California Breast Cancer Research Program
Special Research Initiatives

Identifying gaps in breast cancer research: Addressing disparities and the roles of the physical and social environment

Editors

Julia G. Brody, PhD
Executive Director
Silent Spring Institute

Marion (Mhel) H.E. Kavanaugh-Lynch, MD, MPH
Director
California Breast Cancer Research Program

Olufunmilayo I (Funmi) Olopade, MD
Walter L. Palmer Distinguished Service Professor of Medicine
University of Chicago Medical Center

Susan Matsuko Shinagawa
Breast Cancer and Chronic Pain Survivor/Advocate, Intercultural Cancer Council;
Asian and Pacific Islander National Cancer Survivors Network

Sandra Steingraber, PhD
Author and Distinguished Visiting Scholar
Ithaca College

David R. Williams, PhD
Department of Society, Human Development and Health
Harvard School of Public Health

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Deborah Bowen, PhD, Professor, Social Behavioral Sciences, Boston University

Judy Bradford, PhD, Director, Community Health Research, Virginia Commonwealth University

Linda Burhansstipanov, MSPH, DrPH, Grants Director, Native American Cancer Research

Christina A. Clark, PhD, Research Scientist, Northern California Cancer Center

Lisa Clarke, MS, Research Associate, Northern California Cancer Center

Richard W. Clapp, DSc, MPH, Professor, School of Public Health, Boston University

Melissa B. Davis, PhD, Postdoctoral Fellow/Scholar, Center for Interdisciplinary Health Disparities Research, University of Chicago

Suzanne E. Fenton, PhD, Research Biologist, Reproductive Toxicology Division, U.S. Environmental Protection Agency,

Maria Feychting, PhD, Professor, Institute of Environmental Medicine, Karolinska Institute

Scarlett Lin Gomez, PhD, Research Scientist, Northern California Cancer Center

Robert B. Gunier, MPH, Research Associate, Northern California Cancer Center

Dawn Hershman, MD, Assistant Professor of Medicine, Columbia University

Chanita Hughes Halbert, PhD, Associate Professor University of Pennsylvania

Susan E. Hurley, MPH, Research Associate, Northern California Cancer Center

Esther M. John, PhD, Research Scientist, Northern California Cancer Center

Lovell Jones, PhD, Director, M. D. Anderson's Center for Research on Minority Health

Sue Joslyn, PhD, Professor of Epidemiology, Associate Dean of Graduate Academic Affairs, University of Northern Iowa

Marjorie Kagawa-Singer, PhD, RN, MN, MA, Professor, School of Public Health and School of Asian American Studies, University of California, Los Angeles

Judith Salmon Kaur, MD, Medical Director, Professor of Oncology, Native American Programs, Mayo Comprehensive Cancer Center

Steve Kaye, PhD, Associate Professor, University of California, San Francisco

Charles Land, PhD, Senior Investigator, National Cancer Institute

Robert Millikan, PhD, Professor, University of North Carolina, Chapel Hill

Rachel Morello-Frosch, MPH, PhD, Associate Professor, Center for Environmental Studies, Department of Community Health, School of Medicine, Brown University

Kirsten Moysich, PhD, Associate Professor, Roswell Park Cancer Institute

Margaret Nosek, PhD, Professor, Baylor College of Medicine

Sharon Perry, PhD, Senior Research Scientist, School of Medicine, Stanford University

Blase N. Polite, MD, MPP, Instructor of Medicine, University of Chicago

Anh-Thu Quach, MPH, Research Associate, Northern California Cancer Center

Peggy Reynolds, PhD, Senior Research Scientist, Northern California Cancer Center

Stephanie Robert, PhD, Associate Professor, School of Social Work, University of Wisconsin-Madison

Ruthann Rudel, MS, Senior Scientist, Toxicologist, Silent Spring Institute

Theresa M. Saunders, BA, Research Program Manager, Northern California Cancer Center

Ted Schettler, MD, MPH, Science Director, Science & Environmental Health Network

Richard Stevens, PhD, Cancer Epidemiologist, Department of Community Medicine and Health Care, University of Connecticut

Joseph Thornton, PhD, Associate Professor, Center for Ecology & Evolutionary Biology, University of Oregon

Julie Von Behren, MPH, Research Associate, Northern California Cancer Center

David Wallinga, MD, MPA, Director of the Food and Health Program, Institute for Agriculture and Trade Policy

Barbour Warren, PhD, Research Associate, Program on Breast Cancer & Environmental Risk Factors, Cornell University

Tom Webster, DSc, Associate Professor, Environmental Health, School of Public Health, Boston University

Mary Wolff, PhD, Professor, Mount Sinai Medical Center

Staff and Consultants

Janna Cordeiro, MPH, Coordinator of Special Projects

Elizabeth Day, Program Assistant

Judy Maclean, BA, Editorial Consultant

Katherine McKenzie, PhD, Manager-External Relations; Biomedical Research Administrator

Marj Plumb, DrPH, MNA, Senior Consultant, Plumbline Coaching and Consulting, Inc.

Patrice Sutton, MPH, Technical Consultant

Catherine Thomsen, MPH, Project Lead

PREFACE

- *What role does the environment play in breast cancer?*
- *Why do some groups of women bear a greater burden of this disease than others?*

The answers to these questions have thus far eluded scientists, yet answering them could lead to great progress against breast cancer. Recognizing the need for more research into these questions, the California Breast Cancer Research Program (CBCRP) is launching our Special Research Initiatives, a five-year effort to find answers that will push breast cancer research forward.

We are setting aside 30 percent of our funds over five years for the Special Research Initiatives, approximately $18 million. To select the research that will lead to the most progress against breast cancer, we are following a carefully-crafted, two-year, publicly-accessible strategy development process. An initial step in the process is this report reviewing previous research.

We are embarking on the Special Research Initiatives because research has been conducted for decades, and yet too many women are being diagnosed with breast cancer, living with the threat of a recurrence, and dying. There is no action women can take to assure they won't get breast cancer. Our goals are:

- To initiate research that will point to actions that can be taken to reduce the burden of breast cancer
- To conduct research that will provide recommendations to advocacy organizations and policy makers for evidence-based change.
- To stimulate more research into the environment-breast cancer connection and the reasons why some groups of women bear a greater burden of breast cancer.

We plan to identify and involve California organizations and institutions who can join forces and increase the resources available to conduct this research.

This report is not a comprehensive review of all research on the environment-breast cancer connection or the reasons why some groups of women bear more of the burden of the disease. It is instead a review of existing research—gathered from widely scattered sources—pointed toward discovering research areas that show some connection with the disease, and recommending further investigations that are likely to make the most difference toward eliminating the death and suffering caused by breast cancer.

The Need for This Research

Breast cancer is a complex disease. Despite decades of intensive research, its causes and basic biology remain unclear. From the 1940s until very recently, the U.S. breast cancer rate has been rising, and this increase is not explained by better detection methods.

Scientific studies have uncovered a number of risk factors for breast cancer. Some of these risk factors can be modified by individuals to lower

their risk, and others cannot. One known risk factor is a family history of the disease, which raises a woman's risk. This can't be modified by individuals. Another known risk factor is not having children or having children later in life. Although this can be modified by individuals, it isn't a feasible strategy for most women in the U.S. economy and culture today. Other risk factors include lack of regular exercise and obesity. These can be modified by individuals and are the focus of a good deal of current research.

However, all known risk factors for breast cancer taken together can only account for some percentage of the disease. The percentage is in dispute, with estimates ranging from 50-70 percent. This means that for 30-50 percent of all cases of breast cancer, we can pinpoint nothing that may have even contributed to causing the illness. Clearly, there is a lot yet to be understood about breast cancer.

Studies of immigrant populations provide evidence that environmental causes may play a role in the 30-50 percent of unexplained breast cancer cases. For decades, researchers have noticed different patterns of breast cancer in different populations. For example, women in Asia have far lower rates of breast cancer than women in the U.S.. Soon after they move to the U.S., Asian women's rates of breast cancer begin to rise. The risk rises further for the next generation of Asian women who grow up in the U.S.. These patterns, which have remained largely unexplained for 50 years, suggest that the environment has a role in causing breast cancer. These patterns also suggest that further study into breast cancer differences among various population groups could not only lead to a decrease in inequality among groups of women with breast cancer, but also reveal crucial information about the disease itself.

One major reason that more research has not already been done on the questions we are addressing is that they are difficult and complicated to research. There's no scientific consensus about where to begin. Previous research, as this report reveals, has been reported in widely scattered sources and conducted under a variety of paradigms and philosophies. These approaches include basic science, epidemiology, toxicology, social justice/critical theory, health services, health policy, and community-based participatory research. Each of these research paradigms has methodological challenges. Multi-disciplinary research combining some or all of the research approaches will be a complex endeavor. It will require establishing communication lines across diverse scientific subcultures.

California: The Unique Laboratory

California has unique resources for investigating the environment-breast cancer connection and reasons why some groups of women bear a greater burden of the disease. This combination of resources creates an opportunity no other state or country can match. These resources include:

- **Geographic variety**, with large rural, urban, and suburban areas.
- **Diverse population**, with a wide spectrum of income, social class, and cultures; many ethnic groups; and first, second, and third

generation immigrants from low-incidence areas such as Asia.

- **Unique databases,** with high-quality data on cancer incidence and data on pesticides and pollutants mandated by state Proposition 65.

- **Excellent research institutions**, including schools of public health and a strong state Health Department, with some experience in collaborative research.

- **Strong environmentalist and breast cancer advocacy groups**.

What We Mean by "Environment"

Some researchers define the influence of environment on breast cancer as everything that is not due to the influence of genes. For the purposes of our Special Research Initiatives, the CBCRP is using a narrower definition. We define "environment" as all of the non-genetic factors that might lead to breast cancer that are also largely outside an individual's control. This definition includes possible causes of breast cancer resulting from exposure to sources such as air pollution, second hand smoke, and pharmaceuticals.

Defining "environment" in this way means that under our Special Research Initiatives, the CBCRP will not pursue further studies into the well-researched connection between breast cancer and lifestyle, including diet. We believe studies of this type are valuable and should be continued. However, the focus of our Special Research Initiatives will be on how the environment directly affects breast cancer or affects lifestyle in a way that can lead to breast cancer. For example, we might pursue an investigation of how the environment shapes American women's diets, by investigating how different neighborhood characteristics affect women's food choices.

"Environment," by this definition, includes the human-created, built environment. We may include investigations of how features of the built environment might impact breast cancer, for example, whether racial segregation makes survival less likely. We may also include ways the built environment has an impact on lifestyle. For example, we would not investigate further the question of whether regular exercise may help prevent breast cancer, but we might study the ways that features of the built environment, such as neighborhood design, create opportunities or barriers to women getting exercise.

Challenges of Investigating the Environment-Breast Cancer Connection

One logical place to look for causes of breast cancer in the environment is to investigate the role of toxic chemicals, pollutants, and other similar agents. This type of research already has led to controversy, with some experts claiming that research has demonstrated that there is no connection, and others saying researchers have barely scratched the surface of these questions.

Researching the connection between toxic exposures and breast cancer presents methodological challenges. These include:

Lack of basic biological knowledge. Researchers do not know exactly what biological

changes a cell goes through as it transforms from normal to cancerous. Therefore, it is hard to determine whether exposure to a particular substance or a particular combination of exposures stimulates the development of breast cancer.

Many subtypes of the disease. DNA analysis shows that breast cancer is not one disease, but many. A particular toxic exposure could be related to just one subtype.

Timing of exposure. A toxic exposure may lead to breast cancer years, or even decades, after the substance has been eliminated from the body. Toxic exposures as early as when a baby girl is still in the womb could predispose her to breast cancer as an adult. Uncovering the connection between the exposure and the disease is difficult.

Dose. Researchers don't know how much the amounts of exposure matter. For example, it is unclear whether one massive dose of a toxic chemical is more or less likely to cause breast cancer than exposures to small amounts of the same substance over a long period of time.

Combinations of exposures. Testing for the role of one toxic substance ignores the fact that most people have experienced a variety of toxic exposures in combination.

Gene-environment interactions. Some toxic exposures may only increase the risk for breast cancer in women who carry certain genes.

Privacy Concerns. Federal privacy regulations make it difficult to conduct studies on large populations of women who may have experienced toxic exposures, because each individual must consent to the use of her medical record.

Lack of tests for exposures. The single biggest challenge to researching the breast cancer-environment connection is that scientists have developed few reliable tests to determine whether a given woman has been exposed to chemicals, pollutants, or other agents that could lead to cancer in breast tissue. Especially needed are tests that can detect biomarkers that provide a trace of past exposure to toxics that the body eliminates quickly.

All of these challenges complicate research into the breast cancer-environment connection.

The Unequal Burden of Breast Cancer

Different groups of women in the U.S. are impacted differently by breast cancer. African American women, for example, get the disease at younger ages. They are less likely than white women to get breast cancer, but once they have it, they are more likely to die from the disease. Some of the disparities between various groups of women can be explained by unequal access to care, but not all of them.

Much of the previous research into why some groups of women bear more of the burden of breast cancer has been descriptive and has not addressed how to decrease or eliminate the inequality.[1]

Challenges of Investigating Why Some Women Bear More of the Burden of Breast Cancer

Investigating why different groups of women are impacted differently by breast cancer presents its own set of challenges. These include:

Problems with definitions. "Race" is more of a social construct than a biologic category. The commonly-used racial groupings in the U.S.—African American, white, Hispanic, Asian, Pacific Islander—do not have consistent genetic profiles within the groups or consistent genetic differences between groups. However, this is an area of scientific controversy, with some geneticists arguing that some genes are commonly distributed among some racial groups. In any case, differences in breast cancer among various groups are probably due to a combination of genetics and differences in the environments in which these groups live and work. This underscores how intertwined are the two questions being investigated under the CBCRP's Special Research Initiatives.

Variations within groups. There are great variations within racial/ethnic groups. "African American" includes people whose ancestors were brought to this country as slaves eight generations ago, and people who immigrated from Kenya last month. Their genetic profiles, environmental exposures and experiences of the human-made environment are likely to be very different. Similarly, "Asian/Pacific Islander" combines people of Japanese ancestry with people from India, who aren't similar. However, if each subgroup in the "Asian/Pacific Islander" population of California is studied separately, the numbers of women are often too small for statistically meaningful research.

Socioeconomic status adds complexity. Higher socioeconomic status is a risk factor for breast cancer. Comparisons of breast cancer incidence and death rates for various ethnic groups often fail to address differences in socioeconomic status. Taking socioeconomic status into account adds another level of complexity.

Confusion between the biological and the environmental. Differences in breast cancer related to race may be biological, environmental, or a combination. For example, African American women being more likely to die from the disease could be due to a genetic predisposition toward more lethal types of tumors. It could also be due to the stress of racism, to lack of access to treatment, to living in neighborhoods that make survival less likely, or to a combination of any of these factors and other unknown factors. Untangling multiple, related causes complicates research.

The Framework for Each Chapter of this Report

Researchers JudyAnn Bigby and Michelle D. Holmes have provided a framework for studying how breast cancer differently impacts various groups of women. Each chapter of this report follows a framework we have adapted from Bigby and Holmes:

1) We begin by defining the factor related to breast cancer.

Chapters in Section I, Exposures from the Physical Environment, define the exposure, for example, pesticides, light at night, or compounds in cosmetics and personal care products.

Chapters in Section II, Disparities in Breast Cancer: Domains of Individual-Level Social Inequality, define the characteristics of groups of women who bear unequal burdens of breast cancer. Examples include ethnicity, age, sexual orientation, and insurance status.

Section III, Disparities in Breast Cancer: Neighborhood Built and Social Environment, defines features of the human-created environment that may underlie geographic differences in breast cancer rates in California. Examples include racial segregation in housing and human-created features of the environment that alter personal behavior.

2) We summarize the biological evidence that this factor is relevant to breast cancer.

3) We review research that links the exposure, characteristic of groups of women, or human-created feature of the environment to breast cancer:

a) incidence

b) etiology/prevention

c) screening

d) diagnosis

e) treatment

f) morbidity

g) quality of life after diagnosis

h) survival

i) mortality

Many chapters discuss only one or a few of the topics above, because each chapter covers only those areas where some research has been conducted. The chapters in Section I, Exposures from the Physical Environment and Breast Cancer, mostly deal with etiology and tumor promotion. For example, no research has been conducted on the relationship between exposure to pesticides and quality of life after diagnosis. Therefore, quality of life after diagnosis is not discussed in Section I, Chapter B.4, Pesticides.

4) We discuss limitations and gaps in knowledge.

5) We recommend the highest priority/highest payoff research for the factor being reviewed. We also recommend other future research and future policy interventions that could result from research.

There is considerable overlap among the chapters that follow. For example, studies of breast cancer and race (Section II, Chapter A), often overlap with studies of breast cancer and culture (Section II, Chapter D).. Some of the same chemicals discussed in Section I, Chapter B.2, Persistent Organic Pollutants, are chemicals of concern in air pollution, which is discussed in Section I, Chapter B.1. Where there is a large overlap in the research, we discuss the issue in detail in one chapter, and refer to it in other chapters.

A General Recommendation

One general recommendation emerges from multiple chapters of this report. It concerns possible future partners for the Special Research Initiatives. Many of the toxic exposures considered here are likely causes of other types of cancer and other diseases. This is also true of features of the built environment. Just as breast cancer impacts various population groups of women in unequal ways, some groups of women bear a greater burden of other diseases and health problems. One way to increase the financial resources for the Special Research Initiatives would be to conduct joint research with organizations investigating other diseases. For example, breast cancer researchers, childhood asthma researchers, and birth defects researchers might team up to study the role of air pollution in causing or exacerbating all three.

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Introduction

The nature and direction of scientific inquiry is neither neutral nor random, but is best explained by its social and political context.[1] Breast cancer research is not exempt from the influence of social and political forces. However, the systemic forces that shape the creation of science are often sufficiently subtle to maintain the illusion that scientific inquiry is free of these powerful influences.[1] Ignoring such forces may constrain contemplation of the full range of possibilities in studying the environment, disparities, and breast cancer. Therefore, the following introduction briefly explores the social and political forces that have helped script what we know and what we do not know about the environment, disparities and breast cancer.

The Gaps in Knowledge

"The best way not to see something is not to look for it."

Alice Stewart, Epidemiologist, discoverer of the link between fetal exposure to ionizing radiation and childhood cancer.[2]

While the science reviewed on the following pages will guide future research efforts by what the studies say, it is equally informative to consider what these studies do not shed light on. Brody et al recently reported that the overwhelming majority of chemicals identified as animal mammary carcinogens or endocrine disrupting compounds have never been included in an epidemiologic study of breast cancer, and the overwhelming majority of chemicals to which we have been exposed have never been included in an animal cancer bioassay.[3]

Of those environmental pollutants for which questions have been asked, the science is dominated by research examining single agents or classes of chemicals one at a time, examined under the toxicological lens of "the dose makes the poison." As described in the introduction to Section I, research exploring the relationship between breast cancer and exposure to chemical mixtures, the influence of when in a lifetime exposure occurs, and a search to understand environmental agents with the power to modify known reproductive risk factors is largely lacking.

The relative amount of information on individual topics in the science review does not imply a relative worth. We may know more about some chemicals than others simply because regulations have led to the scrutiny of some chemicals but not of others. For example, the fact that there is not a lot to say about the relationship between antibiotics and growth hormones in food and breast cancer does not mean that these exposures are not important. It only means these questions have not been addressed.

The research reviewed on disparities also has systemic shortcomings. Although the U.S. Public Health Service has been documenting the nation's health and related disparities for a century, there has been a lack of progress in undertaking the research needed to address the unequal burden of disease including breast cancer. While in the 1950s African Americans had lower rates of cancer mortality than Whites, they currently have higher rates. But we do not yet fully know why such disparities exist. As described in Section III, in many cases, the broad, socially-constructed categories used to group individuals by race and ethnicity tend to obscure rather than illuminate underlying differential patterns of disease.

The scientific evidence presented on the following pages also suffers from the compartmentalization of the research between three discrete areas: the physical environment, disparities, and the social environment. The reality of the lives of people of color and the poor is more likely to resemble a coming together of the physical and social environment and disparities. Twenty years after the 1987 United Church of Christ Commission for Racial Justice released its groundbreaking study that found race to be the most potent variable in predicting where commercial hazardous waste facilities were located in the U.S., significant racial and socioeconomic disparities persist in the distribution of the nation's commercial hazardous waste facilities.[4] The perfect storm of the geography of environment risk, race and social vulnerability is profoundly visible in the wake of Hurricane Katrina.[4]

The atomized nature of these prevailing models of inquiry is incongruous with the mechanisms of breast cancer, which reflect a complex web of potential interactions among multiple factors to produce the circumstances in which breast cancer develops, is promoted, and becomes clinically apparent (Table). The current understanding of the mechanisms of cancer indicates that all cancers arise from a convergence of the environment and genes,[5] and that neighborhood and social factors such as racism, the physical and chemical exposures incurred where people live, work, and play, biology, and other factors may all have a role. But most epidemiologic studies of breast cancer have focused on a narrow range of personal behaviors or genetics, ignored a broader spectrum of potential environmental risk factors, and neglected the question of how these exposures interact with genes.[6]

Table 1. Mechanisms of Breast Cancer Development

Mechanism	Description
Initiation	Tumor initiation may occur as much as 20 to 40 years before diagnosis, and consists of permanent changes in a cell.[7] Carcinogens that initiate tumor formation are genotoxic or able to directly damage DNA.
Promotion	Promotion involves the stimulation of cell proliferation or tumor growth and is thought to require repeated exposure to endogenous or exogenous compounds. Estrogen is believed to influence mammary carcinogenesis through promotion. Wolf and Weston state that tumor growth may be promoted by exposure to endogenous hormones or exogenous environmental hormone mimics.[7]
Progression	Progression is the transition from a benign to malignant tumor and also involves some level of genotoxicity.[8]
Epigenetics	Epigenetic mechanisms cause heritable changes in gene function without a change in the sequence of the DNA. There is evidence epigenetic mechanisms are involved in the regulation of critical tumor suppressor and growth regulatory genes in breast cancer that are important for DNA repair, cell cycle control, as well as cell growth and differentiation.[9, 10]

Where Does the Money Go?

Research follows the money. The gaps in the science review echo where the money has not gone. Of those resources directed to cancer research, only a small amount of funding has been allocated to explore avoidable exposures to a wide range of occupational and environmental industrial carcinogens. Only 10 percent of the National Cancer Institute's (NCI's) $5.9 billion 2008 budget request is allocated to "cancer prevention and control," and based on a review of NCI's stated research goals, most of NCI's expenditures in the field of prevention appear to be in search of improved detection and other control measures.[11, 12]

Money has also not flowed to disparities research. Although health disparities have been documented for a century, as recently as 1999, an Institute of Medicine committee charged with reviewing the programs of research at the National Institutes of Health (NIH) relevant to ethnic minority and medically underserved populations concluded that an inadequate one percent of the NCI's 1997 budget was allocated to research and training programs relevant to these populations, and that "no blueprint or strategic plan to direct or coordinate [health disparities] research activity appears to exist."[13]

Historically, breast cancer research has focused primarily on identifying targets for therapy and treatment. Prioritizing funding for treatment and related research while neglecting primary prevention research-related activities parallels the overall imbalance among health care and public health resource allocations. An analysis of U.S. state and local public health agency expenditures found that mean per capita spending for public health in 2004–2005 was $149, compared to $6,423 for overall health care.[14] Public health, charged with creating healthful conditions for all, has competed unsuccessfully for resources supporting technologically intensive disease treatment aimed at individual consumers.[15, 16] In 2006, America's pharmaceutical and biotechnology research companies set a new record for biopharmaceutical research, spending $55.2 billion to develop new medicines and vaccines, or about double the entire NIH budget of $28.4 billion budget in the same year.[17]

Gaps in knowledge that stem from the lack of resources directed towards understanding the impact of environmental pollution on breast cancer feed back into society as messages that "there is no evidence" that pollution plays a role.[3] NCI's breast cancer prevention advice to patients explicitly downplays environmental etiology, stating "studies have not proven that being exposed to certain environmental exposures (such as chemicals, metals, dust, and pollution) increase the risk of breast cancer."[18] The "no evidence" message informs clinicians' perceptions about the role of the environment in the etiology of cancer, may influence the likelihood that clinicians ask their patients about workplace and community exposures, and thus may diminish the important historical role of clinicians as sentinel reporters.[19]

Finally, the decline in cancer funding – funding of federal grant applications for cancer research has fallen from about 30 percent to about 9 percent – is further reducing progress in cancer prevention research. An academic researcher and NCI grant reviewer stated recently in the New York Times that due to decreases in cancer funding, "a whole generation of American scientific researchers is at risk; careers are ending because of a lack of

federal dollars … in effect, American mothers have been asked to swallow their objections instead of their tamoxifen; breast cancer is simply not an administration priority anymore."[20]

What Questions Are Asked?

Institutional racism and prejudices impact what questions are asked and what knowledge is included in science. To address disparities, we must understand how the legacy of racism and prejudice against people of color, sexual minorities, the disabled, immigrants, the poor and others in all its manifestations, (i.e., stressful experiences on the individual level, residential segregation, etc.) interacts with social, physical and other factors to impact health. Such research challenges our notions of ourselves, our nation, and our policies and practices that sustain inequalities and prejudices. The scientific infrastructure, the individuals and institutions that establish research priorities and disperse funding, are uncomfortable with this type of research. Their discomfort gets translated into policy that is reflected in the science review.

On a practical level, segregation serves to make the experience of others invisible and therefore questions are not formed in the first place. For example, clinicians who by virtue of the segregated nature of our society do not see young African American women dying of "triple negative" breast cancer would be less likely to ponder the reasons for this disparity than physicians who must relate this devastating news to their patients.[21]

Whether disparities research is framed as a social or biological question has profound implications. While in historical hindsight, the assumptions that led some scientists to search for biological answers to social inequalities were clearly racist in nature, it would be perilous to assume science is free of such blinders in the present day.[22] The role of race in biomedical science has been and remains an area of fierce controversy.[21-25]

Advances in genetics have made it possible to characterize the genetic differences between individuals and populations and have led to the abandonment of "race" as a biological category during the last quarter of the twentieth century.[25] The fact that race is not a scientific category but rather captures socially-determined distinctions provokes skepticism about the study of race and genetics among some scientists, including Harold Freeman, former director of the NCI Center to Reduce Cancer Health Disparities.[21] Schwartz maintains in the New England Journal of Medicine that attributing differences in a biologic end point to race is imprecise and of no proven value in treating an individual patient, warns of the dangers inherent in practicing race-based medicine, and recommends that any investigation involving so-called racial distinctions should begin with a plausible, clearly defined and testable hypothesis.[26]

Other scientists, while acknowledging the historic and current inequities based in perceived racial or ethnic identities, believe there can be validity and benefit in the use of racial/ethnic self-categorizations in scientific research.[23, 27, 28] These scientists believe that ignoring race and ethnic background would be detrimental because this information serves as a necessary surrogate measure to identify, track and investigate health disparities and risk factors, and to facilitate testing, diagnosis and treatment when genetic factors are

involved.[23] They argue that because racial and ethnic groups differ from each other on a variety of social, cultural, behavioral, and environmental variables as well as gene frequencies, "race-neutral" epidemiology that relies solely on genotype cluster analysis could lead to spurious genetic inferences due to confounding by the many other ways the groups might differ.[27]

Who Frames the Questions?

The 1999 Institute of Medicine review of the health disparities research portfolio at the NIH spoke to the fundamental difference between inclusion as a research subject versus individual and group inclusion in processes that pose what questions are asked and how they are answered. The report found "diverse study populations do not, in and of themselves, address the research needs of ethnic minority and medically underserved populations unless meaningful research questions relevant to these groups can be posed a priori and answered based on the appropriateness (i.e., diversity and generality) of the study population."[13]

Following the Institute of Medicine's findings that the research priority-setting process at NCI and NIH fails to serve the needs of ethnic minority and medically underserved groups, the National Center on Minority Health and Health Disparities was established with the goal of promoting minority health and to lead, coordinate, support, and assess the NIH effort to reduce and ultimately eliminate health disparities.[29] In FY 2008 NIH proposes to spend $12 million dollars to support community-based participatory research on health disparities.[30]

This laudable effort on the part of NIH as well as foundations to fund disparities research also reveals the systemic tensions that are perpetuated throughout the production of science that greatly influence the outcome of research. For example, while institutional decision-makers may place much value on the scientific merits of a well-written grant proposal, populations that are directly impacted by disparities are more inclined to judge expertise by researchers' demonstrated commitment to developing the trust of the population under study. Research that incorporates the perspective of communities who are directly impacted by disparities faces many other hurdles. The concerns of community advocates include: (1) the resources committed for disparities research may be unequal to address the task at hand; (2) pre-existing systemic inequalities in educational opportunities make it difficult to generate qualified researchers with roots in the impacted population; and (3) differences in the maturity of programs across racial and ethic populations place communities new to disparities research at a structural disadvantage compared to other populations. The concern is that the sum of these tendencies may produce the "scientific" conclusion that community-based health disparities research has been a failed experimental model.

Research has often fallen short of ensuring the incorporation of the direct knowledge of the activities, experiences, and ideas of workers, clinicians, community members, minority populations and others with insights relevant to scientific discovery, a practice that has adversely impacted environmental epidemiology. While exposure assessment conducted without the incorporation of such local knowledge is inherently limited, research funding rarely values the time and resources essential to gain the trust,

and to gather the first hand knowledge, of directly-impacted populations. Illustrative of this problem, reconstruction of radiation doses incurred by Native Americans as a result of the production and testing of nuclear weapons was severely flawed by a failure to include Native Americans' knowledge of their diet, activities, and housing. Important pathways of exposure were missed including exposures to radioactive iodine from eating small game.[31]

Summary

There are many limitations in the science review on the following pages. Methodological issues discussed throughout the review do not alone account for these shortcomings. Non-scientific economic, social and political forces have and continue to shape our knowledge of the environment, disparities and breast cancer. How funding priorities were set, money was awarded, questions asked and not asked, framed in one way versus another, all help explain the deficiencies in our knowledge. The examples provided are by no means an exhaustive accounting of the non-scientific currents that are embedded in the papers that follow.

We are moving towards answers to questions about the environment, breast cancer and disparities as a direct result of political action on the part of advocates who waged a successful campaign that led to the passage of the Breast Cancer Act in 1993 leading to the establishment of the California Breast Cancer Research Program, and in turn to the Special Research Initiative. While patient, environmental and community-based advocates have had great success in promoting changes at NCI and other academic funding mechanisms regarding the nature and extent of research on disparities and environmental pollution, their influence is likely dwarfed by the historical factors, social, and political described above. A clear understanding of the impact of these forces can inform strategic thinking about how to effectively bolster the influence of communities impacted by breast and other cancers in setting a new research agenda. Only in this way can we frame the right questions and find the path to relevant answers about the relationship between the environment, disparities and breast cancer. The limitations of the current science as reflected in this review speak volumes about the need to proceed with a sense of urgency.

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Breast Cancer and Exposures from the Physical Environment:

Introduction and Overarching Issues

In May 2007, 200 leading environmental scientists convened in the Faroe Islands north of Scotland to consider the human health effects of early-life exposures to environmental toxicants. This gathering, the International Conference on Fetal Programming and Developmental Toxicity, resulted in a signed declaration that made headlines around the world, for example, in the Los Angeles Times.[1] The Faroes Statement warned that low-level exposures to common environmental chemicals during fetal life and early infancy increase risks for various health problems later in life. According to the document, these problems include diabetes, attention deficit disorders, obesity, infertility, and thyroid disorders. They also include breast cancer.[2] Singled out for mention were the common pesticide atrazine and the common plastics ingredient, bisphenol A, which, according to the document's consensus statement, can alter breast development in early life in ways that increase susceptibility to breast cancer in adulthood.

The Faroes Statement goes on to call for a fresh approach to research on breast cancer and other diseases that recognizes a new paradigm of toxicologic understanding:

> "The old paradigm, developed over four centuries ago by Paracelsus, was that 'the dose makes the poison.' However, for exposures sustained during early development, the most important issue is that 'the timing makes the poison.' This extended paradigm deserves wide attention….Among the mechanisms involved, particular concern is raised about changes in gene expression due to altered epigenetic marking, which may not only lead to increased susceptibility to diseases later in life, but the effects may also be passed on to subsequent generations."[2]

Andreas Kortenkamp, a toxicologist at the University of London, has likewise called for a new approach to breast cancer that recognizes the existence of *critical periods* in early life and during development that sensitize the breast to carcinogenesis by hormonally active chemicals. Emphasizing the biological plausibility of such an approach, Kortenkamp points out that the majority of cancers arise from the terminal end buds of the breast ducts. Any environmental chemical that increases the number of cells in the end buds during early life or that delays the maturation of these structures can raise the risk for cancer—even without direct genetic damage.[3, 4] The weed killer atrazine, to which 60 percent of the U.S. population is exposed daily, is such a chemical. In laboratory animals, atrazine exposure *in utero* retards the maturation of the mammary gland in puberty and increases the number of end buds.[5, 6] The insecticide DDT may also be such a chemical. A study of women in Oakland, California has found that high serum levels of DDT predicted a five-fold increased risk of breast cancer among women exposed prior to age 14. Women exposed

after age 14 showed no link between blood levels of DDT and breast cancer.[7]

For environmental exposures that do induce genetic damage, such as ionizing radiation, timing of exposure also matters. Among atomic bomb survivors in Hiroshima and Nagasaki, for example, breast cancer increased significantly only among those exposed during puberty.[8] More recently, a study of breast cancer patients who had been treated previously with radiation therapy for childhood cancers found a link between timing of radiation exposure and the development of HER2-positive tumors: the highest risk occurred in patients irradiated within four years of menarche.[9] And yet, in spite of evidence such as this, conventional epidemiological and toxicological testing does not routinely take into account developmental differences at the time of exposure.

Many leading researchers, including Kortenkamp, have also urged increased attention to *chemical mixtures* in environmental health research. Real-life exposures to environmental agents, these researchers point out, are not limited to one chemical but, most often, result from low-level exposures to a changing kaleidoscope of chemicals, some of which may operate down similar molecular pathways.[3, 4, 10-12]

A recent Spanish study, for example, demonstrated that breast cancer risk among women was associated with the body burden of all estrogenic chemical contaminants, excluding natural hormones.[13] Among grazing sheep in Scotland, males exposed *in utero* to a cocktail of chemicals found in sewage sludge developed testicular abnormalities,[14] while females reared on pastures treated with sewage sludge showed abnormalities in mammary gland development.[15] In lab animals, exposure to dioxin in fetal life sensitizes mammary glands to carcinogenic assault by other chemical agents in later life.[5] More specifically, dioxin-exposed breast tissue is less able to fend off the damage caused by subsequent free radical exposure.[16] And yet, again, conventional testing has not routinely taken into account the effects of low-level exposures to chemicals in combination. Like atrazine, bisphenol A has been detected in ground water and private wells.[17, 18] What is the risk for a young girl whose drinking water contains both?

Exposures from the physical environment may also play a role in the breast cancer story if they *amplify the effects of known risk factors*. Early puberty – especially early menarche – is a well-established risk factor for breast cancer. As age of menarche decreases, overall risk of breast cancer increases.[19] Menarche before age 12, for example, raises breast cancer risk by 50 percent when compared to menarche at age 16.[20] Environmental factors that hasten the timing of sexual maturation may thus contribute to breast cancer risk. Some researchers have posited that greater use of estrogen- or placenta-containing hair preparations may be contributing to the falling age of puberty among U.S. black girls.[21, 22] If so, they may also contribute to racial disparities in breast cancer. In addition, chemicals in the physical environment may contribute to early puberty – and thereby to breast cancer risk – if they shorten human gestation, lower birth weight, or increase the risk for obesity and insulin disregulation. All of these factors are associated with earlier sexual maturation in girls.[20, 23-25]

In contrast to early puberty, breast-feeding is a reproductive factor known to lower breast cancer risk, especially among post-menopausal women.[26] Thus, chemical exposures that interfere with lactation may increase the risk for breast cancer. Some organochlorine chemicals have been associated with shortened duration of breast-feeding among nursing mothers in North Carolina and Mexico[27, 28] and decreased milk volume among mothers in the Netherlands.[29] And yet, although pubertal timing and duration of breast-feeding are both known to modify breast cancer risk, little research has explored the impact of the physical environment on these two reproductive factors.

In sum, a fresh approach to the question of breast cancer's environmental roots would take up the question of chemical mixtures, would consider the timing of exposure, (with an emphasis on exposures that happen in utero and in early life), and would expand the search to include environmental agents with the power to modify known reproductive risk factors.

The chapters of this report that follow do not, for the most part, take this tack. Instead, they summarize the evidence—from *in vitro*, animal, and human studies—for individual environmental agents in isolation from one another. While there are obvious shortcomings to this kind of analysis, the hope is that the atomized organization of these chapters will, nevertheless, inspire the reader to consider the various ways in which these individual agents might interact with one another in a web of causality and, in so doing, will reveal potential avenues of inquiry that would be fruitful to pursue. As two new papers reveal, exposure to mammary gland carcinogens is widespread.[30] Many of these have not yet been included in human studies.[31] Among the 216 compounds identified as mammary carcinogens in animals, 73 are found in food or consumer products; 35 are air pollutants; and 29 are produced in the U.S. in large amounts.[30] Thus, even using old-fashioned criteria – investigating one mammary carcinogen at a time using conventional toxicological research – we still have much to learn about how to identify chemical contributors to breast cancer and eliminate them from the environment.

Understanding the role of industrial chemicals and other environmental factors in the story of breast cancer, a disease characterized by complexity and multi-causality, will require bringing the best time-honored techniques of traditional toxicology and epidemiology together with holistic approaches that, so advise the authors of the Faroes Statement,[2] focus on systems and tissue biology.

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Environmental Tobacco/ Second Hand Smoke

Introduction

It is widely acknowledged that tobacco smoke is a known human carcinogen.[1] Approximately 60 percent of nonsmokers in the U.S. show biological evidence of exposure.[2] In California, where smoking rates are below the national average (14.8 percent currently smoke versus 20.9 percent nationwide)[3, 4] and strict antismoking legislation is in place, environmental tobacco smoke (ETS) exposures are likely to be less pervasive, yet remain significant.[3] There is consistent evidence that ETS exposure, also referred to as second hand smoke (SHS), is an established risk factor for lung cancer.[1-3] Over the course of the last 30 years, nearly 100 studies of tobacco exposures and breast cancer have been published, with recent studies re-conceptualizing causal models in ways that promise to clarify the role of tobacco smoke exposures in the etiology of breast cancer.[5, 6]

In keeping with the CBCRP's emphasis on environmental, rather than lifestyle, factors for the purposes of this report, the focus of this chapter is the role of ETS exposure in breast cancer etiology. However, because much of the research and discussion of ETS exposure has been interwoven with that of the potential effects of active smoking, we include some discussion of the active smoking literature where we feel it helps clarify the role of ETS exposure.

Concept/Exposure Definition

Following the abundance of research documenting the adverse health effects of active smoking, researchers began to investigate the health consequences of exposure to ETS among nonsmokers. ETS is comprised of a mixture of exhaled mainstream smoke and sidestream smoke released from the smoldering end of a cigarette or other smoking device. Other terms used to describe this exposure include passive smoking, second hand smoke, and involuntary smoking. As there currently is considerable debate over the most appropriate term, for the purpose of this report we will use the combined term environmental tobacco smoke/second hand smoke (ETS/SHS) throughout.

ETS/SHS is composed of both vapor and particles. Its composition changes during its dilution and distribution in the environment over time. The concentrations of ETS/SHS components in a physical space depend on the number of smokers, the rate at which they smoke, the type of smoking device used (e.g. filter versus non-filtered cigarettes, cigars, pipes, etc.), and the volume and ventilation characteristics of the space in which smoking is occurring.[1, 2] ETS/SHS is a complex mixture comprised of thousands of different compounds. The volatile phase contains 400–500 compounds, while more than 3,500 different compounds have been identified in the particulate phase. At least 50 known or suspected carcinogens have been identified in ETS/SHS, including the widely-studied known carcinogens polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines.[2, 3, 7] Furthermore, at least twenty constituents of tobacco smoke (listed in Table 1 below) have been identified as mammary carcinogens.[3] These carcinogens are not exclusive to tobacco smoke. Women can be exposed through many other sources, including occupational exposures, diet, and pesticides.[7]

Table 1. Mammary Carcinogens Identified in Tobacco Smoke

Benzene	N-nitrosodiethylamine	Acrylamide
Benzo[a]pyrene	N-nitrosodi-n-butyl-amine	Acrylonitrile
Dibenz[a,h]anthracene	4-Aminobiphenyl	1,3-Butadiene
Dibenzo[a,e]pyrene	Nitrobenzene	Isoprene
Dibenzo[a,h]pyrene	Ortho-Toluidine	Nitromethane
Dibenzo[a,I]pyrene	Propylene oxide	Vinyl chloride
Dibenzo[a,l]pyrene	Urethane	

Source: California Air Resources Board (ARB).[3]

Because the smoldering end of a cigarette burns at lower temperatures, leading to incomplete combustion of organic materials, the concentrations of many carcinogens can be considerably higher in sidestream, compared to mainstream, smoke.[2, 7, 8] While the actual exposure to carcinogenic compounds is much higher in active smokers, ETS/SHS exposures can amount to the exposure equivalent of actively smoking several cigarettes a day.[7]

Assessing exposure to ETS/SHS in epidemiologic investigations of breast cancer has been challenging. Problems include the lack of adequate long-term biomarkers or physical measurements, as well as difficulties in assessing ETS/SHS exposure via epidemiological instruments. Cotinine, the primary metabolite, or breakdown product, of nicotine, is presently the biomarker of choice for assessing ETS/SHS exposures. It is easily measured in a number of biologic media (e.g., blood, urine, saliva), is highly specific to tobacco smoke exposures, and has proved useful in distinguishing active from passive smokers.[2] Its usefulness in breast cancer research, however, is limited in that measurements can only capture recent exposures. Furthermore, it only represents one component of a complex mixture and may not reflect exposures to other compounds of concern. Finally, cotinine levels are not simply a function of exposure but also reflect individual variations in metabolism and excretion rates. Thus, no good biomarker of chronic long-term exposure to ETS/SHS currently exists. Air monitoring and personal sampling are other approaches utilized to assess SHS exposures. Again, these are of limited usefulness in breast cancer research because they cannot be used to measure prior/long-term exposures.

Consequently, the majority of epidemiologic studies of tobacco exposure and breast cancer rely on questionnaires to estimate exposure. The quality of the data captured by epidemiological questionnaires is a function of reliability and validity. A questionnaire is considered reliable if the same person gives the same response when asked multiple times. Further, an instrument is valid if it actually measures what it is intended to measure. Reliability and validity studies of ETS/SHS questionnaires have shown that they are reasonably good at capturing current or recent exposures, demonstrating good agreement with cotinine levels.[2] However, evaluating the validity

of questionnaires to capture lifetime or early exposures is problematic, as there is no biological measure against which to compare. Evidence on the reliability of questionnaire answers is mixed. While people give consistent responses about the presence of spousal smoking, which is a key measure of adult exposure, the reliability of quantitative information about these exposures (i.e., how many cigarettes a spouse smokes in the woman's presence) may be less than optimal.[2]

Early studies of ETS/SHS exposure and breast cancer often relied on 'living with a smoking spouse' as the index of exposure. Thus, these studies were typically limited to evaluating adult household exposures. Prior to 1970, this may have been adequate at capturing the predominant source of ETS/SHS exposures for women during adulthood.[9] However, as more women entered the workforce in the latter part of the last century, this measure missed the substantial contribution of workplace exposures. Prior to the enactment of restrictive legislation, California workplaces likely were the source of some fairly significant ETS/SHS exposures.[10] More recent studies have attempted to assess ETS/SHS exposures across settings (household, workplace, social) and over time. This body of literature, however, is still relatively small (see Critical Review of the Literature subsection below). The vast differences in ETS/SHS exposure assessment are likely to have greatly contributed to the observed inconsistencies in findings of studies aimed at investigating ETS/SHS exposure in breast cancer etiology.

Biologic Plausibility

From a toxicological perspective, the relationship between tobacco smoke and breast cancer risk is likely to be complex, as there is evidence that tobacco smoke may both be genotoxic and anti-estrogenic. As described above, tobacco smoke contains a multitude of known or suspected carcinogens, several of which are mammary carcinogens.[2, 3, 7] Many of these carcinogens are lipophilic and accumulate in adipose tissue throughout the body, including the adipose-rich tissue of the breast.[6, 7] Metabolites of cigarette smoke have been found in the breast fluid of non-lactating smokers.[11, 12] The presence of smoking-specific DNA-adducts and p53 gene mutations in breast tissue are reportedly more prevalent in smokers compared to non-smokers.[13-19] Thus, there is evidence that tobacco carcinogens not only reach the breast tissue, but also are able to induce biological effects that are common in breast carcinogenesis.

At the same time, breast cancer is an estrogen-mediated disease and there is considerable evidence that tobacco smoke has anti-estrogenic properties. Smoking has been linked to early menopausal age with fewer total years of menstruation, higher incidence of osteoporosis, and lower breast density,[6, 20-24] all of which would suggest a protective effect for breast cancer. Whether these effects appear in nonsmokers exposed to ETS/SHS has not generally been explored, although two recent studies have reported results to the contrary, with earlier age at menarche found among girls exposed to ETS/SHS.[9, 25]

Thus, tobacco exposures may work to both increase breast cancer risk through its genotoxic properties and decrease risk through its anti-estrogenic properties. How these mechanisms ultimately affect breast cancer risk may in part be determined by both the timing of exposure and the genetic susceptibility of an individual.

Genetic susceptibility to the genotoxic effects of tobacco smoke is reflected in an individual's inherited capacities in carcinogen metabolism and detoxification, DNA repair, and various cell-cycle-related and apoptotic pathways. Thus, smoking women with a genetically-determined high capacity (i.e., CYP1A1 variant genotype) to metabolize nongenotoxic pro-carcinogens to genotoxic ultimate carcinogens might be at greater risk of breast cancer than women who smoke, but are less effective in these metabolic processes. On the other hand, women exposed to tobacco who carry genotypes associated with higher detoxification of genotoxic carcinogens (i.e., NAT2 rapid acetylator genotype), might be at lower risk of breast cancer than are women with similar exposures and lower capacity to detoxify carcinogens. These same principles apply for genes relevant in DNA repair, cell cycle control, and apoptotic processes.

The idea that timing of exposure is critical in influencing risk is predicated on the fact that the rate of breast tissue proliferation and levels of cellular differentiation vary over the course of a woman's life and are tied to reproductive events.[26, 27] During times of rapid proliferation, breast tissue is likely to be more susceptible to the harmful effects of carcinogens. Highest rates of proliferation occur during childhood and decrease markedly after puberty, pregnancy, and lactation, as well as gradually with aging. Cellular differentiation of the breast tissue also occurs episodically with puberty, pregnancy, and lactation, reaching its fully differentiated state only after lactation occurs.[28] Less-differentiated tissue is likely to be more susceptible to carcinogenic insults. Thus, it has been suggested that the genotoxic effects of tobacco smoke may be most evident when experienced early in life, especially before a woman's first pregnancy. Conversely, the anti-estrogenic effects of tobacco smoke may prevail when exposures are experienced later in life.[26, 29]

Critical Review of the Literature

Over the past three decades, a large body of epidemiologic studies has evaluated the role of tobacco exposures (both active and passive smoking) and breast cancer risk. In the last five years, a number of U.S and international agencies have reviewed the research on tobacco exposures and breast cancer. While there is some dispute on this issue, as evidenced by the recent concurrent assessments by the U.S. Surgeon General and the California EPA, at least one report maintains that the weight of the more recent evidence supports an association in younger women, with remaining uncertainty about the effect on post-menopausal women. It is important to consider this current evidence in the context of the succession of expert reviews over the last few years, as summarized in Table 2.

One of the problems in evaluating the evidence for ETS/SHS exposure and breast cancer has been reconciling the findings for active and passive smoking. Early studies of tobacco exposures and breast cancer have yielded inconsistent findings, with some studies demonstrating risk reductions, but most studies showing null results or very small risk elevations.[5, 33] The vast majority of these early studies on active smoking, however, did not account for ETS/SHS exposures in their analyses.[6, 34-37] Given the pervasiveness of ETS/SHS exposures, it is likely that the 'unexposed' referent group used in these studies included substantial numbers of individuals exposed to ETS/SHS. If tobacco exposures are in fact causally related to

breast cancer risk, the inclusion of passive smokers in the referent category would serve to dilute the risk estimates for active smoking towards the null. This argument has been cited as a possible explanation for the apparent association of breast cancer with passive, but not active, smoking in the few of these early studies that measured ETS/SHS exposure.[6, 37]

Consequently, many of the next generation of studies on active smoking, especially those published within the last few years, carefully measured ETS/SHS exposures.[9, 26, 38-47] The most recent large-scale reviews of active smoking and breast cancer conducted by IARC and the U.S. Surgeon General, both of which concluded there was no evidence of an association, were published before most of these results became available and therefore were not included in their assessments. Of the 11 recent geographically and

Table 2. Summary of conclusions from recent reviews by international, national, and state agencies on the relationship between smoking and breast cancer

Agency, Year Published	Type of Smoking Evaluated	Latest year of studies included	Conclusions
Surgeon General 2001[30]	Active and Passive	2000	"The totality of the evidence does not support an association between smoking and the risk for breast cancer" "…several issues were not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether ETS exposure affects risk"
IARC 2004[1]	Active and Passive	2001	"There is evidence suggesting a lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast"
Surgeon General 2004[31]	Active and Passive	2001	"The evidence is suggestive of no causal relationship between active smoking and breast cancer." "in light of the evidence showing no overall association between active smoking and breast cancer, passive smoking would also be expected not to be associated with breast cancer risks, assuming that the same mechanisms apply to both active and passive smoking"
Surgeon General 2006[2]	Passive	2005	"The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer."
CAL EPA 2006[3, 32]	Passive	2005	"Overall, the weight of evidence…is consistent with a causal association between ETS exposure and breast cancer in younger, primarily pre-menopausal women. In contrast to the findings in younger women, in studies which reported statistics for women diagnosed with breast cancer after menopause, risk estimates cluster around a null association."

methodologically diverse studies that excluded women with ETS/SHS exposures from the referent group, all but two[39, 45] reported an increased breast cancer risk associated with active smoking.[9, 26, 38, 40-44, 48]

These more recent studies of active smoking and breast cancer have also begun to test some of the hypotheses suggested by the postulated competing anti-estrogenic and genotoxic effects of tobacco smoke. A number of these studies have suggested that an early age at smoking initiation imparts an increased risk, while a later age does not[9, 38, 40, 41, 43, 46, 49, 50] which is consistent with the idea of adolescence being a particularly vulnerable period of the breast to the genotoxic effects of tobacco smoke. These results, however are not in agreement with many earlier studies[51-58] as well as some of the later studies.[6, 59] The use of different cut-points for age at initiation, the increasing proportion of smokers initiating smoking during adolescence among more recent birth cohorts,[60] different referent groups (with most of the more recent positive studies removing ETS/SHS exposures), and the mix of pre- and post-menopausal populations across studies might explain such heterogeneity in results.

Overall, however, there is emerging evidence that the effects of smoking on breast cancer risk may be limited to women who began smoking at an early age. Because early smoking initiation is so highly correlated with duration of smoking (for which there also is substantial evidence of an effect), it is difficult to determine whether this is truly an age effect or simply a duration effect. Furthermore, some studies have suggested that the risks associated with early smoking may vary by menopausal status,[29, 42, 44, 61] endogenous estrogen levels,[49] tumor hormone responsiveness,[38, 39] and certain genetic polymorphisms.[47, 48]

There also is mounting evidence that active smoking prior to a first pregnancy may increase a woman's risk of breast cancer,[9, 26, 38, 40, 43, 46, 62] which also supports the hypothesis that breast tissue may be especially vulnerable to carcinogens prior to terminal differentiation of the breast cells. It has been suggested that the best strategy for discriminating the competing effects that smoking may have on breast cancer risk would be in situations where the carcinogenic effect was maximized and the putative anti-estrogenic effect less evident and vice versa.[29] So, the chances of detecting the potential carcinogenic effects would be maximized by studying breast cancer in women who smoked only before and/or during a first pregnancy and then stopped. Conversely, smoking's anti-estrogenic effects would best be discerned in women who started smoking after a first pregnancy when the breast tissue is no longer as susceptible to carcinogenic insults. While only a few studies have been able to employ such a strategy,[9, 43, 46, 63] the results tend to suggest elevated risk in women who smoked only before a first pregnancy, and a reduced (or no different risk) among women who solely smoked after their first pregnancy. This analytic strategy is difficult to implement, given the generally small proportion of women who take up smoking after having children.

In summary, at least some of the rationale for initially rejecting a causal relationship between ETS/SHS exposures and breast cancer has been based on the apparent lack of an association of active smoking with breast cancer.[1, 31] The flurry of studies recently published tend to show a positive association between breast cancer and active smoking, at least within certain

subpopulations or those exposed early in life or over the course of many years.[3, 64] It should also be noted that some of these recent studies with positive findings were specifically designed to investigate the association between smoking and breast cancer. On the other hand, almost all of the earlier studies were so-called secondary data analyses, meaning that these studies were designed to examine different exposures (i.e., diet or physical activity), and smoking was collected as a potential confounder. Thus, the quality of smoking data, especially ETS/SHS exposure, differs significantly between these groups of studies.

There is a significant body of research that has focused on the effect of genetic polymorphisms relevant to tobacco carcinogens on the association between active smoking and breast cancer risk. These studies have focused on a variety of genes involved largely in carcinogen activation and detoxification. Results from these studies have largely been inconsistent, with the exception of the NAT2 slow acetylator and the GSTM1 null genotypes. The inconsistency is likely due to differences in methodologies, smoking cut-off points, and small samples sizes.[65] A more detailed discussion of this body of work goes beyond the scope of this review, which is aimed at ETS/SHS exposure.

As pointed out above, a number of studies have directly investigated the role of ETS/SHS exposure in breast cancer etiology. To date there have been eight prospective cohort studies[9, 40, 42, 43, 66-69] and 15 case-control studies.[26, 37, 39, 41, 44, 45, 55, 61, 70-76] Results have been fairly mixed, with four of the eight cohort studies yielding positive results and ten of the 16 case-control studies reporting positive findings. The most recent large-scale reviews published in the last year[2, 3] have considered nearly all of these studies in their assessments. In addition to a qualitative assessment of the literature, both the California EPA and the U.S. Surgeon General performed quantitative meta-analyses to generate summary risk estimates (see Table 3 below).

While each agency employed slightly different methods and included slightly different subsets of studies, the summary point estimates are generally

Table 3. Summary of results from recent ETS/SHS exposure meta-analyses

Agency	Exposure	Subset of Studies	Number of studies	Summary RR (95% CI)
CAL EPA	Lifetime	All	19	1.25 (1.08–1.44)
CAL EPA	Lifetime	Those with full exposure assessment	5	1.91 (1.53–2.39)
CAL EPA	Lifetime	Pre-menopausal women	14	1.68 (1.31–2.15)
Surgeon General	Lifetime	All	10	1.40 (1.12–1.76)
Surgeon General	Any	Cohort	7	1.02 (0.92–1.13)
Surgeon General	Any	Case-control	14	1.40 (1.17–1.67)
Surgeon General	Best	Pre-menopausal women	11	1.64 (1.25–2.14)

similar, yet the conclusions from each agency are different. California EPA felt the evidence was strong enough to declare a causal relationship between ETS/SHS and breast cancer among pre-menopausal women. This conclusion was bolstered by their analysis, in which they only included those studies with full lifetime exposure assessment (including childhood residential and adult residential and occupational sources) and found even stronger risk elevations. The U.S. Surgeon General's office, however, while noting the strength of the association among pre-menopausal women, cited the lack of association among cohort studies, the strong potential for recall and selection bias among many of the case-control studies—where many of the positive findings tended to come from hospital-based, rather than population-based, studies—and evidence of publication bias as arguments limiting their ability to declare causality. These differing conclusions highlight the state of the evidence to date and point towards needed future directions.

Conclusion and Future Directions

While overall the evidence to date suggests there may be a causal association between ETS/SHS exposure and breast cancer, there remains substantial variability in results. Clearly more research is needed to discern whether such discrepancies are a function of methodological flaws related to study design or are a reflection of varying risks associated with differing times of exposure and/or subpopulations of susceptible individuals. Most of the positive findings are derived from case-control studies. These case-control studies tend to have more fully characterized exposure assessments (taking into account timing, duration, and intensity in various settings) than the cohort studies, and thus may be less likely to have misclassified exposure. Only one cohort study has been published to date that has been able to characterize ETS/SHS exposures in settings other than the home and for a variety of time periods.[42] In keeping with the conclusions of the California EPA report, this study reported an effect for both active smoking (RR = 3.9, 95% CI = 1.5–9.9) and ETS/SHS exposure (RR = 2.6, 95% CI = 1.3–5.2) for pre-menopausal women, but not post-menopausal women (RR = 1.1, 95% CI = 0.8–1.6 for active smoking; RR = 0.7, 95% CI = 0.4–1.0 for ETS/SHS).[42]

On the other hand, the case-control studies tend to be smaller and more susceptible to the possibility of selection and recall biases. A few of the key positive findings from the case-control studies were from studies in which participants were re-contacted specifically and solely to ask about ETS/SHS exposures, raising the likelihood of differential recall between cases and controls.[41, 55] However, those studies that employed the most detailed ETS/SHS exposure assessment[37, 41, 44, 73, 77] consistently reported statistically significant risk elevation for women with the highest levels of ETS/SHS exposure. The need for more cohort studies with full characterization of ETS/SHS exposures across time periods and settings (home, workplace, social) is glaringly apparent. It also is critical to create a 'clean' referent group in all these studies that includes lifetime never smokers with no ETS/SHS exposures for any time period or from any setting. To date, investigators from only one cohort study characterized their referent group according to these criteria.[42]

Given the likely complexity of mechanisms underlying the relationship between smoking and breast cancer, it is very important not only to construct a full lifetime exposure profile for ETS/

SHS exposure, but also to examine the risks in the context of the hormonal milieu in which the exposure occurs. The provocative finding recently reported by Manjer and colleagues[49]—of an increased risk of breast cancer associated with active smoking only among women with high levels of endogenous estrogens—deserves more attention. Furthermore, consideration of genotypes both that affect the activation, detoxification, DNA repair, and cell cycle control/ apoptotic processes in tobacco-related carcinogens, as well as estrogen metabolism, may help to reveal the mechanistic pathway by which smoking exposures may differentially influence risk during different time periods of life.

Finally, while most of the studies to date have taken into account confounding by other known breast cancer risk factors, more attention to some covariates may be warranted. The large collaborative pooled analysis of active smoking and breast cancer published in 2002 suggested that the smoking-related risk of breast cancer reported in the literature was entirely an artifact of alcohol consumption.[78] In this pooled analysis of over 50,000 cases of breast cancer, it was reported that when the analysis was limited to nondrinkers, there was no longer a smoking-related risk. In the recent analysis by Reynolds, et al., stratifying the data by alcohol consumption did not eliminate the smoking-related risks.[9] Nevertheless, given that both active and passive smoking are strongly correlated with alcohol consumption, this issue deserves further attention and highlights the importance of going beyond simple covariate adjustment to examining the potential for effect modification for this and other covariates.

California has one of the lowest rates of active smoking and some of the strictest anti-tobacco legislation in the country. Consequently, most Californians are fortunate not to have to endure substantial exposures to ETS/SHS. From an attributable risk perspective, ETS/SHS exposure (if it is in fact related to breast cancer), is unlikely to be a large contributor to breast cancer incidence in California. There are, however, certain subpopulations that remain at risk for substantial exposures. Children, especially those riding in motor vehicles with smoking adults, are at risk for fairly high exposures.[79] Women working in the hospitality industry (bars and restaurants) are also at particular risk for high exposures. In fact, waitresses (an occupational group often dominated by young women), experience the highest occupational exposures to ETS/SHS (72.3 percent nationwide).[80] While California legislation prohibits smoking in such workplaces, compliance, although improving, is still far from complete.[81] Legislation is currently pending in California that would ban smoking in cars with young children present.[79] Thus, elucidating the breast cancer risk associated with both active and passive smoking during early life may be particularly important in helping to provide the impetus to eliminate these exposures.

From a public health perspective, if tobacco smoke is found to be causally related to breast cancer, it could point to one of the few modifiable avenues for preventing this disease. Furthermore, research has suggested that women fear breast cancer more than other smoking-related diseases that carry a higher mortality threat.[82, 83] If tobacco smoke exposure is found to be linked to breast cancer risk, it may serve as an especially strong motivating factor in reducing tobacco use and its accompanying host of related adverse health outcomes.

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Air Pollutants from Fuel, Additives, and Combustion

Introduction

Air pollutants are chemical, physical, and biological agents that modify the natural characteristics of the atmosphere. Air pollution is generated by combustion of fossil fuels and other materials; industrial, agricultural, and residential activities, including chemical releases and use; and natural events, such as wildfires. Fuels such as gasoline, diesel, and coal are particularly of concern because of the vast quantities extracted, formulated, transported, and used in vehicles (on- and off-road) and by industry, particularly utilities.

A great deal of research has demonstrated the impact of air pollutants on respiratory health, including lung cancer, and cardiovascular disease. There is also evidence that ambient air pollutants affect birth outcomes, including the quality of fetal growth and development[1] which may affect susceptibility to adult diseases, including breast cancer.[2] The number of suspected mammary carcinogens that are air-borne makes air contaminants an intriguing area for breast cancer research.

Levels of these contaminants vary greatly in California, given the tremendous geographic and meteorologic diversity. The state is currently organized into 15 regional air basins to monitor and model air quality.[3] The South Coast air basin (which includes Orange county and parts of Los Angeles, Riverside and San Bernardino counties) historically has some of the highest air pollution levels due to the relatively high temperatures, concentration of population and industry, and surrounding mountains that trap pollutants. The Great Basin Valleys (Alpine, Mono and Inyo counties) are more rural and very dry, with winds blowing over dried up lakes creating some of the highest particulate matter concentrations in the U.S. Wind and rainfall impact air conditions, such that pollution levels vary greatly across and even within these air basins.

This subsection will address air pollutants that may be measured individually and some that are constituents of particulate matter. For some, such as polycyclic aromatic hydrocarbons (PAHs), there has been a great deal of research, while fuels, including additives, are much less studied. Dioxins are another combustion by-product of concern. While dioxin exposure is mentioned here, this environmental pollutant is discussed in more detail in Section I, Chapter B.2, Persistent Organic Pollutants.

A number of other air pollutants may also be associated with breasts cancer. Rudel et al. identified 35 pollutants of outdoor or indoor air that are possible animal mammary gland carcinogens, and listed several other chemicals that are known air toxics.[4] Several volatile organic compounds of concern for breast cancer risk are monitored by the California Air Resources Board (CARB) as hazardous air pollutants. Benzene, for example, is a natural constituent of crude oil and has been used in the past as an additive in gasoline, but much higher exposure is associated with its use as an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber, and dyes. Therefore, benzene is discussed in Section I, Chapter B.5, Solvents and Industrial Chemicals. Other combustion by-products and air

pollutants of concern covered in other chapters of this report include 1,3-butadiene, nitromethane, isoprene, styrene and ethylene oxide (also in Section I, Chapter B.5); DCBP, atrazine, chlordane, dichlorvos, and simazine (in Section I, Chapter B.4, Pesticides); and metals (in Section I, Chapter B.7).

PAHs

Polycyclic aromatic hydrocarbons (PAHs) are a group of over 100 different chemicals that are formed by the incomplete combustion of coal, oil and gas, garbage, or other organic substances like tobacco or charbroiled meat. PAHs are usually found as a mixture of two or more of these compounds, such as soot. Some PAHs are manufactured. These pure PAHs are usually colorless, white, or pale green solids. PAHs are found in coal tar, crude oil, creosote, and roofing tar; a few are used in medicines, or to make dyes, plastics, and pesticides. Of the 15 PAHs listed as reasonably anticipated to be human carcinogens according to the 11th Report on Carcinogens (RoC),[5] six are monitored by CARB as part of CARB's ambient toxics data collection.

Concept/Exposure Definition

Mixtures of PAHs are present in ambient air, tobacco smoke, and in foods that are grilled, smoked, or contaminated by air pollution. The primary route of exposure is inhalation of contaminated air, with some PAHs ingested in contaminated water and in foods. PAHs inhaled through the lungs can be carried through the bloodstream to the breast, where they can be stored, concentrated, and metabolized, and affect the types of cells where breast cancer arises.[6]

Benzo[a]pyrene is of particular concern because of its ubiquitous exposure pattern. It is found in gasoline and diesel exhaust, cigarette smoke, other types of smoke, soot, grilled foods, coal tar, petroleum asphalt, creosote, shale oil, and solvents.[4] The main sources of human exposure are tobacco smoke, ambient air pollution from exhaust and coal-fired power plants, and foods. Nitropolycyclic aromatic hydrocarbons (nitro-PAHs) are formed at high levels from diesel oil combustion.[7] In addition to exposure from ambient air, the general population may be exposed to nitro-PAHs via drinking water and dermal contact.

Background levels of PAHs are much higher in urban areas than rural. PAH emission levels and composition vary over time and geography, as do those of other air pollutants, which may influence their potential for affecting health, including carcinogenicity.[8]

Critical Review of Literature

The International Agency for Research on Cancer (IARC) has listed soot and other PAH mixtures as known human carcinogens, and individual PAHs as probable human carcinogens.[9] PAHs are genotoxic and potentially carcinogenic to the human breast.[7] Nitro-PAHs and PAHs are both associated with increased mammary gland tumors in animals, with some, although not entirely consistent, evidence from studies in humans of an association with both male and female breast cancer.[4, 9]

In vitro

Gilli et al. found that PAH concentrations extracted from the ambient air were statistically correlated with mutagenicity in Salmonella assays. This occurred both with and without metabolic activation, suggesting they are both direct mutagens and promoters.[8] They did not, however, observe a linear dose-response relationship with either benzo[a]pyrene or total PAHs, mutagenicity ratios were highly variable, and the levels of fine particles (PM2.5) and unsubstituted PAHs did not account for the total observed mutagenicity. The researchers noted that the role of other pollutants was not studied and should be investigated, as should nitro-PAHs and ultra-fine particulate matter.

In vivo

PAH mixtures and some individual PAHs are mammary carcinogens in animals. Five of eight studies on one nitro-PAH, 1-nitropyrene, reported increased benign and/or malignant mammary tumor development in exposed animals.[4] When administered by subcutaneous injections, 1-nitropyrene induced mammary tumors, including adenocarcinomas, in female rats.[5] One study in female rats injected intraperitoneally with 1-nitropyrene showed increased mammary tumors, while another found an increase that was not statistically significant. Mammary gland tumors were also increased following oral administration of 1-nitropyrene to female rats.[5] Further, benzo[a]pyrene, administered either by gavage or intraperitoneal injection, induced mammary tumors in female rats.[4]

Human

Brody et al.[9] identified seven case-control studies of the association between breast cancer risk and environmental exposure to PAHs, including several that evaluated air pollution in a limited geographic area. One study found an association between exposure to total suspended particles (TSP), a surrogate for PAH exposure, and breast cancer risk.[10] These investigators reported a statistically significant trend (p-trend < 0.05) for higher breast cancer risk among women who lived at birth in areas with higher TSP levels. Among post-menopausal women, odds ratios were elevated but statistically unstable for higher TSP at birth, menarche, and first full-term pregnancy. The lack of an association at menarche and first full-term pregnancy for pre-menopausal women could be due to declining TSP levels in more recent years, shorter lag time (the time between a woman's exposure and when the researchers assessed the health effect), or other factors.

Another study used indicators of industrial and traffic density to estimate exposure to air pollution and PAHs. Lewis-Michl et al. reported a statistically significant higher risk associated with living near industrial air pollution sources in one county (OR = 1.61; 95% CI, 1.06-2.43), but not another county.[11] Results for living near high-density traffic were inconsistent.

A Belgian study found that exposure to PAHs from the ambient air was associated with a significant delay in breast development in a cohort of 200 adolescents (15.8–19.6 years old).[12, 13] The delay was also associated with a doubling of serum dioxin concentrations.

Many studies of breast cancer risk among women with work exposure to PAHs have been small and/or did not control for known breast cancer risk factors. Brody et al. identified two occupational studies of exposure to gasoline and vehicular exhaust that found elevated risk of breast cancer among females and males.[9] Men who worked for more than three months in an exposed job were particularly at risk if their first exposure was before 40 years of age (OR = 3.7; 95% CI, 1.7-7.9 with no lag time; OR = 5.4; 95% CI, 2.4-11.9 with 10 years lag time).[14] Women with occupational PAH and benzene exposure had higher breast cancer risk in a New York study (OR = 1.82; 955 CI, 1.02-3.16).[15]

The Long Island Breast Cancer Study assessed PAH exposure by measuring PAH–DNA adducts, a gauge of DNA damage caused by these compounds. This case-control study found the odds ratio for detectable versus non-detectable adducts was 1.32 (95% CI, 1.00-1.74).[16] Women with the highest compared to lowest PAH-DNA adducts had about 50 percent higher breast cancer risk, taking into account an extensive list of breast cancer risk factors. Results showing the strongest effects in premenopausal women are consistent with the Cal-EPA Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant" that concluded tobacco smoke is associated with higher breast cancer risk in women under age 50.[17] The Long Island results did not show a dose-response relationship. However, dose may not be well-characterized in this study: measurements were taken after diagnosis and therefore represent exposure over the previous months to a few years, not consistent with the known latency of breast cancer; and they do not consider the effects of DNA repair mechanisms. The study did not identify a relationship between grilled food or tobacco and PAH–DNA adducts, suggesting that other sources, perhaps air pollution, may be important or that women's recollections of diet and tobacco exposure are not relevant to recent blood measurements.[9] Additional analyses of the Long Island data suggest that certain genetic polymorphisms may influence the relationship between PAH exposure and breast cancer risk; and it will be informative to see whether these associations are observed in other studies as well.[9]

The small, hospital-based studies of PAH-DNA adducts in breast tissue are limited by low statistical power and lack of breast tissue samples from healthy controls for comparison.[9, 18-21]

Biological Mechanisms

Combustion byproducts are well known for causing oxidative stress, which leads to respiratory and cardiovascular diseases. Oxidative stress can disturb redox homeostasis, resulting in OH-adducts in breast tissue, and distort the geometry of the DNA in measurable ways that are predictive of breast cancer.

PAHs are known to damage DNA and researchers are looking into the possible association between breast cancer, PAHs, and polymorphisms in carcinogen activation, detoxification, and DNA repair genes.[9, 22] Studies have investigated interactions with polymorphisms in XRCC1, XPD, SULT1A1, and GSTM1, yielding some positive and some null results.[9] It will be important to see whether consistent associations

emerge in multiple studies of these or other polymorphisms.

PAHs and their metabolites have been associated with mutations in the tumor suppressor gene p53, which are associated with poorer breast cancer outcomes.[23, 24]

Some studies have found p53 mutations to be more common among African American than white women or differences in the pattern of mutations between racial groups. A study found that African American women were significantly more likely than white women to have mammary tumors that over-express p53.[25] A previous study had not found a difference.[26] PAHs and their metabolites can also be agonists or antagonists in hormonal pathways.[23]

Dioxins

Dioxins are organochlorine compounds, discussed in Section I, Chapter B.2, Persistent Organic Pollutants. However, because the primary source of dioxins is the combustion of organic material in the presence of chlorine, and they are commonly released into the air, some exposure issues are addressed here.

Concept/Exposure Definition

Nearly 80 percent of dioxin emissions come from coal-fired utilities, metal smelting, diesel trucks and equipment (on- and off-road), land application of sewage sludge, and burning of treated wood and trash. After incineration, dioxins can reform in the atmosphere above the stack. With new emissions rules from 1995-97, the EPA estimated that incinerator emissions of dioxins would be reduced by more than 95 percent, making it a minor contributor to atmospheric dioxin.[27] Dioxins are also present in smoke from typical cigarettes, particularly in those with chlorine-bleached paper and residues of chlorinated pesticides.

For the general population, most dioxin exposure occurs through the diet, with more than 95 percent of dioxins stemming from consumption of fats in milk, fish and meat. A much smaller proportion of exposure comes from inhalation of trace amounts of dioxins on particles in ambient air and in vapor form, from inadvertent ingestion of soil containing dioxins, and from absorption through the skin contacting air, soil, or water containing minute levels.[28] The ambient environmental contribution would be higher for people living near point sources where emissions are not adequately controlled. Workers may be exposed to dioxins in the chemical industry, or in the application of chemicals, notably herbicides.

Dioxins are commonly found in human adipose tissue, serum, and milk. Children are exposed to dioxins in utero and from breast-feeding. Animal experiments indicate the most sensitive stages to disruption of mammary gland development by dioxin occur in the womb and from infancy to sexual maturity [12]

Critical Review of Literature

Evidence regarding dioxins is sparse and methodologically limited, but suggestive of an association with breast cancer. One dioxin congener, Tetrachlorodibenzo-p-dioxin (TCDD) is a known human carcinogen, based on an increase in all cancers.[5] TCDD binds strongly to the aryl hydrocarbon receptor (AhR), which is involved in

signaling and activating genes in mammary and other tissues. This binding can change gene expression, metabolism, and cell growth and differentiation, and can also disrupt hormone and growth factor pathways. The offspring of mice treated with TCDD during pregnancy had significant impairment of mammary gland differentiation, and slight impairment of hormone production.[29]

TCDD and other dioxins are also reported to have multiple endocrine effects, including estrogenic and anti-estrogenic activity;[30] although they cause cancer in animal models, they have been explored as possibly protective against breast cancer. Human evidence of the role of dioxins in breast cancer has come primarily from occupational studies and increasingly from the residents of Seveso, Italy, who were highly exposed from an industrial accident.[9, 31] The Belgian study cited above found that dioxins were also present in the ambient air, and that the significant delay in breast development in the adolescents was also associated with a doubling of serum dioxin concentrations.[12] Dioxins are discussed further in Section I, Chapter 2.2, Persistent Organic Pollutants.[13]

Fuel Additives

With increases in fossil fuel prices and the stricter regulation of fuel economy and emissions, fuel formulations have been changing, particularly for motor vehicles. This leads to the production of different levels and mixtures of combustion byproducts. These changes are often made in response to economic, political and/or environmental concerns, before a thorough study of potential long-term health effects has been conducted.

The main source of exposure to fuel additives among the general population is from inhalation while fueling at gasoline filling stations, driving, and in parking garages or homes with attached garages.[32] These products vary in solubility; some but not all may affect ground water quality.

Fuel Oxygenates: Under the 1990 Clean Air Act amendments, oxygenates must be added to gasoline to reduce carbon monoxide (CO) emissions. The oxygenate methyl tertiary-butyl ether (MTBE) reduces engine knocking and improves combustion, thereby minimizing CO and aromatic hydrocarbon emissions.[33] Nonetheless, MTBE is listed as a toxic in the volatile organic compounds monitored by the CARB, and combustion of MTBE results in increased formaldehyde, tertiary-butyl alcohol (TBA) and isobutene emissions. Due to concern for MTBE contamination of ground water and drinking water supplies, MTBE use in gasoline was discontinued at the end of 2002.[34]

MTBE is widely distributed in body tissues and can metabolize to formaldehyde, a genotoxic agent, within the body.[35] The weight of the evidence does not support a genotoxic mode of action for MTBE.[33] MTBE does not affect the estrogen receptor, but it increases estrogen catabolism. It has been associated with decreased incidence of endometrial hyperplasia and changes in other estrogen-sensitive organs, but serum estrogen levels and ER functions were not affected.[36]

MTBE is listed as unclassifiable as to its carcinogenicity to humans. Carcinogenicity by oral and inhalation routes has been observed in animals,[34] and as have weak tumorigenic responses,[33] but neither was observed specifically in breast tissue. No human cancer studies were identified. Some experts note that such actions either do not occur in humans, or that humans are less susceptible to these effects, concluding that it is unlikely that humans would be exposed to sufficient levels of MTBE to cause these tumorigenic responses.[33] One model predicted that the overall health effect of increased MTBE use would include a decrease in all cancers compared to gasoline that has not been reformulated, primarily due to the reduction of volatile organic compounds—specifically a decreased exposure to 1,3-butadiene and benzene.[32]

Ethyl tertiary-butyl ether (ETBE) and tertiary-amyl methyl ether (TAME) are alternative oxygenates used in gasoline. California limited the amount of these and other fuel additives shortly after the MTBE ban.[37] Data on ETBE and TAME are even more limited than MTBE, but the latter is considered more acutely toxic and from in vitro study, a dose-related chromosome aberration has been reported.[32] The single rat study of ETBE carcinogenicity found increased incidence of neoplasms at several sites, including malignant Schwannoma in the uterus.[38] The study design and interpretation have been questioned and it is not listed by IARC, National Toxicology Program, or other organizations classifying cancer risk. ETBE toxicity is sometimes inferred from data on MTBE. Computer modeling of the ETBE chemical structure has predicted that it is neither genotoxic nor carcinogenic.[32]

TBA, another oxygenate and a fairly persistent metabolite of both MTBE and ETBE, is not believed to be genotoxic.[33] TBA has not been classified as to its carcinogenicity by any major organization. One review found that while TBA exposure in drinking water was associated with adenomas and carcinomas at certain sites, it was associated with a decreased incidence of mammary adenomas, fibromas, and carcinomas in female rats.[38] At least one study found that there is great inter-individual variability in the metabolism of MTBE, ETBE and TAME, suggesting that the genetic polymorphism of a critical enzyme (CYP2A6) is important in determining individual sensitivity to these oxygenates.[39]

Ethanol/Acetaldehyde: The increasing use of ethanol as a substitute and oxygenate for gasoline will result in higher atmospheric concentrations of acetaldehyde (the first metabolite of ethanol oxidation) from motor vehicle exhaust, as well as peroxyacetylnitrate (PAN),[35] and ozone.[40] When unburned ethanol is released, it is also converted to acetaldehyde and eventually to PAN and formaldehyde.[35] Acetaldehyde is used in chemical production, including flavorings, fragrances, pesticides, disinfectants, drugs varnishes, and dyes, from which it is commonly released into the air.[5] It also occurs naturally in plant respiration and alcohol fermentation. Acetaldehyde is a Hazardous Air Pollutant listed as a Toxic Air Contaminant in California based on evidence of carcinogenicity (reasonably anticipated to be a human carcinogen per the 11th RoC[5]).

In addition to vehicle exhaust, the general public may be exposed to acetaldehyde in ambient and indoor air from cigarette smoke, wood burning

and other fuel combustion, and air deodorizers. It has been detected in breast milk.[5] Ethanol use in gasoline may increase the spread of benzene and other volatile organic chemicals (VOCs) in ground water.[32] While it has been assumed to pose a lower risk for ground water contamination than MTBE, the California Air Resources Board felt it would not affect the public health impact of air pollution.[32]

The vast majority of the research on acetaldehyde's role in cancer has focused on the direct consumption of alcohol, where it is suspected of co-carcinogenic effects, including dysregulation of proliferation and apoptosis.[41] Researchers have found that cancer risk related to acetaldehyde levels and metabolism is affected by genetics;[41] no literature on this genetic linkage was identified for inhalation exposure.

Among the limited inhalation research, some studies have found an association with other cancers,[5, 42] but there is no evidence regarding mammary gland tumors. Acetaldehyde binds to proteins and DNA, resulting in impairment of cellular morphology and function, and which could provide a mechanism for replication errors and/or mutations in oncogenes or tumor suppressor genes.[41]

Research indicates that ethanol can also interact with cellular macromolecules and produce DNA damage through free radical mechanisms.[35, 41] While this risk may be most significant for the increasing number of people working with ethanol, it remains to be seen whether this can occur with atmospheric ethanol. Exposure to peroxyacetylnitrate (PAN) is not well documented.[43] While PAN has not been tested for carcinogenicity, it is reportedly genotoxic[35] and a weak point mutagen.[32] Further evaluation could also be directed at the potential impact of increased levels of acetaldehyde and PAN.

Air Pollutants

1,3-Butadiene: Carcinogenicity Potency Database, National Toxicology Program and the National Library of Medicine Chemical Carcinogen Research Information System list 1,3-butadiene as a probable human carcinogen. 1,3-Butadiene is a component of gasoline, vehicle exhaust, and cigarette smoke. It is used to produce other compounds, including synthetic rubber, which also involves the use of styrene (see Section I, Chapter B.5, Solvents and Industrial Chemicals).

The most common route of exposure is inhalation. Air levels are higher near petrochemical facilities, while industrial releases have decreased.[5] Although some food packaging contains residual 1,3-butadiene, data suggest that it does not usually migrate to the food.[4] Certain cooking oils, such as rape oil (canola) release 1,3-butadiene when heated.

1,3-Butadiene metabolites are known to be mutagenic and carcinogenic and have been found in the urine of exposed workers. Metabolites appear to alter proto-oncogenes and/or tumor suppressor genes.[5] Three studies found increased levels of mammary tumors in mice and rats.[4] One of the rat studies found that mammary tumor formation involved the endocrine system.[44]

Nitromethane: This compound is primarily used to synthesize derivatives used as pharmaceuticals, agricultural soil fumigants, and industrial antimicrobials, and is also addressed in Section I, Chapter B.5, Solvents and Industrial Chemicals. Moreover, nitromethane is used as a fuel or an additive with methanol in racing cars and boats, and in the production of explosives.[5] The most common nitromethane exposure sources are motor vehicle exhaust and tobacco smoke. However, people working with or near this hazardous substance may be exposed to higher levels through inhalation of fumes. Nitromethane is reasonably anticipated to be a human carcinogen. Administered by inhalation, it significantly increased benign and malignant tumors at multiple sites in both mice and rats, including mammary gland tumors in female F344/N rats. However, no human studies were found in the published literature and the mechanism by which nitromethane causes cancer is not known.[5]

Conclusions and Future Directions

People are thinking about much too narrow a set of chemicals in relation to breast cancer, so it is important to think about all of the chemicals for which we have animal evidence that they are mammary carcinogens. With the advent of ethanol, continued use of oxygenates and other changes in fuel formulations, additional study of the impact of the parent compounds, metabolites and combustion byproducts is critical. Primary research into these issues is needed to identify possible links to breast cancer.

It is critical to study oxygenates, such as methyl tertiary hexyl ether and methyl tertiary octyl ether, before they are introduced.[45] Using these products in fuel ensures their introduction into the environment and the potential for human exposure; therefore these compounds should be thoroughly tested.[35] Acetaldehyde and PAN are potentially significant carcinogens, indicating a need to better understand their health effects and the toxicokinetics of ethanol.

Methodological problems include inadequate dioxin and TCDD exposure assessment, lack of unexposed populations, and lack of preclinical markers to identify associations that may be obscured by disease latency. Work on identifying an appropriate biomarker is continuing.[46] It may also be important to study specific congeners, rather than look at total dioxins.

Perhaps most promising would be research into the polycyclic aromatic hydrocarbons (PAHs). Studies to date are suggestive of causal and promotional relationships between PAHs and breast cancer. It has been difficult to measure or estimate exposure to PAHs, since exposure occurs over a lifetime from multiple sources. Biological measurements in blood are intrusive and expensive, and would require repeated testing to represent long-term exposure. Ambient air monitoring and mapping of traffic and industrial sources to estimate exposures from outdoor pollution do not directly indicate exposure to individuals and do not account for time indoors.[22, 47] Self-reported exposures from tobacco smoke and diet involve errors and often bias in recall. Improvements in biomonitoring methods, additional ambient and personal air pollution monitoring, and refined modeling of relationships between environmental databases and individual

exposure will improve future epidemiologic studies.

Given the variety of PAHs and the mixtures encountered, further research needs to be carried out on nitro-PAHs and fine particles to understand the dose and mechanism for a mutagenic effect.[8] The relative contributions to adduct formation and breast cancer of the various PAH sources also need further study and may help distinguish between dietary and ambient air exposures. The development of new methods may help; for example, Binkova et al. reported that exposure to cigarette smoke and ambient air pollution, and a single polymorphism, were predictive of a PAH-DNA adduct specific to benzo[a]pyrene.[22]

While it is possible to directly measure the genotoxic effect (PAH-DNA adduct) in target tissue, this adduct is short-lived and it has been argued that higher levels may be "a biomarker of greater susceptibility."[23] Better biological measures are needed and work is underway to develop new biomarkers.[48] To better understand the role of PAHs in breast cancer risk, epidemiologists could identify and monitor susceptible subpopulations or highly-exposed workers over time, improving the exposure estimates.

Other than PAHs, data on exposure to hazardous air pollutants, such as MTBE, acetaldehyde and 1,3-butadiene, are very limited. These exposures vary geographically in California. One attempt to model the cancer risk from volatile organic compounds (VOCs) in the ambient air in Los Angeles found levels from two to 100 times the U.S. EPA benchmark.[49]

Assessment of actual exposure to these pollutants has been challenging. Data from monitors is limited, so the CARB also uses emissions inventory and air quality models to evaluate air quality.[50] Their periodic air quality modeling may not be frequent enough or on a geographic scale that is useful for health studies, however they make an extensive collection of modeling software available to researchers and the public.

More robust, validated exposure assessment methods are needed to examine the relationship between various air pollutants and breast cancer, as well as other adverse health outcomes. Researchers at California universities and the California Department of Public Health's Environmental Health Investigations Branch (EHIB) have been working on health effects associated with air pollution and evaluating models to estimate exposure for their usefulness in health studies.[51-53] It may be most useful to study air contaminants together, given that actual exposure is never limited to a single component. Future studies should also take into account that ambient concentrations of pollutants are not a good indicator of indoor where people spend most of their time.[54]

Finally, future research into the relationship between air pollutants and breast cancer should consider the significant potential confounding with neighborhood level disparities. Air pollution levels are often higher in lower income areas, given their proximity to traffic, industry and other sources of contamination. While the correlation is not perfect, racial and ethnic minorities are disproportionately exposed to air and other toxics, and associated health risks even across economic

strata, but most pronounced in neighborhoods with high levels of poverty.[55-59] Recent research suggests that disparities associated with ambient air toxics are affected by segregation and that these exposures may have health significance for populations across racial lines.[60] These interactions between the physical environment and social disparities deserve additional research.

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Persistent Organic Pollutants

Introduction

Persistent organic pollutants (POPs) are a family of synthetic, carbon-based chemicals defined by their behavior. They are toxic, lipophilic, and resistant to degradation. Their structural durability means that POPs persist in the environment and can circulate globally – far from where they are produced, used, and discarded. Most POPs are semi-volatile, which means their transport is temperature dependent. They evaporate from warm regions and condense in cold regions and, hence, tend to drift toward the Poles and mountainous areas. Their ability to dissolve in lipids means that POPs bioaccumulate in the fatty tissues of living organisms. Many also biomagnify, which means that their concentration in fatty tissues increases by a factor of 10–100 with each rung of the trophic ladder ascended. Organisms at the top of the food chain thus bear the highest body burdens of POPs. Traces of POPs are found in the blood and body fat of all Americans, including newborns. Indigenous peoples in the Arctic, who are located at the receiving end of POPs transport and whose traditional diets are heavy in animal fat, have some of the highest recorded levels of POPs in the world.[1]

POPs serve many different functions. Most famously, POPs include a raft of chlorinated insecticides that were introduced into the U.S. economy after World War II: aldrin, chlordane, dichlorodiphenyl-trichloroethane (DDT), dieldrin, endrin, heptachlor, hexachlorobenzene (HCB), lindane, mirex, and toxaphene. POPs also include industrial compounds, such as polychlorinated biphenyls (PCBs), which were used as heat exchange fluids, in electric transformers and capacitors, and as additives in paint, carbonless copy paper, sealants, and plastics. Polybrominated flame retardants (polybrominated diphenyl ethers/PBDEs) are another subgroup of POPs that offer fire protection to plastics, textiles, and furniture. The insecticide mirex has also been used as a fire retardant in plastics, rubber, and electrical products.[2]

Because of their toxicity, longevity, affiliation for fatty tissues, and tendency toward long-distance transport, many POPs have been banned for production and use in the United States. Consequently, body burdens for these POPs have been decreasing in recent decades among members of the general public. An exception is PBDEs, which are still used widely in the United States as flame retardants and for which human body burdens are increasing exponentially.[3] Another POP still in widespread use is perfluorooctanoic acid (PFOA, also known as C8), which is used in the manufacture of non-stick cookware and in stain-resistant, grease-resistant, and water-proof materials, such as food packaging and upholstery finishes.

Some POPs are of no commercial use but are generated as unintentional byproducts during other industrial processes, such as pesticide manufacturing, metal recycling, pulp and paper bleaching, or combustion. Unintentional POPs include dioxins and furans, and certain polycyclic aromatic hydrocarbons. Another unintentional POP is methylmercury, which is created, for example, when elemental mercury released during coal burning combines with carbon as a result of bacterial action in soils and sediments.[1]

Many, but not all, POPs are suspected carcinogens. One dioxin congener, for example, tetrachlorodibenzo-*p*-dioxin (TCDD) is classified as a known human carcinogen by the International Agency for Research on Cancer.[4] The agency classifies PCBs as a probable human carcinogen and considers chlordane, DDT, heptachlor, HCB, mirex, and toxaphene as possible human carcinogens.

Many POPs, including TCDD, are endocrine disruptors, and some behave like steroidal estrogens. This realization – together with the ubiquitous presence of POPs chemicals in breast milk and breast fat – has raised long-standing questions in the minds of both breast cancer activists and breast cancer researchers about the role of POPs in breast cancer etiology.[5-7] The strong evidence linking endogenous estrogens to breast cancer risk has lent biological plausibility to a causative role for POPs. Accordingly, considerable research has been directed toward illuminating the possible contribution of POPs to breast cancer. The results of these studies are summarized below.

This chapter is limited to a discussion of POPs for which the main route of exposure is dietary. Polycyclic aromatic hydrocarbons, an ingredient of air pollution, are described in Section I, Chapter B.1. on air pollutants. PBDEs, for which household dust appears to serve a second major vector of exposure and for which exposures are rising rather than falling, are considered in a companion chapter, which immediately follows this one. Organochlorine pesticides are considered here in this chapter as well as in the preceding chapter on pesticides. This redundancy reflects that fact that some epidemiological studies have considered chlorinated pesticides in the context of POPs exposure, while others have examined their role in the context of exposure to pesticides of all kinds. Not intended to serve as a comprehensive review of the POPs literature, which is considerable, this chapter spotlights new discoveries and draws heavily on material contained in Brody et al.'s recent systematic critical review in *Cancer*, which represents an up-to-date assessment of the epidemiological studies of these and other pollutants.[4]

Regulatory History of POPs

POPs enjoyed three decades of extensive use. Most were introduced after World War II and quickly insinuated themselves into the food chain. By 1950, produce free of pesticide residues was so scarce that the Beech-Nut Packing Company began allowing detectable levels of residue in baby food.[8] By 1951, DDT metabolites were discovered in human breast milk.[9] Thus, women of the baby boom generation were the first to be exposed to POPs in utero, in infancy, in childhood, and/or during puberty. This cohort is just entering the age of maximum breast cancer risk.

With the passage of the Toxics Substances Control Act in 1976, many POPs were phased out of domestic use, including PCBs and several chlorinated pesticides. However, this generalization obscures important waxings and wanings among individual chemicals. For example, DDT reached its peak usage in 1959, whereas toxaphene, which replaced DDT after its ban in 1972, did not peak until the early 1970s, when it quickly became the most heavily used

insecticide in the United States. Toxaphene was finally banned in 1990.[10, 11] While dieldrin was banned in 1975, aldrin, which converts to dieldrin in soil and in human tissue, was allowed as a termite poison until 1987.[12] Thus, even within the baby boom generation, different age cohorts were exposed to a changing kaleidoscope of different chemicals during different stages of early breast development.

POPs are currently being phased out globally in accordance with the United Nation's Stockholm Convention on Persistent Organic Pollutants. This treaty was adopted in Sweden in May 2001 and became international law in May 2004. Over 90 countries, including Canada, have joined as parties; the United States has not. The Convention has targeted 12 POPs for eventual worldwide elimination. It also provides a mechanism for adding additional chemicals to the list and compels member states to submit national implementation plans to the Stockholm Convention Secretariat. The original 12 POPs named in the treaty are aldrin, chlordane, DDT, dieldrin, dioxins, endrin, furans, heptachlor, hexachlorobenzene, mirex, PCBs, and toxaphene. There is variation in the manner in which different chemicals are treated under the treaty. For example, all production and use of endrin and toxaphene is banned outright, while DDT is restricted to controlling disease vectors, such as malarial mosquitoes. Under the treaty, governments are required to minimize the release of dioxins and furans as combustion byproducts with the goal of complete elimination where feasible.[1] The Convention gives governments until 2025 to phase out electrical equipment containing PCBs.

The nine pesticides regulated under the Stockholm Convention are no longer registered for sale or distribution in the United States. Uses were cancelled between 1969 (aldrin) and 1990 (toxaphene).[13] PCBs were banned domestically in 1978, although stocks still remain in electrical equipment.

By 2015, PFOA will be voluntarily phased out of consumer products but will still be allowed in manufacturing processes. The long residency times of POPs – which often exceed a human generation – ensure that POPs will be part of the ecological world long after their economic prohibition.

Routes of Exposure

More than 90 percent of human exposure to POPs comes from diet, with freshwater fish the source of highest exposure. The primary source of exposure to PCBs is fish. The primary source of exposure to dioxins is dietary fat, particularly dairy products, fish, meat, and breast milk.[4] A major dietary source for young children is breast milk.[14] A breast-feeding mother transfers 20 percent or more of her body burden of POPs during the first six months of breast-feeding. This quantity leaves breast-fed children with higher body burden levels of POPs contaminants than their formula-fed counterparts. Nevertheless, breast milk serves to protect infants from the neurological and immunological risks posed by prenatal exposures to these same chemicals[14] and appears to counteract the adverse developmental effects of PCBs and dioxins.[15]

Other than PBDEs, the most prevalent POPs found in human tissues are DDE (the major metabolite of DDT) and PCBs. Levels in human tissues rise with

age and are consistently higher in African Americans than in Caucasians.[5]

Since the discontinuation of the use of chlorinated pesticides and PCBs in the 1970s, levels of these POPs detected in food and human tissues have declined in western nations, including the United States.[5]

Critical Review of the Literature

In vitro Studies

The ability of many POPs to act as endocrine disruptors was first appreciated by Rachel Carson in her 1962 book *Silent Spring*. Her observations were based on animal and human studies. They have since been corroborated by in vitro studies. Many POPs are weakly estrogenic in experimental models. The pesticides endosulfan, toxaphene, and dieldrin, for example, have estrogenic effects on human estrogen-sensitive cells.[16] The ability to use estrogen-sensitive cell lines to screen POPs for endocrine disruption was perfected with the development of the E-SCREEN assay by Soto and others in 1995.[17]

Most illuminating are the bioassays that attempt to replicate the real-life mixtures of POPs to which human populations are exposed. For example, a mixture of POPs, including DDT and HCH, acted together to create proliferative effects on MCF-7 cells, even when each mixture component was present at levels below its no-observed-effect concentration. Combined effects were both additive and synergistic.[18]

In vitro studies have demonstrated that, while DDT itself is estrogenic, its persistent metabolite, DDE, does not bind with estrogen receptors and instead acts an anti-androgen. While some PCB congeners are estrogenic, the most persistent forms are actually anti-estrogens.[19] Thus, the hypothesis that guided much early epidemiological research – that PCB and DDT/DDE exposure may raise breast cancer risk via increased estrogenicity – is based on a false presumption.

In vivo Studies

Animal studies point to the importance of early life exposures, that is, exposures that take place at the time of birth or around puberty.[20] Compounds that retard development of the mammary gland are associated with increased risk of breast cancer.[21]

Mammary gland development is guided by cells at the blind ends of the ducts called terminal end buds. These are the branching and dividing points in the ductal tissue that blaze the trails for new networks of epithelial ducts in the growing mammary gland.[21] With each menstrual cycle before a full-term pregnancy, estrogen directs the elongation and branching of the duct system.[22] Terminal end buds are especially vulnerable to carcinogenic damage. Rodent studies indicate that the number of terminal end buds exposed to the carcinogen is related to the risk of tumor formation. The sooner the terminal end bud differentiates into adult structures, the more protected the animal is against mammary carcinogenesis.[21] POPs known to delay mammary gland development in laboratory animals following early-life exposure include dieldrin, TCDD dioxin, organochlorine mixtures, PCBs, and PFOA.[21] PFOA has been identified as a mammary gland carcinogen in animal studies.[23]

Exposure to PFOA in mice is associated with stunted mammary gland development. Female mice exposed during pregnancy exhibited diminished epithelial branching of mammary glands that disrupted the ability to lactate. Exposed female offspring also displayed stunted mammary growth and branching patterns.[24] This finding is significant, in that delayed mammary development is associated with increased susceptibility to carcinogenesis.[21] In rats, prenatal exposure to dioxins can increase the susceptibility of the mammary gland to subsequent carcinogenic insults.[20]

Human Studies

A large number of epidemiological studies have investigated the role of PCB body burden in breast cancer etiology. Overall, the vast majority of these studies have not provided strong evidence for an association between PCBs and breast cancer. However, the evidence to date generally supports an association between breast cancer and PCB exposure for subpopulations of women who have inherited polymorphisms in cytochrome P450 genes.[4] More specifically, women with a variant of the CYP1A1 gene called m2 are at greater risk for breast cancer when they are exposed to PCBs. Cytochrome P4501A1 (CYP1A1), which is involved in the metabolism of steroid hormones and polycyclic aromatic hydrocarbons in humans, is induced by PCBs. About 10–15 percent of U.S. white women possess the variant genotype. Another CYP1A1 polymorphism with presumed similar function is present in an even larger proportion of African American women. Women with high PCB body burden and the CYP1A1 variant genotype have a two- to three-fold increased risk of breast cancer, compared to women with lower levels and without this genetic trait. This risk elevation is higher than the excess risk reported for many established breast cancer risk factors.[4, 25]

Regarding dioxins and breast cancer, evidence is sparse but suggestive. Occupational cohort studies of dioxin-exposed female workers and studies of Russian women living near a dioxin-contaminated chemical plant yielded positive findings, but these studies involved women exposed to many chemicals. Moreover, some of the studies were not controlled for confounding by established risk factors.[4] Much of our knowledge about dioxin and breast cancer comes from a cohort of women exposed by a 1976 industrial accident in Seveso, Italy. Early studies with limited follow-up time showed no links between dioxin exposure and breast cancer incidence.[26, 27] But by 2002, researchers had found a statistically significant, dose-response-increased risk for breast cancer incidence with individual serum dioxin level among women in the Seveso Women's Health Study. More specifically, a 10-fold increase in dioxin level – as measured shortly after the accident – was associated with a two-fold increase in breast cancer incidence.[28] This study highlights the significance of long latency periods and the importance of having knowledge of chemical exposures decades before diagnosis. Breast cancer incidence may continue to increase in this cohort of 981 women and further follow-up is warranted. Many members in the cohort, who, at the time of the explosion ranged from infancy through 40 years old, are just now old enough to be at risk for breast cancer.[4]

More than 50 investigations have been published that ask whether women with breast cancer have elevated body burdens of organochlorine chemicals. The results are conflicting and unpersuasive. Many of these studies focused on PCBs or DDT and its metabolites. While early, small-scale studies found higher levels of, for example, DDE in cases than in controls, newer, larger, better-designed studies, by and large, have not replicated these results. Meta-analysis of prospective studies, as well as pooling of retrospective studies, has failed to yield odds ratios above unity. In other words, women with breast cancer, as a group, do not have higher body burdens of particular POPs contaminants than women without breast cancer.[4-6, 29] While some earlier studies seemed to suggest that high body burdens of organochlorines may increase risk in African American women, results from a recent case-control study of nearly 700 African American women did not confirm these results.[30]

Researchers are divided on the significance of these negative findings. Some believe these results reassuring.[5] Others argue that the putative role for endocrine-disrupting POPs should not be dismissed prematurely, because most epidemiological studies have so far not considered timing of exposure and genetic polymorphisms relevant in the biological pathways by which certain POPs might influence breast cancer risk. Further, recent evidence from in vitro models demonstrates that estrogenic pollutants – POPs and non-POPs alike – can act together at low levels to influence cancer risk.[6] Moreover, as one researcher points out, the demonstration that hormone replacement therapy contributes to breast cancer risk required an investigation of more that 150,000 women. By contrast, the pooled analysis of prospective studies, which relied on only 1857 women with breast cancer, has limited statistical power. From this point of view, the jury is still out on POPs and breast cancer.[6]

Epidemiological studies of POPs and breast cancer are limited due to three important methodological shortcomings. One is the presumption that contemporary measures adequately reflect past exposures.[5] However, as indicated above, the PCB congeners that are estrogenic are short-lived and more difficult to measure in biological samples. Hence, existing studies may not be able to assess the importance of POPs that are most quickly metabolized.[5] One Danish study that examined a bank of blood samples drawn many years prior to the development of breast cancer found higher levels of dieldrin in women who went on to develop breast cancer. Women with the highest levels of dieldrin had more than double the risk of breast cancer compared to women with the lowest levels.[19] However, this study also measured other POPs with similar biological activity and observed no excess risk associated with these chemicals. It is therefore possible that the excess risk associated with dieldrin could be due to chance alone.

The second limitation of epidemiological studies of POPs and breast cancer is that many studies have not considered combined effects of environmental estrogens.[6] Some researchers have therefore called for studies that measure the total effective xenoestrogen burden. One recent Spanish study measured levels of 16 organochlorine pesticides in the adipose tissue of 198 breast cancer patients at the time of diagnosis and compared them to 260 women without breast cancer matched on age.

Researchers found an increased risk for breast cancer in leaner, post-menopausal women that was related to the total body burden of all estrogenic chemicals, excluding natural hormones. The pesticides aldrin and lindane were also individually associated with risk.[31]

A third problem is that many studies do not consider the timing of exposure. The results of animal studies suggest that future epidemiological studies need to focus on exposures that occur when the mammary gland is most sensitive to hormones in order to capture time-specific responses.[20, 32] A new study that used banked blood samples gathered from young women from 1959–1967 in Oakland, California did find an association between exposure to DDT before age 14 and breast cancer risk before age 50. By contrast, women who were not exposed to DDT before age 14 showed no association between DDT levels and breast cancer.[33] In other words, girls' and younger adolescents' DDT exposure during the years of peak DDT usage in the U.S. was linked to breast cancer risk, while DDT exposure at older ages was not. As the authors note, many baby boom women heavily exposed to DDT in childhood have not yet reached age 50. The significance of early-life exposure to DDT for breast cancer risk may not yet be fully understood and may be quite large.[33]

Two others areas of research are noteworthy. The first examines the effect of POPs exposure on breast cancer survival or relapse. A few studies have found a significant association between high PCB levels and the risk of death among women with estrogen-positive breast cancer. Another found that higher levels of PCBs were associated with more aggressive breast cancer.[4] Dieldrin has also been linked to higher breast cancer mortality,[34] and organochlorine exposure has been linked to higher rates of breast cancer recurrence.[35] In light of the higher POPs body burden in African American women and their higher mortality rate from breast cancer, this line of inquiry seems worth pursuing.

The second examines the effects of POPs exposure on lactation. A small body of evidence suggests that some POPs contaminants interfere with human milk production, possibly by inhibiting prolactin. In studies conducted in both North Carolina and Mexico, women with the highest levels of DDT in their breast milk had poorer lactational performance and consequently weaned their infants sooner than mothers whose pesticide levels were lower. Similar studies come from the Netherlands, where mothers with high levels of PCBs and dioxins in their breast milk had significantly lower volumes of milk and lower fat content.[15, 36-38] These studies support animal studies, described above, that indicate that POPs can interfere with the ability to lactate. Such studies indirectly affect breast cancer risk, as breast-feeding has a protective effect against breast cancer.[39]

Conclusions and Future Directions

POPs exposures are pervasive and, indeed, universal. The absence of an unexposed population and the long latency period between exposure and onset of disease make epidemiological study challenging. In vitro studies indicate the importance of considering mixtures of chemicals that share pathways of endocrine disruption. In vivo studies indicate that early-life exposures to POPs can alter the development of the mammary gland in ways that make the breast more

susceptible to later carcinogenic assaults. Human studies that measure exposure at the time of a breast cancer diagnosis are not helpful in explicating the role that POPs may play in breast cancer etiology. Epidemiologists, chemists, and toxicologists should work together to develop methods to study the associations between complex mixtures of POPs and breast cancer, as well as other health outcomes.

Outstanding questions include:

- Do POPs contribute to a cocktail of estrogenic chemicals that act in concert to raise the risk of breast cancer? Or, in practical terms, does the blood sera of women with breast cancer exhibit increased mitogenicity?
- Can bioassays such as the E-SCREEN test provide a measure of internal exposure to estrogen-like chemicals?
- Does exposure to POPs interfere with the ability to lactate? (Longer duration of breast-feeding affords increased protection against breast cancer.)
- How do POPs exposures during crucial periods in early life – especially prenatal and pubertal – alter mammary gland development in girls?
- Do POPs exposures make breast cancer more lethal? And do the higher POPs body burdens in African American women explain their higher rates of breast cancer mortality?
- Finally, which are the most relevant POPs to study? As pointed out above, many studies have focused on the role PCBs and DDE may play in breast cancer development, yet resources may be better directed at other compounds in light of the fact that neither DDE nor most PCBs are estrogenic or mammary carcinogens.

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Polybrominated Flame Retardants

Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of persistent halogenated organic compounds widely used as flame retardants. Like dioxins and PCBs, PBDE molecules resemble bicycles. They consist of two phenyl rings studded with bromine atoms (the wheels) and attached by an oxygen bridge (the frame). When PBDE molecules are exposed to heat—a s in a house fire—the bromines detach and quench the flames.

PBDEs, like PCBs, exist as more than 200 potential congeners. However, only three mixtures have been available for commercial use, as identified by the average number of bromines in the dominant congener: Deca, Octa, and Penta. Deca, with ten bromine atoms, is used in hard polystyrene plastics, textiles, and electronic equipment such as televisions. It is also used in polyethylene for wires, cables, and pipes. Octa-PBDE, with eight bromine atoms, has primarily been used in the plastic housings of computer monitors and in circuit boards. With five bromine atoms, Penta-BDE has been used in flexible foam products, such as polyurethane furniture cushions, carpet padding, and mattresses. Penta has also been used in rigid foams.[1-4] These three mixtures are not strictly homogeneous and can contain PBDEs with other numbers of bromine; for example, Penta can contain some fraction of Tetra-BDE. The only mixture currently available in the United States and the European Union is Deca-BDE. The European Union banned Octa and Penta in 2004, and the sole U.S. manufacturer voluntarily stopped production in the same year.[5]

PBDEs first became commercially available as flame retardants in 1960[4] and have been widely used throughout the world for the last 30 years. Usage has tripled during the previous two decades.[6] In 2001, approximately 67,440 metric tons of PBDEs were manufactured, with the majority of use occurring in North America.[7] The U.S. has been, by far, the predominant producer and user of Penta.[8] Over time and under ordinary conditions of use, PBDEs have diffused out of the polymer matrices in which they were embedded and are now a ubiquitous contaminant of indoor and outdoor environments.[3, 8-10] By the late 1990s, Swedish researchers had documented exponential increases in PBDE levels in breast milk samples collected from 1972 to 1997. These findings were one factor that inspired a ban on PBDE manufacture in the European Union. Between 1998 and 2002, levels in human milk in Sweden decreased significantly.[3, 4, 8, 10]

Here in the United States, PBDE levels in Great Lakes fish rose rapidly during the 1980s and 1990s and doubled in less than three years. PBDEs have also turned up in commonly consumed fish, including salmon, mackerel, swordfish, herring, catfish, and shellfish; and they have been detected in many types of wildlife around the world, with some of the highest levels found in harbor seals in the San Francisco Bay.[4] This discovery, together with the Swedish breast milk results, prompted researchers to measure levels of PBDEs among U.S. human residents. U.S. inhabitants have the highest documented levels of PBDEs in the world. These levels are 10- to 100-fold higher than levels observed in Europe, Asia, or New Zealand.[7, 8, 11-13] Moreover, as seen in fish and wildlife, body burdens appear to be increasing.[4, 10, 11, 14, 15]

Owing to their similar molecular structure and toxic profile, PBDEs are often referred to as the 'PCBs of the future.'[8, 16] The less-brominated forms—Penta and Octa—are the more persistent, lipophilic, and biologically active. Some of the congeners contained in Penta-DBE have been identified as estrogenic.[4] By contrast, Deca-BDE is less well absorbed and less bioaccumulative. Its bulky size and high molecular weight restrict its toxicity and ability to biomagnify. Furthermore, Deca-BDE binds strongly to soil and sediments, limiting its bioavailability.[2, 3, 8, 10, 17] Ominously, however, debromination of Deca can generate the lighter, more toxic forms. The degree to which Deca degrades to the less brominated congeners in the environment is a source of ongoing debate.

Despite their widespread use, very little is known about the human health effects of exposures to PBDEs. Only a few epidemiological investigations have been conducted.[18, 19] Limited data from animal studies suggest that these compounds may exert endocrine-disrupting effects at levels close to those being documented in the current U.S. population, especially among children,[20] making them of particular concern for breast cancer.

Regulatory History of PBDEs

The banning of PBDEs in Sweden in the late 1990s inspired a European Union-wide ban of the Penta and Octa formulations in 2001, which became effective in 2004.[10, 21] In 2003, California followed suit and became the first U.S. state to enact a ban of Penta and Octa, which will go into effect in 2008. Since that time, eight other states have enacted legislation to ban these two congener formulations and, in 2004, the sole American manufacturer of PBDEs voluntarily removed Penta and Octa from the U.S. market. Subsequently, the U.S. EPA issued a regulation to ensure no new manufacture or import of Penta and Octa after January 2005. These various legislative efforts effectively ceased the introduction of new sources of Penta- and Octa-DBEs from entering the U.S. marketplace. They do not, however, eliminate exposures from products currently in use or the manufacture of new products with recycled materials containing PBDEs or from the disposal of products containing Penta and Octa.[22]

There are no comprehensive bans on the use of Deca-BDE anywhere in the U.S. In April 2007, the Washington state legislature passed a bill, now signed by the governor, that bans the use of Deca from mattresses by 2008 and from televisions, computers, and furniture by 2011.[23] Maine recently introduced similar legislation and has already passed some of the strictest laws to date.[24] However, in both states, the bills contain a number of loopholes/exemptions for Deca, including provisions that proven safer alternatives must be available prior to phasing it out. It remains unclear if the use of Deca-BDE will actually decline in these states after 2008. As of March 2007, nine states had introduced legislation to restrict or prohibit uses of PBDEs, including Deca, for specific purposes. More states will likely follow. The National Caucus of Environmental Legislators monitors PBDE legislation. An annotated compilation of enacted laws, executive orders, and introduced bills that seek to limit the use of PBDEs can be found on its website, www.ncel.net.

PBDEs in the Environment

PBDEs are detectable in many environmental media, including air, soil, household dust, clothes

dryer lint, sewage, fish, and wildlife.[1, 2, 10, 11, 13, 25-33] In North America, Penta-BDE is the primary contaminant found,[11] although Deca is often dominant in house dust. A recent meta-analysis of environmental PBDE concentrations reported exponential increases over the last 30 years, with a doubling time of approximately four to six years.[11] This study also demonstrated especially high levels of contamination in North America compared to Europe and Japan, the other two regions of the world with available data.[3, 11, 13, 29]

Sources of contamination have not been fully evaluated. One important non-point source of contamination is thought to be household trash, which often contains furniture, bedding, foam cushions, and electronics loaded with PBDEs. No information, however, is currently available on the degree to which incineration and landfills contribute to environmental contamination.[8] Recent work in Great Britain along urban-rural transects suggests that cities themselves may be sources, possibly from leakage of PBDEs from indoor to outdoor air.[34] Because incomplete combustion may produce brominated dioxins and furans, concern has also focused on incomplete incineration and accidental fires as additional sources of exposure.[8, 10] Sewage sludge is a well-documented source of persistent environmental contamination, especially for Deca, which binds strongly to sediment.[11, 29] Concentrations of PBDEs in water generally haven't been assessed due to their low solubility in water.[8, 29] Fish and marine mammals tend to have higher levels than do their terrestrial counterparts.[11, 29]

PBDEs in People

PBDEs have been detected in human blood, breast milk, umbilical cord blood, and in adipose, brain, liver, and placental tissue.[7, 8, 10, 12, 13, 35-40]

Over the past three decades, PBDE body burden levels have increased 100-fold, representing a doubling time of approximately five years. On average, U.S. blood levels (35ng/g lipid, which equals 35 ppb) are 17 times higher than in those seen in European populations (2 ng/g lipid or 2 pbb).[11] PBDE levels in the breast milk of U.S. mothers are 10–100 times those seen in the breast milk of European mothers.[40] Within the U.S., human body burdens of PBDEs vary wildly. Most PBDE researchers report levels between 4 and 400 in human blood and breast milk. However, in 2005, a team of researchers found individuals in New York City with levels as high as 9,630 ppb (in a 32-year-old man) and 4,060 ppb (in a 23-year-old woman). These levels are 4 to 9.5 times higher than any previously reported in people anywhere in the world.[41, 42]

The exponential rise in body burden levels of PBDEs stands in stark contrast to the temporal trends of other well-known organohalogenated compounds, many of which have markedly declined over the last few decades.[7, 15] A recent analysis comparing body burden levels of PBDEs, dioxins, furans, and PCBs measured in current and archived sera from 1973 in a U.S. population demonstrated this dramatically changing exposure profile.[7] PCBs, dioxins, and furans all declined dramatically during the 30-year span (1973–2003) marked by the collection of the two sets of sera, presumably reflecting the banning and regulation of these compounds. In contrast, PBDEs were

virtually undetected in the 1973 samples but were the predominant compound in the current sera. On average, these levels were more than twice those of current levels of PCBs, and 100 to nearly 2,000 times those of the dioxins and dibenzofurans. These levels may decline in the U.S. population with the recent ban of Octa and Penta. Initial reports from Sweden indicate that body burden levels there may be leveling off or even declining after exponential increases observed during the 1980s and 1990s.[11] However, the Swedish ban on PBDEs is more comprehensive.

Routes of Exposure

Routes of human exposure to PBDEs and the relative contribution of different sources depend on the congener or congener group, the country, and the life stage of the individual.[1, 8, 43, 44] Food is a vector for exposure but appears to play a lesser role than it does for other common persistent organic pollutants.[45-47] There is now good evidence that both diet and the indoor environment (probably inadvertent dust ingestion) contribute to exposure to Penta-BDE in adults in the U.S.[47] The indoor environment – both dust ingestion and dust inhalation – may dominate for exposure to Deca-BDE in the U.S.[43]

The Debromination Question

Some human exposure to bioactive Penta- and Octa-PBDE may come from the degradation of Deca. In contrast to industry claims, several studies now indicate that Deca can debrominate under ordinary environmental conditions, including through exposure to sunlight and via metabolism. Bacteria and fish, for example, can convert Deca into lighter brominated congeners [10, 17, 32, 48-52] and there is some evidence for metabolic debromination of Deca in mammals.[53] While Deca is not easily absorbed across the gut wall, its less brominated congeners are.[10, 11] Moreover, recent studies of workers exposed to Deca indicate that some fraction of Deca is absorbed. Deca has also been detected in blood and breast milk samples from the general population.[4]

Occupational Exposures

Occupational exposures may be important for workers in computer and electronic manufacturing, recycling, and disassembly plants and in PBDE formulation facilities.[1, 3, 8, 11, 54]

Diet

Diet is not the sole significant route of exposure to PBDEs and appears to explain only a portion of the variability in PBDE levels.[10, 35, 38, 44, 47]

Several lines of evidence suggest a smaller role for diet than the lipophilic nature of PBDEs might suggest.[12, 35, 37] First, research has established a link between Penta-BDE concentrations found in people with the quantities found in dust from their homes, independent of diet.[47] Second, although levels of fish contamination are orders of magnitude higher in North America than they are in Japan or Europe, analyses in U.S. populations tend not to see a large correlation between fish consumption and body burden levels of PBDEs.[11, 14, 47] Third, PBDE levels are not positively correlated with age. Indeed, children have higher body levels than adults. Two recent studies reported that PBDE levels in U.S. children are two to five times those found in adult populations.[36, 55] One case study of a San Francisco Bay Area

family[36] found blood levels of Deca comparable to levels seen in Swedish workers manufacturing and/or dismantling Deca-treated products.[56, 57] Total PBDE levels in the children, which ranged from 151–651 ng/g lipid, approached the 95th percentile of what has been reported in U.S. adult populations.[7]

All together, these results suggest that diet is not the sole or primary route of exposure for children and adults. Ingestion of breast milk does appear to be the primary route of exposure among breast-feeding infants.[1] PBDEs can also pass through the placenta.[1] Liver tissues from seven live-born and four stillborn U.S. infants attest to prenatal PBDE transfer from mother to offspring. The mean level was 23.1 ppb in these infants, and the median 15.2 ppb, lipid.[39]

Household Dust Ingestion and Inhalation

Among children and adults, dust appears to be an important vector for exposure. Unlike PCBs, PBDEs are a pervasive indoor pollutant found at high levels in household and office dust.[7, 31, 32, 47] A recent analysis of PBDE levels in breast milk samples reported a strong correlation with household dust samples, and to a lesser degree, with dietary consumption of dairy and meat products.[47] Thus, inhalation and ingestion of dust may be a particularly significant route of human exposure, especially among young children.[36, 58] Allen et al.[43] found that inhalation of dust may be important for exposure of adults to Deca.

The degree to which leaching of PBDEs from products in the home or office—directly into the indoor environment or through direct dermal absorption from furniture/mattresses—contributes to human exposures requires further exploration. House dust samples from the Washington DC area found no correlations between total PBDE concentration and year of house construction, type of flooring, presence of carpeting, or number of television sets or personal computers in the home.[32] A new study focusing on house dust likewise found no direct connection between household products known to contain PBDEs and levels of PBDEs in dust.[47] However, when using x-ray fluorescence to screen for bromine, researchers in Boston did definitively link PBDE concentrations in dust with bromine concentrations of household furnishings, including TVs, power strips, CD players, VCRs, alarm clocks, chairs, couches, mattresses, pillows, and futons.[45]

Critical Review of the Literature

In spite of the widespread usage of and documented human exposures to PBDEs, remarkably little data on the health effects of PBDEs exist. The full-bore introduction of PBDEs into electronics and furniture manufacturing in the 1970s preceded a systematic investigation of their toxicological properties. Concerns about the environmental health impacts of PBDEs were greatly heightened after documentation of an exponential rise in PBDE levels in national breast milk samples in Sweden. This report was published in 1998.[59] Thus, research on the health impacts associated with these widespread exposures is less than a decade old. To date, no breast cancer studies have been conducted in humans. However, the virtual absence of PBDEs in human sera prior to 1973 means that the oldest cohort of U.S. women exposed to PBDEs in

infancy is now only in their 30s – too young for most to develop breast cancer. For women who are old enough to be at risk for breast cancer, PBDE exposure occurred in adulthood, not during fetal, infant, or pubertal life when the mammary gland was under development and when exposures may raise the most risk for harm. Moreover, widespread human exposure to PBDEs may not yet have exceeded the latency period for carcinogenesis. Meaningful retrospective epidemiological investigations into PBDEs as a contributor to breast cancer risk are thus decades away. The suggestion that some congeners, especially Penta, act as endocrine disruptors, nevertheless, make PBDEs of particular interest with respect to breast cancer etiology.

In Vitro Studies

A number of in vitro studies have suggested potential endocrine-disrupting activity for PBDEs. PBDEs, which structurally resemble thyroid hormone, have been shown in vitro to disrupt thyroid activity by competitively binding to the T4 receptor site.[3, 60, 61] They may also bind to the plasma carrier protein transthyretin, causing more rapid metabolism of thyroid hormone.[62]

However, the resemblance between PBDEs and thyroid hormone is not the whole story. Additional studies have shown that PBDEs – or their hydroxylated and methoxylated metabolites – can bind with estrogen receptors in vitro,[63-65] while one study reported anti-androgenic activity.[66] Furthermore, PBDE metabolites disrupt cytochrome P45017 (CYP17) enzyme activity in vitro.[67] Because CYP17 catalyzes key steps in sex hormone synthesis in humans, these results may be particularly relevant to breast cancer, although such effects have yet to be evaluated in vivo.

In Vivo Studies

Carcinogenicity studies in animals have only been conducted for Deca-BDE, the least toxic mixture. Based on very limited bioassay data from chronic oral dose studies in rats, the U.S. Environmental Protection Agency classified Deca-BDE as a Class C (Possible Human Carcinogen). This classification, published in 1986, was based on no human data and limited evidence of carcinogenicity in rodents, specifically increased incidences of neoplastic liver nodules in male and female rates and increased incidences of hepatocellular adenomas in male rats.[68] All of the PBDE mixtures have been shown to disrupt thyroid balance in vivo, although Deca-BDE appears to be the least potent in this regard.[3]

The mechanism by which PBDEs lower thyroid levels has not been fully characterized. Furthermore, the degree to which these findings are applicable to humans, who are considered to be less sensitive to disruption of thyroid function than rodents, is not currently known.[3] Finally, the relevance of these findings to breast cancer is not known. While there have been reports of an elevated incidence of thyroid diseases among breast cancer patients, a causal link has not been established; but this is an area of growing and intense interest to breast cancer researchers.[69]

A handful of animal studies have examined the reproductive effects of PBDEs. Structural changes were observed in the ovaries of PBDE-treated female rats,[70] and sperm function decreased in male mice exposed to Deca.[71] Furthermore, a

number of studies have reported delays in puberty onset in both male and female rats exposed to PBDEs.[66, 72-74] Stoker and colleagues reported delayed puberty in male rats as well as suppressed growth of androgen-dependent tissues following a peri-pubertal exposure. This disruption appeared to indicate that PBDE was acting as an androgen receptor antagonist.[66, 74]

No studies have examined the effect of PBDEs on mammary gland development.

Human Studies

To date, no epidemiologic study of breast cancer and PBDE exposures has been conducted. Two small studies from Sweden, however, suggest potential carcinogenic effects in humans. In 1998, Hardell and colleagues reported a non-significant two-fold elevated risk of non-Hodgkin's lymphoma associated with adipose levels of Tetra-BDE.[75] A later study by the same research group in Sweden reported an increased risk of testicular cancer (OR = 2.5, 95% CI = 1.02–6.0) associated with maternal, but not case, sera levels of PBDEs.[76] These latter findings are particularly intriguing with regards to breast cancer, as risk for testicular cancer is thought to be at least partially mediated by pre-/peri-natal exposures to endogenous and exogenous hormone levels. The maternal blood levels in this study, however, were collected at the time of the son's diagnosis and may not reflect the *in-utero* exposures experienced by the sons from decades prior.

Two new birth cohort studies have found associations between PBDE concentrations and health effects other than cancer. In a Danish-Finnish study, the concentration of PBDEs in breast milk was significantly higher in boys with cryptorchidism (undescended testicles) than in controls.[19] A study in Taiwan found a relationship between PBDE levels in breast milk and birth outcome: higher PBDE levels were associated with lower birth weight and shorter birth length.[18]

Conclusions and Future Directions

PBDE exposures to humans are pervasive and, in contrast to other PCBs and dioxins, human body burden levels are increasing, with a doubling time of about five years.[16] While recent regulatory action to restrict the use of some PBDEs may stem the extraordinary increases in exposures observed over the last three decades, human exposures are likely to continue for decades to come, because PBDEs persist and bioaccumulate in the environment. Despite known widespread exposures, the health effects remain largely unknown. Retrospective epidemiology studies to illuminate breast cancer risks are unlikely to yield insights in the near future because the widespread commercialization of PBDEs occurred only within the last thirty years. However, it is feasible to investigate the developmental effects of PBDEs on the human mammary gland now. Outstanding questions include:

> What are the main routes of human exposure among both adults and children?
>
> How are the various PBDE congeners metabolized and excreted? What are their half-lives in humans? To what degree does Deca-BDE break down into more toxic congeners?

What is the environmental fate of PBDEs, in particular Deca-BDE, which is still being produced and used in the U.S.?

Do workers with high levels of occupational exposures have higher-than-expected risks of cancer?

Are body burden levels of PBDEs able to serve as early indicators of breast cancer risk? Do they affect menstrual function, onset of puberty, development of mammary glands, or timing of menopause?

Are Octa- and Penta-BDEs carcinogenic? Basic cancer bioassays are needed.

How do PBDE congeners affect endocrine pathways that may play a contributory role in breast carcinogenesis?

How do PBDEs contribute to the overall body burden of estrogenic and mitogenic synthetic chemicals, such as chlorinated persistent organic pollutants, pesticides, and pharmaceuticals, and, in so doing, are there important additive or synergistic effects?

Does thyroid hormone disruption play a role in breast cancer risk?

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Pesticides

Introduction

Pesticides are, by definition, poisons. Designed to kill living organisms, they are one of the few substances that are both toxic and deliberately released into the environment. These twin properties make pesticides unique as environmental contaminants.[1] Pesticides are present in almost every environmental media that has been monitored – including surface water, ground water, ambient air, household dust, soil, fog, rain, and snow.[2] A recent national survey by the U.S. Geological Survey found pesticide residues in every stream monitored.[3] Of common foods sampled by the U.S. Department of Agriculture's (USDA) Pesticide Data Program, pesticide residues were found in more than 70 percent of fruits and vegetables, more than 60 percent of wheat samples, and 99 percent of milk samples.[1, 4] They are also found in the bodies of nearly all U.S. adults and children.[1, 5]

California leads the nation in pesticide use.[6] Indeed, California is responsible for one-quarter of all pesticides used in the U.S.[7] Along with New York, Massachusetts, and Oregon, California is also one of few states that maintains a comprehensive pesticide registry. All agricultural pesticide use in the state must be reported monthly to the California Department of Pesticide Regulation (CDRR). However, individual consumers and institutions are not required to report their pesticide applications.[8]

Concerns about a possible link between pesticides and breast cancer are longstanding in both the research community and the cancer activist community. Ten common pesticides have been associated with increases in mammary gland tumors in at least one animal study.[9] The endocrine-disrupting abilities of many other pesticides, especially those that act as estrogens, have raised questions about possible contributory roles for these chemicals in breast cancer etiology.[10] Recently, concern has been expressed over the widespread use of organophosphates (e.g. malathion) and pyrethroids (e.g. permethrin) in residential areas for public health programs, such as vector control to contain West Nile Virus. There is also concern, but more limited information, about synergists, surfactants, and other "inert" ingredients.

Of particular concern among many researchers and activists are the triazine herbicides. These include the weed killer atrazine, the most common pesticide used in the U.S. and the most common pesticide contaminant of drinking water. Restricted for use in the European Union, atrazine increases estrogen production in vitro and induces mammary gland tumors in one strain of laboratory rat.[11] Recent animal studies also suggest that early-life exposures to atrazine can alter mammary gland development in ways that may predispose the breast to cancer.[12, 13]

In this chapter, we review the evidence for a pesticide-breast cancer link, with an emphasis on pesticides in current use. Widely-studied organochlorine pesticides are also considered here. This particular class of insecticides is further explored in the subchapter on persistent organic pollutants (POPs) that immediately follows. This redundancy reflects that fact that some studies have considered chlorinated pesticides in the

larger context of POPs exposure – which includes non-agricultural chemicals such as dioxins and PCBs – while other studies have considered chlorinated pesticides along with agricultural chemical exposures of other kinds. While most organochlorine pesticides have been phased out of use and body burden residues are falling,[5] a few still remain in common use. Notable among these are methoxychlor and endosulfan.

Regulatory History of Pesticides

Before World War II, the agrichemical industry was small and depended on a handful of chemical compounds, including petroleum products (such as diesel fuel) and arsenicals (such as Paris green). Between 1917 and 1942, lead arsenate and calcium arsenate were the most common pesticides in use.[14] Lead arsenate was commonly used in apple orchards during this time period. In the 1930s, fluoride-based pesticides, such as cryolite and barium fluorosilicate, were introduced by western fruit growers. The chronic effects of exposure to petroleum-, heavy metal-, and fluoride-based pesticides were never systematically evaluated by the U.S. government.[14] However, soil and household dust samples collected in and around homes constructed on land previously used as orchards frequently show ongoing contamination by heavy metals, including arsenic and lead.[15, 16]

Synthetic organic pesticides were introduced into agriculture at the end of World War II. Within ten years, carbon-based pesticides captured 90 percent of the agricultural pest-control market and had almost completely routed the pest-control techniques of the prewar years.[17, 18] Hence the baby boom generation is the first to experience lifelong exposures to synthetic organic pesticides. This cohort is just beginning to reach the age of maximum risk for breast cancer.

Many pesticides were developed under the secrecy of wartime and with military purposes in mind. For example, DDT was first deployed in wartime Naples to halt a typhus epidemic. The phenoxy herbicides (2,4D and 2,4,5T) were developed with the goal of destroying the Japanese rice crop. Organophosphates were developed by a German company as nerve gasses. The first generation of organophosphate poisons were tested on prisoners in the concentration camps of Auschwitz.[19-21] The peculiar origins of chemical pesticides as weapons of warfare have meaning for our current toxicological understanding of these chemicals, which is notably incomplete. Little advance testing was conducted for chronic, low-level exposures prior to their reinvention as a civilian tool of pest control.

Since 1972, pesticides have been regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which subjects them to more scrutiny than other toxic chemicals.[1] For example, FIFRA requires registration for all pesticides, which includes mandatory data collection on potential health risks. Regulatory decision-making under FIFRA is based on risk-benefit standards, with weight given to the economic benefit of controlling the pest, rather than a strictly health-based standard. In 1988, FIFRA was amended to bring data collection up to date for older pesticides that went on the market before such testing was required. This process is still ongoing.[22]

The U.S. Environmental Protection Agency (EPA)

sets standards called tolerances for allowable levels of pesticides on food. The U.S. Food and Drug Administration (FDA), charged with enforcement, monitors the food supply for pesticide residues, with the exception of meat and poultry, which is monitored by the USDA. From 1958 to 1996, the Delaney Clause prohibited the presence of cancer-causing pesticides in processed foods. However, this law was openly flouted. In 1993, a report from the National Research Council found that federal regulations were inadequate to protect children, due both to their increased susceptibility to harm and their unique food consumption patterns.[18] As a result, the Delaney Clause was replaced in 1996 by the Food Quality Protection Act. This law lifted the strict prohibition on pesticides in processed foods in order to allow detectable levels, but required the EPA to provide an additional margin of safety for tolerance limits when the risks for children are uncertain. It also required that the EPA consider the cumulative impact of pesticides that have a common mechanism of toxicity and gave the agency until 2006 to review the safety of the estimated 800 pesticides in use in the U.S.[23]

Additionally, the Food Quality Protection Act directed the EPA to develop a battery of screening tests for hormonally-active pesticides and gave it a 1999 deadline. However, the Endocrine Disruptor Screening Program has been crippled by funding problems and the repeated disbanding of its advisory panel. The deadline for validating test screening points has been pushed back to the end of 2007 and commencement of testing pushed back until 2008.

In May 2007, the EPA released a draft list of 73 pesticides that will be tested under the program. This testing will take place in two phases: tier 1 tests will be in vitro screening assays to identify potential endocrine disruptors; tier 2 tests will be rodent assays. The Natural Resources Defense Council, an advocacy group, along with some leading researchers, have questioned the protocols on the grounds that (1) they favor rodent strains known to be unresponsive to endocrine disruptors in the tier 2 tests,[24] (2) they fail to consider prenatal exposures,[25] (3) they allow test animals to eat chow that may mask the effects of endocrine disruption,[25] and (4) they do not sufficiently test for very low-dose exposures.[26] In other words, according to these critics, the choice of lab animal and their diet, as well as the chemical dose range and the timing of exposure, are biased toward missing, rather than finding, effects.[25]

Another recent regulatory action on pesticides undertaken by the EPA involves an organophosphate insecticide. In May 2006, the EPA proposed the continued sale of dichlorvos, although the agency had been poised to ban this pesticide two decades earlier.[23] In February 2007, the Natural Resources Defense Council filed a lawsuit against the EPA for failing, for 20 years, to finish an expedited review of dichlorvos, an organophosphate insecticide that is currently in used in pest strips, aerosol sprays, “bug bombs,” and pet collars.[27] Dichlorvos is one of ten pesticides identified by Rudel[9] as a mammary carcinogen in lab animals.

For regulatory purposes, pesticide ingredients are divided into two categories: active and inert. This is an arbitrary distinction with little toxicological meaning, as more than 500 inert ingredients are

also used, or have been previously used, as active ingredients in other pesticide formulations. In the parlance of regulation, "inert" does not mean biologically inactive or non-toxic, but instead refers only to its function in the formulated product. Inerts can work as solvents, surfactants, potentiators, or preservatives, for example. On average, common household pesticides contain 86 percent inert ingredients. These are rarely identified on the product label, nor are they subject to chemical testing under FIFRA.[1]

Pesticides in drinking water are regulated in much the same way as those in food. Just as food has tolerances, drinking water has maximum contaminant levels. These represent the highest limits allowable by law of particular toxic substances, including pesticides. Maximum contaminant levels are not health-based standards. Instead, they take into consideration costs and available technology to reduce contaminants to particular levels, which then become the legal benchmark. In 1974, the Safe Drinking Water Act brought all community water systems under federal and state regulation and required the EPA to set legal limits for contaminants. Individual states are in charge of enforcement. The promulgation of maximum contaminant limits for pesticides was established with the amendments of 1986. Routine monitoring of agricultural chemicals in drinking water began in the state of Illinois in 1992 and now includes all fifty states. Thus, an historical chronicle of pesticide contamination of drinking water does not exist for women old enough to be at risk for breast cancer. Since 1996, amendments to the Safe Drinking Water Act have compelled water utilities to make information about pollutants in drinking water available to the public in their water bills at least once per year. The law also mandated the creation of a national database of contaminants found in drinking water.[28]

Pesticides that drift in the air are regulated under the federal Clean Air Act. In California they are also regulated under the Toxic Air Contaminant Act of 1983.[6] The California Department of Pesticide Regulation has been taken to task for failure to enforce the Toxic Air Contaminant Act through the creation of enforceable drift laws.[6]

In 1990, responding to demands for more realistic and comprehensive pesticide use data, California became the first state to require full reporting of agricultural pesticide use. Under the program, all agricultural pesticide use must be reported monthly to the county agricultural commissioner, who in turn, reports the data to Department of Pesticide Regulation. California has a broad legal definition of agricultural use, so the reporting requirements include pesticide applications to parks, golf courses, cemeteries, rangeland, pastures, and along roadside and railroad rights-of-way. In addition, all post-harvest pesticide treatments of agricultural commodities must be reported, along with all pesticide treatments in poultry and fish production, as well as some livestock applications. The primary exceptions to the reporting requirements are home and garden use and most industrial and institutional uses.[8]

Routes of Exposure

Pesticides have many routes of exposure, and the relative importance of each depends on at least three factors: the type of pesticide, the pest control practices of the community, and the age of the

exposed individual. In general, food is the main route of exposure to organochlorine pesticides, which are persistent and tend to biomagnify in the food chain. Food also appears to be an important route of exposure to organophosphate pesticides. Studies of preschool children in the Seattle area found significantly lower organophosphate pesticide metabolites in the urine of children fed organic diets, compared to those on conventional diets. When children fed conventional diets were shifted to organic diets, through one-to-one substitutions of food items, median concentrations of organophosphate pesticide metabolites in urine fell dramatically, indicating that food was the source of exposure to these pesticides.[29, 30]

Drinking water is the main route of exposure to triazine herbicides such as atrazine, which is highly mobile in soil and not subject to biomagnification.

Air can be an important route of exposure to many types of pesticides. More than 90 percent of the pesticides used in California are prone to drift. "Second hand pesticides," like second hand tobacco smoke, create involuntary exposures through inhalation. A 2003 analysis of pesticide air monitoring data showed widespread pesticide drift. Farmers and farmworkers were the most highly exposed. However, building fumigations can also be important as airborne routes of exposure for urban and suburban residents.[6]

For children of farmers and farmworkers, exposure can occur through the so-called take-home pathway, when adults track pesticides into their homes. Children of pesticide applicators have higher levels of pesticide metabolites in their urine than the children of non-agricultural workers, and these levels correlate with metabolite levels in the urine of adults living in the same household, as well as with pesticide levels in vehicle and household dust, as was demonstrated in a recent study of apple and pear workers in Washington state.[31] Similar results have been reported in California's Salinas Valley by the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS). Eighty-five percent Hispanic, this intensely agricultural region is home to an estimated 38,000 farmworkers. A 2002 quantitative exposure analysis study revealed elevated levels of recently-applied pesticides in the household dust where farm worker families live, and on the clothes and in the urine of farm worker children, particularly toddlers.[32, 33]

The CHAMACOS cohort study has also found an inverse relationship between pesticide exposure during pregnancy and length of gestation: higher levels of the organochlorine hexachlorobenzene were associated with shorter gestations.[34] Similarly, higher levels of organophosphate pesticides in maternal urine during pregnancies were associated with shorter gestations. Markers of organophosphate exposure in umbilical cord blood were also correlated with shorter gestations.[35] These results may have relevance for breast cancer research, because preterm birth is a risk factor for early puberty, which itself raises the risk for breast cancer in adulthood.[36] In other words, pesticide exposure in prenatal life may alter fetal programming in ways that indirectly increase susceptibility to breast cancer as, for example, by accelerating the pace of sexual maturation. This potential pathway toward breast cancer requires further investigation.

Critical Review of the Literature

In Vitro Studies

In the human breast epithelial cell line MCF10F, the organophosphate pesticide parathion was able to alter gene expression, induce malignant transformation, and appeared to act as an initiator of breast cancer. Interestingly, atropine, which is used as an antidote to parathion in pesticide poisonings, significantly inhibited the genetic alterations triggered by parathion exposure.[37]

The weed killer atrazine increases aromatase expression in some human cancer cell lines and thereby increases estrogen production. According to one recent study, it does so by binding to and inhibiting phosphodiesterase, which results in elevated cAMP, which, in turn, stimulates transcription of the aromatase gene.[11] However, the precise molecular mechanism is incompletely understood and appears to vary between cell types.[11]

Several pesticides have been shown to exhibit estrogenicity in the ESCREEN assay developed by Soto and others.[38] Notable among these is the chlorinated pesticide endosulfan, which is still in current use and is a common contaminant in California's Alamo River (Imperial County). A 2000 survey of pesticides in California surface water found endosulfan in 64 percent of all samples collected from the Alamo.[39]

The ESCREEN assay also revealed that estrogenic chemicals may act cumulatively: when mixed together, they induce estrogenic responses in human breast cell lines at concentrations lower than those required when each compound is administered alone.[40] These results have particular significance for pesticides, which are, more often than not, found together in environmental media. California's Alamo River, for example, contains not only endosulfan but also diazinon and chlorpyrifos.[39]

Phenol derivatives generally contribute to estrogenic activity. One of these, 2,4-dichlorophenol (2,4-DCP), is the primary metabolite of the widely used phenoxy herbicide 2,4-D, which is classified by the International Agency for Research on Cancer as a class 2B, possible carcinogen. Gene-expression profiling in some, but not all assays, has shown that the activity of genes related to proliferation was altered after treatment with 2,4-DCP.[41] Very little is known about human exposure to 2,4-DCP, and health effects in animal models and humans are poorly understood.[42]

In Vivo Studies

Animal studies reveal that atrazine can affect mammary gland development. Early-life exposure to atrazine delays mammary gland differentiation in ways that prolong the presence of terminal end buds in the gland.[13, 43] The lingering presence of terminal end buds in the breast has been demonstrated to raise the susceptibility of the breast to carcinogenic damage.[13, 43] Moreover, among Long-Evans rats, very low levels of atrazine metabolite mixtures administered during late pregnancy were able to perturb mammary gland development of female offspring in ways that persisted into adulthood and that were unrelated to pubertal timing.[12]

Atrazine does not induce mammary gland tumors in female F344 rats, but it does induce tumors in Sprague Dawley rats. These tumors are generally presumed not to be relevant to humans, based on the observation that atrazine also induces premature reproductive aging in Sprague Dawley rats, which is thought to be associated with elevated estrogen levels. By contrast, in humans, reproductive aging is associated with lower estrogen levels. However, data do not exist to support this presumption.[9]

In addition to atrazine, the pesticides demonstrated to cause mammary gland tumors in animal studies are 1,2-dibromo-3-chloropropane (DBCP), captifol, chlordane, clonitralid, dichlorvos, fenvalerate, nifurthiazole, simazine, and sulfalate.[9] Of these ten, seven are banned or restricted. DBCP is a fumigant that was heavily used on grapes, tomatoes, and pineapples until its ban in 1985.[44] Captifol is a phthalate fungicide for which registration was cancelled in 1986.[45] Chlordane, a chlorinated insecticide once used in fire ant control, is now also restricted.[45] Fenvalerate, once widely used as a flea and tick repellant and a termiticide, is a pyrethroid insecticide that has been cancelled for use.[45] Sulfalate is a carbamate herbicide that was phased out of use in the early 1990s. Clonitralid is restricted and is used primarily to kill sea lampreys and snails. However, there is widespread potential for human exposure in the Great Lakes area.[46] Nifurthiazole is an antibacterial agent no longer produced in the U.S.[47]

The remaining three – dichlorvos, simazine, and atrazine – are both legal and common. Dichlorvos is an organophosphate insecticide. As described above, it is used in no-pest strips, flea collars, bug bombs, and ant and roach sprays for the home. It is also used in barns.[45] Simazine is a triazine herbicide that remains in wide use as a soil sterilant and weed killer, although its use as an algaecide in swimming pools and hot tubs has been prohibited.[48] Indeed, it is the 20th most common agricultural herbicide in the U.S.. California receives the highest use of simazine in the U.S.[49] Simazine has been detected in California well water[50] as well as in the San Joaquin River and its tributaries. According to a 2000 analysis, simazine was among the five most frequently detected pesticides in California surface water.[39] Atrazine, the number-one pesticide used in the U.S., is also present in California ground water in the northern third of the state and throughout the Central Valley.[50]

Human Studies

Studies that examine breast cancer risk among women with occupational exposures

Some, but not all, epidemiological studies of women farmers report increased risks for breast cancer.[7, 10, 51] Breast cancer risk doubled among North Carolina women farmers who did not wear protective gear while spraying pesticides or who worked in the fields during or shortly after spraying.[52] Most epidemiologic studies of breast cancer among women farmers and farmworkers have relied on estimations of past exposure, which can be subject to exposure misclassification. They have often presented results for all pesticides or multiple classes of pesticides, which makes it difficult to evaluate the role of an individual

compound, but accounts for the fact that exposure generally does not occur to individual pesticides.[10]

The ongoing Agricultural Health Study has examined pesticide use and breast cancer among farmers' wives in a large prospective cohort study in Iowa and North Carolina. So far, overall pesticide use is not associated with increased risk of breast cancer, but follow-up time is still relatively short, and it may be too early to observe statistically significant associations. Nevertheless, risk was elevated modestly among wives whose homes were closest to areas of pesticide application. Moreover, breast cancer risk was related to the use of several specific pesticides, with the strongest link to husbands' use of 2,4,5-TP (2,4,5-trichlorophenoxypropionic acid). Also known as silvex, this phenoxy herbicide is known to be contaminated with dioxin. As of 1985, it is no longer available for use in the U.S.[45] Weaker links were found with the chlorinated insecticide dieldrin (outlawed in 1971) and the phthalate fungicide captan (outlawed in 1989). This cohort will be followed further.[10]

In California, 81 percent of women farmworkers are Hispanic.[7] These women typically begin their work in the fields as children and teenagers and are thus potentially exposed to multiple pesticides from a young age onward.[7] A nested case-control study of 128 newly-diagnosed breast cancer cases within a cohort of Hispanic women farm workers found increased breast cancer risk among younger women and those with early-onset breast cancer. Those women in the highest quartile of pesticide use had odds ratios that were 40 percent higher than those in the lowest quartile. Risk of breast cancer was not associated with any particular single crop except mushrooms, where exposed women were at six-fold increased risk, compared to non-exposed women. All women in this study were members of the United Farm Workers (UFW) union.[7]

Studies that examine breast cancer risk among women living in agricultural areas

For adults, living in a crop-production area where pesticides are used increases the risk of several cancers, including lymphomas, leukemias, ovarian cancer, and brain cancer; Kelsey provides a review.[6] Results for breast cancer have been mixed. This possible association between breast cancer and living in areas where pesticides have been heavily used outdoors has been difficult to study, because several important breast cancer risk factors, including reproductive history, physical activity level, and body weight, are likely to vary geographically and be associated with rural/urban living. So, for example, hypothetically, an increase in risk due to pesticides could be offset by decreased risk due to earlier childbearing, higher physical activity, or lower obesity rates. In fact, one ecological study that looked at pesticide-use data and cancer-incidence data in California deliberately excluded breast cancer from its correlation analysis because other factors, such as reproductive histories, also varied between counties.[53]

Three studies aimed at evaluating whether breast cancer rates in California are related to recent pesticide use have reached different conclusions. Using data from both the state cancer registry and from the pesticide use registry, a 2005 study found no evidence that California women living in areas of recent, high agricultural pesticide use

experience higher rates of breast cancer.[54] Proximity to pesticide-intense farm fields during childhood or puberty, however, was not investigated.

Similarly, a 2004 study found no association between residential proximity to recent agricultural pesticide use and invasive breast cancer incidence among members of the California Teachers Study cohort, which has been followed for cancer incidence since 1995.[55] It should be noted, however, that exposure classification was based on the current address of participants and no comprehensive residential history was available for these analyses. Conversely, a third study that focused solely on Hispanic women in California observed an association between pesticide use and breast cancer incidence. Specifically, risk of breast cancer was positively associated with pounds of two organochlorine pesticides, methoxychlor and toxaphene. No association was found for the triazine herbicides atrazine and simazine. In this study, no distinction was made between Hispanic women who worked in agricultural operations and those who simply lived near the fields.[56] It is possible that there is less variation in other breast cancer risk factors, such as reproductive history, in an analysis that is limited to Hispanic women. There may also be better differentiation between highly-exposed (farm worker) women and low-exposed women.

Some studies have demonstrated associations between residential proximity to areas of past pesticide use and increased risk of breast cancer. In Long Island, a more than six-fold increase in risk of breast cancer was seen in long-time residents who lived on land previously used for agriculture and who also had never given birth or were older than 26 years old at the time of first childbirth (OR 6.4 (2.2–18.2)). In other words, there was an interaction between agricultural history and reproductive history. This study also found an increased breast cancer risk among women residing within one mile of a hazardous waste site containing organochlorine pesticides.[57]

The Cape Cod Breast Cancer and Environment Study, a case-control study of 2,100 women, reconstructed in detail historical exposure to pesticides used in insect control and agriculture, and on roadside rights of way, and estimated women's annual exposure at each Cape Cod address where they lived since 1948. Results from this study did not demonstrate consistent associations between breast cancer and living in areas where banned or currently-used pesticides were applied.[58] However, this and another study conducted on Cape Cod[59] did find weak, statistically non-significant associations between breast cancer and living near cranberry bogs.

One ecologic cohort study in Kentucky found an association between breast cancer and atrazine-contaminated well water.[60]

Studies that examine links between breast cancer and residential pesticide use

In a recent report from the Long Island Breast Cancer Study, self-reported use of lawn and garden pesticides was associated with a 40 percent increased risk of developing breast cancer, but there was no dose-response relationship. In this study, which is the first to investigate self-reported pesticide use in a residential setting, 1,508 women

with newly-diagnosed breast cancer and 1,556 women without breast cancer were questioned about their pesticide practices.[61]

Studies that examine links between breast cancer and organochlorine pesticides

Because pesticides have so many possible routes by which they may enter the body, assessing real-life exposures is challenging – Especially for highly polar, water-soluble chemicals that have short half-lives. For persistent chemicals that are stored in body fat, such as organochlorine pesticides, exposures can be measured in blood or fat samples, often many years after exposure. By the early 1990s, several descriptive studies had suggested that blood levels or adipose levels of DDT and its DDE metabolites, as well as that of other organochlorine pesticides, might predict breast cancer risk.[62] A causal link between organochlorine exposure and breast cancer seemed to make biological sense. Many organochlorines act as weak estrogens, and pesticides such as DDT, chlordane, and dieldrin were known to cause other types of cancer.[62] And indeed, a prospective, nested, case-control study from Denmark did report positive results with dieldrin exposure: women with the highest blood levels of dieldrin had double the risk of breast cancer.[63]

However, the results of most recent case-control studies – which have focused on white, Western adult women – have been largely negative (reviewed by Brody et al.,[43] Clapp et al.,[64] Engel et al.,[10] Khanjani et al.,[65] and Mills et al.[7]). It is still unclear if particular subpopulations of women – of different racial or ethnic backgrounds, for example – may have higher breast cancer risks from past or current organochlorine pesticide exposure.[62] At least one small study found that black women with breast cancer, as a group, had higher blood levels of DDE than black women without breast cancer.[66] Not yet investigated is the question of whether exposure to organochlorine pesticides during breast development in early life plays a contributory role. Also unknown is the effect of organochlorine pesticide exposure on age at diagnosis, breast tumor progression, metastatic potential, or morbidity. Emerging research on gene-environment interactions highlights the need for future analyses that focus on genetically-susceptible subpopulations.[43] According to a review by Brody, certain genetic polymorphisms appear to play a role in modulating the carcinogenicity of another group of organochlorine compounds, the PCBs,[43] and could play a role in dampening or magnifying the effects of organochlorine pesticides as well. These effects may be masked in exposure studies of the general population.

For further discussion of DDT and other organochlorine pesticides, see Section I, Chapter B.2, Persistent Organic Pollutants.

Studies of breast cancer and currently-used pesticides

Other than the organochlorine insecticides, which are now mostly outlawed, few pesticides have been investigated in relation to breast cancer risk. There is a particular dearth of information about currently-used pesticides and breast cancer risk. Among currently-used pesticides, researchers have established connections in some studies, but not all, to breast cancer and atrazine, 2,4D, and malathion.[7, 10, 64]

Conclusions and Future Directions

There are many reasons to explore further the possible link between pesticides and breast cancer risk in California: Human pesticide exposure is ubiquitous. California leads the nation in pesticide use. Many pesticides are known endocrine disruptors, and several pesticides in common use are known to cause mammary tumors in laboratory animals. The epidemiological data are inconsistent and difficult to evaluate because of limitations in the methods and data available to estimate exposures across a lifetime. In light of recent animal studies that reveal effects of early-life exposure on mammary gland development, further epidemiologic study should take timing of exposure into account. The following are suggested avenues for further inquiry:

1) Environmental epidemiology needs to be integrated with disparities research. Hispanic women in California experience a 42 percent lower risk of breast cancer than do non-Hispanic white women. Reproductive patterns probably explain part of this difference. Among Hispanic farmworkers, the intense physical activity required by farm labor may also have a protective effect.[7] Accordingly, Hispanic women living in intensely agricultural areas and/or working as farmworkers need to be compared to Hispanic women without such exposures. Simply comparing rates of breast cancer among women of all races among counties with varying pesticide use patterns may blur important associations within and among subpopulations. That is, pesticides in agricultural counties may be significantly contributing to the burden of breast cancer among Hispanic farmworkers, but comparing their rates to populations of predominantly white women in non-agricultural areas will not reveal this association.

2) The biologic impact of combined exposures remains unknown.[10] New methods in epidemiology, analytical chemistry, and toxicology need to be developed to explore real-life mixtures. Evidence from in vitro studies indicates that effects of pesticides can be cumulative and additive.[67]

3) The biological impact of pesticide exposures at early developmental stages remains unknown.[10] Animal studies, particularly of atrazine, indicate the importance of cellular events taking place many years before breast cancer develops.[13] Pesticide use patterns at the time of diagnosis do not reflect conditions at the time that these cellular changes take place. This is especially problematic for many currently-used pesticides, which are not persistent. Future studies should focus on pesticide exposures at biologically relevant time points (i.e. *in utero*, puberty, before childbirth).

4) Known mammary carcinogens in common use, such as atrazine, simazine and dichlorvos, deserve closer scrutiny. The commonly-used herbicide 2,4D and its phenolic metabolite, 2,4DCP, also deserve further investigation. California's pesticide reporting program can pinpoint areas of intense use of these pesticides.

5) Studies should focus on commercial formulations, including the inert ingredients, and not just the active ingredients.

6) Interactions between reproductive history and pesticide exposure deserve further investigation.

7) Future studies should also consider interactions between pesticide exposure and genes relevant in the biological pathways by which these chemicals influence breast cancer risk.

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Solvents & Industrial Chemicals

Introduction

A recent review found that more than 30 industrial chemicals were shown to have caused mammary gland tumors in at least one animal study.[1] While exposure is highest in certain workplaces, many of these solvents and other chemicals are commonly found in ambient air, drinking water, and consumer products. In this chapter we address some organic solvents: benzene, ethylene oxide, methylene chloride, styrene, tetrachloroethylene and other dry cleaning agents, and urethane; and industrial chemicals: acrylonitrile, isoprene, nitrobenzene, toluene diisocyanate mixtures, and nonylphenols. A discussion of consumer cleaning products and air fresheners is also included. Other related compounds mentioned here, but covered more completely elsewhere in this report, are: acetaldehyde, 1,3-butadiene, ethanol and nitromethane (see Section I, Chapter B.1, Air Pollutants); and perfluorooctanoic acids (see Section I, Chapter B.2, Persistent Organic Pollutants). Solvents are also addressed in Section I, Chapter C, Compounds in Personal Care Products.

Organic Solvents

Solvents are used to dissolve or extract other substances in industrial and consumer products such as paint thinners (e.g. toluene), nail polish removers, spot removers, detergents (e.g. terpenes, nonylphenols), and perfumes (e.g. ethanol). They are also employed in processes like dry cleaning (e.g. tetrachloroethylene) and chemical syntheses. Solvents are widely and routinely used and can enter the human body by ingestion, inhalation, and skin absorption. Detection of organic solvents in breast milk confirms their availability to breast tissue.[2] Organic solvents or their metabolites are suspected of initiating or promoting breast carcinogenesis through genotoxic or related mechanisms.[2, 3] Table 1 provides an summary of the likelihood of exposure, mechanisms of concern and evidence of a link with breast cancer for selected organic solvents.

Evidence that common organic solvents are animal mammary carcinogens makes these compounds important targets for human studies.[4] However, relatively few human breast cancer studies have assessed solvent exposure and controlled for potential confounding by other breast cancer risk factors.[2] One well-designed epidemiologic study found elevated risk of breast cancer among younger Danish women in occupations with greater overall exposure to solvents (Hansen,[5] reviewed in Brody et al.[2]). Risk was about doubled for women with more than ten years in an exposed job and 15 years lag time (OR = 1.97; 95% CI = 1.39–2.79). A registry-based case control study of Canadian women found elevated incidence among both pre- and post-menopausal women employed in two industries with higher chemical exposure, with particularly high rates among those in dry cleaning which used tetrachloroethylene.(Band,[6] reviewed in Brody et al.[2]).

However, findings from other studies examining breast cancer risk associated with industries and/or occupations with exposure to solvents have not been consistent. Ray et al. did not find a greater risk in exposed versus unexposed textile workers,[7] while Peplonska et al. observed higher breast

cancer rates among Polish textile machine operators and tenders.[8] The latter also found an association among those who worked in electronics manufacturing or as printing machine operators, but not among janitors or among health care workers likely to be exposed to ethylene oxide. Occupational studies are often limited in their ability to evaluate the association between exposure and disease outcomes, especially longer-latency cancers. These limitations are outlined in the "Conclusions and Future Directions" subsection below.

Table 1. Selected Organic Solvents Linked to Breast Cancer

Compound(s)	Potential for Exposure	Mechanism(s) of Concern	Human/Animal Evidence
Benzene	More likely (HPV*, air, water, consumer products)	Mutagen (conflicting evidence) Mammary carcinogen	Measured in human milk; increased incidence of mammary gland tumors in rats and/or mice
Ethylene oxide	Undefined (HPV*, air, water, occupational)	Mutagen Mammary tumorigen and carcinogen	Increased incidence of mammary gland tumors in mice (lower dose); some human evidence (occupational, drinking water)
Meythlene chloride	HPV*, consumer products, air, water, occupational	Mammary carcinogen, fibroadenomas possible genotoxicity	Measured in human milk; increased incidence of mammary gland tumors in rats and/or mice
Styrene	More likely (HPV*, occupational, air, food)	Mutagen	Limited animal evidence; one occupational study of mortality
Tetrachloroethylene (Perc)	Undefined (occupational)	Possible genotoxicity	Measured in human milk; limited human evidence of increased incidence from worker study and drinking water
Urethane	More likely (HPV*, occupational, food)	Mammary tumorigen	Increased incidence of mammary carcinomas in mice and mammary tumors in hamsters.

* HPV – High Production Volume refers to chemicals produced in or imported into the U.S. in amounts over one million pounds per year.

Benzene: This volatile organic compound is widely used in chemical production; gasoline production, storage, transport, vending, and combustion; and is a by-product of other processes (e.g. coke ovens).[1] Some consumer products contain benzene, including carpet, pesticide products, and adhesive removers. Benzene is a toxic air contaminant monitored by the California Air Resources Board and is also a water contaminant of concern.

Exposure to benzene is highest in urban areas, in workplaces where there is heavy traffic or machinery, and around gasoline filling stations. Exposure also occurs by inhaling tobacco smoke (see Section I, Chapter A), drinking contaminated water, or eating contaminated food.[1] Benzene is a known human carcinogen by all routes of exposure, based on animal and human evidence. When administered orally, benzene caused mammary gland carcinomas and carcinosarcomas in female mice in four studies.[1]

Ethylene oxide: Ethylene oxide is used to sterilize medical equipment and other products, such as foods, clothing, cosmetics, and beekeeping equipment. It is found in tobacco smoke, vehicle exhaust, and in some foods and spices. The general population may be exposed to ethylene oxide in tobacco smoke, ambient air pollution, or use of products that have been sterilized. Those who work with ethylene oxide are at greater risk of exposure to higher levels of the compound.

Two animal studies found a higher incidence of mammary tumors in mice exposed to lower doses than those exposed to higher doses (an inverse dose-response).[1] Ethylene oxide is a known human carcinogen, but evidence of breast cancer risk from several occupational studies has been somewhat inconsistent. In an ethylene oxide-specific study, Norman et al. found about a two-fold increased risk of breast cancer (standardized morbidity ratio) in women who worked in a plant with documented exposure.[9] Several studies have assessed risks in nursing and in health and science laboratories, which may involve exposures to ethylene oxide, but may also involve exposures to other risk factors, such as shift work and light at night (discussed in Section I, Chapter H). Many of the studies of nurses were well designed and findings for chemical exposures are unlikely to be confounded by established breast cancer risk factors. For example, Band et al. found an elevated risk for nurses in British Columbia (OR = 1.54; 95% CI = 1.05–2.28) and Gunnarsdottir et al. found similarly elevated risk.[1]

Methylene chloride: Although this highly volatile compound was discontinued as a propellant for hair spray, it is still used in other consumer products such as fabric cleaners, paint strippers, wood sealant and stains, spray paints, adhesives, furniture and shoe polish, and art supplies.[1] Due to its common use and volatility, methylene chloride is ubiquitous in ambient air and ground water. Exposure occurs during production and industrial use of methylene chloride and of dichloromethane, and during the use of nearly 1,000 methylene chloride-containing consumer products.

Methylene chloride is a probable human carcinogen.[10] High levels of methylene chloride have been associated with benign mammary tumors in rats, as well as an increase in the number

of mammary tumors per animal. Inhalation of methylene chloride increased the incidence of fibroadenomas of the mammary gland in female rats and appeared to do the same in male rats.[1]

Styrene: This compound is used in and is a byproduct of polystyrene manufacturing (plastics labeled #6) and the synthetic rubber industry. It is present in a number of building materials and consumer products including carpets, paints, adhesives, hobby and craft supplies, and home maintenance products.[1, 2] Exposure is common in the general population from inhalation of ambient air and tobacco smoke, and consuming food that has been in contact with polystyrene.[1]

Styrene is classified as a possible carcinogen.[10] It has been associated with increased mammary tumors in some animal studies, but not consistently.[1] Human data on a possible relationship between styrene and breast cancer are limited, but at least one study reported elevated breast cancer mortality associated with occupational exposure to styrene based on death certificate data.[11]

Tetrachloroethylene: The solvent tetrachloroethylene, also known as perchloroethylene or Perc, replaced the acutely toxic solvent carbon tetrachloride in dry cleaning. Exposure has occurred among workers, residents near dry cleaning facilities and through ingestion of contaminated water. Elevated levels of breast cancer have been found in women working in dry cleaning (OR = 5.25; 95% CI = 1.41–19.5).[6]

One population-based case-control study of women who were accidentally exposed to Perc leaching from improperly prepared water pipes found an elevated risk of breast cancer associated with exposure, although the increase in risk was not monotonic (Adjusted OR = 1.6; 95% CI = 1.1–2.4 for exposure > 75th percentile).[12] Possible confounders were extensively evaluated and this "natural" experiment provided an unusual ability to define the exposed population.

Carbon tetrachloride: While no longer used in dry cleaning due to its acute toxicity, carbon tetrachloride may still be present in paint and varnish removers; and in cleaning, auto, and hobby products.[1] This compound is detected at low levels in ambient air and water, and has been detected in human breast milk.[3] When administered by subcutaneous injection, carbon tetrachloride induced mammary adenocarcinomas and fibroadenomas in female rats.[10]

D5: Some dry cleaners are now replacing Perc with decamethylcyclopentasiloxane or D5, an unregulated solvent which is also used in personal care and automotive products.[13] D5 is a common air contaminant,[14] but there is little information about potential health effects. A recent study found that D5 was not hormonally active in estrogenic and androgenic assays.[15]

Toluene diisocyanate mixtures: These are highly reactive compounds used in the production of polyurethane foams and coatings; paints, varnishes, and sealants; and binders. Exposure to toluene diisocyanates from inhalation or dermal contact can occur in all phases of its manufacture and use.[10] Household products employing polyurethane varnishes or foam such as furniture, carpet underlay, and bedding may volatize unreacted toluene diisocyanates.[1] The FDA has determined that levels of toluene diisocyanates in

food, food additives, and food packaging are very low. In testing on female rats, these mixtures, administered by gavage, induced mammary gland fibroadenomas.[1]

Urethane: This solvent is used on organic materials and as a co-solvent in the manufacture of pesticides, fumigants, and cosmetics, where workers may be exposed. Urethane also is naturally produced in fermented foods, such as beer, bread, wine, soy sauce, yogurt, and olives.[1] Exposure may occur by ingesting these foods and beverages.

When administered in drinking water, urethane induced mammary carcinomas in mice of both sexes, and mammary tumors in hamsters of both sexes.[1] When injected intraperitoneally, urethane increased incidence of mammary tumors in rats of both sexes. X-irradiation combined with administration of urethane led to the induction of mammary carcinomas in mice. Vinyl carbamate epoxide, a metabolite of urethane, causes mammary gland tumors.[1]

Industrial Chemicals

Many industrial chemicals have been examined for their potential health affects. While these are more often a concern for workers, such compounds are often released during manufacturing or from end products. Table 2 provides a summary of the likelihood of exposure, biolobical mechanisms of concern and evidence of a link with breast cancer for selected industrial chemicals.

Acrylonitrile: This chemical has been detected only rarely and at low levels in ambient air and water.[1] The general population may be exposed from use of acrylic carpeting, rubber, and toys. Exposure from food containers is generally very low, because acrylonitrile monomers do not readily migrate.[1, 16] Administered orally, this chemical increased the incidence of mammary gland carcinomas in female and male rats. While inhalation studies in female rats found increased mammary tumors, at least one mouse study did not find an increase.

Table 2. Select Industrial Chemicals Linked to Breast Cancer.

Compound	Exposure Potential	Mechanism(s) of Concern	Human/Animal Evidence
Acrylonitrile	Less likely (air, water, consumer products, food)	Mammary tumorigen and carcinogen	Inconsistent – mammary gland tumors in rats, not mice
Isoprene	More likely (air, occupational)	Oxidation Tumorigen	Neoplasms of the mammary gland in both rats and mice
Nitrobenzene	Undefined (ambient air, consumer products, water)	Mammary tumorigen	Mammary gland tumors in at least one mouse species
Nonylphenols	More likely (HPV*, consumer products, water, food)	Endocrine disruption	Affects reproduction of aquatic species, accelerates rate of mammary gland development

* HPV – High Production Volume refers to chemicals produced in or imported into the U.S. in amounts over one million pounds per year.

Isoprene (2-methylbuta-1,3-diene): Isoprene is formed naturally in plants and animals, including humans (estimated at 17 mg/day for a 150 lb. person). Low levels of isoprene are common in many foods. The chloroplasts of certain tree species are a main source of isoprene, with especially high emissions (~5–20 mg/m^2/hr) on hot, sunny days.[10] About 95 percent of the isoprene manufactured is used to produce natural rubber. Sources of emissions include ethylene production by petroleum processing, wood pulping, oil fires, wood-burning stoves and fireplaces, other biomass combustion, tobacco smoke, gasoline, and exhaust from turbines and automobiles.[1] Workers involved in the manufacturing and use of isoprene in the 1940s and 1950s may have been exposed to high levels.[17] While current engineering controls have increasingly reduced exposure, some isoprene is likely to be released during production of the original monomer and even more likely released during subsequent polymer production, so some workers are exposed.[17]

Isoprene is closely related to butadiene (see Section I, Chapter I.B, Air Pollutants), but its metabolism and chronic toxicity appear to differ.[18] Isoprene is reasonably expected to be a human carcinogen based on evidence for carcinogenicity at multiple organ sites in both mice and rats exposed by inhalation.[10] Inhalation exposure of rats to isoprene vapors induced increased incidence of neoplasms of the mammary gland. Common sites of neoplasm induction by isoprene and butadiene included the mammary gland in mice.[1] There is no epidemiologic evidence of

cancer among workers exposed to isoprene;[19] no adequate human studies of isoprene exposure and cancer were identified.[1]

Nitrobenzene: This compound is found in soaps and in shoe and metal polishes, and it is used in spray paints, floor polishes, the perfume industry, and as a substitute for almond essence. It is commonly detected in surface and ground water.[1] The general public may be exposed to nitrobenzene through inhalation of ambient air, ingestion of water, or dermal contact with products or water containing nitrobenzene.[1] Exposure to nitrobenzene caused mammary gland tumors in female B6C3F1 mice.

Nonylphenols

Nonylphenol is an organic chemical produced in large quantities in the U.S. for manufacturing nonylphenol ethoxylates, surfactants used in cleaning and other products, most notably laundry detergents.[20] Nonylphenols are often found in streams and waste water treatment plant effluent as a breakdown product from surfactants and detergents; they are persistent and do not readily degrade in water. The U.S. EPA is working with several companies to eliminate the intentional use of nonylphenol and nonylphenol ethoxylates in detergents.[20, 21] Nonylphenol ethoxylates are also used in paper and pulp production, latex paints, pesticides, flotation agents, industrial and automobile cleaners, and in the textile industry.[22] Besides the predominant use of nonylphenols for manufacturing nonylphenol ethoxylates, they are also used in the form of tris(nonylphenol)phosphites as antioxidants in plastics. Ethylene oxide (see above) is also used in nonylphenol ethoxylate production.

A German study found that nonylphenols were ubiquitous in food.[22] Although nonylphenols are lipophilic, their concentration was not related to the fat content of the food or to the packaging, leading the authors to hypothesize that food contamination could be occurring at multiple stages of food production. The authors also hypothesized that nonylphenols may be breakdown products from cleaning agents or pesticides used in agriculture or processing, or may migrate into food from plastic packaging materials.

Although nonylphenol exposure appears ubiquitous, biological samples found measurable levels of nonylphenol in just over half of adults tested[23] and fewer than six percent of girls tested.[24] The relatively low frequency of detection of nonylphenol (compared, for example, to Bisphenol A) could be explained by a lower human exposure to nonylphenol, by different pharmacokinetic factors (i.e., absorption, distribution, metabolism, elimination), by the fact that 4-n-nonylphenol (the measured nonylphenol isomer) represents a small percentage of the nonylphenol used in commercial mixtures, or a combination of all of the above. Additional research is needed to determine the best urinary biomarker(s) to assess exposure to nonylphenol.[23]

Nonylphenols are known to cause reproductive effects in aquatic organisms, with suspected effects on human endocrine, reproductive, and immune systems. Nonylphenols have been shown to be weakly estrogenic in human cell cultures and in vivo rat bioassays by competitively binding to the estrogen receptor.[22] In rat models,

nonylphenols accelerated mammary gland development.[25]

Amsonic acid: Like nonylphenols, amsonic acid is used in laundry detergents (as an optical brightener) and is also used in the manufacturing of dyes. Potential for human exposure to amsonic acid is quite possible from clothing, packaging materials, and foods such as fish; it is produced and used in great volume in the U.S. While little toxicologic or other information is available on amsonic acid, at least one animal study found a dose-related increase in mammary fibroadenomas.[1]

Related Compounds

1,3-Butadiene is an industrial chemical used as a monomer in the production of synthetic rubber, generally mixed with styrene or acrylonitrile, both also shown to cause mammary gland tumors in animal studies.[1] It is a probable carcinogen and of particular concern for certain industries. However, many of the studies to date have focused on styrene-butadiene rubber workers, who are exposed to both industrial chemicals. Because the most common route of exposure for the general population is inhalation from vehicle exhaust, this compound is discussed at greater length in Section I, Chapter B.1, Air Pollutants, Fuels and Additives.

Nitromethane is primarily used to synthesize derivatives used as pharmaceuticals, agricultural soil fumigants, and industrial antimicrobials. While the most common exposure sources are motor vehicle exhaust and tobacco smoke, exposure may occur from the use of solvents (manicuring preparations or rubber adhesives), aerosol propellants, and fuels containing nitromethane.[26] Nitromethane has been detected in air, as well as ambient and drinking water.[1]

Perfluorooctanoic acids are used in non-stick and stain-resistant coatings on rugs, furniture, clothes, cookware, fire-fighting applications, cosmetics, lubricants, paints, and adhesives. In the past, their use in insecticide and herbicide formulations resulted in direct releases into the environment. They are widely detected in blood samples in the US. Two studies demonstrate that perfluorooctanoic acid is a multi-site carcinogen. The single study that included females observed mammary gland tumors in female rats.[1] Perfluorooctanoic acids are discussed in Section I, Chapter B.2, Persistent Organic Pollutants.

Consumer Cleaning and Air Freshening Products

Some cleaning and air freshening products contain volatile organic compounds, such as glycol ethers and terpenes. The former are toxic air contaminants. The latter include terpene hydrocarbons, terpene alcohols, and related compounds which are often derived from pine, orange, and other plant oils, and used as scenting agents or as active solvents.[27] Terpenes react with ozone to form a variety of secondary pollutants. However, relatively little is known about the resulting indoor concentrations.[28] In addition to formaldehyde, the terpene-ozone reaction produces acetone and acetaldehyde (see Section I, Chapter B.1), the latter at much higher levels in the presence of nitrogen dioxide.[29] Exposure to these compounds is very likely, given the common use of cleaning products and air fresheners.[28]

Conclusions and Future Directions

There are thousands of other organic solvents and industrial chemicals, some of which have not been adequately tested for carcinogenicity or endocrine disruption or other potential effects that might impact breast cancer risk. We lack information on the levels of exposure and relative contribution of various sources to our body burden. The fact that no one is exposed to just one of these chemicals at a time highlights our lack of understanding of possible additive effects, interactions or synergies. A single animal study was identified in this review that looked at a combination of exposures: urethane and x-irradiation, which led to the induction of mammary carcinomas in mice.[1]

The Occupational Safety and Health Administration (OSHA) produces cancer risk estimates to determine permissible exposure limits (PEL) for their regulation of many of these compounds in workplaces, including ethylene oxide, benzene, methylene chloride, and 1,3-butadiene. While these risk estimates are not specific to breast cancer, the overall risks are as high as one percent[30] indicating that workers may face a substantial hazard.

While workers may have some of the highest exposures, occupational studies often face serious limitations. Breast cancer has a relatively long latency. It is difficult to estimate women's exposure. Employment records provide limited job histories because women's length of employment in a "usual" job may be short, and job exposure matrices have not been designed specifically to assess women's experiences, which may typically differ from men in the same job category. Many occupational exposures are correlated: solvents are often correlated with each other, reducing researchers' ability to attribute risk to individual compounds or subgroups of compounds. When many occupations are analyzed, it is difficult to link job categories to specific exposures, interpret inconsistencies across jobs with overlapping exposures, and evaluate the role of chance. It is also difficult to assess consistency between the occupational studies, as job classifications are not often comparable from one study to another.

Finally, in addition to confounding specific to breast cancer, studies of occupational exposures may understate risk because of the "healthy worker effect" or because workers with sensitivity to the exposure leave due to acute or short-term illness (e.g., skin rashes or respiratory distress), so that they may not be included in long-term follow-up studies. If short-term workers are not included, and they develop cancers that were caused by their exposures, these may be missed and the true effect of the workplace exposures will be underestimated. Further work is needed in exposure assessment, toxicology, and susceptibility to make future epidemiologic studies more useful. One of the most promising lines of research would be an on-going study of a large number of exposed women workers, with government ensuring access to this population. There is an on-going Agricultural Health Study; we need something like this for industrial workers.

For nonylphenol and nonylphenol ethoxylate, work is needed to determine how exposure to these compounds disrupts the endocrine system, including determining the toxicologically active form(s) and the pharmacokinetics and

toxicokinetics of nonylphenols and metabolites. Other congeners in this group may also be of concern,[22] but no data were identified, making this another area for possible study. Canada and the European Union have banned nonylphenol ethoxylates in detergents, and the Sierra Club has called for similar action in the U.S.[31]

While formaldehyde and acetaldehyde are important indoor toxicants, little is known about the toxicology of many terpenoid oxidation products. Several reaction pathways involving ozone and reactive compounds that are present in the formulation of household products are still not well characterized and deserve further attention.

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Water Contaminants

Introduction

Sixty-five percent water by weight, the human body is intimately associated with the ecological water cycle, which includes, most directly, sources of drinking water. In the United States, drinking water comes from one of two places: ground water, which is drawn up from wells sunk into aquifers (i.e., geological formations containing water), or surface water, which is pumped from sources open to the atmosphere, such as river, lakes, and streams. More than 80 percent of public water systems in the U.S. draw from subterranean aquifers.[1] Nevertheless, the majority (about 60 percent) of U.S. inhabitants drink from surface water sources, with only 40 percent of the U.S. population drinking ground water.[2] This is because large metropolitan areas rely on rivers and reservoirs to supply tap water. Thus, women in large cities tend to drink surface water, whereas women living in rural areas or smaller cities tend to drink well water. Eighty-five percent of the U.S. population lives in areas serviced by public water systems; the remaining 15 percent use private sources of water, the vast majority of which are ground water wells.[2]

The distinction between surface and ground water is a permeable one.[3] Ecologically speaking, aquifers and surface water are interconnected sources. All running surface water was at one time ground water, aquifers being the source of rivers and streams, and ground water is recharged with precipitation, which itself is evaporated surface water.

The average American uses 90 gallons of water each day in the home.[4] Only a small fraction of this total is actually ingested. However, exposure to chemical contaminants in drinking water sources can come from inhalation of volatile compounds in indoor air, as well as direct transfer through the skin, as during bathing and showering. Thus, an understanding of the possible role of drinking water contaminants in breast and other cancers necessitates investigations into the flow of toxicants through entire watersheds, as well as investigations into the water-use patterns of individual households, including showering, bathing, and dishwashing habits, for example.[5]

Water, a universal solvent, is prone to many types of contamination. Surface and ground water are both vulnerable to chemical contamination, but in different ways. In general, ground water is more protected from chemical contamination by its overlaying lid of soil and other geological materials. However, once adulterated, ground water remains contaminated longer. This is especially true for contamination with volatile organic compounds, such as solvents, which readily vaporize from surface water. With no oxygen, sunlight, or turbulence to facilitate their breakdown, nor open air to encourage evaporation, volatile contaminants persist far longer in ground water aquifers than in rivers and streams.[6] In general, chemicals from run-off (storm water, urban, or agricultural), atmospheric deposition, and sewage effluent – which can include pharmaceuticals and personal care products – are a bigger threat to surface water sources than to ground water.[3]

By contrast, lightweight, volatile substances, such as solvents, are a bigger threat to ground water sources. Leaking underground storage tanks and leachate from landfills also pose special risks for ground water,[3] as does waste water from septic tanks – which, like sewage effluent, can contain pharmaceuticals and personal care products.[3, 7] However, ground water aquifers are not all equally vulnerable to contamination. Shallow wells in sandy soils are more vulnerable than deeper wells in clay-rich soils. Thus, in the case of ground water, the potential for drinking water contamination is a function not only of the industrial and agricultural activities that go on above it, but of the geological substrate that lies over it.[3]

Nitrates from fertilizers and from animal waste affect both surface and ground water. Human nitrate production has increased rapidly since 1950 and now exceeds, by 30 percent, nitrogen fixed by natural sources. Nitrates migrate both to streams and to ground water. Nitrate is the most common chemical contaminant found in ground water.[8] In both surface and ground water, nitrates are highest in drinking water sources in agricultural areas. In such areas, one in every five domestic wells exceeds EPA limits for nitrates.[8]

Persistent organic pollutants, which are fat-soluble and tend to bind to sediments, are rarely found in drinking water.[3] However, pesticides that are water-soluble and highly polar, such as atrazine, are common contaminants of drinking water drawn from both surface and ground water sources. Found in 98 percent of streams sampled in the Midwest, atrazine received the highest hazard quotient of all pesticides evaluated from treated municipal water in a 2002 risk assessment.[3]

In addition to pesticides, municipal drinking water can also contain disinfection by-products. When chlorine is used as a water disinfectant, it reacts with organic matter and forms hundreds of different halogenated organic compounds, many of which have been linked to cancer in animals. One of the most mutagenic compounds formed during water disinfection is 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5h)-furanone, referred to as "mutagen X" or MX.[9] Other disinfection by-products include trihalomethanes (THMs), e.g. chloroform, and haloacetic acids, e.g. the human carcinogen dichloroacetic acid.[10] DCP (2,4-dichlorophenol) is a water contaminant formed when chlorine spontaneously reacts with phenolic compounds. It is also a metabolite of the herbicide 2,4-D (see Section I, Chapter B.4). A weak estrogen, DCP thus has at least two origins in drinking water: as a disinfection by-product and as a metabolic breakdown product of a common pesticide.[11, 12] Among U.S. adults sampled, 64 percent had detectable levels of DCP in their urine.[13]

Because surface water contains more organic material than ground water and because it requires more chlorine for disinfection, levels of disinfection by-products tend to be higher in treated tap water that is pumped from surface water than in tap water drawn from ground water. The EPA has identified only half of the total number of disinfection by-products found in chlorinated water.[14] Considerably less is known about the by-products of newer-generation

disinfectants. These include ozone, chlorine dioxide, and chloroamine.[15]

More than most states, California relies on surface water sources for its drinking water. In normal years, ground water provides only 30 percent of the state's water supply. During drought years, the state's reliance on ground water increases.[16] Approximately 20 million southern Californians depend on the Sacramento-San Joaquin Delta for drinking water. The Colorado River basin also supplies southern California. In the north, the Sacramento River, the state's longest river, with headwaters near Mt. Shasta, serves as a drinking water source. Fed by melting snow, the Sacramento empties into the San Francisco Bay. It is polluted by heavy metals from abandoned mining operations in its upper watershed and by agricultural chemicals in its lower watershed. In the mid-1980s, herbicides used in rice production were detected the lower Sacramento River, which serves as the drinking water source for the city of Sacramento.[17]

Two discoveries in 1979 revealed the vulnerability of California's ground water to chemical contamination. The first was the presence of two industrial solvents, perchloroethylene (PCE) and trichloroethylene (TCE), in drinking water in the San Gabriel Valley, which is located in southern California, east of Los Angeles.[18] The second was the discovery of a soil fumigant, 1,2-dibromo-3-chloropropane (DBCP), in drinking water wells in the Central Valley. By 1987, DBCP was the most widespread pesticide contaminant in California aquifers, with more than one thousand wells in the Central Valley declared undrinkable due to DBCP. A reproductive toxicant, DBCP was first used in 1955 to kill nematodes, and was outlawed in California in 1977.[19] Organic solvents were subsequently found in drinking water wells near military bases and electronic industries in the state.[19]

Water pollutants remain common. Methyl tertiary butyl ether (MTBE), a water-soluble gasoline additive, has contaminated 10,000 ground water sites across California and contaminates the drinking water of 15 million Americans in 29 states.[20] With 127 drinking water systems reporting detections, California has the most severe MTBE contamination of drinking water in the United States, according to a recent analysis of data from state environmental agencies.[20] This includes drinking water sources in population-dense areas. Most notably, in 1996, city officials discovered MTBE – at levels as high as 610 parts per billion – in two of Santa Monica's drinking water wells.[21] Perchlorate, a water-soluble rocket fuel, pollutes 292 ground water sources throughout California, especially in communities located near military bases and missile manufacturing facilities, while the pesticide DBCP pollutes the drinking water of one million residents across the Central Valley.[18] In Fresno, nitrates from agricultural fertilizer and leaking septic tanks have seeped into drinking water supplies.[18] Solvents from electronic industries have affected drinking water sources in Silicon Valley, due to leaking underground storage tanks.[17]

Another emerging issue in California is the increasing reuse of wastewater to augment fresh water supplies. Within the State Water Resources Control Board, the Water Recycling Funding

Program promotes the use of treated waste water for such purposes as crop irrigation, landscaping, irrigation of playing fields for sports, and recharging ground water.[22] Several studies have found endocrine-disrupting chemicals in reclaimed wastewater, including pharmaceuticals and personal care products.[15] For example, anti-convulsants, muscle relaxants, cholesterol-lowering drugs, insect repellants, synthetic musks, and flame retardants have been detected in runoff from farm fields irrigated with treated waste water.[23]

This chapter describes the evidence for a link between breast cancer and drinking water contaminants. It considers some of the same chemicals described in other chapters – pesticides, solvents, pharmaceuticals, and personal care products – but from a mixtures perspective. The chapter also focuses on exposure to a group of chemicals unique to drinking water: the by-products of water disinfection that are created during chlorination. The role of drinking water contaminants in breast carcinogenesis is an under-studied question.

Regulatory History

Public drinking water is regulated nationally by the Safe Drinking Water Act (SDWA), which became law in 1974. Under SDWA, the EPA has set standards for 90 contaminants in drinking water. These include four radionuclides (but not radon); inorganic contaminants such as lead and arsenic; synthetic organic contaminants, such as pesticides; volatile organic compounds, such as benzene and other solvents; and the by-products of water disinfectants, such as trihalomethanes and haloacetic acids. For each of these, the EPA sets a legal limit, called a maximum contaminant level.[24] MCLs are not health-based standards. They are set to reflect both the economic cost of removing contaminants and the technological feasibility of doing so.

Since 1999, water utilities are required to divulge to their customers an inventory of contaminants found in drinking water in an annual consumer confidence report.[4] According to these reports, ten percent of the nation's water systems are out of compliance with EPA standards for tap water quality.[1]

Maximum contaminant level *goals* (MCLGs) are also promulgated by the EPA for each of its 90 regulated contaminants. These are health-based standards, and they are not legally enforceable. Often, there are discrepancies between the MCL and the MCLG. For example, the MCLG for the dry-cleaning solvent PCE is zero, whereas the MCL is five parts per billion.[24] Standards are not always set with cancer in mind. The MCL for nitrates, for example, was promulgated to protect formula-fed babies from a type of anemia. Recent studies indicate possible adverse outcomes for other endpoints, such as cancer and diabetes, at levels below the MCL.[8]

States may create and administer their own stricter drinking water standards. Therefore, the quality of California's tap water is governed both by federal regulations and by state regulations under the California Safe Drinking Water Act. The Office of Drinking Water within the California Department of Health Services oversees the quality of the state's drinking water. Local communities are responsible for making decisions

about whether or not to add fluoride to drinking water. The FDA sets standards for bottled water.

Of the 216 chemicals and pollutants identified as mammary carcinogens by Rudel,[9] at least 32 are often found in drinking water. Of these 32, only 12 are regulated under the Safe Drinking Water Act. They are acrylamide, the triazine herbicides atrazine and symazine, DBCP, 1,2 dibromoethane, 1,2-dichloropropane, 1,2,dichloroethane, benzene, carbon tetrachloride, 3,3-dimethoxybenzidine, styrene, and vinyl chloride.

Many drinking water contaminants have no SDWA standards and are thus not federally regulated.[24] These include 20 known mammary gland carcinogens, as identified by Rudel.[9] Among the chemicals with no drinking water guidelines are two that are known to pose significant risks to California's drinking water – the gasoline additive MTBE and the rocket fuel perchlorate.[25, 26] Also federally unregulated in drinking water are pharmaceuticals and ingredients found in personal care products. Three of these – conjugated estrogens, estradiol-17b, and ethinylestradiol – are mammary gland carcinogens.[9]

Hormones, pharmaceuticals, and personal care products were found in 80 percent of U.S. surface water sampled by the U.S. Geological Survey.[27] The known endocrine disruptors included antibacterial agents, insect repellants, nonylphenol, and estradiol. These substances are not completely removed in the process of sewage treatment, have no drinking water guidelines, and are not routinely tested for by water treatment plants.[27, 28] Hormones, pharmaceuticals, and personal care products are carried into the general aquatic environment and can eventually turn up in drinking water.[28, 29] A study conducted jointly by the U.S. Geological Survey and the Centers for Disease Control identified many unregulated chemicals in drinking water sampled at a water treatment facility in an urban area where surface water streams were affected upstream by sewage-treatment plants. Contaminants included prescription and non-prescription drugs, cosmetics, fragrance compounds, flame-retardants, and plasticizers. At least 11 and as many as 17 organic wastewater compounds were detected in samples of finished drinking water.[29]

The phenolic compound triclosan is an antibacterial agent of emerging concern as a drinking water contaminant. Used in dish and hand soaps, toothpaste, mouthwash, plastic cutting boards, children's toys, cosmetics, and deodorants, triclosan is now found in many U.S. streams at a median concentration of 0.14 ppb.[27] Although this phenolic compound is not classified as carcinogenic or mutagenic, it is thought to combine with chlorine in drinking water to form chloroform gas (a known carcinogen) and other chlorinated contaminants such as chlorinated phenoxy phenols.[30] Use of triclosan in hand soaps can increase individual exposure to chloroform by as much as 40 percent above background levels from tap water.[15]

The U.S. Geological Survey has also found intersex fish – such as male fish with ovaries – in many streams and rivers throughout the nation, including the Colorado River, an important drinking water source for southern California. Endocrine-disrupting chemicals from wastewater appear to be the cause, but precise methodologies

to evaluate the effect of environmental estrogens on wild fish populations have not yet been developed.[31] Endocrine-disrupting chemicals found in U.S. rivers have been demonstrated to cause alterations in sexual development and reproduction in aquarium fish.[32]

Concept/Exposure Definition

Routes of exposures for drinking water contaminants include ingestion, inhalation, and dermal absorption. The relative importance of each route varies for different contaminants, depending on the volatility and polarity of the chemical, and on the age and personal habits of the individual. Compared with adults, very young children, for example, have greater overall surface area and more permeable skin. What follows here is brief overview of chemicals with identified routes of exposure. For most, the relative contribution of each route of exposure is not known.

Exposures from Ingestion

Direct ingestion is the major route of exposure to nitrates in drinking water. In the gut, nitrates are converted to nitrites. Nitrate is also a precursor in the formation of N-nitroso compounds, which, as a class, are genotoxic and potent animal carcinogens.[8]

Oral intake, along with dermal absorption, is also the primary route of exposure to the antimicrobial phenol, triclosan, which has been detected in human breast milk and serum samples from the general population[33] and in the urine of 61 percent of six- to eight-year-old girls from various parts of the U.S.[34]

Exposures through Inhalation and Dermal Absorption

For volatile organic contaminants – including many disinfection by-products – exposure through inhalation and skin absorption appears to be more significant than ingestion.[15, 35] One study reports that a ten-minute shower or a thirty-minute bath can contribute a greater internal dose of volatile organic compounds than drinking a half a gallon of tap water.[36] Showering in an enclosed stall appears to contribute the greatest dose, probably because of the inhalation of the steam. Both showering and bathing significantly increase exhaled breath and blood concentrations of chloroform.[37] One study in Rockford, Illinois, where drinking water wells were contaminated with chlorinated solvents, found that blood levels of solvents correlated more closely with household air levels than with actual water levels. In turn, air levels were correlated with length of shower run times.[38] Dishwashers, with their combination of high temperatures and high turbulence, are an especially efficient means of transferring volatile organic compounds from drinking water into indoor air.[5, 37] as is machine-washing of clothes.[37] Bleaches in both laundry and dishwashing detergents are an additional source of indoor chlorinated air pollutants.[39]

Exposures from Swimming Pools

Disinfection of swimming pool water produces trihalomethanes when body fluids, sunscreens, natural organic matter, and cosmetics react with chlorine. Trihalomethanes have been detected in the blood and exhaled breath of swimmers and non-swimmers at indoor pools.[40] Swimming pool water test kits contain 3,3'-dimethylbenzidine, a

mammary carcinogen.[9] Human exposure may occur if these chemical solutions enter the pool.[9]

Exposures from Bottled Water

More than 70 percent of Californians use bottled water for some or all of their drinking water.[41] However, little information is available about bottled water quality. A four-year investigation by Natural Resources Defense Council, completed in 1999, found that bottled water rarely violated federal drinking water standards but sometimes contained chemical contaminants. These included volatile organic compounds, arsenic, and plasticizing ingredients such as DEHP phthalate. California legislation to regulate bottled water as strictly as drinking water – and which would have compelled disclosure of its source and the number and concentration of its contaminants – was defeated in 2004.

Critical Review of the Literature

The toxicological profiles of many common water contaminants – pesticides, solvents, personal care products – are described in other chapters. Disinfection by-products are considered here. The summary of human studies includes additional drinking water contaminants.

Of the 500 different by-products that have been reported in the literature, almost no quantitative occurrence data exist for most, and only a limited number have been studied for genotoxicity and other health effects.[42]

One disinfection by-product for which there is toxicological evidence is MX, a mammary gland carcinogen that is unique to drinking water. MX is not routinely monitored in U.S. drinking water nor regulated under the Safe Drinking Water Act. The absence of occurrence data for MX in finished drinking water means that its potential hazard as a breast carcinogen for women cannot be evaluated.

However, a preliminary nationwide survey of disinfection by-products in drinking water samples conducted by the EPA in 2002 revealed troubling results. First, researchers found MX at much higher levels than had previously been reported. The drinking water samples with the highest MX levels were collected from utilities using chlorine dioxide for primary disinfection. Second, researchers discovered brominated forms of MX. These appear to be even more carcinogenic than their chlorinated analogues. Third, the survey identified several new classes of disinfection by-products that had never before been described. These included brominated acids, iodo acids, and a new brominated ketone. Fourth, carbon tetrachloride was detected in some of the samples of finished drinking water. However, its source is unclear. Carbon tetrachloride could be a disinfection by-product or it could be a contaminant from the cleaning of chlorine cylinders.[42]

In Vitro Studies

In standard bacterial test systems, MX is a potent mutugen and a clastogen (that is, it can cause chromosomes to break; for a review, see McDonald and Komulainen[43]). Much lower in concentration than trihalomethanes or haloacetic acids, MX nevertheless accounts for as much as 20–50 percent of the total mutagenic activity measured in chlorinated drinking water samples.[42] Although its precise mechanism is unknown, MX

appears to cause DNA damage by ionizing DNA bases due to its high reductive potential. It also may cause mutations through DNA adducts.[43]

In Vivo Studies

MX is a multi-site carcinogen in both male and female rats[43] and is a mammary gland carcinogen in females.[9] MX increases malignant mammary gland tumors, and appears to be significantly more potent than other disinfection by-products in causing cancer in animals.[43]

Brominated nitromethanes, another disinfection by-product, have also been recently demonstrated to act as genotoxic agents in mammalian cells.[42]

The antimicrobial triclosan has been shown to disrupt thyroid-hormone-associated gene expression in frogs and can accelerate the pace of post-embryonic development.[44] Very little is known about the implications of this emerging endocrine disruptor for human health.

Human Studies

Epidemiologic studies of chemical contaminants in drinking water have mostly focused on cancers other than breast cancer. These have revealed immunologic effects, bladder cancer, and hematopoietic cancers.[45] One study examined communities in 339 U.S. counties with hazardous waste sites that had contaminated ground water which served as the sole drinking water source. Women living in these areas suffered significantly more mortality from breast cancer (and also bladder, colon, and stomach cancers). Counties with hazardous waste sites were 6.5 times more likely to have elevated breast cancer mortality rates than counties without such sites.[46]

Epidemiologic data on nitrates and cancer of any kind are not sufficient to draw conclusions,[45] with the possible exception of bladder cancer, the risk for which is elevated with nitrate-contaminated drinking water, according to several studies.[47] Nitrates in municipal drinking water were not associated with increased breast cancer risk among older women in the Iowa Women's Health Study.[47]

Disinfection by-products have been consistently linked to bladder and, to a lesser extent, rectal cancers in multiple studies.[10, 37, 45] Few studies have evaluated associations between disinfection by-products and breast cancer,[9, 48] and none have high statistical power. For example, a 1992 meta-analysis of case-control studies that investigated links between chlorination of drinking water and cancers of various kinds found a relative risk of 1.18 for breast cancer – but only four of the 12 studies reported on breast cancer.[48, 49]

Disinfection by-products have been linked to adverse pregnancy outcomes in some epidemiologic studies, according to a review by Afzal.[50] These results may have relevance to breast cancer if they indicate endocrine-disruption pathways that affect ovarian functioning. For example, one study found that increased exposure to trihalomethanes was associated with decreased length of menstrual cycling that resulted from earlier ovulation.[51] Shorter cycles raise lifetime exposure to endogenous estrogen and are associated with higher breast cancer risk.[51]

Human studies of breast cancer and drinking water contaminants other than water disinfection by-products are sparse, and most suffer from exposure assessment problems.[7] In Wisconsin, researchers did not find an association between risk of breast cancer and adult exposure to atrazine. However, the range of exposure in this study was extremely limited, and few women were exposed at levels above the MCL. (For more evidence on the link between atrazine and breast cancer, see Section I, Chapter B.4.)

Only one other epidemiologic study has investigated possible links between endocrine-disrupting chemicals in drinking water and breast cancer risk. Using a case-control design on Cape Cod, Massachusetts, researchers did not find a link between adult exposure to drinking water contaminated by wastewater and the risk of breast cancer.[7] However, the range of exposures was small, with few women unexposed and none exposed at high levels. On Cape Cod, where public water is drawn from more than 100 shallow wells sunk into sandy soils, septic system effluent and surface pollutants have seeped into ground water. Previous research had demonstrated that septic waste on the Cape was a source of exposure to endocrine-disrupting compounds, including alkylphenols from detergents.[52]

Cape Cod, which has a history of unexplained elevated breast cancer risk, was also the study site for the sole investigation of organic solvents in drinking water and breast cancer. In this case, results did provide evidence of a link. Investigating PCE exposure from vinyl-lined water pipes, researchers found a small but significant increase in breast cancer among women with the highest levels of PCE exposures in their drinking water.[53] One strength of this study was that it used residence history and inspection of water pipe systems to estimate individual exposure. In addition, traditional breast cancer risk factors were extensively evaluated as possible confounders.[48] A follow-up analysis that included further information on tap water consumption and bathing habits – in order to capture various routes of exposure – supported the original study.[54]

Conclusions and Future Directions

At least four chemicals identified by Rudel[9] as mammary gland carcinogens are common contaminants in drinking water: MX (a by-product of water disinfection), perchloroethylene (a dry-cleaning solvent), atrazine, and DCBP (both pesticides). Other than these, very little is known about breast cancer's relationship to drinking water contaminants, and almost nothing is known about the effects of exposures to mixtures of contaminants. Future research should focus on exposures to real-life mixtures as well as early-life exposures. The rate of tap water consumption per body weight is highest in early childhood, with formula-fed infants receiving the greatest exposure to contaminants in tap water.[43] Moreover, atrazine, one of the most common contaminants of drinking water drawn from both surface and ground water sources, is known to disrupt mammary gland development in prenatal and neonatal life. (See Section I, Chapter B.4 for details.) Outstanding questions include:

1) How does childhood exposure to MX, a direct-acting mutagen, affect breast cancer induction? Oxidative metabolism is

known to detoxify MX, but oxidative enzyme systems (such as liver CYP2E1) are not fully active in early life.[43]

2) What is the total mutagenicity of finished drinking water? Mixtures of chlorination by-products, triclosan, pesticides, and gasoline additives, for example, may exhibit toxic effects that are complex and not predicted from the effects of single compounds.[43]

3) What are the indirect effects of water disinfection by-products on breast cancer risk, via pathways such as shortened menstrual cycles? These pathways may be important for women living in large urban areas, where trihalomethane levels in drinking water are high. San Francisco, for example, has a history of high trihalomethane levels and, on this basis, received a grade of "poor" for drinking water quality from the Natural Resources Defense Council in 2003.[55]

4) What can data on water contaminants available through the Safe Drinking Water Act reveal about breast cancer risk in different geographic areas? These data have been underused in breast cancer studies. Together with databases mandated by California's Proposition 65, they provide a means to reconstruct historical exposures to water-borne carcinogens. Tools for GIS computer mapping, already developed for use in the Cape Cod Breast Cancer and Environment Study, are also available for these studies.[7, 48, 56]

5) How many chemicals identified by Rudel[9] as mammary gland carcinogens in animals are found in California's drinking water? And are they associated with elevated breast cancer risk?

6) Is PCE-contaminated drinking water associated with elevated breast cancer rates in California, as it is in Cape Cod?

7) What potential human exposures may be associated with the growing use of reclaimed wastewater in California?

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Hormones and Contaminants in Food

The hormonal activity of veterinary medications and additives used in food production has raised concern about the potential effect on breast cancer. Many animals are intentionally exposed to growth hormones to maximize meat, egg or dairy output. In some cases, hormone residues end up in the food itself. In other cases, as with cow's milk, hormone additives can raise the levels of endogenous hormones in the finished food product.

While most work has focused on hormones, other signaling molecules and growth factors that work through receptor based mechanisms may also play an important role. In addition, changes in production methods have also influenced endogenous hormone levels. The potential effects of both exogenous hormones and changing levels of endogenous hormones are considered in this chapter, which focuses on the potential cancer-promoting and endocrine-disrupting compounds used in animal food production and their potential for affecting breast cancer risk. Extensive and on-going research has been and is being devoted to the role of diet in breast cancer risk, particularly on dietary fat, therefore this discussion will be limited to the use of hormones in food production, rather than the diet composition or other more frequently addressed topics.

Other exposure issues associated with diet are addressed elsewhere in this document. Animal fats often contain measurable amounts of probable or known human carcinogens, such as hexachlorobenzene, polycyclic aromatic hydrocarbons (see chapter I.B.1), dioxins, furans, and PCBs (see chapter I.B.2). Pesticide use in animal feed may also be a concern and is addressed in section I.B.3. Nonylphenols, an endocrine disruptor discussed in chapter I.B.4, are also found in food. Production and storage practices may also increase hormonal activity in food by introducing compounds such as phthalates. In the past, cow's milk and maple syrup were often collected in plastic tubing, allowing plasticizers to leach into the food products. The potential effects of phthalates on breast cancer are addressed in I.B.10. Antibiotics are routinely and extensively used in poultry and pork production; chapter I.D discusses the relationship between antibiotics and breast cancer.

Milk and Dairy Products

On average, U.S. dairy cows produce six times more milk than they did a century ago.[1] Most of this increase is attributable to selective breeding. The vast majority of dairy cows are now conceived through artificial insemination and are sired by just a few individual bulls. Because milk production is regulated hormonally, some researchers speculate that the breeding for higher milk production has selected for endocrine variants, and this in turn, may have altered hormonal microconstituents in milk.[1] Evidence for an overall increase in the hormonally activity of cows' milk does not currently exist. However, lack of high-quality milk banks means there is an absence of data to enable researchers to understand whether and how hormonal profiles of dairy milk may have changed over time.

Cows cannot give milk until they have given birth. The gestation period of a cow is about nine

months long, and dairy farmers attempt to impregnate adults about every 13 months. Cows are typically milked early in their pregnancies and then allowed to dry up during late pregnancy. Some researchers speculate that simultaneous pregnancy and lactation is more common now than in years past and that the contemporary practice of milking cows into late pregnancy has boosted estrogen levels in the milk,[2] however, there has been little research into whether contemporary milk supplies have a higher proportion of milk from pregnant cows than in previous years. It is nonetheless an important question because dairy cow pregnancy status and stage affect estrogen and progesterone levels in milk.[2] A major estrogen in milk of particular concern is estrone sulfate. When ingested, this compound is highly absorbed in the gut (high oral bioactivity)…..) and has a long plasma half-life. It can be readily converted to estrone and estradiol in the body. One study found that almost 47% of estrone intake in a standard human diet came from dairy products.[2, 3] Milk and dairy products have been estimated to account for approximately 60–80% of the estrogens and progesterone consumed in the average U.S. diet overall.[4]

One notable change in dairy production occurred in 1993 when the FDA approved the use of recombinant bovine growth hormone (rBGH), also known as recombinant bovine somatotropin (rBST).[5] The use of rBGH is not approved in Canada or the European Union. While rBST is still used to maximize milk production in dairy cattle, less than 30% of U.S. dairy cattle are now treated and that number is decreasing.[5]

The human health concern about rBGH in milk production is its potential for increasing levels in milk of another compound made by the cow itself, insulin-like growth factor I (IGF-I). In response to concerns about rBGH, the FDA contended that it is not recognized as a hormone in the human body and that, because it is a protein hormone, it is broken down during human digestion. Industry and governmental bodies have found that milk from rBGH supplemented cows does not differ from that of untreated cows in the composition of macronutrients, such as lactose, total solids, and relative percentages of, for example, casein and lactalbumin.[6] However, there is little data on the effect of rBGH on levels of hormonally active agents. Monsanto, the manufacturer of rBGH, has reported the milk from rBGH-treated cows does have significantly higher levels of IGF-1,[7] and these findings have been reported by others (for example, Gulay et al.[8]). Casein, however, can protect IGF-1 from digestion. A 1990 paper by FDA staff reported that pasteurization of rBST milk could increase IGF-1 further and that the undigested protein could cross the intestinal wall in humans.[9]

IGF-1 in cow's milk is identical to IGF-1 in humans where it is used to regulate the growth of cells. It has also been demonstrated to promote tumor growth on a cellular level, including mitogenic, anti-apoptotic, pro-angiogenic and cell migration and is linked to chemically and genetically-induced mammary tumors in vivo.[10] IGF-1 and estrogen interact and share regulatory functions. IGF-1 receptors and estrogen receptor sites in the brain appear to affect one another (cross-talk). IGF-1 appears to be a key part of the mechanism for estradiol signaling and is required

for the priming actions of estradiol on the hypothalamus pituitary gland axis and in this way is involved in pubertal timing.[11-14]

Animal studies show that dairy consumption has estrogenic effects. A study of rats found that ingestion of commercially available cow's milk (i.e. with normal levels of estrogen) for 7 days had a weak but biologically significant hormonal effect in both young ovariectomized rats and sexually immature rats. This study used uterotrophic assay to test for estrogenicity, incorporating both metabolic effects and pharmacokinetics.[15] Another study found that commercially available low-fat milk promoted the development of DMBA-induced mammary tumors in rats, and only to a slightly lower degree than those fed 0.1 μg/ml estrone sulfate.[16] The authors hypothesized that the high estrogen content in the milk may be responsible for the promotional effects, acting in concert with other hormones such as IGF-I.

Drawing firm conclusions about the role of dairy hormones in breast cancer causation from human studies is made difficult because of at least four factors. First, rBGH was introduced in the dairy industry only within the last two decades; therefore, not enough time has passed to detect an effect. Second, not all dairy farmers use rBGH, and the milk from rBGH-treated cows is not evenly distributed within the national milk supply. Third, many studies of milk consumption and cancer risk combine human data from many nations, including those where rBGH is not used and where the milk practices regarding pregnant cows may be very different. Fourth, dairy consumption by itself, regardless of artificial hormones used in the production of the milk, may have a relationship to cancer risk. Dairy consumption does appear to elevate IGF-1 levels in humans.[1] IGF-1 levels vary considerably within and between individuals. While levels can be influenced by meat and dairy in the diet, it is not known how much rBGH-treatment may contribute to IGF-1 increases.

The association between milk consumption and breast cancer has been inconsistent in case-control and cohort studies, particularly when they did not control for menopausal status.[17-19] One meta-analysis observed a small increase in breast cancer risk with high milk consumption,[20] while a pooled analysis of cohort studies found no significant association.[21] An analysis of the Nurses' Health Study data found that among premenopausal women, higher intake of lowfat dairy foods was associated with reduced risk of breast cancer.[22] They also found that the lower risk was associated with specific components of dairy foods—calcium and vitamin D, but independent associations were difficult to distinguish. Milk in the U.S. is usually fortified with vitamin D, a prosteroid hormone thought to prevent cancer and associated with lower of developing premenopausal breast cancer.[23] However diet, including consumption of dairy products, provides a relatively small part of vitamin D dosage. For a more in-depth discussion of vitamin D, please see Section I, Chapter I.

The association between milk consumption and circulating IGF-1 levels is clearer. In an analysis of samples from more than 1000 women participating in the Nurses' Health Study, the most consistent positive association with plasma levels of IGF-1 was greater milk intake.[24] This

association held when adjusting for other factors and in an analysis of the biologically active fraction of IGF-1. Likewise, a 2007 IARC study found a modest association between circulating IGF-1 levels and intake of milk and cheese among European women.[25]

The association between circulating IGF-1 levels and breast cancer is not consistent and is currently under revision. The data have become less clear just during the past few years as results from large-scale cohorts have been published. One meta-analysis found that higher concentrations of IGF-1 were positively associated with increased risk of breast cancer in pre-menopausal but not post-menopausal women [pooled odds ratio = 1.93 (CI 1.38–2.69)]. The IGF-I binding protein IGFBP-3, was also associated with breast cancer [pooled odds ratio = 1.96 (CI 1.28–2.99)].[10] The authors suggested that IGF and its binding protein could have both potentiating and attenuating associations. They also took exception with conclusions of no association between IGF-1 and breast cancer from analyses of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort[26] and the Nurses Health Study II.[27]

Beef

The European Union has forbidden the use of exogenous hormones as promoters of animal growth since 1989.[28] By contrast, six hormones are approved for use in beef cattle in the United States. One is estradiol. Another is zeranol, a non-steroidal hormone with estrogenic activity.[29] Also used by the beef industry are two androgens—testosterone and trenbolone acetate, and two hormones with progesterogenic activity—progesterone and melengestrol acetate.[30] Many animals are dosed with more than one hormones. Synovex C, for example, is a calf implant that contains 100 mg of progesterone and 10 mg of estradiol. It is used to increase the rate of weight gain in suckling beef cattle.[31] Zeranol, trenbolone acetate (TA), and melengestrol acetate (MGA) are not metabolized as quickly as estradiol, progesterone and testosterone.[32] More than 90% of US livestock are currently injected with these hormones to increase production of veal and beef.[33]

The FDA has reported that "concentrations of the hormones in edible tissues remain within the normal physiological range that has been established for untreated animals of the same age and sex."[32] These estimates assume that veterinary products are used as directed, which may not always be the case. Additionally, steroid hormones (in contrast to protein hormones) are not digested in the human gut and may pass into the bloodstream, making even low doses of concern, particularly during critical stages of development.

Additionally, federal risk assessments for safe threshold levels for estrogens in meat are based on overestimates of children's own endogenous production of estrogen, which are now known to be many times lower than presumed by previous models.[28] This means that estrogenic chemicals in food contribute a higher proportion of sex hormone levels in prepubertal girls than was presumed when federal risk assessments established legal limits for estrogen levels in meat. Moreover, the three synthetic hormones given beef cattle—trenbolone acetate, zeranol and melengestrol acetate—were found to cross the

placental barrier of pregnant rabbits that were treated. Fetuses had detectable levels of both parent compounds and their metabolites.[34]

The form of estradiol used in beef production (17β) is a cancer promoter and has shown genotoxic activity in certain conditions.[35] In addition to hormonal action, it is suspected of acting as a chemical carcinogen by binding to cellular macromolecules. Some evidence suggests that certain catechol metabolites induce free-radical damage of DNA in cell and laboratory animal test systems.[30]

It also is biologically plausible that estrogens in meat could contribute to the falling age of menarche in U.S. girls; early menarche is a known risk factor for breast cancer. Estradiol is known to accelerate hypothalamic maturation, which controls pubertal timing.[36] In addition, known exposures to estrogens in personal care products and ingested pharmaceuticals have been documented to induce precocious breast development in young girls.[28, 36]

There are also reasons to be concerned about the synthetic estrogen zeranol, which is also used in beef production. The estrogen receptor-positive MCF-7 human breast cancer cell line showed estrogen-dependent growth in vitro, as well as estrogen-dependent tumorigenicity *in vivo* in the presence of zeranol.[29, 37] Zeranol has induced estrogenic responses in primary cultured breast cells and breast cancer cell lines. Meat and serum from zeranol treated cattle were mitogenic (heat-stable) for cultured breast cells, and both normal and cancerous human breast cells exhibited estrogenic responses to zeranol.[16]

Human epidemiological studies sometimes have shown an association between meat consumption and breast cancer incidence. However, many analyses blended data from nations that do and do not use hormone supplements. Analysis of dietary data from 40 countries found meat was the most closely correlated with breast cancer incidence ($r = 0.827$), followed by milk (0.817) and cheese (0.751).[2] A step-wise regression again found the highest correlation with meat, while breast cancer mortality was most closely associated with cheese. An Italian study found that, after parity, only dairy consumption had a significant positive correlation with breast cancer mortality.[38]

Increased breast cancer in humans and increased mammary gland tumors in animals has been associated with the form of estradiol used in beef production (17β).[39] Recent findings from a large prospective cohort study found a link between increased breast cancer incidence and red meat consumption in premenopausal women. They found a strong positive relationship (test for trend, $P = 0.001$) between the amount of red meat younger women reported consuming and rates of estrogen receptor positive breast cancer in the 12 years of follow-up.[40] Meat consumption was reported at three times during this prospective study, limiting potential recall bias and error. Previous negative findings were based on studies of older women, did not account for menopausal status and/or did not account for cancer hormone receptor status.

Poultry

Little information is available about nithiazide, a veterinary medicine used in poultry production. It may persist in the tissues and eggs of treated

poultry and when administered in the diet, it increased the incidence of fibroadenomas and cystadenomas of the mammary gland in female rats.[39] It was also found to be positive for mutagenicity.[41]

In addition to nithiazide, roxarsone, an organic arsenic derivative, is routinely used in poultry feed in order to kill parasites in broiler chickens and to promote growth.[42] A percentage of roxarsone converts to inorganic arsenic within the chicken, and also is rapidly transformed into inorganic arsenic when poultry litter is applied to fields. From here, it may easily move to groundwater. There are, thus, two important routes of human exposure for arsenic used the poultry industry: consumption of chicken and drinking water.

Data published in 2004 by Lasky and her colleagues at the USDA calculated that some heavy consumers of chicken—who include children, senior citizens, and African Americans--may be ingesting more arsenic than the WHO/FAO tolerable daily intake (2 micrograms/kg/day inorganic arsenic).[43] Moreover, consumption in the United States is on the rise, having increased by 2.5 fold between 1966 and 2000.[42] Arsenic may also be ingested with groundwater, fish and some brands of rice, adding to total exposure.

Arsenic is a known human carcinogen.[44] It is also an endocrine disruptor. Arsenic alters the ability of glucocorticoid receptors, progesterone receptors, and mineralocorticoid receptors to respond to their normal hormonal signals. It does so by affecting the regulation of gene expression. The dose-response curve is non-monotonic: at very low doses, arsenic enhances gene expression. At higher doses, it inhibits these receptors.[45] These results suggest that arsenic may have very different carcinogenic influences at lower and higher doses. Arsenic also disrupts estrogen receptors both in vivo and in MCF-7 cell cultures. Specifically, arsenic significantly inhibited E2-mediated gene activation of an ER-regulated reporter gene and the native ER-regulated GREB1 gene in human breast cancer cells. Arsenic is also discussed in I.B.8. Metals.

Discussion & Conclusions

The relationship between diet and cancer is very complex, involving not only potential exposure to risk factors for breast cancer, but also protective effects of nutrients. It is difficult to distinguish between carcinogens produced by cooking meat and those in animal fat, or between endogenous and exogenous hormones in meat and milk. Given this conflicting evidence, some researchers call for further work to identify the relationship between specific components of milk and the development of breast cancer.[16] The use of equipment and containers with hormonally active compounds, such as plastics with the potential to leach phthalates, is an additional factor that may confound research on the role of food and should be considered in future studies.

Studies cited here offer evidence of a positive association between IGF-1 levels in humans with milk consumption; however, more information is needed about the effect of IGF-1 levels in milk on the levels in humans. It is also important to evaluate differences in human response to treated and untreated milk, as well as responses to milk from dairy cow by pregnancy status and stage. While governments in Canada and the EU have

banned the use of rBST, consumers concerns about human health are driving change in the U.S. Following a few other large producers (Tillamook, some Safeway and Kroger plants), California Dairies Co., which supplies about 10% of U.S. milk, is eliminating rBST in the milk it handles by mid-2007.[46] Kroger will finish eliminating rBST from milk it processes and sells by early 2008.[47]

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Metals

Introduction

Metals are naturally occurring elements that readily form positively charged ions. Metals are found in air, food, and water. They exist primarily as salt compounds in food and water, but may also be present as oxide dusts or elemental fumes in air. Metals are used in many industrial processes and some metals are released into the air as by-products of combustion. The metals that have been studied most frequently in relation to breast cancer include cadmium, chromium, lead, and nickel. Biological and other evidence supports the plausibility that exposures to cadmium, chromium, lead, or nickel compounds could be associated with breast cancer. These heavy metals are considered known or probable human carcinogens and also have demonstrated estrogenic properties. Evidence for an association between breast cancer and exposure to other metals—including arsenic, cobalt, and mercury—has been inconsistent across studies. Although there were some positive findings, the overall evidence is weak. Exposure to zinc may be protective against breast cancer. There are few epidemiologic studies evaluating exposure to metals and breast cancer, and most of these are limited in power due to small numbers of subjects and have been published very recently; but the findings to date are intriguing and highlight the need for future studies.

Concept/Exposure Definition

Environmental Exposures

Metals are widely distributed elements, usually occurring at low levels in the earth's crust, although some geographic areas have naturally high levels in soil. Metals are released into the environment during mining operations, industrial and manufacturing processes, and as by-products of combustion.[1-3] Metals are generally present at low concentrations in ambient air, although much higher concentrations have been measured near metal processing facilities.[1-3] The overall median air concentration at 20 monitoring sites in California from 2000–2002 was 3 ng/m^3 for total chromium, 7 ng/m^3 for lead and 3 ng/m^3 for nickel.[4] The median concentrations for arsenic and cadmium were around 0.5 ng/m^3, based on the most recent air monitoring data in California during the 1990s.[4] Drinking water, especially groundwater and well sources, can also be contaminated with metals. Testing in California from over 6,700 drinking water sources between 2002–2005 found that arsenic concentrations exceeded the new maximum contaminant level (10 μg /L) in about 10 percent of sources and chromium concentrations exceed recommended levels (1 μg /L) for over 33 percent of sources.[5] Lead contamination of drinking water is a result of leaching from pipes in the home. Lead levels in California tap water are not well known, due to a lack of testing. For most metals, food is the primary source of exposure for the general population. Duplicate diet analyses conducted in the National Human Exposure Assessment Surveys (NHEXAS) in Maryland and Arizona found median daily intake rates of 30–50 μg /day for arsenic, 10–23 μg/day for cadmium, 100 μg / day for chromium, 8–15 μg /day for lead and 214 μg /day for nickel.[6, 7] Assuming standard breathing and water consumption rates, the average dietary intake of these metals is about an order of magnitude higher than intake from drinking water, and several orders of magnitude greater than the intake from air. However, the metabolism and toxicity of a chemical can vary significantly by exposure route.

Cigarette smoke is another source of exposure to metals, including cadmium,[8, 9] lead,[9] and nickel.[10] For example, smokers may double their daily intake of cadmium, compared with nonsmokers.[1] Urinary levels of cadmium[11] and lead[12] were also elevated among people exposed to second-hand smoke.

Occupational Exposures

Occupational exposure to heavy metals occurs in several industries. Concentrations in workplace air can be up to two orders of magnitude higher than ambient levels experienced by the general population.[13] Metal workers are exposed to cadmium, chromium, and nickel fumes during plating operations.[1, 14, 15] Welders had significantly higher levels of cadmium, chromium, lead, and nickel in both their blood and urine than controls who were not exposed to welding fumes during work.[16] Battery manufacturing workers are exposed to cadmium, lead, and nickel salts used in production.[1] Bridge and auto body painters had higher levels of blood lead and urinary cadmium and chromium than unexposed controls.[17, 18] Workers employed in paint and pigment manufacturing are also be expected to have higher exposure to metals, due to the use of these compounds in the products they produce.[1]

Extent of Human Exposures

Laboratory techniques are available to quantify metals in a variety of biologic media, including urine, blood, hair, and toenails to evaluate exposure levels. Urine concentrations provide a good measure of cumulative lifetime exposure to cadmium.[19] The National Health and Nutrition Examination Survey (NHANES), a representative sample of about 5,000 persons each year around the United States, observed a median urinary cadmium concentration of 0.3 µg /g creatinine for people 20 years of age and older during the 1999–2002 survey.[20] Occupational cadmium exposure can produce urinary levels as high as 50 µg /g creatinine and the occupational level of concern in the United States is set at 3 µg /g creatinine.[1] However, the occupational level of concern is based on renal damage and does not include consideration of breast cancer or hormonal mechanisms relevant to breast cancer.

Chromium levels in urine are considered a marker of recent exposure and a population-based median reference value of 0.4 µg /g creatinine was identified in the late 1980s.[21] More recent population-based measurements in Germany found a median level of 0.1 µg /g creatinine for chromium.[22] Occupational exposure studies of urinary chromium levels have observed median concentrations of 5 µg /g creatinine for boilermakers[23] and 20 µg /g creatinine for welders.[16] In the general population, average nickel concentrations in urine range from 1 to 3 µg /g creatinine.[24] Urinary nickel concentrations resulting from occupational exposure range from 4 µg/g creatinine for welders[16] to 11 µg/g creatinine among exposed refinery workers.[25]

Whole blood is the most commonly measured biologic media for evaluating exposure to lead. Geometric mean blood lead levels among adults in the United States have declined dramatically over the past 25 years, from 12.8 µg /dL during 1976–1980 NHANES to 2.9 µg /dL during 1988–1991 NHANES, and, most recently, 1.6 µg /dL during the 1999–2002 NHANES.[20] The occupational level of concern in the United States is 25 µg /dL, and the highest lead exposures occur among welders, painters, and construction workers.[26]

Critical Review of the Literature

In Vitro Studies

The mutagenicity of cadmium, chromium, lead, and nickel depends on the form, but they are generally mutagenic in either mouse lymphoma cells or the Ames Salmonella test.[27, 28] Several heavy metal salts, including cadmium chloride, chromium chloride, and lead acetate, have been found to be estrogenic using an estrogen-receptor-dependent transcriptional expression assay or E-screen assay systems.[29, 30] A range of estrogenicity has been observed for different species of lead and chromium, suggesting that the valence state of a metal may be an important determinant of estrogenic activity.[30] Chromium, lead, and nickel chlorides can also stimulate cell proliferation in the estrogen-receptor-positive human breast cancer cell line, MCF-7, through the formation of a high-affinity complex with the hormone-binding domain of the estrogen receptor.[31]

In Vivo Studies

Cadmium, chromium, lead, and nickel compounds have been shown to be carcinogenic in numerous rodent studies, producing excess lung, liver, and kidney tumors.[27] Cadmium chloride also has exhibited potent estrogen-like activity in ovariectomized rats, increasing uterine wet weight and promoting an increase in the side branches and alveolar buds in the mammary gland.[32] This study also found that *in utero* exposure to cadmium chloride mimicked the effects of estrogen by causing an earlier onset of puberty and increasing the number of terminal end buds in the mammary gland of female offspring. In female mice infected with murine mammary tumorvirus, chromium and selenium have interactive effects on mammary tumor development and growth. Chromium counteracts the inhibitory effect of selenium on tumor development and shortens the tumor latency period.[33]

Studies in Humans

Hexavalent chromium and nickel oxide dusts are classified as known human carcinogens, while cadmium and organic lead compounds are considered probable human carcinogens.[28] These cancer classifications are based primarily on associations with increased rates of lung cancer in occupationally-exposed individuals. Several recently-published studies, although limited in power due to small numbers of subjects, have observed elevated levels of metals in women with breast cancer, compared to controls. Higher levels of cadmium, chromium, lead, and nickel were found in 20 breast cancer tissue biopsies than were present in eight healthy biopsies, suggesting that accumulation of these metals in breast tissue may be closely related to the malignant growth process.[34] A study in India found higher levels of lead and cadmium in both blood and breast tissue of 25 women with malignant breast lesions, compared to 25 women with benign breast lesions.[35] Cadmium levels in urine were compared between 24 women with breast cancer and 254 age-matched controls.[36] Women in the highest quartile of creatinine-adjusted cadmium level had more than twice the breast cancer risk (OR = 2.3, 95% CI = 1.3–4.2) of women in the lowest quartile, after adjustment for established breast cancer risk factors. There was also a statistically significant ($P_{trend} = 0.01$) increase in risk with increasing cadmium level in this study. It is not known whether increased biological levels of metals are causal factors for breast cancer, or a reflection of the disease state or treatment.

A case-control study of breast cancer and metal exposure based on an assessment of occupation using mortality records found an increased risk for women exposed to a group of metals (chromium, arsenic, beryllium, and nickel), as well as exposure to lead and cadmium individually.[37] The odds ratios were approximately 1.1, after adjusting for socioeconomic status for each metal exposure group, and were either significant or borderline significant for both probability and level of exposure in both white and black women. The limitations of this study include (1) an inability to control for most recognized breast cancer risk factors, and (2) potential exposure misclassification, resulting from the use of a job exposure matrix based on occupation and industry codes instead of task-based personal interviews.

An ecological study in Texas, which utilized Toxics Release Inventory data to estimate exposure to numerous pollutants, found significantly higher ($p < 0.01$) breast cancer rates in counties with reported releases of chromium and nickel, but not arsenic or cadmium.[38] Although the results of this study are provocative, the exposure assessment methods used the county of residence, which is a poor estimate of proximity to chemical releases. The study did not utilize the volume of reported releases to estimate the magnitude of exposure and test for a trend with increasing exposure.

Intake of certain essential metals may be protective against breast cancer. A case-control study of dietary intake conducted in Germany observed a significant protective effect for breast cancer risk between the highest quartile of zinc intake and the lowest (OR = 0.35), and a significant trend ($p <0 .01$) with increasing zinc intake.[39] Although selenium intake has been shown to be protective against some types of cancer, there does not appear to be an association with breast cancer.[40]

In summary, recent studies in humans suggest that there may be a relationship between exposure to certain metal compounds and the risk of breast cancer, but these studies have been limited by small numbers of exposed subjects, a lack of information on speciation of metals (salts, oxide dusts, or metal fumes), and potential exposure misclassification.

Future Directions

Given that there is widespread exposure to several metals that are likely to cause other types of cancer in humans and that these compounds are estrogenic, more breast cancer studies of cadmium, chromium, lead, and nickel are warranted.

Some first steps might include:

- Occupational studies to monitor breast cancer incidence rates in occupations with exposures to cadmium, chromium, lead, and nickel, along with better characterization of exposures to these metals by job type and task.
- A prospective study evaluating biological levels of these metals in blood or urine and the associated breast cancer risk. Metals are easily measured in blood or urine. Due to their persistence, a single biological measurement is likely to be representative of exposure levels over a relatively long period of time.
- Since the existing human evidence of a relationship between exposure to metals

and breast cancer is weak, a prospective case-control study of breast cancer that accounts for environmental exposures to potentially carcinogenic metals by all major pathways (air, water, or diet) is needed.

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Exposures from Polyvinyl Chloride (PVC)

Introduction

Produced since the 1930s, polyvinyl chloride (PVC) was one of the first plastics to be manufactured. Today it is the second most commonly-used plastic in the world,[1] with an estimated 59 billion pounds produced globally in 2002. Plastic pipes and other construction materials account for the majority (75 percent) of PVC consumption in North America.[1] PVC is also used in a wide range of products, including kitchen flooring, shower curtains, wallpaper, children's toys, garden hoses, three-ring binders, credit cards, and food packaging. It is one of the only common plastics to contain chlorine. PVC is 56 percent chlorine by weight, and it is this ingredient that has raised questions about PVC's effect on human health.

While the carcinogenic risks posed to workers occupationally exposed to vinyl chloride during the production of PVC were recognized over twenty years ago,[2] it is only recently that attention has focused on other potential health consequences in the general population posed by PVC throughout its entire life cycle – from production, to use, to disposal. Two U.S. advocacy groups have recently published extensive reviews of research in this regard that provide more detailed discussion of the overall health and environmental dangers associated with PVC.[1, 3] The summary presented here is focused on the exposures and potential effects of PVC only as they may be relevant to breast cancer risk.

Definitions and Sources of Exposure

PVC is a polymer made from vinyl chloride molecules. PVC products, however, are typically not the pure polymer itself, but contain a variety of additives and stabilizers that impart the desired qualities specific to the various uses of PVC. The most widely used of these are the phthalate plasticizers, used to soften and make the products more flexible, and metallic stabilizers used to extend the life of the products. Thus, in considering the potential breast cancer risks associated with PVCs, it is important to include a consideration of potential exposures to these additives.

Potential human exposures associated with PVCs vary throughout the life cycle of PVC (Table 1). Vinyl chloride exposures are primarily a concern associated with PVC production. Heavy metals and phthalates are of concern during the use and disposal of PVC products, while dioxins and other persistent organic pollutants are an exposure of concern throughout the entire life cycle of PVC. The extent of human exposures to each one of these compounds is described in more detail on the following pages. In addition to these compounds, there are a myriad of other chlorinated hydrocarbons released as by-products during PVC production and combustion, including hexachlorobenzene, chlorinated phenols, PCBs, hexachloroethane, hexachlorobutadiene, and carbon tetrachloride.[3] With the exception of PCBs, the relationship of these compounds to breast cancer risk has not been widely investigated. For a summary of the breast cancer evidence for PCBs, please see Section I, Chapter B.2, Persistent Organic Pollutants.

Table 1. Potential Human Exposures to Hazardous Substances from the Production, Use and Disposal of PVCs.

Compounds of Concern	Source of Exposure	Likely Extent of Human Exposures
From Production:		
Vinyl Chloride	• Environmental contamination from facilities that produce PVC and its feedstocks	• Minimal, except in small areas in close proximity to these facilities, where exposures could be quite high
	• Workers involved in PVC manufacturing	• Minimal due to industrial hygiene efforts to reduce exposures & the relatively small number of women likely to be employed in this industry
Mercury	• Used and released in some processes to make elemental chlorine	• May be high in some small areas/populations. • Not likely to be widespread
Dioxins & Other Persistent Organic Pollutants	• Manufacturing by-products released into environment by facilities that produce PVC and its feedstocks; released into environment directly or via disposal of wastes.	• Universal due to these compounds' ability to persist and bioaccumulate
From Use:		

Phthalates	• Leach out of products during normal use	• May be fairly extensive; biomonitoring data of phthalates indicate widespread exposures but all sources have not been elucidated
Heavy Metals	• Leach out of consumer and building products during normal use	• Not known
Dioxins	• Produced during accidental building and vehicle fires	• Universal due to these compounds' ability to persist and bioaccumulate
From Disposal:		
Phthalates	• Environmental contamination from landfill leachates	• Not known; biomonitoring data of phthalates indicate widespread exposures but not all sources have been elucidated
Heavy Metals	• Environmental contamination from landfill leachates, incinerator air emissions and ash	• Not known
Dioxins	• Environmental contamination from incinerator air emissions and ash	• Universal due to these compounds' ability to persist and bioaccumulate

Vinyl Chloride

Vinyl chloride was previously used as a refrigerant, an extraction solvent, and in aerosol propellants, including hairsprays, but these uses were banned in 1974.[4] Today, vinyl chloride is released into the environment primarily through effluents and emissions from vinyl chloride and PVC manufacturers.[5] Due to its high volatility, vinyl chloride does not appear to bioaccumulate in terrestrial or aquatic food chains.[6] Although vinyl chloride has been detected in air, water, soil, and food, levels are generally very low. The exceptions are areas in close proximity to hazardous waste or PVC manufacturing sites, where levels can be orders of magnitude higher

than general ambient levels and have been found to exceed health-based standards.[5-7] Vinyl chloride has been detected at nearly 40 percent of the hazardous waste sites on the EPA's National Priorities List[5] and at 24 out of 251 California landfills tested in the 1990s.[6]

Workers involved in PVC manufacturing are primarily exposed to vinyl chloride through inhalation, but some dermal exposure may also occur.[5] The National Occupational Exposure Survey conducted by NIOSH in the early 1980s estimated that approximately 28,000 women were employed at manufacturing facilities where potential vinyl chloride exposures were likely.[8] These data probably do not adequately reflect exposures in today's workforce, but more recent occupational survey data on potential PVC exposures do not exist. Due to improvements in industrial hygiene efforts over the last 30 years, however, workers involved in PVC manufacturing today likely experience much lower levels of exposures than previous generations.[3]

Vinyl chloride is a Class A carcinogen because of its known effects on the liver, with other reported toxicities of the nervous system.[9] As is true for many environmental contaminants, the effect of this component of PVC on the development of mammary tissue or breast cancer risk is unknown. However, the fact that this compound can cause irreversible damage to the neonate deserves further attention to PVC's possible effects on reproductive tissues such as the breast.

Mercury

There are currently three different processes used to extract the chlorine gas needed to produce PVC. The mercury process, the oldest and most energy-intensive, can result in substantial releases of mercury into the environment.[3] One estimate puts the annual release of mercury into the atmosphere from the production of PVC in the U.S. in the range of six to 26 tons.[7] The vast majority of mercury's effects on the brain/central nervous system are thought to derive from developmental exposures. The effects that it may have on the endocrine system are not known, but there is some evidence that mercury exposures are related to premature pregnancy loss. Mercury is discussed further in Section I, Chapter B.8, Metals. Fortunately, production of chlorine gas via the mercury process is being phased out.[3]

Dioxins

Dioxins are associated with every part of the PVC life cycle. During production of feedstocks for PVC, they are produced and released directly to the environment or indirectly via hazardous wastes, which are disposed of in incinerators or landfills. Dioxins are also produced as by-products of incineration of other chemicals in the wastes from PVC production.[3] During use, dioxins are released into the air from the estimated one million annual accidental building and vehicle fires often laden with PVC-containing materials.[1] During disposal, dioxins are released into the air through incineration. With an estimated 500-600 million pounds of PVC burned in municipal incinerators each year,[1] this is a significant source of dioxin pollution. While there are many other sources of dioxins, it has been suggested that when the entire life cycle of the product is considered, PVC may be the largest single source of dioxin formation in this country.[3]

Dioxins are highly toxic, persistent, widely-dispersed and they bioaccumulate, making them of great concern to human health. Dioxin is a well-documented mammary developmental toxicant, having significant effects on mammary gland development and breast cancer risk in both animal models and in humans.[10] A more comprehensive discussion of the extent of human dioxin exposures and how they may relate to breast cancer appears in Section I, Chapter B.1, Air Pollutants, Fuels and Additives and in Section I, Chapter B.2, Persistent Organic Pollutants.

Phthalates

With global production of at least three million metric tons annually,[11, 12] phthalates are a family of compounds with widespread and diverse use. By far their greatest use, however, is as a plasticizer to soften and impart flexibility to products made of PVC. Approximately 90 percent of phthalates produced are used in the PVC industry.[3] In the U.S., where 75 percent of PVC is used in building materials, phthalates are used to soften PVC products such as cabling, vinyl flooring, roofing membranes, and wall coverings.[3] Approximately 5.4 million tons of phthalates are used annually for this purpose, with an estimated 83 million tons of phthalates contained in the reservoir of building materials in existing structures worldwide.[3]

While there are several forms of phthalates in commercial use today, di-(2-ethylhexyl) phthalate (DEHP) is the most heavily-used phthalate, as it is the primary plasticizer of PVC.[13, 14] In addition to DEHP, di-isononyl phthalate (DiNP), benzyl-butyl phthalate (BBP) and Di-isodecyl phthalate (DiDP) are also used in PVC, although to a much lesser extent. Soft PVC can consist of up to 40 percent DEHP by weight.[15] Some products commonly made of soft PVC that contain phthalates include breast pumps and other medical devices (such as plastic tubing, syringes, and blood bags), toys, food storage and packaging materials, furniture, pool liners, home accessories (such as shower curtains, window blinds, and tablecloths), children's backpacks, and auto parts and interiors.

Because phthalates are not bound to the PVC polymers in which they are embedded, they readily migrate, or leach from the product into the surrounding media, including air, water, saliva, blood, IV solutions, and nutritional formulas. It has been reported that up to 50 percent of the phthalate content of a product can be released over the product's lifetime, depending on the circumstances of use.[14] While the release process is still not fully characterized, it does appear that phthalates can leach out of building products during normal use. Indoor air levels of phthalates are five to 20 times higher than ambient levels in outdoor air.[3]

In the U.S., environmental contamination with phthalates is well documented.[13, 14] PVC disposal is the largest source of phthalates in the solid waste stream.[1] Soil and water contamination tend to be greatest in areas of industrial use and waste disposal,[16] but widespread contamination has been documented even in areas as remote as Antarctica and in deep-sea jellyfish found at depths of more than 3,000 feet in the Atlantic Ocean.[14]

Potential pathways of human phthalate exposure include ingestion, inhalation, intravenous transfer, and skin absorption through either direct contact with consumer products or through general

contamination of the ambient indoor and outdoor environment.[16-19] While for the general population, ingestion of contaminated food has been considered the major route of exposure, this conjecture is based on relatively little and outdated data.[17] A recent study of pregnant women reported correlations between personal air samples and urinary biomarkers of phthalate exposures, suggesting that inhalation may also be a route of substantial exposure for the general population.[13] Dermal absorption, especially of phthalates common in personal care products, may also provide a significant pathway of exposure, especially among women of reproductive age, who appear to have some of the highest urinary monobutyl phthalate levels in the U.S.[14, 16, 20]

While there is clear evidence of widespread human exposures to phthalates, a number of key data gaps remain with respect to fully elucidating the sources and pathways of human exposures. Recent data on phthalate exposures from dietary intake are lacking. Exposures from pharmaceuticals, herbal preparations, and nutritional supplements, some of which are intended for use during pregnancy, may be significant and are largely unexplored.[17] The degree to which inhalation and ingestion of ambient sources of phthalates in dust and air contribute to overall exposure also remains largely unknown. Among susceptible subpopulations such as premature infants, medical sources of phthalate exposures may be significant and need to be more fully characterized.

Regardless of the source, it is well documented that people in the general population are heavily exposed to phthalates. Virtually all people tested (85–100 percent depending on the study and the metabolites measured) have detectable markers of phthalate exposure in their urine or blood.[15, 16, 19, 20] Given that phthalates are rapidly metabolized and excreted,[15, 18, 19] the nearly universal detection of phthalate exposure is evidence for chronic, continuous exposures. Of particular concern with respect to breast cancer risk is the fact that women of reproductive age and young children appear to have some of the highest urine levels.[15, 16, 20]

While phthalate exposures appear to be nearly ubiquitous, body burden levels vary widely between people, and within people vary considerably by the predominant type of phthalate metabolite detected.[16, 20] It is unclear whether such variations are due to variations in exposure, individual differences in metabolic profiles, or differing toxicokinetics of the different types of phthalates. Many of the studies prior to 2004 measured diester and nonoxidative monoester metabolites, which are readily available in the air and may be detected due to contamination. Recent advances in our understanding of the differing toxicokinetics between the four major phthalates and the recent development of biomonitoring methods to measure secondary oxidized metabolites of the major phthalates,[15, 21] which have longer half-lives and are immune to the external contamination common in most earlier studies, provide a promising avenue for pursuing these issues. Elucidating the primary sources and routes of exposures to phthalates is a clear research priority.

Heavy Metals

The other primary additives of concern are heavy metals, which are used as stabilizers in hard PVC

materials to extend the life of the products.[3] While used in levels much lower than phthalates, heavy metals—including lead, cadmium, organotins, zinc, and magnesium—are commonly used as stabilizers in PVC building materials. The degree to which these metals leach out of the building materials and contaminate the indoor environment is largely unknown, but significant releases of lead have been documented from PVC window blinds and into water carried by PVC piping.[3] Following a 1996 Greenpeace study on serum lead levels in children, there was a global movement to remove lead from vinyl blinds.[22] During disposal of PVCs, the heavy metals persist in incinerator ash and landfills. The degree to which PVC waste contributes to overall environmental contamination and human exposures to these metals has not been evaluated, although it has been suggested that PVC serves as the major source of lead and cadmium in the municipal waste stream.[23]

Critical Review of the Literature

Summarizing the evidence of an association between breast cancer risk and PVC exposures is complicated, given the numerous potential hazardous exposures originating from PVC, many of which are not unique to PVC. Also, there has been little research to determine the effects of these several compounds on endocrine disruption or developmental effects on reproductive tissues. Dioxin, a compound associated with PVC throughout its entire life cycle, is a known carcinogen and endocrine disruptor. A review of the potential breast cancer risks associated with dioxins and other persistent organic pollutants is contained in Section I, Chapter B.2 and will not be discussed here.

During the use of PVC products, the primary compounds of concern are the phthalates and heavy metals that can leach out of the polymer into the environment and into food and other products wrapped in PVC packaging. Phthalates are of particular concern for breast cancer, because of their well-documented endocrine-disrupting effects in animals and potential carcinogenic effects. A review of the literature on the health effects of phthalates is included in Section I, Chapter C, Compounds in Personal Care Products. Although a few metals are known to have endocrine disrupting effects,[24] virtually nothing is known about a potential relationship between metals and breast cancer; a review of the limited literature on this topic is presented in Section I, Chapter B.8.

The toxicity of vinyl chloride, released in the production of PVC, is well-characterized.[2, 5, 6, 25] In 1987, the International Agency for Research on Cancer (IARC) classified it as a Group 1 (known) human carcinogen,[25] based on a substantial body of animal and human studies. In animal studies, vinyl chloride has been shown to be mutagenic, carcinogenic, and have adverse reproductive and developmental effects.[5, 25, 26] Similarly, carcinogenic, reproductive, and developmental effects have been documented in epidemiologic studies of workers occupationally exposed to vinyl chloride.[2, 18, 25, 26] In animals, vinyl chloride exposures have been associated with an excess number of cancers, including those of the mammary gland.[6, 25] In humans, the evidence for carcinogenicity is strongest and most consistent

for liver angiosarcoma, with more limited evidence for brain cancer, lung cancer, and lymphoma.[6] Due to the small numbers of women working in occupational settings with PVC exposures, it has not been possible to fully assess the risk of breast cancer associated with vinyl chloride exposures in women.

Conclusions/Future Directions

In summary, the use of PVCs in building materials and consumer products grew dramatically in the latter half of the last century. While these materials are inexpensive and have some useful and convenient qualities, we are now discovering many of the hazards associated with these products. PVC production, use, and disposal result in myriad potentially harmful exposures to humans. PVC has contributed substantially to the contamination of our indoor and outdoor environments with a number of compounds that could be implicated in breast cancer incidence due to their carcinogenic and endocrine-disrupting potential. Vinyl chloride itself, although a known human carcinogen, is probably the least worrisome, because environmental contamination levels are generally low and direct exposures from use of PVC products are unlikely. More problematic are the by-products formed during PVC production and disposal and the migration of additives from the PVC during use and disposal. Phthalates, dioxins, and heavy metals top the list of priority compounds associated with PVC plastic. Please consult Section I, Chapters C, B.1, B.2, and B.8, respectively for a review of the evidence for the role of these compounds in breast cancer etiology.

Elucidation of the portion of the human body burden levels of these compounds that is attributable to the PVC life cycle is a necessary step towards reducing such exposures. Research aimed at investigating the risk of breast cancer associated with PVC plastics focusing on these individual compounds—considering the toxicokinetic properties of each, the probable timing of exposures in relationship to critical periods of breast and brain development, and the latency of breast cancer—could be fruitful. Alternatively, given the complex mix of potential endocrine disruptors and carcinogens produced in the PVC life cycle, examining potential breast cancer risks in communities living near industrial sources of these exposures may allow for a more comprehensive evaluation of breast cancer risks associated with all exposures originating from PVCs. Given the nearly universal exposure to some of these compounds among people living in the U.S., epidemiologic studies may be particularly difficult to conduct and in vitro and in vivo studies may prove more fruitful.

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Bisphenol A

Introduction

Bisphenol A (BPA) is a synthetic chemical that was originally developed for use as a synthetic estrogen. It is now one of the highest-volume chemicals produced in the world, with over six billion pounds manufactured each year.[1, 2] BPA is used as a monomer in the manufacture of polycarbonate plastics, in the resin lining of food and beverage cans, as a component of dental sealant, in digital media such as CDs and DVDs, and as an additive in other types of plastics.[2, 3] The first reported synthesis of BPA was in 1905.[4, 5] Bisphenol A was first used in epoxy resin in 1939 and in 1966 was incorporated into vinyl ester polymers.[6] Large-scale production of BPA began in the late 1950s, when commercial uses for polycarbonate plastics and epoxy resins were developed.

BPA is known to leach under normal conditions of use from the plastics and resins that contain it, but especially during heating and washing, which has led to widespread human exposure. An estimated 95 percent of Americans tested, including young girls, show detectable levels of BPA in their urine.[7, 8] The ubiquity of human exposure to a chemical with reported estrogen-like characteristics has created considerable concern about BPA's potential role in breast cancer. In rodent studies, early-life exposure to BPA alters mammary gland development in ways that may alter the risk for breast cancer: changing mammary gland morphology, steroid receptor expression/responsivity, and pre-neoplastic lesions. BPA also increases the sensitivity of mammary tissue to endogenous estrogen.[9, 10]

Definitions and Sources of Exposure

Environmental Exposures

BPA is a ubiquitous environmental contaminant.[3, 11] It has been found in the waste water from factories that produce BPA[3] and has been identified as the compound responsible for the majority of estrogenic activity of landfill leachate.[2] In the U.S., the presence of BPA has been documented in surface water and drinking water,[3, 12, 13] ground water and private wells,[14] soil,[3] ambient air,[3, 15, 16] and residential dust samples.[15] A sampling of dust from 120 homes in Cape Cod, Massachusetts detected BPA in 86 percent of samples tested.[15]

Environmental degradation of BPA is thought to be fairly rapid and complete.[11] Atmospheric degradation occurs by reaction with hydroxyl radicals with a half-life of several hours.[17] In surface water, abiotic degradation is negligible, but degradation by bacteria is common, resulting in a half-life of a few days.[3, 11] BPA released to ground or surface water can be absorbed to soil or sediments. Levels of BPA in sediments are generally higher than those in surface waters; the half-life of BPA in soil is estimated to be less than three days.[3] Thus, while environmental contamination is widespread, due to BPA's relatively fast degradation, levels of contamination appear to be generally low.[3, 11, 12] Consequently, environmental contamination is not considered a primary source of human exposure.[2, 3, 11]

Occupational Exposures

The extent of human exposure to BPA through occupational sources is not known,[2, 11] but

potentially could be considerable, given BPA's widespread industrial and commercial use. Occupations in which workers could be exposed include those involved in the manufacture of BPA, polycarbonate plastics, items made from polycarbonate plastics, epoxy resins, liquid epoxy paints, laquers, and powder coatings.[11] The only published data available on occupational exposures to BPA in the U.S. was collected over 20 years ago. In a National Institute of Occupational Safety and Health (NIOSH) occupational exposure survey of selected industries, the greatest number of female employees potentially exposed to BPA worked as electrical and electronic equipment assemblers; cementing and gluing machine operators; machine operators, not specified; welders and cutters; and assemblers.[18] The number and type of consumer products containing BPA has changed substantially over the last 20 years, with notable increases in the use of BPA in digital media and electronics. There clearly is a need for more current information on the prevalence of occupational exposures to BPA in today's workforce. Furthermore, the degree to which these occupational settings may result in biologically meaningful exposures has not been investigated.

Exposures from Consumer Products

By far the greatest sources of concern with respect to BPA are exposures from consumer products. Most of the BPA that is produced is used for the manufacture of polycarbonate plastics and epoxy resins, which are widely used in consumer products that come into contact with food and beverages.[11, 19, 20] Plastic water and milk jugs, recyclable beverage containers, baby bottles, children's "sippy cups," and other food and beverage storage containers are commonly made from polycarbonate plastic. Epoxy resins are most commonly used as part of the protective linings in food and beverage cans. They are also used in resin-based adhesives, protective coatings, and printed circuit boards. Similar BPA-containing resins are used in some dental sealants.[19, 20]

While initially it was thought that human exposure to BPA from these consumer products would be minimal, given the stability of the BPA polymer, it is now well documented that BPA can leach out of these food and beverage containers under normal conditions of use. Migration of BPA into food and drink occurs when the polymer is hydrolyzed due to contact with acidic compounds or due to heating.[3, 11] BPA has been detected in myriad canned foodstuffs, including coffee, vegetables, fish, meat, beverages, diary products, and infant formula.[3] The levels and presence of BPA in such items appear to be influenced by the duration of and temperatures used in the heating process during manufacture and may also be influenced by storage times.[3] Migration of BPA into food and beverages from polycarbonate plastic containers is also well documented.[2, 3] BPA leaching increases as the polymer degrades with use, and appears to be expedited by heating and repeated washing.[21, 22] This has created considerable concern over potential exposures to infants from baby bottles, which are typically heated and washed multiple times a day. Additional data has suggested that BPA can even leach from new polycarbonate plastic into water at room temperature.[23, 24]

Extent of Human Exposures

The extent of human exposures from environmental, occupational, and consumer product sources has not been fully elucidated. Estimations of BPA levels in food and beverages stored in polycarbonate plastics and epoxy-resin-lined cans have been the primary focus, since these are believed to be the sources of the greatest potential for exposure. Initial estimates of human exposures to BPA were based on models predicated on assumptions of leaching rates observed in the laboratory, measurements of actual levels of BPA in canned goods, and/or average consumption rates of various foods and beverages.[20] Models generated on those assumptions generally predicted daily human consumption of BPA from food and beverage sources and through an oral route would be very low (<1 μg/kg body weight).[3, 20]

With the advent of laboratory techniques to detect BPA levels in a variety of biologic media, including sera, saliva, and urine, we are now able to measure BPA in humans at very low levels. Recent biomonitoring data from NHANES III reported 95 percent of participants had detectable levels of BPA in their urine, with a median concentration of 1.28 μg/L.[7] Measurements of BPA in biologic media from other studies conducted in the U.S., Europe, and Japan have yielded remarkably similar levels, with detection rates generally between 95 percent and 100 percent.[2, 8, 25, 26] In addition to urine, BPA also has been measured in plasma of adult men and women.[25] Furthermore, its presence in human fetal plasma, placental tissue, amniotic fluid, and breast milk[11, 27-31] has fueled considerable concern with respect to potential breast cancer risks, as much attention has recently focused on the role of early-life estrogen exposures in breast cancer etiology.

Welshons and colleagues note that the nearly universal detection of BPA in human biologic media is not consistent with exposure prediction models predicated on low consumption and rapid metabolism/elimination, suggesting that BPA exposure must be virtually continuous, that there may be unidentified sources of BPA exposures, and/or that we may not fully understand the pharmacokinetics of this compound.[2]

In 1988, the U.S. Environmental Protection Agency set a maximum acceptable level (reference dose) for BPA at 0.05 mg/kg/day.[32] This level was based on toxicologic studies conducted in the 1980s that relied on the administration of high doses of BPA to rodents and recorded the lowest level at which adverse effects were observed, which was 50 mg/kg/day (the lowest dosage tested).[33] Then, as is common practice in risk assessment, this level was divided by a 1,000 (an "uncertainity factor") to account for potential differences in effects in humans. In 2002, the European Union, taking a more conservative approach, established a temporary tolerable daily intake of 10 μg/kg/day (0.01 mg/kg/day) based on the now well-documented liver, reproductive, developmental, and hormonal effects observed at relatively low doses of BPA.[34] However, several papers published in the last five years suggest effects at even lower levels.[11, 35]

In summary, there is well-documented evidence of widespread human exposures to BPA. The most likely exposure route is ingestion through food and

beverage containers made from products containing BPA, although we have not yet fully elucidated the primary determinants of levels in humans. It appears pre- and peri-natal exposures are also likely through transplacental transport of BPA and ingestion of BPA-contaminated breast milk. Detectable levels of BPA in humans, while extremely prevalent, are generally low. Until recently, most monitoring of BPA has been in urine.[36] A large body of literature from studies in rodents, however, mostly published within the last few years, has suggested that adverse health effects can be caused even at these very low levels. The interpretation of these findings and their pertinence to breast cancer risk in humans remains a source of considerable debate (see discussions below).

Biologic Plausibility

BPA is not currently classified as a carcinogen by any large health regulatory agency. This is largely based on the results from carcinogenic bioassays conducted in the 1970s-80s in which mice were administered large doses of BPA and no increase in the incidence of malignant tumors was observed.[11, 33] These assays, however, are designed to capture direct genotoxic effects and may fail to detect the promotional and other potential indirect routes by which endocrine disruptors may affect carcinogenesis. While it has been argued that a lack of carcinogenic effect at high doses makes carcinogenicity at lower doses implausible, others have noted that endocrinology boasts numerous examples of compounds that at low doses can stimulate a response, while they can inhibit the same response at much higher doses.[37] As breast cancer research has begun to focus more attention on the potential role of endocrine disruptors, BPA has received intense scrutiny due to its well-documented estrogenic properties. Within the last few years, many studies have been published documenting estrogenic effects of BPA at levels currently observed in human populations (see Critical Review of the Literature, below). Whether these estrogenic effects result in an elevated breast cancer risk has not yet been determined, but two recent studies suggest that prenatal exposure to very low levels of BPA can induce mammary gland neoplasias in the absence of further insults.[9, 10]

In addition to estrogenic activity, it has been suggested that low doses of BPA may act to increase breast cancer risk by a number of other mechanistic pathways. There is some evidence, both in vitro [11] and in vivo,[38] of BPA disrupting microtubule formation, and increasing the risk of aneuploidy. There also is evidence emerging that BPA may disrupt thyroid function[2, 39] and may stimulate prolactin release.[11] Furthermore, very low levels of BPA may act via non-genomic receptors to activate cell signaling pathways and promote proliferation.[2] The lines of evidence supporting these various mechanisms are discussed in the next section. Nearly the entire body of literature to date has focused on the estrogenic mechanisms of BPA, with very little devoted to these other potential modes of action.

Critical Review of the Literature

The majority of findings to date have been from in vitro or in vivo studies, with almost no human health data available. As discussed previously, while results from these kinds of studies can be informative, they are fraught with limitations.

Nearly all studies have focused on documenting BPA's estrogenic properties. In this regard, most studies have examined the effects of BPA on intermediate endpoints (such as timing of pubertal development and mammary gland morphology), rather than mammary tumor susceptibility or incidence. Recently-published evidence suggests that BPA affects the fetal mammary gland in a significant and persistent manner, leading to increased mammary epithelial cell proliferation in adult animals.[9, 10, 40] With nearly ubiquitous exposures occurring in a complex milieu of endogenous and exogenous hormones, the study of BPA and breast cancer is highly challenging and will require creative multi-disciplinary thinking.

In Vitro Studies

BPA consistently has been shown to bind to estrogen receptors with an affinity approximately 2-4 orders of magnitude lower than that for estrogen,[41-46] and it was noted by Nagel and colleagues that in MCF-7 breast epithelial cells, the presence of human serum increased the binding affinity of BPA.[47] Recently, Welshons and colleagues followed up on this finding with a novel in vitro assay that considers the effects of plasma-binding proteins on the uptake of estrogenic chemicals into cells. They found that BPA bound only weakly to albumin in blood, and therefore was delivered to cells with a physiologic advantage compared to estradiol.[2, 37] This suggests that the estrogenic potential of BPA may be greater than what is suggested by most of the in vitro studies conducted to date.

There is strong evidence that BPA can elicit a proliferative response in MCF-7 cell strains with an order of magnitude approximately three to five times less potent than 17 β-estradiol.[11, 48] In vitro studies also have suggested the ability of free BPA to stimulate prolactin release,[49] progesterone activity,[11] and anti-androgenic activity,[11] and to disrupt microtubule formation and increase the risk of aneuploidy,[11] although these findings are not as well documented as BPA's estrogenic properties.

In Vivo

For the most part, in vivo studies of BPA have focused on the developmental toxicity of BPA in rats and mice. In a recent review of this literature, Vom Saal noted that through the end of 2004, 115 in vivo studies had been conducted to investigate low-dose effects of BPA, 94 of which reported significant findings.[37] Thirty-one of these studies reported effects at doses below the current standard of 5.0 mg/kg/day.[37] In fact, within the last year, a committee of experts on BPA convened to review the literature on the low-dose health effects of this compound and made several sound conclusions on low-dose effects of BPA, existing below the current NOAEL (no observed adverse effect level).[35] A number of these effects, including morphologic changes in the mammary glands, and alterations in the onset and cyclicity of estrus, could have potential impacts on breast cancer risk.

Perhaps most worrisome is the growing body of evidence that low doses of BPA administered prenatally can result in a variety of changes in the mammary glands of female rodent offspring.[2, 8-10, 35, 40, 50] Such morphologic changes are likely to be irreversible and permanent. It has been noted that the mammary glands of the female offspring of exposed animals also demonstrate precocious

development, often resembling the gland in early pregnancy.[51] Morphologic changes of the mammary gland associated with low doses of in-utero exposures in rats and mice include: an increase in terminal end buds;[10, 50-53] a decrease in apoptotic activity (programmed cell death) in the terminal end buds;[50] an increase in ductal density;[10, 40, 51] and an increase in progesterone receptor-responsive ductal epithelial cells.[50] These morphologic changes could potentially be linked to increased mammary tumor risk, because the tumors are known to arise from the cells of the terminal end buds. Perhaps the most convincing evidence of a direct association between low doses of BPA and breast cancer in vivo comes from a recently-published report in which rats exposed prenatally to very low doses of BPA were significantly more likely to develop pre-neoplastic lesions and carcinoma in situ of the breast.[54] To our knowledge, this is the first report to directly link prenatal exposure to very low levels of BPA to subsequent breast cancer in laboratory animals.

Other effects of prenatal BPA exposures that could potentially increase breast cancer risk include: larger size of offspring and an increase in postnatal growth,[51, 55] earlier onset of sexual maturation,[37, 51] alterations in estrus cyclicity,[51, 56] earlier mammary gland development in female offspring,[37, 51] and altered immune function.[37] Furthermore, it has been reported that animals exposed in utero to BPA have significantly-increased sensitivity to estradiol throughout their life[10, 50] and greater susceptibility to known breast carcinogens when exposed subsequent to prenatal exposures to BPA.[9] Replication of these findings is a clear priority.

However, results from in vivo studies have not been entirely consistent across studies and replication of some of the key findings has proven problematic.[11, 19, 35, 57] A great deal of discussion has ensued concerning the sources of the disparate findings. This highlights a number of key issues in studying the effects of endocrine disruptors in rodents, including the wide variation in effects by species, and even within strains of a single species. For example, the Charles-River Sprague Dawley strain of rat was commonly used in many of the studies that failed to find any effects of low-dose BPA. This strain, however, is well known for its low sensitivity to estrogens.[35, 58]

The variation in sensitivity to estrogenic effects within and between species underscores the importance of using positive controls in these types of studies, something that was inconsistently done for this body of literature. When positive controls were used, DES (a well-documented estrogenic compound and developmental toxicant) was the most common choice and in those studies, BPA effects essentially mirrored those of DES. The inconsistency in findings across laboratory studies may also be due to the wide variability in the phytoestrogen content of the animal feed used in various laboratories.[2, 57-59] Finally, it has been noted that the source of research funding appears to be correlated with study results. Vom Saal and Hughes recently pointed out that while no industry-funded studies have reported effects of BPA at low doses, 90 percent of government-funded studies have reported significant findings.[58] They further note that industry-funded studies often use inappropriate animal models (such as the Charles-River Sprague Dawley rat)

and fail to use (or fail to report that they used) positive controls.[58]

While industry continues to debate the estrogenic effects of BPA, during the last few years, solid evidence for low-dose estrogenic effects in rodents has emerged.[35] Development of in vivo studies to extend these findings to more directly investigate BPA exposures and breast cancer, such as the ones recently published by Murray and Durando and colleagues[10, 54] is a necessary next step.

Studies in Humans

The wide variation in sensitivity to estrogenic effects in different species/strains of animals highlights the limitations in making inferences about BPA's effects in humans based on observed effects in rodents. Another complication of inferring effects from rodents to humans for this compound is that the major pathway for metabolizing ingested BPA in rats involves glucuronide conjugation. The glucuronide form is absorbed by the gut and demonstrates less estrogenicity than the free form of BPA. Humans do not glucuronidate BPA as efficiently as rodents, thus we may underestimate the potency of this compound in humans if directly translating dose to effect from rodent data.[9, 11] Furthermore, the large variation due to feedstuffs in rat studies is slight compared to the enormous variation in the daily diets of U.S. children and adolescents.

To our knowledge, no epidemiologic studies of breast cancer risk and BPA exposures have been published. There are, however, some very limited human data on other endocrine-related effects in humans that may have some relevance to breast cancer risk. Results from a small study recently conducted in Japan found a significant relationship between serum levels of BPA in women and obesity, ovarian dysfunction, and blood androgen concentrations.[25] It also has been reported that BPA levels are positively correlated with repeated miscarriage[60] and inversely correlated with endometrial hyperplasia.[61] Another recent study measuring BPA in the adipose tissue of women may help us understand the amount of this compound that actually reaches the breast.[36]

Future Directions

Given the well-documented and widespread human exposures to BPA, in conjunction with some clear evidence of estrogenic effects at low levels, more study of effects in humans is warranted. Unfortunately, the study of a non-persistent—but nearly continuous and ubiquitous—exposure at relatively low levels for a disease, such as breast cancer, with a long latency period is fraught with difficulty. There is, however, a rapidly emerging literature on exposure assessment issues surrounding this compound. For example, recent data suggests fair-to-excellent intrapersonal variability for BPA urinary metabolites, despite BPA's short half-life.[62] New biomonitoring methods and data from NHANES may help establish better references ranges.

The potential of BPA to hasten the onset of breast development in girls needs to be explored. Clearly, a multi-disciplinary approach is needed, requiring creative thinking from a team including endocrinologists, toxicologists, epidemiologists, and geneticists.

Some first steps might include:

- Conduct occupational studies to identify groups at high risk for exposures, paying special attention to women of childbearing age.
- Document the degree to which body-burden levels change over time, i.e., how representative of lifetime exposures are a single or a few body-burden measurements?
- Conduct a body-burden study to examine age of puberty and amount of BPA in umbilical cord blood at birth, or BPA in urine of young children (a current aim of epidemiological studies by the Breast Cancer and Environment Research Centers, jointly funded by the National Institute of Environmental Health Sciences and the National Cancer Institute).
- Elucidate major factors that determine body-burden levels in humans. While it is assumed that oral ingestion from contaminated food and drink is the main route of exposure in humans, this is mostly based on models and speculation, not real data. Welshons and colleagues have emphasized the importance of considering inhalation and transdermal exposures through bathing with contaminated water.
- Further investigate BPA pharmacokinetics in humans, especially in infants and children.
- Consider BPA effects in context of mixtures.

BPA exposures may be curtailed by regulatory action before we figure out if there is a breast cancer connection.[63] If so, documenting past and persistent exposures may become critically important to studying and understanding BPA's health effects.

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Compounds in Personal Care Products

Introduction

The widespread rise in the use of personal care products among women and men has coincided with increasing rates of breast cancer, leaving some to wonder if there is a connection. Of greatest concern are the natural and synthetic chemicals included in these products that are known or suspected carcinogens and those that may alter the body's endocrine activity. Most women use personal care products on a daily basis over an extended period of time, often applying a liberal amount to the skin. While many argue that these products contain a "safe" level of compounds of concern, below the regulatory standards,[1] the health effects of chronic exposure in humans have not been well studied.

Recent research has shown that some compounds commonly used in cosmetic and personal care products can mimic or block the action of natural hormones, including estrogens.[2] Some experts hypothesize that exogenous carcinogens, tumor promoters, and endocrine disruptors – along with altered breast sensitivity to these exposures – contribute to increased breast cancer incidence,[3-6] and that the widespread and extended use of personal care products provides a potential source of such exposures.

The U.S. Food and Drug Administration (FDA) only minimally regulates chemicals in cosmetics and personal care products.[7] Industry funds the Cosmetics Ingredient Review Panel to oversee its members, but relatively little is known about the potential health effects of the 5,000 or so ingredients in personal care products.

Definitions and Sources of Exposure

Three classes of compounds that have received considerable public attention are parabens, phthalates, and organic solvents. While these compounds are quite common in personal care products, they are also often found in other commonly-used consumer products and may be ubiquitous in the environment, making it very difficult to distinguish between sources of exposure. Many of the compounds of concern are also not identified on personal care product labels. The FDA cosmetic labeling law excludes fragrance components (such as phthalates) in commercial products produced for and sold solely to professional salons.[7] The latter exemption particularly affects the large number of women who work in salons and are exposed to such products daily.

The FDA is only able to regulate cosmetics after products are released to the marketplace. Although the FDA must prove the likelihood of harm in order to regulate cosmetic compounds, manufacturers are not required to report inert ingredients. Laboratory analyses of cosmetic products sold in California have found products that contain substances known to or likely to cause cancer and not identified as an ingredient on the product's label. California recently passed the California Safe Cosmetics Act. This new law requires cosmetics manufacturers to disclose to the California Department of Health Services (CDHS) any ingredients "identified as causing cancer or reproductive toxicity."[8] CDHS is authorized to investigate the chemicals' health impacts, and plans to make information about the products' components available to the public and

researchers. Whether the mandated reporting of compounds such as phthalates and benzene will lead manufacturers to reformulate their products remains to be seen. Regardless, many of these compounds are likely to remain in the environment at measurable levels.

Parabens, phthalates, and organic solvents are the three main chemical classes that will be discussed here. Other compounds of concern – including placenta/estrogens; plant oils; phenols found in UV filters (sunscreens), toothpaste, and antibacterial hand soaps; musks; and nanoparticles will also be addressed.

Parabens: Because of their antimicrobial and preservative properties, parabens have been used for 50 years to extend the shelf life of cosmetics, food, and other consumer products. Animal studies have shown that parabens are quickly absorbed from the gastrointestinal tract and from the blood, and the glucuronide conjugated form is excreted in urine.[9-11] Studies have also shown that parabens can be absorbed rapidly through the skin.[11-13] The six most commonly used parabens (methyl-, ethyl-, n-propyl-, isobutyl-, n-butyl-paraben and benzyl-paraben) have all been shown to have endocrine-disrupting properties – with weak estrogenic effects.[11] Substantial literature reviews have recently been conducted on these components of personal care products.[14, 15]

Phthalates: As a principal component of polyvinyl chloride (PVC) products, building materials, pesticides, and personal care products, phthalates are used to render PVC softer and more flexible and to extend the scent stability in fragrances, cosmetics, and shampoos. Although phthalates are not persistent, they can be detected in the blood or urine of nearly everyone because exposures are ubiquitous and frequent. These compounds have also been found in breast milk,[16] but do not bioaccumulate in humans; they tend to be excreted through the urine and feces.[17, 18]

The most widely used phthalates are di (2-ethylhexyl) phthalate (DEHP), di-isodecyl phthalate (DIDP), dibutyl phthalate (DBP), diethyl phthalate (DEP) and di-isononyl phthalate (DINP). The first of these is common in fragrances, but primarily used in plastics (see also Section I, Chapter B.9, Polyvinyl Chloride). DBP, DEP and butyl benzyl phthalate (BBP) are among the most commonly found in personal care products, including nail polishes, perfumes, soaps, lotions, and moisturizers[19, 20] where they can reach up to 20 percent of the product volume.[21]

Phthalates may be absorbed through the skin when using personal care products; inhaled in household dust contaminated with phthalates from personal care products, vinyl flooring, shower curtains, adhesives, plastic toys, clothing, and building materials; or ingested eating food with phthalates from flavorings or leached from plastic wrap and containers. Exposures may also occur from medical treatment that uses equipment made with certain plastics, or from living near a facility that produces phthalates.[22]

The relevance of exposure via personal care products has been demonstrated by the relationship between self-reported product use and levels of MEP, a urinary metabolite of DEP.[23] MEP levels are also higher among African Americans and among women.[24]

Although there are conflicting published reports of estrogenic activity for phthalates in vitro, most studies demonstrate that their primary activity is anti-androgenic and that they may also affect enzyme activity.[25, 26] In vitro studies have shown that one phthalate, DEHP, is associated with the dose-dependent suppression of aromatase and has the ability to activate peroxisome proliferator-activated receptors (PPARs), possibly through receptor-mediated signaling.[27]

Solvents: These chemical compounds are capable of dissolving, extracting, or dispersing/ suspending other substances. They are widely used and can enter the human body by ingestion, inhalation, and skin absorption. Exposure can occur through ingestion of polluted water sources or inhalation from working with or near solvents. Dermal absorption can be significant when the solvents are applied to or come into direct contact with the skin.

Solvents are used in the manufacturing of and can be a primary component of personal care products, including shampoo and hair styling products, perfumes, cosmetics, and nail products. They are used to extract and deliver other ingredients, create desired consistency, and extend color. While many are of low toxicity, solvents of some concern include:

Acetone (in nail polish and remover) is a suspected mutagen, but has not been classified for carcinogenicity. Breathing moderate-to-high levels for short periods of time can cause a shortening of the menstrual cycle in women, among other health effects.[28]

Ethanol (in perfume, facial cleansers and moisturizers, and mouthwash) is readily absorbed, but in relatively low quantities from these products. It is generally not ingested in the quantities that link alcohol consumption with breast cancer.[29] Inhalation of ethanol is more associated with its use as a fuel and is addressed in Section I, Chapter B.1 of this report, Air Pollutants, Fuels, and Additives.

Ethylene glycol (in facial, acne, and hair treatments) may contain toxic impurities or contaminants, and there is limited evidence of reproductive or developmental toxicity.

Triethanolamine or TEA (in soaps, lotions, facial cleansers and treatments, perfume, hair and acne treatments, eye makeup and remover, antiperspirants, and baby products) and the less common Diethanolamine or DEA (in mascara, sunscreen, and body wash) are amines. If combined with nitrosating agents on the skin or in the body, amines can form carcinogenic nitrosamines. TEA is also a suspected endocrine disrupter.[30]

Toluene (in nail polishes and treatments) is a possible human reproductive and developmental toxicant. Toluene is not classifiable as to carcinogenicity to humans according to the International Agency for Research on Cancer (IARC), but is often contaminated with small amounts of benzene. Toluene may also have endocrine-disrupting effects.[31]

Methylene chloride has been a common component of nail products. While it was used at low levels, many consumers and, especially, workers were exposed over long periods of time.

This solvent, and its predecessor, benzene, have been measured in human breast milk and linked to increased incidence of mammary gland tumors in rats and/or mice.[32]

Other solvents, including benzene and methylene chloride, are addressed in Section I, Chapters B.1, Air Pollutants, Fuels, and Additives, and B.5, Solvents and Industrial Chemicals.

Other Personal Care Product Exposures: Other additives to personal care products are also of concern. Hair products that contain *placenta and estrogens* are hormonally active. These products are heavily marketed to African Americans to induce hair growth.[33] At least one study reports use by a majority of African Americans, including more than half of their young children.[34] Hair products containing placenta and estrogens are suspected of affecting the hormonal system, including altering the timing of puberty in girls.[35] Repeated topical use of personal care products with *natural plant oils, particularly lavender and tea tree*, has been associated with breast development in males as young as age four.[36] Growth receded after product use ended, and in vitro studies in human cell lines indicated that these oils were both weakly estrogenic and anti-androgenic.

Ultraviolet (UV) filters are extensively used in sunscreens and to promote product stability in other personal care products at concentrations exceeding 10 percent.[37]

Several of these compounds appear to be estrogenic or anti-androgenic. In particular, benzophenone-3 (BP-3), homosalate (HMS), octyl-dimethyl-PABA (OD-PABA), octyl-methoxycinnamate (OMC) and 4-methylbenzylidene camphor (4-MBC) have been shown to have estrogenic effects on cultured human breast cancer cells (they stimulated MCF-7 cell proliferation); more evidence of these compounds' estrogenic effects comes from in vivo experiments with rats.[38, 39]

One of the most common sunscreen chemicals, 4-MBC, has exhibited the highest in vivo activity.[38] In water-dwelling animals, 4-MBC has been shown to cause potential change to the physiological and developmental processes mediated by estrogen receptor signaling mechanisms.[40] Due to concern for protecting skin from aging and skin cancer, use of such products has increased. These products are lipophilic and appear to be bioaccumulating in aquatic environments and fish.[40] While the major route of exposure for humans is likely direct dermal application, there is also likely some exposure through fish or other food consumption.[41] At least one UV filter, BP-3, is easily absorbed through ingestion and has been detected in human urine and breast milk.[37] Another UV filter, octyl-methoxycinnamate or OMC, has also been detected in breast milk.

These and other UV filters, including 4-methylbenzylidene camphor or 4-MBC, have been increasingly studied over the past ten years. The limited evidence to date suggests that BP-3, 4-MBC, and several other of these compounds are estrogenic, anti-androgenic and anti-progestegenic.[42] OMC was a weak estrogen alpha agonist but a strong progesterone antagonist. 3-BC and 4-MBC have both been shown to stimulate MCF-7 cell proliferation, and the latter

has been linked to uterotrophy in rats.[38, 39, 41] After daily application on humans, UV filters were measured in urine, but did not appear to affect levels of endogenous reproductive hormones in young men or post-menopausal women.[43]

Musks are another compound of concern about which relatively little is known. They are used in almost all scented products, including perfumes, cosmetics, and even laundry detergents, and are found in all aquatic environments and in fish, where they are persistent.[44] Various musk compounds have been detected in human adipose tissue and breast milk.[45] Like UV filters, many of the musk compounds have been identified by in vitro and in vivo tests as hormonally active. Some appeared to be weakly estrogenic in vitro but were not estrogenic in an assay using human MCF-7 cells.[45] Two polycyclic musks appear to be anti-estrogenic at high levels, and anti-progestegenic at very low levels.[42]

The following table is a general summary of many of the compounds discussed above in relation to endocrine disruption, carcinogenicity, and disposition of the compounds in body fluids and tissues. Information about phthalates exposure from other than personal care products can be found in Section I, Chapter B.9, Exposures from Polyvinyl Chloride. Solvents are addressed elsewhere; ethanol in Section I, Chapter B.1, Air Pollutants, Fuels, and Additives and all others in Section I, Chapter B.5, Solvents and Industrial Chemicals.

Table 1. Select chemical constituents of personal care products and their link to endocrine disruption and cancer.

Compounds	Source	Mechanism(s) of Concern	Human/Animal Evidence
Parabens	Preservatives in cosmetics, food, and pharmaceuticals	Estrogen agonists	Measured in human milk and human breast tumors
Phthalates	Plasticizers, nail and hair care products	Estrogen agonists Androgenic antagonist Aromatase suppressor	Measured in human milk; animal studies indicate link with mammary carcinogenesis; adverse reproductive and development effects in animals; altered hormone levels
Solvents	Nail care products		
Benzene and Meythlene chloride	Artificial nail products	Possible carcinogens	Measured in human milk; increased incidence of mammary gland tumors in rats and/or mice
Toluene	Nail polish	Endocrine disrupting effects	Measured in human milk
Acetone	Nail polish remover	Suspected mutagen	Affects menstrual cycle length
Other			
UV Filters (4-MBC, BP-3, OMC)	Sunscreen and cosmetics	Estrogen agonists Androgen and progesterone antagonists	Measured in human milk and urine MCF-7 cell proliferation, uterotrophic in rats
Musk	Fragrance in perfume, cosmetics, detergents	Estrogen antagonists Androgen and progesterone antagonists Potentially carcinogenic (non-genotoxic)	Measured in human milk, adipose tissue, and blood
Estrogen/placenta	Hair products marketed to African Americans	Earlier onset of puberty in African American girls	None

Nanoparticles: One overriding area of controversy is the use of nanoparticles in personal care products. These microscopic particles are added to consumer products to enhance skin penetration and to extend component stability. Conflicting evidence has been presented on skin penetration. There is evidence that they can penetrate broken or flexed skin and pass into the lymphatic system and regional lymph nodes, then potentially into the circulatory system.[46] There is concern that some nano-sized substances may be toxic to human tissue and cell cultures, resulting in adverse health outcomes. While an industry study of titanium dioxide and zinc oxide nanoparticles found that the weight of the evidence shows they pose no threat to human health, they advised caution in using nano-sized particles of compounds that are able to penetrate the skin and/or have inherently toxic constituents.[47] There is still very little known

about potential exposure or about the deposition, translocation, and biopersistence of the myriad nanoparticles that are being used in personal care products and elsewhere, and new methods may be needed to identify potential risks.[48]

Critical Review of Literature

Parabens: The use of personal care products has been implicated as a risk factor for breast cancer among women, particularly in the western countries where they are heavily used. One controversial hypothesis is that the estrogenic ingredients in underarm cosmetics (mainly deodorants and antiperspirants) have contributed to the rising breast cancer incidence in women over the recent decades.[49] Darbre called for more research into this potential link, given that: 1) underarm cosmetics are frequently and repetitively applied to and left on an area directly adjacent to the breast; 2) a large population is exposed due to widespread use, including higher-risk subgroups such as young adults; 3) personal care products contain compounds that are endocrine disruptors (e.g. parabens); and 4) there is suggestive evidence of intact paraben esters in breast tumor tissues, indicating a non-oral exposure route.[14]

While several chemical culprits were listed in the hypothesis (including aluminum salts and triclosans), parabens have received the most attention, mainly because of their estrogenic properties.[49] Parabens have been shown to have estrogenic effects in assay systems, both in vitro in human MCF-7 and ZR-75-I breast cancer cell lines[50-52] and in vivo in rodent uterotrophic assays.[52-54] Parabens have also been shown to be dermally absorbed in animal and human studies,[13, 55] lending further support to the hypothesis that parabens from underarm cosmetics are absorbed through the skin. Conversely, some argue that parabens are only weakly estrogenic and that exposure occurs only at doses lower than those required for effect,[15, 56] and, thus, that parabens are unlikely to cause any health effects. Proponents counter that no human health studies have examined chronic effects of low-level exposures to parabens to safely claim no adverse effect. Accordingly, the role of parabens and personal care products in breast cancer etiology should not be dismissed, particularly given their estrogenic activity.[14, 57]

Other suggestive human evidence includes the relatively high proportion of carcinomas arising in the upper outer quadrant of the breasts, which is local to where the cosmetics are applied.[52] A recent descriptive study in Nottingham using core breast biopsies, however, reported that the proportion of malignant to non-malignant histological findings between the four quadrants and the retroareolar region were not significantly different. While the results were not sufficient to refute the hypothesis of underarm cosmetics and rising breast cancer incidence, the author suggested that the trend for the high proportion of carcinomas in this area may be a reflection of the greater amount of breast tissue in this quadrant, and less likely a result of the personal care products used in that local area.[58]

The epidemiologic data examining the relationship is also scant. To date, only two recent studies have attempted to address this question. A population-based case control breast cancer study found no difference in risk between women who used antiperspirants and those who used deodorants in

an analysis limited to women who also shaved their underarms.[59] Since both types of products may contain parabens, this study does not clarify the role of parabens, though it weighs against the hypothesis that blocking perspiration increases risk. Because use of underarm products is so common in the U.S., it would be difficult or impossible to assess risks in an epidemiologic study here because of the lack of unexposed women. A case-based study of breast cancer patients found that increased frequency of antiperspirant/deodorant usage and earlier age at onset of use was associated with an earlier age of breast cancer diagnosis.[60] While this study asked about age at menarche, it did not appear to control for the age of puberty onset. Some girls develop apocrine glands, those responsible for adult body odor, before their breasts and others develop breasts first and pubic hair and apocrine glands second. Pubertal timing would affect the relative sensitivity of breast tissue to exposure to the deodorant components during the crucial period of breast development.

Phthalates: In a report issued by the Centers for Disease Control and Prevention (CDC) in 2000, researchers found significant levels of seven phthalate monoesters and their metabolites in urinary samples from a reference population of 289 adult humans.[17] While women of childbearing age in that study had higher levels of one phthalate, larger samples did not see a difference from children or older women.[24] Additionally, phthalates have been measured in human milk, implying their presence and availability to breast tissues.[16] The findings of phthalates and their metabolites in urine and breast milk do not explain their origins, since these compounds are ubiquitous in the environment. However, the findings that women had higher levels of phthalates than did men suggests that women's personal care products may be a potential source. A smaller Korean study estimated that women's daily exposures to DEHP (41.7 µg/kg) was much higher than children's (male 9.9 µg/kg, female 17.8 µg/kg) and exceeded the European Union tolerable daily intake of 37 µg/kg, suggesting a significant difference in exposure.[61] Childhood exposures are still of interest for future research. In a pilot study of six- to eight-year-old girls by the Breast Cancer and the Environment Research Centers, 94 percent had intermediate levels of concentrations of 9 out of 10 phthalate metabolites, with some significant racial differences.[19]

Although there is some evidence of reproductive and developmental effects from phthalates, no epidemiologic studies have been undertaken to examine the relationship between phthalates and breast cancer.[62] Furthermore, animal studies have not considered the effects of phthalate monoesters on mammary gland development or pubertal timing in the female. Concern about a possible link between phthalates and breast cancer exists, however, because of phthalates' controversial in vitro estrogenic properties[51, 63] and because they can act as endocrine-disrupting chemicals.[6, 64-66] These endocrine disruptors can potentially affect breast cancer through promotional mechanisms, by affecting mammary gland development and the receptor populations normally expressed, or by responding to other carcinogens.[6] Animal studies have reported suggestive evidence for the

protective effect of phthalates on the various stages of mammary carcinogenesis.[63] In contrast, in vitro studies reported that exposure to pharmacological levels of phthalate diesters can increase the proliferation of MCF-7 breast cancer cells.[64-67] However, these studies do not agree on the concentrations of these compounds needed to stimulate cell proliferation of estrogen-receptor effects. These findings underscore the need to further explore the role of phthalates in the etiology of breast cancer, particularly given their ubiquitous presence in the environment and the significant body burden levels of these agents in the general population.

In the absence of clear evidence from human health studies, breast cancer advocacy groups and environmental organizations have taken a precautionary principle approach to phthalates. In 2005, U.S. Assembly Bill 908 proposed to ban dibutyl phthalate (DBP) and diethylhexyl phthalate (DEHP) from personal care products. The ability of cosmetic manufacturers to reformulate products to be phthalate-free, in order to comply with the European Union ban on DBP and DEHP, indicates that alternatives exist. However, U.S. legislators concluded that the current scientific evidence was inadequate to prove a public health risk. More and better evidence is needed to counter the strong industry lobbying on this issue.

Solvents: Several hypotheses have supported the biological plausibility of organic solvents causing breast cancer. One theory is that the estrogenic properties of halogenated hydrocarbons may be linked to breast cancer etiology.[68] Another theory is based on the lipophilic properties of organic solvents, which allow them to pass more slowly from alveolar air to blood. Once in the blood, organic solvents can easily be transferred to the fat tissues.[69] This theory suggests that since organic solvents are lipophilic, they can migrate to the adipose tissue in the breast and can be stored there for significant amounts of time, where they can thereby initiate or promote carcinogenesis through genotoxic or related mechanisms.[69]

Once organic solvents are in fatty tissue, they can be metabolized and expressed in human milk.[70] Biomonitoring studies have detected significant levels of solvents in breast milk, including benzene, methylene chloride, and toluene.[69, 71-73] Breast milk levels of solvents may be higher than blood levels partly because breast fat does not eliminate solvents as quickly as does blood;[69] thus, their presence in breast milk indicates their bioavailability to breast tissue, possibly from a much earlier exposure.

Despite the suspected carcinogenicity of organic solvents in cosmetic products, a dearth of information exists on human health effects. A few occupational studies have reported a positive relationship between solvents and breast cancer among solvent-exposed workers[74-76] but only one has been specific to solvents in cosmetic products. The California Occupational Mortality Study (COMS), a statewide population-based study that evaluated mortality data from 1979–1981 for different workforces compared to the general population, found significantly elevated breast cancer mortality rates – nearly two-fold – for cosmetologists, even after adjusting for smoking, alcohol, and SES.[77] Unfortunately, this mortality study did not specifically examine the relationship

between solvents and breast cancer; thus, the question about the role of organic solvents in breast cancer development still remains.

Health concerns have been particularly pronounced for hair and nail care service workers. Hair and nail services involve frequent and intense use of volatile chemicals, including organic solvents, which may present a health threat to the workers, consumers, and neighborhood residents. Of particular concern are the workers themselves, who have daily exposures to these agents over an extended period of time. The cosmetology industry in California is the largest professional licensee population of any industry or profession in the country, with nearly 400,000 licensees, including 206,000 cosmetologists and 83,500 manicurists.[78] The size and racial/ethnic composition of the workforce has also changed dramatically in the last few decades, notably, with a large composition of Vietnamese female immigrants working in this sector.[79] This demographic shift suggests a different set of risk factors for breast cancer (including genetic susceptibility and historical exposures) in this workforce and future studies should take these changes into account.

Other Personal Care Product Components: *UV Filters*: A single human study was identified related to UV filters. Janjua et al. found that young men and post-menopausal women who applied a combination of three sunscreen agents (BP-3, OMC and 4-MBC) in high concentrations (maximum to twice the maximum permitted) to their entire bodies daily had detectable plasma and urine levels of these sunscreen compounds.[43] The researchers found only minimal to no effect on serum concentrations of reproductive hormones in either sex. This study suggests that there was substantial skin penetration, systematic uptake, and urinary excretion of the three sunscreen compounds, yet the compounds did not appear to have any influence on the levels of endogenous reproductive hormones in young men or post-menopausal women.

Estrogen/placenta: Several studies have been conducted on hair products containing estrogen/placenta. There is evidence that girls in the U.S. were starting puberty at an earlier age, with breast and pubic hair development appearing on average one year earlier in white girls and two years earlier in African American girls.[80] Obesity was found to be an important contributing factor for the overall earlier onset of puberty, but it did not account for all the interracial difference in onset of breast development; additional factors are needed to explain the higher prevalence of early puberty in African American girls compared to white girls.[81]

Some preliminary evidence points to the more frequent use of hormone-containing hair products among African Americans as the culprit for a higher prevalence of sexual precocity in this population. A survey of the frequency of use of certain hair-treatment products containing hormones or placenta among different racial groups attending the pediatric clinics of military treatment facilities reported that 55.5 percent of African American parents used these products on their children, compared to 6.9 percent among white parents.[34] A study examining advertising for women's personal care products from 1950 through 1994 in widely-read, long-lived

magazines reported that hair products containing hormones or placenta were much more likely to be advertised in magazines with a predominantly African American readership (e.g. Essence and Ebony), compared to magazines such as Mademoiselle and Ladies' Home Journal.[2] These findings suggest that African American women and girls are likely to have different patterns of use of personal care products, particularly hair products that may contain hormones or placenta.

Two case series suggested that exogenous hormones in hair products may be associated with early pubertal development in African American girls. In 1998, Tiwary reported that four African American girls, aged 14 to 93 months, developed breast or pubic hair two to 24 months after the parents started using estrogen- or placenta-containing hair products on them. These symptoms decreased after the discontinuation of such products in three of the four patients.[35] Another study reviewed records of children referred for evaluation of sexual precocity and found that the eight African American children with symptoms of early puberty were using products containing exogenous hormones.[82] With so many other suspect substances for earlier puberty and with the scant literature on the relationship between estrogen-containing hair products and earlier puberty onset, further studies are needed. However, if there is a causal relationship, this may have implications for breast cancer risks among African American women, particularly since breast cancer rates are higher for pre-menopausal African American women compared to pre-menopausal white women. A more recent study found no association between hair relaxer use and risk of breast cancer.[83]

Summary and Future Directions for Research

Parabens: Given the significant role of estrogen and endocrine disruptors in breast cancer, widespread use of cosmetic products among a potentially vulnerable population of young women, and mildly suggestive toxicological data, it is logical to include parabens in the research agenda to explore etiologic factors that contribute to this disease. Future research should combine both toxicologic and epidemiologic methods, with more attention focused on exposure assessment, particularly historical exposures, given the long latency period for breast cancer. In summary, the hypothesis remains controversial and further research is needed to shed light on this question.

Phthalates: Despite the lack of human health studies, toxicologic evidence exists suggesting a possible link between phthalates and breast cancer. Cosmetic products have been shown to contain varying forms and amounts of phthalates and the presence of phthalates in urine and breast milk indicates that these compounds are bioavailable and remain in the body after environmental exposure. Future research is needed to examine the role of phthalates in mammary carcinogenesis, taking into account individual exposures levels and their sources of exposure in order to plan for future risk-reduction efforts. Since phthalates are widely used in the cosmetics industry, including in nail polish, hair products, fragrances, and skin creams, future research should include studies of hairdressers, nail care workers, perfume counter technicians, makeup artists, and other occupational groups who routinely handle many of these products.

Solvents: In summary, few human studies exist on the influence of organic solvents in cosmetic products on breast cancer, despite the mammary carcinogens widely used in these products. Because of the widespread use of potential mammary carcinogens in many nail and hair care products, organic solvents should become a high priority for the breast cancer research agenda. Future research should include studies of cosmetologists; particularly nail salon workers who have daily exposures to these volatile chemical compounds. These studies should focus on valid and reliable exposure assessment methods that take into account individual historical exposures. While biomonitoring methods exist to indicate recent exposure to some solvents, air monitoring may be more reflective of the current levels of exposures, which may differ greatly from past exposures, given the dramatic changes in this industry in recent decades. Air monitoring may also help distinguish the source of exposure, i.e. workplace exposure as opposed to second hand smoke at home or outdoor air pollution. Identifying the source of organic solvent exposure can help with interventions to reduce levels of exposure for both workers and consumers of cosmetics. Breast cancer research related to nail salon worker exposures may be particularly of interest, as this type of business did not exist 40 to 50 years ago, workers are often younger, and it could indicate if infant and young girls are at increased risk from using nail products.

UV Filters: Given the suggestive evidence of hormonal activity, further research is warranted into how these compounds act in humans and their role in breast cancer etiology. Greater attention should be paid to 4-MBC because of its common use and higher in vivo effect.[38]

Discussion: While there are some noticeable differences among parabens, phthalates, and solvents with respect to their chemical properties and their purpose in products, they share very common characteristics of potential concern – estrogenic properties, other hormonal effects, and absorption into breast tissues. Curiously, there have been no systematic research efforts to examine their effects in human populations that are vulnerable to such exposures. The lack of epidemiologic studies appears to be mainly due to study design limitations (i.e. difficulties in conducting exposure assessment) and minimal resources, rather than lack of a clear rationale for further exploring these environmental links. Finding a population that is not exposed to parabens, phthalates, or solvents would be extremely difficult; therefore future studies may be best focused on in vitro and animal models, and longitudinal biomonitoring to compare relatively higher and lower exposures, such as the BCERC study. Reliance solely on animal studies has been criticized as providing insufficient evidence. However, evidence from these studies that indicates early-life exposures stimulate effect, when adult exposures do not, should be heeded.

Industry scientists are working on estimating exposure to personal care products as part of their safety assessments.[84] Most effective would be to require more extensive testing before these products are marketed, similar to the system used for drugs. Such testing would be useful not just for synthetic compounds, but also for natural components of personal care products. For

example, tea tree and lavender oils were recently suspected of causing breast growth in young boys and found to have estrogenic and anti-androgenic activity in human cell lines.[36]

Different interest groups, including industry and nonprofit organizations, have sought to influence the regulation of compounds in personal care products. Public policy appears to have been driven more by interest groups than by human health evidence, especially given the lack of human studies in this area. Often, the lack of scientific endeavors has been spun as a lack of supporting evidence for the link between the compounds and breast cancer, a misinterpretation that needs to be clarified with policy makers. Given that research has been trailing policy changes, it is imperative that more resources be dedicated to conducting human health studies on this issue to inform sound public policy and better serve the public's interest.

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Pharmaceuticals

Introduction

Prescription and over-the-counter medications are very widely used in the U.S. and many western countries. A recent study of medication use in the ambulatory adult population of the U.S. revealed that during the previous week, 81 percent of participants had used at least one medication, and half had taken at least one prescription medication. This survey also demonstrated that women aged 65 or older were the highest medication users; specifically, 12 percent of women in this age group took at least 10 different medications and 23 percent took at least five prescription drugs.[1] More recent data from the Slone Survey[2] indicate that overall and prescription medication use has increased between 1999 and 2005. This study also reinforced earlier estimates that more than 90 percent of women 45 years or older use some medication(s). Further, prescription medication use rates for women 45–64 years old and 65 or older were 68 percent and 82 percent, respectively. Thus, medication use in the U.S. represents a ubiquitous exposure. With breast cancer being the most common cancer in women, a careful evaluation of the potential chemopreventive or carcinogenic effects of common medications is warranted. In this review, we focus on commonly-used medications previously researched in epidemiological studies of breast cancer, including antibiotics, antidepressants, statins, antihypertensives, and non-steroidal anti-inflammatory drugs (NSAIDs).

Exposure Definition and Study Designs

The existing body of literature concerning the use of common medications and breast cancer risk is largely inconsistent. A primary reason for the divergent findings likely relates to the vast differences in methodologies employed in these studies. In addition to the obvious differences, such as study design (cohort studies vs. case-control studies) previous studies vary greatly with respect to exposure assessment, exposure classification, and adjustment for potential confounding variables. For instance, with respect to exposure assessment, many studies focused on NSAID use and breast cancer risk have only measured aspirin exposure, but have no data on more-recently-used NSAIDs, such as ibuprofen or selective COX-2 inhibitors. Thus, it is possible that women who do not report aspirin use, but are in fact frequent ibuprofen users, might be erroneously classified as “non-NSAID users” because use of these newer drugs was not assessed in some studies.

Further, using the existing research on antibiotic use and breast cancer risk as an example, there are great differences in exposure assessment. Some studies classify antibiotic use as crudely as "ever vs. never," whereas others have detailed information based on prescription data. Results from cohort studies might be difficult to interpret, as many studies rely on a single measurement of medication use, which does not take into account that medication use is subject to change over time. Many studies of medication use and breast cancer utilize large general practice databases, which improves exposure assessment, but does not allow for adjustment for potential confounding variables, as these are generally not available in these data resources.

Finally, the vast majority of previous studies are so-called secondary data analyses, indicating that these studies were not specifically designed to

address the relationship between common medications and breast cancer risk. Rather, medication use was collected as a potential confounder or within the context of a medical history. While it is standard practice in epidemiological research to analyze data for secondary associations, such studies are always methodologically inferior to those that were specifically designed to assess the link between specific medications and risk of breast cancer.

Studies of medications and breast cancer risk are also complicated by the medications containing non-active ingredients that may affect breast cancer. These ingredients can include phthalates (see Section X, Chapter X of this report), dyes and fillers.

Antibiotics and Breast Cancer Risk

Biological Mechanisms. Antibiotics may influence breast cancer risk via two main biological mechanisms: disruption of intestinal microflora and impact on immune and inflammatory function.[3] Naturally occurring gut microflora have been shown to play a role in the conversion of phytochemicals derived from the consumption of plant-based food products into biologically-active substances[4-6] suggested to be protective against cancer. For example, phytochemicals such as lignans, can be converted by microflora to enterolactone,[7] which has been correlated with reduced breast cancer risk.[8, 9] Antibiotics could also theoretically decrease breast cancer risk by affecting the ability of microflora to modulate levels of circulating estrogens through deconjugation of bound estrogens in the gut, freeing them for re-absorption and circulation.[10-13] However, the disruption of the microflora by antibiotics is not uniform, and may vary by dose and specific drug formulation.[14]

Breast cancer risk may also be mediated by the effect of antibiotics on the human immune system and inflammatory response. Numerous specific biological mechanisms have been suggested, but these remain largely speculative.[3] Some antibiotics may have an anti-inflammatory effect by limiting the production of cytokines, or a group of several proteins involved in the immune and inflammatory response.[15] Inhibited cytokine production may be important in limiting estrogen synthesis in the peripheral fat,[16, 17] potentially decreasing cancer risk. There is also limited evidence that some antibiotics may increase the production of prostaglandins, or markers of the inflammatory response.[3]

Summary of Existing Research. The potential role of antibiotic use in breast cancer etiology gained wide public attention after results from a recent large case-control study became available. In this study of 2,266 breast cancer patients and 7,953 controls who were enrolled in a non-profit health plan, Velicer et al.[18] used computerized pharmacy records to assess exposure to antibiotic drugs. Results indicated that compared to women who never used antibiotics, women with the longest durations of antibiotic use had a two-fold increase in breast cancer risk (OR = 2.07; 95% CI = 1.48–2.89). Similar risk estimates were observed when non-users were compared to women with the greatest number of antibiotic prescriptions (OR = 2.31; 95% CI = 1.69–3.15). Results were very similar for pre- and post-menopausal women and risk was increased for all sub-types of antibiotic drugs. These findings, which sparked considerable public concern about antibiotic use, are somewhat similar to those from a Finish cohort study[19] where ever

having used antibiotics was associated with increased risk of breast cancer among pre-menopausal women (RR = 1.74; 95% CI = 1.13–2.68), but not post-menopausal women (RR = 0.97; 95% CI = 0.59–1.58). Subsequent population-based[20] and nested case-control studies[21-23] did not report strong associations between antibiotic use and breast cancer risk. Most recently, Friedman and colleagues[24] conducted a nine-year follow-up study of over two million women enrolled in the Kaiser Permanente Medical Care Program in northern California. They observed a modest breast cancer risk elevation for women with the highest number of days using tetracyclines (RR = 1.23; 95% 1.11–1.36) and an even more attenuated, non-significant estimate for macrolides (RR = 1.16; 95% CI = 0.98–1.36).

Overall, there is little consensus on whether antibiotic use is associated with breast cancer risk. Any definitive conclusion is complicated by the fact that epidemiological studies cannot distinguish between the potential carcinogenic effect of antibiotic drugs and the potential influence on breast cancer development of the underlying conditions for which these drugs have been prescribed.

Antidepressants and Breast Cancer Risk

Biological Mechanisms. There are several biological mechanisms by which antidepressants may play a role in breast cancer development. One frequently cited laboratory study found that the administration of antidepressants resulted in a significant increase in the development of mammary tumors in rodents.[25] This positive association may be due to the structural similarities among common antidepressants and the cell growth regulating compound N,N-diethyl-2-[4-(phenylmethyl)phenoxy] ethanamine HCl, or DPPE. Tricyclic and selective serotonin reuptake inhibitor (SSRI) types of antidepressants have been shown to bind to the same intracellular histamine receptors associated with anti-estrogen binding sites as DPPE.[25] However, the presumed effect of antidepressants on tumor growth was not replicated in subsequent *in vitro* studies of human breast tumor cell lines.[26]

The cytochrome P450 enzyme system has been recognized as an important route of endogenous hormone metabolism, potentially affecting estrogen-dependent breast cancers. Myriad antidepressants have been shown to variably inhibit the cytochrome P450 system,[27-30] increasing the availability of endogenous estrogens, thereby increasing the risk of breast cancer. Antidepressants are also thought to increase levels of prolactin,[31, 32] itself a suspected breast tumor promoter. Finally, antidepressants may play a role in immune suppression by suppressing lymphocyte proliferation[33-35] suggesting an additional route for increased risk.

Summary of Existing Research In a somewhat recent paper, Lawlor et al.[36] conducted a systematic review of previous investigations of the association between antidepressant use and breast cancer risk. This review included seven relevant epidemiological studies published until 2002: two prospective cohorts,[37, 38] two retrospective cohort studies,[39, 40] and three case-control studies.[41-43] None of the case-control studies generated significant associations between antidepressant use and risk. One prospective cohort study[37] reported a significant increase in risk with use of any antidepressant at baseline only (RR = 1.75; 95% CI = 1.06–2.88). In contrast, a

significant decrease in risk (OR = 0.50; 95% CI = 0.30–0.80) was found in one retrospective cohort study.[40] In light of these inconsistent findings, the authors concluded in their review that the current epidemiological evidence does not support an association between antidepressant use and breast cancer.

Eight epidemiological studies have been published subsequent to the review paper by Lawlor.[36] Results from two population-based[44, 45] and one hospital-based[46] case-control studies did not demonstrate elevated breast cancer risk among antidepressant users. Similarly, two additional studies using general practice[47] and health care plan[48] databases did not reveal significant associations with antidepressant use. Further, Fulton-Kehoe et al.[49] utilized a large health care plan database and reported a modest increase in risk associated with ever having used amitriptyline (OR = 1.27, 95% CI = 1.10–1.47). However, no dose-response relationship was noted when number of prescriptions were considered, nor were breast cancer risk elevations observed for tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs). Finally, Chien et al.[50] reported results from a recent population-based case-control study where they observed significantly higher risk of progesterone receptor negative (OR = 1.8; 95 % CI = 1.1–3.6) and estrogen receptor positive/ progesterone receptor negative (OR = 2.0; 95% CI = 1.1–3.8) breast cancer among those who had ever used SSRIs compared to those who never used them.

Overall, these additional reports also do not provide strong evidence that would implicate antidepressant use in the etiology of breast cancer. More detailed analyses by tumor hormone receptor status in existing data sets might be warranted.

Statin Drugs and Breast Cancer Risk

Biological Mechanisms. There is considerable interest and controversy around whether statins may play a role in carcinogenesis. An early laboratory study suggested that these lipid-lowering drugs cause cancer in rodents at amounts that would be comparable to clinically-effective doses in humans.[51] However, several studies published subsequently have called those findings into question. The best-studied route of action for statins appears to be their inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, a key enzyme in the mevalonate pathway of cholesterol synthesis. Inhibition of HMG-CoA reductase inhibits prenylation, a protein synthesis process that leads to cell signaling processes involved in cell proliferation.[52, 53] Preclinical studies have showed that a variety of statins working through disruption of the mevalonate pathway decrease cell proliferation by promotion of G1 cell cycle arrest and apoptosis in breast cancer cell lines.[54-57] Statins have also been shown to decrease mammary tumor formation and metastasis in a mouse model.[58]

Interest in the mevalonate synthesis as target for cancer therapies has grown with the observation that statins may show a synergistic effect with chemoradiation,[59] chemotherapies,[60-62] and COX-2 inihibitors.[63] Independent of the mevalonate pathway, statins have been suggested to have anti-cancer properties through an anti-inflammatory effect and via inhibition of the proteasome.[52]

Summary of the Existing Evidence The association between statin use and breast cancer

risk has been the subject in recent attention in the field of pharmaco-epidemiology. Many of these studies utilized prescription or heath care plan record databases. Results from these investigations have consistently not revealed strong associations between statin use and risk.[64-71] While findings from these geographically-diverse investigations are consistent, they may have to be cautiously interpreted, due to significant methodological shortcomings such as lack of adjustment for confounders and crude exposure assessment (ever vs. never) in many of these studies. Coogan and colleagues[72] reported findings from a hospital-based case-control study in which prolonged statin use was associated with a two-fold increase in breast cancer risk (OR = 2.1; 95% CI = 1.1–4.0). However, more detailed analyses revealed that this estimate was largely driven by women with in situ disease (OR = 3.4; 95% CI = 1.5–8.0) rather than women with invasive breast cancer (OR = 1.5; 95% CI = 0.7–3.1). Results from a recent population-based case-control study did not demonstrate an increased risk of breast cancer for women who used statin drugs.[73] Further, analyses from two large cohort studies, the Nurses Health Study[74] and the Women's Health Initiative Observational Study[75] did not reveal significant associations. In contrast, Cauley et al.[76] described results from a smaller cohort study where ever having used statin drugs was associated with a significant risk reduction (OR = 0.28; 95% CI = 0.09–0.86). However, this estimate was based on only six statin-exposed breast cancer patients and results should be interpreted cautiously. Finally, two recent meta-analyses on this topic did not provide evidence that statin use is linked to breast cancer risk. Thus, considering this diverse and largely consistent body of evidence, it is unlikely that statin drug use is an important factor in breast cancer development.

Antihypertensive Medications and Breast Cancer Risk

Biological Mechanisms Research into the biological mechanisms by which antihypertensive agents may affect carcinogenesis has focused on calcium channel blockers (CCBs) and Angiotensin-II-converting enzyme inhibitors (ACEis). Pahor has suggested that CCBs could play a role in increased cancer risk,[77] due to inhibition of apoptosis resulting from diminished intracellular calcium ion concentrations.[78-80] However, as reviewed by Mason,[81] the role of calcium ions in apoptosis has been shown to be inconsistent, with intracellular calcium levels yielding both increased and decreased apoptosis across a range of cell types. Additionally, research has shown that CCBs may actually inhibit carcinogenesis by limiting cell proliferation in breast cell lines,[82, 83] making it difficult to draw firm conclusions about their ultimate effect on cancer risk.

ACEis have been suggested to offer a potential protective effect against cancer risk through the inhibition of angiogenesis. More specifically, ACEis target the action of angiotensin II, part of the rennin-angiotensin system involved with renal blood flow, fluid homeostasis, and blood pressure control.[84] Angiotensin II has also been shown to promote neovascularization,[85] a necessary process for tumor development. Early studies showed that angiogenesis and tumor growth were slowed following administration of ACEis in preclinical studies.[86, 87] Later, Yoshiji and colleagues [88] hypothesized that the inhibition of angiotensin II inhibits the action of vascular endothelial growth

factor (VEGF), a key enzyme in the angiogenesis process. Although cell proliferation has not been shown to be directly affected,[89] use of ACEis alone or in combination with other agents decreased VEGF concentrations and angiogenesis,[90-92] and reduced blood vessel formation around tumors.[89]

Summary of Existing Evidence. An increasing number of studies have focused on the potential role of antihypertensive drug use in breast cancer development. These studies have largely focused on CCBs, beta-blockers and ACEis; we will restrict our discussion to these widely studied drugs. As with many pharmaco-epidemiological efforts, most of these prior studies were registry-based and utilized data from prescription plan or health care plan records. The limitations of this approach are outlined above. Nevertheless, results from these studies do not indicate that ever having used, or prolonged use of, CCBs, beta-blockers or ACEis were related to elevated breast cancer risk.[93-99] Similarly, results from a large hospital-based case-control study[100] and the Nurses Health Study cohort[101] do not suggest that these drugs are related to breast cancer risk. In contrast, findings from a smaller cohort study[102] have linked ever having used CCBs to a significant increase in risk (OR = 2.57; 95% CI = 1.47–4.49). No risk elevations were observed for use of beta-blockers or ACEis. Finally, Li et al.,[103] in a large population-based case-control study, observed a significant increase in risk for prolonged use (15 years or longer) of beta blockers (OR = 2.1; 95% CI = 1.2–3.7), but no associations with long term use of CCB and ACEis. While most studies on this topic generated null findings, the majority of these investigations could only crudely classify participants as ever or never having used these drugs. Further, one study with more sophisticated exposure assessment demonstrated an association between breast cancer and prolonged use of beta blockers.[103] Thus, future studies employing solid epidemiological designs and sophisticated exposure assessment might be needed to definitively rule out a role of antihypertensive medication use in breast cancer development.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Breast Cancer Risk

Biological Mechanism. NSAIDs—including aspirin, ibuprofen, and naproxen—appear to exert an anti-cancer effect through inhibition of the cyclooxygenase (COX) enzyme system. COX-2, in particular, promotes the synthesis of prostaglandins, such as PGE_2, thought to play an etiologic role in tissue generation and tumorigenesis. Additionally, COX-2 has been found to be over-expressed in human breast tumors in multiple studies.[104-106] Preclinical research has shown that the administration of NSAIDs inhibits production of COX enzymes with resulting reduction in tumor progression.[107-109] Moreover, it has been suggested that NSAIDs reduce neovascularization and promote apoptosis.[110, 111] Some NSAIDs that do not effect the COX system have been shown to induce cell cycle arrest and apoptosis in breast cancer cell lines.[112] Taken together, multiple lines of research into the biological mechanisms by which NSAIDs impact cancer risk point to a potentially valid agent in chemoprevention.

Summary of Existing Evidence A large and diverse body of literature exists on the potential chemopreventive effect of NSAIDs use on breast cancer development. Exposure assessment, however, differs widely across studies, including the definition of regular use and prolonged use. Nevertheless, results from most studies have been remarkably consistent. Two registry-based studies[113, 114] showed significant breast cancer risk reductions for prolonged aspirin use. Several hospital-based studies[115-117] and population-based studies[118, 119] have generated statistically significant risk reductions for regular and prolonged aspirin use. Less consistent evidence exists for ibuprofen use, which was associated with decreased risk in one investigation,[117] but not in others.[115, 119] Such discrepancy might not be surprising, given that ibuprofen is still a relatively new drug and to date few people will have had significant exposures to this agent. Findings from the WHI observational study indicated that prolonged use (10 years or more) of any NSAIDs or aspirin was associated with statistically significant breast cancer risk reductions (RR = 0.72; 95% CI = 0.56–0.91 and RR = 0.79; 95% CI = 0.60–1.03, respectively).[120] Similarly, findings from the CLUE cohort in Washington county[121] point to a chemoprotective effect of aspirin use in breast cancer etiology (RR = 0.46; 95% CI = 0.22–0.98), but results were not influenced by tumor hormone receptor status or COX-2 genetic polymorphisms.[122] Further support for a chemopreventive role of aspirin comes from the NHANES I[123] and Iowa Women's[124] cohorts, where current or prolonged (six years or longer) use were associated with significant risk decreases (RR = 0.70; 95% CI = 0.56–0.96 and RR = 0.71; 95% CI = 0.58–0.87, respectively).

In contrast, initial analyses from the Cancer Prevention Study II Nutrition cohort,[125] as well as results from the California Teachers[126] and Nurses Health Study[127] cohorts did not demonstrate associations between use of aspirin or other NSAIDs and breast cancer risk. In fact, in the California Teachers cohort, prolonged use (five years or more) of both aspirin and ibuprofen was associated with significant risk elevations for women with hormone receptor negative tumors (RR = 1.8; 95% C1.2–2.92 and RR = 1.50; 95% CI = 1.1–2.03, respectively). In a recent randomized low dose aspirin (100 mg) chemoprevention trial, with an average of ten years of follow-up, women who were randomized to the aspirin intervention arm were not at lower risk of breast cancer compared to women who received the placebo (RR = 0.98; 95% CI = 0.87–1.09). In response to results from this trial, Jacobs et al.[128] very recently conducted further analyses in the Cancer Prevention Study cohort and focused on long-term (five years or longer) daily use of adult-strength aspirin preparations (≥ 325 mg). The authors speculated that the lack of a protective effect in the randomized trial may be due to the low dose of aspirin, which may not have been sufficient to produce a chemoprotective effect. Results indicated that daily long-term use was associated with a non-significant risk reduction (RR = 0.83; 95% CI = 0.63–1.10).

The existing body of literature on the associations between various NSAIDs and breast cancer risk is complicated and difficult to interpret. While most studies on this topic have demonstrated statistically significant risk reductions, the majority of these studies were either registry-based or employed a case-control design. The former approach is methodologically limited due

to insufficient adjustment for potential confounders, whereas the latter study design is known to be prone to selection and information bias. Further, evidence from cohort studies is inconsistent, although results from most cohort studies point to a role of aspirin in breast cancer chemoprevention. Most importantly, however, the only randomized trial, considered the gold standard in epidemiological study designs, did not demonstrate a chemoprotective effect of aspirin use. It is possible, as suggested by Jacobs et al.[128] that higher-dose aspirin preparations may be needed to produce a chemoprotective effect. Additional randomized trials with higher aspirin doses may be needed to resolve this important question. It is also possible that selective COX-2 inhibitors have much stronger chemopreventive properties than aspirin. However, in light of the serious side effects revealed in previous trials with these drugs, the use of these drugs in cancer chemoprevention trial is unethical.

Conclusions and Future Directions

The existing literature on the use of common over-the-counter and prescription medications has not definitely linked any of the drugs covered in this review to either increased or decreased risk of breast cancer. Important contributing factors to this apparent inconsistency are likely the numerous methodological issues, discussed throughout this review, associated with the various study designs employed in these investigations. In summary, there is inconclusive evidence on the association between antibiotic use and breast cancer risk; no strong evidence pointing to a significant role of antidepressant and statin drugs in breast cancer development; somewhat inconclusive evidence on the effect of antihypertensive drugs; and suggestive evidence implicating aspirin use in the chemoprevention of breast cancer.

Future studies with detailed lifetime medication histories are needed to further clarify these important associations. While methodologically superior to case-control studies, it is unlikely that such an assessment can be accomplished with a cohort study design, where repeated detailed medication measurement would be difficult to achieve. Thus, future case-control studies should consider in their design strategies for obtaining detailed and valid lifetime medication histories, which will likely involve a combination between self-report and prescription and/or health care plan data. Further, in light of the strong and largely consistent findings from epidemiological studies that link prolonged higher-dose aspirin use to reduced risk of breast cancer, an adult-dose (325mg) chemoprevention trial might be warranted. Other medications that have not been subjects of epidemiological studies on their relationship to breast cancer may also warrant further investigation. These include medications that supplement thyroid hormones; anti-seizure medications such as Dilantin; steroidal drugs, including those used to treat asthma and those used and abused by young female athletes; and Ritalin, for its possible impact later in life after use in childhood.

As pointed out above, medication use constitutes a ubiquitous exposure in the U.S. and in many countries worldwide. Given that breast cancer is the most common cancer in the U.S. and elsewhere, it is essential that we increase our understanding of the role of commonly used drugs in the etiology of this disease.

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Infectious Agents

Introduction

Chronic microbial, parasitic, or viral infections are thought to contribute to the carcinogenic pathway of many different cancers. These include gastric cancer and gastric lymphoma (Helicobacter pylori), cervical cancer (human papillomavirus), non-Hodgkin's and Hodgkin's lymphoma (Epstein-Barr virus), T-cell leukemia/lymphoma (human T-cell leukemia virus--HTLV-I virus), Kaposi's sarcoma (human herpesvirus-8), bladder cancer (Schistosomiasis haetobium), cholangiocarcinoma of the liver (liver flukes), and liver cancer (hepatitis B and C viruses). Infectious agents may account for nearly 18 percent of the global cancer burden, with H. pylori, HPV, and hepatitis viruses each contributing about 5 percent.[1]

Breast cancer incidence varies both geographically and by birth cohort, variations that also parallel differences in the extent of individual exposure to infections and microbes. People in western, industrialized countries where breast cancer rates are highest, experience substantially less exposure to infection than those in developing nations, where breast cancer rates are lower. Populations in industrialized societies have lower rates of gastrointestinal infections and substantially less exposure to parasites; they also receive routine vaccination against a multitude of viral illnesses. With industrialization, exposure to many microbes once considered a part of the natural human ecosystem has been altered by urbanization, public health infrastructure changes such as indoor plumbing and advanced sewage treatment systems, and widespread personal and domestic use of antibiotic pharmaceuticals, antiseptics, and detergents. As an example, H. pylori infection (still the most common chronic infection in the world and once almost universally acquired in early childhood) is rapidly disappearing from western societies, a trend that has been accompanied by dramatic reductions in gastric cancer rates over the past century.[2] Yet there has been little research of these global epidemiologic transitions as they might relate to observed breast cancer patterns.

Most work to date examining infections and breast cancer has focused on possible etiological roles of specific microbes, as well as infectious complications of breast cancer treatment. However, emerging evidence suggests that infectious agents could potentially alter breast cancer risk through three other pathways:

1) by potentiating other risk factors, such as chemical exposures;

2) by altering the timing of sexual maturation during childhood and/or by altering the levels of circulating sex hormones; or

3) by influencing particular immune responses to breast cancer that alter its initiation, progression, metastasis, or response to treatment.

Exposure Definition

This review focuses on environmental exposures to pathogenic microbes, including viruses, bacteria, and parasites, as well as benign/commensal microbes (e.g. intestinal microflora), as they might relate to breast cancer incidence, etiology, and outcome.

Biologic Plausibility

Infectious agents may play a contributory role in breast cancer if they work in combination with other causative agents, such as chemical carcinogens. In an example of this contributory role with another type of cancer, a nested case-control study of non-Hodgkin's lymphoma and serum organochlorine residues revealed a synergistic relationship between PCB exposures and Epstein-Barr virus infection with regard to lymphoma risk.[3] A possible interactive role for chemical agents and Epstein-Barr--or any other infectious pathogen--with regard to breast cancer has not yet been explored.

Infectious agents in childhood may serve to lower breast cancer risk if they delay the onset of sexual maturation and, in particular, menarche. As age of menarche decreases, overall risk of breast cancer increases.[4] Conversely, for each year menarche is delayed, the risk of breast cancer declines by 5–20 percent.[5] The presence of chronic disease is associated with later onset of puberty and is believed to influence the endocrine regulation of that part of the hypothalamus that governs pubertal onset.[6] Most recently, a study of Bangladeshi women who migrated to the United Kingdom found that those who migrated as infants and young children reached puberty earlier and had significantly higher levels of circulating progesterone than women who migrated at a later age or than those who stayed in Bangladesh. Poor sanitation and higher exposure to infectious agents were posited as possible explanations for the slower sexual maturation of Bangladeshi women who grew up there.[7]

Mechanisms of action by which infectious agents might cause cancer include: 1) direct carcinogenesis through DNA damage; 2) induction of chronic inflammation or rapid cell proliferation; 3) suppression of immune responses against cancer; and/or 4) immune stimulation of cancer growth factors. In the case of infectious agents, virulence factors, host genetic polymorphisms, concomitant infections, and lifestyle can also play important roles. For breast cancer, there is some evidence that inflammation may contribute to the alterations in estrogen metabolism that are involved in carcinogenesis or growth. Provocative evidence of an association with inflammation derives from animal studies showing that NSAIDs inhibit mammary carcinogenesis, as well as case-control and prospective epidemiologic studies generally reporting that long-term users of anti-inflammatory medications have markedly lowered risk (> 20 percent) of breast cancer,[8-10] especially for hormone-receptor positive types.[9-12]

Criteria for establishing a cause-effect relationship between a microbe and cancer are evolving along with technology.[13, 14] At present, useful criteria include: consistency of association; molecular evidence of oncogenicity (consistent observation of genomic particles within a host cell line, or of translocational correlates enabling cell proliferation and immortalization); and isolation of functional mechanisms of the agent that are responsible for perpetuating the malignant phenotype. Not all discoveries follow a consistent path to these conclusions or subscribe to a common physiologic model. Some agents, such as DNA-containing tumor viruses, are latent infections. Some, like hepatitis viruses and H. pylori, are chronic active infections that induce

tumorigenesis. Interdisciplinary approaches—involving basic laboratory, animal models, as well as population-based epidemiology and clinical trials—are increasingly needed to understand causal relationships.

Critical Review of the Literature

Most work to date examining infections and breast cancer has focused on possible etiologic roles of specific infections, as well as infectious complications of breast cancer treatment. However, it is possible that a wide spectrum of single or cumulative microbial exposures influence particular immune responses to breast cancer, affecting its initiation, progression, metastasis, and response to treatment.

Incidence/Etiology

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a persistent herpesvirus known to transform lymphocytes in vitro. In addition, B-cell lymphoproliferation is observed in patients with immunosuppression.[15] EBV is considered a Group I carcinogen by IARC and has been implicated in the etiologies of several cancers, including Burkitt's lymphoma, non Hodgkin's and Hodgkin's lymphomas, other lymphoma subtypes, and nasopharyngeal carcinoma.[16, 17] Studies have also been conducted to explore possible associations of breast cancer with EBV.

EBV seropositivity is nearly universal by late adulthood, although ages of primary infection may differ among populations in patterns that also correlate with economic development. One analysis of U.S. SEER registry data reported a two- to five-fold increase in rates of breast cancer associated with older age at diagnosis of infectious mononucleosis or tonsillectomy.[18] A study of women under age 40 did not observe case-control differences in seropositivity to EBV or another herpesvirus, cytomegalovirus (CMV), but did note higher CMV antibodies in breast cancer cases than controls, independent of other factors, suggesting an association with later age at primary CMV infection.[19] In support of a role of infectious mononucleosis in breast cancer etiology, authors have cited circumstantial associations between breast cancer and Hodgkin's disease, a lymphoma associated with history of infectious mononucleosis, including strong correlations of incidence rates internationally,[18] and, in a Connecticut registry series, similarities in birth-cohort-specific incidence patterns.[20] However, an elevated rate of breast cancer was not detected in women with hospital-treated infectious mononucleosis in a Scandinavian cohort.[21] In addition, other explanations for international correlations, such as ethnic differences, have been posed,[22] and in a large population-based prospective study of individuals with confirmed infectious mononucleosis, the standardized incidence ratio was 1.01 (0.92–1.23), suggesting no excess rates of breast cancer were detected.[23]

Epstein-Barr viral proteins have been variably detected in breast cancers. However, use of immunohistochemical techniques for detection of the viral antigen, EBNA1, may be confounded by cross-reactivity with other common proteins.[24, 25] These studies have concluded that there is little evidence to support the consistent involvement of EBV.[25] Thus, despite the presence of EBV viral

material in some breast tumor cells, there is no evidence to date that EBV plays any etiologic role in the carcinogenesis of breast cancer.

Mouse Mammary Tumor Virus (MMTV) Analogs

MMTV is a mouse betaretrovirus. MMTV was first identified in the 1920s, when it was found that a breast cancer-causing agent was passed through milk from mouse mother to mouse daughter.[26] This transmissible agent caused almost 100 percent of the mouse daughters to develop breast cancer. However, when the newborn daughters of mice from a strain with a high rate of breast cancer were nursed by foster mothers from a strain that had a low rate of breast cancer, the virus was not transmitted and the daughters did not develop breast cancer. Milk is the only clearly established mode of transmission of infectious MMTV in mice.

Interest in the idea that human breast cancer could also be caused by a virus was renewed when MMTV-like sequences were detected using polymerase chain reaction methods in more than 30 percent of human breast cancer samples in at least two clinical series.[27, 28] However, subsequent studies using more advanced technologies found some of these sequences were of human origin, that the sequences were found in surrounding tissues and not tumor cells, or that the observations otherwise could not be replicated. Serologic studies to identify antibodies to an MMTV-like virus were initially plagued by similar methodological difficulties and yielded uneven results.[29] With more advanced techniques, a considerable proportion of sporadic breast cancer samples have been observed to contain an MMTV-like env+ gene sequence.[30] Using cDNA microarray to compare two sublines of the MCF-7 breast cancer cell line, one team reported differential expression of interferon, TNF-alpha, and TGF-b, cytokines associated with the inflammatory phenotype.[31]

However, there is little corroborating epidemiological support for a milk-borne, MMTV-like-induced breast cancer in humans. Population-based case-control studies have not shown increased incidence of breast cancer in daughters who were nursed by mothers who later developed breast cancer, compared with daughters who were not breast-fed.[32, 33] These studies do not support evidence of a transmissible agent in breast milk.[33]

Recently it has also been suggested that the MMTV could be transmitted directly from mice to humans. This zoonotic mode of infection was proposed because geographic areas of high breast cancer incidence (Western Europe and North and South America) overlap with the distribution of the Mus domesticus species of house mouse.[34] Recent National Cancer Institute assessments of MMTV antibody prevalence utilizing state-of the-art methods and examining multiple strains of MMTV support very low population prevalence (no greater than 3 percent) of MMTV antibodies in representative women with breast cancer.[35] Thus, support for MMTV or for MMTV-like viruses causing human breast cancer is weak or confined to experimental systems at the present time.

Bovine Leukemia Virus (BLV)

BLV is an oncogenic bovine retrovirus that causes a B cell leukemia/lymphoma in 1–5 percent of all infected cattle. The tax subunit of the pXBL genetic region is responsible for malignant transformation[36, 37] and may be relatively conserved in evolution.[38] As BLV is present in infected cows' milk and breast tissue, it was hypothesized that it could be transmitted to humans via dairy products and other cattle-based foods. In one serologic survey, 74 percent of 257 human serum samples were reactive to the BLV p24 capsid protein.[39] However, numerous surveys have failed to find a link between contaminated milk products and human leukemias, including the related human lymphoma, HTLV-1.[40, 41] With respect to breast cancer, assays of human breast tissue have yielded variable detection of BLV genes and gene products. In a case-control comparison, breast cancer cases were significantly more likely to have evidence of BLV genes in their unaffected breast tissue (Odds Ratio = 5.4; 95% CI = 2.42–11.9) than healthy women, after adjustment for age, but not after adjusting for other breast cancer risk factors.[42] Work is ongoing to further isolate the location of BLV material in breast tumor cells, but the variable detection of BLV antibodies and genetic material do not support a major role of BLV in breast carcinogenesis in humans. While evidence linking adult dairy consumption with breast cancer risk is inconsistent (see I.B.7. Hormones in Food for a discussion of these studies), studies are ongoing to examine early-life exposure to dairy products.[43]

Human Immunodeficiency Virus (HIV)

HIV is a widespread human retrovirus that destroys specific lymphocytes, T-helper cells. At least two studies have reported lower rates of breast cancer outcomes in women with HIV infection: a European cohort (RR = 0.43; 95% CI = 0.24–0.73),[44] and a large population-based series in the U.S. (Standardized Incidence Ratio 0.69; 95% CI = 0.62–0.77).[45] The lowest risks were found in those with greatest immunosuppression (women 4–27 months after AIDS diagnosis RR = 0.5; 95% CI = 0.3–0.8).[46] Notably, reduced risk in AIDS patients appears to be largely independent of reproductive history, such as lower parity. Furthermore, the introduction of highly active AIDS therapies appears to be attenuating this breast cancer deficit. Possible explanations for reduced breast cancer outcomes in the setting of T-cell mediated immunodeficiency may include down-regulation of hormone metabolism or other inflammatory processes, impairment of cell proliferation by the virus, or differential ascertainment bias.

Sexual Activity/Sexually Transmitted Diseases

Many factors or co-factors potentially associated with breast cancer are also related to sexual history, including reproductive history, lifestyle, and hormone production. In adulthood, a theoretical correlate of microbial exposure is sexual activity, particularly with multiple partners. Among white women in Seattle, an increasing number of male sex partners was associated with decreased breast cancer risk in a dose-response fashion (15 or more partners vs. 1 partner OR = 0.6; 95% CI = 0.3–1.0), after adjustment for

reproductive characteristics, alcohol use, education, and religion, but not for contraceptive practices like condom use.[47] To the extent that marital status correlates with more frequent sexual activity (albeit with fewer partners), similar interpretations can be made from several other studies: lower breast cancer rates have been reported among married nulliparous women compared to unmarried women;[48] among postmenopausal women married multiple times compared to those married once, after adjusting for parity and other factors;[47, 49] and in Islamic countries--where extramarital sexual activity has been uncommon among women--among ever-married women compared to never-married women, after consideration of nulliparity, age and other confounders.[50, 51]

Perhaps the best example of a sexually-transmitted cancer is the human papilloma virus (HPV). Considered a true human tumor virus, genotypes 16 and 18 are consistently associated with cervical cancers. HPV genes E6 and E7 have the ability to immortalize breast cell lines, as well as human target cells in vitro.[52] Several reports have detected high-risk HPV genotypes in breast carcinoma samples, although variation in laboratory methods, as well as the ubiquity of different papilloma infections in humans, make the specificity of these findings difficult to establish.[53, 54] HPV DNA has been detected in ductal cancer specimens, including histologic features consistent with HPV, but no correlations with tumor grade or p53 expression have been observed.[52, 55] It has been speculated that the virus, which requires cell surface contact, may be transmitted to the breast by autoinoculation during sex, or even bathing and showering. However, evidence of an oncogenic role for HPV in the breast remains circumstantial.

To our knowledge, no epidemiologic studies have addressed associations of breast cancer with history of common sexually-transmitted diseases other than HIV (see above). Other sexually-transmitted infections, including Chlamydia trachomatis and syphilis, have been inversely associated with prostate cancer, but have not been studied for breast cancer.

Parasites

The inflammatory immune response is a key factor in the development of many cancers. Overexpression of cyclooxygenase (COX) -2, and the cytokine TNF-alpha, are found in a variety of breast tumors and associated with poor prognosis. Conversely, drugs to inhibit this cascade are targets for new chemotherapies.[56, 57] Some parasite infections, in particular those caused by the geohelminths, induce a strong, even polarizing, non-inflammatory or Th2-type immune response to infection. In mouse models of gastric cancer, helminth infection has been associated with attenuation of Helicobacter-associated gastritis and metaplasia.[58] In high-risk cancer populations, serologic response to H. pylori infection may also vary with respect to helminth burdens.[59] Given the virtual disappearance of helminths from areas with the highest rates of breast cancer, and the fact that these chronic infections are profoundly immunomodulatory, one could hypothesize that systemic parasitic infections might also interact with risk of breast cancer. In the laboratory, Sheklakova[60] detected a directly inhibitory effect of Trypanosoma cruzi, a protozoan, on cultured breast cancer (MCF-7) cells in vitro. Schistosoma

haematobium, a water cestode found in Africa and Asia, is linked to increased risks of bladder cancer. In some Egyptian studies, it has been associated with increased risks of breast cancer in men.[61] Although rates of helminth infection can be significantly higher in recent U.S. immigrants than in U.S.-born, to our knowledge, no epidemiologic studies have explored a comparison of breast cancer rates in this context.

Non-Specific Microbial Exposures: Probiotics and Persistent Gastrointestinal Infections

Intestinal bacteria may influence breast cancer development through effects on inflammatory responses or cytotoxic anti-tumor responses, or through their influence on metabolizing ingested hormones or phytoestrogens as well as endogenous estrogens. Helicobacter pylori, a pre-eminent cause of gastric cancers,[62] induces a chronic Th1 inflammatory state in the gut. Strains containing the pathogenetic island (PAI) can, in combination with host genetic polymorphisms, dramatically multiply the risk of gastric cancer.[63, 64] In an animal model, irritable bowel disease (IBD)-resistant mice rapidly developed mammary tumors after Helicobacter infection, a "surreptitious" result that was subsequently tracked to TNF-alpha triggered effects of infection.[65] This animal model lends further support to the speculation of cross-talk between intestinal bacterial infections and extraintestinal immunoregulatory systems.

Probiotics are fermented foods and supplements, including beneficial bacteria like lactobacillus that presumably make intestinal microflora composition more beneficial. To the extent that gut bacteria might be involved in the metabolism of protective phytoestrogens, studies have addressed relationships between probiotic consumption and serum levels of endogenous estrogens and phytoestrogens in post-menopausal women. These did not detect associations between probiotics and estrogen levels.[66] One breast cancer case-control study addressing consumption of fermented dairy products reported a negative association,[67] implying a protective effect. Although molecular technologies to describe intestinal microflora are newly developed, there is little other extant work to understand how characteristics of intestinal bacteria may regulate hormone levels or affect breast cancer risk.

Antibiotic use plays an important role in modifying intestinal microflora at both population and individual levels. In the industrialized world, for example, counterposing trends in incidence of esophageal and gastric cancers beginning in the last century parallel the disappearance of H. pylori infections, an infection that is susceptible to many common antibiotics.[68] See Section I, Chapter D for a discussion of antibiotics and breast cancer risk.

Other Non-Specific Microbial Exposures: "The Hygiene Hypothesis"

The "hygiene hypothesis" proposes that cumulative exposure to common infections and other microbes, particularly in early life, protects against the development of childhood asthma, allergy and other immune-mediated diseases.[69] This literature suggests that immune system development is adaptive, that is, influenced by cumulative exposures[70, 71] to a variety of microbes,

innocuous microbial by-products like endotoxin,[72, 73] and perhaps even intestinal microflora.[74] From this, one can speculate that negative influences of insufficient microbial exposures in early life on immune system development may impact the ability of the immune system to fight off breast tumor cells in later life. By analogy, as rates of non-cardial stomach cancer have plummeted in the industrialized world, rates of upper stomach and esophageal diseases--such as GERD, Barrett's esophagus, and pancreatic cancers--have surged. One hypothesis is that loss of H. pylori from the gut microflora has disturbed a historically important niche of adaptive immune response to this chronic infection.

While some studies have examined associations between breast cancer and some relevant markers of microbial exposure identified in the allergic disease literature, this inquiry has occurred as secondary analyses and has focused on single rather than cumulative measures of infection. Case-control studies to examine associations of post-menopausal breast cancer with markers relevant to the hygiene hypothesis are currently ongoing.

Mortality/Survival

The idea that infectious agents might be effective cancer treatments was first posed in the 1900s by William Coley, who observed that patients with advanced soft tissue sarcomas who went on to develop streptococcus infections sometimes experienced spontaneous regression of the tumors. He went on to develop "Coley's toxins" which were not uniformly produced, but nonetheless were tested broadly as a cancer remedy, mostly to no avail. Today, there is one FDA-approved infectious-agent-based treatment for cancer, the Bacille-Calmette-Guerin (BCG) vaccine against M. tuberculosis for treatment of bladder cancer. Little is known about how infections occurring during the course of breast cancer treatment might influence propensity for recurrence or lengthen survival. To the extent that breast cancer differs from other tumors in its propensity for recurrence, and can recur up to 20 years after initial treatment, the idea of immunosurveillance of malignant breast cells is intriguing.

Discussion

Carcinogenesis is a complex process involving the contribution of many different factors. Rarely is a single factor implicated as both sufficient and necessary on this pathway. Nevertheless, the possibility that infectious agents might influence breast cancer development and outcome has not been well studied. Furthermore, genetic technologies needed to identify novel viral causes of breast cancer are constantly being developed and refined. Recognizing these, the National Action Plan on Breast Cancer (NAPBC) held in 1997 a workshop entitled "Viruses and Human Breast Cancer: Exploring the Links."[75] First, this workshop recommended conducting large epidemiologic studies of breast cancer and established viral antibodies or other biomarkers. They specified that such efforts should proceed even in the absence of a specific suspected causal entity, noting that HPV was determined to be the cause of cervical cancer only after persistent and diverse investigations over many years. They also recommended comprehensive viral characterization studies to identify and describe viral material in a variety of specimens relevant to

breast cancer (e.g., sera, blood, normal tissue, tumor tissue, breast milk), reasoning that identification of novel breast cancer viruses will come only from careful cross-checking of newly-identified sequences with those already published or reported.

In the ten years since the workshop was convened, searches for novel viral causes of breast cancer--including mouse mammary tumor virus, its possible human analogs, and bovine leukemia virus--have generally followed these recommendations. As yet, research has not identified consistent molecular evidence of viral involvement in carcinogenesis. Similarly, efforts to detect EBV in breast tumors have not yielded strong evidence of involvement. However, there may be progress in this area as technologies for identifying, sequencing, and communicating novel viral sequences in breast cancer-relevant biospecimens are improved. The inauguration in September 2006 of a new, open-access medical journal, Infectious Agents and Cancer, focusing entirely on viral and infectious causes of malignancy, should provide a welcome forum for improved communication of findings and research issues.

As indirect causes of breast cancer, chronic viral and parasitic infections, including aspects of age at infection (and/or vaccination), are promising candidates for future study, especially as the immunologic sequelae of these kinds of exposures--including chronic inflammation, and dysregulation of Th2 cytokines and regulatory T-cell functions--are increasingly understood to influence steroid hormone metabolism. Several small European studies and a recent large, population-based U.S. study have consistently demonstrated that HIV infection is associated with lower rates of breast cancer occurrence, with risk that decreases as immunosuppression becomes more profound. Some evidence for a link of infectious agents and breast cancer also comes from studies illustrating the antithetical trends associated with NSAID and antibiotic use.[11] These findings additionally support an important regulatory role of immune factors on the expansion of nascent breast tumor cells, or on hormones or other determinants of breast tumor growth and spread. Other data hint at inverse associations with other sexually-transmitted microbes. Inverse associations with many of these infections, especially early age at or intense exposure, would be consistent with many aspects of the descriptive epidemiology of breast cancer, particularly the incidence variation with socioeconomic status, race/ethnicity, and immigration status.

Limitations

An important limitation for investigations into the effect of infectious agents on breast cancer is the need for a developmental model of cumulative, including concomitant, exposure. Chronic infections frequently co-exist within the same host, while diagnostic agents are designed to capture "one disease-one pathogen." Second, infections potentially related to breast cancer tend to be ubiquitous when they are prevalent at all. To this extent, the challenge is to establish specific, sentinel biomarkers that can be informative for birth cohort studies. One approach is to incorporate a definitive temporal marker, like H. pylori infection, that has a known secular

influence on the distribution of cancers over time. Third, studies considering the timing of infection, of vaccination for childhood diseases, or severity of infection have to rely on self-report or medical records. Especially in the setting of a life-defining event like breast cancer, recall of antecedent exposures can be difficult to validate. If complete medical records are needed, this can introduce bias into ascertainment systems. As was the case with H. pylori and stomach cancer, where induction periods or mechanisms are uncertain, nested case-control designs within large subscriber populations can be useful for matching pre-diagnostic biologic specimens to identify infectious exposures of interest.

Gaps in Knowledge

There are several gaps in our understanding that, if filled, might shed light on the potential role of microbes in influencing breast cancer occurrence and outcomes. These gaps stem largely from the absence of any epidemiologic studies designed specifically to examine associations of microbial exposures with breast cancer or its probable precursors (e.g. hormone levels or mammographic density). In particular, there is a paucity of literature addressing the associations of sexually transmitted diseases and parasitic infections in breast cancer development, despite biologic and epidemiologic consistencies. Also virtually unstudied is the relevance of the intestinal microflora to breast carcinogenesis, despite its known influence on the metabolism of endogeneous and exogenous hormones, and emerging information on extraintestinal effects of gastrointestinal infections. Infectious causes of inflammatory breast cancer, a rare and virulent breast cancer subtype characterized by vigorous inflammation of the tumor site, are suggested by the clinical features of the disease, but remain poorly understood. In addition, no studies have examined the influence of acute infections, which might influence the likelihood of breast cancer recurrence and/or survival time.

Conclusion and Future Directions

Infectious and immunologic conditions predisposing to or protecting against breast cancer are plausible but have not been well studied. In this effort, we have reviewed available evidence for only a few of the infectious agents that could be relevant to breast cancer development. Many common infectious agents, including Helicobacter pylori and all classes of parasites, have been rarely considered as they might associate with breast cancer risk.

As a first step, associations of relevant markers of infections and microbial exposure should be examined in a study population with adequate exposure variation. The diversity of the California population with respect to race/ethnicity, socioeconomic status, and immigration status would be important to ensuring appropriate heterogeneity. However, the very low prevalence of some of the infectious exposures of interest (e.g. parasites) might support an international or other multicenter study design. To the extent that serologic (e.g. antibodies) markers are available for exposures of interest, these studies should be designed to rely upon these measurements for exposure classification.

Future studies should pursue interactive links between infectious agents and environmental

contaminants. Research should also examine the role of chronic infectious disease in altering pubertal timing and circulating hormone levels in ways that might lower breast cancer risk.

Although an infectious etiology for breast cancer remains elusive, the field of infectious disease oncology is only in its infancy. With the advent of translational medicine modalities in research, there is an historic opportunity to integrate basic science, immuno-epidemiology and clinical trial disciplines. New technologies, such as DNA and protein microarrays, have potential to identify molecular signatures and gene expression profiles associated with different cancers. The UC campuses have been in the vanguard of this movement, and are well equipped to assist in this challenge. The human immune system has co-evolved with infectious agents. The adaptive and homeostatic features of this extraordinary system enable the vast majority of hosts to escape the long-term consequences of infection, including cancer. Through our own cross-talk, the cross-talk of the host-pathogen ecosystem may be revealed. The future of this branch of breast cancer research may well hold the clues to our past.

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Ionizing Radiation and Breast Cancer

Definition and Sources of Exposure

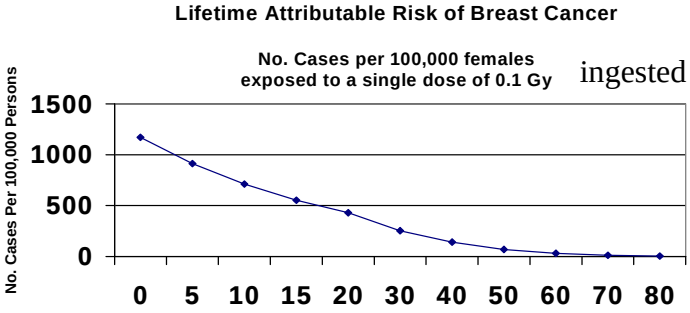
Radiation is energy that travels in the form of high-speed particles or waves. When radiation has enough energy to break chemical bonds in molecules or remove tightly bound electrons from atoms it is referred to as "ionizing" radiation. Ionizing radiation takes the form of energized sub-atomic particles such as protons, neutrons, beta particles (electrons), and alpha particles, and electromagnetic radiation in the form of x-rays and gamma rays. The types of ionizing radiation differ in their ability to penetrate the body. Most medical x-rays, gamma rays and neutrons are highly penetrating. In contrast, electrons and alpha particles are relatively non-penetrating and can affect internal organs only if the radiation source is inhaled, ingested, injected, or otherwise able to enter the body.

Exposure to ionizing radiation results from: (1) background sources, i.e., cosmic radiation from our sun and distant stars, and terrestrial radiation emitted during the decay of radioactive elements in rocks, soil, water, and the atmosphere; and (2) human-made sources, i.e., radioactive materials used in medicine, research, nuclear weapons, nuclear power, and other industries.

Estimates made as recently as 2006 attributed about 82% of total radiation exposure in the United States to background sources.[1] The largest background source of exposure to radiation is to alpha particle radiation from inhaled radon gas that collects in mines and poorly ventilated basements. However, a study by the National Council on Radiation Protection to be released in 2008 reportedly calculates that diagnostic imaging procedures have now displaced natural background radiation as the leading source of human exposure.[2] The per-capita dose of ionizing radiation from clinical imaging exams in the United States increased almost 600 percent from 1980 to 2006.[2] Consumer products, such as tobacco, certain building materials, television and computer screens, and smoke detectors, occupational exposure, nuclear fallout, and the nuclear fuel cycle are also human made sources of radiation that contribute to population exposure. However, exposures are not distributed uniformly over the population. An individual's exposure can vary above relative population averages, for example, due to increased use of radiation for medical purposes, smoking, working near ionizing radiation such as in medicine, mining, milling, nuclear power, or nuclear weapons industries; living in areas affected by weapons testing or planned or accidental releases from nuclear power plants or other nuclear facilities; and/or being a veteran exposed directly at a distance to nuclear weapons testing.[1]

The type of radiation affecting breast tissue is almost entirely by gamma rays and (to a lesser extent) neutrons from cosmic rays and terrestrial sources, and, in the case of the survivors of the nuclear weapons dropped on Hiroshima and Nagasaki, from those bombs, and from medical x-rays. However, the possibility that alpha particles can reach and therefore be emitted within breast tissue is not well described but cannot be dismissed. Historical exposures to alpha radiation among radium dial painters, who ingested radium in the course of using their lips to bring their brush tips to a point, resulted in the development of bone

sarcomas from radium in bone surfaces and bone matrix. The excess of breast cancer risk among radium dial painters has been ascribed to the penetrating gamma rays given off by the radium paint pot in front of the painters, not to the radium



Source: National Academy of Sciences, National Research Council Committee to AssessHealth Risks from Exposure to Low Levels of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation: BEIR VII – Phase 2. Washington, D.C.: National Academies Press, 2006: Table 12 D-1 p. 311

ingested while pointing the brush tips.[3] However, as radium is chemically similar to calcium, there is the potential that ingested or injected radium might end up in lactating breast tissue. The possibility that alpha radiation could impact breast cancer is also supported by the finding of a dose-related excess of breast cancer among German patients with tuberculosis of the bone who were treated by injection of Ra-224.[4]

Biologic Plausibility

Mechanism

Ionizing radiation is harmful to human health because it has sufficient energy to remove electrons from atoms and disrupt molecular bonds, for example in DNA. During the last decade, major advances have led to increased understanding of the molecular and cellular responses to ionizing radiation and of the nature of the relationship between radiation exposure and the types of damage that underlie adverse health outcomes.[1] The main effects of ionizing radiation on DNA are mediated by secondary electrons energized by interactions with gamma rays, x-rays, and neutrons (also possibly by any alpha particles emitted within breast tissue). The resulting DNA damage is handled by cellular repair mechanisms that are error-prone, often resulting in mutations. A single electron track can induce complex damage[5] and the number of electron tracks in a small amount of tissue is roughly proportional to the dose to that tissue. Additional mechanisms by which radiation may influence breast cancer risk include the creation of genomic instability and bystander effects on neighboring cells that are not directly exposed.[6] However, there is currently insufficient knowledge of adaptive responses, genomic instability, and bystander signaling among cells to incorporate these potential mechanisms in a meaningful way into modeling cancer risk.[1]

Radiation Dose and Cancer Risk

Radiation dose is measured in units called grays (Gy) or sieverts (Sv), which, when describing exposures from x-rays and gamma rays, are equivalent measures of the amount of energy deposited in living tissue. In 2006, The National Academy of Sciences (NAS), National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR VII) updated the estimated relationship between exposure to low levels of ionizing radiation and harmful health effects.[1] The NAS/BEIR VII report reaffirmed the prevailing model used for radiation risk estimates, that every exposure to radiation produces a corresponding increase in cancer risk. Excess cancer risk is well quantified for a given exposed population by a linear dose response over the range 200–2000 mSv. Continuing the linear dose-

response down to zero dose fits the data well, but dose-response data are, for statistical reasons, increasingly uninformative about excess risk per unit dose at very low doses.[1, 5, 7] In a review of the evidence for what is the lowest dose of x- or gamma-radiation for which good evidence exists of increased cancer risks in humans, Brenner et al concluded the epidemiological data suggest that it is approximately 10–50 mSv for an acute exposure and 50–100 mSv for a protracted exposure.[8]

Radiation exposures during infancy, childhood, and adolescence appear to confer the greatest increased breast cancer risks (Figure 1).[1, 9, 10] Breast tissue may proliferate from stem cells during adolescence and if some cells have previously been damaged by radiation there may be more chance for carcinogenesis to occur.[9]

The levels of radiation needed to induce human carcinogenesis may vary by whether the exposure is acute or chronic. There may be more time for DNA repair to occur when the exposure is given over a longer period.[11] There is also some evidence, based on very small numbers, that radiation exposure received during pregnancy may also convey highly increased risk to the exposed mother.[12] Pregnancy represents a highly estrogenic and proliferative stage of development. Postmenopausal breast tissue does not proliferate to the same extent, which may be why there is a smaller increased breast cancer risk with postmenopausal radiation.[9]

Genetic factors may also influence radiation-related cancer risk. Subgroups of women appear genetically susceptible to radiation-induced breast cancer. Certain genes, including BRCA-1, BRCA-2, ataxia-telangiectasia mutated gene (ATM) and CHEK2, are associated with increased breast cancer risk, and they appear to decrease the efficiency of DNA repair.[13-16] Women who are carriers of these genes exhibit increased breast cancer risk with exposure to diagnostic x-rays, especially to the chest, which may be due to the decreased ability to repair DNA damage following radiation exposures.[14-16] There are no published direct measures of the prevalence of clinically important BRCA-1 or BRCA-2 mutations in the general non-Jewish U.S. population; models have estimated the population prevalence to be less than one-half percent.[17]

Ataxia-telangiectasia (A-T) is a rare genetic disease that causes a hypersensitivity to radiation.[18] The ATM gene encodes a protein that plays a key role in the detection and repair of DNA double strand breaks.[19] An estimated one percent of the U.S. population, about two and a half million people, may be carriers for A-T (carriers have one normal and one mutated copy of the gene and usually do not know that they are carriers).[20] Some studies suggest that mutations on the ATM gene may be associated with greatly increased risk of breast cancer, however not all studies are consistent in this finding.[18]

The risk of exposure to ionizing radiation may also be modified by exposure to chemical agents.[21-24] The synergistic relationship between exposure to tobacco smoke and ionizing radiation is a well studied, albeit complex, example of how co-exposure to chemicals and radiation increases risk beyond additive effects.[21] Mineral dusts and fibers, including asbestos show supra-additive interaction with radiation at historical workplace exposure levels.[21] The interaction between radiation and chemical exposures is leveraged by cancer therapies

that irradiate tumors in combination with drugs that inhibit cellular repair of radiation damage.[21]

A 2000 review of the combined effects of radiation and other agents by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) describes many other chemicals present in the human environment that interact with radiation, and these examples and the limitations of the existing data are summarized in Table 1. In general, interactions between exposure to ionizing radiation and a wide range of agents having a variety of mechanisms of action have been demonstrated at high levels of exposure; it is difficult to infer the nature of potential interactions at levels of exposure encountered in the workplace and ambient environment from the existing data.

There is no guidance for conducting risk assessment for two agents with different mechanisms of action (i.e., energy deposition from ionizing radiation versus DNA interactions with chemicals) but similar biological endpoints (i.e., chromosomal aberrations, mutations, and cancer).[24] Of potentially greatest concern are interactions that are multi-step mechanisms for which two different agents would promote different steps that normally have low probability of occurrence, such as radon (initiation) and smoking (promotion).[23] UNSCEAR recommends that substantial evidence that hormones modify cancer risk be incorporated into radiation risk analyses.[21] In general, assessing the cumulative health risks from aggregate exposures to ionizing radiation and chemicals is an important area of future research.[24] As a supra-additive relationship between endocrine disrupting chemicals and radiation is biologically plausible, this interaction may be an untapped and productive avenue for breast cancer research.

Incidence and Etiology

Exposure to Nuclear Weapons

More is known about the relationship between radiation dose and cancer risk than any other human carcinogen, and female breast cancer is the most accurately quantified radiation-related cancer, according to Charles Land, Co-Chair of the National Action Plan on Breast Cancer's 1997 Workshop on Medical Ionizing Radiation. Much is known about the effects of radiation and cancer risk due to long-term studies of the survivors of exposure to nuclear weapons in Hiroshima and Nagasaki, Japan. For breast cancer in these women, the strength of the radiation dose response and the generally low level of population risk in the absence of radiation exposure provide a clear description of excess risk and its variation by age at exposure and over time following exposure.[25] The female survivors in this cohort had higher breast cancer risk that was strongly associated with dose,[26] and risk was highest in women who were less than 20 years old at the time of the bombings.[10, 26] Male atomic bomb survivors also exhibited a statistically significant association between ionizing radiation and breast cancer.[27]

Exposure to Ionizing Radiation in the Workplace and Community Environment

Further, albeit much weaker, evidence for an association between exposure to ionizing radiation and breast cancer comes from studies of workers who incur on-the-job exposure and community members living near nuclear power and weapons facilities. There

are many limitations to the interpretation of these studies (Table 2). Whereas increased incidence of breast cancer has been demonstrated among radium dial workers,[3] flight attendants[28-30] and radiologic technicians,[31] studies of (mostly male) nuclear workers have shown a weak or no association between exposure to radiation and breast cancer risk.[32-34] Moreover, it is important to note that Pukkala et al. state that the estimated cumulative cosmic radiation dose (15–20 mSv) to flight attendants would be expected to barely affect the relative risk at all (RR = 1.01) based on a linear low dose extrapolation from the A-bomb data and therefore conclude that cosmic radiation does not account for the excess risk in female flight attendants. Studies of populations living near nuclear weapons and power facilities exposed to radiation from unintentional and routine releases into the environment are also plagued by methodological limitations, and have demonstrated an impact on breast cancer risk in some (Chernobyl),[35] but not all (Hanford, Washington; Pennsylvania) communities that have been studied.[36, 37]

Exposure to Ionizing Radiation in Medical Diagnostic and Therapeutic Procedures

The use of ionizing radiation in medicine produces health benefits and also causes extra cases of cancer. Exposure to ionizing radiation for disease therapy and diagnosis has been linked to increased breast cancer risk across a variety of patient populations. Radiation-related treatments for tuberculosis in the 1930s and 1940s,[9] scoliosis, enlarged thymus glands, skin hemangiomas, and Hodgkin disease,[9, 47-49] and primary breast cancer[9] have all been linked to increased breast cancer risk. Radiation therapy for breast cancer has also been linked to the creation of angiosarcomas within the chest wall.[50] John et al. found increased risks for breast cancer among women who had radiotherapy for a previous cancer (OR = 3.55, CI = 1.47–8.54) and diagnostic chest x-rays for tuberculosis (OR = 2.49, CI = 1.82–3.40) or pneumonia (OR = 2.19, CI = 1.38–3.47). Risks were highest for women with a large number of exposures at a young age or exposed in earlier calendar years.[51]

Cancer risk in the general population due to routine use of medical x-rays has not been well studied.[15] One estimate is that in the United States 5,695 cancer cases (all types) annually are attributable to medical x-rays (cumulative risk up to age 75 years).[52] Computed tomography (CT) scans screen the whole body in a series of x-rays and result in more exposure than a single diagnostic x-ray. The estimated effective radiation dose from a CT scan is 12 mSv,[1] although the dose to breast tissue may be higher for certain procedures, (i.e. 20 mGy during pulmonary CT angiograms,[53] and there is the potential for high cumulative doses (i.e., ranging from 19 to 153 mSv in a six-year period among patients being treated for renal colic.[54] While CT use has increased substantially in the past decades, little is known about the possible long-term effects, and most physicians are unaware of the radiation risks associated with CT scans.[55]

Much more is known about the risks and benefits of using ionizing radiation for breast screening, although key questions of much practical importance remain unanswered. Whereas the average annual background dose to breast tissue is about 1 mSv, almost all of it from gamma rays with a relatively small contribution from neutrons, the average breast dose of radiation per single screening mammogram is about 3 mSv.[8] Lower energy photons, like the softer x-rays s used for mammography, have a greater effect per unit dose than higher-energy x-rays, like those used for chest x-rays, or the gamma rays from the use of nuclear weapons in Japan.[56]

Generally, the numbers of lives saved by mammography is presumed to outweigh the harm. Whereas mortality reductions from detected breast cancer appear to be greater than the radiation risks in women 50 years and over,[57] the risk/benefit for women below age 50 is not fully characterized, and this issue remains a source of debate.[58]

Reasons why the risk/benefit analysis of mammography is less clear for women age 40 to 49 include that breast tissue in younger women is denser making mammograms less effective,[59] and it is also more sensitive to radiation. Many studies have examined the efficacy of mammography screening in women under age 50 years. In a meta-analysis the summary relative risk was 0.85, showing a reduction in mortality.[57] However, a randomized screening trial of mammography conducted in Canada did not find that annual mammograms reduced breast cancer mortality in women age 40 to 49 years.[60] Another large observational study, however, also from Canada, found a relative risk of death of 0.6 for women having a first mammogram between 40 and 49; this study followed about 600,000 women in British Columbia from 1988 to 2003.[61] A recent analysis of the radiation risks compared to the decreased breast cancer mortality benefits in the United Kingdom determined that a relative risk of 0.8 (a 20% reduction in mortality) would be needed to outweigh the increased risks in this age group.[59]

The risk/benefit ratio for mammography may also be different for women under age 50 years who have a family history of breast cancer. Current consensus advises earlier mammograms for these women.[62] The benefits from mammography may be greater in these women, because of the greater probability of detecting life-threatening disease. However, the risks of mammography may also be greater for these women, some of whom may have inherited genetic factors that might make them more sensitive to radiation-induced breast cancer. Those women who are at most risk for breast cancer are precisely those who are often screened the most intensely and thereby exposed to the highest amount of ionizing radiation through early and frequent screening. There have been no randomized controlled trials of screening mammography specifically in younger women with a family history of the disease.[62]

Another factor that may modify the risk-benefit equation of mammography is reproductive status. Women who give birth at older ages, women who have never given birth, premenopausal women, and women with a history of benign breast disease may represent radiation susceptible subgroups.[12] Women who have never given birth are at higher risk of breast cancer, but their breasts are also physiologically more susceptible to radiation

damage. A case-control study of breast cancer among atomic bomb survivors found that interactions between reproductive history and radiation exposure (nulliparity, age at 1st full-term pregnancy, cumulative lactation, number of births) were consistent with a multiplicative interaction but not with an additive model.[25, 63] For example, an early age at 1st full-term pregnancy was protective against both baseline and radiation-related breast cancer risk, whether the pregnancy occurred before or after the exposure. On the other hand, the fact of being American (high baseline risk) or Japanese (low baseline risk) interacted additively with radiation dose (the increment in breast cancer rate per unit dose was approximately equivalent for high-risk Americans and low-risk Japanese).[64] The US-Japan difference in baseline rates is not genetic – Americans of Japanese descent tend to have rates comparable to those of other Americans – but whatever it is that is responsible for the difference appears to interact additively with radiation dose.

Regarding the interaction of dose with reproductive history, Russo et al found evidence suggesting that differentiated breast cells are less susceptible to chemical carcinogens,[65] and experimental studies have concluded that mammary cells differentiated for milk secretion are less susceptible to radiation carcinogenesis.[66, 67] The risks and benefits of irradiating lactating breasts is a matter of great interest and debate within the lactation community as well as the breast cancer community.

There are factors other than radiation to consider when evaluating mammography risks such as false positives and unnecessary biopsies.[57] Because it is difficult to quantify all of the potential risks and benefits of mammograms in women under age 50, various government and medical groups disagree upon the recommended age and frequency for early mammograms. The U.S. Preventive Services Task Force, the American Medical Association and the American Cancer Society support guidelines advising mammograms every one to two years for all women starting at age 40.[57] However, the Canadian Task Force on Preventive Health Care and the American Academy of Family Physicians recommend beginning mammography at age 50 and counseling women ages 40 to 49 about the risks and benefits.[57] The American College of Physicians recently recommended that for women between the ages of 40 to 49 years, physicians should periodically perform an individualized assessment of breast cancer risk, inform women of the risks and benefits of mammography, and base screening mammography decisions on the risks and benefits as well as a women's preferences and breast cancer risk profile.[68] In the United Kingdom women are offered mammograms every three years between ages 50 and 70.[59]

Summary and Research Directions

Ionizing radiation is a well-established, extensively studied carcinogen.[69] The prevailing model used for radiation risk estimates is that every exposure to radiation produces a corresponding increase in cancer risk, and exposures during infancy, childhood, and adolescence confer the greatest risks. The relationship between exposure to ionizing radiation and breast cancer risk has been clearly demonstrated in studies of the survivors of the nuclear weapons dropped on Hiroshima and Nagasaki. Further evidence comes from studies of individuals exposed to ionizing radiation at work, as a result of living near a nuclear facility, or due to

the use of radiation in medical diagnostic and therapeutic procedures.

The use of ionizing radiation for breast cancer screening and treatment and for other medical procedures produces health benefits and also causes extra cases of cancer. Cancer risk in the general population due to routine use of medical x-rays has not been well studied, and while CT use has increased substantially in the past decades, little is known about the possible long-term effects, and most physicians are unaware of the radiation risks associated with CT scans.Generally, the numbers of lives saved by mammography outweigh the harm; however the risk/benefit for women below age 50 is not fully characterized, and this issue remains a source of debate. Moreover, subgroups of women appear to be more susceptible to the harmful effects of radiation, for example due to inherited genes or reproductive status, and all together, these represent a large subset of the total number of women receiving annual mammograms.

Therefore, research is needed to improve our understanding of the relationship between low-dose exposure to ionizing radiation and breast cancer, and to identify, implement, and monitor policies and practices that ensure the benefits of the use ionizing radiation outweigh the harm. A key area of research is related to the possibility that genetic factors may modify radiation-related cancer risk. The National Research Council has recommended further study of gene mutations and functional polymorphisms that are involved in the body's response to radiation and cancer risk in order to better understand the DNA repair capacity, especially for the double strand and multiple stand breaks at low doses of radiation.[1] In addition, research is needed to assess the cumulative health risks from aggregate exposures to ionizing radiation and chemicals.[24] Because of the complexity of this problem, future research on breast cancer and radiation should involve a diverse group of scientists with expertise in molecular and clinical genetics, radiation biology, physics, medicine, and epidemiology.[18]

Increased understanding of the risks of low-dose radiation is also of much importance in that exposures are prevalent across issues as varied as screening tests for cancer, the future of nuclear power, nuclear weapons, occupational radiation exposure, and air travel. Epidemiologic studies of exposed occupational and community-based populations such as nuclear industry workers, radiologic technicians, and exposed community members near Chernobyl are needed and should include improved dose measurements to gain more insights into risks associated with low dose exposures.[1]

Research is also needed to identify and implement steps to reduce occupational exposure to ionizing radiation. Ionizing radiation is used extensively in a wide range of industries and while its use has grown significantly in recent years, for example in the use of x-rays in security screening, the U.S. Occupational Health and Safety Administration (OSHA) workplace exposure limits for ionizing radiation have not been updated since they were promulgated in 1971. Workers covered by the current OSHA regulations are permitted to incur annual exposures of 50 mSv (29 CFR 1910.1926), a level of exposure that corresponds to a cancer risk of 1 in 200.

Finally, many questions related to the use of ionizing radiation for medical diagnostic and therapeutic procedures remain unanswered. The use of radiation in breast cancer screening and treatment for subpopulations of women with increased susceptibilities to its harmful effects should be evaluated. Breast cancer advocates have called for alternative screening tools that do not expose the breast to a known carcinogen. There is also the related need to investigate the impact of exposure among people receiving CT scans and other x-rays, especially children.[1] The U.S. Food and Drug Administration (FDA) classifies medical x-rays as a known carcinogen although the agency does not monitor clinical practices other than mammography. The FDA should closely regulate all radiologic medical devices and create guidelines for maximum acceptable doses, acute and cumulative, especially for CT scans[55] Research is needed to identify ways to reduce the dose of radiation from CT scans,[55] minimize exposure to x-rays to girls' and young women's breasts,[9] include measured doses of radiation in patient medical records and calculate dose through the lifetime of each individual, quantify the exposure to the general population over time, and educate physicians about radiation risks.[55]

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Electric and Magnetic Fields (EMFs)

Introduction

Electromagnetic fields (EMFs) are invisible lines of force that surround any electrical device and are produced by the generation, transmission, and use of electric power. Electric fields are produced by voltage, while magnetic fields result from the flow of current through wires or electrical devices.[1] Interest in magnetic fields and breast cancer was initially sparked by reports of elevated breast cancer rates among men working in electrical occupations.[2-5] In addition, Stevens presented a hypothesis proposing that magnetic fields could suppress melatonin levels in the same way as light at night, thereby inhibiting a protective effect of melatonin on breast cancer risk.[6] These reports, in conjunction with ubiquitous magnetic field exposures in industrialized areas where breast cancer rates tend to be elevated, have led to a great deal of interest in the potential role of magnetic fields in breast cancer etiology. Despite considerable research over the last few decades, no consistent evidence, either experimental or epidemiologic, has emerged to support an association between magnetic fields and breast cancer. In addition, experimental research has not been able to consistently confirm the ability of magnetic fields to suppress melatonin production, as was suggested by some early studies. These results undermine support for a plausible mechanistic pathway by which EMFs could exert an etiologic effect.

Concept/Exposure Definition

The term EMF encompasses two distinct exposure fields – magnetic fields and electric fields, both of which are created by the generation, transmission and use of electric power. Because electricity is pervasive in our environment, so are EMF exposures. In the workplace, sources of EMF exposures include: electronic office equipment such as computers, fax and copy machines, scanners, and printers; fluorescent lights; security systems; and any kind of power tools, such as saws, sewing machines, and welding equipment.[1, 7] In the home, electrical appliances such as electric blankets, hairdryers, microwave ovens, electric shavers, air conditioners, electric heaters, television sets, vacuum cleaners, and toasters all generate EMFs.[1, 7] In addition to electronic and electrical equipment, the internal electrical wiring, meters, service panels, and grounding systems in a home or workplace also generate EMFs. Sources of EMFs exist outside of the residence or workplace and include high-voltage power lines, distribution lines, underground cables, substations, transformers, and transportation systems.[7]

The strength of both magnetic and electric fields decreases rapidly with increasing distance from the source.[1] Electric fields are easily shielded by materials that conduct electricity, even poor conductors such as trees, buildings, and skin. Magnetic fields, however, are not easily shielded and can penetrate buildings and human skin.[1, 8] Since magnetic fields are more likely to penetrate the body than are electric fields, most cancer research has focused on the magnetic component of EMFs.

Electric fields are produced by voltage and thus are only created from an appliance when the power is turned on. Since voltage in power lines typically doesn't change much, the electric fields

from power lines are relatively stable.[1] Magnetic fields, however, are created from the flow of electric current. Thus, magnetic fields from appliances are only generated when the power is turned on. Magnetic fields from power lines can fluctuate greatly as current changes in response to changing electrical loads.[1] Although magnetic fields near many electrical appliances are higher than near power lines, appliances contribute less to a person's total exposure to magnetic fields, because appliances are typically only used for short periods of time and not often used close to the body.[8] Furthermore, the magnetic field strength decreases more rapidly from point sources, such as appliances, than from power lines. Given the multiple potential sources and transient nature of magnetic field exposures, characterization of exposure is complex and challenging.

Because magnetic field exposures are imperceptible, they do not lend themselves to self-report. In most of the epidemiologic studies of cancer and magnetic fields conducted to date, crude proxy measures of exposure have been used. Occupational sources of magnetic fields have been based on job classifications, with or without supplemental field measurements. Residential sources of magnetic fields typically have been characterized by proximity to electric/transmission sites, self-reports of household appliance use, and/or estimated by characteristics of power lines outside of the home (i.e. wire codes or calculations of magnetic field levels generated by the power lines).

The development of fairly sophisticated magnetic field monitors in recent years has improved understanding of exposure in different occupations and in homes. A remaining limitation in assessing magnetic field exposures for a breast cancer study, however, is the lack of knowledge as to which attribute of exposure (e.g., frequency, intensity, peak, variations, etc.) is likely to be most biologically relevant.

Biologic Rationale/Mechanism

The leading biologic mechanism that has been explored with respect to magnetic field exposures and breast cancer is the melatonin hypothesis. In 1987, Stevens and colleagues first suggested that magnetic fields might increase breast cancer risk by suppressing melatonin output.[6] Initially, it was thought that decreases in melatonin would lead to increases in estrogen levels that would then increase breast cancer risk.[6] Other mechanisms mediated by melatonin also have been suggested, including a suppression of breast cancer by a melatonin-mediated boost in immune function and by direct suppression of breast cancer cell growth.[7] While substantial evidence now exists for a protective role of melatonin in breast carcinogenesis (see Section I, Chapter H, Light at Night), the evidence that magnetic fields can affect melatonin levels is, at best, equivocal.

Despite considerable research aimed at assessing magnetic fields' effect on melatonin levels, the evidence is inconsistent.[1, 7, 9-12] Among at least 60 laboratory animal studies, some have shown a suppression of melatonin associated with magnetic field exposures, while others have not. However, two interesting human breast cancer cell line studies showed that environmentally relevant magnetic fields interfered with melatonin's oncostatic action on MCF7.[13, 14]

Clinical studies of human volunteers exposed to EMFs in a controlled environment have reported no effect of magnetic fields on melatonin levels. Some studies of people exposed to magnetic fields at home or in their workplace have reported small reductions in melatonin levels, but these findings are difficult to interpret for several reasons. The effect has generally been confined to subgroups and the characteristics of the people in the subgroups in which effects were observed have varied between studies.[15-18] In addition, because there is no control for other factors that might affect melatonin levels in such studies, we don't know whether the melatonin reductions are due to magnetic fields, some other environmental or behavioral factor, or occupational exposure.[1, 7] The fact that similar reductions are not seen in the controlled clinical studies supports the supposition that some other exposure is the responsible agent. A few of these studies have suggested that magnetic fields' ability to suppress melatonin production may be limited to subgroups of women using exogenous estrogens or other prescription drugs,[15, 16] a possibility that, if confirmed, would be important.

A multitude of laboratory studies have been conducted to evaluate other potential mechanistic pathways for magnetic fields' potential carcinogenic effects outside of the melatonin pathway. Over 1,000 studies have sought to identify cellular effects associated with EMF exposures, including changes in cell proliferation and differentiation, gene expression, enzyme activity, and DNA damage. In its 2000 report of the health effects of EMFs, NIEHS reviewed this body of literature and concluded that there is "little convincing evidence of cellular effects of EMFs at environmental levels."[1] Furthermore, the NIEHS reported that most evidence to date "suggests EMF is not genotoxic."[1] The few studies that have reported evidence of genotoxicity have not been replicated. Given the lack of evidence for any direct genotoxic effect, some investigators have focused on multistage carcinogenesis studies in rodents to assess whether EMFs exert promotional effects on breast carcinogenesis after genetic damage has been induced by known carcinogens such as UV light, by chemical carcinogens, by radiation, or in mice genetically pre-disposed to mammary tumors. While the data are still sparse and results fairly mixed, some of these studies have suggested a cancer-promoting effect of EMFs.[1, 10] In an intriguing example of possible interactions between EMFs and other exposures, Loscher and colleagues in Germany (e.g., Mevissen et al. 1996;[19] Thun-Battersby et al. 1999[20]) have consistently reported that exposure to an environmentally-relevant magnetic field increases chemically-induced mammary tumor formation in rats. This result was not replicated by two other labs,[21, 22] but the choice of rat strain may be the difference.[23, 24] Little or no further work has been conducted in the U.S. on this potentially important science.

In summary, the biologic evidence to date of a mechanism for magnetic field exposures inducing breast carcinogenesis is weak. While the 'melatonin hypothesis' initially provided a theoretic framework for a potential effect, laboratory research generally has not supported this hypothesis. Melatonin levels in humans do not appear to be affected by magnetic field exposures. There is substantial evidence that magnetic fields are not genotoxic and no physiologic effects at the

cellular level consistent with tumor initiation have been consistently identified. There is some evidence that magnetic fields could play a role in cancer promotion or interact in some way with other exposures, but so far that evidence is limited.

Review of the Epidemiologic Literature

In the last five years, a number of national and international agencies have reviewed the literature on the health effects of magnetic field exposures and published reports summarizing their findings.[1, 10, 25] Additionally, a number of review articles have appeared in the peer-reviewed scientific literature discussed below.

As part of the state of California EMF Program's review of the literature, Erren and colleagues conducted a meta-analysis of magnetic fields and breast cancer, including all relevant studies published through January 2000.[11] Risk estimates from the 24 studies that reported on breast cancer and magnetic fields in women ranged from 0.6 to 1.64, with a pooled estimate of 1.12 (95% CI = 1.09–1.15). There was, however, substantial heterogeneity of results, with 14 studies reporting relative risks between 0.9–1.2, five reporting risk estimates below 1.0, and five reporting risk estimates greater than 1.35. Sample sizes tended to be small and confidence intervals wide, with only five of the 24 studies yielding confidence intervals that did not include one. There was significant heterogeneity in results, such that variations in findings between studies were greater than those expected by chance (*p* value = 0.035). Thus, despite the significantly elevated pooled estimate of risk, the author stated that "it is premature to conclude that the observations reflect a real, rather than an artifactual association," citing the lack of consistency in study findings, doubts that differing indices of exposure really capture the same phenomenon, and concerns about inadequate covariate adjustment.[11]

This conclusion has been echoed by all the major reviews conducted to date.[1, 7, 10, 11, 25, 25-28] While lack of experimental evidence to support the hypothesized biological mechanism (as discussed previously) is central to the conclusions made in these reviews, the lack of consistent epidemiologic evidence is also cited. The primary limitations in the epidemiologic studies include: incomplete or indirect exposure assessment; limited ability to control for confounding factors; and small numbers of cases. Epidemiologic investigations of magnetic fields and breast cancer have tended to focus either on occupational or residential sources of exposure. Only two studies to date have incorporated exposures across both the home and workplace.[29, 30]

Since the publication of the large-scale reviews by IARC, NIEHS, and the California Department of Health Services (which included the meta-analysis by Erren), a number of additional epidemiologic studies of magnetic fields and breast cancer have been published. While these more recent studies tend to have more comprehensive exposure assessment methods, they continue to generate inconsistent, but generally null, findings. Six of these studies have focused on residential exposures[30-35] and most have vastly improved on the exposure measures of the earlier studies.

The first of these, a case-control study conducted in Seattle and published in 2002 by Davis and colleagues, used several different metrics of magnetic field exposure, including survey data to

collect information on household electrical appliance use, nighttime spot measurements of magnetic fields in subjects' bedrooms in the home in which they lived at the time of study enrollment, and wire coding of current and all residences within the previous ten years.[32] None of these exposure measures was significantly related to breast cancer, either in the whole study sample or among subgroups of interest (e.g., defined by tumor estrogen receptor status, menopausal status). The odds ratio for the highest quartile of mean nighttime magnetic field measurements in the bedroom was 0.9 (95% CI = 0.7–1.3); for highest quartile of estimated exposure based on wire codes was 0.8 (95% CI = 0.5–1.3); and for highest quartile of estimated exposure based on appliance use was 1.1 (95% CI = 0.8–1.5).

A later analysis of data from the Multiethnic Cohort in Los Angeles used a similar approach, collecting both measured nighttime magnetic field values in subjects' homes at study entry, as well as wire coding for every residence during the previous ten years.[31] Similar to the Seattle study, no significant findings were reported for either of these magnetic field exposure metrics with an odds ratio of 0.76 (95% CI = 0.49–1.18) for the highest exposure category based on wire configuration and an odds ratio of 1.31 (95% CI = 0.82–2.09) for the highest quartile of mean measured nighttime magnetic field levels.[31]

While the exposure assessment in these studies is improved over earlier studies, no 'perfect' metric has been utilized. The magnetic field measurements probably better capture actual personal exposures experienced during nighttime (the most biologically relevant time if melatonin is the mechanistic pathway), but they are limited in that they cannot estimate prior exposures. Conversely, the wire coding estimations were calculated for ten-year periods, but the degree to which they reflect actual personal exposures of subjects is not known. In fact, Davis et al. reported that in their study, the wire codes of the current house did not correspond well to the measured values in the home (Spearman Rank correlation coefficient = 0.26; $p < 0.001$).[32]

In a similar study of magnetic fields and breast cancer conducted on Long Island, NY, researchers also collected a plethora of exposure data, including survey information on electric appliance use, both spot and 24-hour magnetic field measurements at various locations in the home, as well as estimated exposure based on wire codes.[34] A previous analysis of the exposure data used in this study demonstrated a high degree of correlation between 24-hour measurements and estimations based on wire codes.[36] Furthermore, this study had the added advantage of being limited to a population of women who had lived at their current residence for at least 15 years. Thus, the measured values in the home at study entry are likely to capture historical exposures, at least to the degree to which measured values of magnetic fields have not changed for a given residence over time. This study's results were also null. The odds ratio for the highest estimated exposure from wire codes was 0.90 (95% CI = 0.54–1.48); the odds ratio for the highest quartile of 24-hour magnetic field measurements was 0.97 (95% CI = 0.69–1.37) in the bedroom and 1.09 (95% CI = 0.78–1.51) in the most lived-in room.

In contrast, a population-based study coming out of Norway recently reported a nearly 60 percent increase in risk of breast cancer associated with residential magnetic field exposures estimated as fields generated by nearby high-voltage power lines (OR = 1.58, 95% CI = 1.30–1.92), although no consistent dose-response pattern was found.[30] Magnetic field exposures were estimated for all residences during the follow-up period (minimum of 13 years) and were expressed as the time-weighted average across all residences. These associations were seen in women with both ER+ and ER- tumors and among both pre- and post-menopausal women. While the strength of this study is its ability to estimate historical residential exposures from high-voltage lines, it is limited by its inability to incorporate information on other sources of residential magnetic field exposures and its lack of measured values of exposure. The authors do note that a previous Norwegian study using similar exposure assessment techniques showed that the magnetic fields from power lines were the major source of exposure among children living close to a power line.[37]

Two other recent studies examined the risk of electric blanket/bedding devices and breast cancer risk, one reporting an association (OR = 4.9, 95% CI = 1.5–15.6 for ≥ 10 years of usage)[35]and one reporting a statistically non-significant increased risk in pre-menopausal, but not post-menopausal, women (OR = 1.4, 95% CI = 0.7–2.6 in pre-menopausal women and OR = 0.8, 95% CI = 0.5–1.3 in post-menopausal women with ≥ 10 years of usage).[33] Reasons for the disparate findings are not immediately apparent but are in keeping with the inconsistent findings of previous studies published on this exposure, some of which have reported an effect,[38, 39] while others have not.[40-43] The authors of the recent positive study,[35] which was conducted among African Americans, note that their findings are consistent with two previous studies on occupational magnetic field exposures involving African American women, which found a stronger association between exposure and breast cancer in African American women than in Caucasian women.[44, 45] The authors of the recent study speculate that African American women may be more susceptible to magnetic field exposures.[35] It is worth noting, however, that the magnetic field analysis in the L.A. Multiethnic Cohort by London and colleagues did not see an effect in any racial/ethnic group, including African Americans.[31]

Five additional studies of occupational magnetic field exposures and breast cancer recently have been published.[46-50] These studies generally addressed a number of the limitations cited in the reviews by IARC and others, including better control for confounding, more refined exposure assessment methods, and evaluating risks in subgroups that may be more susceptible to magnetic field effects.

In a population-based case control study from the U.S.,[50] magnetic field exposures were assessed using a combination of job titles and measured magnetic fields to estimate occupational exposures for six broad categories of occupation. Approximately 200 study volunteers wore personal magnetic field monitors and filled out a questionnaire about occupation. Cumulative measures of exposures were then estimated for all study participants, based on the two longest-held jobs. The association for cumulative occupational

magnetic field exposures was not statistically significant (OR = 1.2, 95% CI = 0.8–1.7 for the 90th percentiles versus 30th percentiles of exposure).[50]

In a Swedish study that included 20,400 breast cancer cases identified from the population registry, researchers linked study participants' occupational histories to a new job-exposure matrix specifically designed to estimate magnetic fields in occupations common to women (previous job-exposure matrices had been developed only for men). The job-exposure matrix was created by measuring magnetic field exposures in 49 of the most common jobs held by women, covering approximately 85 percent of women employed in Stockholm. This study reported that all risk estimates examined, regardless of the choice of cut-points or exposure parameters, were close to unity, with an overall odds ratio of 1.01 (95% CI = 0.93–1.10) for women exposed to 0.30+ μT.[49] The large size of this study allowed for good precision in subgroup analyses.

In contrast, three recent studies reported an excess of breast cancer associated with occupational magnetic field exposures.[46-48] In a case-control study nested within a cohort of Norwegian female radio and telegraph operators, exposure estimates were based on years and workload according to ship type, an assessment that could not separate exposure to extremely low frequency magnetic fields from radiofrequency fields or light at night.[48] The study reported a statistically significant trend of increased breast cancer risk with increasing cumulative exposure. Stratified analyses showed an increased risk of estrogen-receptor-positive breast cancer in women under age 50, while the older age group had an elevated risk of estrogen-receptor-negative breast cancer.[48] The other two studies, one a hospital-based case-control study conducted in Canada,[47] and the other a U.S. population-based case-control study,[46] used occupational surveys reviewed by industrial hygienists to assign exposure categories. The U.S. study, which included over 6,200 cases and nearly 7,400 controls, reported a modest increase in risk compared to background levels that ranged from 1.06 in the lowest-EMF-exposure category to 1.16 in the highest category. While point estimates for each exposure level did not achieve statistical significance, there was evidence for increasing risk with increasing exposure (*p* value for trend = 0.03). A number of specific job titles were also evaluated. Data entry clerks were the only group to have a statistically significant increased risk (OR = 1.47; 95% CI = 1.06–2.04).[46] The Canadian study, which was limited to post-menopausal women, found an elevated risk associated with lifetime occupational exposures to magnetic fields in women who were exposed before the age of 35 among cases with progesterone-receptor-positive tumors. A similar, although not statistically significant, risk was found for estrogen-receptor-positive tumors. Most of the highly exposed women in the Canadian study were sewing machine operators and textile workers.

Overall, the epidemiologic evidence generally does not support an association between magnetic field exposures and risk of breast cancer. Early studies on this topic were limited by small numbers, crude measures of magnetic fields, incomplete control for confounders, and inability to evaluate risks in potentially susceptible

subgroups. Later studies have generally addressed these limitations with much larger sample sizes, more comprehensive measures of magnetic field exposures (incorporating some actual measurements), control for most known risk factors for breast cancer, and subgroup analyses. These later studies continue to provide equivocal results. The evidence for an association between breast cancer and residential exposures is particularly weak. Studies that have examined risks in particular subgroups have reported excess risks in some subgroups, but not in the same subgroups across studies.[26] This suggests these may be chance findings.

Occupational studies have provided some slightly more provocative findings, although in these studies, too, occasional positive findings are often confined to subgroups within the studies. Furthermore, these studies generally suffer from the inability to consider other occupational exposures of potential importance. One such exposure of intense recent interest is light at night, which has been hypothesized to operate via melatonin suppression, and has been shown much more convincingly to affect melatonin levels than EMFs (see Section I, Chapter H, Light at Night).

Conclusions and Future Directions

Overall, there is a lack of evidence for an association between magnetic field exposures and breast cancer etiology in women. The lack of evidence is not from lack of effort. Hundreds of studies, both experimental and epidemiologic, have been conducted to evaluate this association. While the earlier studies suffered from major limitations, later studies—with large sample sizes, improved exposure assessment, and sufficient statistical power—do not provide evidence of association. A new insight into mechanism, a new exposure assessment strategy, or the identification of a different group of highly-exposed women for study would likely be needed to change the balance of evidence in this field.

Further epidemiologic evaluations of residential EMF exposures are especially unlikely to be fruitful. Exposure levels in the home are typically much lower than are those experienced in occupational settings and are difficult to estimate retrospectively.

Occupational studies also are difficult, given that, historically, few women have been employed in occupations known to have high levels of EMF exposures. Recent efforts have been made to identify high-EMF occupations dominated by women and to characterize EMF exposures in those occupations. Female-dominated occupations with high EMF exposures recently identified in a large occupational exposure study among Swedish women included: cashiers, working proprietors in retail trade, flight attendants, dental nurses, cooks, post-office clerks and kitchen maids.[51] Additionally, seamstresses, (who typically do not work in the garment industry in Sweden), were not identified as highly exposed in this study. But seamstresses have been reported to have some of the highest EMF occupational exposures among female workers in other studies.[52] If an interest in EMFs persists, a focus on the occupations posing the greatest potential exposures to EMFs among women may be warranted. Studies within these high-exposure occupations, utilizing measured EMF levels, and controlling for other occupational exposures, may prove worthwhile.

Ultimately though, the ability of epidemiologic studies to detect EMF-related breast cancer risks hinges on the ability to better elucidate the etiologic framework by which EMFs could affect breast cancer risk, so that exposure measurements are relevant to a biological mechanism. The biggest limitation of most epidemiologic studies to date has been inadequate exposure assessment. With the development of hand-held EMF exposure monitors, this limitation is no longer about instrumentation but about knowledge. We still do not know what attribute of magnetic field exposures might be most etiologically relevant. As Dr. Feychting notes in her 2005 review of the literature, the "absence of a clearly elucidated, robust, and reproducible mechanism of interaction of EMFs with biological systems deprives epidemiologic studies of focus in their measurement strategies."[28] Thus, substantial misclassification of exposure in epidemiologic studies is likely. Given the large body of experimental data that has not yet been able to identify a plausible biologic mechanism by which EMFs could affect breast cancer, new evidence of an underlying biologic mechanism should precede future epidemiologic investigation.

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I.H. Light at Night

Introduction

Breast cancer incidence rates vary dramatically across geographic regions, both internationally and within the U.S..[1, 2] The observation that breast cancer rates are higher in more urbanized areas,[3, 4] coupled with the slow but persistent increase in incidence rates during the latter half of the last century,[2, 4] has led breast cancer researchers to investigate etiologic factors related to industrialization. Electricity is a fundamental hallmark of industrialization and a great deal of interest has focused on the potential health effects of exposures to artificial light at night and electromagnetic fields (EMF) associated with the advent of widespread electrical usage.[5]

Early work in this area was more focused on EMF exposures. Recently, however, attention has been redirected towards the role of exposures to light at night, because epidemiologic studies of shift workers have provided compelling results that light at night may be a risk factor for breast cancer. Laboratory studies have also provided a strong biologic rationale for an effect. Furthermore, the U.S. and other industrialized nations are moving towards '24-hour societies.'[6] As the number of people employed in alternative work schedules increases,[7] exposures to both occupational and environmental sources of light at night will increase.

Most work to date has been focused on breast cancer incidence, with little attention paid to the other outcomes on the breast cancer continuum. There is, however, evidence emerging that light at night (and corresponding levels of melatonin, the hormone that mediates the body's response to light at night), may affect disease progression and thus could provide avenues for new treatment regimens.

Concept/Exposure Definition

The idea that light at night may increase breast cancer risk is predicated on earlier hypotheses surrounding the role of melatonin output by the pineal gland in breast carcinogenesis.[8] Stevens and colleagues suggested that if high levels of melatonin could decrease breast cancer risk, then light at night, by lowering levels of melatonin, could increase breast cancer risk.[5, 9]

While substantial evidence exists that exposure to light at night suppresses nocturnal production of melatonin by the pineal gland,[10-15] there is uncertainty as to how much and what kind of light is necessary to produce a clinically-relevant reduction in melatonin production. Melatonin suppression will likely depend on the color of the light, its intensity, and the duration of the exposure.[15] Laboratory evidence suggests that even relatively dim light (such as that equal to twice the illumination provided by a full moon) can suppress nocturnal melatonin production in animals.[15] Recent evidence in humans suggests that melatonin production may be especially sensitive to blue light at levels as low, or lower than, those documented in rodents.[16] This is an important area of further inquiry.

Epidemiologic studies have used a wide variety of approaches to characterize exposure in evaluating this hypothesis, some of which focus more on light-at-night exposures (or surrogates thereof), while others focus more directly on melatonin

levels. Incidence studies of breast cancer have been conducted among blind women who lack light perception and thus experience no light at night. Other researchers have relied on occupations that typically involve a great deal of night-shift work, such as nurses and flight attendants. Some of these studies have information on duration and frequency of night-shift work,[17-19] while others have relied on occupational titles as proxies for nighttime work.[20, 21] Other investigators have used sleep times and durations as a proxy for exposures to light at night.[17, 22, 23]

A number of epidemiologic studies have aimed to more directly address a link between melatonin levels and breast cancer. Most of the earlier studies were case-control studies that relied on measurements of plasma concentrations of circulating melatonin collected at the time of, or after, diagnosis.[24-28] Thus, while these studies generally found lower levels of plasma melatonin in cases than in controls, they were unable to distinguish whether such differences were a cause or a consequence of breast cancer.

Recently, two prospective studies have been published that have relied upon urinary, rather than plasma, measures of melatonin.[29, 30] Sulphatoxymelatonin (aMT6), the primary metabolite of melatonin, is excreted in the urine, and correlates well with plasma melatonin levels (as discussed by Schernhammer et al.[31]). Urinary measures of aMT6 appear to be particularly good at capturing peak nocturnal levels of plasma melatonin,[32] which is thought to be the most biologically relevant metric. Furthermore, there is evidence that spot measurements of aMT6 can provide reasonably reliable estimates of chronic plasma melatonin levels, at least over a span of several years.[31, 33] These measures have the advantage of being less invasive and easier and less expensive to collect, making them more useful in prospective study designs. The potential disadvantage of using urinary aMT6 levels is that this is a somewhat less direct measure of melatonin output from the pineal gland; aMT6 levels may be affected by individual differences in melatonin metabolism.

Finally, the most comprehensive evaluation of exposures comes from animal studies, which have the ability to measure both light at night and plasma melatonin levels simultaneously. Furthermore, the effect of these exposures can be examined in conjunction with the effects of pinealectomy, blindness, and the administration of exogenous melatonin. It is from these studies that some of the most convincing evidence has arisen (see subsection on biologic plausibility below).

Biologic Plausibility

There are several lines of evidence that support the biologic rationale for a connection between light at night and breast cancer etiology.[34, 35] Most of this evidence is directed at testing the hypothesis that light at night suppresses the pineal gland's production of melatonin, which, in turn, stimulates mammary carcinogenesis. The most convincing evidence supporting this hypothesis arises from a large body of laboratory studies, mostly in rodents. These studies have shown that both removal of the pineal gland and exposures to constant light can independently result in an increase in mammary carcinogenesis, while administration of exogenous melatonin and light deprivation decrease mammary carcinogenesis.[10, 12] That these

relationships may also exist in humans is bolstered by the observations that melatonin receptors are present in both normal and tumor tissue in the human breast, that melatonin levels are lower in breast cancer patients than in women without breast cancer, and that nocturnal melatonin levels are suppressed by exposure to light at night.[36, 37]

In 2005 a landmark paper was published by Blask and colleagues that pulled together these different threads of evidence and provided compelling data to support the hypothesis that light at night, mediated by a suppression of melatonin, promotes carcinogenesis in human breast tissue.[38] By measuring the response of rats bearing human breast cancer xenografts to increasing intensities of ocular light exposures during normal periods of darkness, Blask was able to demonstrate a dose-dependent suppression of nocturnal melatonin levels, as well as a dose-related increase in tumor growth rates. Furthermore, the time to tumor onset decreased as the light intensity increased. Perhaps more importantly, though, this study also measured the responses of the human breast cancer xenografts to perfusion in situ with blood from pre-menopausal women collected during the day, at night, and at night following 90 minutes of light exposure. As predicted, melatonin levels were substantially higher in the nighttime-collected blood, compared to both the daytime collected blood and the blood collected at night following 90 minutes of light exposure. Furthermore, they found that the tumors perfused with daytime-collected blood exhibited high-proliferative activity, compared to those perfused with nighttime-collected blood. The breast cancer xenografts that were perfused with human blood collected after 90 minutes of light at night exhibited the same high-proliferative activity as those exposed to daytime-collected blood. Finally, to test whether these effects were mediated by melatonin, the investigators added melatonin to the melatonin-depleted blood that was collected after 90 minutes of light-at-night exposures and found that the high-proliferative activity was prevented. These results, while needing to be replicated, provide some very strong evidence that light at night, through the suppression of melatonin output, stimulates breast carcinogenesis.

Initially, the mechanistic pathway by which melatonin was thought to inhibit breast carcinogenesis was through its ability to reduce levels of circulating estrogens.[39] Evidence for this pathway has been somewhat mixed.[31, 37, 40, 41] Furthermore, recent positive findings for other cancers[42] suggest effects may not be mediated (or entirely mediated) by melatonin's effect on estrogen levels. Consequently, researchers are now considering a number of other potential pathways for melatonin's inhibitory effect on breast carcinogenesis. These are nicely summarized in four recent review articles.[12, 34, 43, 44] Mechanisms receiving the most attention include:

1. a direct anti-proliferative effect, mediated by lowered levels of estrogen
2. increased immune response
3. antioxidant activity, scavenging free radicals
4. changes in the metabolism of linoleic acid by tumor cells

5. modulation of cell life cycle length through the p53 pathway

In summary, the biologic plausibility for an etiologic effect of light at night is strong and generally supported by a large body of laboratory evidence. While the data generally support the idea that the effects of light at night are mediated by reduced output of melatonin, the exact pathway by which melatonin exerts its inhibitory effects remains to be determined. There also is growing interest in other hormones that are controlled by circadian rhythms that could be disrupted by exposures to light at night. These include cortisol, dopamine, somatotropin and growth hormones.[22] To date, little is known about the role of these hormones in breast cancer etiology. Evaluation of the role of pineal peptides has also been suggested as a course of further study.[12] There is some evidence emerging that these polypeptides, which have been found in the pineal gland and whose biologic function is largely unknown, may have antigonadotropic and tumor-inhibiting activity.[12] Finally, while most rodent studies have shown a strong and positive association between light exposures and mammary tumors, one recent study found the opposite was true.[45] This recent study began the light exposures later in life (the equivalent of human adolescence), which suggests there may be a window of vulnerability to light exposures. This avenue of inquiry deserves further attention.

Critical Review of the Literature

Literature to date on this topic has almost entirely focused on incidence and etiology. There are only a limited number of epidemiologic studies that have used a wide range of approaches, but these have produced remarkably consistent results overall. The comparatively large body of laboratory studies also supports a relationship between light at night/melatonin and breast cancer risk. There is some evidence, mostly from laboratory studies, which suggests light at night/melatonin can affect disease progression, and thus may ultimately be useful in breast cancer treatment.

Incidence

Epidemiologic studies addressing this question fall into several categories: occupational studies; studies of blind women; studies of sleep duration/timing; and studies of melatonin levels. Findings for each are summarized below.

Occupational Studies

The majority of occupational studies examining light at night and breast cancer risk are focused on airline flight crews.[46-52] Originally the rationale for looking at cancer incidence among flight attendants was based on concern over the elevated levels of cosmic radiation experienced by these workers. After publication of initial findings, it was suggested that the reported increases in risk of breast cancer also could be due to melatonin deficiencies resulting from occupational exposures to light at night.[53] A recent meta-analysis of the seven flight attendant studies published up to 2005 reported an elevated risk of breast cancer with a summary standardized incidence ratio (SIR) of 1.44, 95% C.I. 1.36-1.61.[43]

All of these studies were retrospective cohort studies using linkage of pre-existing data sources. Specific details of night-shift work were not

available, nor was information on most breast cancer risk factors. Thus, the results from these studies are remarkably consistent, but are limited by lack of good 'exposure' data, small numbers (the largest study had 60 cases of breast cancer), and inability to completely control for other breast cancer risk factors. Since the publication of this meta-analysis, results have been published from a small nested case-control study which sought to evaluate breast cancer risks associated with lifestyle and occupational factors among a group of airline cabin attendants.[54] This study, which was relatively unique in its ability to control for other breast cancer risk factors, reported a slightly increased risk of breast cancer in cabin attendants who reported disruption in sleep rhythms ("sometimes or often" compared to "never"), but this finding was not statistically significant.

As a whole, the flight attendant studies have not been able to directly assess the role of light at night on breast cancer risk. They were, however, the first group of occupational studies in women to suggest that disruptions in circadian rhythms may impact risk. The rationale for the early studies of breast cancer in flight attendants was based on putative elevated exposure to cosmic radiation. Pukkala et al.[49] specifically addressed this possibility. They calculated the cumulative excess radiation exposure for the study subjects on the basis of low-dose extrapolation from the Japanese atomic bomb cohort and estimated that radiation would yield a relative risk of 1.01, not close to the 1.87 they observed.

The other occupational group that has received considerable attention in this arena is nurses. The results from these studies also suggest an increased risk of breast cancer associated with night-shift work. In both the original Nurses Health Study (NHS), a prospective study of breast cancer in predominantly post-menopausal women, and in the Nurses Health Study II, a companion study focused solely on pre-menopausal women, nurses who worked rotating night shifts for many years had a higher incidence of breast cancer.[18, 19] In the NHS, which included both pre- and post-menopausal women, a moderate increase in breast cancer risk was observed, with risks increasing with increasing duration of rotating night-shift work (RR = 1.36, 95% CI = 1.04–1.78 for 30+ years of night-shift work, p-trend = 0.02).[18] These results were similar, although no longer statistically significant, when the data were stratified by menopausal status. Case counts, especially for the pre-menopausal group, were very small.

In the NHS II, which was limited entirely to pre-menopausal women, elevated rates of breast cancer were observed for the highest duration of night-shift work (RR = 1.79, 95% CI = 1.79, 1.06–3.01 for 20+ years), but there was no evident trend of increasing risk with increasing years of night-shift work (p-trend = 0.65). These results were based on small numbers, with only 15 cases in the highest exposure category. Similarly, a large prospective study of Norwegian nurses also reported an increased risk of breast cancer associated with working nights for 30+ years.[55] These prospective studies generally had good information on potential confounding by established risk factors, though no effort was made to investigate possible confounding by exposures to the many chemical agents in medical settings, including sterilants, solvents, and therapeutic

agents, many of which are animal mammary carcinogens or hormonally active. Detailed information on duration and frequency of night-shift work is a strength of these studies.

The evidence of an increased risk of breast cancer associated with night work from population-based studies is a bit more mixed. Both a Danish study[20] and a Seattle study[17] reported increased risks of breast cancer among women who worked at night. In contrast, a study conducted among participants of the Electromagnetic Fields and Breast Cancer on Long Island Study reported that women who worked non-day shifts were not at increased risk (OR = 1.04; CI = 0.79–1.38); a post-hoc analysis found that for evening-shift work, the OR was 1.08 (CI = 0.81–144) and for night work, the OR was reduced, at 0.55 (CI = 0.32–0.94).[56] Reasons for these disparate findings are not readily apparent, although each of these studies relied on slightly different definitions of night-shift work and considered different windows of exposure, with the Seattle study considering shift work only within the last ten years, the Long Island study considering shift work within the prior 15 years, and the Danish study considering shift work over a lifetime.

Finally, two studies have approached this issue from an entirely different angle by studying women who are in darkness most of the day. Both of these studies reported reduced risks of breast cancer among photo processors, who typically work in darkness for several hours during the day.[57, 58]

In summary, although the number of epidemiologic studies conducted to date is limited, there is consistent evidence that women who work at night are at an increased risk of breast cancer. This is supported by data from a number of occupations that are not likely to share any other common exposures (i.e., nurses, telegraph operators, flight attendants), with the possible exception of ionizing radiation exposures, which are likely to be high in flight attendants and among some nurses. Many of these studies, in particular the flight attendant studies, did not have full information on established breast cancer risk factors. While it is possible that at least some of the excess risk is due to incomplete control for confounding, it is unlikely to fully explain the elevated risks among nighttime workers. In the meta-analysis of 13 studies on night shift work and breast cancer performed by Megdal et al., the summary risk ratio for the seven flight attendant studies was virtually the same as that based on the remainder of the studies, which, for the most part, were adjusted for the main breast cancer risk factors.[43]

Aside from possible confounding by established breast cancer risk factors, other characteristics of night-shift workers might underlie the associations with breast cancer risk. There has been emerging interest surrounding the hypothesis that vitamin D from sunlight exposure may reduce breast cancer risk (see Section 1, Chapter E). The degree to which night-shift workers may suffer from reduced sunlight exposure has not yet been investigated in this regard. It is possible that women working on a permanent night-shift schedule may be better able to adapt and less likely to experience circadian disruption than women who work rotating night shifts; further evaluation of whether permanent and rotating night-shift work confer the same risk may be

fruitful. The intriguing, although preliminary, findings of reduced risk of breast cancer among photo-processors deserves further attention.

There have recently also been studies of hormone production in shift workers. Four studies have reported melatonin production to be reduced in shift workers.[31, 59-61] One of the studies also reported elevated estrogen levels, [31] although the others did not.

Studies of Blind Women

Much of the early interest in light at night was fueled by the observation of lower breast cancer incidence among blind women.[62-65] The reduced risk of breast cancer among blind women appears to be limited to the totally blind and severely visually impaired,[62, 65] although one study reported reduced risks across most categories of visual impairment and a decreasing trend with greater level of impairment.[64] Generally, the results from these studies are consistent with a hypothesized reduced risk of breast cancer in blind women due to higher levels of melatonin secretion by the pineal gland in response to the lack of ocular light perception.[62, 66] These studies, however, tend to be limited by small sample size and lack of information on other breast cancer risk factors that may co-vary with visual impairment. Information on nulliparity, a well-established risk factor for breast cancer was available from one study, which suggested that blind women are much more likely to be nulliparous than sighted women.[65] This would increase, not decrease, breast cancer risk. Future incidence studies of breast cancer among blind women would be strengthened by incorporation of measured levels of circulating melatonin, greater sample sizes, and information on age of onset of visual impairment and on other breast cancer risk factors.

Studies of Sleep

Another approach to evaluating the melatonin hypothesis has been to examine sleep habits in relation to breast cancer risk. To date, two case-control studies have been published on the risk of breast cancer associated with sleep habits and the lighting of the bedroom environment, yielding conflicting results.[56, 67] The study conducted in Seattle found an increased risk of breast cancer among women who frequently experienced 'non-peak sleep' (i.e., they did not sleep between 1 and 2 a.m., when nocturnal melatonin levels are typically at their highest). They found no association between breast cancer risk and several measures of bedroom light exposures, including number of times during the night that the subject turned on a light, the percentage of time that a light was on in the bedroom, and reported ambient levels of light in the subjects' bedrooms.[17] In contrast, the study conducted on Long Island reported no association with non-peak sleep (defined in the same way as the Seattle study), but an increased risk associated with frequency of turning on a light during sleep hours.[56] Reconciling these findings is difficult, as the exposure definitions used in these two studies are quite similar, although the time period for the Long Island study was more recent and shorter than that examined in the Seattle study.

Using a slightly different approach, a Finnish cohort study examined sleep duration with respect to breast cancer risk.[22] The rationale for the study was based on the observation that an increase in sleep duration may be associated with greater

nocturnal melatonin secretion.[22] Sleeping habits were ascertained prospectively from questionnaires administered six years apart. While there was no overall effect of sleep duration, when the analysis was restricted to 'stable sleepers' (i.e. sleep duration categorization was the same across the two questionnaires), breast cancer risk significantly decreased with increasing sleep (p-value for trend = 0.03), such that those who slept six hours or less had an increased risk (HR = 1.10, 95% CI = 0.59–2.05) and those who slept for nine hours or more had a decreased risk (HR = 0.28, 95% CI = 0.09–0.88), compared to those who slept an average of eight hours a night. While these findings are consistent with an increased risk of breast cancer associated with light at night mediated by melatonin secretion, the authors of this study also note that sleep duration is likely to impact other circadian rhythms, including rhythmic fluctuations in secretion of cortisol, dopamine, somatotropin, and growth hormone. The relation of these hormones to breast cancer is largely unknown.

In contrast to Verkasalo et al.,[22] Pinheiro et al.[23] reported on sleep duration and breast cancer risk in the Nurses' Health Study I, and found no overall association. Among women reporting the same sleep duration on questionnaires from 1986 and 2000, there was a modest increased risk in those who slept more than nine hours, compared to those who slept less than seven. There are many differences between these two cohorts, not the least of which is that the NHS cohort is made up of nurses, most of whom currently work, or in the past worked, a non-day shift.

The results from these studies are intriguing and warrant further study. It might be useful to elucidate which characteristics of sleep behavior (i.e., sleep duration, timing, ambient lighting) have the largest impact on the secretion of melatonin and some of the other hormones that are tied to circadian rhythms, particularly cortisol, for which there appears to be growing interest with respect to its role in breast cancer etiology.[68-70]

Studies of Melatonin Levels

As much as 25 years ago, it was noted that plasma melatonin levels tend to be depressed in women with breast cancer.[24, 25, 27, 28, 71-74] Because levels were measured at the time of, or after, diagnosis, it was impossible to assess whether this was a cause or a consequence of the disease. With the recent identification of a useful urinary biomarker for plasma melatonin,[32, 75, 76] it is now possible to prospectively evaluate melatonin levels in relation to breast cancer risk.

To date there have been two epidemiologic studies published that have made use of this biomarker. Both of these studies were large, well-conducted, prospective breast cancer studies that relied on urinary measures of Sulphatoxymelatonin (aMT6) as a marker for plasma melatonin levels. The first of these was a case-control study nested in the Guernsey III study, a large prospective cohort study of hormones and breast cancer conducted in Britain.[30] This study, which measured aMT6 in 24-hour urine samples collected at the time of cohort enrollment, found no association between breast cancer and aMT6 levels (OR = 0.99, 95% CI = 0.58–1.70, comparing the highest to lowest categories). In contrast, a nested case-control analysis within the Nurses Health Study II

found lower breast cancer risk associated with higher aMT6 levels as measured in first morning urine (OR = 0.59, 95% CI = 0.36–0.97, comparing the highest to lowest quartiles of aMT6). The design of these two studies was very similar, but the critical difference that may explain the disparate findings is the use of 24-hour versus first-morning urine. Use of a 24-hour urine sample, as was used in the British study, cannot capture nocturnal duration or peak concentrations of melatonin, which are likely to be important in determining cancer risk.[77] Furthermore, the British study, which did control for many of the important risk factors for breast cancer, did not have information on night-shift work, alcohol consumption, or exposures to light at night, all of which are well-documented determinants of plasma melatonin levels.[20, 31, 40, 41]

While more research is needed to evaluate the degree to which melatonin levels in 24-hour urine samples correlate to those measured in first morning urine, and the degree to which timing and duration of sleep might affect these levels, this approach holds great promise. The use of a urinary marker for melatonin levels that can be collected prior to the onset of disease is extremely valuable in directly assessing the 'melatonin hypothesis' with respect to breast cancer etiology.

Circadian Disruption During Pregnancy

The idea that exposures to a woman during her pregnancy that alter her sex hormone levels could result in increased lifetime risk of breast cancer in her daughters has gained wide interest and mounting scientific support.[78-80] The hypothesized mechanism is by altering the normal development of breast tissue. For example, Stevens and Hilakivi-Clarke[81] proposed that low and moderate alcohol intake during pregnancy would increase risk of breast cancer in the daughters. This idea was based on observations that ethanol can affect estrogen and/or testosterone production[82, 83] and lower melatonin production.[84, 85] Hilakivi-Clarke et al.[86] tested this hypothesis in rats and found that female rats fed low and moderate amounts of ethanol during pregnancy had female offspring that were more susceptible to chemically-induced mammary cancer than offspring from pregnant rats not fed ethanol. The alcohol levels were far below those required to result in fetal alcohol syndrome, being as little as the equivalent human consumption of one drink per day. Alcohol can also be a circadian disruptor.[87] Similarly, other circadian disruption during pregnancy may affect the lifetime risk of breast cancer in the daughters. Specific tests of this idea are that shift work during pregnancy leads to increased risk in daughters. This could be tested in case-control studies. Prospective studies would be considerably more difficult, but intermediate endpoints might be possible, such as breast density in early adulthood, based on the Child Health and Development Study led by Barbara Cohn at the Public Health Institute in Berkeley (e.g., Cohn, et al.[88] and Stevens et al.[89]).

In summary, the incidence studies conducted to date are supportive of an association between light at night and breast cancer risk. While the body of literature is still fairly small, the results from occupational studies, which generally report an approximate 50 percent elevated risk of breast cancer among night-shift workers, are extremely consistent. The incidence studies among blind women, while hindered somewhat by lack of

information on breast cancer risk factors and small numbers, also support this hypothesis. The studies of sleep patterns and those using urinary markers of melatonin are too few to draw solid conclusions from at this point, but suggest future research is needed.

Etiology

Studies addressing etiology have already been summarized in the prior subsections on biologic plausibility and incidence. There are also a number of cross-sectional exposure studies focused on identifying determinants of melatonin levels in humans; these studies both indirectly address etiology and raise some methodologic dilemmas in studying this exposure. There have been quite a few studies examining the effects of light at night on melatonin levels in humans, yielding somewhat mixed results, with some studies showing a relationship, while others not.[31, 37, 40, 41] Differences in results are likely due to inconsistencies in exposure metrics. More research is needed to determine the effects of timing, duration, and intensity of light at night on levels of nocturnal melatonin levels.

Furthermore, melatonin levels appear to be affected by a number of known breast cancer risk factors, including age, alcohol consumption, BMI, physical activity, and height, as well as use of a number of medications (e.g. NSAIDS, psychotropics). A summary of this literature appears in Table 1. Calcification (for example from exposure to fluoride[90]) may also effect on the pineal's ability to produce melatonin, but is difficult to study.[91]

Table 1. Factors that have been identified as determinants of melatonin concentrations in humans.

Factor	Direction of relationship associated with an increase in the factor	References
Age	↓	Knight et al.,[41] Travis, et al.[30]
BMI	↓	Davis et al.,[67] Schernhammer et al.,[40] Travis et al.[30]
Height	↑	Knight et al.[41]
Alcohol consumption	↓	Davis et al.[67]
Smoking	↓	Schernhammer et al[40]
Vegetable intake	↑	Nagata et al.[92]
Exercise	↑	Knight et al.[41]
Parity	↑	Schernhammer et al.[40] Travis et al.[30]
Hours of daylight	↓	Davis et al.,[67] Knight et al.[41]

These results are important for two reasons. First they suggest a potential melatonin-mediated pathway of breast carcinogenesis for these risk factors. Second, they highlight the importance of careful modeling when evaluating the risk of breast cancer associated with melatonin levels. If

these factors are in the causal pathway, then adjustment for them in models examining melatonin and breast cancer could obscure a true association. For example, if light at night disrupts fertility, resulting in nulliparity (which increases breast cancer risk), then controlling for nulliparity in study of melatonin could mask a true effect.

While these exposure studies have identified a number of important predictors of melatonin exposures, overall we have yet to identify the most important predictors, as the percent of variability explained by these studies is quite low. Given the fairly strong evidence that melatonin is likely to play an etiologic role in breast cancer, identifying the determinants of melatonin levels should be a research priority.

Finally, in evaluating the role of melatonin in breast cancer etiology, genetic susceptibility must be considered. The genes that regulate circadian rhythms are emerging as key players in expression of a wide variety of genes that regulate cell cycle length and apoptosis.[34, 93, 94] A number of genes have been identified that play a critical role in sleep-related conditions and diurnal preferences.[93] Diurnal preference (i.e. night owls versus morning larks) predicts tolerance to evening or overnight shift work and may be related to melatonin levels. Of particular interest is new evidence that polymorphisms in the Period (Per) gene family, which is central to regulation of the circadian rhythm, can affect tumor suppression and DNA damage response in mice and may be related to breast cancer (as described by Davis et al.[93]).

Treatment

Much of the etiologic evidence from animal studies seems to indicate that melatonin/light at night may act during the promotion, rather than the initiation, phase of carcinogenesis.[95] This suggests melatonin and/or manipulation of the light/dark cycle may be useful in treating breast cancer. Studies to this end, especially in humans, are limited. A number of clinical trials have shown that administration of exogenous melatonin in conjunction with other oncostatic drugs slows disease progression and improves quality of life in patients with a variety of cancers.[96-99] Clinical trials of the effectiveness of melatonin alone in the treatment of breast cancer are lacking. While a number of laboratory studies have provided compelling evidence that light at night exposures can affect progression of chemically-induced tumors,[95] the effectiveness of 'darkness therapy' as a treatment for breast cancer has not been evaluated in humans.

A related area of emerging interest in breast cancer treatment that taps into the importance of circadian rhythms is that of 'chronotherapy.' Chronotherapy, which aims to administer anticancer drugs at optimal times of the circadian clock, has been extensively evaluated in rodents and has been shown to alter the toxic effects of more than 30 different anti-cancer drugs.[100] Very limited data from clinical trials in humans suggest this may be a promising avenue to pursue. In a recent clinical trial among metastatic colon cancer patients, it was found that patients who received anticancer drugs at selected times considered to be optimal with respect to the circadian clock, instead of the constant-rate infusions typically done,

experienced fewer side effects, more shrinking of tumor size, and increased survival times[101] (as described by Ross[100]).

Conclusions and Future Directions

There is mounting evidence that disruptions in the circadian rhythm play a role in breast carcinogenesis. This is supported by data from a large body of both laboratory and epidemiologic studies. The timing, duration, and intensity of light-at-night exposures are likely to modify risk and warrant further investigation. There is substantial evidence that these effects are mediated by melatonin, although there are a number of other potential mechanisms that deserve further attention. The recent identification of a urinary marker for melatonin levels in humans offers the opportunity to more directly evaluate the role of melatonin in mediating the effects of light at night. To date, only two studies have utilized this marker, offering conflicting results.

The recent identification of a number of 'clock genes,' which regulate the circadian rhythm and appear to be important in cell cycle regulation and apoptosis throughout the body, calls for investigation of how these genes may alter an individual's susceptibility to disruptions of the circadian clock by exposures to light at night.[34] Substantial and provocative findings from laboratory studies on the effectiveness of melatonin in cancer treatments highlights the need to further pursue the usefulness of melatonin/light-dark therapies in breast cancer treatment regimens. Another potentially critical topic is circadian disruption (such as from shift work) during pregnancy and its effect on the daughter's risk of breast cancer later in life.

While the mechanism by which disruptions in circadian rhythm affect breast cancer risk have yet to be fully elucidated, the evidence that nighttime shift work increases breast cancer risk is internally consistent and makes biological sense.

No other occupational exposure with known or potential carcinogenicity is as common as work at night.[20] Identifying factors which may limit or reduce the harmful effects of night-shift work should be a research priority.

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Vitamin D and Breast Cancer Risk

Introduction

Human beings are photosynthetic organisms. In the presence of sunlight, a form of cholesterol stored in the skin is transformed into vitamin D. More specifically, the energy from solar ultraviolet B radiation converts 7-dehydrocholesterol into vitamin D_3 (cholecalciferol), an inert form of vitamin D that becomes biologically activated through a two-step metabolic process involving both the liver and the kidney (Figure 1). From here, fully functional 1,25-dihydroxyvitamin D travels through the blood on carrier proteins to various target tissues. Most famously, vitamin D stimulates the expression of proteins involved in transporting calcium and phosphorus across the gut wall and thus facilitates the mineralization of bone and electrochemical signaling.[1, 2] But many tissues in the body – including lymphocytes and the breast – also display vitamin D receptors or synthesize 1,25-dihydroxyvitamin D outright from its inactive precursor form.[3] As such, vitamin D is not actually a vitamin at all (that is, an essential micronutrient that catalyzes chemical reactions) but is more properly regarded as a hormone (that is, a chemical messenger involved in signaling and regulatory pathways). Through mediation by nuclear hormone receptors, the misnamed hormone called vitamin D acts as a transcription factor that alters the expression of many genes.[3] In so doing, it modulates inflammatory responses and participates in regulating cell growth and differentiation. In the breast, vitamin D exerts anti-proliferative, pro-differentiating, and apotoptic effects.[2]

In the last 10 to15 years, vitamin D has become the subject of growing interest as an environmental factor that may be associated with the reduction of risk of a spectrum of cancers, including breast cancer.[4-6] In 1990, an ecological study conducted by Garland and coworkers reported an inverse correlation between U.S. breast cancer mortality rates and exposure to solar radiation and hypothesized that vitamin D produced by sunlight exposure might have more than a correlative role in the regional differences in breast cancer mortality.[7] Since then, a substantial body of experimental evidence has accumulated that 1,25-dihydroxyvitamin D has anti-cancer effects both *in vitro* and *in vivo*. Human epidemiologic studies are conflicting but mostly provide support for cell culture and animal studies. All together, prospective and retrospective studies suggest that vitamin D deficiency is associated with a 30–50 percent increase in breast cancer risk and with poorer survival among those so diagnosed.[8] These studies also suggest that the apparent cancer-preventive effect of vitamin D can involve various pathways, including calcium-dependent processes. In addition, there is much ongoing interest in the possibility that vitamin D could be used as a treatment for cancer.[9]

This chapter focuses narrowly on the influence of vitamin D on breast cancer risk and mortality. It does not review the evidence for its effects on the development of other cancers – including colon, prostate, and lung – where it is also apparently involved in risk reduction[10] – or on other disorders, such as cardiovascular disease and multiple sclerosis (see Holick[8] for a review). Nor does it comment on the ongoing controversy regarding the opposing public health goals of sun

protection to prevent skin cancer and sun exposure to promote vitamin D_3 synthesis. (See Gilchrest,[11] who argues that the controversy is being fueled, in part, by the indoor tanning industry. See also chapter I.C., which examines compounds in personal care products, including sunscreens, as a source of exposure to endocrine-disrupting chemicals.)

Perhaps more than any other single factor, vitamin D has profound connections with all three sectors of this report. As a photosynthetically produced hormone, vitamin D is deeply involved with physical environment. Air pollution, for example, is known to interfere with sunlight-induced vitamin D synthesis. Vitamin D synthesis is also influenced by season, latitude, altitude, time of day, and cloud cover.[12]

Because the skin pigment melanin competes with 7-dehydrocholesterol for solar UV B radiation, darker-skinned people require more time in the sun to generate adequate stores of vitamin D than do lighter-skinned individuals. Thus, vitamin D may potentially be involved with racial and ethnic disparities in breast cancer progression and survival. African American women, for example, are ten times more likely than white women to suffer from hypovitaminosis D, according to data collected as part of the National Health and Nutrition Examination Survey.[13] Individuals confined to nursing homes are often sunlight and vitamin D-deprived, raising questions about vitamin D's role in breast cancer among disabled women who are homebound or confined to institutions.

Because, the structures of workplaces and neighborhoods mediate sunlight exposure, vitamin D is also a dimension of the built environment. Indeed, vitamin D was first identified – and misclassified as a vitamin – during attempts to prevent and cure the scourge of rickets among urban children in 19th century Europe. The rise of rickets – a bone-deforming disease that is the result of acute vitamin D deficiency – corresponded to a dramatic change in the built environment that was ushered in with the advent of the Industrial Revolution when indoor factory work, tenement living, and smoggy air of industrial cities replaced outdoor farm life. As a consequence, sunlight exposure for a large sector of the European and British population markedly decreased.[1]

Vitamin D's involvement with the physical environment, race, and the built environment make it an intriguing topic for California-based breast cancer research. With the longest latitudinal gradient of any state, areas of high air pollution, a diversity of built environments ranging from urban to rural, and a population containing many different skin colors, California is a good laboratory for a study of vitamin D's influence on breast cancer incidence and outcome.

Concept/Exposure Definition

During the race to find a cause for rickets, two independent discoveries were made: sunbathing could cure rickets in children, and cod-liver oil could cure rickets in dogs that had been confined indoors away from sunlight. By 1924, U.S. children began consuming milk and bread that had been irradiated with ultraviolet light, and the epidemic of rickets quickly dwindled.[1] Because of this unusual history, the term vitamin D is used in reference to two fat-soluble compounds,

cholecalciferol (vitamin D_3), which is manufactured by irradiated skin, and ergocalciferol (vitamin D_2), which is created during the irradiation of foods. Both were originally named and defined by their ability to both prevent and cure rickets. Both of these compounds require a two-step metabolism, as described above, for conversion to their active form, $1,25(OH)_2$ D.

Sources of Exposure

(The following sections are summarized from several comprehensive reviews on various aspects of vitamin D and health[14-22].)

There are four contemporary sources of vitamin D. The leading source by far is sunlight exposure. Another source is dietary and includes a limited number of foods contain naturally occurring vitamin D_3. These are egg yolk, liver, and oily saltwater fish such as herring, salmon, and sardines. Certain mushrooms (for example, shitake) are a natural source of vitamin D_2. A third source is foods that are naturally low in vitamin D but which have been fortified with synthetic vitamin D_3 or D_2. These include liquid milk (but not cheese or ice cream, which are not fortified) and certain brands of cereals, bread, orange juice, and margarine. Last are supplements in the form of multivitamins containing vitamin D, vitamin D tablets, or cod liver oil. These may contain either vitamin D_3 or D_2. While excessive exposure to sunlight does not lead to overproduction of vitamin D_3, overdosing on vitamin D supplements can produce intoxication. Indeed, baits laced vitamin D are sometimes used as rat poison.[3]

Whatever the source, vitamin D must undergo metabolic activation as shown in figure 1 and discussed below.

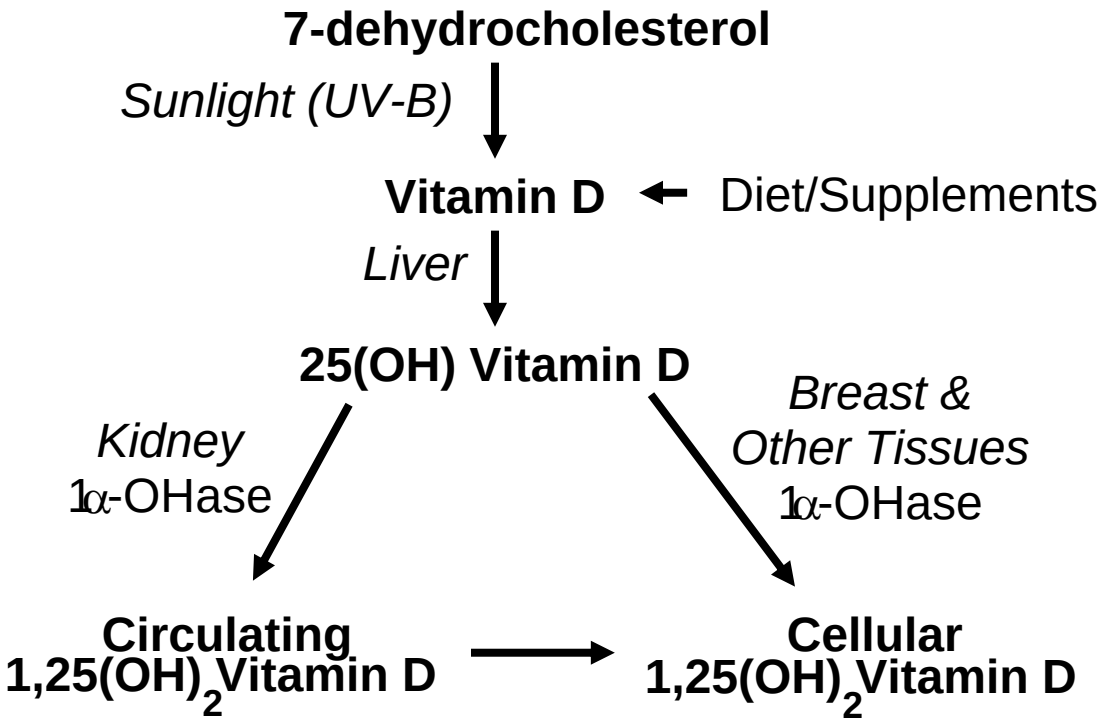

Figure 1. Synthesis and Metabolism of Vitamin D

Vitamin D from Sunlight

In the United States, sun exposure accounts for up to 90% of the circulating 1,25$(OH)_2$ D precursor, 25-dihydroxyvitamin D [25(OH)D, calcidiol] levels.

Cutaneous vitamin D production is modified by both *personal, social,* and *environmental* factors.[18] *Personal factors* include constitutive skin pigmentation, age, body type, use of sunscreen, and wearing of protective clothing. As described above, people of different races diverge in the level of expression of melanin within melanocytes. Melanin contained within the melanocytes competes with 7-dehydrocholesterol for UV-B radiation. Humans differ in the levels of melanin expressed in epidermal melanocytes and higher levels of melanin in the epidermis decrease vitamin D production.

In fact, given an equal amount of sun exposure, light-pigmented individuals are 5–10 fold more efficient in converting 7-dehydrocholesterol to previtamin D.[23]

Age is also an important variable. Levels of 7-dehydrocholesterol decrease linearly with age such that the epidermis of an 80-year-old has levels that are about half that of a 20-year-old. Thus, at any given sun exposure, a college student can produce twice the vitamin D_3 as her grandmother can.

Body type may also play an important role in the bioavailability of vitamin D. Vitamin D_3 is fat-soluble compound that is stored in body fat compartments. In this way, vitamin D produced during the summer months can be used in the winter when ambient light may be insufficient to create more. Accordingly, individuals with different BMI values may differ both in their bioavailability and reserves of vitamin D.

Sunscreens are very effective inhibitors of cutaneous vitamin D photosynthesis. A sun protection factor of 15 effectively halts vitamin D production.

Environmental factors also influence cutaneous vitamin D_3 photosynthesis. These factors include geographic latitude, altitude, season, time of day, cloud cover, and air pollution. The solar zenith angle – which varies with season, latitude and time of day – is a major determinant of the amount of solar radiation that reaches the earth's surface. The more oblique the sun's zenith angle is in the winter, the fewer UV-B photons per unit area strike the earth's surface. Consequently, at northern (or southern) latitudes, no vitamin D is produced by photosynthesis during the winter. The length of the season that is prohibitive of vitamin D production varies with latitude. For example, in Boston, which is situated at 42ºN, vitamin D synthesis is not possible from November through February. California's northern border is also located at 42ºN. Below 37ºN, which is the latitude of San Francisco, winter UV-B irradiation is sufficient, and vitamin D_3 photosynthesis takes place year-round. Vitamin D production is also affected by changes in the angle of the sun throughout the day; the photosynthetic period is thus limited to the hours of 10 am to 3 pm. Complete cloud cover reduces UV irradiance by half, and complete shade reduces it by 60 percent. Industrial pollution increases shade and decreases

sun exposure and can even contribute to the development of rickets.[24]

Vitamin D metabolism

Vitamin D made in the skin or absorbed from the diet or supplements does not have biologic activity and must undergo a two-step metabolic process to its biologically active form. The steps in this process are illustrated in Figure 1.

Whatever its source, vitamin D that enters the circulatory system is bound largely to vitamin D-binding protein. This protein also binds metabolically modified forms.

Upon circulatory delivery to the liver, vitamin D is hydroxylated at the 25 position by a cytochtrome P450-like enzyme. This reaction produces 25(OH) vitamin D [25(OH)D or calcidiol], the major circulating vitamin D metabolite. The production of 25(OH)D is not tightly regulated and its serum levels reflect the degree of vitamin D photosynthesis in the skin and that absorbed from the diet. Because of its longer half-life, 25(OH)D is thought to provide the best estimate of vitamin D exposure.

25(OH)D is converted to the active hormone $1,25(OH)_2D$ by the enzyme 25-hydroxyvitamin D1α-hydroxylase (1α-hydroxylase). This enzyme is also cytochtrome P450-like and is localized in the kidneys, as well as other tissues including mammary tissue. The renal enzyme is best studied and has been found to have tight regulation. Parathyroid hormone and low level of serum phosphate have been found to induce the activity of this enzyme whereas calcium and the end product $1,25(OH)_2D$ repress its activity. 1α-hydroxylase is expressed in both normal and malignant tissues including that of the breast. While the non-renal enzyme is thought to be identical to the renal enzyme, it has been found to be unaffected by the regulators of renal activity.

$1,25(OH)_2D$ has both endocrine and paracrine activities. Following its formation in the kidney, it can function as an endocrine hormone to act as a positive regulator of calcium (and phosphate) homeostasis. $1,25(OH)_2D$ accomplishes this in three ways: a) by increasing calcium and phosphate absorption in the small intestine; b) by interacting with parathyroid hormone to enhance calcium and phosphate mobilization form bone; and c) by decreasing renal excretion of these ions. At the molecular level these processes occur following the binding of $1,25(OH)_2D$ to the vitamin D receptor (VDR). The VDR is a member of the steroid and thyroid hormone receptor supergene family and is present in most tissues including normal and malignant breast tissue. The VDR bound to $1,25(OH)_2D$ acts by forming a heterodimer with the retinoid-X receptor and inducing transcription of target genes. $1,25(OH)_2D$ also has biologic effects which occur too rapidly to involve transcription induction and may possibly involve a recently identified membrane receptor the 1,25,D3-membrane-associated rapid response, steroid-binding protein. The functioning of this protein is at this time not fully understood.[25]

The affinity of the VDR for $1,25(OH)_2D$ is about 1000 times that of any of the other circulating vitamin D metabolites. Nonetheless, the total serum concentration of 25(OH) D is about 1000 times higher than $1,25(OH)_2D$. Because of the

high total serum 25(OH) D concentrations, this compound could potentially compete for VDR binding and affect the biological activity of $1,25(OH)_2D$. However, differential binding affinities of 25(OH)D and $1,25(OH)_2D$ to the vitamin D binding protein has a modulating effect such that the free concentration of 25(OH)D is only twice that of $1,25(OH)_2D$. This effect eliminates any potential VDR binding competition between these two compounds. Knock-out mice of the vitamin D binding protein display mild dysfunction and are susceptible to vitamin D deficiency.[26]

25(OH)D, the product of hepatic metabolism may also have paracrine activity. It is now known that 1α-hydroxylase is expressed in many non-renal tissues, including breast cells[27, 28] and the delivery of this compound via the circulation may allow for synthesis of[28] $1,25(OH)_2D$ synthesis in the breast and other tissues containing this enzyme. However, this effect remains theoretical as formation of $1,25(OH)_2D$ has not been measured in any of these tissues.

Both 25(OH)D and $1,25(OH)_2D$ are hydroxylated at the 24 position by another cytochtrome P450 enzyme 24-hydroxlaase. It is considered a key enzyme in vitamin D catalysis. Dysregulation of 24-hydroxlyase expression has been demonstrated to occur in breast cancer cell lines and breast tumors. This enzyme may play an important role in the functioning of vitamin D during the carcinogenesis process.

Daily vitamin D requirements

In 1997, the Institute of Medicine of the National Academy of Sciences made age-dependent daily recommendations for vitamin D intake. These were: 1) 200 IU for children and adults up to age 50; 2) 400 IU for adults aged 50 to 70 years; and 3) 600 IU for adults older than 70 years. Based on clinical trials examining reduction of bone fractures, a group of prominent nutritionists have recently suggested that these recommendations are far too low. Potential for cancer risk reduction were also mentioned in this statement of concern. The body's daily needs for vitamin D have been estimated at an average of 3,000–5,000 IU.[21] Such needs are clearly not being met. For example, typical multivitamins contain 400 IU of vitamin D (in the form of D_3 or D_2). Casual sun exposure (on face, arms and hands) of 5–15 minutes/day 2–3 times a week (depending on latitude, season, and skin pigmentation) supplies the equivalent of 1000 IU of vitamin D_3. Garland et al.[29] found that individuals with a serum level of 52 ng/ml of 25(OH)D had a 50 percent lower risk of breast cancer compared to individuals with less than 13 ng/ml. A serum level of 52 corresponds to an intake of 4000 IU/day.

Vitamin D Deficiency

Vitamin D deficiency has been reported in all races as well as in areas with potentially adequate solar exposure. This deficiency is especially prominent in the black population. A recent NHANES based study found that 42% of black women of reproductive age exhibited hypovitaminosis D. By contrast, only 4 percent of white women did.[13] Hypovitaminosis D is also common in sunny countries in which cultural practices prescribe that women be heavily veiled in public.[3]

Biologic Plausibility

The biological activity of vitamin D and calcium support the idea that these entities may play a role in breast cancer etiology. *In vitro* and *in vivo* studies in normal and malignant breast cells have shown that $1,25(OH)_2D$ can inhibit proliferation, induce differentiation, stimulate apoptosis, and inhibit angiogenesis.[9, 30-34] High intake of vitamin D has also been demonstrated to inhibit proliferation and tumor formation in a rodent model of mammary carcinogenesis.

As vitamin D plays an important role in the regulation of calcium, it is possible that any activity associated with vitamin D may involve calcium, which itself has anticancer activity. Like vitamin D, calcium is involved in the regulation of proliferation, differentiation and apoptosis in mammary cells *in vitro*. In addition, some studies suggest interplay between vitamin D and calcium. Studies have also demonstrated activity for calcium in rodent models of mammary carcinogenesis. At high levels of intake, calcium is able to inhibit carcinogenesis in two rodent models of mammary carcinogenesis, one involving tumor induction by 7,12-dimethylbenzanthracene and the other by a high-fat diet.

Review of the Epidemiologic Literature

The epidemiologic evidence on vitamin D and breast cancer is more limited than the in vitro and in vivo data but certainly suggests a protective role for vitamin D in the pathogenesis of breast cancer, especially in halting progression. Low levels of vitamin D are associated with more advanced cancers.[35]

A wide range of ecological studies has linked low levels of sunlight with high breast cancer rates.[29] However, until recently, it was not possible to estimate the dose-response relationship. A pooled analysis conducted in 2007 to assess the association between vitamin D metabolite 25(OH)D in the serum and breast cancer risk found that individuals with the highest circulating vitamin D had a 50 percent lower risk of breast cancer than those with the lowest levels. Pooled odds ratios for breast cancer from lowest to highest quintile were 1.00, 0.90, 0.70, 0.70, 0.50.[29] Human studies show that vitamin D levels are higher in controls than in cases and decrease further in patients with bone metastases. Moreover, circulating vitamin D levels are lower in patients with advanced breast cancer than in those with early breast cancer.[35]

The ecological studies that focus on latitudinal gradient find stronger associations with mortality than with incidence. Garland et al. noted in 1990[7] that U.S. breast cancer mortality rates in white women were highest in the Northeast and lowest in the South, and based on correlation with solar radiation levels they proposed the hypothesis that vitamin D from sun exposure and diet may lower breast cancer mortality. A geographic gradient for breast cancer incidence has been evident for white women in all 5-year periods between 1950 and 1994,[36] and inverse correlations with solar radiation have been reported for both white and black women.[37, 38] However, a recent analysis of more detailed mortality data showed that in white women aged 20–49 years, the breast cancer mortality gradient had disappeared by 1990–1999, largely due to a greater decline in mortality rates in the Northeast than in the South.[39] A similar

trend was seen in women aged ≥50 years: the Northeast/South gradient diminished over the last three decades as breast cancer mortality rates increased in the South.

Higher mortality rates may reflect exposure to factors (e.g., vitamin D deficiency) that increase tumor progression and metastasis, thereby shortening survival and increasing mortality. Recent epidemiologic data by John et al.[40] provide some support for this hypothesis.

In contrast to the results for breast cancer mortality, the results of studies examining breast cancer incidence over geographic gradients are not supportive of the importance of solar exposure in breast cancer etiology. SEER incidence data for breast cancer do not show a Northeast-South gradient,[41] though a recent analysis of the incidence data for the year 1999 from additional high-quality cancer registries shows lower breast cancer incidence rates in the South than in the Northeast (cited in Sturgeon 2004[39]). In the Nurses' Health Study, which utilizes a large, national U.S. cohort, incidence rates in both premenopausal and postmenopausal women were similar across four major U.S. regions, after adjustment for individual risk factors of the participants.[42] In California, where latitude spans from 32–42ºN, breast cancer incidence rates among participants of the California Teachers Study did not display a north-south gradient. Following adjustment for personal and ecologic risk factors, incidence rates were 33% higher in the urban areas of San Francisco and 29% higher in Los Angeles than in the remainder of the state.[43] These findings emphasize the importance of other factors in explaining the results of studies examining regional differences in incidence rates. The true importance of sun exposure in these studies cannot be assessed, as it was not examined in this occupational cohort of school employees that works largely indoors.

Three ecological studies have examined the relationship of place of residence, with and without consideration of average sunlight exposure, and breast cancer risk. Residential solar radiation levels was inversely associated with breast cancer mortality in a nationwide death-certificate based case-control study.[44] A statistically significant reduction of 18% was reported but solar radiation levels were based on state averages and risk was only adjusted for age. A case-control study examined breast cancer risk in Marin County California, viewing this as a high incidence population. This study found increased risks of premenopausal breast cancer in women under age 50 years who were born in the Northeast (OR = 6.2; 95% CI = 1.0–7.9) or who had ever lived in the Northeast before age 21 years (OR = 6.2; 95% CI = 2.2–17.8).[45] Small and non-significant effects were reported for postmenopausal breast cancer risk. In addition, no correlation was made to sunlight exposure. A better-designed and more complete nationwide cohort study was conducted using NHANES data. Data on sunlight levels in the state of longest residence were combined with a physician-conducted sun-exposure evaluation.[46] A statistically non-significant but substantial (42%) decrease in breast cancer risk was reported for women with moderate-to-considerable sun exposure who lived in a state with high solar radiation.

Four studies have assessed breast cancer risk in relation to personal sun exposure histories. A Canadian population-based case-control study found reduced breast cancer risk associated with increasing sun exposure from ages 10–19.[47] The NHANES based study by John et al. discussed above reported moderate decreases in risk among women who self-reported frequent (vs. rare or never) recreational activity (OR = 0.66; 95% CI = 0.44–0.99) and occupational sun exposure (OR = 0.64; 95% CI = 0.41–0.98).[46] A second study utilizing national death certificates and sun exposure based job titles reported weak statistically non-significant decreases in the risk of breast cancer mortality.[44] Decreases were reported for women living in areas of high sunlight and working as farmers (OR = 0.90) or outside (OR = 0.75). In contrast, in the Nurses Health Study, the decrease in cancer risk associated with total or dietary vitamin D (discussed below) was not affected by adjustment for outdoor activity (or place of residence).[48]

A novel measure of sun exposure based on skin pigmentation measurements has been developed to serve as an index of past sun exposure.[40, 49, 50] The index is calculated as the difference between skin color on the upper inner arm (a site with very little to no exposed to sunlight) and the central forehead (a site with high sunlight exposure). These studies, which are as yet unpublished, reported an inverse association between the sun exposure index and advanced breast cancer. However, no association was found with localized breast cancer.[40]

Serum measures of vitamin D concentration have the distinct advantage that they provide direct measures of exposure and the disadvantage that they may represent exposures over a relatively short time period in the life span. Such studies have used two measures – that of the active metabolite of vitamin D, $1,25(OH)_2D$ and that of its precursor, 25(OH)D. Some scientists have justifiably argued that 25(OH)D is the more relevant measure for several reasons. First, the circulating concentration of $1,25(OH)_2D$ provides a poor measure of vitamin D status as its plasma concentrations are tightly regulated and change only in cases of extreme deficiency. Second, 25(OH)D levels provide a measure of the availability of vitamin D from diet, supplements, and skin photosynthesis and are accordingly more valid. In addition, they may also be a more relevant measure for breast cancer risk assessment since 25(OH)D may be converted to its active metabolite, $1,25(OH)_2D$, by 1 α -hydroxylase in breast tissue.

Three studies assessed breast cancer risk in relation to circulating 25(OH)D. A hospital-based study found no differences in cases and controls.[51] In contrast, a case-control study nested within the Nurses Health study reported an inverse relationship between high 25(OH)D levels and breast cancer risk (OR = 0.73 for highest compared with lowest quintile).[52] The results were suggestive, but not statistically significant (P trend = 0.06). A hospital based case-control study in Britain found a strong statistically significant association with breast cancer risk (OR = 5.83) for women with low compared with high circulating levels of 25(OH)D.[53]

Three studies have assessed serum levels of $1,25(OH)_2D$ for an association with breast cancer risk. The first of these studies is a small nested

case-control study which reported no association between pre-diagnostic $1,25(OH)_2D$ levels and postmenopausal breast cancer risk.[54] A second small hospital-based case-control study reported a strong statistically significant association (OR = 5.3) comparing low and high $1,25(OH)_2D$ levels.[51] The third study was a large case-control study nested within the Nurses Health Study. This study reported a modest (OR = 0.76), statistically insignificant association between high versus low $1,25(OH)_2D$ levels and breast cancer risk.[51, 52, 54]

A number of studies have examined dietary vitamin D intake and breast cancer risk. Interpretation of these studies relative to vitamin D is complicated as vitamin D and calcium intake are highly correlated. This is especially important as they have similar activities against breast cancer cells, share regulatory pathways, and may act in conjunction with each other. According to a prospective investigation of 30,000 women in the Women's Health Study, higher dietary intakes of calcium and vitamin D were associated with lower breast cancer risk among premenopausal, but not postmenopausal, women. Moreover, premenopausal women with low calcium and vitamin D intake were more likely to have large and poorly differentiated tumors.[55]

Six other studies have also explored the association of dietary vitamin D intake and breast cancer risk.[34] Consistent with the Women's Health Study, a statistically significant reduction in breast cancer risk was found in the large cohort Nurses' Health Study for premenopausal women (RR = 0.72) for women whose total daily intake was more than 500 IU compared to women whose intake was less than 150 IU [Shin 2002]. Dietary vitamin D intake was associated with a similar but marginally statistically significant risk reduction. Further adjustment for residential area and history of sunlight exposure did not change these relationships. As in the Lin study, this investigation found no association with breast cancer risk for postmenopausal women.[48]

Similarly, a national U.S. cohort of 68,567 women found no association between total and dietary vitamin D and breast cancer risk among postmenopausal women as a whole.[56] However when estrogen-receptor positive (ER+) and negative (ER-) cases were examined separately, a weak, statistically significant reduction in risk was found for postmenopausal women with ER+ tumors (RR = 0.74). The comparison groups in this examination were women with dietary intakes greater than 300 IU/day relative to women with intakes less than 100 IU/day. There was also a significant dose-response relationship.

Cellular studies support such an ER-related effect. Experimental studies, using mammary cell lines, have reported that ER+ cell lines are more sensitive to $1,25(OH)_2D$ than ER- cell lines.[31] Surprisingly, examination of total (rather than merely dietary) vitamin D intake, was not associated with risk. These authors also reported a potentially important modifying effect of UV exposure for women from cloudy localities. Among women from states with little sunlight, vitamin D intake had a significant effect on breast cancer risk. Risk was statistically significantly reduced (RR = 0.81) for daily intakes of > 300 IU/day vs. ≤ 100 IU/day. On the other hand, for women from states with higher sunlight exposure levels, vitamin D intake (> 300 IU/day vs. ≤ 100

IU/day) was not associated with breast cancer risk (RR = 1.05).

Three other small, case-control studies have examined women of all ages and reported no association between dietary vitamin D and breast cancer risk.[57-59] No statistically significant association with vitamin D intake was reported by an NHANES based cohort study.[46]

Animal studies and some human epidemiologic studies have suggested that adolescence may be a critical period affecting future breast cancer risk. Frazer and coworkers have conducted two studies that retrospectively examined vitamin D intake during adolescence. In both studies they found no association with breast cancer risk.[60, 61]

Preliminary data (published abstract) from the Women Health Initiative (WHI), a randomized clinical trial, suggest that daily intake of 400 IU of vitamin D_3 and 1000 mg of elemental calcium did not reduce the incidence of invasive breast cancer among postmenopausal women after 7 years of follow-up (HR = 0.96, 95% CI = 0.85–1.09).[62] However, in the placebo group, total vitamin D intake at baseline was associated with reduced risk.

The studies conducted to date do not provide a completely clear picture on the effect of dietary and supplemental vitamin D on breast cancer risk. However, examination of the results as a whole may add some potentially encouraging clarity. Beneficial effects have been reported for some subgroups of the women studied, including premenopausal women, postmenopausal women with ER+ tumors, and women living in sunless areas. Accordingly, inclusion of these three subgroups along with others in the analyses could potentially obscure the results.

The finding of reduced risk in regions of low UV is consistent with lower circulating levels of 25(OH)D due to lack of vitamin D synthesis during the winter months and higher prevalence of vitamin D insufficiency/deficiency. Thus, high dietary vitamin D intake is a more important contributor to circulating levels of 25(OH)D in individuals who live in low-UV regions without year-round vitamin D synthesis, than in individuals who live in high-UV regions. Thus, the effect of dietary vitamin D on breast cancer risk may be masked in high-UV regions. An alternative interpretation is that a daily intake of 400 IU may be too small to influence breast cancer risk. Among fair-skinned Caucasians, casual sun exposure for 10–15 minutes corresponds to an oral intake of 1000 IU. A serum 25(OH)D level of 52 ng/mL, which corresponds to oral intake of 4000 IU/day, has been associated with a 50% reduction in breast cancer risk.[29] Thus, oral intake much higher than 400 IU may be necessary to reduce breast cancer risk.

A number of studies have assessed associations of common polymorphisms in several regions of the vitamin D receptor (VDR) gene and breast cancer risk.[34, 63] The most commonly studied SNPs include a polymorphic site in exon 2 near the 5' end of the gene that is identified by *FokI* restriction enzyme, which has two potential translation initiation sites and results in VDR proteins that differ in length by three amino acids and differ in transcriptional activity. At the 3' end of the gene, two polymorphic sites in intron 8 are identified with *BsmI* and *ApaI* restriction enzymes,

and a third in exon 9 is identified by *TaqI* restriction enzyme. The *BsmI*, *Apa, I* and *TaqI* SNPs are not functional, but are strongly linked with the *poly(A)* microsatellite repeat located in the 3' untranslated region (UTR) which may influence VDR mRNA stability.

Studies of associations between breast cancer risk and VDR variants, while inconsistent, are largely null. Three relatively large case-control studies in white women from the US,[64] the UK,[65] and Sweden[66] found no association with *TaqI*. Other smaller studies found no association in white, Hispanic and African-American women from California[40] or increased risks in relation to the *TaqI* T allele in women from Australia,[67] China[68] or Taiwan.[69] Several studies found no association with *FokI*.[40, 64, 65, 70] In the largest study conducted to date, *Fok*I ff (vs FF) was associated with a significantly increased risk (OR = 1.34, 95% CI = 1.06–1.69),[71] as previously reported for Hispanics.[72] Most of these studies had design limitations such as small size or limited adjustment for confounding factors. More study will be required to clarify this potentially complex area of research.

Since any potential effect of the VDR protein on cancer development is dependent on the availability of its transactivation ligand, 1,25(OH)D, it may be critical to consider the association between VDR variants and breast cancer in the context of substrate availability. A nested case-control study within the Nurses Health Study reported no effect of serum levels of 25(OH)D or $1,25(OH)_2D$ on the association of the *FokI* genotype with breast cancer risk.[71] In agreement with these results, an unpublished case-control study found that the inverse association of the sun exposure index with breast cancer risk was not modified by VDR genotype, though stratification produced relatively small groups for analysis.[40] In contrast, a small, British case-control study reported a strong, statistically significant increase in breast cancer risk (OR = 6.82) associated with the *BsmI* bb VDR genotype and low levels of 25(OH)D,[53] It should be noted that there was also a statistically significant trend for this relationship but that the analysis was limited as there was only adjustment for age and menopausal status.

Breast density – the relative proportion of glandular tissue to fat tissue in the breast – is also affected by vitamin D. High breast density (lots of ductal tissue and little fat) is strongly related to breast cancer risk and has been proposed as an intermediate marker in breast cancer prevention efforts. Emerging evidence shows that vitamin D is associated with lower breast density, especially among premenopausal women,[73, 74] perhaps reflecting vitamin D's antiproliferative effects, as seen in cell culture experiments. Moreover, a Canadian study has found that breast density changes seasonally, reaching a peak in early spring when circulating blood levels of vitamin D are lowest. Changes in blood vitamin D were inversely related to breast density and were seasonally synchronized.[75]

As $1,25(OH)_2D$ has been shown to decrease proliferation, increase differentiation and inhibit metastasis, it is plausible that various aspects of vitamin D availability and functioning and availability might play a role in survival from breast cancer. As early as 1989, Colston and

coworkers reported significantly longer survival for breast cancer patients with *VDR* positive tumors.[76] Two studies of women from Norway have also supported this idea. Both studies examined how seasonal variation in UV radiation at the time of diagnosis may affect survival from breast and other cancers. Norway is well suited to such a study as it has a spread in latitude of more than 10 degrees (as does California); long summer days and long winter nights provide considerable seasonal variation. In Norwegian women, survival was highest when the season of diagnosis occurred during the summer or fall months when vitamin D photosynthesis was potentially highest.[77] The second study also found a summer effect. Recently, Lim and coworkers[78] published similar findings for breast cancer mortality rates among women in the United Kingdom.

Very few studies have examined diet after breast cancer diagnosis and survival. Holmes and coworkers conducted such a study of the Nurses' Health Study Cohort.[79] This study reported a 27% decrease in breast cancer risk for women with the highest dietary vitamin D intake (not including supplements) relative to those with the lowest levels of intake. This decrease bordered on statistical significance, and there was a statistically significant trend across the quantiles of intake (P value, trend = 0.05). A decrease in risk was also reported when supplements were included in intake values (RR = 0.86) but these results were not statistically significant.

Demonstration of anti-proliferative effects of $1,25(OH)_2D$ has led to the active investigation of $1,25(OH)_2D$ as an agent in cancer therapy.[4, 30] Administration of $1,25(OH)_2D$ can lead to life-threatening hypercalcemia. This effect is the major challenge in the use of $1,25(OH)_2D$ chemotherapeutically and in the design synthetic vitamin D analogues. Hundreds of analogues have been developed, many have been assessed for their effects on breast cancer cell growth versus their hypercalcemic activity. Some of these analogs are currently being tested in clinical trials. Vitamin D analogues may have potential as cancer chemopreventive agents but this remains an unexplored area.

Discussion and Future Directions

All together, the experimental and human studies provide evidence for a protective effect of vitamin D on the breast. In vivo and in vitro studies show clear anticarcinogenic effects that manifest as a result of vitamin D's hormonal regulation of cell proliferation, differentiation, and apoptosis in both normal and malignant breast cells.[34] In some, but not all, human studies, sunlight exposure and serum levels of vitamin D are inversely related to breast cancer risk among subgroups of women. The benefits of vitamin D for the breast appear strongest for premenopausal women. Possibly because of its anti-proliferative effects, vitamin D is also inversely associated with breast density, which is itself a risk factor for breast cancer. The finding that 4 of every10 young African American women exhibit hypovitaminosis D – a rate 10-fold that of their white counterparts – raises public health concerns, especially in light of the fact that low vitamin D levels are associated with more advanced breast cancers.

Outstanding questions include:

1) What are the racial/ethnic differences in sunlight exposure and circulating vitamin D levels among women in California?

2) Can differences in blood serum levels of vitamin D explain racial disparities in breast cancer progression, mortality or aggressiveness? Palmieri[35] notes that darker skin pigmentation has been associated with larger-sized tumors and increased frequency of lymph node involvement. Are racial differences in vitamin D status – and perhaps access to sunlight--playing a role here?

3) How does air pollution interfere with UV B irradiance and thereby vitamin D photosynthesis among women in California?

4) Is timing of exposure important for the anti-carcinogenic benefits of vitamin D?

5) What aspects of the built environment – housing density, sidewalks, safety, playgrounds, community gardens, workplace policies, distance to shopping and schools – influence vitamin D levels among inhabitants and thereby the pathogenesis of breast cancer?

6) Recommendations for beneficial sunlight exposure presume light-colored skin. Among fair-skinned Caucasians, for example, casual sun exposure for 10–15 minutes is said to correspond to an oral intake of 1000 IU. What are the correspondences and recommendations for black, Hispanic, and Asian women? And how do these recommendations vary by latitude within California?

7) Vitamin D is fat-soluble. How does body mass index affect bioavailable vitamin D metabolites?

8) What are the vitamin D profiles for teachers, nurses, and other occupational groups known to have high rates of breast cancer, and how do these compare to the general population?

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Race/Ethnicity

Introduction

This chapter provides an overview of research aimed at elucidating disparities across racial/ethnic groups in breast cancer incidence and outcomes. Following a discussion of race and ethnicity, their conceptual frameworks, and some general issues surrounding how these concepts are typically categorized for health research, the review of the literature is organized according to the continuum in breast cancer burden, from incidence to mortality.[1]

Historical and Political Conceptualization of Race and Ethnicity

The concept of race in this country is interwoven with a contentious sociopolitical history. Probably no other health research concept has generated so much passionate debate.[2-4] Freeman states that race is "perhaps the single most defining issue in the history of American society," despite the fact that there is no genetic basis for racial classification.[5] Views in this debate range from calling for the elimination of race and its commonly-used categories altogether from health research, as continuing their use perpetuates racism in society;[6, 7] to viewing race as strictly a sociocultural construct with no biological basis;[3, 4, 8] to affirming that the modern concept of race and its categorization indeed have biological significance and ramifications in biomedical science.[2]

Categories of race and ethnicity have been used inconsistently across research efforts.[9] The classification scheme established by the Office of Management and Budget (OMB; Executive Office of the President) is used for federal reporting purposes, including the U.S. Census. In 1997, and in preparation for Census 2000, OMB revised its Statistical Policy Directive No. 15 by modifying its established categories for race and ethnicity to include five race groups: "White", "Black or African American", "Asian", "American Indian and Alaska Native", and "Native Hawaiian and Other Pacific Islander."[10] This classification scheme appears to emphasize ancestry.[2, 11, 12] Ethnicity is a concept based more on cultural traditions, reflecting commonalities in history and possibly genetic heritage,[2, 11, 12] and is addressed by OMB in reference to "Hispanic origin" in two categories: "Hispanic or Latino" or "Not Hispanic or Latino". According to the OMB, race and ethnicity are not mutually-exclusive categories; individuals of any race can be "Hispanic or Latino."[10]

The definitions for race and ethnicity commonly used in epidemiologic research appear to be fairly similar to the OMB definitions, with race reflecting more on ancestry and geographical origins, and ethnicity emphasizing shared cultural heritage.[11, 13] By law, federally-funded research (including collection and reporting of data) must use OMB classifications and definitions.[10] In epidemiologic studies, however, it is fairly common for Hispanic or Latino to be considered a separate race category. Relatedly, ethnicity is often used in reference to subpopulations within the major race categories. For example, Chinese, Cambodian and Sri Lankan are three of more than 30 ethnic subpopulations that fall under the rubric of "Asian"; Samoan, Chamorro and Fijian are three of more than 30 ethnicities within the

"Native Hawaiian and Other Pacific Islander" rubric.[14] Furthermore, due to their relatively small census (in comparison with larger race groups), epidemiologists often combine Asians and Pacific Islanders into a single category – "Asian/Pacific Islander" (API) – for strengthened statistical significance.[14] American Indian/Alaska Native populations are often combined into a potpourri category of 'Other,' if referenced at all. These federally-used broad categories of race and ethnicity are described below.

Hispanic or Latino: OMB defines Hispanic or Latino as "a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race."[10] Persons from the Dominican Republic are also considered Hispanic. Of over 40 million "Hispanics or Latinos" responding to Census 2000, 49 percent identified their race/ethnicity combination as "Hispanic White", 48.2 percent as "Hispanic-Hispanic", and 3 percent as "Hispanic Black." The term Latino is preferred by the American Public Health Association because it reflects the integration of Spanish, indigenous, and African cultures among the people of Latin America.[15]

White: White is commonly used to describe persons of lighter skin hue with origins in the populations of Europe (except Spain) and Caucasia. The U.S. Census Bureau defines the "White race" as "people having origins in any of the original peoples of Europe, the Middle East, or North Africa"[10] and includes people who checked the box "White" on the census form or wrote in entries like Irish, German, Italian, Israeli, Lebanese, or Scottish.

Black or African American: Black is commonly used for persons of darker skin color with origins in sub-Saharan African populations. The Census Bureau describes "Black or African American" people as having "origins in any of the Black racial groups of Africa"[10] and includes people who checked the "Black, African American, or Negro" box on the census form or provided write-ins of African American, Afro-American, Haitian, or Nigerian when asked to describe their race/ethnicity.

American Indian and Alaska Native (AIAN): The Census Bureau defines American Indians and Alaska Natives as persons "having origins in any of the original peoples of North and South America (including Central America) who maintain tribal affiliation or community attachment."[10, 16] They also include those who report their race as American Indian/Alaska Native or who wrote in their tribal affiliation for the U.S. Census. American Indian/Alaska Native populations are heterogeneous, with many distinct cultures and languages. As Cobb points out, American Indian/Alaska Natives "live in environments ranging from the deserts of the Southwest to the Alaskan tundra."[17] Currently, there are 562 federally-recognized tribal entities in the U.S. and many more recognized by individual states. One-hundred and seventy-five Native American languages are still spoken in the U.S.

Asian or Pacific Islander (API): Beginning with Census 2000, the U.S. Census Bureau collected and reported its decennial census data using new and separate definitions for "Asians" and "Native Hawaiians or Other Pacific Islanders." "Asians" are defined as "people having origins in any of the

original peoples of the Far East, Southeast Asia, or the Indian subcontinent," including, but not limited to, people from China, Japan, Korea (Far East); Cambodia, Thailand, Vietnam (Southeast Asia); and India, Pakistan, Sri Lanka (Indian subcontinent).[10]

Native Hawaiians or Other Pacific Islanders (NHOPI) are defined as "people having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands."[10] Although OMB classified Native Hawaiian and other Pacific Islanders in their own race category in 1997, the National Cancer Institute (NCI), and other cancer research entities; e.g., the American Cancer Society (ACS), continue to collect and report national cancer surveillance data for these two distinct population groups in the "Asian/Pacific Islander" aggregate, and most research studies do not distinguish between the two broad categories.

The Need for Disaggregated Racial/Ethnic Data

The practice of collecting and reporting health data in the broad and heterogenous categories "Asian/Pacific Islander" and "American Indian/Alaska Native" is motivated by the desire for sufficient number of health outcomes to achieve statistical significance when evaluating the data. Unfortunately, this may result in obfuscating important health disparities among subpopulations within these groups.

Unaware of (or perhaps insensitive to) the complexity of heterogeneity of the more than 60 distinct population subgroups contained within the "Asian/Pacific Islander" rubric, the policy and practice of collecting and reporting aggregate Asian/Pacific Islander breast cancer rates serves to obscure those Asian/Pacific Islander subgroups with high incidence and/or mortality rates. Additionally, breast cancer control, research and funding decisions based on aggregate Asian/Pacific Islander data serve to further perpetuate the myth that breast cancer incidence and mortality rates remain low across all Asian and Pacific Islander populations; ultimately, these practices will result in even greater breast cancer disparities among some Asian and Pacific Islander women.

For example, in "Cancer Incidence and Mortality in California: Trends by Race/Ethnicity, 1988 – 2001," the California Cancer Registry (CCR) reports that invasive female breast cancer incidence rates for Asian women remain lower than other groups.[18] However, disaggregation of Asian/Pacific Islander breast cancer data reveal substantial increases in breast cancer incidence rates for Japanese, South Asian, Chinese and Korean women. Since 1988, California breast cancer mortality rates have either decreased or exhibited minimal change, while mortality rates among the state's South Asian women and Filipinas rose slightly during this period. However, in a recent joint ACS/CCR report,[19] trend tables of breast cancer incidence and mortality showing aggregate Asian/Pacific Islander breast cancer rates over the same time period all but obscure rate increases seen in specific Asian populations when such data are disaggregated.

Key to understanding critical breast cancer surveillance data for U.S. Asian, Native Hawaiian and other Pacific Islander women is knowledge of

their U.S. census and demographics, and the impact of nativity, immigration, and generation in the U.S. for Asian/Pacific Islander subpopulations on reported cancer surveillance data.[14] Nationally, the Asian/Pacific Islander census has doubled each decade since 1970, from 1.5 million to nearly 13 million for Census 2000. Since 1990, the Asian/Pacific Islander population has grown 41 percent – faster than any other U.S. race or ethnic group. In 2005, the aggregate Asian/Pacific Islander census was 15,366,331, of which 989,673 were Native Hawaiian and other Pacific Islander (6.4 percent) and 14,376,658 were Asians (93.6 percent). Comprised within the aggregate "Asian/Pacific Islander" rubric are more than 30 different Pacific Islander subpopulations and more than 30 diverse Asian ethnic groups. Globally, more than 2,000 distinct Asian and Pacific Island languages and dialects are spoken, of which ~100 are commonly spoken in the U.S.[20]

In Census 2000, 69 percent of Asians and ~20 percent of Pacific Islanders reported nativity outside the U.S. Research reveals immigrant populations are more likely to experience significant language barriers and social isolation, and to be socioeconomically disadvantaged.[21] An important but often-overlooked factor in Asian/Pacific Islander heterogeneity is the bimodal distribution of socioeconomic status between subpopulation groups.[22] Spanning the socioeconomic status continuum, within the Asian/Pacific Islander rubric exist those groups with the highest and lowest levels of English language proficiency, educational attainment, income, coverage and quality of medical insurance, and numerous other markers of social class in the U.S. Although Census 2000 reports Asian/Pacific Islander (aggregate) populations to have the lowest (11 percent) poverty rate in the U.S., second only to non-Hispanic whites (8 percent), only three Asian American subgroups (Filipino, Japanese and Asian Indian) and no Pacific Islander subgroup had poverty rates at or below the U.S. national average (12 percent). Hmong (38 percent) and Cambodian (29 percent) populations had the highest poverty rates. Despite the number and extent of poor and medically underserved subgroups within the Asian/Pacific Islander rubric, aggregate collection and reporting of demographic and health data continue to obscure troubling health disparities.

Of course, there are valid situations in which aggregate data reporting is useful and desired. The ability to track trends over time and between major population groups are examples of such situations; the advent of health disparity research has relied heavily on these important contributions to the literature. Nonetheless, it is important to recognize the adverse impact aggregate reporting of data has had on communities. Advances in detailed, population-specific research aside, studies reporting aggregated race/ethnicity data continue to dominate the biomedical literature. Thus, for our review of the literature, we will try to highlight studies that provide detailed race and ethnicity data as much as possible. Where the research limits our efforts, we will cite the available literature, cautioning the reader regarding the reliability (or lack thereof) of aggregate data across all or most Asian and Pacific Islander populations.

Genetics and Race/Ethnicity

The degree to which health disparities are the result of genetically-driven biologic differences between racial/ethnic groups has long been a source of contention. The recent advent of bioinformatics has given researchers new tools to evaluate this issue. Some researchers argue that genetic clustering generally corresponds with the continental groups described above, while others find that genetic groupings diverge from traditional racial/ethnic categories.[12, 23] In addition, relatively little is known about the interaction of environmental and genetic factors.

The initial analysis of human genome commonalities between individuals and racial/ethnic groups has yielded complicated results. There are no "African," "Caucasian" or "Hispanic" genes, but a differential proportionate distribution of alleles across populations. There is greater variation between individuals than between groups (no matter how they are defined), even though individuals with the same geographic ancestry are more similar to each other on average than to individuals with different geographic ancestries.[24] Some researchers report that they find good correlation between the self-reported race and racial groupings based on continental origins.[12] However, others warn that the groupings may not be as clear-cut as they first appear, because of possible overclustering[25] and a lack of true diversity in the sample population.[24] Additionally, there is disagreement about whether the broad continental groupings will be predictive of the presence of specific variants in individuals based on their group membership. The admixture of populations, particularly in the U.S., could require genetic assignment on the individual level according to a continuum, rather than discrete separations into categories. This debate becomes important when trying to determine whether this method of grouping populations can ultimately be used to inform individuals about biological risks and whether it could be used to predict drug responses.[12, 26, 27] However, it is still unknown whether race categories and/or the continuum of race groupings are biomedically useful or predictive of treatment response, independent of genetic factors.

Efforts to characterize the magnitude and impacts of these issues as well as strategies for addressing them have been attempted, and more have been proposed and are underway. The National Institutes of Health (NIH) has released at least two relatively recent program announcements to address these broader methodological issues, and resources such as the International HapMap database[28] and the Human Genome Diversity Cell Line panel[29] are being developed to investigate the relationship between genetic clustering in populations and race. While acknowledging the need for these methodological efforts that are necessary to improve research on race/ethnicity,[30, 31] we focus this section on documenting the breast cancer disparities across the standard OMB racial/ethnic groups, with attention to identifying gaps and future directions for moving beyond these categories to better understand underlying factors responsible for the disparities.

Overview of the literature, by outcomes in breast cancer continuum

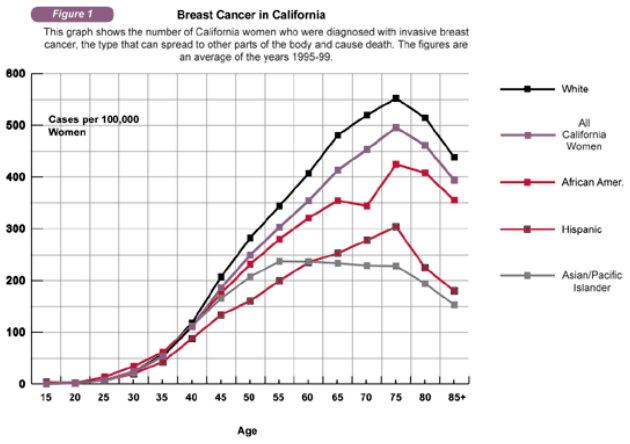
Incidence

Breast cancer incidence varies markedly by race/ethnicity in the U.S., with the highest age-adjusted rates (130-140 per 100,000) in non-Hispanic white and Native Hawaiian women, intermediate rates in African American, Japanese and Filipina women (80–120 per 100,000), and lower rates in Hispanic, Chinese, South Asian, Vietnamese, and Korean women (50–79 per 100,000).[18] Thus, among women living in the same country, breast cancer rates can have up to a three-fold variance solely on the basis of racial/ethnic classification.

Racial/ethnic differences in age-specific incidence of breast cancer are well-described for the broad OMB-defined racial/ethnic groups. For example, Figure 1 below summarizes age-specific incidence of invasive breast cancer in California (1995–1999) as described in a recent report from the California Cancer Registry.[32] It illustrates the high rates among non-Hispanic white women and the relatively low rates among Asian/Pacific Islander and Hispanic women. It also illustrates the long-recognized 'cross-over' phenomena where the rates for young women are higher for black than for non-Hispanic white women but then reverse in older women, such that non-Hispanic white women have the higher rates.[33]

The presentation of aggregate data such as these, however, masks the high incidence rates among certain Asian/Pacific Islander subpopulations, such as Native Hawaiians and Japanese Americans.[34] Furthermore, it suggests that age-specific incidence rates among Asian/Pacific Islander women level off after menopause. Disaggregated California data, reported by National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (although for a slightly earlier time period), paints a very different picture, with increasing age-specific rates after age 55 for Chinese, Filipina, Japanese, and Native Hawaiian women.[34]

Temporal trends in breast cancer incidence also vary by racial/ethnic group. However, because of historical constraints in the level of detail collected by population-based registries, most of this evidence has been limited to the last decade or so, and much of it has been limited to the broad



aggregate racial/ethnic groups. Interestingly, incidence rates in women age 50 and under have been stable in most racial/ethnic groups, but have been significantly decreasing in African American women,[19] to the point where the previously observed higher rate among younger African American women relative to white women[33, 35] may no longer exist.[19, 36]

An interesting phenomenon in breast cancer incidence for black and white women is what has been labeled the "crossover" effect. While breast

cancer incidence is highest in non-Hispanic white women, African American women under the age of menopause (approximately 40 – 50) have higher breast cancer incidence rates compared to white women, but have lower rates in older ages.[33, 37] Studies have suggested a relationship between the crossover effect and reproductive factors related to socioeconomic status, although previous research is not conclusive.[33, 38, 39] This shifting disparity of the crossover to lower incidence rate in older women differs by stage at diagnosis. The crossover occurs at age 35–39 years for localized stage, and at ages 55–59 for regional stage. For distant stage, black women of all ages experienced higher incidence compared with white women. Similar crossover effects do not exist for American Indians or Asians/Pacific Islanders compared to white women, or for Hispanic women compared to non-Hispanic women.[37]

Another relevant age-related phenomenon is Clemmenson's Hook, which describes a shift in the slope of breast cancer incidence rates around the time of menopause. Incidence rates continue to increase following menopause for women of all race and ethnic groups in the U.S., although at a much slower rate of increase compared to pre-menopause increases. The rate of increased incidence following menopause for Asian/Pacific Islander women in the U.S. is even lower than that of whites and blacks, but is important to note, because for at least one subpopulation of Asians/Pacific Islanders, Japanese women born in Japan, incidence rates decline following menopause.[40, 41] This significant difference indicates the impact of environment on breast cancer incidence.

While incidence rates appear to be stable in most of the broad racial ethnic groups from 1988-2001, a more detailed examination of the disaggregated statewide data reveals some alarming trends. Most notably, incidence rates increased among Japanese, South Asian, Chinese, and Korean women.[18] Furthermore, in a detailed study of breast cancer diagnosed in Los Angeles (L.A.) County, California, significant differences were noted among the more detailed subgroups of Asian/Pacific Islander women, with a greater than two-fold difference in the 1997 incidence rates for Filipinas over Korean women, and for Japanese over Chinese women.[42] This study also reported a very sharp rise in incidence rates for Japanese American women, such that continuance of this trend may result in Japanese American breast cancer incidence rates in L.A. County exceeding those of non-Hispanic-white women in the near future.[42]

Breast cancer incidence among American Indians and Alaska Natives has been challenging to monitor, owing mostly to difficulties in accurate identification of these groups in cancer registry settings, lack of reliable denominator data, and unstable rate estimates due to small numbers. This misclassification bias is a significant problem with no easy solution. Misclassification could explain the particularly low incidence rates for American Indian and Hispanic women. Prior to expansion of SEER, the only American Indian data came out of the relatively healthy American Indian groups in New Mexico, thus limiting the numbers and reliability of the data. Often rate estimates are so unstable that they are not presented separately for American Indians/Alaska Natives. Historically, it has been reported that American Indian/Alaska

Native women have low breast cancer incidence rates.[43] Recently, however, it has been argued that data are really inadequate for fully ascertaining the breast cancer experience in this group of women. Most data on American Indians/Alaska Natives come from either SEER or the Indian Health Services (IHS).[44] Approximately 75 percent of the American Indian population in the SEER data come from Arizona and New Mexico, but only 19 percent of the American Indian population live in these states.[45] Furthermore, breast cancer rates may be lower among southwestern American Indians than other American Indians/Alaska Natives. Data from the IHS also potentially undercount breast cancer cases because they are based on hospital discharges only and because many American Indians/Alaska Natives do not receive care at the IHS.[44] Linkages with the IHS have improved classification. However, over half of all American Indians/Alaska Natives live in urban areas, are part of unrecognized tribes, or otherwise may not have access to IHS. Regardless, IHS-enhanced estimates of incidence rates for American Indians in New Mexico and Alaska Natives in Alaska suggest that rates for American Indians/Alaska Natives may be substantially higher, perhaps as much as four-fold higher, than rates in U.S. white women.[46]

By virtue of their close interrelationships, it is difficult to interpret racial/ethnic differences in breast cancer incidence without consideration of socioeconomic status and immigration status. However, joint relationships among these factors are difficult to study using population-based cancer registry data, owing to deficiencies in available numerator and denominator data. Several studies[47, 48] have documented that racial/ethnic differences in invasive breast cancer incidence persist after adjustment for area-level socioeconomic status. For example, among Californians living in areas of the highest socioeconomic quintile, rates were 87 percent higher in non-Hispanic whites, 52 percent higher in African Americans, and 31 percent higher in Hispanics, compared to Asian women.[47]

While there appear to be few recent studies assessing racial/ethnic differences according to immigration status, there is a well-established body of literature documenting differentials in breast cancer risk among Asian women according to acculturation status. These studies show that breast cancer risk increases with generational status in the U.S., and with time since migration, even within a woman's lifetime.[49] In women under age 54, risk almost doubled in foreign-born women who lived in the U.S. for 18 years or longer, compared to those who lived in the U.S. for two-seven years.[50] However, even among long-term foreign-born residents, risk remained lower than in U.S.-born Asian Americans. As with Asians, the incidence of breast cancer in Hispanic women is strongly influenced by migration patterns and acculturation. Incidence rates are twice as high in U.S.-born Hispanics as in foreign-born Hispanics, and increase with increasing duration of residence in the U.S. and over successive generations.[51]

Certain racial/ethnic groups in California are markedly heterogeneous with respect to immigration status. Higher breast cancer incidence rates in acculturated subgroups may be masked by very low rates in recent immigrants. The changing associations of incidence rates with

socioeconomic status over time observed by Krieger support an interactive role of acculturation and socioeconomic status having an impact on incidence among Asians, Pacific Islanders, and Hispanics.[48]

Breast cancer subtypes

Potential racial/ethnic disparities in the incidence of specific subtypes of breast cancer generally have not been explored at the population level. A recent study, however, suggests that substantial differences in tumor characteristics exist across racial/ethnic groups in the U.S.[52] This study reported that relative to non-Hispanic whites, the risks for estrogen/progesterone receptor-negative breast cancers were elevated for African Americans, American Indians, Filipinos, Chinese, Koreans, Vietnamese, Indians/Pakistanis, Mexicans, South/Central Americans, and Puerto Ricans, with risk estimates ranging from 1.4 to 3.1. The investigators' analysis of rates by histologic subtype confirmed previously documented reports of higher rates of lobular cancers among non-Hispanic white women compared to all other groups.[32] and revealed significantly different risks across racial/ethnic groups for five of the seven histological subtypes examined. Similar racial/ethnic differences in tumor characteristics have been documented in California populations as well.[53, 54]

DNA microarray analysis of breast tumor characteristics has led to a new classification scheme.[55] Tumors can be divided into clinically relevant subcategories (luminal A, luminal B, basal-like and erb-B2) that have biologically distinct mechanisms.[56, 57] Using this classification, a recent study has found that the basal-like subtype, which correlates with the worst prognosis, was more prevalent in pre-menopausal African Americans than in any other population examined.[58]

Differences in tumor biology may reflect differential genetic susceptibilities and/or differential exposures to environmental contaminants or established risk factors (e.g., association of HRT use with lobular subtype), and may relate to certain clinical differences in breast cancer observed among racial/ethnic groups, including later stage at diagnosis and poorer outcomes. The California Cancer Registry now routinely collects information on tumor hormone responsiveness, histologic subtype, and Her-2-neu status. More studies similar to the one conducted by Li and colleagues,[52] including those in younger women, may help elucidate the degree to which such differences in tumor biology may play a role in racial/ethnic disparities in breast cancer treatment, survival, and mortality.

Incidence: Conclusions and future directions:

Overall, non-Hispanic white women bear the greatest burden of breast cancer incidence. An important area for future research is to identify groups with possibly under-recognized risk. This most certainly should involve examination of racial/ethnic differences in breast cancer incidence by detailed racial/ethnic subgroup, socioeconomic status and immigration status. Racial/ethnic disparities in the incidence of breast cancer by histologic subtype and tumor hormone responsiveness generally have not been well documented and warrant further attention. Because it appears that recent temporal trends in

breast cancer incidence rates vary by racial/ethnic group, it is important to continue to monitor these patterns of incidence, both to generate hypotheses related to etiology and to target prevention and cancer control strategies.

The very limited data on American Indians and Alaska Natives suggesting potentially high rates of breast cancer incidence[46] warrants further attention and underscores the need to develop better data ascertainment methods to document the cancer experience of this population in the U.S.

Population-based cancer registry data represent the major source for measuring and tracking racial/ethnic disparities in breast cancer incidence. Cancer registry data, however, are narrow in scope, consistent with mandates to broadly collect information for all cancers diagnosed in defined geographic areas, and the data are based on medical records. They do not include important information available from other sources on personal risk factors for breast (e.g., pregnancy history, hormone replacement therapy use) or on potential exposures to chemical contaminants in the environment or occupational settings. Supplementing CCR data--through linkages to administrative data from Medicare, Medicaid and large health maintenance organizations such as Kaiser--could greatly enhance the use of these data to evaluate cancer disparities. While tumor registries have limitations for assessing etiology, their use has been increasing in evaluating treatment patterns and quality of care.

Etiology

The reasons for the pronounced racial/ethnic disparities in breast cancer incidence are only partially understood, because until recently, relatively few epidemiologic studies have been conducted in non-white populations. Several large cohort and case-control studies that include non-white women were initiated in the 1990s and have started to produce important data towards a better understanding of breast cancer risk factors in African American, Hispanic, and Asian American women. Examples include the Multiethnic Cohort Study,[59] Women's Health Initiative,[60] Black Women's Health Study,[61] WISH Study,[62] New Mexico Women's Health Study,[63] Carolina Breast Cancer Study,[64] CARE Study,[65] San Francisco Bay Area Breast Cancer Study,[66] Northern California Family Registry for Breast Cancer,[67] Los Angeles Breast Cancer Study in Asian Americans,[68] and the Four Corners Breast Cancer Study.[69] For American Indian and Alaska Native women, information on breast cancer risk factors is still very limited.[70]

Differences in the *prevalence* of known risk factors (hormonal and lifestyle factors) are likely to contribute to racial/ethnic disparities in incidence. It remains uncertain whether the *magnitude* and *direction* of associations with known risk factors differ between racial/ethnic groups. Few studies have examined the contribution of environmental exposures to the observed racial/ethnic disparities in breast cancer incidence. Differences in genetic susceptibility and in combined effects of genetic and hormonal/lifestyle/environmental factors may also

influence breast cancer incidence and contribute to disparities.

Racial/ethnic differences in hormonal and lifestyle factors

Most research to date aimed at elucidating etiologic factors underpinning the noted racial/ethnic disparities in incidence has focused on the degree to which racial/ethnic differences in the *prevalence* of established risk factors are likely to contribute to racial/ethnic differences in incidence. Epidemiologic studies that reported on breast cancer risk factors in African Americans,[35, 59-62, 64-66, 71-79] Hispanic,[59, 60, 63, 66, 69, 80, 81] or Asian Americans[50, 59, 60, 68, 77, 82] demonstrate wide variation in the prevalence of risk factors between racial/ethnic groups in the U.S. The prevalence has been shown to vary by place of birth (U.S.-born versus foreign born)[59, 81, 83] and acculturation [81] and to change over time.[84] While in general, the prevalence of factors that increase or decrease risk tend to parallel incidence rates, there are numerous exceptions and inconsistencies, suggesting a complex interplay of multiple factors and the likely importance of yet-to-be identified factors that underlie the risk in specific racial/ethnic groups.

There is some evidence that the relationship of breast cancer risk with known risk factors may not be the same (in *direction* and/or *magnitude*) across all racial/ethnic groups. For example, in non-Hispanic white women, it has been well established that breast cancer risk increases with decreasing age at menarche.[85, 86] This relationship, however, has not been as consistently documented among African American women, with some studies reporting an inverse association[64, 72] and others reporting a positive or no association.[62, 75, 79, 87] Likewise, studies in Hispanic women have produced mixed results. Later menarche has been associated with increased risk in some studies,[63, 80] and decreased risk among foreign-born, but not U.S.-born, Hispanics.[87] For Asian/Pacific Islander women, an inverse association has been reported that is similar to that seen in white women.[83]

Similar inconsistencies across racial/ethnic groups in either the *magnitude* and/or *direction* of the risk relationship have been reported for several other risk factors, including parity, age at first full-term birth, breast-feeding, and oral contraceptive use.[61-65, 79, 87] These inconsistencies may in part be due to the relatively small numbers of non-white women included in the above studies and heterogeneity in risk due to immigration status. Differences in underlying biologic mechanisms may also play a role, as has been suggested, for example, for the effect of body size.[69]

Racial/ethnic differences in genetic/biologic factors

There is emerging evidence that genetic factors that contribute to the development of breast cancer may also differ by race/ethnicity and may contribute to racial/ethnic differences in incidence. For example, deleterious mutations in BRCA1 and BRCA2 are more common in Ashkenazi Jewish women than non-Jewish white women and non-whites, and African Americans appear to have a different spectrum of BRCA1 and BRCA2 variants than white women. Few studies to date, however, have investigated BRCA1 and BRCA2 mutations in non-white populations. The prevalence of common genetic variants, such as

single nucleotide polymorphisms (SNPs), also varies by race/ethnicity, as documented in various HuGE reviews.[88]

Researchers have linked risk disparities to germ line mutations such as BRCA1/2 and/or differential gene/environment interactions in culturally-shared behavior or geography.[89, 90] Fewer studies have been performed looking at differences in epigenetic changes,[91, 92] but studies in this area may give more clues to differential gene/environment interactions.

Increasingly, molecular epidemiologic studies assess breast cancer risk in relation to genetic variants in specific pathways, primarily comparing Caucasians and African Americans. Porter et al.[93] conducted a study looking at the expression of cell cycle regulatory genes, among other factors, in grade-matched tumors from African American and Caucasian women. They found reduced levels of cyclin D and elevated levels of cyclin E and p21 in the tumors of African American women, which are all hallmarks of tumors with poor prognosis. Other studies have reported that the ethnic disparity in genetic mutation may lie in the types of mutations rather than the frequency. For example, Shiao et al.[94] found similar rates of p53 mutation rates in African Americans and Caucasians, but observed that African Americans had more G:C to A:T mutations and Caucasians had more A:T to G:C mutations. This variation in mutations may indicate a difference in carcinogen exposures.

Many associations are based on small sample sizes, and often not replicated in larger studies. Several studies in non-white populations cited above have collected blood samples (e.g., the Multiethnic Cohort Study, Carolina Breast Cancer Study, CARE Study, San Francisco Bay Area Women's Health Study, Northern California Family Registry for Breast Cancer) and have begun assessing breast cancer risk in non-white populations in relation to genetic variants in different pathways, as well as the modifying effect of lifestyle and environmental factors.[95-101]

There has been speculation that racial/ethnic differences in endogenous hormone levels may partially explain some of the racial/ethnic disparities in breast cancer incidence, particularly with respect to the high rates among Native Hawaiians and young African American women, both of whom have been reported to have high levels of pre-menopausal estrogen and progesterone. Pike et al.[59] speculated that the strikingly high incidence of breast cancer seen among Native Hawaiians in the Multiethnic Cohort Study may be due to a) higher endogenous pre-menopausal serum estrogen and/or progesterone levels, which may have a carryover effect on post-menopausal breast cancer risk; b) elevated post-menopausal serum estrogen levels and differences in the distribution of genetic polymorphisms in the sex steroid and gonadotropin metabolism pathways; c) elevated insulin-like growth factor levels; or d) dietary factors.

Interactions of Genetics, Lifestyle/Environment, Socioeconomic Status, and Race/Ethnicity

Differences in proportions of tumor markers by specific race/ethnic group are most likely due to variables other than race for women diagnosed with breast cancer in the U.S., where it is widely

known that race is strongly correlated with socioeconomic status. In addition, several significant lifestyle/environmental etiologic factors for breast cancer are strongly correlated with race and socioeconomic status. These known and suspected etiologic factors include lactation history, patterns of oral contraceptive use and menopausal hormone use, age at first birth, parity, BMI/obesity, physical activity, and alcohol use.

The impact of the interaction of these factors with genetics, race, and socioeconomic status is mostly unknown, but hypotheses are beginning to emerge from the literature. For example, studies show that increased parity and younger age at first birth are associated with decreased risk of breast cancer. These protective factors are more prevalent among African American women and women of low socioeconomic status.[102, 103] However, these factors that reduce the risk of breast cancer are associated with poor prognostic markers and breast cancer subtypes.[104] It is hypothesized that these risk factors are partially responsible for African American women diagnosed with breast cancer presenting with disease characteristics associated with poor prognosis, such as younger age, advanced stage, and biologically aggressive tumors, as found in several studies including.[105-108]

Results of studies that examine the combined effect of race and socioeconomic status have been mixed in determining whether race is an independent significant predictor of breast cancer prognosis apart from socioeconomic status.[105-107, 109-114] However, the majority of well-done studies have concluded that if socioeconomic status, treatment, prognostic tumor markers, and comorbidity are equivalent--or are all controlled in multivariate statistical analyses--race is not a factor in breast cancer outcome. Studies show these confounders are not equally distributed by race and/or socioeconomic status in women diagnosed with breast cancer.[108, 115, 116]

Etiology: Conclusions and future directions

We have yet to fully understand the etiologic factors underpinning the observed racial/ethnic disparities in breast cancer risk. Much of the research to date has been aimed at comparing the prevalence of known risk factors across racial/ethnic groups. Several studies have concluded that known risk factors do not fully explain the differences in incidence[59] or risk[51, 60] between racial/ethnic or migrant groups.[51, 59] These studies generally have focused on reproductive and menstrual factors, while dietary and other behavioral risk factors, such as physical activity and smoking, have received comparatively less attention. Almost completely ignored in the literature to date is an examination of the degree to which exposures to environmental contaminants play a role in racial/ethnic disparities in risk. The currently known breast cancer risk factors, which were primarily identified by studying white women, explain only about half of all breast cancers in white women.[62, 117-121] Furthermore, it is not entirely clear that these factors impart the same risk in other racial/ethnic groups. Thus by limiting our evaluation of racial/ethnic differences to these factors, we are inherently hindering our ability to fully explain racial/ethnic disparities in breast cancer.

One of the fundamental challenges in studying racial/ethnic disparities in breast cancer is

disentangling the effects of genetics, socioeconomic status, immigration status, and potential exposures to environmental contaminants. There is evidence that racial/ethnic disparities persist after adjustment for socioeconomic status and vice versa. While difficult to conduct, research focused on women that are discordant for these factors may help tease out the independent effects of these highly correlated factors.

Consideration of exposures to chemical contaminants through the workplace or ambient environment generally has not been considered in the body of literature on racial/ethnic differences in breast cancer incidence and risk. The strong regional variations observed in breast cancer incidence, with rates highest in urban and industrialized areas, suggest a potential role for these types of exposures. While overall, non-white populations (who tend to have lower rates of breast cancer incidence), are more likely to live in highly polluted areas, there may be some specific exposures more common to white women that have yet to be identified. Furthermore, the potential role of environmental contaminants in explaining the modestly higher rates of breast cancer incidence among young African American women largely has been ignored. Future research aimed at elucidating factors responsible for racial/ethnic disparities in incidence needs to move beyond considering solely the known breast cancer risk factors to identify and include occupational, environmental, and social factors.

Screening

Historically, non-white women have had lower rates of mammography screening than have white women in the U.S. After nearly two decades of health promotion efforts to improve mammography screening rates, racial/ethnic disparities have been greatly reduced, especially in California. In its publication Healthy People 2010 (HP2010), the CDC set out as a national objective to achieve 70 percent of women age 40 and older having received a mammogram in the previous two years.[122] Most recent data reported by the 2001 California Health Interview Survey (CHIS),[123] indicate this goal has been reached in nearly all racial/ethnic groups in California, with the rate exceeding the HP2010 goal in white and African American women, and lagging slightly among Native Hawaiians and Pacific Islanders (Table 1).

Table 1. Women in California age 40+ who reported having a mammogram during the last two years by race/ethnicity, 2001.*

	Mammography use	
Race/Ethnicity	**% Screened in past 2 years**	**% Never Screened**
White	78.1	8.1
African American	78.5	9.4
Hispanic	69.9	17.7
Asian	67.2	17.2
Native Hawaiian/other Pacific Islander	63.4	§
American Indian/Alaska Native	68.8	10.0
All Women age 40 and older	75.5	10.7

* Source: 2001 California Health Interview Survey[123]

While the increases in mammography utilization over the last twenty years can be counted as one of the great successes of health promotion efforts within the public health community, these summary data mask some important pockets of remaining disparities in utilization. Specifically, an examination of screening rates by age indicates that screening rates among women age 40-49

years of age still fall short of the HP2010 goal for all racial/ethnic groups except African Americans.[32] Additionally, disparities in mammography utilization among subpopulations within these broad racial/ethnic groups persist.

A recent analysis of the 2001 CHIS data with a more detailed categorization of Asians revealed significant differences in mammography screening among specific Asian ethnic subgroups, with Cambodians and Koreans having significantly lower rates of utilization (Table 2).[124] Although no recent California data has been published by specific subgroups within Hispanic women, there is evidence that screening rates within the Hispanic population are likely to vary by country of origin, socioeconomic status, and level of acculturation.[125]

Table 2. Women in California age 40+ who reported having a mammogram during the last two years by detailed Asian ethnicity, 2001.*

Population subgroup	% Reporting mammogram in past 2 years
Chinese	64.6
Filipino	71.5
Japanese	76.4
Vietnamese	71.3
Korean	53.1
South Asian	69.6
Cambodian	56.6

* Source: 2001 California Health Interview Survey[124]

Major research efforts have sought to explain the factors underlying the well-documented underutilization among some Asian and Pacific Islander women. Asian/Pacific Islander women often share many of the structural barriers with other minority women, including lack of insurance, lack of health care access, low socioeconomic status, lack of a usual source of care,[90, 126-129] and lack of encouragement by physicians.[90, 130] Sociocultural factors, including low level of education,[127, 131] limited knowledge of breast cancer,[130] and low English proficiency[90, 132] have been found to be associated with low mammography utilization among Asian/Pacific Islander women. Furthermore, level of cultural assimilation, often measured by length of U.S. residency and English proficiency, has also been a critical determinant of mammography.[90, 132] Additionally, some qualitative studies using focus groups and key informant interviews have explored cultural beliefs that underlie health-seeking behaviors.[129, 130, 133] These studies have identified other perceived barriers to utilization, including having a male physician, fear of being exposed unnecessarily to radiation,[90] and the lack of sensitivity from hospital staff regarding their embarrassment of having to undress for a mammogram, which often discouraged them from returning for subsequent visits.[133] Similarly, other studies have shown a potential interaction between immigration status, cultural beliefs, and income (or other socioeconomic status-related variables) for perceived barriers to breast cancer screening.[134, 135] Unfortunately, many of these variables overlap with one another and are hard to measure quantitatively. Regardless, these studies illustrate the complexity with which the structural and sociocultural barriers operate in this heterogeneous population.

Screening: Conclusions and future directions

Health promotion efforts in the last few decades have greatly increased mammography screening rates and have helped reduce racial/ethnic disparities in mammography utilization. With the few notable exceptions discussed above, mammography rates in California have generally reached HP2010 goals across all broad racial/ethnic groups. More detailed analyses suggest that sociodemographic characteristics beyond race/ethnicity may be more important predictors of mammography utilization. Recent data from both CHIS and the California Women's Health Survey (CWHS) suggest that lack of health insurance may be one of the largest contributors to underutilization of screening mammography among all racial/ethnic groups.[123, 136] Only half of uninsured California women ages 40-64 report having a mammogram in the past two years, with uninsured Asians reporting the lowest screening rate (39.5 percent).[123] Having a usual source of care also appears to be an important predictor of mammography utilization, with women who have no usual source of health care reporting screening rates below 45 percent, regardless of race/ethnicity.[123, 137] (For more, see Section II, Chapter E.) These data suggest that rather than targeting specific racial/ethnic groups, it may be more effective to target interventions towards lower-socioeconomic-status women, particularly recent immigrants, and women with no health insurance and/or usual source of health care.

The ultimate goal of increasing screening rates and reducing racial/ethnic disparities in screening is to reduce the corresponding mortality associated with late-stage diagnoses. Controversy remains as to whether further efforts to increase screening will significantly improve racial/ethnic disparities in survival.[138] As discussed later in this chapter, despite having the highest mammography screening rates, African American women continue to be diagnosed at later stages and have worse survival rates than all other groups. This begs the question in terms of both the biology and post-diagnostic treatment of these cancers.

It may be that the HP2010 goal of 70 percent having had a mammogram in the last two years is not the yardstick by which to measure success. Debate persists over the ideal interval between screening mammograms, especially among women age 40–49.[139] Some consider 'full breast cancer screening' to also include annual clinical breast exams.[136] The American Cancer Society (ACS) and the California Department of Health Services recommend that women age 40 years and older receive both an annual mammogram and annual clinical breast exam.[140, 141] Recent California survey data suggest that only a little more than half of women 40 years of age and older meet this guideline, with similar racial/ethnic patterns as those seen for mammography usage within the last two years.[136] However, the efficacy of mammography screening in women under age 50 years remains a source of debate.[142] Breast tissue in younger women is more sensitive to radiation and is denser, making mammograms less effective.[143]

Finally, while the relatively small differences in screening rates seem to suggest that racial/ethnic differences in stage and survival are not due to disparities in screening, others would argue such a

conclusion is premature.[144] Dr. Smith-Bindman recently noted that these observations have been largely based on surveys of mammography use that are self reported, only consider recent use, and do not take into account reasons for mammography and frequency of use.[144] In her linkage-based study utilizing mammography registry data, in which she took these other aspects of mammography use into account, Dr. Smith-Bindman and colleagues found that compared to white women, African American, Hispanic, Asian, and Native American women were more likely to receive inadequate mammography screening.[144] Furthermore, this study reported that the higher rates of late-stage, high-grade tumors among African Americans disappeared when the data were stratified by screening interval. The results from this study underscore the need to firmly identify the optimal level and components of screening necessary to minimize late-stage diagnoses and ultimately maximize reductions in breast cancer mortality.

Diagnosis

Stage of disease at diagnosis is one of the strongest predictors of survival. Among women diagnosed with localized disease (tumor is confined to the breast tissue), the five-year survival rate is 97 percent, but it falls to 26 percent among women diagnosed with late-stage disease (when the tumor has spread to distant organs).[145] Known factors that contribute to later stage at diagnosis include infrequent mammography, delays in follow-up after abnormal mammographic findings, limited access to health care, and more aggressive tumor characteristics.[19, 60] Tumor size is often used as an indicator of delayed detection, because tumors smaller than one centimeter are primarily found by screening mammography, whereas larger tumors are often detected by additional modalities such as clinical examination. Both stage at diagnosis and tumor size are used as surrogate indicators of screening utilization and to evaluate potential inequities in quality and timeliness of follow-up.[146]

In California in situ and localized breast cancer incidence rates are highest in non-Hispanic white women and lowest in Hispanics, while the rates of late-stage disease are highest among black women and lowest among Asians/Pacific Islanders.[32] In a recent analysis of national cancer registry data, African Americans, American Indians, and Hispanic whites were all about twice as likely to be diagnosed with stage IV breast cancer as non-Hispanic white women.[147] This same study found that African Americans and Hispanics were somewhat more likely to be diagnosed with larger-sized tumors.[147] In these analyses, Latinas and Asians were also disaggregated into specific ancestry groups. Some variation in the likelihood of advanced-stage disease was seen across Hispanic ancestry groups (Mexican, South/Central American, Puerto Rican, and other Hispanic) with the highest risk in Puerto Ricans (OR = 3.6 compared to non-Hispanic whites), though the risk in all Hispanic sub-groups was statistically significantly elevated. Among Asians and Pacific Islanders, Hawaiians (OR = 1.4 compared to non-Hispanic whites), South Asian Indians/Pakistanis (OR = 2.3) and "other Asians" (OR = 1.7), were more likely to present with late-stage cancer, while Japanese women were less likely to present with late-stage disease (OR = 0.7).[147]

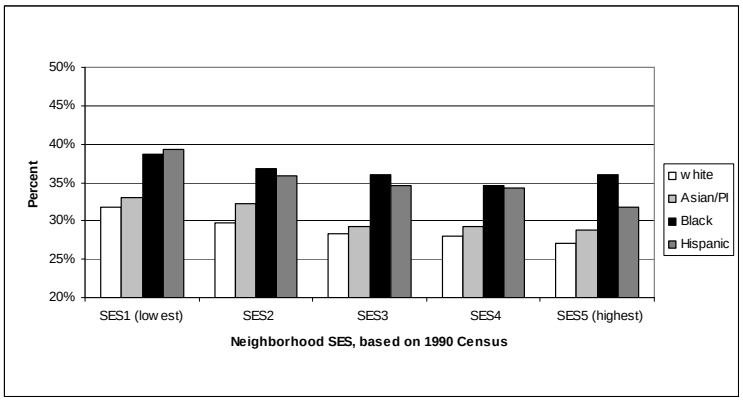
Potential risk for advanced-stage disease and larger tumor size among Asian Americans and Pacific Islanders by specific ancestry groups has been reported in several other studies.[147-152] The risk for larger tumors among Asian women appears to vary by both birthplace and place of ancestry.[153] Hedeen et al. reported that the risk for tumor size greater than one centimeter was significantly increased for all Asian-born Asian American women relative to white women (OR = 1.6), yet no elevated risk was observed for U.S.-born Asian American women, except for U.S.-born Filipinas.[153] These researchers also observed increased risk for advanced-stage diagnosis among U.S.-born Filipino women and Korean women, compared to U.S. white women. These results suggest that acculturation may influence beliefs and behavior with regard to accessing preventive services. However, approximately a quarter of the women in this analysis were missing information on place of birth, which could have biased the estimates of association between birthplace and risk of more advanced disease.[154, 155]

Birthplace and acculturation may also be important issues to consider when examining the differences in stage and tumor size among Hispanic women. A study based on SEER data found that Hispanic women born in Latin America had an increased risk for tumors larger than two centimeters, compared to their U.S.-born counterparts (OR = 1.72)[156] However, there was no significant difference in risk of advanced-stage disease by birthplace in this study (OR = 1.09).

Most studies have found that American Indian women are diagnosed at a later stage than white women.[147, 157-159] Several of these studies have used data from the New Mexico Tumor Registry.[157-159] However, a study in Washington state found that the distribution of breast cancer stage at diagnosis for American Indians was not significantly different from the distribution for whites.[160] These disparate results could be due in part to misclassification of American Indians, a frequent problem with cancer data, or because of heterogeneity between American Indians living in New Mexico and Washington State.[157] There are very little California-specific data on stage of breast cancer diagnosis in American Indians.

Differences in socioeconomic status do not fully explain the differences in breast cancer stage. At all levels of socioeconomic status in California, the disparities by race/ethnicity exist. As shown in Figure 1, in every socioeconomic status group, Blacks and Hispanics have the highest proportion of cases diagnosed at late stage (regional and remote) while whites and Asian/Pacific Islander women have the lowest percentage.

Figure 1. Percentage of breast cancer cases diagnosed at late stage (regional and remote) by neighborhood socioeconomic status (SES) and race/ethnicity, California, 1995-1999.*



*Source: California Cancer Registry Data, 1995–1999

Diagnosis: Conclusions and Future Directions

Disparities exist in staging and tumor size across racial/ethnic groups in all socioeconomic groups in California. These differences remain despite relatively small differences in rates of screening mammography, as previously noted. Determining the underlying reasons for these disparities will require the consideration of factors in addition to mammography. Several other possible reasons for delayed detection could include less frequent clinical breast exams, lag-time in follow-up on abnormal results, rapid tumor growth, or other biological factors. In addition, there may be more complex reasons for these disparities that relate to acculturation and other social and physical aspects of the environment.

Treatment

A number of studies have noted systematic differences in patterns of treatment between racial/ethnic groups of women presenting at comparable stages of disease. This section briefly summarizes the current evidence regarding these differences, with a focus on recommended treatment modalities thought to have a proven impact on breast cancer outcomes, particularly for quality of life and survival: 1) surgical treatment (vs. none); 2) breast conserving surgery for in-situ and invasive stage I and II breast cancers; 3) adjuvant radiation following breast conserving surgery and 4) use of adjuvant systemic therapy, such as chemotherapy and hormonal therapy. This section relies heavily on a recently-conducted comprehensive review of 23 studies of racial/ethnic patterns in cancer treatment by Shavers and Brown,[161] with additional information from a few studies that were not included or have been published since that article.

Brief overview of treatment options

The treatment regimen for an individual patient is determined by a complex series of clinical, demographic, and personal factors influencing both the treating physician(s) and the patient. Standard tumor-specific factors include stage, axillary lymph node status, histologic and nuclear grade, presence of lymphvascular space invasion, estrogen receptor and progesterone receptor status, and Her-2-neu status. Additional factors that also influence clinical treatment options are patient age, menopausal status, presence of comorbid conditions, presence of multifocal disease, and access to treatment. The specific standard treatment for given patient and tumor

characteristics are detailed in the Physician Data Query.[162] The social, cultural, and fiscal situation of the patient further influences the initial treatment plan.

In the late 1980s, clinical trial results established that survival following breast-conserving surgery with radiation therapy was equivalent to survival following mastectomy for women diagnosed with early-stage breast cancer. In 1990, the National Institutes of Health Consensus Panel recommended breast conserving surgery and radiation therapy to be preferable to mastectomy for early-stage breast cancer because of the potential for better quality of life. However, there continues to be substantial geographic, socioeconomic, and racial/ethnic variation in the use of breast conserving surgery in the U.S.,[163-165] raising concerns about "over-treatment" in some groups.[166] Radiation adjuvant to lumpectomy results in lower local recurrence rates, and possibly better survival, compared to lumpectomy alone.[167-171] Adjuvant chemotherapy or hormonal therapy (e.g., Tamoxifen) is also recommended for some women diagnosed with early-stage breast cancer. For advanced-stage cancer (stage IV), treatment usually involves chemotherapy and/or hormone therapy, and is given for palliation instead of cure.

Breast conserving surgery

The use of breast conserving surgery has increased in all race groups since the issuance of the 1990 NIH Consensus recommendation,[163-165, 172] but racial/ethnic differences in breast conserving surgery persist. Studies of patients diagnosed in the 1980s suggest that breast conserving surgery was less often used among blacks than whites.[161] However, more recent studies demonstrate few differences between blacks and whites in the utilization of breast conserving surgery, with some more recent studies.[112, 154, 164] showing slightly higher utilization among blacks. In an analysis of California Cancer Registry (CCR) data for stages 0-II breast cancer cases diagnosed from 1988-1995, Hispanics and Asians were approximately half as likely to have breast conserving surgery, while blacks were 16 percent more likely to have breast conserving surgery, compared to whites.[164] Lower rates of breast conserving surgery among Hispanic women were also recently noted among a population of Florida women diagnosed with early-stage breast cancer.[173]

A small but interesting analysis is based on 1996–1997 Detroit cancer registry diagnoses which were linked to Medicaid data and 1990 Census tract poverty information[112] considered the relative effects of black race and poor individual- and neighborhood-level socioeconomic status (as represented by Medicaid enrollment status and census tract poverty, respectively) on breast cancer stage at diagnosis, treatment, and survival. They found that blacks were 63 percent *more* likely than were whites to have breast-conserving surgery. However, patients who were on Medicaid fee-for-service and those who lived in census tracts with five percent or more below poverty were significantly *less* likely to have breast-conserving surgery. This suggests that in this population, blacks are receiving breast-conserving surgery at a higher level than are whites with comparable sociodemographic and clinical characteristics, but the most economically disenfranchised segments of the population, irrespective of race, are not. Lack of access to modern radiation therapy

facilities is a contributor. However, radiation treatment facilities are most often found in larger urban areas, where racial and ethnic diversity is greatest.

Lower utilization of breast conserving surgery among Asians has been consistently documented. In the study based on CCR data from 1988-1995, the proportion receiving breast conserving surgery was not only lowest among Asians/Pacific Islanders , but they also experienced the smallest increase in breast conserving surgery over the eight-year time period.[164] Studies that have considered Asian subgroups separately have found that certain subgroups, including Chinese, Filipinos, and Vietnamese, are more likely to undergo mastectomy for their early-stage tumors, a pattern not completely explained by the sociodemographics of the patient or clinical characteristics of the tumor.[53, 154, 174] Similarly, in a California interview study of 379 women residing in the greater Bay Area, Chinese women were more than three times more likely than non-Hispanic whites to have mastectomy (OR = 3.3; 95% CI = 1.5–7.1), attributable in part to language, education, and recency of immigration.[154] Linkage of Hawaii Tumor Registry data with health claims data determined that Japanese and Filipinas were 25 percent and 50 percent less likely than whites to have breast conserving surgery, respectively.[175]

In a recent large and comprehensive analysis of SEER data from five registries (Hawaii, Los Angeles, San Francisco/Oakland, San Jose/Monterey, and Seattle), comprising over 66,000 stage I and II breast cancer patients, 10,000 of whom were Asians, Goel et al.[176] found that breast conserving surgery for early-stage tumors was lower only among the foreign-born, with 43 percent of foreign-born Asians/Pacific Islanders having had breast-conserving surgery, compared to 56 percent of U.S.-born Asians/Pacific Islanders and 59 percent of whites. These results contribute to the idea that cultural and language factors may underlie some of the disparities in use of breast conserving surgery observed for Asian subgroups. Several qualitative studies are currently underway to address these cultural and language issues that may serve as barriers to receiving standard of care treatment, and their impact on patient-provider communications, treatment decision-making processes, and quality of life. (See additional discussion of this in Section II., Chapter D., Culture.)

Taken together, these studies focusing on factors responsible for the considerably lower receipt of breast conserving surgery among Asian women suggest that the pattern cannot be explained by known demographic or clinical factors. There appears to be some association of breast conserving surgery utilization with immigration and acculturation factors, and with institutional and provider factors, prompting further research into the role of specific cultural factors and patient-provider communication in the treatment decision-making process. This, together with the apparently lower rate of breast conserving surgery utilization in lower-socioeconomic-status black women, suggests that factors associated with available resources may further influence these treatment differences.

Adjuvant Radiation Therapy

According to the Physician Data Query,[162] adjuvant radiation is recommended following breast conserving surgery to minimize risk of recurrence. The impact on survival is well documented. Adjuvant radiation may be difficult for certain populations because it requires a nearly daily administration for an average of six weeks. Indeed, previous studies report lower breast conserving surgery usage and lower adjuvant radiation therapy among the aged and those living a farther distance from radiation facilities.[177-183] It has been estimated that 20-30 percent of women treated with breast conserving surgery do not receive radiation,[184, 185] and that adjuvant radiation therapy is lower among minority women than non-Hispanic white women.

Similar findings were reported among Latinas in Florida.[173] In a recent analysis of 10 years of SEER data (1988–1998), Joslyn reported that African American women with early-stage breast cancer were less likely to receive follow-up radiation therapy than their white counterparts.[108] This difference was observed in every age group, with the exception of those over the age of 85. Certain Asian subgroups also may be less likely to receive adjuvant radiation therapy following breast-conserving surgery. In a San Francisco Bay Area study, Chinese women were significantly less likely than white women to receive recommended adjuvant radiation or hormone therapy, while Japanese and Filipina women did not differ from whites in their use of adjuvant therapy.[174] In the study based on Hawaiian claims data, Filipinas were slightly, although non-significantly, less likely than white women to have adjuvant radiation, while Japanese were significantly more likely to have chemotherapy for node-positive disease.[175]

Adjuvant Systemic Therapy

Systemic adjuvant treatment provides undisputed benefits for women with early-stage breast cancer, but there has been little research on the risks and benefits for minority groups other than African Americans.[186] Studies have suggested that black women are less likely to receive optimal systemic adjuvant therapy than are white women and this may account in part for the disparities in survival outcomes. Several studies have evaluated early discontinuation of therapy and found that African American women were more likely to discontinue adjuvant chemotherapy early,[115] black patients are less likely than other patients to be prescribed tamoxifen,[187] and that they are less likely to be adherent when it is prescribed.[188] The disparity in outcomes became more pronounced in the mid to late 1980s, corresponding to the introduction of adjuvant therapy for this disease. This is particularly important, because if the reasons for disparities in the treatment of breast cancer can be elucidated, they may be modifiable.

One of the factors that may lead to the receipt of suboptimal adjuvant therapy is access to cancer treatment services, which is associated with income, education, and insurance [161, 189, 190] Adjuvant treatment for breast and other cancers is also associated with race.[191] For example, black patients receive less aggressive intravenous chemotherapy, [192] have fewer consultations with medical oncologists, and have a significantly higher risk of recurrence than whites. Only 50 percent of black women appropriate for adjuvant

chemotherapy for breast cancer are estimated to be receiving it.[193] Treatment delays, while uncommon, also may contribute to worse outcomes among black women.[194] Gwyn et al. found a relationship between black race and delays in both initial diagnosis and subsequent surgical treatment.[195]

Less is known about outcomes and treatment disparities in other racial groups. With the exception of blacks, differences in breast cancer incidence rates between most racial/ethnic groups are explained by risk factor distribution. To date, Hispanics and Asians have been underrepresented in the SEER database and, therefore, less is known about health care delivery to these minority subsets. One study looking at delay found that Spanish-speaking Latinas are more likely to experience a delay of three months or more from diagnosis to surgical treatment for breast cancer (36.4 percent vs. 9.1 percent for non-Latina whites, 18.6 percent for blacks, and 12.7 percent, for other Latinas, $p < 0.001$).[81, 196] Latinas were recently reported to be less likely to experience appropriate adjuvant therapy than were non-Latino white women. In this study, underuse was defined as omissions of radiation therapy after breast-conserving surgery, adjuvant chemotherapy after resection of hormone-receptor-negative tumors greater than or equal to one centimeter, or hormonal therapy for receptor-positive tumors greater than or equal to one centimeter.[197]

Similarly, for Asians, most research to date has focused on risk. Chinese women were also more likely than were white women not to receive adjuvant therapy, be it radiation after lumpectomy or hormonal therapy for estrogen receptor-positive disease. One population-based study identified differences in treatment for localized breast carcinoma by race/ethnicity that were not explained by differences in demographic, medical, or socioeconomic characteristics.[174]

As individualized therapy becomes an achievable goal, some researchers are re-examining how race should be incorporated into clinical assessments. The technology is not completely available yet and would require extensive institutional reorganization to disseminate broadly,[198] so the question also becomes what is the best stopgap approach until we reach that goal. Some researchers argue that we should take a race-blind approach to diagnosis, where the genetic profile of the tumor or disease markers should be the sole source of diagnosis and drug development. Others advocate for continuing to diagnose on the basis of both genetic profiling and race/ethnicity.[12, 24, 199, 200] By completely ignoring race/ethnicity, contributory factors to drug efficacy such as underlying genetic factors, cultural practices and institutional barriers could be overlooked. For example EGF-targeted therapies hold some promise for treating basal-like tumors, since they express EGFR, but initial clinical trial results are mixed.[201, 202] Jimeno and Hidalgo hypothesize that one reason for the failures of EGFR-targeted therapies is the variations in EGFR polymorphisms in different ethnicities. Including race/ethnicity in the arsenal as a surrogate for underlying genetics and cultural features is an imperfect, but useful, tool.

Other treatment issues

Racial/ethnic disparities exist in other domains of breast cancer treatment and treatment-related factors. For black compared to white patients, these include a longer period from diagnosis to treatment initiation, longer follow-up times after an abnormal mammogram, and less frequent minimum expected therapy or follow-up mammogram after diagnosis and treatment of breast cancer.[161] These patterns point to possible lag times in progressing from one aspect of care to another, and reflect poor continuity in cancer care among blacks. In a large multi-center study of disparities in black/white survival, treatment delays were attributed to institutional, rather than individual, factors. However, such delays did not appear to differ between black and white patients.[203, 204]

In a comprehensive analysis of national SEER data, Li et al. examined the differences between racial/ethnic groups who received appropriate and inappropriate treatment for stage I and II breast tumors less than 5.0 centimeters. Inappropriate treatment was defined as not receiving any treatment, adjuvant radiation, or axillary lymph node dissection, or receiving a subcutaneous mastectomy. Blacks, Asians/Pacific Islanders, and certain Hispanic subgroups were more likely than whites to receive "inappropriate" treatment.[147]

It has been theorized that racial/ethnic disparities in cancer treatment may arise in part from a failure of providers to engage patients in the decision-making process. Among blacks, mastectomy was more likely when the decision was perceived to have been made by the surgeon. However, in contrast to this belief, mastectomy over breast conserving surgery was in fact more likely among patients with greater decision-making involvement, as reported by Katz et al. for a population-based group of 1,844 patients from Detroit and Los Angeles.[205] Black women also visited more surgeons than white women, had more visits before surgery, and were less likely to have made the surgical decision during the first consultation. The authors suggest that these patterns reflect more treatment uncertainty among blacks, but they could again reflect discontinuity in care settings among minorities and the poor. Black women also reported receiving less information about breast conserving surgery. In an accompanying commentary, Nattinger reinforced the idea that decision making regarding early stage breast cancer is complex, and that innovative research on methods to improve the quality of the process is needed. Nattinger also pointed out that social factors may affect not only receipt of information to facilitate decision-making processes, but that the interpretation and synthesis of information may also differ by social factors and context. For example, some patients may have difficulty with the abstract notion that "an irradiated cancer is just as gone as a cancer that has been surgically removed."[206] It also requires "a high level of faith in medical science and clinical trial results to accept the idea that the possibility of local recurrence or new cancers in a conserved breast does not translate into any survival decrement."[205]

The observation that Asian women are more likely to receive mastectomy over breast conserving surgery for early-stage cancer has stimulated several qualitative studies aimed at identifying the cultural issues at hand in the breast cancer

treatment decision-making process. In addition to language and financial barriers, these studies identified a number of sociocultural factors unique to Asian women that may influence their treatment.[207-209] These studies are described in more detail in Section II, Chapter D of this Report.

Treatment: Conclusions and future directions

Apparent racial/ethnic disparities in treatment, particularly for early stage disease, are not necessarily explained by differences in tumor characteristics or clinical attributes of the patient. It is also not clear to what extent women of different racial/ethnic groups are being offered comparable treatment options. Cultural and economic factors appear to play large roles in differing treatment patterns. Black/white differences appear to be better explained by socioeconomic status than by race. Disparities observed for several Asian/Pacific Islander and Latina groups, particularly among recent immigrants, appear to be largely influenced by cultural beliefs, language barriers, and economic resources. Future work in this area will require attentiveness not only to the heterogeneity of breast tumors, but also to the heterogeneity of the patient population, as well as associated inequalities in socioeconomic resources and access to care.

Quality of life

A focus on cancer outcomes and survivorship has become an increasingly important area of research.[210, 211] Quality of life is a major component of survivorship research, particularly with the increasing population of breast cancer survivors due to improvements in survival and the sheer numbers of women coming into age groups at highest risk of breast cancer. Psychometric research has identified several relevant domains of importance in considering quality of life. For breast cancer, these generally include relationships with family, self-image, relationships with friends, social enjoyment, attractiveness, sexuality,[212] physical function, and symptoms. Determination of quality of life is highly subjective, relying predominantly on patient ratings, and is often subject to errors in reliability and validity. There are also several validated tools for assessing general quality of life, quality of life specific to cancer patients, and quality of life specific to breast cancer patients. Variations in results across studies could in part reflect differences in measurement tools. To date, there has been very little research on the impacts of breast cancer on the quality of life for specific racial/ethnic groups. Existing studies have mostly been qualitative in nature, though there have been a few studies that have applied more quantitative approaches.

Ashing-Giwa et al. conducted a qualitative study with breast cancer survivors of various race groups and reported some important similarities and differences between African American, Asian American and Latina women.[213] They found that all three groups expressed difficulties in adjusting to physical changes from cancer. These negative feelings about body image are of particular interest for Latina and Asian American women, who are more likely to have been diagnosed at a younger age and to undergo mastectomies. Asian American women, like African American and Latina women, cited spirituality and family support as critical factors in their recovery and

coping with their illness. However, unlike African American women, Asian American and Latina survivors identified language barriers and lack of time with their doctor along with lack of insurance (i.e. insurance status) as concerns for their health care and treatment. Such findings may correlate with their "choice" of mastectomy. Similarly, another qualitative study of Asian American women also found that these women expressed negative feelings about their bodies after their cancer surgeries, including feelings of inadequacy, loss of self-confidence and self-worth, unhappiness, and depression.[209] Asian women also expressed concerns related to worry about children and burdening their family. Since Asian American breast cancer survivors tend to seek professional assistance for psychosocial problems at a significantly lower rate than white women,[207] the burden of psychosocial stress may be more pronounced; no research has explored the implications of such psychosocial stress in this group.

Ethnic variations in quality of life exist among Asian/Pacific Islander women. In a population-based multiethnic study in Hawaii, Gotay and colleagues found that Filipina breast cancer survivors reported worse emotional functioning, as well as significantly more nausea, vomiting and overall symptoms, compared to other racial/ ethnic groups.[214] However, the observed difference may be attributable, in part, to Filipinas defining quality of life differently than other groups.[215]

A qualitative study of Chinese breast cancer patients reported important differences between American-born and foreign-born Chinese women in their beliefs about, perceptions of, and experiences with breast cancer.[216] Cancer carries a stigma for both groups, but is more prominent in the immigrant group. Furthermore, whereas American-born women named independence and freedom to describe quality of life, foreign-born Chinese women viewed wealth as an important dimension of quality of life.[216] These findings suggest that acculturation can influence quality of life and can have varying impacts on different dimensions of quality of life.

The most-studied group for quality of life, besides non-Hispanic whites, has been African American breast cancer survivors, for whom breast cancer diagnosis and treatment has been reported to negatively influence family and marital relationships, employment security, economic well-being, and satisfaction with body image and sexuality.[217] Qualitative research to identify and understand possible means of coping with these quality of life challenges have identified several distinctive factors in the African American breast cancer survivorship experience. For example, as compared to other ethnic groups, African American breast cancer survivors tend to rely more heavily on their spiritual faith as a source of support and on the church community as an important source of social support. The long history of African American resilience and survivorship has also been identified as an important coping resource.[213] A focus group including rural African American breast cancer survivors identified several intriguing areas for further research into breast cancer-related quality of life. This study identified as major concerns finding "safe," respectful sources of social support in light of the stigma of cancer, finding ways to feel comfortable and optimistic about the future,

and finding help with adjustment to the role of and the pressure of serving as a cancer survivor role model. Focus groups reinforced the important roles that spiritual faith and prayer, ensuring family support, and other social networks have for addressing these concerns.[218]

Studies of quality of life among Latinas after breast cancer suggest that Latina survivors have lower quality of life than do white women. Latinas in northern California reported higher rates of pain and numbers of symptoms after breast cancer treatment than white women.[219] In a study by Carver et al. of long-term breast cancer survivors diagnosed at early stage, Latinas reported more frequent negative feelings, more social avoidance, more distress about their family's future, and more distress about the possibility of recurrence than did other women. These differences did not appear to be rooted in differences in socioeconomic status.[220] Focus groups also found that Latina breast cancer survivors may experience more financial burden than other groups.[213]

Few studies specifically examining quality of life among American Indian/Alaska Native breast cancer survivors have been published. Several cancer survivor support groups exist, including the National Native American Breast Cancer Survivor's Network, a project conducted by the Native American Cancer Initiative of the Denver Indian Center and "A Gathering of Cancer Support." The project is designed to improve survival from breast cancer and quality of life.[221] Bauer also examined social networks and perceived social support among American Indian cancer survivors. The investigator found that family appears to be the principal source of social support compared to close friends, church, or community.[222] Palliative care has only recently formally been addressed for Indian Health Service and tribal health programs. Kitzes describes the needs for and barriers to palliative care, and several successful programs.[223]

Quality of Life: Conclusions and future directions

In summary, little research has been dedicated to exploring quality of life among specific racial/ethnic groups of breast cancer survivors. The few studies conducted in this area offer some insights into understanding the impact of the illness on these women, but more refined efforts are needed, especially in a population with such cultural diversity. To date, the studies seem to indicate some common themes of negative body image and other forms of emotional burden. Research attention should be given to examining some of the specific sociocultural burdens of psychosocial stress on breast cancer survivors and ways to reduce such stress in each of these groups. In order to evaluate ethnic variations across studies, reliable and valid measurement tools to measure the quality of life construct need to be developed and used.

Survival/Mortality

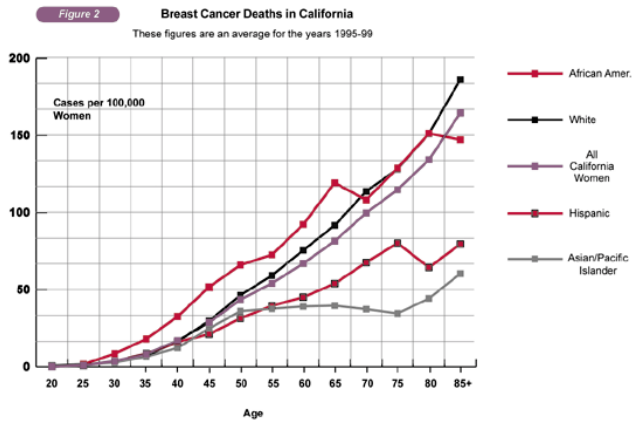
Breast cancer mortality rates vary widely by broad racial/ethnic group (Table 3, Figure 2). Most notable is the persistently higher death rate among African Americans compared to whites, despite a lower incidence rate.

Table 3. Average annual female breast cancer mortality rate (cases per 100,000), U.S. SEER data, 1998-2002[36]

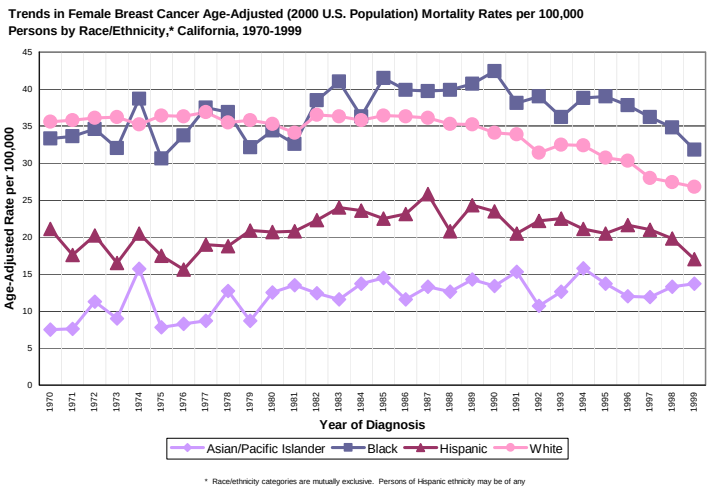
Race/ethnicity	Breast cancer mortality rate (per 100,000)
White	25.9
African American	34.7
Hispanic	16.7
Asian/Pacific Islander	12.7
American Indian/Alaska Native	13.8

While breast cancer mortality has been steadily decreasing since 1990,[19] this decline has not been realized equally among all racial/ethnic groups in the U.S.. In fact, although rates are decreasing over time among both African Americans and whites, the rate among whites is decreasing faster, so the net effect has been a widening disparity in breast cancer mortality.[19] In the 1980s there was no difference in breast cancer mortality rates between African Americans and whites; in 1990, the mortality rate among African Americans was 16 percent higher than among whites; in 2002-03, that difference increased to 36 percent.[19, 36]

The disproportionately high death rate and worse survival among African American women has been the focus of a large body of research. While



African Americans do tend to be diagnosed at a later stage, it is well established that survival disparities persist even after adjusting for stage.[32, 203, 224] Research on the impact of treatment differences between blacks and whites on survival outcomes has not been entirely consistent. As previously noted, it is well documented that while African Americans are more likely to have breast-conserving surgery than are whites, they are less likely to receive a full course of adjuvant radiation therapy. In a recent examination of these treatment differences on subsequent survival,[108] Joslyn found that adjustment for these treatment differences attenuated, but did not completely eliminate, survival differences between blacks and whites. These results support a previous study that found significantly worse survival among African Americans compared to whites given equivalent treatments,[225] but conflict with the findings of another study which reported no residual mortality disparities after adjusting for treatment among a population with equal access to care.[106]



It also has been suggested that racial/ethnic disparities in breast cancer survival may be a function of differential responses to treatment (reflecting underlying biological differences). A

recent review of clinical trials evidence where tumor biology was assessed using classical pathological classifications suggests that there are few or no major underlying biological differences between blacks and whites that influence the effectiveness of breast cancer treatment.[161] However, in 2006 researchers are reporting that young blacks are prone to developing more types of tumors that are more resistant to current therapies than other groups.[58, 226, 227] Data on this issue is fairly limited and not entirely consistent. One study at the University of Kansas Medical Center found higher systemic recurrence rates (but not local recurrence rates) and shorter time to recurrence among blacks compared to whites treated with breast conserving surgery and radiation for stage II cancer.[228]

The degree to which black/white differences in tumor characteristics may impact survival has been an area of intense interest. Because different tumor characteristics may require different treatment protocols, it is important to take these differences into account when evaluating the degree to which treatment differences explain racial/ethnic disparities in survival. It has long been noted that African American women are at higher risk for being diagnosed with more aggressive tumors that are more likely to be non-hormonally responsive and of a higher grade.[224, 229, 230] Recently, evidence has emerged that African American women are also more likely to have tumors with a variety of molecular genetic compositions (e.g. higher mitotic index, over-expression of cyclin E and p53, higher S-phase fractions, basal-like subtypes) that are associated with shorter disease-free survival times.[58, 231] While treatment decisions are complex and multifactorial, it is important to try to disentangle differences required by clinical profile versus those that are due to modifiable factors such as access to care, cultural beliefs, and potential discrimination.

It is likely that the persistently worse stage-adjusted survival seen among African Americans compared to whites is a function of a myriad of factors discussed throughout this Report, including lower socioeconomic status and poorer access to medical care, receipt of lower-quality cancer treatment, existence of more comorbidities, and more aggressive tumor biology. Studies that have examined these factors in univariate analyses (socioeconomic status, treatment, life expectancy, and comorbidities) have found that these variables appear to attenuate, but not fully explain the differences in breast cancer survival.[116, 224, 232-236] However, to date no studies have controlled for all of these factors concurrently along with prognostic tumor/disease characteristics.

Comorbidity appears to be a strong predictor of overall survival and breast-cancer-specific survival and is likely to explain much of the black/white disparity in all-cause mortality, but it does not fully explain racial disparities in breast-cancer-specific survival.[116] Two studies out of the MD Anderson cancer center have found that equal treatment of tumors with similar characteristics in African American and Caucasian women may not lead to equivalent clinical outcomes.[226, 227] Woodward et al. also compared clinical outcome in Hispanics, who had a similar referral process and socioeconomic status profile to African Americans in their study, and found that Hispanics had similar overall survival rates to Caucasians.

Institutional factors, however, such as health insurance coverage, hospital characteristics, delay in treatment, and continuity in care are increasingly being recognized as perhaps the more important contributors to the disproportionate burden of breast cancer mortality experienced by African American women.[106, 112, 161, 237-241] For example, in a recent study from data in the Metropolitan Detroit Cancer Surveillance System, the risk of death from breast cancer among African American women was not statistically different from white women after adjustment for age, marital status, stage, Medicaid status, census tract poverty, and surgical treatment. In fact, Medicaid status was a larger contributor to mortality than was race.[112] In a large meta-analysis explicitly designed to examine the respective roles of cancer biology and differential access to treatment on survival in black vs. white patients, Bach et al.[232] reported a significantly elevated (20 percent higher) breast cancer mortality rate for black women, even after accounting for treatment differences. However, difficulties inherent to the meta-analysis study design sometimes mitigate its increased power to detect significant differences. Difficulties include inability to control for quality of original studies included in the meta-analysis, varying factors analyzed among the different studies, large numbers in the combined studies that result in statistically significant but clinically insignificant results, and individual studies designed to answer hypotheses different that those examined in the meta-analysis.

Compared to the large body of research focusing on breast cancer mortality and survival disparities between white and African American women, relatively little has been done to document and explain other racial/ethnic disparities in breast cancer survival. While compared to non-Hispanic whites, mortality rates for other racial/ethnic groups are lower on an absolute scale, important racial/ethnic differences in relative survival exist. In a recent analysis of SEER data for 1975-1999, breast cancer survival rates were significantly better for Asian American women compared to non-Hispanic white women.[242] All other racial/ethnic groups examined—including Native Hawaiians, Hispanics, African Americans, and American Indian/Alaskan Natives--experienced worse survival. This study, however, did not examine more specific subpopulations within the Asian American population.

As was previously noted for other breast cancer outcomes, further examination of more detailed racial/ethnic subgroups may reveal important survival disparities masked by these broad categories.[147, 243, 244] For example, it has been noted that Latina women have worse survival than non-Hispanic white women, while Asians/Pacific Islanders, as a broad group, tend to have better survival, even after adjustment for stage at diagnosis.[19, 234, 242, 245] More detailed analyses of Latina women have shown important survival differences depending on country of origin, with those of Mexican ethnicity having 30 percent higher mortality than whites after diagnosis, while survival among South and Central Americans, Puerto Ricans, and other Hispanics were comparable to whites.[147]

In similar analyses among Asians/Pacific Islanders, mortality among Japanese American women was 40 percent lower compared to whites,

while mortality among Native Hawaiians was 30 percent higher, and mortality rates among the other Asian subgroups were similar to whites.[147, 244] To our knowledge, there have been no studies of cancer treatment effectiveness or biological differences in response to treatment in racial/ethnic groups other than African Americans.

Given that we still cannot completely explain racial/ethnic disparities in breast cancer survival, it is important to look beyond issues of treatment and biology towards other factors that are likely to impact survival. There is a substantial and growing body of work devoted to understanding psychosocial factors such as stress, social support, and coping strategies in relation to breast cancer survival.[246-250] Immune systems are affected negatively by stress and the mitigating effect of some positive psychosocial characteristics on a patient's anxiety level may have an indirect, but potentially significant, effect on cancer survival. Effects on survival have been reported for some of these factors, yet few studies have considered psychosocial factors among racially/ethnically diverse populations. While some notable racial/ethnic differences have been observed for these factors that have included both white and non-white study participants, the degree to which such differences may explain disparities in survival is not known. This avenue of research remains largely unexplored.

Survival/Mortality: Conclusions and future directions

The greatest burden of breast cancer mortality is borne by African American women. Compared to non-Hispanic whites, all racial/ethnic groups, other than Japanese American women, have worse relative survival. These differences persist after adjusting for stage at diagnosis. Clearly issues related to socioeconomic class, such as access to care and treatment, play a role in the worse survival experience among minority women but they are not the whole story. As yet unidentified biological factors may play a role in survival disparities. Identifying the factors that impart better survival among Japanese Americans may provide important clues to improving survival among other groups.

4. Conclusions and future directions

A number of well-documented racial/ethnic disparities exist across the breast cancer continuum. With the exception of incidence, which is markedly higher among non-Hispanic white women, minority women bear a disproportionate share of the burden of breast cancer. They are more likely to be diagnosed at a later stage, less likely to receive timely, appropriate, and complete treatment, and have worse survival rates than non-Hispanic white women. Most notable of all the disparities identified to date is the persistently higher breast cancer mortality rates suffered by African American women in this country. The fact that this disparity has widened over the last twenty years represents one of the most troubling failures of our efforts to address racial/ethnic disparities in breast cancer.

By far, the bulk of the research conducted to date on racial/ethnic disparities in breast cancer incidence has focused on the degree to which differences in the prevalence of established risk factors between racial/ethnic groups explains the differences in breast cancer incidence rates. This

research suggests that reproductive and behavioral risk factors (especially age at first birth and parity, but also body mass index, alcohol consumption and use of exogenous hormones) explain some, but not all, of the racial/ethnic disparities in incidence. Because most of the established risk factors were primarily identified in populations of white women, and in fact, only explain about half of breast cancers among white women, this approach is particularly limited for evaluating disparities in breast cancer incidence. Addition of risk factor information to the California Cancer Registry database could greatly enhance this avenue of research, by providing population-based data on breast cancer risk factors in a large and ethnically diverse population.

Determining the degree to which individual behaviors explain some of the noted disparities in breast cancer outcomes other than incidence is complex. While the choice to obtain screening or seek treatment, or choose specific treatments, ultimately lies with the individual, such a decision is embedded in complex layers of sociocultural, physical, financial, and institutional factors. The challenge in disparities research is to disentangle these factors in a way that can identify inequities in opportunities for behaviors that can increase screening, improve treatment, and ultimately eliminate disparities in survival. Thus in evaluating rates of breast conserving surgery usage, for example, it is critical to be able to distinguish between the woman who chooses a mastectomy over breast conserving surgery because of a strongly-held cultural belief, versus the woman who makes that choice based on insurance coverage or other economic challenges, versus the woman who is not presented with any choice at all because her physician believes (based on her race/ethnicity or socioeconomic situation) that she will not be likely to complete adjuvant therapy and therefore mastectomy is the only option offered. Disentangling such complex factors is critical for identifying avenues for reducing disparities, and cannot be achieved through studies solely based on large registry data, but must come from thoughtfully-designed, culturally-sensitive qualitative studies.

A small but growing body of literature aimed at identifying racial/ethnic genetic differences may explain noted disparities in breast cancer. The findings that there are racial disparities in breast cancer incidence and mortality are almost exclusively based on data from studies using the social definition of race, whether it is through self-reporting or observer assessment. Sequencing of the human genome has given scientists new tools to examine how closely genetic constructs correlate with social definitions of race. If the genetic constructs correlate, then it lends support to the argument that there could be a biological component to the observed disparities in socially defined race. If not, then there is an opportunity to redefine populations with high or low susceptibility to disease at the genetic level.

A good deal of research directed toward understanding contributions of biology to disparities in breast cancer has been concentrated on understanding how pathological and genetic risk markers are distributed between races and ethnicities and how to target them for risk assessment, diagnosis, and the development of treatments. Scientists are moving away from the primarily morphological prognosticating protocols

of the past. DNA tissue microarrays, proteomics and other bioinformatics analyses are uncovering new, more predictive systems for classifying breast tumors.[56, 57, 251] This has allowed researchers to categorize cancers in a way that could not only predict which tumors would respond to specific therapies, but provide clues regarding the exposures that caused the tumors.

The significance of race in the context of disease research is that it serves as a proxy for other susceptibility factors, in which genes and physiology interact to some extent with cultural attitudes and behaviors, geography, and environment. Migrant studies have consistently demonstrated that there is a strong cultural/environmental component to breast cancer incidence, although some portion of observed disparities may still be due to differences in genetic make-up. Studies that definitively tease out the biological contributions from the sociocultural ones will not only inform our understanding breast cancer etiology, but also speed the development of therapies that will be effective in diverse populations.

Because race/ethnicity and socioeconomic status are so highly correlated in the U.S., it is impossible to examine racial/ethnic disparities in health without considering socioeconomic status. Although non-whites are over-represented in lower socioeconomic status groups, it is clear that race/ethnicity is not simply a proxy measure for socioeconomic status.[86] Racial disparities in breast cancer outcomes generally remain even after adjusting for socioeconomic status, although much of the research seems to suggest stronger effects of socioeconomic status than of race/ethnicity. Differences by race that remain after adjustment for socioeconomic status do not necessarily mean that there are underlying biologic differences or mechanisms.[252] Differences can be due to remaining confounding and incomplete understanding of the influences of the social and physical environments on breast cancer outcomes. It has been well documented that people of color and people living in low-income areas are disproportionately exposed to environmental pollutants.[253-255] Institutional factors such as discrimination, insurance status and usual source of care are also very important to consider when examining socioeconomic status differences. To better understand racial/ethnic disparities in breast cancer outcomes, researchers will need to more comprehensively examine the complex interactions between socioeconomic status, race/ethnicity, physical exposures, occupations, stress, and social environments. A growing number of researchers, community activists, and policy makers have taken a broader, more inclusive view of the environment that incorporates all of these factors in ways that consider the effects of multiple stressors and multiple exposures.[253, 256, 257] For more on this topic, see Section III of this Report.

While there is a small, but growing body of literature suggesting psychosocial factors such as stress and social support are important determinants for breast cancer outcomes such as quality of life and survival, this avenue of research generally has not been pursued in the literature examining racial/ethnic disparities in breast cancer. One study which explicitly examined black/white breast cancer patient differences in social support and coping suggested that while

these are important independent predictors of survival, they do not explain the black/white disparities.[246, 247] Racial discrimination has been implicated as a race-specific stressor and potential predictor of racial inequalities in health (see Section III of this Report). In other health outcomes research, physiological changes such as elevations in blood pressure have been documented in response to discrimination.[258, 259] Additionally, research in other fields has shown that individual coping behaviors, particularly in dealing with discriminatory actions, and social support networks may mediate or buffer negative effects due to stress and are important to consider.[259-264] Beyond the stresses associated with discrimination, the numerous barriers to access to care encountered by minority women suggest there may be racial/ethnic differences in stress and support presented specifically by the process of seeking care for breast cancer. Examining the role of psychosocial stress in explaining racial/ethnic disparities in breast cancer outcomes is a glaring gap in the research conducted to date.

This review highlights a number of examples that underscore the need to disaggregate the data to look at more detailed ethnic and ancestry subgroups whenever possible. This need is particularly acute for American Indian/Alaska Natives for whom reliable data are lacking. Furthermore, the Asian/Pacific Islander population in California is particularly heterogeneous with respect to a number of factors which are likely to contribute to breast cancer disparities, such as immigration status, acculturation, and socioeconomic status. Thus, aggregate data on this population may be especially problematic.

To date, there has been little consideration of the role of differential physical exposures, in the general environment and in the workplace, in breast cancer disparities research. The large body of literature on breast cancer incidence among migrants underscores the importance of looking at both environmental and behavioral aspects of breast cancer etiology. To determine which specific aspects of race/ethnicity are associated with breast cancer risk and outcomes, a multidisciplinary approach is needed to comprehensively examine the complex interactions between race/ethnicity, socioeconomic status, physical exposures, stress, acculturation, genetics, and social environments. California, with its large, racially and ethnically diverse population of women, is the ideal place to study this important topic. More than merely study this topic, California is also the most appropriate place to address and reduce disparities in breast cancer outcomes.

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Sexual Minority Women

Introduction

There is a paucity of information about the cancer experience of the approximately six percent of women in the U.S. who are sexual minorities.[1, 2] Until recently, sexual orientation measures were not included in national health data systems, making it impossible to accurately estimate the prevalence of cancer among sexual minority women (SMW). Persistent efforts by lesbian, gay, bisexual, and transgender (LGBT) scientists and colleagues in the past half-decade have resulted in the incorporation of sexual orientation measures in an increasing number of government surveys.[3, 4] These and other efforts are expanding the range of national population data relevant to determining cancer prevalence rates among sexual minority women compared to heterosexual women. Despite definite progress in understanding the extent to which sexual minority women are affected by cancer, two significant areas of research are underdeveloped and warrant specific attention. First, the research that has been conducted on cancer among SMW to date has focused primarily on breast cancer screening. There is a vital need to improve the understanding of other aspects of cancer among SMW in the U.S.. Second, at their best, government surveys provide only gross estimates of population subgroup prevalence, and, due to sample size and number of measures, they are limited in their applicability to exploring differences within groups. Population-based studies are needed to explore the social, cultural, and behavioral factors that may influence differences within groups in cancer rates and in response to treatment options.

As the Institute of Medicine (IOM) Lesbian Health report points out, SMW women "have historically been the target of prejudice."[5] In community and population-based surveys, lesbians have reported discrimination in routine health care and lack of trust with providers.[6-11] The dearth of information on breast cancer among SMW stems in part from the prejudice that has dominated professional and societal attitudes toward SMW's health needs, and this lack of information may also affect the health of sexual minority women.[5]

Methodological limitations of sample size, lack of consensus on how to define and measure sexual orientation, and non-inclusion of sexual orientation measures on government surveys (related in part to a lack of accepted definitions) have presented obstacles to more rapid advancement of lesbian health research.[5] While there are still large gaps in information about the health of SMW, scientific interest has increased over the past decades. As described at The 2000 Scientific Workshop on Lesbian Health, the hypothesis that breast cancer incidence may be higher in lesbians garnered a great deal of media attention in the 1990s.[12, 13] During the same time period, the National Lesbian Health Advocacy meetings with federal agencies began, leading to an increased focus by the Department of Health and Human Services on SMW health.[13, 14] Also noted at the Workshop on Lesbian Health was how questions regarding sexuality included in the Women's Health Initiative and the Nurses Health Study allowed the field to further develop.[13] Furthermore, in 1999 and 2000, several reports were published describing health disparities among SMW, the lack of research focusing on

SMW, and recommendations for future research.[5, 13, 15, 16]

Concept/Exposure Definition

As Dean et al. note, SMW "are defined by their sexual orientation," and the definition varies throughout history and across cultures.[10] Therefore the meaning of sexual orientation, as described in the IOM Lesbian Health report, differs based on one's culture and race/ethnicity.[5, 17] Although many measures have been developed to identify SMW, there is not a standard definition. Generally speaking, SMW include lesbians, bisexuals, women who partner with women, and women who have sex with women. Moreover, the report explains that sexual orientation is often described as being predicated on three factors: desire or attraction, behavior, and identity.[5]

In a nationwide study of randomly sampled adults examining issues of sexuality, Laumann et al. measured sexual orientation based on the following criteria – sexual contact with another woman, attraction to another woman, and identifying as a lesbian.[17] This study found that the prevalence of women classified as SMW varied depending on several factors including socioeconomic position, race/ethnicity, religious beliefs, and region. The authors also point out that many women who reported having sexual relations with woman did not necessarily self-identify as lesbian. Women of lower socioeconomic position were more likely to report being attracted to or having sexual contact with women, but to not identify with being a lesbian.

Referencing a table in the Laumann report,[17] the IOM report notes that SMW are incredibly diverse and can be of any race/ethnicity, socioeconomic position, or age.[5] The authors of the report emphasize that "there is no single type of family, community, culture, or demographic category fully characteristic of [SMW]."[5] Analysis of data from the United States Census has provided more specific information about diversity among same-sex female-headed households.[18-21]

Biologic Plausibility

Sexual orientation is a proxy for many individual and social risk factors that potentially influence breast cancer risk and outcomes. Risk factors associated with SMW include nulliparity, older age at first birth, alcohol consumption, smoking, and obesity.[22-27] As Cochran points out, none of these risk factors is exclusive to lesbians, but all may be more prevalent among this population.[27]

Critical Review of the Literature, by Outcomes in Breast Cancer Continuum

Introduction

The overall effect of sexuality is not well understood because few studies have explored its role in breast cancer. The studies that have been conducted have generally focused on risk factors, screening behaviors, and quality of life.

Incidence and Etiology

The incidence of breast cancer among SMW is not known. However, SMW make up about six percent of women in the United States and should, thereby make up about six percent of all cases of breast cancer.[26] Dibble points out that this may be a conservative estimate, if breast cancer is higher among SMW,[26] as some studies suggest.[12] Though

few studies have examined the incidence of breast cancer among SMW, a study by Kavanaugh-Lynch et al. examined breast cancer risk among lesbians using three surrogate correlates of sexual orientation: no male sexual partners ever, never married and not currently using contraceptive, and not currently married and not using contraceptive. She found an elevated risk for all three measures.[28] In contrast, a pooled analysis of seven independently-conducted surveys of SMW found no difference in the prevalence of self-reported history of breast cancer among self-identified SMW, compared to all U.S. women combined, despite the higher prevalence of a number of breast cancer risk factors reported by SMW in these surveys.[27] The pooled analysis by Cochran and colleagues, however, had a number of limitations. Breast cancer risk was estimated by self-report of breast cancer and thus, by definition, was limited to survivors. If SMW have different survival rates than the general population of women, this could introduce a survival bias in estimating breast cancer risk. Furthermore, none of the seven studies were population-based and the authors note that a healthy-volunteer bias likely resulted in some underestimation of the prevalence of disease and risk factors in these studies. Finally, the SMW in the pooled analysis were young (mean age = 36 years) and not representative of the age group most at risk for breast cancer nor probably of the full population of SMW. Despite the limitations of the pooled analysis by Cochran, a recent in-depth review of studies on this issue by The Safeguards Project & The LGBT Health Resource Center led them to conclude that Cochran and colleagues' pooled analysis provides "the best possible picture at this time."[29] Ultimately, the limitations of the Cochran analysis reflect those of the underlying studies and underscore the need to develop better strategies for capturing a representative sample of the full SMW population in which true breast cancer incidence can be measured.

The research that has been conducted among SMW suggests that they may be at higher risk of developing breast cancer than heterosexual women, based on perceived differences in prevalence of risk factors associated with breast cancer in community and population-based studies. Most research suggests that lesbians differ from heterosexual women in that they are more likely to be nulliparous and they are more likely to consume alcohol, smoke, and be overweight.[27] Thus, while the existing data strongly suggest that SMW are at increased risk of breast cancer, both the reality of increased risk and the magnitude of the presumed increase remain uncertain.

Screening

Breast cancer screening frequency among SMW may differ from that of heterosexual women. SMW receive mammograms less frequently than do heterosexual women,[24] potentially increasing their risk for later-stage diagnosis and worse prognosis. A study by Diamant et al. found that lesbian, but not bisexual, women were less likely than were heterosexual women to have had a clinical breast exam in the past two years.[11] In an analysis of pooled data from multiple studies of over 11,000 lesbian and bisexual women, Cochran also found that SMW had a lower lifetime breast cancer screening prevalence rate than what was expected, using population-based norms.[27]

Several researchers have also explored the reasons why SMW may receive less screening. Lauver et al. found that they include cost, scheduling, discomfort, competing life demands, fear, and embarrassment.[30] Conversely, reasons for seeking mammograms included good health practices, responding to the perception of being at high risk of cancer, and the desire to ensure early detection.[30] Among lesbians with a first-degree relative with breast cancer, Burnett found that the odds of obtaining a mammogram was positively associated with being concerned about developing breast cancer and socioeconomic position.[31] In addition, Dean and others suggest that SMW may have decreased access to appropriate health care, due in part to lower average household incomes and to the fact that health insurance rarely covers the partners of SMW.[10, 24] Research suggests that even SMW with health insurance and financial resources may have difficulty obtaining appropriate care due to homophobia among health care providers[24, 27] or simply due to ignorance among physicians about lesbian health issues.[27]

Few interventions have been developed to improve breast cancer screening rates among SMW. Bowen, in a randomized controlled trial, found that lesbian and bisexual women who received breast cancer risk counseling intervention had reductions in anxiety and fear about breast cancer, and also had increased screening for up to two years after the intervention.[24] Dibble et al. conducted a pilot study to determine whether lesbian-specific educational interventions would impact cancer-screening behaviors among lesbians over the age of 50. It was not possible to obtain conclusive results, due to loss to follow-up and small numbers, but the authors stress the need to develop appropriate interventions for this underserved population.[32]

Research suggests that SMW have lower screening rates than do heterosexual women. Several barriers to screening have been identified, as have interventions that increase screening among this population. However, compared to most racial/ethnic minority groups, SMW have had little research dedicated to improving their screening rates.

Diagnosis and Treatment

Dibble conducted one of the few studies investigating breast cancer diagnosis and treatment in SMW.[26] She found no significant differences in diagnostic or surgical procedures, or chemotherapy or radiotherapy regimens between lesbians and heterosexual women.[26] However, lesbians did report significantly more side effects from chemotherapy.[26] Further research with larger samples is necessary to determine if these results are consistent across different SMW populations.

Nothing is known about participation of SMW in clinical trials.

Morbidity

Little is known about morbidity associated with breast cancer treatment and survivorship among SMW, but several studies have examined quality of life among SMW diagnosed with breast cancer. Matthews found that although SMW and heterosexual women similarly rated their overall quality of life, lesbians were less happy with their medical care, lacked support on an emotional level, and experienced higher levels of stress.[33] In

a different study, Boehmer et al. found that women with breast cancer had a more positive experience when they were able to discuss their sexual orientation and when they had less "helpless-hopeless coping."[34] In another study, Boehmer et al. found that women who identified themselves as being lesbian or bisexual used healthier coping mechanisms than women who reported "partnering with women," but did not self-identify as being lesbian or bisexual.[35] Fobair et al. found that lesbians reported fewer body image problems, were more likely to obtain social support from partners and friends, and were more likely to report anger than were heterosexual women.[36] In a different study, Fobair et al. also found that a 12-week support program for lesbians was helpful in reducing emotional distress and improving coping.[37]

Overall, current research findings conclude that SMW experience quality of life similar to that of heterosexual women after breast cancer diagnosis, though their qualitative experiences may differ.

Nothing is known regarding survival and mortality differences among SMW and heterosexual women.

Discussion

Limitations

Limitations to the literature are driven by the lack of data collected about women of diverse sexual orientations. This is likely caused by potential discrimination regarding sexual orientation in both clinical and research settings. Discrimination is a serious barrier in SMW health research. The IOM Lesbian Health report suggests that SMW participating in studies may not discuss being gay because they do not trust researchers.[5] Moreover, there has been little funding support for research on SMW health topics and several investigators report difficulty in publishing data on SMW.[5, 38] Dean notes that before Healthy People 2010 included "persons defined by sexual orientation," there was virtually no funding to support the study of SMW health.[10, 15] However, limited, discernible progress has been made since publication of the Healthy People 2010 Companion Document on LGBT Health.[21] Of particular note, National Center for Health Statistics (NCHS) staff and LGBT scientists have conducted cognitive testing studies to determine the most acceptable measures for sexual orientation to include on government and other surveys.[39] This work has facilitated the inclusion of sexual orientation measures on government surveys, as noted earlier.

There are several limitations in the study of breast cancer among SMW. Perhaps most importantly, there is no simple and accurate measure of sexual orientation.[40] Different studies define SMW in various ways, making it difficult to compare results across studies.[5] There may be sampling bias in studies of SMW because lesbians who are actively involved in the lesbian community may be more likely to participate than other lesbians.[40-42, 42] The IOM Lesbian Health report also points out that SMW are a relatively small group "dispersed throughout the population [making] it difficult and expensive to obtain a population-based sample (or probability sample)."[5] Furthermore, the use of small sample sizes and non-randomization of participants preclude generalizability of study results.[5]

Gaps in Knowledge

The paucity of SMW breast cancer data is due, in large part, to the limitations described above. Existing data come from studies focused on screening, to the exclusion of other parts of the breast cancer continuum, including diagnosis, treatment, morbidity, mortality, or other aspects of breast cancer survivorship.

Conclusion and Future Directions

Several recent reports have provided recommendations for enhancing future research in SMW's health.[5, 15, 16] First and foremost, funding for research about SMW is essential. The 2000 Scientific Workshop on Lesbian Health specifically recommended the federal government solicit and fund such research.[13] Dean also makes several important suggestions.[10] First, the study population needs to be specifically defined, perhaps through a large-scale probability survey to collect data on sexual orientation in general,[10] as well as women's self-perceptions of their sexual orientation. Second, there is a related need to develop valid measures of sexual orientation.[10] Third, the development of methods for sampling "hidden populations" will greatly improve future studies,[10] not only for SMW, but for other underserved groups. Fourth, further development of methods for soliciting information on "sensitive topics," such as computer-assisted interviews, is also needed.[5, 10] In addition, Healthy People 2010 reports that federal surveys need to include questions regarding sexual orientation.[15] Other government-supported efforts are also underway to address these concerns and definite progress has been made as evidenced by the numerous surveys that now include these types of questions.[3] The Scientific Workshop on Lesbian Health further highlighted the need for research to include the diversity of lesbian populations.[13]

Following results from Laumann,[17] SMW research should address race/ethnicity, socioeconomic position, age, disability, other population characteristics, and regional differences among SMW.[13] Furthermore, to reduce barriers and improve access to quality cancer and other health care for SMW, there is a critical need for additional education and SMW cultural competency training among health care providers (including all positions within the health care and public health workforce), educators, researchers, and students.[13, 15] The CDC-funded "Removing the Barriers" program was developed and implemented by the Mautner Project for Lesbians with Cancer to improve health care providers' knowledge and competence for treating sexual minority women.[7] Enthusiasm for this program and positive evaluations over time indicate that such programs meet a recognized need and warrant expansion.

Integration of Research on Sexual Orientation with Research in Other Domains

The study of SMW can be and has been included in the study of overall women's health, making these investigations diverse and efficient. Sexual orientation has been added as an additional demographic variable in several large-scale studies of women's health.[22, 43] Inclusion of simple questions on sexual minority status has not affected the response rate of the participants, and including these variables has enabled the field to

move forward in ways that research using smaller, less representative, samples cannot.

Policy intervention opportunities for the study of and improvement of breast cancer outcomes for SMW are plentiful. Policy in the area of research activities could include the required inclusion of sexual minority variables in all federally funded studies, and reporting of SMW status in final and status reports to funding institutions. Including gender, ethnic, and racial status in these reports resulted in a clear jump in awareness of demographic distribution of samples recruited for general research and improved our understanding of the role of these key differences in health.[44] National surveys that monitor the health of the nation's population should be the first targets for inclusion of sexual minority variables, along with large federal- and state-funded surveys and studies.

While many other recommendations have been made to improve SMW health research, the recommendations discussed in this section have been the most frequently cited. If implemented, important research will begin to address the many critical questions that, to date, remain unanswered.

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Disability Status

Introduction

According to 2005 data from the U.S. Census Bureau, 15.5 percent of California adult women living in the community have disabilities, or 2.1 million women; among women 65 years and older, 42.1 percent have a disability.[1] An additional 87,000 California women with disabilities live in institutions such as nursing homes, or about 0.7 percent of adult women.[2] As the population ages and as the life expectancy of women with disabilities is increasing,[3] the number of women aging with disabilities is growing.[4] Very little, however, is known about the cancer experience of women with disabilities. To date, the literature on breast cancer among women with disabilities has almost entirely focused on issues related to screening, and to a lesser degree, treatment. There remain critical gaps in our knowledge of breast cancer in this large segment of the U.S. population.

The dearth of information on breast cancer among women with disabilities is reflective of a more general neglect of research interest in the health of people with disabilities. Historically, most public health resources have focused on preventing disability in the healthy population, rather than promoting health among people with disabilities.[5] In the early 1990s, the glaring absence of baseline data on people with disabilities was highlighted by the U.S. government's report Healthy People 2000.[6] Nine years later, in its follow-up report,[7] the Center for Disease Control and Prevention (CDC) for the first time set out specific goals addressing the health and well-being of people with disabilities: 1) promote health of adults with disabilities; 2) prevent secondary conditions among people with disabilities; 3) eliminate health disparities between people with and without disabilities.[7] In response, there has been considerable research in the last five years on health promotion efforts targeting people with disabilities. Now is the ideal time for breast cancer researchers to seize this momentum and build upon these efforts to lessen the burden of breast cancer among this large and growing segment of the population.

Concept/Exposure Definition

The concept of disability has evolved over time. Thirty years ago, disability referred solely to an underlying physical, cognitive, or psychological impairment or health condition. Today, disability is conceptualized as a combination of the condition, the individual's ability to function in various domains, and the interaction between the person and the environment in a way that enhances or prevents full social participation.[8] Disability is usually defined according to the presence of functional or activity limitations, which are part of the definition used by the Americans with Disabilities Act (ADA), and in population surveys such as the CDC's National Health Interview Survey (NHIS) and Behavioral Risk Factor Surveillance System (BRFSS), and the U.S. Census Bureau's Survey of Income and Program Participation (SIPP) and American Community Survey (ACS). These surveys, which offer widely divergent prevalence estimates of disabilities in the U.S. population according to the particular questions asked, were designed to capture a broad population with any type of activity or functional limitation. More traditional

measures of disability identify limitations in Activities of Daily Living (ADL), which are self-care activities such as bathing or dressing; limitations in Instrumental Activities of Daily Living (IADL), which are activities often associated with independent living, such as going out to shop or to a doctor's visit; and limitations in a person's ability to work.[9] The World Health Organization, striving to codify a standard classification of disability, developed the International Classification of Functioning, Disability, and Health (ICF). Since an individual's functioning and disability are considered to depend, in part, on the person's environment, the ICF does not provide a single way to determine disability status. Instead, the ICF suggests a classification scheme to define disability in the context being studied.[10]

In the context of studying the impact of breast cancer on women with disabilities in the U.S., it clearly is necessary to define disability in a variety of ways, depending on the research question being studied. Unfortunately, however, there has not been any systematic approach to identifying the pertinent definitions of disability status with respect to the various breast cancer outcomes of interest. Even breast cancer studies designed to address the same research question have had little consensus on the definition of disability. Some studies have focused only on long-term disabilities such as deafness or blindness,[11, 12] while others have utilized the more traditional definitions focused on ADL and IADL, which may include both long-term and short-term disabilities.[13] Disabilities associated with chronic medical conditions such as obesity or severe asthma are often, but not always, included in the disability literature. Consideration of cognitive/developmental disabilities separate from physical disabilities is likely to be of critical importance,[14] as is consideration for the degree or severity of disability and how it impacts mobility.[15-17] Other studies use Medicare eligibility or receipt of Social Security Disability benefits as a de facto definition of disability among non-elderly women.[18, 19] Such a definition can be faulted for two reasons. First, it excludes many women with significant disabilities who may not qualify for these benefits, either because their disability does not meet the restrictive Social Security definition based on inability to work, or because they lack sufficient work histories. Second, it includes some women without disabilities who qualify for benefits for reasons other than disability, such as the transfer of benefits from a deceased parent. A functional measure of disability, though often not available in the datasets being analyzed, would be far superior to using program participation as a proxy for disability status.

In summary, there is a clear need to systematically identify the population of women with disabilities of particular interest when performing research related to specific aspects of breast cancer. When available, existing data should be used to inform such studies. As discussed below, it is likely that even within one area of the breast cancer continuum, it will prove useful to sub-categorize disability to better pinpoint the sources of disparities between women with and without disabilities.

Biologic Plausibility

There is no observed overarching unifying mechanism by which "disability" directly affects breast cancer risk. The question has not even been asked yet about whether there is overlap between genetic markers for breast cancer and genetic markers for specific disabling conditions. However, research on breast cancer among disabled women stands to offer unique insights into the disease. Perhaps the best example of biologic plausibility arises from the small body of literature on breast cancer among blind women. The observation that blind women appear to be at a reduced risk of breast cancer led to what is now known as the 'melatonin hypothesis.'[20] This hypothesis states that women who are blind, by virtue of having no light stimuli, have high levels of melatonin, which, in turn, reduce breast cancer risk. This hypothesis has spurred an entire area of breast cancer research which has offered important clues into both the etiology and treatment of breast cancer (see Section I, Chapter H, on Light at Night). By neglecting the breast cancer experience in the large segment of the U.S. population with any type of disability, we may be overlooking important clues into the disease's etiology.

Critical Review of the Literature

Prevention

Primary breast cancer prevention could take the form of exercise, chemoprevention (such as the use of tamoxifen or raloxifene),[21] prophylactic oophorectomy, or prophylactic mastectomy.[22] There have been no studies of the degree to which women with disabilities engage in these preventive strategies.

Many of the factors that have been established to influence risk for breast cancer (e.g., age at menarche, age at menopause, parity, age at first birth, family history) are difficult, if not impossible, to modify. Behavioral factors (e.g., alcohol consumption, physical activity, breast-feeding), which should be more amenable to change, have also proved fairly resistant to modification, at least at the individual level. Some macro-level primary prevention activities recently have been proposed by Willett and colleagues.[23] Included in these recommendations are changes to society's infrastructure, which can help promote physical activity and healthful eating habits; development of social norms for low alcohol intake by women; and facilitation of childcare and breast-feeding for working women.[23] In addressing these and other potential breast cancer prevention strategies, the accessibility needs of women with disabilities need to be considered.

Primary breast cancer prevention that focuses on reduction of behavioral risk factors in general has been the subject of a small number of intervention development studies in populations of women with disabilities.[24-30] These interventions addressed the needs of women with physical disabilities and took the form of face-to-face workshops, generally employing psycho-educational and behavior modification approaches. Their effectiveness was limited, however, by several factors that inhibit participation by women with physical disabilities. One recent study identified four major barriers to participation in a health promotion program by women with

physical disabilities: transportation, cost of program, lack of energy, and lack of knowledge concerning program availability. When these barriers were eliminated by providing free transportation, charging no fee for the program, reducing the fatigue that often occurs getting to a site by providing door-to-door transportation, and developing an accessible and individually-designed exercise program at a fitness center, attendance in the program was over 85 percent and every participant completed the program.[5]

Recent qualitative studies of health promotion efforts among Deaf women highlight the need to address the barriers specific to the type and/or severity of the disability.[11, 12] These two studies report that even a group of Deaf women with fairly high levels of education had an alarming lack of knowledge about the meaning or value of standard health screenings, the purposes of prescribed medications such as hormone therapy, or the necessity for other medical or surgical interventions such as hysterectomies.[12] Since prevention strategies are contingent upon knowledge and education, improving health communication to women with disabilities is a requisite first step.

Incidence

There is scant data on the incidence of breast cancer among women with disabilities. Prevalence data from the 2005 California Health Interview Survey indicate that California women with broadly defined disabilities are much more likely than their non-disabled counterparts ever to have been diagnosed with breast cancer (4.4 versus 1.9 percent), but that these differences can be accounted for by the older age distribution of the sample with disabilities.[31] Similar prevalence rates do not necessarily imply similar incidence, however, because survival rates may also vary.

As for specific disability groups, the little information that is available is almost entirely for blind women, for whom the reported incidence of breast cancer is lower than in the sighted population.[32-35] The reduced risk of breast cancer among blind women appears to be limited to those with total blindness or severe visual impairments,[32, 35] although one study reported reduced risks across most categories of visual impairment and a decreasing trend with greater level of impairment.[34] Generally, the results from these studies are consistent with a hypothesized reduced risk of breast cancer in blind women due to higher levels of melatonin secretion by the pineal gland in response to the lack of ocular light perception.[20] These studies, however, tend to be limited by small sample size and lack of information on other breast cancer risk factors that may co-vary with visual impairment. Information on nulliparity, a well-established risk factor for breast cancer, available from one study, suggested that blind women are much more likely to be nulliparous than sighted women.[35] This would increase, not decrease, breast cancer risk. Future incidence studies of breast cancer among blind women would be strengthened by incorporation of measured levels of circulating melatonin, greater sample sizes, and information on age at onset of visual impairment and on other breast cancer risk factors.

Beyond the incidence literature among blind women, there is virtually no information concerning the incidence of breast cancer among

other groups of women with disabilities. While a 1998 analysis of the Iowa 65+ Rural Health Study reported a decreased risk of breast cancer among women with disabilities,[36] a follow-up study using data from the Longitudinal Study on Aging failed to replicate these findings.[37] There is some limited information available on cancer incidence among people with developmental disabilities in Scandinavia. These studies suggest that while the overall incidence rate of cancer in people with developmental disabilities may be similar to that of the general population, the pattern of malignancies appears to be different.[3, 38] A small study in Finland reported no difference in breast cancer incidence among a cohort of people with developmental disabilities, compared to the general population, although this result was based on only 23 cases and included both men and women.[3]

Observational studies have suggested that the distribution of many of the known breast cancer risk factors is different among people with disabilities, compared to the general population (see Etiology subsection below). This suggests that breast cancer incidence is likely to be different among people with disabilities, compared to those without disabilities. There is a clear need to better document the incidence of breast cancer among people with disabilities. Studies designed to do so should be specific as to type, severity, and age at onset of disability. Results from such studies could help prioritize and target breast cancer prevention efforts among this population.

Etiology

For women with physical limitations, the etiology of breast cancer stems from biologic factors, combined with increased risk on the array of health conditions and behavioral factors that are associated with breast cancer. Associated sociodemographic characteristics and health behaviors among disabled persons have received a fair degree of attention, although results have not been entirely consistent and studies often have failed to take into account the type and severity of disability.

According to the American Cancer Society,[39] women have an increased risk of breast cancer if they experienced menarche before age 12, gave birth for the first time after age 30, have never breast-fed, have a history of diabetes or hypertension, use alcohol, use oral contraceptive or hormone replacement therapy, are obese and have a high fat diet, or are physically inactive. Women with disabilities, particularly physical disabilities, are at higher risk of breast cancer on many of these factors. Some types of disability, such as spina bifida, are associated with early menarche.[40] Many women with physical disabilities have never had children and, therefore, have never breast-fed.[41] Blind women are also more likely to be nulliparous.[35] Some studies have suggested greater hormone therapy use among disabled women,[42-44] while one earlier study suggested the opposite.[45] We also know that there is a disproportionately high prevalence of diabetes, hypertension, obesity, and physical inactivity in the population of women with physical disabilities,[14, 46-48] characteristics that are likely to yield a higher risk of breast cancer.[23] Lower rates of physical activity have also been reported for women who are blind compared to their sighted counterparts.[49]

Although evidence is mixed about the link between smoking and breast cancer, studies have shown that certain segments of the disabled population (including both men and women) are more likely to smoke and be heavier smokers.[50-54] However, one study found no differences in tobacco use by disability status.[14] Smoking habits may[51] or may not[53] vary by the type and severity of disability. One population-based study found that women with physical disabilities between the ages of 18 and 44 were twice as likely to smoke as women without disabilities in the same age group.[46] The role of smoking in breast carcinogenesis remains unclear, although recently evidence for a risk relationship has been mounting (see Section I, Chapter A, on Secondhand Smoke).

Better information on the characteristics and health behaviors of women with disabilities, in conjunction with better information on incidence, could provide useful insights into etiology. Disentangling some of the seemingly incongruous findings may help illuminate the importance of competing risks and alternative pathways of breast carcinogenesis. Identifying which risk factors are more prevalent among the various groups of disabled women could provide avenues for targeted breast cancer prevention efforts.

Screening

Comparatively, research on breast cancer screening among women with disabilities has received more attention than other areas of the breast cancer continuum. Most of the literature on this topic to date has focused on mammography utilization. Nearly every study has reported lower rates of screening mammography among women with disabilities compared to women without disabilities.[13-15, 17, 46, 55-58] Some studies, however, found this only to be true among women with more severe disabilities[15-17, 46, 55, 59] or among women with specific types of disabilities, such as developmental disabilities[14] or disabilities involving mobility limitations of the lower extremities.[59] Furthermore, one study reported that mammography use was less frequent among women with long-term but not short-term disability.[13]

Data from the 2005 California Health Interview Survey show gaps in receipt of mammograms during the prior year between women 40 years of age or older with and without disabilities, differences that are statistically significant when age differences between the two populations are controlled. While 64.7 percent of women without any type of disability reported prior-year mammograms, only 61.3 percent of women with broadly defined disabilities did so. The gap is much larger when a narrower definition of disability is used. For example, only 54.4 percent of those who reported difficulty leaving the home alone had received a mammogram in the prior year, as had 56.3 percent of those reporting difficulty with self-care activities such as bathing and dressing.[31] Prior analyses of California data also found disparities by disability status.[60, 61]

Data from the 1998 and 2000 Behavioral Risk Factor Surveillance System (BRFSS) suggest that disparities in mammography use by disability status may be lessening.[15] Data from the 1998 survey showed women with severe disabilities were less likely to receive mammograms, while the 2000 survey suggested women with severe disabilities were slightly more likely to receive

mammograms than the population without disabilities.[15] No similar changes, however, were seen in the prevalence of clinical breast exams among women with disabilities for the same time period.[15]

Identifying barriers to screening in the population with disabilities is the first step to eliminating those barriers. Research to date has identified a number of physical and attitudinal barriers to breast cancer screening. Physical barriers cited include: transportation difficulties; heavy doors; inaccessible offices, bathrooms, exam tables, and mammography equipment; and inadequate time allotment for appointments.[16, 17, 57, 62-64] A 1999 study reported that nearly 20 percent of primary care physicians surveyed had offices that were not compliant with the ADA and these physicians were unable to serve their patients with disabilities as a result.[65] Attitudinal and/or informational barriers, both among women with disabilities and their health care providers, also impede breast cancer screening efforts. Health care providers receive very little, if any, training in health promotion efforts for patients with disabilities. Consequently, many are ill equipped to interact with patients with disabilities and are uninformed of their needs. Women with disabilities have reported that healthcare providers often neglect to address screening even after being directly asked[16, 17] and many cite the 'negative attitude of health care providers' as the most difficult barrier to health care access.[66, 67] For patients with certain disabilities, clinicians may believe that life expectancy is not sufficient to warrant preventive screenings.[17, 68] Patients with disabilities may believe that they do not need a mammogram because they are at low risk for breast cancer[68] or they do not understand the purpose of it. Steinberg and colleagues reported the belief among some Deaf women that mammography is only necessary for women who are experiencing symptoms of breast cancer.[12]

As is true of the other aspects of the breast cancer prevention continuum, barriers to screening are likely to vary by the type and severity of disability. Language barriers may be particularly acute for Deaf women who are often not provided with a qualified sign language interpreter during health care visits.[11, 12] Many Deaf women, in fact, do not use interpreters and are limited by a knowledge of medical vocabulary similar to that of non-English speaking immigrants.[12] Perceived physical barriers to mammography may pose especially strong barriers for women with severe lower extremity disabilities who incorrectly assume that one must stand for a mammogram or who find that the clinic's mammography equipment is indeed inaccessible to them.[13, 17, 62, 64, 68] Many women with disabilities have health conditions requiring a great deal of contact with healthcare providers, and they may be resistant to scheduling additional visits for preventive services; bad experiences during prior attempts at mammography may further dissuade them.[63, 67, 69]

A small number of projects have attempted to develop education campaigns or interventions aimed at increasing mammography among women with disabilities. These include a CDC-funded public education campaign,[70] a CDC-funded pilot project testing two interventions targeting women with disabilities in the San Francisco Bay Area,[71] and an ongoing CBCRP-funded project to develop an intervention for Latinas with disabilities living

in California's Central Coast.[72] The CBCRP-funded Breast Health for Women with Disabilities, in the San Francisco Bay Area, has used telephone survey data to develop a manual with best practices on making breast cancer screening accessible to women with disabilities and to educate disability and breast cancer screening agencies.[73]

In summary, while disparities in breast cancer screening for women with disabilities are well documented, there remain critical gaps in our knowledge of the factors that underlie these disparities. In order to develop effective and targeted intervention strategies to promote breast cancer screening among women with disabilities, future research must focus on identifying the specific financial, physical, and attitudinal/informational barriers to breast cancer screening, taking into account both the type and severity of disability.

Diagnosis

If disparities in screening exist, as the discussion above suggests, then presumably disparities in stage at diagnosis would exist as well. There is, however, a dearth of evidence to support or deny this supposition. Two studies have suggested that women with disabilities are diagnosed at a later stage than women without disabilities,[18, 74] while another did not.[4] The varying ways that disability was defined across these three studies may partially explain the disparate findings. There is evidence that women who are obese tend to be diagnosed at a later stage.[75, 76] Obesity, however, in the context of disability research is complicated. While obesity can be considered a cause of disability in and of itself, it also is a frequent consequence of another disability.

Access to Clinical Trials

As a matter of protocol, women with disabilities are usually excluded from participation in clinical trials.[77] The mere presence of disability or any of its frequent co-morbid conditions are almost always listed as exclusion criteria. The *de facto* exclusion of women with disabilities from clinical trials often results from inaccessibility of the trial facilities or the lack of equipment that can accommodate the needs of women with mobility impairments.[78] Consequently, no information is available on optimal treatment protocols for women who have a disability.

Treatment

A recent, groundbreaking study found substantial differences in treatment between women with disabilities who were diagnosed with early-stage breast cancer and their non-disabled counterparts. In a large study using registry data from several geographical areas in the U.S., women under age 65 who qualified for Social Security Disability Insurance (SSDI) and Medicare coverage were found to be much less likely to have received breast conserving surgery (as opposed to mastectomy) than similar women who were not on SSDI or Medicare.[19] The researchers were unable to determine the extent to which these differences were attributable to patient preference versus physician recommendation.

Previous studies were much less definitive. Caban and colleagues studied treatment in a small cohort of women undergoing surgery for breast cancer

(n = 234 women, 39 of whom had disabilities). In this study, in which disability was defined as 'having a physical disability that interfered with mobility or activities of daily living,' lower rates of breast conserving surgery and neoadjuvant chemotherapy were found, although they were not statistically significant.[4] Recently, results from a study of patients with Alzheimer's disease suggested dramatically different treatment protocols for this set of patients.[74] Women with Alzheimer's disease were less likely than those without the disease to receive surgery, radiation, and chemotherapy for their breast cancer.[74] Reasons for these disparities were unclear.

More information on breast cancer treatment received by women with disabilities clearly is needed to identify potential disparities in breast cancer treatment by disability status. Furthermore, it is important to identify and distinguish between differences that are necessitated by the disability itself, versus disparities that are a consequence of misinformation and/or discrimination. For example, the inability to lie flat or adequately abduct the arm (as is common with some types of physical disabilities) may make it difficult or impossible to deliver radiation therapy[4] and consequently would preclude breast conserving surgery as well. Likewise, there have been reports of severe side effects of radiation therapy when administered to women with active lupus.[4] Unfortunately, such observations are often anecdotal and undocumented.

There is no information on how breast cancer treatment affects a woman's disability-related functional limitations. Women who rely on their arms for transferring and conducting their daily activities or who use crutches for ambulation would have a severe reduction in functioning after surgery and while recovering. How they manage to meet their functional needs during recovery is unknown. No studies have examined whether their rehabilitation needs are met. How chemotherapy or radiation therapy affect their functioning is unknown. It is also unknown whether they are ever able to achieve their pre-breast-cancer-treatment level of functioning. There is no documentation about how the course of their recovery from breast cancer differs compared to women with no preexisting disabilities. The exclusion of women from clinical trials and from health research in general has created a void of information on how the presence of a disability should or should not influence therapeutic treatment modalities.

Survival

There are some characteristics that are more prevalent in people with disabilities (e.g. poverty, smoking, depression, stress, social isolation, publicly insured, obesity) that could negatively impact survival. Furthermore, treatment differences (see above) may also affect survival among women with disabilities. More study is clearly warranted.

Co-Morbidity

There have been no systematic studies of overlap between cancer co-morbidities and disability co-morbidities. Previous research has identified pain, weakness, and fatigue as the most common co-morbid or secondary conditions reported by women with physical disabilities.[48] Other common problems that often accompany disability

are overweight,[48, 79] depression,[80, 81] and mobility limitations.[80] Each of these six conditions could also be a consequence of breast cancer treatment and recovery. The fatigue and weakness that result from radiation therapy would likely compound pre–diagnosis fatigue and weakness. No studies, however, have examined levels of these conditions prior to cancer diagnosis compared to post treatment. Breast surgery often results in temporary or permanent limitations in the use of the arm on the affected side. If this arm is needed for propelling a wheelchair or crutch use, its impairment could result in additional mobility limitations. Many women take steroids to manage the inflammation that is part of joint and connective tissue diseases and must deal with the side effect of weight problems. If steroids are then needed as part of breast cancer treatment, it is not known whether weight problems will increase or if the pre-morbid dietary coping behaviors will serve to minimize the effect of additional medication. Similarly, coping behaviors for depression associated with disability may transfer to dealing with the diagnosis of cancer. On the other hand, being confronted with two stigmatizing and life-altering conditions simultaneously may exceed some women's coping capacity and lead to increased needs for psychotherapy and antidepressive medication. In many cases, it is impossible to separate the effect of disabilities from the effect of cancer treatment on these co-morbid conditions. Studies that compare the status of these conditions pre-diagnosis with post-treatment would offer valuable information.

Quality of Life

Quality of life after breast cancer for women with disabilities may be influenced by factors that go beyond those experienced by women in general. These factors include: 1) the quality of treatment for the minimization of complications; 2) attentiveness of medical personnel to disability-related functional needs that may be heightened due to breast cancer treatment; 3) the willingness of family and other assistance resources to compensate for temporarily impaired functioning; 4) the availability of assistive devices to compensate for temporarily impaired functioning; 5) care by medical personnel who are knowledgeable in the treatment of pain, fatigue, weakness, and other secondary conditions commonly reported by women with disabilities; and 6) the availability of individual peer support and support groups that are accessible, knowledgeable, and sensitive to the emotional and physical needs of women with disabilities who are recovering from breast cancer.

Mortality

There appears to be only a single study on breast cancer survival among women with disabilities, the same study that found differential treatment rates. Working-age women with disabilities who had been diagnosed with early-stage breast cancer were found to have higher all-cause and breast-cancer-specific mortality rates than women without disabilities, even after stratifying by stage of diagnosis and adjusting for other factors.[19] It is not clear whether differential mortality rates are related to differences in treatment or to other disability-related factors.

Beyond the one study, virtually nothing is known about breast cancer mortality among women with disabilities. Presumably the lower rates of screening among women with disabilities (as discussed above) would translate to higher mortality rates, but there is currently little evidence to support this. A study of Social Security Disability Insurance (SSDI)-qualifying women reported that those with disabilities had higher all-cause mortality rates than non-SSDI-qualifying women, but similar breast-cancer-specific mortality, despite being diagnosed at a later stage.[18]

In the first study to evaluate cause-specific mortality among people with cerebral palsy (CP), it was reported that women with CP were three-times more likely to die from breast cancer than comparable women in the general population.[82] Since this was a mortality linkage study, the investigators were unable to evaluate the degree to which the excess breast cancer mortality was a reflection of differences in staging and treatment versus differences in incidence. The authors suggest that these findings may be partially explained by the high prevalence of nulliparity among women with CP, but argue this is unlikely to fully explain the three-fold increase in mortality.[82] These findings are alarming and certainly warrant more in-depth investigation. Linkage mortality studies such as this one that make use of preexisting databases are relatively inexpensive and quick to perform. They provide a valuable tool for identifying disparities among segments of the population and determining areas of more focused research.

Conclusions and Future Directions

Despite the large and growing number of women with disabilities in the U.S., there is a paucity of information on the burden of breast cancer among these women. Given that women with disabilities constitute one of the most economically disadvantaged populations living in this country (an estimated 26 percent of California women with severe disabilities live in poverty),[31] large disparities in breast cancer are likely to exist. The limited data we have to date suggest that women with disabilities face higher risk, are less likely to be screened, are more likely to be diagnosed at a later stage, are less likely to receive breast-conserving surgery compared to mastectomy, and may be ultimately at greater risk from dying of breast cancer than their non-disabled counterparts. Conspicuous by its absence is any information about whether their specific disability-related needs are met or even addressed in the processes associated with breast cancer diagnosis, treatment, and recovery. These conclusions, however, are based on very sparse data and may be limited to certain types and/or levels of disability. In order to eliminate potential disparities in breast cancer associated with disability status, we must first identify who is most at risk for such disparities and elucidate the factors that contribute to them.

Comprehensive studies are needed to understand the breast cancer-related experiences of women with a broad spectrum of disabilities, from risk factors to screening to treatment to recovery to long-term survival and quality of life. Research must focus not only on the extent that such women, viewed as a minority group, face increased risk, greater prevalence, and disparities

in treatment methods and survival rates, but also on the specific barriers to prevention, screening, and treatment experienced by subgroups within the disability community, and on strategies for overcoming such barriers.

For example, to what extent do information and communication barriers prevent Deaf women or women with cognitive disabilities from seeking and obtaining preventive screenings, or from obtaining optimal treatments? How does the physical inactivity of many women with mobility limitations affect their breast cancer incidence, and what can be done to reduce their risk? To what extent do inaccessible facilities and equipment prevent women with physical disabilities from gaining access to preventive services, breast cancer screenings, and treatment? What is the interaction between a preexisting disability, along with secondary conditions often associated with that disability, and additional functional limitations caused by the cancer and/or its treatment? How do women with mental health disabilities, or mental health issues secondary to some other primary disability, cope differently with issues related to screening, treatment, recovery, and survival?

Clinical practice guidelines are needed to ensure that the specific functional concerns and complex, multifaceted life situation of women with physical, sensory, and intellectual disabilities are considered in the development of breast cancer treatment plans. Concurrently, education and awareness campaigns are needed that focus on women with disabilities and their families to increase their interest in and pursuit of cancer screening, to empower them to be equal partners in the development of their treatment plans, and to encourage them to demand the highest quality cancer care services that address their disability-related needs, enable them to maintain their level of functioning, minimize complications during recovery, and maximize their chances for survival.

Research shedding light on these and related issues has the potential to substantially reduce breast cancer risks and disparities in screening, treatment, recovery, and survival, thereby lessening the burden of breast cancer for women with all types of disabilities.

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Culture

Introduction

Culture is a set of shared and socially transmitted values passed through generations as learned beliefs and behaviors.[1, 2] The concept of culture carries with it the idea that people who interact on a regular basis know the same unwritten rules and criteria for social life that confer status as a member of the group.[3] Groups of individuals with similar heritage, usually based on race or ethnicity, tend to share cultural characteristics and address problems in approximately the same way.

Despite significant efforts over past years, ethnic and racial minority groups in the U.S. continue to experience excess rates of morbidity and mortality from breast cancer.[4] Migrant studies of Asian American women and Hispanics/Latinas have shown that breast cancer rates change when women move to a new country, providing evidence for possible environmental and lifestyle risk factors.[5-7] Moreover, these lifestyle changes may reflect different levels of acculturation.[8, 9] Since fewer than 5 percent of cancers can be attributed to genetic causes, lifestyle and environmental factors, which are informed by culture, appear to be the more salient causative factors.[10]

Cultural differences between the myriad of ethnic groups in the United States greatly impact health care delivery and effectiveness. Cultural factors are increasingly recognized as being important in health disparities, including influences on breast cancer screening behaviors, decisions about breast cancer treatment, and quality of life. This chapter focuses on the evidence for the association between cultural factors and breast cancer among ethnic and racial minority groups in the United States, including African Americans, American Indians/Alaska Natives, Hispanics/Latinas, Asian Americans, Pacific Islanders, and immigrant populations, who may overlap with most of the preceding categories.

Increasingly, researchers are making a distinction between race, ethnicity, and culture. For example, ethnicity is defined as subgroups within a larger society who share a common origin and practices, while ethnic identity is an individual's perception of group membership, including the importance of belonging to this group, and actual participation in group practices and customs.[11-14] As a result, many investigators are focusing their research on disaggregated subpopulations, as well as different generations within subpopulations.[15-17]

However, not all subgroups have been equally studied; studies on immigrant populations have focused primarily on Mexican, Chinese, Japanese, Vietnamese, and to a lesser extent, Korean immigrants.[18] With the advent of the Community Network Programs (formerly the Special Population Networks) funded by the National Cancer Institute through the NCI's Center to Reduce Cancer Health Disparities (CRCHD), 25 networks are doing research and education focused on other disaggregated subpopulation groups, including Samoan and Tongan (Pacific Islander groups), and Puerto Rican, Cuban, and Guatemalan (Latin groups), and others.

Concept/Exposure Definition

The state of health within any minority population in the United States cannot be fully addressed

without assessing the effects of racism, personal prejudice, marginalization, oppression and acculturation (the extent to which minority-group individuals adopt the beliefs, values, and behaviors of the majority group). For example, the forced relocation of Africans to this country for slave labor resulted in severe acculturation and racism influences that still exist today. As another example, over 560 federally-recognized American Indian/Alaska Native tribes and over one hundred state-recognized tribes each have their own unique cultures, languages, and health care needs and patterns. Historical trauma and contemporary abject poverty impact their health, however, as do strong family ties and respect for tribal history and elders.

Immigrant and refugee populations are often subjected to discrimination by structural systems, including the health care system, due to their lack of English proficiency and lack of understanding of majority U.S. culture. In addition, most immigrants arrive with no historical basis for understanding the paradigm of western medicine, and often distrust the U.S. government. This can translate into distrust of health care providers and the health care system. This distrust is also high among U.S.-born racial/ethnic minorities,[19, 20] and they experience differential care due to their membership in racial/ethnic groups of color.[21]

Cultural beliefs and values regarding the nature of reality (spiritual, material), interpersonal relationships and behaviors (individual, group), and the nature of time (past, present, future) create motivational force.[22] Culture provides the underlying rationale or impetus to behave and think in a certain way and ultimately, influences an individual's perceptions, cognitions, affect, and behaviors.[23, 24] Previous research has demonstrated that ethnic and racial groups differ in terms of beliefs and values related to spirituality and religion, interpersonal relationships, behavior orientation (individual or collective), and temporal orientation.[23-26] For example, cultural beliefs and values for the majority group, European Americans, include individualism, materialism, and future temporal orientation, whereas cultural values for African Americans and Latinos/Hispanics include interdependence, collective responsibility, spirituality, and present temporal orientation.[24, 27-30] Cultural beliefs of American Indians/Alaska Natives include tribal-specific spirituality that connects all living things and nature, including what western scientists consider to be inanimate objects, such as mountains and water.

Additional factors have been considered when working with immigrant populations. For example, there is evidence that acculturation is important to breast cancer risk-related factors in groups who immigrate to the U.S. Researchers have developed a number of measures of culture and acculturation for various racial and ethnic groups, but the concept remains poorly conceptualized and defined.[31] Currently used acculturation scales usually include questions about country of origin, years living in the host country, and language use, preference and proficiency,[18] whereas measures of culture assess beliefs, values, and behaviors related to religion and spirituality, temporal orientation, and collectivism.[32-34] Because of logistic or cost constraints associated with collecting more comprehensive measures of culture and

acculturation, human health studies frequently use more easily available cultural indicator variables such as race, birthplace, length of residency in the U.S., English language proficiency, and/or citizenship status.[35] Although the concept of acculturation is fraught with both conceptual and construct issues, some researches have used creative methods to indirectly estimate proxies for acculturation, although these seem to indicate less about culture than about familiarity with and ability to navigate our health care system. Some studies have also incorporated folk health beliefs to assess the level of culture and acculturation for ethnic and racial minority groups, including immigrants. Because researchers use different definitions of culture and acculturation, it is difficult to make comparisons between studies.

Biologic Plausibility

Breast cancer incidence is lower among most groups of minority women, but the disease is also more deadly. For example, despite lower incidence, mortality from breast cancer is significantly higher among African American women compared to white women.[4] Among American Indian/Alaska Native women, mortality rates are high and incidence is still increasing.[36, 37] Native Hawaiian women have the highest breast cancer incidence rate in Hawaii; nationally they rank second to white women, and the breast cancer mortality rate of Native Hawaiian women approaches that of their African American counterparts.[29, 38, 39] As the mortality and morbidity rates have decreased for U.S. white women over the past twenty years, minority women have gained limited benefit, and in some cases have lost earlier gains, from the progress made in breast cancer diagnosis, prognosis and treatment.[40-42]

Several hypotheses have been put forth to explain the relationship between cultural factors and breast cancer among ethnic and racial minorities in the U.S. As noted earlier, immigrant studies report that women migrating to a country with higher risk of breast cancer have a higher incidence of breast cancer than women in the country they leave behind. These immigrant women may change their lifestyle in ways that increase risk; migration may also profoundly change a woman's exposure to environmental contaminants and her breast cancer risk. Newer immigrant groups may have different cultural beliefs or knowledge that makes them less likely to seek screening or treatment for breast cancer. Minority immigrants may not have the same access to medical care as their non-immigrant counterparts due to language, but may suffer the same barriers of cultural differences, low socioeconomic status, lack of insurance, or discrimination.[43-45]

Cultural beliefs and values for all non-European American groups may influence motivations and decisions about cancer screening, strategies used to make decisions about cancer treatment, and resources used to cope with cancer diagnosis. For instance, individuals may be motivated to engage in cancer screening depending on whether cancer, and cancer risks, are perceived as controllable or uncontrollable, if their focus is on short- or long-term outcomes, and whether the strategy serves individual or group interests. Attention to a particular aspect of these attributes (e.g., greater focus on short-term outcomes, preference for serving group interests) is likely to be influenced by cultural

beliefs and values. For example, religious and spiritual values may influence perceptions of control,[46, 47] and temporal orientation may influence the extent to which individuals focus on the short- or long-term outcomes of cancer screening.

While there is a growing body of literature about the relationship of breast cancer in Askenazi Jewish women and a founder gene mutation, little is known about the genetics of breast cancer in other minority populations. The historical impacts of dramatic and systematic acculturation events have certainly constrained the gene pools of several minority populations, which may also have led to biological susceptibilities. For instance, the concept of a genetic bottleneck that occurred during the Middle Passage of Africans to America[48] is cited as a contributor to the prevalence of diseases such as sickle cell in the U.S. black population. This concept can also be associated with the decimation of 50 to 90 percent of the American Indian/Alaska Native populations by the end of the nineteenth century, as European diseases reached epidemic proportions among people who had no herd immunity to them.[49-57]

It is well documented that "triple negative" breast cancer (tumors negative for estrogen, progesterone, and HER2/neu, and typically diagnosed at young age) occurs more frequently among African American women.[58-60] Few American Indian/Native Alaskan breast cancer survivors have taken part in genetic testing for BRCA1 or BRCA2, but of those few who have, none have shown this mutation.[61]

Critical Review of the Literature, by Outcomes in Breast Cancer Continuum

Incidence

Limitations in cancer data based on nativity, language, or culture--along with poor conceptualization of culture and inaccurate use of the concepts of race and ethnicity on the part of researchers--hamper research on the effects of cultural factors on cancer incidence and mortality.[1]

Generally speaking, it is difficult to obtain information on cancer incidence data based on nativity, language, or culture for certain ethnic groups because few sources that collect these data are available to researchers. The North American Association of Central Cancer Registries (NAACCR) is working with its member researchers, registries and organizations to improve reporting accuracy of race and ethnicity, and address the need for inclusion of important socioeconomic measures and smaller geographic identifiers, while maintaining and protecting patient confidentiality. However, challenges remain.

To meet the need for improved surveillance of cancer status in isolated tribal populations, several partnerships have been established that can confidently report that cancer incidence in these populations has dramatically increased, though cancer was once quite rare. Through partnerships with NCI's Community Network Programs and similar partnerships funded by other agencies, in 2007 improved data on the incidence of cancer in American Indian/Alaska Natives is being reported. The federal 2007 Report to the Nation on American Indian/Alaska Native cancer incidence is the first time there has ever been such an effort

to improve the accuracy of this data. Based on these preliminary data, Alaska Natives have the highest age-adjusted breast cancer incidence rate (139.1), followed by Northern Plains (115.4), and Southern Plains (112.9). The average age-adjusted breast cancer incidence rates for American Indians/Alaska Natives for the total U.S. is 85.8. The Pacific Coast rate is slightly lower, at 80.1. In comparison, the total U.S. breast cancer incidence rate is cited in this report as 62.9.[62] This document finally clarifies both the regional differences and under-counting of incidence data from previous federal publications.[63-65, 65, 66]

Cancer for American Indians/Alaska Natives is under-reported in most state and federal databases, often due to racial misclassification.[67-75] Misclassification occurs for a number of reasons[76] and has been one of the most difficult obstacles in the path of accurate and informative data for the American Indian/Alaska Native population.[77] Hence, improving prevalence estimates must be a priority for policy efforts.

Mack et al. examined breast cancer among Hispanics/Latinas in Los Angeles County, using social security numbers to estimate age of migration to the U.S. They found that Hispanics/Latinas had a lower risk of developing breast cancer than non-Hispanic white women and that Hispanics/Latinas who immigrated as children had only a slightly higher risk than those who immigrated as adults.[78] Eschbach and colleagues used SEER and census track data to investigate whether cancer incidence among Hispanics/Latinas increased with acculturation. Using lower percentage of Hispanic/Latino residents and higher Hispanic/Latino income within a census tract as a proxy for increased levels of acculturation, they found breast cancer rates to be significantly higher among Hispanics/Latinas residing in census tracts deemed to be high-acculturation than those who lived in census tracts deemed to be low-acculturation.[79]

A population-based case-control study in California found that foreign-born Hispanics/Latinas had a 50% lower breast cancer risk than U.S. born Hispanics/Latinas.[9] Furthermore, risk was lower among Hispanic/Latina immigrants who moved to the U.S. at age 20 and those who spoke mostly Spanish.[9] This study also supported the idea that differences in reproductive factors, such as parity and breast-feeding, could partially explain increased risk among more acculturated Hispanics/Latinas.[9] However, when Abraido-Lanza and colleagues used National Health Interview Survey (NHIS) data of Hispanics/Latinas to assess the association between acculturation and screening for cancer of the cervix, they found the association to be inconsistent.[80] Other researchers investigating breast cancer risk among immigrant Hispanic/Latina and Asian populations also found increased risk to be associated with increased levels of acculturation.[6, 29, 81]

Many of these conflicting findings may be due to the lack of consensus on the definitions of culture as well as acculturation, so attributions of causation to these concepts will be inconsistent at best.

In addition, several special studies have examined the role of acculturation in the development of

breast cancer among Asian American and Pacific Islander populations. A 1996 population-based case-control study of breast cancer among Chinese-, Japanese- and Filipino-American women in selected areas of California and in Oahu, Hawaii concluded that parous Asian American women had a significantly lower breast cancer risk over nulliparous Asian American women. However, other reproductive factors, such as duration of breast-feeding or average age at menarche between U.S.-born and foreign-born Asian American women account for only non-significant differences in breast cancer risk, suggesting that lower breast cancer rates in these Asian populations may be primarily due to other environmental and/or lifestyle factors.[82] Wu and colleagues examined tofu (soy) consumption among Chinese-, Japanese- and Filipino-American women in two regional areas of Northern and Southern California, and Oahu, Hawai`i. They found a two-fold greater intake of tofu among Asian immigrant women over U.S.-born Asian American women, and observed a protective effect against breast cancer with increased tofu intake.[83] A follow-up investigation conducted by Wu and colleagues in 1998 in which they analyzed the results of their 1996 study with those of three other studies conducted in China, Singapore and Japan – while indicating a possible relationship between breast cancer risk and soy intake – was inconclusive.[84]

Tseng and colleagues recently published a study on foreign-born Chinese American women examining the relationship between acculturation and breast density, which is associated with increased breast cancer risk. Using a survey instrument to elicit information on the respondents' demographic, cultural, and lifestyle factors, including reproductive history, these investigators found a positive correlation between higher acculturation levels and denser breast tissue. They also found that more highly-acculturated Chinese American women tended to have higher education levels, were more likely to be born in Hong Kong or Taiwan (versus The People's Republic of China), had longer U.S. residence, and were more likely to have immigrated at younger ages. Although the study was limited by a relatively small sample size, foreign-born Chinese American women's reproductive risk factors (including lower age at menarche, fewer live births, higher age at first live birth, and shorter duration of breast-feeding) also correlated with increased levels of acculturation.[85] Despite these findings, Tseng and colleagues report that differences in lifestyle and reproductive factors could not explain the acculturation-breast density association. Further, these investigators did not find an increased breast cancer incidence among women with higher breast density in this small study sample.

Of all U.S. Asian populations, Japanese Americans have the lowest percentage of first-generation immigrants, and they are the only U.S. Asian ethnic group with a negative population growth. Now in their fifth and sixth generations in the U.S., Japanese American women are more likely to be born in the U.S. and are the most acculturated of all U.S. Asian populations.[30] In a detailed study of breast cancer by race and ethnicity in Los Angeles (LA) County, California in women age 50 and above, Deapen and colleagues found the five highest breast cancer incidence rates to be in (1) non-Hispanic white

women, (2) followed closely by Japanese American women, and (3) Filipina American, African American, and Chinese American women. These investigators also found Japanese American women to have the sharpest rising breast cancer rates over all other women in LA County.[86]

In American Indian/Alaska Native populations, breast cancer incidence and mortality rates vary significantly among tribes and geographic regions.[87-91] The distinctive patterns of low incidence and mortality rates in Southwestern tribes and high rates in Northern Plains, Southern Plains and Alaska require research into etiology, access issues and cultural contributors to the observed patterns. Alaska, for example, now has rates of breast cancer equivalent or slightly higher than the U.S. non-Hispanic white incidence rate.[62] Among American Indian/Alaska Native populations, studies also show that people anecdotally report cancer clusters, but the small populations of the communities confound these reports because they do not reach statistical significance.

Studies have shown that cultural beliefs and values may be important to behaviors that may affect breast cancer risk. For American Indian/Alaska Native women, the phrase "brown and round" indicates a cultural acceptance of obesity, possibly culturally transmitted over generational cycles of feast and famine (tribes historically had population counts recorded on blankets documenting years of thin and fat). Future temporal orientation – which, as noted above, has been found to be more common among whites and less common among some minority groups – has been positively associated with health promotion behaviors, such as exercise.[92-94]

Screening

Nativity, immigration history, culture, and level of acculturation impact health screening practices of individuals and communities. While Chen and colleagues[95] found no significant relationship between acculturation and knowledge of breast cancer risk among 135 Chinese women in the New York metropolitan area, they did find a two-fold association between women with higher income/higher education and increased knowledge of breast cancer risk. However, most studies report an association between higher levels of acculturation and increased breast cancer screening for Asian American, Pacific Islander, Hispanics/Latinas and other U.S. minority populations.[26, 96, 97] Specifically, being proficient in English, having been born in the U.S., having moved to the U.S. at a young age, or residing longer in the U.S. are associated with increased mammography and clinical breast exams for Asian American and Pacific Islander women and Hispanics/Latinas.[9, 35, 92-94, 98-122]

Nativity, immigration history, legal status, and citizenship are also important factors in breast cancer screening among immigrant Hispanics/Latinas and Asian American women. Several studies have found that being without legal status and being foreign born serve as barriers to breast cancer screening among both of these groups.[8, 9, 100, 101, 104, 107, 123-127]

In some ethnic and racial minority groups, cultural factors appear to be important to health beliefs and cancer-related behaviors. In research with African American women recruited from public housing

facilities, present temporal orientation was positively associated with greater perceptions of barriers to mammography and was negatively associated with mammography utilization.[16] Other work has shown that future temporal orientation is positively associated with participation in genetic counseling and testing for inherited breast cancer risk among African American women at increased risk for having a BRCA1 or BRCA2 mutation.[34] Although individualism and collectivism have not been directly measured in prior studies on cancer screening, results suggest that collectivist values influence screening behaviors. For example, greater levels of social integration and the size of one's social network were associated with adherence to breast and cervical cancer screening among Mexican, Cuban, and Central American women.[128, 129]

Additionally, cultural beliefs often have considerable influence on U.S. minority women's health behaviors and decision-making. A number of studies have reported that fatalism and fear serve as barriers to screening practices in many communities.[24, 28, 99, 129-136] The misconception that symptoms must follow disease ("I don't feel sick, so I must be healthy.") has also been established as a barrier to screening.[104, 128, 137, 138] The additional fear of becoming a burden on family members could also discourage breast cancer screening.[44, 110, 139, 140] Other studies have pointed to modesty about the body as a salient barrier to breast screening among many Hispanic/Latina, Asian American, and Pacific Islander subgroups, including Vietnamese, Chinese, Filipino, Asian-Indian, and Asian-Islamic women.[44, 113, 114, 117, 137, 141-149] Although modesty was not found to be a barrier among Japanese American women, caution must be taken in interpreting these results, because the study sample was small, at a single site[150]and also because the percentage of foreign-born Japanese in the U.S. is on the rise, one-third having arrived since 2000.[151] Many Hispanics/Latinas and Asian American women, especially immigrants, as well as other minority or poor women, report distrust of the U.S. health care system, and disrespectful or insensitive treatment by health care workers as significant barriers to breast cancer screening and re-screening.[21, 131, 152-154]

Despite these barriers, numerous studies have demonstrated that community-specific, language-appropriate and culturally-tailored interventions are successful in increasing breast cancer screening, specifically among immigrant Asian American, Pacific Islander, Hispanic/Latina and American Indian/Alaska Native communities, as well as other populations who contend with health disparities.[25, 43, 102, 121, 155-179] Such interventions frequently include low-literacy resource materials developed in the target population's language, rather than by translating materials from English. These materials also incorporate cultural values, themes, and symbols to address the importance of screening practices in a manner that is both relevant and respectful to the target population.[25, 102, 105, 163, 164, 167, 180-185] Kreuter and colleagues[186] found that mammography utilization and fruit and vegetable consumption were significantly greater among African American women who received health magazines that were tailored to cultural and behavioral beliefs compared to those who did not receive these magazines and women in the control group.

In contrast, Becker et al.[187] found that the cultural association of cancer with bad spirits that must not be spoken of, compounded by distrust due to cultural injustices within the health care system, prevented effective screening practices in specific American Indian/Alaska Native populations. In fact, only 52 percent of American Indian women aged 40 and older reported having mammograms within the previous two years, compared with 70 percent of white women.[188] The Native WEB program (Women Enjoying the Benefit of screening) was developed to increase access to much-needed screening in Native American/Alaska Native communities and to address these women's request that they be examined by other women.[189]

Critical to the success of any culturally-tailored cancer screening intervention is identification of the specific population group for whom the intervention is targeted. While U.S. cancer surveillance data are still most often collected and reported by aggregate race/ethnicity, each of the more than 30 subpopulation groups within the category of "Asian American"[190] and the more than 30 subpopulation groups within the category of "Pacific Islander"[191] has its own distinct culture, beliefs and practices. Approximately 2,000 Asian and Pacific Island languages and dialects are spoken worldwide. In California, more than 45 distinct Asian and Pacific Island ethnic groups speak 28 different languages and many more unique dialects.[192] Of the ten most commonly spoken languages in California, six are Asian.[193] Similarly, California's Latino/Hispanic populations originate from more than 22 Spanish-speaking countries (including the U.S.), plus Puerto Rico. Spanish is the second most commonly spoken language in the U.S. But while many believe there is a single Spanish language, numerous dialects and regional variants are spoken throughout the world and across the U.S. Diversity, not only across the primary U.S. race/ethnic population groups, but also within each subpopulation, is vast. Within American Indian/Alaska Native communities, over 217 different languages are spoken.[65] Thus, disaggregation of race/ethnic groups in cancer research and along the cancer care continuum is critical.[92, 194-196]

Today, among the most successful interventions across the breast cancer care continuum are those being developed by investigators in partnership with communities via community-based participatory research. The California Breast Cancer Research Program has led the way in promoting this type of research, and now many traditional funders, including the National Cancer Institute, American Cancer Society, Susan G. Komen for the Cure, and others incorporate funding mechanisms to support such partnerships.

It appears that efforts have begun to examine the role of culture on screening practices among African American, American Indian/Alaska Native, Asian American/Pacific Islander and Hispanic/Latina women. Additional studies need to be conducted among American Indian, Alaska Natives, Native Hawaiian, other Pacific Islanders and the smallest Asian American communities, such as Bangladeshi, Hmong, Indonesian, Iwo Jiman, Malaysian, and Nepalese,[151] along with the appropriate methodology and instruments to study these populations. Barriers have been identified, as has the need for more culturally appropriate

means of increasing breast cancer screening among minorities. However, despite targeted efforts at intervention with culturally-appropriate strategies,[180-182] the underutilization of breast screening still persists, and much more needs to be done to better define the concepts of race, culture, ethnicity, and acculturation to be able to compare the findings from these various studies. The studies conducted thus far leave lingering concerns of the impacts of low screening among immigrants, and other minority and medically underserved populations.

Diagnosis

Very little research has been dedicated to examining the role of culture on breast cancer diagnosis and post-screening follow-up among African American, American Indian/Alaska and Hawaii Natives, Asian American/Pacific Islanders and Latinas. However, previous research has shown that religious and spiritual beliefs influence decisions about seeking treatment for breast cancer symptoms.[44, 197-199] For example, Lannin and colleagues[200] found that religious and spiritual beliefs—such as prayer about cancer—can lead to healing, but they were also associated with greater delay in seeking treatment for breast cancer symptoms. African American women were significantly more likely than Caucasian women to endorse these beliefs.[197] Similar findings have been reported for Hispanics/Latinas and many Pacific Islander communities;[201] faith in God was influential in determining the length of time between symptom recognition and seeking care in Latino/Hispanic men and women.[110] Several studies have documented the perception of cancer in American Indian/Alaska Native women and the associated cultural barriers that prevent timely diagnosis.[187, 202-209]

In an analysis of SEER data, Hedeen et al. reported that Asian-born American women have a greater percentage of tumors larger than 2 cm than both U.S.-born Asian-American women and white women, suggesting that birthplace may be correlated with stage of diagnosis. Hedeen found the same results for women born in Latin America and living in the U.S., compared with U.S.-born Latinas and non-Hispanic white women.[210] The authors reasoned that lower utilization of breast cancer screening by foreign-born Asians and Latinas is likely to be responsible for the observed differences in tumor size. This further lends support to the hypothesis that more acculturated U.S.-born women tend to get screened more and, consequently, are less likely to be diagnosed with larger tumors.[210] However, the interpretation of the results may be affected by the relatively large proportion of Asians and Latinas in the cancer registry sample with unknown birthplace who were excluded from the analysis. Recent findings suggest that patients in the registry with unknown birthplace are twice as likely to be U.S.-born than patients with known birthplace.[211]

Later stage at diagnosis may result not only from screening underutilization but also fear of the disease. Two qualitative studies of South Asian and Chinese American immigrant women found that women are likely to delay seeking follow-up assessment after screening positive for a breast lump for fear of the disease and the real or perceived impact it would have on their lives.[130, 212] These findings underscore the importance of targeted health education and outreach to allay

fear and misconceptions among these subpopulations.

Similarly, Moy and colleagues[213] surveyed a small group of Asian, African American and Hispanic/Latina women to determine their cultural perspectives regarding barriers to repeat mammography. They found fatalism among some African American women precluded repeat mammography for fear of finding a breast cancer, which they believed would lead to imminent death. Several studies confirm high rates of late-stage diagnosis among African American women.[27, 214, 215] Wojcik et al.[216] determined that equalizing mammography utilization among African American, white and Hispanic/Latina women would also equalize survival among these groups. However, biologic differences in hormone receptor status and histology among African American women diagnosed with breast cancer, as compared to their non-Hispanic white counterparts, complicate this assumption, especially regarding younger African American women.[194, 217]

In summary, stage of disease at diagnosis is highly correlated with screening practices; women who undergo routine breast cancer screening are more likely to be diagnosed with early stage disease.[27, 213-216] However, there is evidence suggesting that cultural beliefs and values may also delay both diagnosis and treatment, as misconceptions and fear about breast cancer and culturally-defined roles of women in the family may be a barrier to adherence to follow-up guidelines after receiving screening services, over and above individual attitudes and knowledge about mammography and breast cancer.[44, 140, 145, 148, 218] More research is needed to understand cultural beliefs that may affect minority or immigrant women's decisions to delay follow-up after an abnormal or positive screening result.[219] Accordingly, future outreach efforts should not be limited to promoting screening but should also encourage post-screening follow-up after diagnosis. As stated above, culturally tailoring these outreach and education efforts via a community-based participatory research effort will provide the greatest opportunity for success.

Treatment

Culture may influence both the timing and type of breast cancer treatment received by African American, Hispanic/Latina, Asian American, Pacific Islander, Native Hawaiian, and American Indian/Alaska Native patients. These groups, and poor and uninsured patients from all population groups, tend to receive substandard treatments more often than their high-socioeconomic status, insured, non-Hispanic white counterparts.[152, 220-225] Katz found that women who prefer to speak Spanish in Los Angeles were more likely to experience a delay of three months or more from diagnosis to surgical treatment, and were the most likely to experience lower levels of satisfaction with their treatment, compared to non-Hispanic whites, African Americans, and Latinas whose primary language is English.[226] Latina/Hispanic, Asian American, and Pacific Islander women have significantly lower rates of breast conserving surgery compared to non-Hispanic white women.[195, 226-235] In fact, Asian American and Pacific Islander women are two to three times more likely than non-Hispanic white women to undergo mastectomy, a difference not completely

attributable to sociodemographic and clinical factors.

Based on preliminary data from the "National Native American Cancer Survivors Support Network," American Indian/Alaska Native patients report finding access to quality care difficult at best. Examples of findings from Native breast cancer survivors from 1996 to 2000 include that none had access to a second opinion for their diagnosis; only one woman who used Indian Health Service Contract Health Service was offered breast conserving surgery; in some regions, no established treatment protocols were followed and no follow-up recommendations were sent back to the woman's home village; and average interval from the time of diagnosis ranged in various geographic regions from three to nine months.[76, 174, 202, 203, 236-239]

However, researchers have only recently begun to explore the role of cultural influences on treatment for breast cancer to determine if there is a link between culture and observed treatment patterns across racial/ethnic groups.

Several investigators have explored the reasons Asian American and Pacific Islander breast cancer patients tend to receive different treatments than other groups. Goel et al. conducted a large retrospective cohort study of foreign-born Asian American and Pacific Islander women, who tend to be less acculturated than their U.S.-born counterparts.[227] Based on national SEER data, they found foreign-born Asian American and Pacific Islander women were more likely to undergo mastectomy over breast conserving surgery than were U.S.-born Asian American, Pacific Islander, and non-Hispanic white women. The investigators offered several explanations, though none have been tested. One possible explanation is that providers may prefer mastectomy for their foreign-born Asian American and Pacific Islander patients, due to concerns about non-adherence to recommended adjuvant therapy among this population. Alternatively, Asian American and Pacific Islander women may place greater value on immediate treatment (mastectomy), which does not require adjuvant therapy.[227, 232] In a study investigating Chinese American women who underwent surgery for breast cancer and their providers, Killoran and Moyer[240] determined that a majority elected to undergo modified radical mastectomy, even when breast conserving surgery was an option. This finding held regardless of the women's age, educational attainment, income level, and legal status. The women believed mastectomy to be safer, and some reported feeling pressured to accept breast conserving surgery. Physicians and patients alike felt miscommunication was a major barrier for those women whose English proficiency was limited; and language barriers were cited as having led to changing or early stopping of treatment regimens.

A few qualitative studies have also pointed to cultural values as an important variable in treatment preferences among Asian American and Pacific Islander women, many of whom have strong spiritual beliefs that breast cancer diagnosis and outcome are in God's control ("karma").[131, 232] This may lead to Asian American women being less inclined to actively participate in treatment decision-making, leaving the decision to their provider.[131] Through these qualitative studies, some theories emerged in helping to understand

breast cancer treatment decision-making processes through a culturally sensitive lens, based on key values that cut across many Asian cultures. First, Asian American women may want to remove the possibility of worry about a recurrence, thus selecting mastectomy, which does not require additional treatments. Second, mastectomy for treatment of early stage breast cancer usually minimizes the period of disability and affords the patient increased ability to retain obligatory roles and family duties. Third, many Asian cultures encourage self-sacrifice, particularly among women; thus, Asian American women may choose mastectomy, which is less disruptive for their loved ones. Finally, self-sufficiency is also highly valued in many Asian cultures. In that regard, selecting breast conserving surgery would mean that the woman would be less self-sufficient during the multiple treatments periods, forcing her to accept outside assistance, which entails an obligation for future repayment of the favor.[232] Overall, these qualitative studies are critical in establishing the range of beliefs and attitudes among various Asian American populations. Quantitative methods can then be used to examine the extent to which these beliefs and attitudes truly impact health in a population; at least two research groups (Kagawa-Singer and colleagues at UCLA, and Gomez and colleagues at NCCC) are currently undertaking such studies.

Breast cancer treatment decision-making among Hispanics/Latinas also differs from other groups. Maly and colleagues found that Latinas may not receive breast conserving surgery due to decision making by family members.[235] Approximately 49 percent of less-acculturated Latinas and 18 percent of more-acculturated Latinas indicated that their family members determined the final treatment decision, compared with less than 4 percent of African American and non-Hispanic white women. Furthermore, patients were less likely to receive breast conserving surgery when the family made the final treatment decision.[235]

Treatment delays experienced by American Indian/Alaska Native women may be caused by under-funding of the Indian Health Service, and may also be due to cultural factors. Native American breast cancer patients may need family assistance to care for children or elders in the family. Also contributing to delays is reliance on subsistence hunting, for example, among Alaska Native women. The Alaska Native breast cancer patient may delay traveling to Anchorage for treatment until the hunting season is over to help the community obtain food and to access appropriate shares of the food supply. A unique cause of treatment delay is the urbanization of the American Indian/Alaska Native populations, while their eligibility for health care referral remains on their reservations. Conversely, members of isolated tribal communities, especially in Alaska, often have to travel hundreds of miles for prescriptions they must refill in person, the cost of which must come from their personal budgets, which are already constrained by the levels of endemic poverty.

Collaboration with traditional healers must be considered as American Indian/Alaska Native patients communicate their desire to have healing ceremonies (which differ greatly among tribes) as part of treatment regimes.[172, 173, 204]

The co-morbidities that are highly prevalent in most of these minority populations—such as

obesity, diabetes and high blood pressure—often constrain the types of treatments available to these individuals. Co-morbidities will also make many minority patients ineligible for clinical trials, which provide the latest and often the best treatment options.[241] For example, 25 percent of Native American breast cancer patients enrolled in the "Native American Cancer Education for Survivors" (NACES) program are diabetic and about one-third have high blood pressure. Either or both conditions are likely to result in the patient being ineligible for a clinical trials.[204] In any case, clinical trials are rarely offered to these women. Although the barriers to participation are well known, there continues to be insufficient culturally acceptable recruitment strategies to address these barriers.[203]

Minority women who do take part in clinical trials may be misclassified. From April 2005 through 2007, approximately 1000 American Indian/Alaska Natives were asked if they have ever taken part in a cancer clinical trial. Data show 10 percent of the respondents are taking part. However, when checking cancer clinical settings, these individuals were not identified as American Indian/Alaska Native, due to racial misclassification. In an ongoing clinical trial,[242] protocols were modified to assure that cancer patients and families had sufficient information to make an informed decision. The high recruitment rate and lack of refusals in this study show that American Indians/Alaska Natives are willing to take part in clinical trials when the trials are set up in a culturally-appropriate manner.[243]

Culturally- and linguistically-appropriate interventions are needed to decrease the time between diagnosis and treatment and to help ensure that women receive the most appropriate treatment. Efforts must also be made to look at ways to be more inclusive of minority populations in clinical trials in order to be able to determine whether new treatment options offer benefit across all populations.

Survival

Virtually no information is available about the role of culture in survival after breast cancer among ethnic and racial minority groups. The limited literature available for Asian American and Pacific Islander women suggests that acculturation to western culture is associated with early diagnosis; presumably this contributes to better survival. However, beyond differences in stage at diagnosis, the impact of cultural factors on survival among breast cancer patients from ethnic and racial minority groups has not been systematically explored.

In a study using SEER data to compare breast cancer survival among Asian immigrants, U.S.-born Asian Americans and white women, there were no significant differences in survival by birthplace within each of the Asian subgroups (Japanese, Chinese, and Filipina) after adjusting for demographic characteristics, stage of diagnosis, and treatment.[30] The study was criticized, however, for using birthplace information from SEER data, which is missing for a greater number of U.S.-born than foreign-born patients. Exclusion of cancer cases missing birthplace information could potentially lead to a biased sample.[195] Conversely, a more recent study using SEER data comparing U.S.- and East Asian-born Chinese Americans reported significantly

lower five-year overall survival among the latter group.[244] These results suggest poorer survival rates among Asian-born women may be due to problems with access to health care due to language and cultural barriers, leading to delayed diagnosis and treatment. These two SEER studies with contradictory results make it hard to evaluate whether acculturation is correlated with better survival among Asian American women. Additional studies comparing more U.S.- and Asian-born American populations, as well as other populations with a portion of more recent immigrants, such as Hispanics/Latinas, will shed more light on this matter.

Interestingly, studies of survival across Asian American subgroups consistently reported that Japanese American women have better survival and are more likely to be diagnosed at an earlier stage.[30, 195] As noted in the Incidence subsection of this chapter above, Japanese Americans are the most acculturated of all U.S. Asian populations,[30] suggesting that acculturation may be correlated with better survival.

American Indians continue to have the poorest five-year relative survival from breast cancer in comparison to all other ethnicities in the U.S.[245, 246] The culture of past generations of American Indians/Alaska Natives dictated that the word cancer is often not even spoken and that the word does not exist in most dialects. A new project within the Navajo Nation is developing a Navajo language cancer glossary to correct prior translations that lumped cancer with descriptions of incurable illness. In addition, traditional roles that require women to make others their life's priority often negatively impact completion and effectiveness of treatment, thereby contributing to mortality. For some, spiritual associations do not allow for ownership of the disease and patients may rationalize that detection and treatments are not valued since all events were predetermined by a Greater Being.[187] Educational outreach efforts, especially those utilizing visible survivors, will be necessary to overcome the fatalism attached to cancer.

In summary, few studies have touched upon the role of culture on breast cancer survival. The dearth of research studies, imprecise definitions of culture, and complex results indicate the need for more research to develop better methods to assess immigration and acculturation in population-based cancer registries and special studies to determine if and how these factors impact survival for all ethnic groups.

Quality of Life

Little is known about quality of life in ethnic and racial minority breast cancer survivors.[247] The studies that have been conducted in African American women have shown that levels of physical, social, and emotional functioning are relatively high among long-term African American breast cancer survivors; however, subgroups of women may have poorer functioning.[248-251] Not surprisingly, African American breast cancer survivors with malignant lymph nodes and those with recurrent disease reported significantly lower levels of quality of life compared to African American breast cancer survivors without these factors.[249] Ethnic differences in quality of life have also been reported among breast cancer survivors. Compared to Caucasian survivors, African

American survivors were found to have significantly lower levels of quality of life[251] and reported greater levels of cancer-specific distress.[252] While ethnic differences in quality of life may be attributed to socioeconomic (i.e., lower income), medical (i.e., co-morbid conditions), and environmental factors (i.e., greater perceptions of life stress), these factors were higher among African American breast cancer survivors compared to Caucasian breast cancer survivors.[251] However, socio-economic status factors were not associated with quality of life outcomes among short- or long-term African American breast cancer survivors.[249]

Cultural beliefs and values may play an important role in coping with breast cancer diagnosis and treatment, and ultimately quality of life. Studies have shown that religion and spirituality are important coping resources following breast cancer diagnosis in African American, Hispanic/Latina and Caucasian women;[253] however, the importance of these needs may differ depending on the woman's racial or ethnic background. For example, while 25 percent of Caucasian cancer patients reported five or more spiritual needs following their cancer diagnosis, significantly more African American (41 percent) and Hispanic/Latina (61percent) women reported five or more spiritual needs.[131] Other studies have shown that African American and Caucasian women use similar sources for social support following their cancer diagnosis, but significantly more African American than Caucasian women reported that they used God as a source of support.[114] In another study, Caucasian women affected with breast cancer used fewer religious coping strategies compared to African American women and use of religious coping strategies were consistent following surgery only in African American and Hispanic/Latina women.[113] In a recent study on ethnic differences in cultural values between African American and white men newly diagnosed with prostate cancer, Halbert and colleagues found that levels of religiosity were significantly greater in African American men after controlling for clinical factors and sociodemographic characteristics.[254]

In the American Indian/Alaska Native population, the overall poor quality of life for cancer patients demands greater resources. A recent study by Burhansstipanov et al.[172] provides a listing of the quality of life issues that are communicated by the members of the native community. From caregiver support to pain management, quality of life needs to be addressed in this population. Most tribal cultures would like to integrate traditional/spiritual healing with western medicine in an effort to expedite recovery by removing anger and bitterness that accompanies a breast cancer diagnosis. A common complaint among the American Indian/Alaska Native populations is the inappropriateness and inaccuracy of pain assessment tools and lack of communication or miscommunication with health care providers. In most cases, chronically ill individuals are unable to obtain pain medications and are often reported to "pass from this life with no relief," with testimonies of family members having to restrain ill patients who were thrashing in pain. These quality of life issues are direct reflections of cultural distinctions that can be overcome with training, combined effort, and better communication. A very recent effort within the Indian Health Service has been made to develop guidelines that are culturally appropriate for

improving end-of-life care and symptom management. A train-the-trainer program involving all 12 regions of Indian Health Service has been initiated in response to very vocal community requests for improvement in this arena. This need to have providers well trained to address end-of-life care in the context of cultural parameters is also seen in other minority populations.

To date, only one study has been published in the biomedical literature examining the role of culture and other socio-ecological factors on quality of life among Latinas[44] and the studies among Asian American breast cancer survivors were qualitative in design, using focus group participants to capture cultural beliefs and attitudes about coping with breast cancer. Studies have shown that Asian American breast cancer patients, particularly those who are less acculturated, do not communicate their distress from breast cancer with others, be it with family members or providers. Kagawa Singer and colleagues reported that "face" and self-sacrifice are fundamental concepts in many Asian cultures. As a result, many women may tend to hide negative emotions and "suffer in silence" in order to maintain harmony in their family and social circles.[232] Additionally, they also found that Asian American breast cancer patients are less likely to seek professional assistance than their non-Hispanic white counterparts. Of course, given the diverse cultures in this heterogeneous population, there are differences between the many subgroups. Filipina patients may be an exception, in that one study found Filipinas tend to report worse outcomes than other Asian American subgroups.[255] Whether their tendency to communicate distress about the disease arises from differences in cultural expression or from their own physical experiences with the disease is unknown.

Asian American breast cancer patients are likely to report family as the main source of support.[44, 131] However, family is also reported as a source of strain for some Asian American women, who expressed concerns about disclosing their illness and burdening family members. Breast cancer can also bring about physical changes that hinder the woman's role as the family caretaker. Some women expressed concerns about their post-treatment functionality and whether they could still care for their families. The choice of mastectomy, as indicated in the Treatment subsection of this chapter above, may have negative repercussions on self-image.

While the tendencies to hide negative emotions and not seek psychosocial services are coping mechanisms congruent with many Asian cultures, they raise concerns about the emotional well-being of Asian American cancer patients. A research group in Hong Kong has been studying the post-treatment quality of life and treatment decision-making processes among Chinese women, using both qualitative and quantitative methods. In one study measuring social impacts of breast cancer for Chinese patients using a social adjustment scale, the resulting scores indicate declines after diagnosis in self-image, enjoyment of social activities, attractiveness, and sexuality.[256]

For Asian American women, and perhaps for women from other groups of color, beliefs about the causes of breast cancer and its management are highly driven by cultural values, including self-sacrifice and self-sufficiency. The choice of

treatments may be driven by the woman's familial role and hesitation to burden others with her illness, such as is the case with American Indian/Alaska Native women. Lack of knowledge regarding navigation of the U.S. health care system and financial accessibility may pose significant barriers to those less familiar or assertive with the process of accessing services. Less acculturated Asian American breast cancer survivors, unfortunately, often lack information about their diagnosis, treatment, and recovery support, as well as the skills to advocate for such information. Of particular concern are more recent immigrants, who typically are monolingual, yet must navigate through the confusing U.S. health care system. Language barriers and a lack of understanding about the American medical paradigm put them at greater risk for further compromised health.[131] While there is constantly a need for more research studies to confirm these ideas about the impact of acculturation and cultural beliefs on quality of life for Asian American breast cancer survivors, resources should also be dedicated to culturally-competent direct services that may aid these survivors during their journey to recovery (e.g. interpreters during treatment sessions, mental health/social workers, transportation services, and cancer navigator peer support).[44, 116, 253, 257]

Limitations/Gaps/Future Directions

Limited breast cancer studies of African American, Hispanic/Latina, American Indian/Alaska Native, Asian American, and Native Hawaiian and other Pacific Islander women as they move through the breast cancer care continuum suggest that all are at risk for poorer outcomes. The breast cancer risk for newer immigrant groups also increases with increasing levels of acculturation.

Research in diverse populations on breast cancer incidence, morbidity, and mortality is hampered by several factors. Three factors are amenable to more short term intervention. First is the constraint of accuracy on collection of data on subpopulations within the larger ethnic categories. Even in California, the error rate in ethnic classification is quite high for some groups, for example, American Indians. For other groups, such as Native Hawaiian and other Pacific Islanders, the categories are either too limited or non-existent. Second, too few researchers of color are interested in this topic or are even trained at this level to conduct such studies. A corollary to this second factor is the lack of clarity and precision in the definitions and use of the terms race, culture, ethnicity, and acculturation.[258] These concepts must be scientifically applied to produce results that are trustworthy and comparable. Third, the structure of the scientific endeavor on positivist designs and outreach strategies perhaps limits our ability to see different cultural realities.

The constructs of culture and acculturation, like race/ethnicity, encompass a multitude of factors. For the purposes of understanding risk factors and strategies for reducing breast cancer risk and adverse outcomes, research needs to focus on these specific factors and mechanisms for their impact on breast cancer. For example, what is it about lower acculturation levels that are associated with possibly worse breast cancer survival? Is it due to lack of access to quality care, language

barriers, cultural beliefs about disease process, a foreign paradigm of health and well-being, or something else? Future research should also explore the impact of legal status (e.g. naturalized citizen, legal resident, undocumented immigrant, refugee) on acculturation and health. The complex immigration history and anti-immigrant sentiments in the U.S., often directed at specific groups, may inhibit the acculturation process.[259] Despite the increasing evidence that acculturation is not a strict dichotomy in which the minority groups' cultures are displaced by the majority/dominant groups' cultures, theories still present a perspective of a unidirectional culture conflict. This enduring view can likely be attributed to the fact that the status of health and economy among all ethnic and racial minority groups cannot be understood without incorporating the effects of oppression, state-sponsored discrimination, and continuing marginalization. However, despite the decimating effects of coerced westernization, each of these groups has retained a significant condition of distinctive cultures. Measures should be developed to appropriately assess, address, and incorporate these cultures into cancer research. Future studies should also measure the impact of public policy decisions on health behavior and on breast cancer outcomes.

Mixed methodology and research paradigms are needed to move the field of research forward in assessing the contribution of culture to breast cancer outcomes. Rigorous inductive qualitative research is a critical step for uncovering the salient cultural factors impacting breast cancer diagnosis, treatment, and outcomes. However, methodologically rigorous deductive quantitative studies are needed as well for assessing the relative impacts of cultural factors on health among diverse African American, American Indian/Alaska Native, Asian American, Pacific Islander and Hispanic/Latino subgroups. The non-Hispanic white category should be disaggregated into its major groups as well. Middle Easterners are not the same as northern Europeans, nor are eastern Europeans or groups from the Mediterranean. Such categories, originally designated in 1977 and revised in 1997 by the Office of Management and Budget, must seriously be re-evaluated for their application to scientific endeavors.

Cancer registry and other population-based data sources used to assess patterns of cancer incidence and mortality should aim to include more complete information on birthplace. Emphasis should be placed on developing methods to obtain additional information, such as imputing years in the U.S. through other information and acculturation characteristics of the neighborhood through census track data. It is important that data on acculturation be validated to ensure quality, completeness, and scientific validity.[31] Immigration history, for example, should have complete data on nativity, reason for emigration, age at entry, and years of U.S. residency. Missing information is most often not random, resulting in selection bias or misclassification bias which may compromise the validity of research findings.

Population-based behavioral risk factor surveys, such as the National Health Interview Survey, Behavioral Risk Factor Surveillance System, and

California Health Interview Survey, are excellent resources for continuing to monitor trends in breast cancer risk factors among diverse population groups of women. Emphasis, however, should be placed on including more questions addressing the concept of acculturation, and on disaggregating the larger ethnic subgroups in analyses.

An overriding theme that must emerge in health disparities is to combine disciplines in an effort to neutralize the burdens on minority populations who suffer from poorer health. When addressing this issue from the perspective of culture, there must first be a thorough understanding and acceptance of cultural differences. Perhaps the first step is to include some level of training for scientists, researchers, and caregivers, so they are "culturally competent." Secondly, the research should not strictly be performed on culturally distinct populations, but in cooperation and partnership with them. Several community-based participatory research studies that relied on multidirectional communication and circular feedback between researchers and the communities studied have been extremely effective in changing the landscape of cancer perception, and in transforming (without acculturating) subgroups to play a more active role in prevention and seeking treatments. Many cultures do not distinguish spiritual, religious, and traditional customs from medicine. Engaging these communities through partnerships with leaders within their populations, retaining cultural distinctions, and applying culturally-appropriate perspectives to screening, navigation, and treatments will greatly benefit the cause of neutralizing breast cancer disparities.

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Health Insurance

Introduction

Insurance status has been implicated as a contributing factor to disparities in breast cancer outcomes. Several studies have reported a correlation between lack of insurance and lower rates of screening, higher risks of advanced stage at diagnosis, lower likelihood of receiving recommended treatment, and lower survival.

The U.S. health care delivery system has undergone widespread changes that have great impact on the medically underserved. While the insurance industry and government public programs provide some access to cancer care services for some newly diagnosed Californians, many people remain untreated. The extensive literature on health coverage assesses how insurance status – a predictor of access and quality of care – impacts breast cancer outcomes.

Background/ Definitions

Health insurance is an important indicator of access and quality of care, yet there is an uneven distribution of coverage across California's (and the nation's) population. California's uninsured rate has persistently exceeded the national average.[1] In 2004, approximately 6.5 million California children and adults under age 65 went without health insurance, representing slightly more than 20 percent of the non-elderly population (ages 0–64 years).[2] For women, the numbers in California are similar, with 21 percent of women lacking health insurance.

Among those with health insurance, there are several main sources, each with potential differences in access and quality of care. For coverage offered by public programs, Medi-Cal and Medicare are the main sources. Generally, eligibility for Medi-Cal includes adults under age 65 who have family incomes below 200 percent of the Federal Poverty Level (FPL). Legal residents and citizens who are 65 or older and disabled persons younger than 65 are eligible for Medicare coverage. Private insurance is obtained primarily through employment-based coverage or self-purchase. While employment-based insurance accounts for more than half of the state's non-elderly medical coverage, it is not equally distributed among the state's diverse ethnic populations and has been steadily declining. While workers in businesses with fewer than 10 employees are most likely to be uninsured, 20 percent of California's uninsured work in businesses with more than 500 employees. Employment-based health insurance is much less prevalent among young adults (ages 18–34) and among working families earning less than $25,000 per year than among adults ages 35–64 and families with higher incomes.[2]

Some population groups are more acutely disadvantaged for health coverage. According to the 2005 California Health Interview Survey (CHIS) data, the distribution of health coverage and insurance type varies for women ages 18 and older by age group, race/ethnicity, family income, employment status and immigration status (Table 1). A significant proportion of non-elderly women lack health insurance and Hispanics are nearly twice as likely as any other racial/ethnic group to be uninsured. Immigrants, particularly non-citizens (35.5%), are much more likely to be uninsured. Even among women who have health insurance, the distribution in type of insurance varies by age, race/ethnicity, family income, employment status and immigration status. Women who are young, American Indian/ Alaskan

Native, poor, or immigrants are more likely to be covered by Medi-Cal whereas employment-based coverage is most common among White and Asian / Pacific Islander women, wealthier women, and U.S. citizens. It is important to make these distinctions in type of insurance since they may influence access as well as quality of care.

Table 1. Current Health Insurance Coverage (%) by Selected Demographic Factors, Women ages 18 and older, California, 2005*

	Uninsured	Medicare	Medi-Cal	Employer-based Coverage	Privately-Insured	Other Public
Age Group						
18–24	22.4%	.5%	22.2%	40.4%	10.5%	3.1%
25–39	17.3%	.5%	14.6%	60.4%	5.5%	1.6%
40–64	13.3%	3.5%	7.6%	66.5%	7.4%	1.7%
≥ 65	0.8%	94.8%	0.8%	2.6%	0.8%	<.01%
Race/ Ethnicity						
African American	11.5%	17.5%	18.7%	45.6%	3.3%	3.0%
American Indian/ Alaska Native	13.0%	16.9%	23.7%	41.8%	2.3%	2.0%
Asian American/ Pacific Islander	14.1%	15.1%	7.6%	55.1%	7.1%	1.7%
Hispanic/Latina	27.7%	7.4%	19.4%	39.9%	2.8%	2.6%
White	7.0%	22.5%	5.2%	56.1%	8.1%	0.9%
Other Single/ Multiple Race	13.1%	15.1%	15.2%	51.3%	4.3%	*1.0%
Family Income (percent of Federal Poverty Level§ (FPL))						
0–99% FPL	28.6%	17.4%	37.9%	11.0	2.4%	2.5%
100–199% FPL	24.0%	23.7%	16.6%	28.2%	4.5%	2.8%
200–299% FPL	12.9%	25.4%	6.2%	46.9%	6.3%	2.3%
≥ 300% FPL	5.8%	12.6%	1.5%	71.5%	7.8%	0.7%
Current Employment Status						
Full-time (≥ 21 hrs/week)	12.2%	2.2%	6.3%	71.6%	5.9%	1.7%

Part-time (≤ 20 hrs/ week)	15.5%	9.4%	11.6%	49.6%	12.2%	1.2%
Employed, not at work last week	17.0%†	4%†	4.3%†	61.7%	11.4%†	2.2%†
Unemployed & looking for work	32.8%	2.7%	27.8%	26.0%	7.3%	3.4%
Unemployed & not looking for work	13.1%	36.1%	13.1%	31.0%	5.3%	1.4%
Citizenship & Immigration Status						
U.S. born citizen	8.3%	20%	8.3%	55%	6.9%	1.3%
Naturalized citizen	13.6%	18.7%	7.6%	52.6%	5.9%	1.6%
Non-citizen	35.5%	3.6%	21.8%	32.5%	3.7%	2.8%

* Source: 2005 California Health Interview Survey (CHIS).

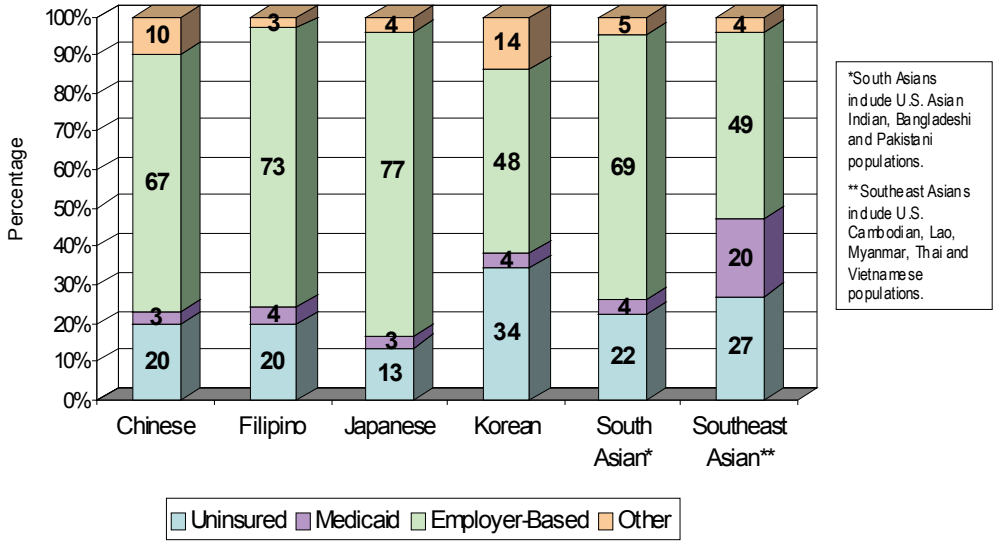
† Statistically unstable; estimate based on sample size.

§ Federal Poverty Level was $16,090 for a family of three in 2005.

Note: Rows may not total 100% due to rounding.

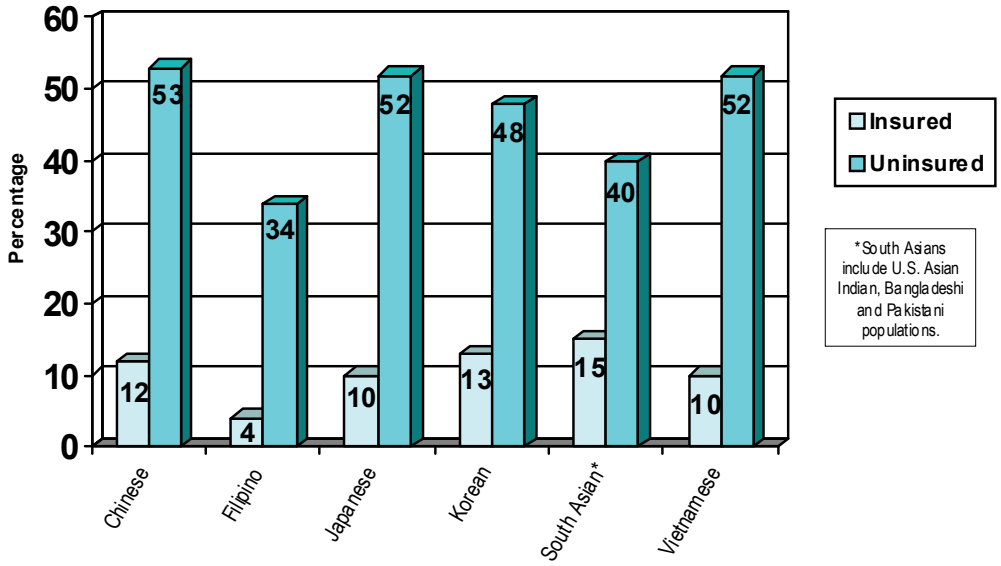
Disaggregation of national data for Asian American populations reveals marked differences between different Asian ethnic groups in insurance status and rates (Figure 1), as well as access to a usual source of care (Figure 2).[3]

Figure 1. Health Care Insurance Status for Selected U.S. Asian Populations, 1997*



* Adapted from Brown et al.[3]

Figure 2. No Usual Source of Care for Insured and Uninsured Selected U.S. Asian Populations, Ages 0-64,



* Adapted from Brown et al.[3]

While the aggregate (federal) uninsured rate for all Asians or Pacific Islanders in 1997 was 20.7 percent, the rate for Korean Americans (34 percent) nearly equaled that of the U.S. Hispanic population (34.2 percent) during that same year.[4] Thus, aggregate federal and state population health (and other) data may not accurately reflect the health status reality of individual population groups

This review will examine the impact of health insurance on the following four areas: 1) receiving screening for breast cancer; 2) being diagnosed with breast cancer, 3) undergoing treatment for breast cancer, and 4) dying from breast cancer. Finally, we will review existing national and state initiatives aimed at addressing the insurance barriers to breast cancer screening and treatment. We will also make specific policy recommendations based on this review of the literature.

Review of Health Insurance Literature

Screening

Screening practices are critical for breast cancer because they can heavily impact the stage of diagnosis and, subsequently, treatment and survival. Numerous barriers to cancer screening have been well documented. In this review, we will focus on three: 1) lack of health insurance; 2) absence of usual source of care; and 3) cost of screening.

Health Insurance

Health insurance has been repeatedly identified as a strong predictor of breast cancer screening.[5-11] A recent analysis of the Behavioral Risk Factor Surveillance System (BRFSS) from 1996–2000 suggests that those without insurance are 50 percent as likely to have undergone mammogram screening after controlling for age, education, urban location, and health status. To put this in further perspective, roughly 35 percent of the

nation's African American women and Hispanics/ Latinas without health insurance were predicted to undergo mammography screening, compared to close to 60 percent of those with Medicaid.[11] Specifically in California, 64 percent of insured women versus 28 percent of uninsured women over age 40 reported having a mammogram in the preceding year.[12] Population-based cross-sectional studies using self-reported information have shown that lack of insurance is a critical structural barrier[8, 13] for immigrant[14] and Hispanic/ Latina women across immigration status.[15] These findings were replicated in smaller studies with specific racial/ethnic groups, including Asian Americans,[16-19] Pacific Islanders,[20, 21] and other minority groups.[22] The overwhelming literature supports health insurance as a strong determinant of screening utilization.

While health coverage is generally thought to be reflective of socioeconomic status (SES), several studies examining insurance while adjusting for sociodemographic variables have suggested that health coverage may also be an independent predictor of utilization of screening services.[11, 14, 15] This independent association between insurance status and screening utilization has been repeatedly shown in studies across racial/ethnic groups.[14, 15, 23-26] These findings indicate that while health coverage is strongly associated with socioeconomic status and race/ethnicity, it can also be a structural barrier that independently influences screening practices.

The findings from studies of screening practices underscore the need for continued efforts to ensure that the medically underserved have adequate access to screening services, especially those who are un- or underinsured. That this strategy can be effective has been confirmed by several real-world examples. A meta-analysis of "access enhancing" strategies suggests mammogram utilization can be increased by 20 percent,[27] and data from the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), which provides federal screening support for mammograms, indicate that as many as one-third of the women utilizing the program had never had a mammogram previously.[28, 29] Unfortunately, current funding levels for this program only allowed 12–14 percent of eligible women to undergo testing between 2002 and 2003.[30]

Usual Source of Care

While providing insurance coverage for screening services is likely a necessary condition for achieving high screening rates, it is probably not sufficient. As we contemplate policy options, we should also emphasize the importance of a patient having one provider or one health center that serves as her primary source for health care. Several studies have clearly shown that even after controlling for insurance status and other sociodemographic factors, those who identified some usual source of care were two to six times more likely to have undergone a screening mammogram.[31-33] In many of these studies, having a usual source of care is more important than insurance status. For example, in one study, Hispanics/Latinas with Medicaid were twice as likely to have had a mammogram than those without insurance, but those who identified a usual source of care were over six times as likely to have had a mammogram.[33] Other studies have also shown that especially among low-income women, having a usual source of care is more important than insurance.[34] Finally, data from the Medical Expenditure Panel Survey suggests that even among the insured, those enrolled in a more integrated health delivery system were more likely

to undergo mammogram screening and that this finding may be most pronounced for ethnic minorities. In this study, Hispanic/Latina patients enrolled in a Health Maintenance Organization (HMO) were three times as likely to have had a mammogram as were other Hispanic/Latina patients, after adjusting for age, income, education and health status.[35]

Cost of Screening

Finally, while providing coverage for screening and ensuring a connection with a usual source of care are critical; these services should also be provided with a minimal financial burden on the patient. The literature shows that cost is a perceived barrier to screening mammography. Women who are uninsured or receive public assistance are less likely to utilize screening services if they believe that they have to pay out-of-pocket.[36] In the recent analysis of the BRFSS, the authors found that those who cited medical cost as a barrier to screening were 30–40 percent less likely to undergo mammogram screening, compared to those who did not cite cost as a barrier. This finding held for all racial and ethnic groups.[11]

Limitations

There are some common limitations in many of the existing studies. Health insurance coverage was often evaluated as a dichotomous variable, with little expansion of the type of coverage (e.g. private vs. public programs). Furthermore, these studies were of cross-sectional design, often based on self-reported practices. The use of telephone-based surveys or convenience sampling is prone to selection or participation bias, with overrepresentation of groups of a certain ethnicity, nativity, language proficiency, and socioeconomic status. Self-reported responses are also subject to recall and social acceptability bias. Widespread campaigns emphasizing the importance of screening, particularly in subpopulations, may often produce a tendency for the respondents to provide a more socially acceptable answer.[15] This may be particularly true in minority populations who have been reported to have over-reporting rates as high as 25 percent.[37, 38]

Although there are potential biases resulting from study design issues, findings have still been fairly convincing in linking lack of health coverage and lack of a usual source of care with failure to utilize screening services. Despite these clear barriers, mammography screening rates for women ages 40–64 years have continued to improve, with close to 60–65 percent of women of diverse racial and ethnic backgrounds reporting having had an appropriate screening mammogram.[11] On the positive side, this indicates the great potential to substantially boost screening rates for ethnic and racial minorities who are more likely to be uninsured and without a usual source of care. On the negative side, it is concerning that despite similar rates of screening, racial and ethnic minorities are still far more likely to present with advanced stages of breast cancer.[39]

Diagnosis

We have established that those without insurance or usual source of care are less likely to undergo screening. This section covers the potential implications of this. That is, does lack of screening lead to increased rates of late stage – and, hence, less curable – breast cancer? Additionally, is there a link between insurance status and stage at diagnosis? Finally, we will explore mechanisms independent of screening that may lead to later stage of diagnosis among the uninsured.

With regard to the issue of screening and stage at diagnosis, there is evidence from large insurance databases (including over 1.5 million women over age 50) that those without screening mammograms are over twice as likely to present with late stage of disease.[40] In addition, data from the NBCCEDP suggest that on initial screening of this uninsured cohort, many of whom had not had previous mammograms, only 40 percent of the screened cancers were stage I disease. On subsequent screenings, 76 percent of invasive cancers were stage I disease.[28] Although not definitive proof, this suggests that providing access to regular screening for this uninsured cohort results in cancers being detected at an earlier and more curable stage of disease. This association between screening rates and stage of diagnosis has been observed by others.[41, 42, 42-44]

Since insurance status is related to screening rates and screening rates are associated with stage at diagnosis, it should come as no surprise that insurance status is also associated with stage at diagnosis. In an analysis of nearly 10,000 patients with breast cancer in the Florida tumor registry, patients without insurance were 50 percent more likely to present with late-stage disease, compared with those who had private insurance, after controlling for age, education, income, race, and co-morbidities.[45] Interestingly, in this same study, those with Medicaid were 87 percent more likely to present with late stage disease compared with privately insured patients. While this suggests that factors other than insurance are at play, caution should be used when looking at single-point-in-time measurements of Medicaid status. The reason is that patients may be enrolled in Medicaid concurrent with their cancer diagnosis. This is suggested by an analysis of the Medi-Cal enrollment files, where nearly 20 percent of women on Medi-Cal diagnosed with breast cancer did not have Medi-Cal benefits in the year prior to their diagnosis. In addition, this affected the likelihood of presenting with late-stage disease, which was reduced by over 40 percent when only those patients enrolled in Medicaid prior to their diagnosis were studied.[46]

While lack of insurance almost certainly leads to lower levels of screening and later stages of diagnosis, one should not assume that the link between insurance status and stage at diagnosis is completely mediated through screening. Just because a patient is screened does not mean that she will necessarily be diagnosed in a timely fashion. First a radiologist must recognize that an abnormality exists, then a patient must be contacted for further evaluation, finally the patient must be able to make and keep the follow-up appointments. Data from the Henry Ford Health system in Detroit suggest that close to 20 percent of their patients with abnormal mammograms had inadequate follow-up.[47] In addition, data from the University of California, San Francisco (UCSF) Medical Center suggest longer time from an abnormal mammogram to diagnosis for minority populations.[48] One can imagine that those without

insurance and without a usual source of care are more likely to have difficulty arranging appropriate follow-up. Efforts to decrease death rates from breast cancer must ensure that every link in the chain of care is strong. In this case, this means that mammograms need to be read by trained breast radiologists, that appropriate systems need to be in place to ensure that patients are contacted about abnormal results, and that patients need to have timely follow-up.

Treatment

One of the final links in the chain is treatment. Two studies from Florida suggest that the uninsured are less likely to receive breast conservation surgery, compared to those who are privately insured.[49, 50] In the study by Roetzheim, et al., uninsured patients were 30 percent less likely to undergo breast conservation, compared to privately-insured patients, after controlling for age, co-morbidities, stage, and ecologic measures of income and education.[49] In terms of other breast cancer treatments, Bickell et al., in a study of 677 women in six New York City hospitals, found that among those patients with greater than stage IA tumors, 49 percent of those with health insurance – versus 24 percent of those without – were referred to a medical oncologist.[51] In this same study, those who were not referred to a medical oncologist were five times as likely to have under-use of appropriate radiotherapy, chemotherapy, or hormonal therapy, after adjusting for age, race, co-morbidities, and stage. In contrast, a small number of studies found no association between insurance coverage and treatment. One study found no significant relationship between insurance type and treatment after adjusting for hospital type.[52] Similarly, Parviz et al. found that there was no influence of patient age, race, surgeon, or insurance status on the rate of mastectomy among medically indigent patients.[53]

Overall, the literature on the link between health insurance and treatment is more limited and somewhat more contradictory than that for screening and diagnosis. However, given the expansion of treatments for early-stage breast cancers using very effective but also very expensive drugs such as trastuzumab (Herceptin), letrozole, and anastrozole, it is very likely that those without the means to pay will find it increasingly difficult to find ways to obtain such care.

Survival

For women with breast cancer, early diagnosis and optimal treatment may greatly enhance survival. As reviewed above, the current literature suggests that access to health insurance promotes screening, earlier diagnosis, and, perhaps, more appropriate treatment, subsequently influencing survival. However, few studies exist on the impact of health coverage on cancer survival. Investigators using population-based cancer registries in several states to examine the relationship between health insurance coverage and survival rates report an increased risk for death among uninsured and Medicaid patients, compared to privately insured patients, after adjusting for stage of diagnosis.[54, 55] Among late-stage patients, Bradley et al. found that Medicaid enrollees enjoyed a two-fold enhanced survival rate for the eight-year study period over non-Medicaid enrollees. However, the study was severely limited by the investigators' inability to state whether non-Medicaid enrollees were uninsured or privately insured.[56] Previously described work in Florida by Roetzheim and colleagues suggests that those without insurance had a 30 percent increase in the

hazard of death compared to those with private insurance. Interestingly, this difference disappears completely when stage at diagnosis is controlled for, suggesting that the increased death rate is indeed being mediated by advanced stage of diagnosis.[49]

A significant limitation in many of the survival studies is the lack of co-morbidity data. Because co-morbidity is often highly associated with economically disadvantaged patients and lack of insurance, it could potentially confound the relationship between insurance status and survival. Indeed, studies focusing on racial differences in survival suggest that among breast cancer patients, competing co-morbidities such as diabetes and hypertension are a more prevalent cause of death than breast cancer.[57] Disparities in survival may also be partly explained by lead-time bias, whereby certain groups appear to have better survival because of their earlier diagnosis (i.e., with a longer lead-time). Another explanation is length-time bias, in which higher screening rates among privately-insured patients may lead to detection of cancers that spread more slowly and are less likely to result in earlier death. Survival studies are prone to these two potential biases, making them difficult to evaluate. Unfortunately, there is no information in the literature about the effect that these biases may have on reported risk estimates.

In summary, disparities in survival across insurance groups are not well documented and are limited by the factors identified above. However the available data suggest that there is a link between insurance coverage and cancer survival that is largely mediated by advanced stage of diagnosis among the uninsured.

Current Policy Initiatives
NBCCEDP and CDP: EWC

Overview

The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) is a federal program, administered by the Center for Disease Control (CDC), which provides grant money to states to provide screening services for breast and cervical cancer. States are asked to provide $1.00 for every $3.00 in federal grant funding. The program was authorized in 1990 as part of the Breast and Cervical Cancer Mortality Prevention Act (PL 101-354). California implemented the program through the Cancer Detection Programs: Every Woman Counts (CDP:EWC) initiative. This initiative is funded through a grant from the CDC, through 50 percent of the revenues from the tobacco tax for breast cancer control, and from funds from Proposition 99.[58] The following individuals are eligible for breast cancer screening under the program in California:

- Women 40 and older who live in California
- Women with a family income below 200 percent of the Federal Poverty Line
- Women without health insurance or who have a co-payment and deductible that they cannot afford

Screening Data

Between 2001 and 2005, 315,000 women received a mammogram through the CDP:EWC in California. Of these, roughly equal proportions were provided to those between 40–49 and those 50–64. In California, Hispanics were the most represented group in the program, representing 67 percent of those who were provided

mammograms, versus 10 percent for whites, 14 percent for Asian/Pacific Islanders, and 3 percent for African Americans.[59] During that same time period, 1,887 breast cancers were detected.

Unfortunately, while substantial progress has been made with this program, only a fraction of those eligible for screening are actually being screened. National data by racial and ethnic group as well as total population data for California is summarized below in Table 2.

Table 2. Number of individuals eligible for screening and number and percent of eligible screened for the NBCCEDP 2002-2003 (2005-2006 for California)

Race/Ethnicity	Number Eligible (thousands)	Number Screened (thousands)	Percent of Eligibles Screened
Total*	4,007	529	13.2%
White	1,972	221	11.2%
African American	714	74	10.4%
Asian/Pacific Islander	221	31	14%
Hispanic	1,016	166	16.3%
Total: California†	1,236	167	13.5%

* From Tangka et al.[30]

† California Department of Health Services, Cancer Detection Section[60]

The small size of the fraction of those eligible being screened mainly has to do with current funding levels for the program. Actual federal funding for this program in fiscal year 2006 was $201.2 million. Using mean cost estimates derived by Mansley and colleagues of $290 per woman served, total state and federal costs for this program would have to total $1.2 billion to provide screening for all those eligible.[61] For California alone, the cost would be close to $360 million per year, which is obviously above the total federal allocation. While funding is certainly the dominant barrier to providing screening to a larger number of eligibles, other chapters in this report examine issues of culture (Section II, Chapter D) and social environment (Section III), which may explain the lower screening rate for certain populations.

Screening Efficiency

Given the limited resources available for screening this population, it is important to examine how efficient screening is under the NBCCEDP. While there are numerous measures of efficiency, we will look at three: the positive predictive value of an abnormal mammogram (percentage of abnormal mammograms that lead to a cancer diagnosis); the recall rate (those in whom further workup is recommended); and the number of cancers detected per 1,000 screening mammograms. We will use comparisons among different groups in the NBCCEDP and between the NBCCEDP and the UK National Health Service Breast Screening Program (NHSBSP) to

provide some relative perspective.

In terms of the positive predictive value, these differed by race and ethnicity in the United States. Examining only patients with abnormal *subsequent* mammograms, the positive predictive value of an abnormal mammogram was 5.8 percent for whites, 6.1 percent for African Americans and only 2.8 percent for Hispanics.[62] This suggests that perhaps for Hispanics, the largest ethnic group served by the California program, efforts to improve efficiency of screening can be undertaken. We will discuss this further below. For recall, the rate for those undergoing subsequent screening mammograms is 6.8 per 100 screens in the NBCCEDP, versus 3.6 in the UK. In terms of cancers detected, the rate for those undergoing subsequent screening mammograms was 3.4 per 1,000 mammograms in the NBCCEDP, versus 5.4 in the UK NHSBSP program.[63] In the UK, fewer patients are recalled, yet more cancers are diagnosed. We will discuss below lessons that can be learned from the UK that may be applicable for the NBCCEDP.

Treatment Provisions: The BCCPTA

In 2000, President Clinton signed the Breast and Cervical Cancer Prevention and Treatment Act into law (PL 106-354). California passed implementing legislation in 2001 and began the program in January 2002. Under the federal program, all individuals who are eligible for and receive a diagnosis of breast or cervical cancer under the NBCCEDP are eligible for treatment of their cancer through Medicaid. In addition, California has expanded the program to include eligible individuals who received their diagnosis outside of the NBCCEDP program, as long as their diagnosis and eligibility are confirmed by a qualified NBCCEDP provider. In addition, in California, individuals under age 65 without satisfactory immigration status are eligible, as well as men and those individuals with insurance whose premiums, deductibles, and co-payments exceed $750 and who have income under 200 percent of the poverty level.

Additional Services: WISEWOMAN

The Well Integrated Screening and Evaluation for Women across the Nation (WISEWOMAN) is a federally-funded demonstration project aimed at Latina women, age 40–64, in California who are eligible for the CDP:EWC program. This project is currently in four pilot clinic sites and aims to provide evaluation, education, and referral regarding cardiac risk factors.[64] As mentioned previously, efforts to decrease the survival disparity of women diagnosed with breast cancer will also have to focus on the competing co-morbid conditions which contribute to mortality differences.

Conclusions and Future Directions

With the limitations and caveats provided in this paper, the bulk of the evidence suggests that health insurance increases breast cancer screening rates, which, in turn, leads to diagnosis of breast cancer at an earlier, more curable, stage of disease and fewer deaths from breast cancer. Fortunately, members of the CBCRP's Strategy Team are able to examine and build upon well-established federal/state programs designed to provide screening, diagnosis, and treatment of breast cancer for the uninsured and underinsured population of California. Our policy recommendations, therefore, suggest that we build upon the knowledge that has been gleaned from these programs and fill the gaps in knowledge

through targeted research initiatives. Our specific recommendations for the Strategy Team are as follows:

- **Work closely with State officials from the Department of Health Services Cancer Detection Section to identify current gaps in the CDP:EWC**.
    - They should be asked to provide a detailed briefing to the entire Strategy Team or to the appropriate subcommittees regarding initiatives (outside of substantial increases in funding) that they believe would more effectively serve the eligible population.
- **Improve the efficiency of screening programs**. In an ideal world, we would ask that the NBCCEDP be fully funded to provide screening for all eligible individuals. While this should remain a goal, the likelihood of such substantial funding increases in the current Federal budget environment is low. Therefore, we must find a way to provide more mammograms under current funding levels.
    - **Improve the quality of mammograms provided**. In practice, this means decreasing the recall rates, while at the same time increasing the number of cancers detected per abnormal mammogram. In the UK, this is partly accomplished through stringent certification guidelines and continued feedback for mammogram readers. These same initiatives could also be applied to the Medi-Cal program.
        - Consider a pilot project that restricts the reading of mammograms in a region or county only to those mammographers who read over 1,000 (or other appropriate number) per year.
        - Provide constant feedback to all mammographers who read for the program regarding their recall rates and their cancer detection rates compared to their peers (average or upper 10 percent of their peers).
    - **Consider decreasing the screening frequency from a yearly to an every-other-year basis.** This approach should be explored with caution, given that it could have clinical consequences. The U.S. Preventive Task Force (USPSTF) recommends screening mammography, with or without clinical breast examination, every 1–2 years for women age 40 and older, although there is evidence that 12-month intervals may be better than 24 months.[65] Thus, decreasing the frequency of screening should be tested to determine if subsequent mammogram follow-up rates decreased substantially and whether this had an effect on subsequent incidence and stage of breast cancer, compared to yearly mammograms.
- **Focus efforts on potentially under-screened populations.**

- California data suggest that only 3 percent of the population screened in the CDP:EWC program are African American. Is this reflective of their proportion of the eligible population or are they underrepresented? If so, do we know why? If not, research initiatives should be aimed at finding out why.

- **Examine strength of patient-provider relationships under the CDP:EWC and Medi-Cal**.
  - As discussed previously, having an identified usual source of care may be more important than insurance status for predicting screening rates.
  - The CDP:EWC has a network of physicians and health care providers that coordinate screening and arrange for diagnostic and treatment services.
  - Do patients view these physicians as a usual source of care? If not, what can be done to better strengthen that relationship?
  - What data do we have for the Medi-Cal program regarding usual source of care? Should efforts be put in place to improve and strengthen those relationships?

- **Evaluate data on breast cancer diagnosis under the CDP:EWC and Medi-Cal.**
  - What percentage of patients with abnormal mammograms under the CDP:EWC and Medi-Cal go on to receive follow-up diagnostic tests?
  - What is the time lag between abnormal mammogram and diagnosis?
  - What are the reasons for lack of follow-up and increased time lag? If not known, then this could be an area of research focus.

- **Evaluate data on treatment provided to those diagnosed under the CDP:EWC.**
  - What percentage of patients diagnosed with breast cancer under the CDP:EWC actually receive treatment under Medi-Cal?
  - What accounts for those who do not undergo treatment? If not known, then this also could be an area of research focus.

- **Consider funding additional pilot projects aimed at providing treatment of co-morbidities identified in women screened under the CDP:EWC program.**

○ Patients could be screened for high blood pressure, diabetes, and obesity while undergoing breast cancer screening. Funding for treatment (including, as an example, diet and exercise interventions with women having a body surface area of over 30) could be provided as part of the pilot project.

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Neighborhood Context and Breast Cancer

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Introduction

Most research on breast cancer incidence and outcomes—including etiology, incidence, screening, diagnosis, treatment, and mortality—has focused on identifying individual-level risk factors such as race, health behaviors, and family history. Yet in research into other medical conditions, there has been a growing interest in how characteristics of place may impact health. In particular, people's neighborhoods can help shape their individual risk factors for a range of health outcomes. Neighborhood context can put people at greater risk for adverse health outcomes, as well as exert protective effects that can preserve or improve health.

Although we have long known that there are regional variations in breast cancer outcomes within the U.S., and across and within other countries,[1, 2] explanations for these variations have focused primarily on examining the extent to which individual-level risk factors (e.g., age, parity, health behaviors, socioeconomic status) account for regional variation. This approach is useful for giving us a basic idea of the role of known individual risk factors in explaining breast cancer distribution. It also helps identify gaps in our knowledge of the range of risk factors that influence breast cancer incidence and outcomes. However, this approach is limited in two ways. First, it overlooks the importance of examining how neighborhoods might shape known breast cancer risk factors, which is important to understand for intervention purposes. Second, it ignores investigation of whether neighborhoods affect breast cancer risk in ways that go beyond shaping known individual-level risk factors. Unique aspects of the neighborhood service environment, social environment, or physical environment may impact breast cancer outcomes. Examples of the service environment include access to risk reduction services, medical care, transportation, employment, food outlets and supermarkets. The social environment includes such factors as crime, neighborhood crowding and social support. The physical environment includes the built environment, environmental pollution, and the health effects of a person's physical surroundings.

Research has only begun to explore how neighborhood context might affect breast cancer. Yet, given what we know about regional variation in breast cancer incidence and outcomes, and about the association between some neighborhood characteristics and cancer incidence and outcomes, breast cancer research is likely to benefit from further investigating the potential role of neighborhood context in putting people at risk for breast cancer.

We begin with an overview of some of the major conceptual and methodological issues related to conducting research on neighborhoods and health. We then review the current evidence of the effects of neighborhood context on breast cancer incidence and outcomes. We conclude by describing priority areas for future research in this area.

Conceptualizing Neighborhood Effects on Health

Much of the recent research on the relationship between neighborhood context and health distinguishes between the compositional and contextual effects of neighborhoods.[3-5]

Compositional effects exist when associations between neighborhoods and health are explained by the population characteristics of residents (e.g., age, race, or socioeconomic characteristics of residents). For example, breast cancer incidence may be higher in some neighborhoods simply because more older women live there. As another example, if breast cancer mortality rates are higher in some neighborhoods, and those neighborhoods have a high proportion of African Americans, a compositional explanation would be that there is no longer an association after controlling for the race/ethnicity of individual residents. Some researchers conclude that neighborhood effects on health can be explained entirely by the compositional effects of individual-level variables. However, even if this were true, it would still be important to understand why people with certain risk factors are clustered in the same neighborhood, whether characteristics of the neighborhood are responsible for the clustering of risk factors, and whether interventions at the individual or neighborhood level might be most effective at improving health outcomes.

Contextual effects are characteristics of neighborhoods that impact residents' health beyond a simple summation of the compositional effects measured among individual residents. In other words, the effect of the whole neighborhood is greater than the sum of the individual parts. Investigation of contextual effects requires that multilevel data be used to examine how characteristics of neighborhoods are associated with individual-level health outcomes, over and above individual-level characteristics. For example, research demonstrates that living in poorer socioeconomic environments is associated with greater risk of heart disease,[6] morbidity,[7, 8] and mortality,[9-11] even after controlling for individual-level socioeconomic factors.

There are a number of ways to conceptualize and categorize the potential contextual effects of neighborhoods. One promising method is to categorize neighborhood context in terms of characteristics of the neighborhood service environment, social environment, and physical environment.

The neighborhood service environment may affect residents' access to and quality of preventive and screening services, medical care, transportation, and supermarkets. These neighborhood service characteristics might impact the risk of higher cancer incidence and poor breast cancer outcomes of all residents, regardless of their own personal factors.

The social environment of neighborhoods can affect multiple risk factors for breast cancer. For example, research indicates that neighborhood socioeconomic context is associated with a higher risk of obesity[12] and smoking,[13, 14] controlling for individual SES measures. Neighborhood social norms may affect individual breast cancer risk factors such as breast-feeding and other health behaviors. Neighborhoods with greater actual or perceived crime rates can affect whether residents are too fearful to leave home to access services in their neighborhood, or too fearful to walk for exercise. Stressful neighborhood social environments may add to an individual's stress, which can adversely affect health.

The physical environment of neighborhoods can expose residents to environmental pollutants that

can put all residents at greater risk of unfavorable health outcomes, regardless of their individual characteristics (see Section I of this paper), although individual-level stressors may modify the potential health impact of pollutant exposures.[15, 16] In addition, characteristics of the built environment affect whether people have healthy housing, workplace, and recreational options.

Characteristics of these neighborhood environments may affect health through direct, indirect, and interactive pathways. Some neighborhood characteristics, such as air and water quality, potentially affect health directly. Most neighborhood characteristics are conceptualized as having indirect effects on health. For example, neighborhood socioeconomic deprivation may indirectly affect the health of residents through a number of pathways, such as through poor service availability, through unsafe places for work and recreation, and by increasing psychosocial stress.

Moreover, neighborhood characteristics may interact with either other neighborhood characteristics or with individual characteristics to affect breast cancer incidence and outcomes. A stressful neighborhood environment can make people more susceptible to the harmful effects of exposure to contaminants in the neighborhood.[17, 18] Neighborhood characteristics may interact with individual-level characteristics, so that some neighborhood characteristics only affect, or are more likely to affect, some people based on their personal characteristics (e.g., age, pre-existing health conditions, or income). For example, being exposed to a low-quality health and social service environment in a poor neighborhood may only or particularly affect poor individuals, whereas higher-income residents might access services both inside and outside of their neighborhood. Interactions between individual-level and neighborhood-level characteristics are crucial to examine as they suggest how neighborhood and individual characteristics can make people either more vulnerable or more resilient to other neighborhood and individual risk factors.

Future research on the impact of neighborhoods on cancer and other health outcomes needs to examine specific direct, indirect, and interactive pathways through which neighborhoods impact health. Attention also needs to be paid to the level of neighborhood or place that is most relevant to the pathway being studied. For example, access to the health and social service environment might be measured using neighborhood boundaries (e.g., municipal boundaries) that are different from the boundaries of neighborhoods considered when examining residents' perceptions of trust, safety, and social networks in their neighborhood (e.g., smaller geographical areas). In addition, neighborhood boundaries may need to be extended based upon place of employment, to include commuting routes and aspects of the built environment of the workplace, since these can also impact health. Studies of neighborhoods also need to address rural, as well as urban and suburban, environments.

Methodological Issues in Studying Neighborhood Context and Health

There have been a number of comprehensive overviews of the methodological challenges of examining neighborhood effects on health.[5, 19-21] We briefly discuss some of the methodological

challenges as they relate to future work on neighborhood effects on breast cancer.

Throughout history, researchers have examined regional variations in health outcomes and have analyzed ecological data to examine how characteristics of place are associated with rates of disease and mortality. Although ecological analyses of aggregate-level data are useful, researchers must be cautious about interpretation of such analyses. The "ecological fallacy" is inferring individual-level relationships from associations observed at the aggregate level. For example, if cities with a higher proportion of African Americans have higher breast cancer mortality rates, one cannot conclude that African Americans are more likely to die from breast cancer. On the other hand, without individual-level data, one similarly cannot conclude that living in a neighborhood with a high proportion of black residents causes higher breast cancer mortality. It may be that the racial/ethnic composition of residents in the neighborhood accounts for the association (compositional effects), with black residents, and not white residents, having higher breast cancer mortality rates. The difference in mortality rates could also result from individual-level confounding, for example, if African Americans have lower socioeconomic status and lower levels of health insurance. Mortality differences could also result from the contextual effects of group-level variables related to physical proximity to medical services, availability and uptake of screening, cultural factors that impact patterns of health care usage, etc. Therefore, data at both the individual and neighborhood level are needed to examine how place affects disease and mortality.

With the introduction of multilevel modeling techniques and more accessible software,[22, 23] there are opportunities to rigorously test how neighborhood contextual factors impact health outcomes, using data at both individual and neighborhood levels. The use of multilevel techniques is one of the best ways to disentangle the complexities of how neighborhood and individual factors separately and jointly relate to health, although these techniques have limitations. Models are only as good as the data that is put into them, and the greatest challenge to multilevel modeling is that researchers often lack the most appropriate data to address important research questions. For example, we may have neighborhood SES variables, but not individual SES variables. What data at the individual and neighborhood level do we need to best address how neighborhoods impact breast cancer outcomes?

When conceptualizing neighborhood effects, we need to measure neighborhood in a way that is consistent with the conceptual framework being employed. Using census tract as a measure of neighborhood, for example, is often a convenient way of categorizing neighborhoods, but it does not necessarily reflect well the borders or boundaries within which people interact or experience their neighborhoods. What level of neighborhood and what neighborhood variables do we need to best examine our questions about neighborhoods and breast cancer? Do we need to use different levels of neighborhood when studying, for example, those from the service environment versus those from the social environment?

Finding an association between neighborhood context and health, independent of individual factors, does not necessarily mean that there is a causal pathway from neighborhood context to health. People may select into or out of neighborhoods based on their health (reverse causation), or there may be other unmeasured factors that affect both where people live and their health (omitted variable bias or selection bias). What data or analytic techniques do we need to best examine causal relationships between neighborhood context and breast cancer?

Other issues related to time are often ignored or understudied in research on neighborhoods and health. Duration of living in a particular neighborhood (exposure to neighborhood) may matter, so may changes in the neighborhood itself over time. Moreover, a woman's age at the time of a critical neighborhood exposure may be particularly relevant with breast cancer. Exposure to toxic environments may be more important in breast cancer etiology at particular critical ages or stages of life.[24]

When using multilevel models to test for contextual effects of neighborhood characteristics while controlling for individual factors, care needs to be paid to not over-control for individual-level variables that are on the causal pathway between neighborhoods and health. This is especially important when a direct individual analog exists for a group-level exposure. For example, if we explore an association between neighborhood-level SES and cancer while controlling for individual-level SES, we are indeed controlling for one of the pathways through which neighborhood SES may affect cancer. For example, living in a low socioeconomic environment may lead to less quality education, lower status occupational opportunities, and lower income, which ultimately impact health. If we want to examine how neighborhood context creates and maintains breast cancer risk factors, rather than examining only whether neighborhood context matters over and above known risk factors, it will be important to ask: What individual-level variables do we need to control for as confounders, and which ones do we need to examine as modifying variables and/or mediators on the causal pathway between neighborhood context and breast cancer? In addition, we need to study how neighborhood-level variables modify individual-level compositional effects. For example, neighborhood or other area-level effects, such as metro-area racial segregation or income inequality, could modify observed relationships between individual-level factors and health outcomes.[17, 18, 25, 26]

Overview of Review on Neighborhood Context and Breast Cancer

Research on neighborhoods and breast cancer has favored some areas of inquiry over others. A fair amount of research has been conducted on how urban/rural status relates to breast cancer, as well as how neighborhood socioeconomic context relates to breast cancer. Our review will therefore begin by discussing these two areas. We then discuss a growing and important area of breast cancer research, neighborhood racial/ethnic context. Next, we provide an overview of research on neighborhoods and breast cancer in three subsections on the neighborhood service environment, the neighborhood social environment, and the neighborhood physical

environment. Although we discuss these literatures separately for simplicity, they have much overlap. Our conceptual model is based on the hypothesis that the urban/rural, socioeconomic, and racial/ethnic contexts of neighborhoods impact breast cancer and other health outcomes. Further, these factors operate through neighborhood service, social, and physical environments. After summarizing limitations and gaps in research in each of these areas, we conclude with recommendations for high priority directions for future research.

Urban/rural differences in breast cancer

"Geographic location is one of the strongest predictors of breast cancer incidence."[1] An urban excess of cancer incidence and mortality has been observed throughout the world, which has generated many hypotheses about place-based environmental exposures and behaviors that can influence cancer risk.[27] Increased incidence rates of breast cancer have also been observed in urban areas in California.[28]

Concept/Exposure Definition

Urbanization is measured by population density, metropolitan area size, or other measures of city or place population.[29] Some researchers have also used percent of the population involved in agriculture as a marker of rural status.[30] The level of urbanization can be measured at different geographic scales. These include state, metropolitan area, county, region, zip code, census tract, or block group. Some researchers call for increased attention to categorizing urban areas into finer categories (e.g., differences between central cities and suburban areas),[28] while others point out that heterogeneity within rural areas needs to be better addressed.[29]

Biologic Plausibility for Urban/Rural Differences

The urban excess of breast cancer incidence could be due to a number of factors. Looking at compositional explanations, it may be that living in urban areas is associated with known individual-level breast cancer risk factors, such as later age at first birth, lower parity, higher alcohol consumption, and higher use of hormone replacement therapy. Although these may be interpreted as simply compositional effects, those with their eye to interventions might also ask why urban living leads to higher rates of these different individual-level risk factors in the first place—investigating the indirect effects of urban/rural residence on breast cancer incidence.

Moreover, there may be contextual characteristics of urban areas that clearly affect breast cancer incidence. Many urban areas have higher levels of hazardous air pollutants from traffic and industrial sources than do rural places.[31] Urban areas also have more industrial waste sites and potential for ground water contamination from industry. Rural women often have more favorable breast cancer risk factor profiles (higher parity, earlier age first full term pregnancy, less alcohol use). On the other hand, rural women are more likely to mix or apply pesticides to crops or livestock and to live in areas with high levels of agricultural pesticide use.[32] Also, there are some rural areas in California that experience high levels of particle air pollution, largely due to dust from agricultural sources.[33, 34] Finally, light at night has been implicated in increased risk of breast cancer in

several epidemiologic studies (see Section I, Chapter H). Disruption of melatonin resulting from night exposure to light could be responsible for much of the urban-rural difference in breast cancer incidence rates.[35] Disentangling the complex effects of all of the possible direct, indirect, and interactive effects of rural/urban residence and breast cancer incidence is extremely difficult. In addition, there are urban/rural differences in access to health care resources that may affect breast cancer screening, diagnosis, treatment, and mortality.

Incidence/Etiology

Although higher incidence rates of breast cancer have been observed in urban areas compared to rural areas throughout the world,[28, 36, 37] the reported urban excesses have generally been modest, in the range of 1.1 to 1.8.[36] Robert et al. found that the urban excess of breast cancer incidence in Wisconsin persisted even when differences in individual-level risk factors and individual and neighborhood SES were accounted for.[38] This study simultaneously modeled individual-level reproductive factors, mammography use, family history of the disease, body mass index, alcohol intake, individual SES, as well as neighborhood-level socioeconomic status and urbanization. In multilevel models, urban women still had higher risk for breast cancer after adjusting for these individual-level and neighborhood-level factors.

A recent study from California considered individual risk factors for breast cancer in combination with neighborhood measures of socioeconomic status and urbanization.[1] The authors examined data from the California Teachers Study, a large cohort study following female professional school employees for cancer incidence since 1995. Within the cohort, breast cancer incidence rates were higher for women residing in the San Francisco Bay area and the Southern Coastal area, compared to women in the rest of California. Adjustment for personal risk factors and neighborhood-level socioeconomic status and urbanization did not diminish regional differences in incidence rates. The authors conclude that regional differences are not attributable to the compositional effects of individual level known breast cancer risk factors or to area measures of socioeconomic status and urbanization. Because individual level socioeconomic status was not available (although as an occupational cohort of professional women it is likely to be somewhat homogenous with respect to individual level socioeconomic status), it was not possible to examine contextual effects of neighborhood socioeconomic status while controlling for individual socioeconomic status.

In a recent ecologic study conducted in North Carolina, Hall et al. compared incidence rates in urban and rural areas among white and non-white women.[36] Urbanization, based on county of residence at diagnosis, was examined in nine categories. The incidence rates for in situ and invasive breast cancer were highest in the most urban areas for white women. For non-white women, rates of in situ cancer were highest among urban women, and rates of invasive cancer were highest among rural women. Although this was limited by being an ecologic rather than a multilevel study, it suggests that future multilevel research attend to urban/rural differences in

different types of breast cancer and their distribution by race.

Reynolds et al. explored the relationship between breast cancer incidence and urbanization, neighborhood SES, and region in California.[28] Because California is considered 85% "urban" by U.S. Census criteria, this study sought to minimize the heterogeneity of areas with this designation to better assess differences between various environments. They categorized urbanization, based on metropolitan area size and population density, into four categories: urban, suburban, city and small town/rural. This classification scheme allowed for the distinction between the densely-populated urban cores and the suburban areas of large metropolitan regions, all of which fall under the U.S. Census rubric of "Urbanized Areas" (i.e. population greater than 1 million). The category of "City" included U.S. Census defined Places with more than 50,000 people outside of an Urbanized Area, thus distinguishing between suburban cities and more remote cities located outside of large metropolitan areas. After adjustment for region, neighborhood SES, and race/ethnicity, women in the suburban and city groups were still at increased risk for breast cancer, but the women in the most urban category were not. This was true for all cases combined as well as for both the ductal and lobular cases that were examined separately. The urban and suburban areas were both located within the largest metropolitan areas of the state. To our knowledge, this is the first study to try to distinguish the difference in breast cancer incidence between urban and suburban women. Its results indicate that there may be important differences within places previously aggregated as urban in many studies. This study assigned urbanization and neighborhood SES at a very detailed level of geography, the census block group, while the two previously mentioned similar studies used zip code level[38] and county level.[36] However, this California study only included invasive cases and did not include individual-level measures of SES. This study did not present analyses for separate race/ethnic groups, which might be considered in the future, in light of the findings of the North Carolina study of different patterns for in situ and invasive cases and for whites and non-whites.

Screening

Women living in rural areas have lower mammography screening rates than women living in urban areas. Based on data from a national survey in 1998-1999, 66.7% rural women vs. 75.4% of urban women ages 40 years and older had a mammogram in the last two years (the Healthy People 2010 goal is 70%).[39] Rural residents also have slightly lower clinical breast examination rates (73.0% of rural women vs. 78.2% of urban women).[39] While these differences in screening rates are statistically significant, they are not very large in absolute terms. Future studies need to address heterogeneity within urban and rural areas with respect to breast cancer screening, using individual-level data on screening uptake and group-level data on screening availability.

Diagnosis

Urban women have greater access to mammography screening and medical facilities, which leads to earlier diagnosis. The rates of

ductal carcinoma in situ, a precancerous lesion detected almost exclusively through screening, have increased faster in urban women than in rural women in the U.S.[40] In California, a recent analysis of cancer registry data indicated that approximately the same proportion of cases in urban and rural areas was diagnosed with early stage disease.[41] This assessment was done at the county level. In California, county-level data is too large to account for heterogeneity within counties or to accurately categorize regions as rural, urban or suburban.

Treatment

Rural women face geographic barriers to obtaining optimal breast cancer treatment, and are less likely than urban women to receive breast conserving surgery.[42-45] Because rural women have to travel greater distances to receive radiation treatment, they are less likely to receive the recommended level of radiation treatment after breast conserving surgery.[46-48] The farther women live from a treatment facility, the less likely they are to receive the appropriate follow-up care.[46, 49] This appears to be particularly true in patients under 65 years of age.[47] Rushton and West used geographic information system (GIS) technology to identify regions of high mastectomy rates in southeastern Iowa and concluded that areas of high rates correlated with areas without radiation facilities.[50]

Mortality

In the United States, breast cancer mortality rates are higher in urban areas compared to rural areas, as is true for incidence rates.[51] However, no clear urban-rural patterns emerge when examining the most recent breast cancer mortality rates by county in California.[52] For example, some of the highest rates were reported in Merced County, which is a largely agricultural county, and the counties with the lowest mortality rates were a mix of rural and urban, such as Santa Clara County and Butte County. These rates were for all races combined. As stated previously, data aggregated by county in California is not adequate to disentangle the effects of rural, urban and suburban residence. No studies have examined breast cancer mortality rates in California by detailed categorizations of urbanization, even though the relevant scales are readily available.

Limitations and Future Directions for Studying Urban/Rural Differences in Breast Cancer

By definition, rural areas have fewer residents, making it difficult to conduct population-based studies that have adequate representation of rural residents. In addition, breast cancer rate calculations in rural areas are sensitive to limitations in the numerator, due to missing cancer cases, or cases that have been miscoded, such as cases coded to the hospital area rather than the patient's residential area. In addition, the breast cancer rate's denominator may be based on inaccurate estimates of population size.

Definitions of urban and rural vary greatly, and the geographic scales used range in size from very small, such as block group, to large, such as county. This makes it difficult to compare results across studies. The large degree of heterogeneity among populations and environments within a county are likely to mask trends at smaller geographical levels, but few studies to date have evaluated patterns of urban/rural risk at finer

levels of geographic detail. Future studies should examine rural/urban status in conjunction with other risk factors at multiple levels of geography (neighborhood block, tract, city, county).

Most research on urban/rural differences in breast cancer does not have accurate information on timing of exposure. How long have individuals lived in a rural or urban environment or neighborhood? Do rural/urban environments exert stronger effects at particular life stages? Most research examines rural/urban residence at time of diagnosis, but does not examine exposures at critical ages or life stages. Future research might examine residential history to help focus analyses on the critical exposures or timing of exposures that lead to greater breast cancer incidence in urban areas.

Most epidemiologic studies of breast cancer to date do not include comprehensive multilevel exposure histories. Ideally, such data would consist of an array of important individual- and neighborhood-level risk and protective factors. Lack of data makes it difficult to separate unique aspects of urban/rural status from neighborhood SES, individual SES, and other individual risk and protective factors. Without multilevel data, it is difficult to conceptualize, let alone measure, how particular individual and neighborhood pathways link urban/rural residence to breast cancer outcomes. However, for research to move forward, we need to have not only better multilevel data, but also clearer analytic strategies for examining specific pathways that may link rural/urban residence to breast cancer.

Although most research has examined rural vs. urban areas, there should be closer examination of more detailed categorization of urban areas (i.e., central city versus suburban) and of rural areas.[29] Moreover, examining what accounts for variation in breast cancer within rural areas and within urban areas might also provide clues about individual- and neighborhood-level factors that work together and separately to influence breast cancer incidence and outcomes.

Rural/urban variations in breast cancer incidence and mortality need to be examined with respect to race and ethnicity. For example, there is a well-documented cross-over in breast cancer incidence rates, with younger black women having higher rates than younger white women, while older black women have lower rates than older white women. No studies have examined in comprehensive fashion how urban, suburban or rural differences might impact these rates. In addition, future research should examine how ethnicity and immigrant status modifies the association between rural/urban residence and breast cancer. This should include investigating the effects of urban/rural status and race/ethnicity using individual- and group-level data on residence history, socioeconomic status, screening, and breast cancer risk factors.

Some of the work on screening and treatment that looks at distance traveled for medical care could examine the interactive effects of SES and race/ethnicity. Having to travel a greater distance for screening and medical care may be more problematic for rural residents with low income than for rural residents with higher income.

Finally, future investigations should also consider different histologic subtypes of breast cancer, especially lobular cases, which appear to be

particularly elevated in the highly urbanized areas of California.[28]

Neighborhood Socioeconomic Context and Breast Cancer Outcomes

A number of articles summarize research on the relationship between neighborhood socioeconomic context and health outcomes.[53-55] Recent research on neighborhood socioeconomic context has emphasized the use of multilevel models to examine how both individual- and neighborhood-level SES relate to health. In breast cancer research, higher SES is consistently related to elevated breast cancer incidence. Indeed, SES is particularly important to examine in relation to breast cancer because breast cancer incidence is one of the few health problems that is associated with higher, rather than lower, SES. Yet little attention has been paid to the potential multilevel nature of the relationship between SES and breast cancer. Most breast cancer studies use either individual SES or neighborhood SES, but not both. At this point, we do not know whether SES has a compositional effect (serving as a proxy for one or more individual-level breast cancer risk factors) or a contextual effect (serving as proxy for a neighborhood-level environmental exposure and/or greater access to screening and medical care). Therefore, examining SES and its effects in a multilevel and comprehensive way may provide better clues about the risk factors and combination of risk factors that need to be addressed to reduce breast cancer incidence and improve outcomes.

Concept/Exposure Definition

Socioeconomic status often refers to a person's standing in a social hierarchy that affords differential access to resources. Individual-level SES is measured in various ways, but often focuses on education, income, and occupation, and, less frequently, on assets, home ownership, car ownership, and other aspects of material circumstances. SES may be estimated using separate measures (i.e., education and income), or by a composite index that combines individual SES measures. SES at the group level is often restricted to household income, or the income of one's spouse, and does not include the status of one's neighbors or neighborhood. When it is measured, neighborhood SES is almost always estimated using census data in the U.S. by block, block group, tract, zip code, or metropolitan statistical area. Sometimes neighborhood SES is measured by aggregating the individual reports of SES of neighborhood residents who participated in a survey. Following the conventions for measuring individual SES, neighborhood SES is sometimes measured using separate indicators, such as percent poverty, median family income, percent of residents with at least a college education, percent of residents who are white collar workers, and unemployment rates. These measures are then combined to create multilevel indices of neighborhood SES or neighborhood deprivation.[56, 57] The idea is that just as people are part of a social hierarchy in society, the neighborhoods people reside in have a hierarchy as well. Those neighborhoods lower on the hierarchy often have fewer resources and greater health challenges. Researchers have yet to agree on the most ideal system for capturing the complex interplay of compositional and contextual effects that contribute to social class and socioeconomic status. But there is little doubt that such factors are integral to achieving a greater

understanding of the etiology and progression of breast cancer.

Biologic Plausibility for Neighborhood Socioeconomic Context

Epidemiologic studies suggest that neighborhood SES may affect breast cancer incidence and outcomes through a number of indirect and interactive pathways. Neighborhood SES over the life course may affect the individual SES attainment of residents, which then impacts personal risk factors for breast cancer incidence and outcomes. Most research also conceptualizes neighborhood SES as having potential contextual effects on health independent of individual SES. Neighborhood SES can affect breast cancer incidence and outcomes through its effects on the service, social, and physical environments of neighborhood residents.[54]

Until recently, there has been little data to suggest that neighborhood socioeconomic context has direct biological links to breast cancer. However, recent data support a conceptual model whereby aggregate-level neighborhood factors could more directly affect biologic pathways that increase risk of breast cancer. For example, recent data on laboratory animals suggest that social deprivation may increase breast cancer incidence through up-regulation of stress-related cell-signaling pathways and modulation of the immune system.[58] Shorter sleep cycles due to noise or crime, combined with higher levels of ambient light, lead to depressed melatonin levels and have been suggested to increase risk of breast cancer among women in specific neighborhoods.[59]

Incidence

While much is known about the association between individual SES and breast cancer incidence, little is known about potential contextual effects of neighborhood SES. The well-documented positive association between breast cancer incidence and higher individual-level SES[37] is partly driven by socioeconomic variations in established breast cancer risk factors, most importantly, later age at first birth and nulliparity or lower parity.[60, 61] However, the association between individual SES and breast cancer remains even after adjustment for these known individual-level risk factors.[38, 62] A number of breast cancer studies use neighborhood SES measures to look at breast cancer incidence, but these studies use neighborhood SES as a proxy for individual-level SES, because no individual SES data are available.[63] Although these studies are useful in detecting SES patterns in breast cancer incidence across neighborhoods, no conclusions can be made about whether neighborhood SES context might contribute independently to breast cancer incidence beyond individual SES.

In a case-control study in Wisconsin, neighborhood SES was still associated with increased risk of breast cancer, even after controlling for individual-level SES.[38] This suggests that there may be something about higher-SES neighborhoods that contributes to breast cancer incidence. However, most epidemiologic studies of breast cancer only examine SES at the level of individuals or households, and not at the neighborhood level.

Screening

Women with lower individual SES are less likely to have mammograms than are higher SES women.[64-66] Based on a national survey, 82.5% of women with annual household incomes of $50,000 or more had a mammogram in the last two years, compared to 68.4% of women with incomes under $15,000.[66] Women with low income are also less likely to have the recommended frequency of clinical breast exams.[67] Reasons for these persistent disparities include financial limitations that restrict access to care, such as lack of health insurance, and no usual source of health care.[65]

As with research on breast cancer incidence, there is little evidence about whether screening rates correlate more strongly with individual-level, as opposed to neighborhood-level, SES. However, Rosenberg and colleagues,[68] using the Black Women's Health Study data, found that among African American women, regular mammography use was associated with higher neighborhood SES, but not after controlling further for individual-level SES.

Diagnosis

Studies have reported that low-SES women are more likely than high-SES women to be diagnosed with late stage breast cancer, and higher-SES women are more likely to be diagnosed with localized disease,[69-73] although these findings have not been entirely consistent.[74-76] Using national SEER data from 1995 through 1999, a higher percentage of women living in areas of high poverty were diagnosed with more advanced stages of breast cancer; conversely, a higher percentage of women in areas of low poverty were diagnosed with localized breast cancer.[73] This disparity in diagnosis by poverty residence was seen across all racial/ethnic groups. Again, limiting SES measurement to either the individual level or the neighborhood level, but lacking information on both, hampers our understanding of how socioeconomic inequalities in diagnosis might be patterned across both individuals and neighborhoods.

In interesting studies, Catalano, Satariano, and Ciemins showed that in situ and local breast tumors in black and white women were less likely to be detected during periods of high area unemployment.[77, 78] Chronic unemployment rates, which are more prevalent in lower-SES and predominantly minority neighborhoods, may also delay cancer detection by the same "distraction" model.

Treatment

Breast conserving surgery (BCS) is currently the preferred method of treatment for stage I and stage II breast cancers.[73] BCS is more common in high-SES neighborhoods, compared to low-SES neighborhoods[73] and in urban areas versus rural areas.[45] BCS rates have increased since the 1980s in all neighborhood SES groups, but rates are still highest in the highest-SES neighborhoods.[73] This finding could be due to the fact that individual high-SES women are more likely to be diagnosed at an early stage, or that high SES results in greater group-level access and awareness of services, or both. Many of these potential relationships have been assumed rather than tested. There may also be treatment norms that vary by neighborhood, and operate independently of the individual SES of women.

Mortality

While women living in the highest-SES neighborhoods have the highest incidence rates of breast cancer, women living in the poorest-SES neighborhoods have the lowest survival rates,[73, 79] including in the San Francisco Bay Area.[80] The reasons for the socioeconomic difference in survival rates are not clearly established,[81-83] and are particularly obscured by lack of multilevel data on SES, information on access and use of health care, and tumor biology data. Potential explanations include disparities in access to health care, which influence stage at diagnosis; disparities in access to optimal treatments; and differences in tumor biology, such as estrogen receptor status, histology, and grade. However these factors do not completely explain the differences in survival.[71, 84]

The recent study by Bouchardy et al. in Switzerland found that adjusting for later stage at diagnosis, different tumor characteristics, and treatment differences explained less than half of the excess mortality in the low-SES women.[83] SES in this study was based on most recent occupation. Rutqvist et al. reported from Sweden that the SES differences in stage-specific survival were mostly explained by non-breast cancer mortality.[85] Lagerlund et al. found that Swedish women of higher SES had a better prognosis for survival than did lower-SES women, even after adjusting for age, tumor characteristics, parity, and cohabitation. The observed survival benefit with high SES was most pronounced in women under 50 years of age.[76] It is interesting to note that socioeconomic disparities in breast cancer survival exist even in ethnically homogenous, affluent countries like Sweden and Switzerland, with excellent health care systems and health care access. Different methods were used to measure and aggregate SES across studies, and there does not appear to be a uniform or agreed-upon method for addressing SES in studies of breast cancer mortality.

Limitations and Future Directions for Studying Neighborhood Socioeconomic Context and Breast Cancer Outcomes

As this review has demonstrated, it is clear that higher SES is positively related to breast cancer incidence, screening, and treatment, but inversely related to stage at diagnosis and mortality. What is not at all clear is how individual and neighborhood SES contribute to these patterns through separate or joint effects. Individual SES or neighborhood SES have been examined separately in studies of breast cancer incidence and outcomes, but rarely together. This is an example of how breast cancer research has been severely limited by the norms of data collection and the ways in which data is analyzed in cancer studies. Whereas many other areas of health research have multilevel socioeconomic data, breast cancer studies have been behind in collecting, accessing, and analyzing such data.[86, 87]

Regarding breast cancer incidence, future research could examine whether there are factors associated with living in high-SES areas that contribute to increased breast cancer risk, over and above individual SES. In terms of the neighborhood service environment, do women living in higher-SES neighborhoods use medical care systems that are more likely to emphasize hormone use? In terms of the neighborhood social environment, are

there particular social norms in higher-SES areas that produce behaviors putting women at greater risk of breast cancer? Examples might be social norms encouraging alcoholic beverage consumption (consumption in excess of two drinks per day is associated with increased breast cancer risk) and aspects of the workplace that discourage breast-feeding or impact childbearing (breast-feeding has a protective effect on breast cancer risk beyond that of parity alone).[88] In terms of the neighborhood physical environment, do higher-SES neighborhoods expose women to more toxic chemicals of a specific kind? A survey in Newton, Massachusetts found that women in areas with the highest incidence of breast cancer were more likely to report use of professional lawn services and higher routine use of home pesticides than women in low-incidence areas.[89] Other studies suggest that dry cleaning and other chemical exposures may contribute to breast cancer risk in high-SES women. These are examples of the kind of research that might link individual- and neighborhood-level SES to increased breast cancer risk.

The influence of neighborhood SES on stage at diagnosis, treatment, and survival needs further attention as well. In these cases, lower SES is related to adverse breast cancer outcomes in the same way it is related to other health outcomes—with lower SES people or places being at a disadvantage. Future research needs to examine the relative and joint roles of individual SES and neighborhood SES in exposing people to neighborhood service, social, and physical environments that increase or decrease breast cancer risk. The idea is not only to examine whether there are independent effects of neighborhood SES on breast cancer incidence and outcomes, but also to explore explanations for these contextual effects. Looking simultaneously at other health conditions and outcomes may also provide clues about the neighborhood conditions that affect risk for all diseases, along with those that may specifically influence breast cancer risk.

One question regarding mammography screening is whether rates of mammographic screening in a neighborhood may be a crude measure of social norms regarding mammography. Perhaps women in neighborhoods with lower mammography rates are less likely to be urged and supported in getting timely and routine mammograms by neighborhood friends and relatives. Indeed, there may even be a level of skepticism of the medical care system or of the importance of screening that varies by the SES of neighborhoods.

It will also be important to examine multilevel interactions between individual and neighborhood SES. Although living in lower-SES neighborhoods might be detrimental to the health behaviors and health care access of all residents, it might be particularly detrimental to those with lower individual SES (a double jeopardy hypothesis). Moreover, neighborhood SES may interact with race, age, and other factors in ways that are detrimental to women's health. As will be discussed briefly below, it is important to examine race/ethnicity and SES simultaneously, especially when investigating neighborhood SES. Racial and ethnic minorities are much more likely to live in lower-SES neighborhoods than are white people, even at the same individual income level.[90]

Little is known about how multilevel SES and age interact over the life course to affect breast cancer

incidence and outcomes. Most studies only look at SES at time of diagnosis. Early life SES may also have an important impact on breast cancer risk and only a few studies have looked at this issue.[91-93] Wrensch et al. noted that there was some indication that early-life high SES was associated with increased risk in women over 50 years of age in Marin County, California.[92] This is consistent with other health research indicating that SES in both childhood and adulthood are related to health and health risk factors in adulthood.[94-96] In the absence of long-term prospective studies beginning in childhood, collecting information on residential histories and asking women about their childhood SES might help us understand whether SES over the life course has a cumulative impact on breast cancer incidence and outcomes, and whether individual and neighborhood SES are particularly important to breast cancer at certain ages or stages of life.

Neighborhood Racial/Ethnic Context and Breast Cancer

Research consistently demonstrates that race and ethnicity are related to all aspects of breast cancer, from incidence to mortality. Section II, Chapter A, of this paper specifically addresses our knowledge of racial and ethnic differences in breast cancer. Despite the importance of race and ethnicity in predicting breast cancer incidence and outcomes, little research has examined how the racial/ethnic composition of neighborhoods might contribute to breast cancer. This is a strong limitation of current research, since minority racial and ethnic groups live, on average, in very different types of neighborhoods than do white people. Indeed, it is wrong to discuss the health impact of race in this country without recognizing that different races live in different neighborhood contexts where health risk factors are developed and maintained.

Concept/Exposure Definition

Racial composition refers to the distribution of racial/ethnic groups within a neighborhood. Racial composition is usually measured in simple ways, such as looking at the percentage of African Americans, Hispanics, or racial/ethnic minorities in a neighborhood. Racial composition is sometimes categorized to indicate whether a neighborhood is racially/ethnically mixed, mostly white, or mostly racial/ethnic minority.

Racial residential segregation (also referred to as "racial segregation") refers to the fact that individuals are unevenly distributed across neighborhoods by race/ethnicity. Historical and discriminatory patterns of uneven industrial development, the movement of economic opportunities away from inner cities, real estate speculation, discrimination in government and private financing, and exclusionary zoning have led to systemic racial segregation among diverse communities, with important implications for community health and individual well-being.[97-103] In a world with no racial segregation, the racial composition of all neighborhoods would be the same, reflecting the racial composition of the nation as a whole. Racial segregation measures the variation in racial composition of neighborhoods. It is commonly measured using smaller residential units, such as census tracts, within a larger area unit, such as a city or county.[104] In essence, it measures whether a specific neighborhood looks similar to or different

from the racial/ethnic composition of other neighborhoods within a given city or county.

Biologic Plausibility for Neighborhood Racial/Ethnic Context and Breast Cancer

There are two general pathways through which racial segregation may impact health.[8, 105-109] First, racial segregation produces and reinforces economic segregation in the U.S.[90, 110, 111] As a result, people of different racial/ethnic groups live in very different types of neighborhood socioeconomic environments. For example, African Americans are more likely than whites to live in lower-SES neighborhoods, on average, even when African Americans and whites at the same income level are compared.[90] Therefore, racial segregation can negatively affect health indirectly through its impact on neighborhood SES, and also through its impact on the individual SES attainment of residents.

Second, living in a racially segregated area may be related to health outcomes over and above socioeconomic pathways. Studies show that racial segregation is associated with differential exposure to a host of health risks, including substandard housing, chemically toxic environments, lack of access to adequate medical services, and social isolation.[15, 105, 112, 113] Moreover, racial segregation may heighten exposure to and perceptions of discrimination, which can cause acute and chronic stress that leads to poor health outcomes. Living in a neighborhood with a high racial/ethnic minority composition may be related to health outcomes in ways similar to those for racial segregation. However, there may also be some protective aspects of living in neighborhoods that have high racial/ethnic minority composition, and/or are racially segregated. As is discussed in Section II, Chapter D of this paper, immigrants with lower acculturation have lower breast cancer incidence. This is likely due in part to their maintaining health behaviors that are protective of health generally, and against breast cancer specifically. Living in ethnic enclaves may help individuals maintain healthy behaviors consistent with the norms of their country of origin.[105] Ethnic enclaves may also protect immigrants from discrimination in housing and the lending industries, which in turn impacts their individual SES status. Moreover, living among people who are racially or ethnically similar may create a social environment that is more supportive, in some ways, than living as a member of a racial/ethnic minority in a white neighborhood.

Evidence for an Association between Neighborhood Racial/Ethnic Context and Breast Cancer Outcomes

Although racial and ethnic minorities often live in very different neighborhood contexts than do whites, research has paid little attention to examining how the neighborhood context contributes to racial disparities in breast cancer incidence and outcomes. In a study on racial differences in obesity, individual SES somewhat attenuated the association between race and obesity among African American and white women. Moreover, controlling for neighborhood SES even further attenuated the association. Neighborhood context helps explain racial disparities in obesity[12] and self-rated health.[114]

There is very little direct evidence for the impact of neighborhood racial segregation on cancer risk, but evidence has accumulated for its impact on other health conditions. Much previous work has focused on neighborhood racial segregation's impact on hypertension and cardiovascular disease. Some studies using aggregate-level data have shown an association between higher levels of racial segregation and infant and adult mortality rates.[106, 108, 108, 115, 116] However, two recent multilevel studies found only modest associations between racial segregation and self-rated health using three national data sets.[8, 117]

In terms of the neighborhood service environment, highly segregated neighborhoods often face limited availability of high-quality preventive care. Research demonstrates a positive correlation between access variables (transportation barriers, increased distance to health care facilities) and suboptimal treatment patterns.[46, 48, 49, 115, 118-121] Zenk, Tarlov, and Sun[122] examined travel distances to facilities providing low- or no-fee mammography screening in Chicago. They found that even compared to other high-poverty neighborhoods with the highest screening needs, neighborhoods with a greater proportion of African American residents had longer travel distances and travel times.

Individuals living in highly segregated areas may have limited access to economic and social resources for promoting health[112] and for moderating breast cancer risk factors. Clustering of disadvantaged neighborhoods, or "ghettos," may further constrain social and economic resources for minority groups by heightening crime rates and limiting access to resources such as supermarkets, parks and recreational facilities in other parts of the metropolitan area.[105]

In terms of the social environment, racially segregated neighborhoods potentially have both positive and negative effects on breast cancer incidence and outcomes. Social norms and practices of ethnic groups may be easier to transmit and maintain in a neighborhood where most residents share cultural norms and values. To the extent that these shared health behavior practices are unhealthy, living in an ethnic enclave may be detrimental to health. Kandula and colleagues[123] used the 2001 California Health Interview study to examine disparities in cancer screening among non-Hispanic whites (NHWs), Chinese, Filipinos, Koreans, Vietnamese, and other Asians. After adjusting for access to care, some Asian subgroups still had lower rates of cancer screening, compared to NHWs. Foreign-born Asians reported that they did not get screening tests because they did not experience problems or symptoms. In this case, living among other recent immigrants might perpetuate the norm of not accessing Western medicine for screening. Distrust of the medical establishment and long-standing perceived barriers to quality care can also lead members of minority groups to forgo treatment for cancer, even when symptoms are present.[124] Living in a minority neighborhood could reinforce this distrust and perception of barriers.

Yet, on the positive side, recent immigrants may maintain their health advantage longer if surrounded by neighbors with protective health behavior norms and values. Studies on migration, acculturation, and breast cancer incidence

demonstrate that incidence rates increase in women who migrate to high-incidence countries from low-incidence countries. For example, focusing on Hispanic women in California, John and colleagues[125] found that breast cancer risk was lower in Hispanic women who moved to the U.S. after age 20, and those who spoke mostly Spanish. The effects of migration patterns were significantly attenuated once known individual risk factors were included. Higher levels of acculturation were associated with characteristics of Western lifestyle that increase breast cancer risk (higher education, early age at menarche, nulliparity or low parity, late age at first pregnancy, no breast-feeding or short duration, hormone therapy use, height, sedentary lifestyle, and alcohol consumption). Research on migration and acculturation is discussed in more detail in Section II, Chapter D of this paper. However, a research agenda that includes examinational of cultural norms within and across different neighborhood racial/ethnic contexts might enhance our understanding of how healthy behaviors may be promoted and maintained.

In terms of the neighborhood physical environment, people of color and people living in low-income or economically disadvantaged areas are disproportionately exposed to environmental pollutants,[15, 126, 127] which adversely affect their health and well-being. An environmental justice conceptual framework can encourage new insights into the junctures of the political economy of social inequality with racial discrimination, environmental degradation, and health. According to the U.S. EPA definition, "Environmental Justice is the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies."[128] Most important, application of an environmental justice perspective to some of the noted disparities in the burden of breast cancer has not been fully explored, but may be relevant, particularly with respect to the greater burden of incidence among young African American women and worse survival rates among some minority and low-income women.

Limitations and Future Directions for Studying Neighborhood Racial/Ethnic Context and Breast Cancer

Few studies have directly examined how the different neighborhood contexts of racial and ethnic groups may affect breast cancer incidence and outcomes. This is an important gap in the literature, conceptually and empirically. For example, in a study of breast cancer mortality in the San Francisco Bay Area, O'Malley and colleagues[80] found that less than 3% of white women in the study resided in poverty neighborhoods, compared to 48% of black women in the study. These different neighborhood contexts must contribute to racial/ethnic disparities in breast cancer, yet they remain generally unaddressed and poorly understood.

Research on racial segregation and breast cancer incidence, screening, diagnosis, treatment, and mortality would further our understanding of the complex barriers that women face, and the contexts in which they face them. Segregation, even when the adverse health effects are experienced by individuals, occurs at a group level, based on social class and racialized

hierarchies. By definition, segregation refers to an imbalance in the distribution of a specific demographic group across a geographic region, such as a metropolitan area. Therefore, the community health effects of segregation must be examined and remedied through policy decisions and interventions at the regional, metropolitan, state, or national levels. In general, the structural forces that create segregation tend to operate regionally, as evidenced by many current political and economic regions where economic growth and environmental quality are not optimal for communities of color, the working class, and the poor.[26] From a public health perspective, the rationale for taking a regional approach to examining links between segregation, environments, and health disparities is twofold: First, economic trends, transportation planning, and industrial clusters tend to be regional in nature, even as zoning, facility siting, and urban planning decisions tend to be local.[101] Second, research that examines how health inequities play out regionally could have implications for the development of interventions and policy initiatives that ameliorate fundamental drivers of environmental health and disease among diverse communities.

As we conduct research on racial segregation and breast cancer, we need to discuss the variety of intervention options implied by our studies. For example, if racial segregation is related to a host of breast cancer risk factors, we likely want to address not only each of those factors, but we would also want to ameliorate the social, political, and cultural factors that lead to and perpetuate residential segregation.[129, 130] Similarly, as we consider how to continue to improve access to breast cancer screening among African American women and in African American neighborhoods, we need to simultaneously consider how to ensure that all women have access to the diagnostic and treatment services that would make early screening worthwhile.[131]

Neighborhood Service Environment and Breast Cancer

Some aspects of the neighborhood service environment may put women at greater risk for developing breast cancer. Some research indicates that there is neighborhood variation in the availability of supermarkets and healthy, affordable food.[132] Availability of recreational resources is related to physical activity levels.[133] Transportation services also vary by neighborhood, and can affect the ability of many residents to access available services, resources, and social and recreational opportunities.[134]

Obviously, aspects of the neighborhood medical service environment may put women at greater risk for poor cancer screening, diagnosis, treatment, and mortality outcomes. A large literature discusses the importance of access to mammography, early diagnosis, and appropriate treatment. This research shows that there is much regional variation in both access to and use of these services, and some of this research has been summarized earlier in this chapter.

A number of initiatives have targeted low-income neighborhoods for increasing access to mammography. For example, the North Carolina Breast Cancer Screening Program used lay health advisor networks to increase uptake of screening mammography among older, minority women in

impoverished rural areas.[135] Similar projects have been established in urban areas.[136] The Witness project, which uses cancer survivors and lay health advisors to increase awareness, knowledge, access to screening, and early detection in the African American population, is now implemented in 22 states at 33 different sites. Results suggest that individual as well as group-level barriers need to be overcome. For example, neighborhood transportation may impede access to medical services, even if appropriate screening, diagnosis, and treatment services are available.

Future Directions for Research on the Neighborhood Service Environment and Breast Cancer

We need to better understand how neighborhoods vary in access to appropriate services that would lead to prevention of breast cancer, earlier diagnosis, and better treatment. It will be important to examine how individual characteristics interact with the available service environment. For example, poor people or older adults may be particularly vulnerable to the lack of appropriate neighborhood services.

There are currently efforts in some cities to improve access to healthy affordable food, and to improve transportation systems. Examining the impact of these interventions on breast cancer and other health risk factors—such as health behaviors (eating habits, nutrition) and health care access and use—would help us understand which risk reduction interventions should be highest priority.

Finally, lack of minority access to state-of-the-art clinical trials and other aspects of optimal breast cancer treatment is a well-documented problem.[136] In the absence of universal health care, it is imminently worth investigating not only individual-level barriers, but also neighborhood characteristics that can be targeted to improve access to preventive and medical care services. The available literature demonstrates that disparities in breast cancer outcomes are related to patient-, provider-, and health system-level factors, but relatively little work has been done at the level of neighborhood.

Neighborhood Social Environment and Breast Cancer

While an increasing body of research has linked racial and income segregation with poor health outcomes,[105, 107] little remains known about the mechanisms that mediate this link. Research suggests that metropolitan-level segregation shapes neighborhood-level social environments in ways that impact health. As discussed above, segregation has been linked with poorer environmental quality, poorer housing conditions, and reduced community access to parks, health care facilities, and transportation. Residential segregation is also linked with neighborhood levels of crime, social cohesion, and trust.[137] Using trust as an index of social capital, the Social Capital Community Benchmark Survey (SCCBS) found that residents of racially diverse communities were less likely to trust other people, including members of their own race. They were also more likely to be personally isolated. In addition, people in racially diverse communities were less likely to connect with neighbors across class lines.[138] Asesina and Ferrar[139] also found lower interpersonal trust in racially heterogeneous communities and communities with high income

inequality. Marcshall and Stolle[140] extend this work by examining the neighborhood conditions in Detroit that foster generalized trust. They found racial differences in how trust develops. Racial heterogeneity was positively correlated with levels of interpersonal trust for African Americans, but was not a significant factor among whites. Neighborhood sociability, or the amount of formal and informal social interactions occurring within the neighborhood, was also positively correlated with the formation of generalized trust for African Americans, but not for whites. What determined white residents' level of interpersonal trust was the socioeconomic status of the neighborhood.

These differences in the way that neighborhood racial and socio-economic context influences residents' levels of interpersonal trust can help us understand how, in the context of a highly segregated metro area, various dimensions of neighborhood racial composition could affect health behaviors potentially linked to breast cancer. In addition, these differences may help us better understand some of the contradictory effects of segregation for whites versus African Americans on various health and social outcomes.[107, 110, 137, 141] Neighborhood social factors that have been studied in recent research on health include, but are not limited to: social connectedness of neighbors, social disorganization, violence, cultural norms and practices, civic engagement, and political environments.[142] However, little research has specifically examined neighborhood social factors and breast cancer. The social environment of neighborhoods can affect breast cancer incidence and outcomes through a number of pathways. Living in more stressful neighborhood environments can "get under the skin"[143] by way of repeated assaults, resulting in chronic stress. Neighborhoods with high crime, high unemployment, low social cohesion and trust, and greater experiences of racism and discrimination can elevate stress in residents.[77, 78, 105] People living in areas with limited access to service facilities may require more effort, energy, and time to achieve the basic tasks of daily living. A diagnosis of breast cancer, which may limit mobility while increasing the need for travel (e.g., to medical facilities), can present an additional challenge for people in neighborhoods with limited resources.

The social environment can also produce social norms and practices that shape the health behaviors and risk factors of individuals. Berkman and Kawachi[144] suggest that neighborhoods with high social capital may be able to reinforce positive social norms and health behaviors. Some behavioral or risk factors that may be affected by neighborhood norms include smoking, exercise, and obesity. Datta and colleagues[145] analyzed multilevel data from the Black Women's Health Study and found that African American women living in neighborhoods with higher poverty had higher smoking prevalence, even after controlling for demographic factors, education, occupation, and several other neighborhood SES variables, which is consistent with previous research.[13, 14] Neighborhood socioeconomic context is associated with a higher risk of obesity,[12] controlling for individual SES measures. Cubbin, Hadden, and Winkleby[146] found that neighborhood socioeconomic deprivation, over and above individual SES, was associated with physical inactivity. Neighborhood

social structures and social norms also have a strong impact on smoking[147] and physical activity patterns[148] among younger women.

Policies and social norms can affect breast-feeding practices at work or in other public spaces. A recent study of women working in semiconductor manufacturing in Taiwan found that "breast-feeding-friendly policies can significantly affect breast-feeding behavior."[149] Internationally, breast-feeding has been demonstrated to have a strong protective effect on breast cancer risk.[88] A variety of barriers discourage breast-feeding among women, even though benefits to mother and child are well established. Women of lower SES are less likely to breast-feed, which may be linked to specific occupations, social conditions, and education. Several aspects of women's reproductive history track very closely with SES,[150] but breast-feeding may be the only factor that can be readily addressed through public health interventions.

In the stress literature, there is a strong body of research on how coping and social support at the individual level moderate health outcomes.[151-153] Several studies have also established an association between social support and breast cancer survival.[154-156] Less attention has been paid to how neighborhood and individual social support may buffer the impact of neighborhood context on breast cancer. An increasing body of animal studies provides evidence that stress and the social environment may impact breast cancer, but little research on this topic has been done with human beings.

Directions for Future Research on Neighborhood Social Environment and Breast Cancer

Gee and Payne-Sturges and Morello-Frosch have developed useful models for conceptualizing the complex interactions between social and physical factors that operate simultaneously at the community and individual levels.[16] Future work should explore how the neighborhood social environment impacts breast cancer, including attention to the neighborhood experiences of: social trust and social capital, social stress, social support and interaction, and social norms and behaviors. Each of these neighborhood social components may lead to risk factors for breast cancer and may moderate the course and outcomes. In particular, social cohesion for whites, African Americans, and Latinas may be a result of different conditions which, in turn, interact with other neighborhood factors to affect health behaviors. More research is needed to determine when and how diverse dynamics of neighborhood racial and ethnic composition promote health, and when they harm. With respect to Hispanic women, California is probably the only state with sufficient numbers to conduct a comprehensive analysis of breast cancer risk factors and outcomes. Howe et al.[157] outline several avenues for investigation among Hispanic women that include country of origin, years living in the U.S., the role of individual and neighborhood level SES, and cultural factors.[26] In addition, see Gee and Payne-Sturges[16] and Morello-Frosch,[26] who have developed useful models for conceptualizing the complex interactions between social and physical factors

that operate simultaneously at the community and individual levels.

Neighborhood Physical Environment—the Built Environment

Our physical environments are the places where we live, work, learn, and play. The quality of our neighborhood physical environment affects our health and well-being. Section of this paper examines biological exposures from the physical environment, focusing on the potential effects of sunlight, artificial light, tobacco smoke, radiation, bacteria, endotoxins (part of the outer cell wall of bacteria), and viruses, so we will not address these topics here.

The built environment is another aspect of our physical environment that affects our health and well-being, and that may be relevant to breast cancer. The built environment includes buildings, housing, parks—any urban, rural and suburban infrastructure—along with the "connective tissue that links these places together," transportation infrastructure.[158, 159] The built environment ranges from large-scale civic environments to the small-scale personal spaces and indoor residential environments where humans spend nearly 80% of their time.

A recent explosion of studies in public health examine how aspects of the built environment (e.g., the availability and accessibility of recreational facilities, pharmacies, stores, and the walkability of a neighborhood) relate to health outcomes such as low birth weight,[160] depression and perceived health status,[161, 162] drug overdose mortality,[163] motor vehicle and pedestrian fatalities,[164] death[165] and several other health outcomes. Moreover, aspects of the built environment have thus far been strongly and consistently associated with levels of obesity and physical activity,[166-168] two established risk factors for breast cancer.

Our physical surroundings can dictate many involuntary physical exposures. The way neighborhoods are constructed influences road patterns, traffic density, noise, and air pollution from vehicle exhaust. The placement of industrial facilities, trucking distribution centers, and waste dumps, which is related to land use policies and zoning, can also greatly impact residents near these sites. The quality of the housing, schools, and other public places, along with the types of building materials used, impact our physical exposures as well. Public policies regarding smoking impact exposures to second-hand smoke. Many involuntary exposures from the built physical environment may be risk factors for breast cancer. For example, the Cape Cod Household Exposure Study, conducted by the Silent Spring Institute has sought to characterize indoor exposures to endocrine disrupting chemicals (EDCs) potentially linked to breast cancer. Testing included household air and dust and women's urine samples from 120 homes for 89 EDCs, including phthalates, alkylphenols, parabens, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), pesticides, and other phenolic EDCs, many of which had not been tested for before in indoor residential environments.[169]

Physical inactivity and obesity are two of only a few known, modifiable, risk factors for breast cancer. There is an emerging literature on the

relationship between obesity, physical activity, and physical attributes of one's neighborhood. These attributes include the number of walkable destinations and the availability of undesirable amenities, such as fast food stores, and desirable amenities, such as supermarkets and recreation facilities. Neighborhood street connectivity and accessibility, high number of non-residential destinations near a home, higher residential density, and greater mix-diversity land use (mixes of residential, office, retail, and public space) have been found to be associated with higher levels of physical activity.[164, 168, 170] In a review of eighteen studies, Owen et al. found that the accessibility of sidewalks, stores, and parks, and perceptions about traffic and busy roads were associated with walking.[171] Less studied is the relation between measures of safety and physical activity levels, although there are suggestions that people who perceive their neighborhood as unsafe are less likely to be physically active.[171, 172]

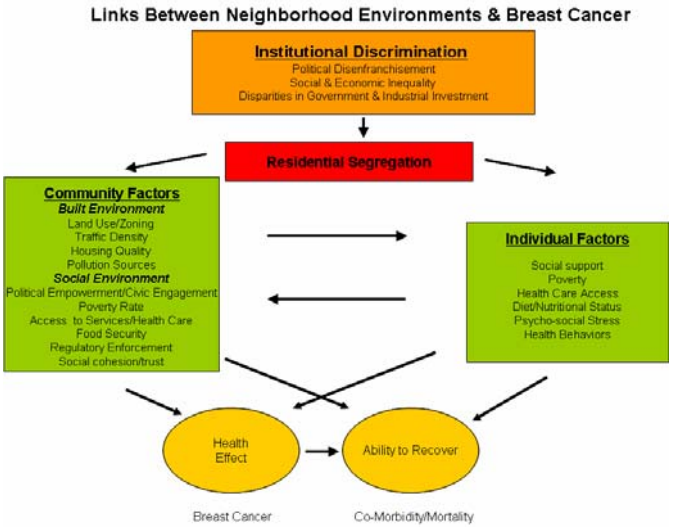
In the literature on obesity/overweight, similar to the physical activity literature, most,[164, 167, 170, 173] but not all,[174] studies have found obesity/overweight to be more prevalent among residents of areas where sprawl makes it more difficult to walk to destinations.[166] Obesity may be related to limited access to food establishments, restaurants and grocery stores that serve healthy food, and/or to increased access to unhealthy food establishments, such as fast-food restaurants.[175] Additionally, there is some evidence that obesity is associated with the amount of time spent in a car,[167] vehicle miles of travel, and commute time.[176] These same measures are highly predictive of polycyclic aromatic hydrocarbon (PAH) exposures from vehicle exhaust,[177] which may also be associated with increased breast cancer risk.

Directions of Future Research on the Neighborhood Physical Environment—the Built Environment *and Breast Cancer*

Addressing the specific aspects of the built environment that may impact breast cancer incidence and outcomes represents a highly productive direction for future breast cancer research. Research into the effects of the built environment may open a new avenue for breast cancer risk reduction by examining how neighborhood attributes may be changed to reduce the burden of breast cancer and other diseases. With greater knowledge about the role of the built environment in determining biological and behavioral risk factors, urban planners, community groups, and public health officials can advocate for changes to the built environment that promote health and reduce risk.

Recent advances in geographic information system (GIS) technology have provided new opportunities to explore the complex relationships between many facets of the physical environment and health. GIS technologies allow for much finer geographic detail in examining environmental exposures. A number of investigators have invested considerable effort in developing GIS-based environmental exposure metrics with an eye towards studying breast cancer. The Cape Cod Breast Cancer and Environment Study, the Western New York Exposures and Breast Cancer Study (WEB Study) and the Long Island Breast Cancer Study have been particularly active in this regard.[178-182]

Some GIS exposure methods have been developed and then applied to case-control studies in which residential histories also have been collected so as to better characterize chronic exposures or exposures in early life. These studies have generated some provocative results regarding biological exposures (see Section I of this paper for detailed descriptions of these studies). The methods used in these studies might be fruitfully used to examine how breast cancer risk factors relate to spatial aspects of the built and social environment and to the interactions among physical and social aspects of the neighborhood environment.



Conclusion: Priority Directions for Future Research

Most breast cancer research has focused on individual-level risk factors, overlooking the potential importance of neighborhood in shaping known individual-level risk factors and itself providing risk factors. Figure 1 provides a framework for how neighborhood environment can be examined in conjunction with individual-level factors in terms of how they might shape breast cancer risk.

Basic Conceptual and Methodological Issues for Future Research

The following are the most important conceptual and methodological issues to be addressed in future research into neighborhood effects on breast cancer.

- Neither individual- nor group-level exposure measurement alone provides sufficient data for understanding breast cancer incidence patterns and outcomes.
- To determine how neighborhood context impacts breast cancer incidence and outcomes for specific social groups, research should proceed at multiple levels, examining both neighborhood characteristics and individual demographic factors (e.g., age, race, individual SES).
- Neighborhood context can be conceptualized as both a risk factor and a protective factor, interacting with individual-level risk factors to affect breast cancer incidence and outcomes.
- Age at exposure and timing and duration of exposure to neighborhood contexts need to be comprehensively explored through detailed residential histories.
- County-level spatial aggregation is insufficient to capture heterogeneity within regions; urban, suburban and rural regions needs to be characterized and evaluated.

- A useful conceptual framework for future investigations would encompass how urban/rural, socioeconomic, and racial/ethnic contexts of neighborhoods impact breast cancer and other health outcomes, and how these factors operate through neighborhood service, social, and physical environments.

High Priority Recommendations

Studies that identify distributions of known risk factors associated with living in metropolitan and affluent areas and also incorporate information on environmental exposures could prove useful. California has a number of population-based surveys that could be combined with existing databases on environmental exposures.[183] We also need studies that examine variations in the breast cancer burden at small levels of geography, in racial/ethnic groups separately, and by tumor subtypes defined by histology, receptor status and stage at diagnosis. In addition, large cohort studies with geographically dispersed populations (e.g. the California Teachers Study) can incorporate both individual and contextual effects. It would be useful for these types of studies to collect information on places of residence at times other than at diagnosis. Likewise, it would be useful to improve the quality and completeness of birthplace information recorded by the California Cancer Registry, and obtain residential history information on study participants whenever possible.

A recent example of the rich and complex nature of neighborhood information is provided by a recent series of articles in the American Journal of Epidemiology.[184] The authors developed a panel of scales that measured seven dimensions of neighborhood environment, with a focus on cardiovascular disease impact (aesthetic quality, walking environment, availability of healthy foods, safety, violence, social cohesion, and activities with neighbors). Many of these factors were strongly correlated with neighborhood socioeconomic position, but the scales provided additional information that was not captured by economic status alone. There are several potential applications of this approach for breast cancer research. First, the authors demonstrate the importance of investigating neighborhood effects tied to specific underlying causal mechanisms. With respect to breast cancer, potential causal mechanisms including a variety of factors that may exert effects independent of individual or neighborhood SES, including social support (e.g. social cohesion), stress (e.g. safety, violence), physical activity (e.g. availability of sidewalks, parks), social norms (e.g. breastfeeding, age at first pregnancy), and environmental contamination (e.g. pollution, air and water quality). When conducting such studies, alternative definitions of neighborhoods should be investigated using clusters of relevant causal factors rather than relying upon census tracts or predetermined geographical boundaries.[185] Second, the authors demonstrate importance of gathering neighborhood-level information from persons who reside in the same neighborhood as study participants. For example, in a case-control study of breast cancer, interviewing neighbors would avoid differential misclassification associated with relying on information from breast cancer cases and controls. Third, the authors demonstrate the ecometric properties of survey measurements, wherein scale items are nested within individuals

who are nested within neighborhoods. In epidemiologic studies of breast cancer, ecometrics principles could be applied to neighborhoods as well as other social groups (e.g. race, ethnicity, specific age groups) for which group-level information may be relevant to the etiology and progression of breast cancer. For breast cancer studies, considerable time and effort will be required to develop the relevant scales and to assess reliability (test-retest agreement) and validity (ability to capture the underlying construct of interest). Particular attention should be paid to the possibility of structural confounding, the presence of "unmeasured influences that facilitate selection into certain environments and discourage selection into others."[185] To the extent that better, more comprehensive neighborhood measurements are taken, the greater the likelihood for identifying political, economic, historical and social processes that cause breast cancer to cluster in specific geographic areas and among particular groups of persons.

Little research has been conducted on specific attributes of the built environment and breast cancer. With advances in GIS technology, scientists now have the ability to more thoroughly explore the connection between attributes of the built environment and breast cancer. Breast cancer researchers could learn from studies of other health outcomes (e.g. cardiovascular disease, diabetes) and the built environment, where most of this research has been conducted to date. We need to examine the degree to which attributes of the built environment may influence breast cancer risk factors and rates. Studies identifying what aspects of the built environment increase physical activity and reduce obesity may be important, especially since interventions aimed at individuals to reduce obesity and increase physical activity have generally not been successful.

Possibilities for applying GIS-based methods to large-scale population-based ecologic studies are more limited. In their studies of childhood cancer,[186-188] and to a lesser-degree, breast cancer,[28] in California, Reynolds and colleagues have used a number of pre-existing databases to characterize potential ambient exposures to agricultural pesticide use, hazardous air pollutants, and automobile exhaust. Since these methods are based on residential address at diagnosis, applying them to studying breast cancer is somewhat problematic, given the long latency of breast cancer and probable importance of exposures during early life and/or during critical periods of mammary growth and development. Addition of residential history information to the California Cancer Registry could greatly enhance the ability of researchers to evaluate these potential exposures. Furthermore, it could be very informative to create a large, geographically-dispersed, cohort of California women in which these GIS-based methods of exposure assessment could be incorporated with individual-level risk factor information and residential histories. Such an approach is currently being utilized by Dr. Reynolds and colleagues in the California Teachers Study, a large cohort of California school professional employees. This cohort is predominantly white and of higher SES. Creating a more ethnically and socioeconomically diverse cohort would provide a better opportunity to study potential exposures to environmental pollutants.

Future research should also focus on the role of health behavior norms and practices that are influenced by neighborhoods. We need to identify social and cultural norms revolving around childbearing, breast-feeding, physical activity, diet, and other factors that may be amenable to interventions aimed at the neighborhood level. Productive areas for future investigation include how neighborhood context reinforce or perpetuate cultural norms among immigrants; how sources of health information that impact behavior may vary by neighborhoods and SES; and what forms of communication (mixed media, bulletins, etc.) are most effective in empowering group and individual decision making to improve health. Research studies and interventions targeted to specific age groups and neighborhood characteristics are likely to be particularly effective.

A growing number of researchers, community activists, breast cancer advocates, and policy makers have taken a more inclusive view of the environment than the definition traditionally used. This viewpoint, which is based on a framework similar to that of the environmental justice movement, includes "holistically considering the effects that SES and other social factors have on exposures to environmental hazards."[189] Research needs to consider models of cumulative risks and multi-stressors, not just single chemicals or single behavioral risk factors.[16, 18, 26, 189] To achieve this goal, future studies of the neighborhood environment will require collaborations between health researchers, policy makers, geographers, environmental scientists, social scientists, and urban planners. Recent advances in GIS, exposure assessments, and methods for examining social processes provide the basis for productive, interdisciplinary research to elucidate the complex connections between breast cancer and the environment.

Research on neighborhood context and health needs to be planned and evaluated in light of future implications for forming policy and planning interventions. Does failure to detect a neighborhood effect on a breast cancer outcome (after controlling for individual risk factors) mean that the neighborhood context does not matter? Or does it mean that there are some neighborhoods that should be targeted for community-based interventions because they have a greater number or proportion of people with known risk factors?[190] Alternatively, if a strong neighborhood effect is found (even after controlling for individual risk factors), what specific economic and/or social policies are needed to improve outcomes in specific neighborhoods? Especially when strong differences in breast cancer mortality or survival are observed by region, the distribution of resources such as access to quality medical care across neighborhoods needs to be targeted as soon as possible to reduce inequalities that adversely impact breast cancer outcomes.

In discussing the importance of neighborhood effects on health, Diez-Roux[19] reminds us: "Neighborhood differences are not 'naturally' determined but rather result from social and economic processes influenced by specific policies. As such, they are eminently modifiable and susceptible to intervention." By comprehensively examining individual- and neighborhood-level risk factors for breast cancer and determinants of adverse breast cancer

outcomes, the California Breast Cancer Research Program will fill important gaps in previous research, and uncover information critical to the design and implementation of interventions that could have a lasting and significant impact on future generations of women.

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