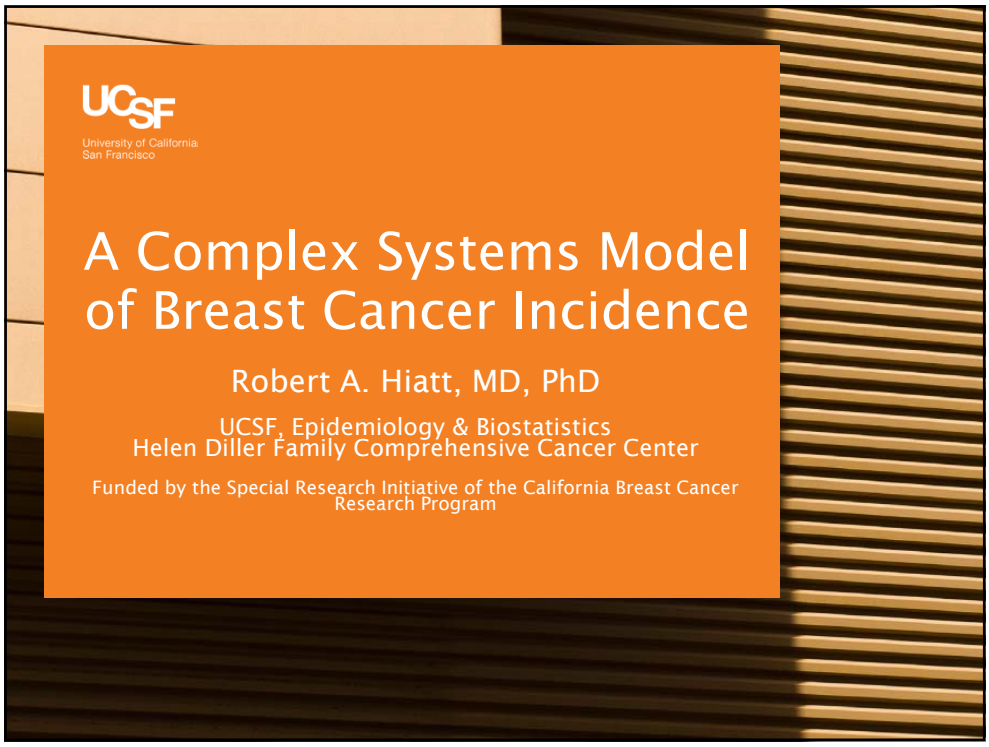


I. Goals of Project

To develop a model of the causes of breast cancer that shows:

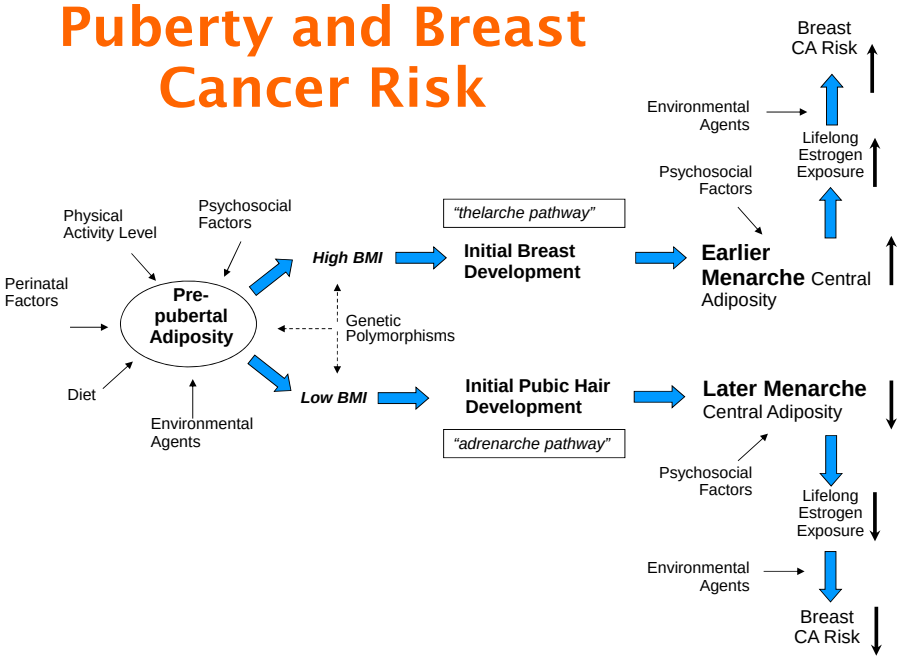
1. Multilevel nature of causation
2. Accessible to a "sophisticated lay audience"
3. Adaptable to add additional factors
4. Recognize feedback and interrelationships between causes

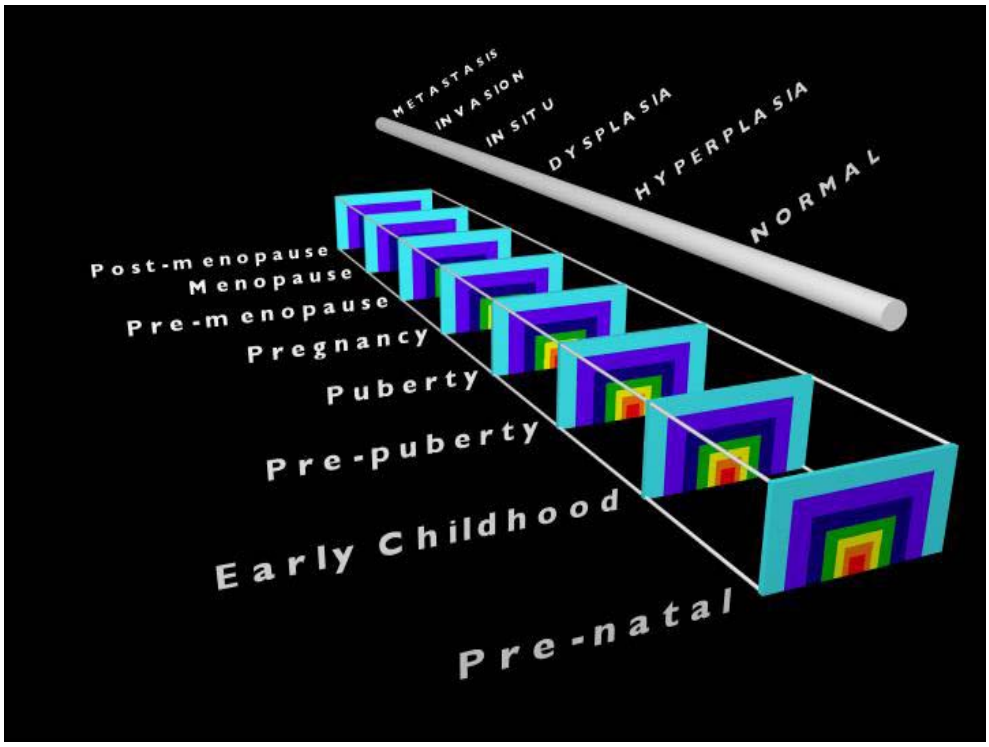
II. Background

Lots of ways to create and use "models":

- Illustrate pathways
- Illustrate relationships and networks
- Prediction models
- Simulation models
- Complex systems models

Puberty and Breast Cancer Risk




METASTASIS
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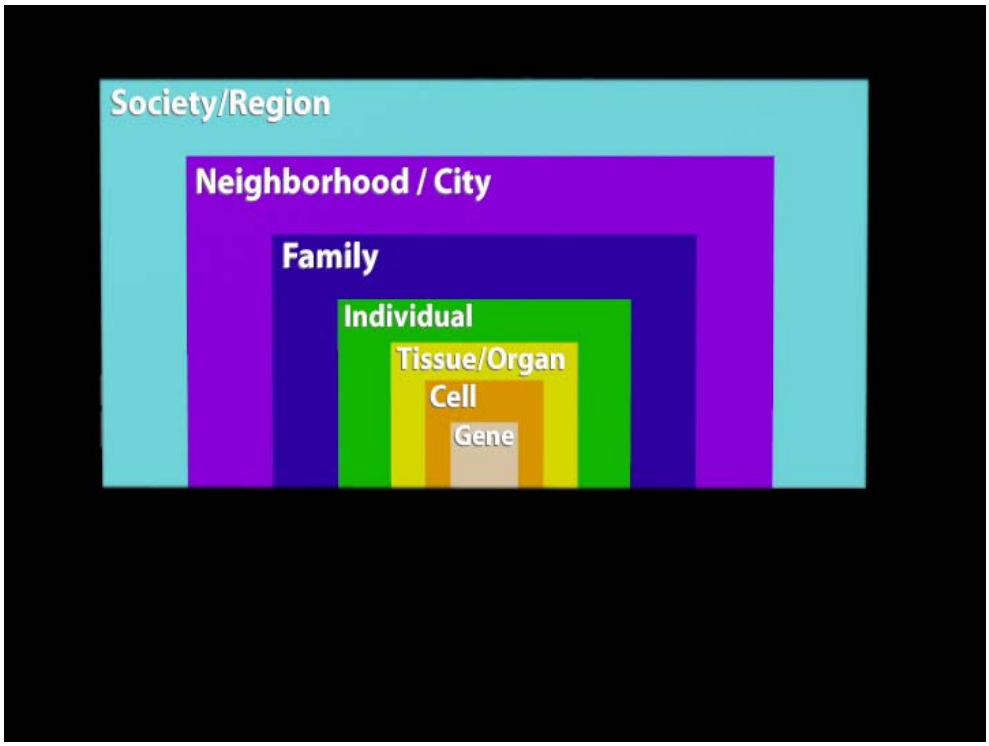
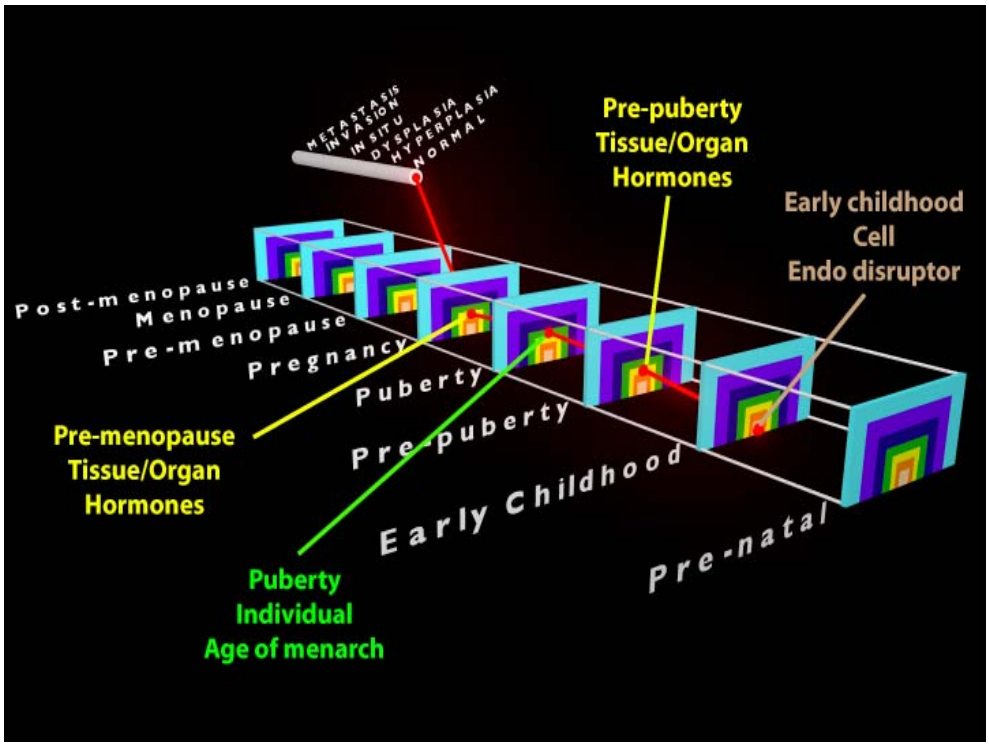
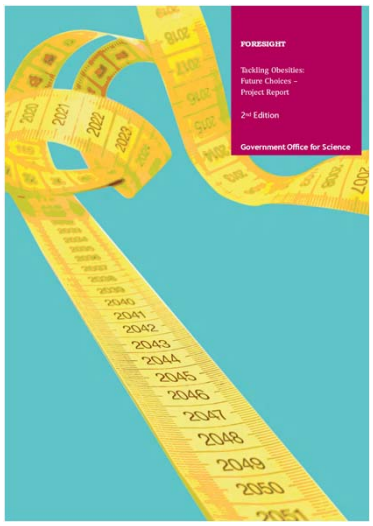
IN SITU
DYSPLASIA
HYPERPLASIA
NORMAL
Post-menopause
Menopause
Pre-menopause
Pregnancy
Puberty
Pre-Puberty
Early Childhood
Pre-natal


Society/Region
Neighborhood / City
Family
Individual
Tissue/Organ
Cell
Gene



Foresight UK



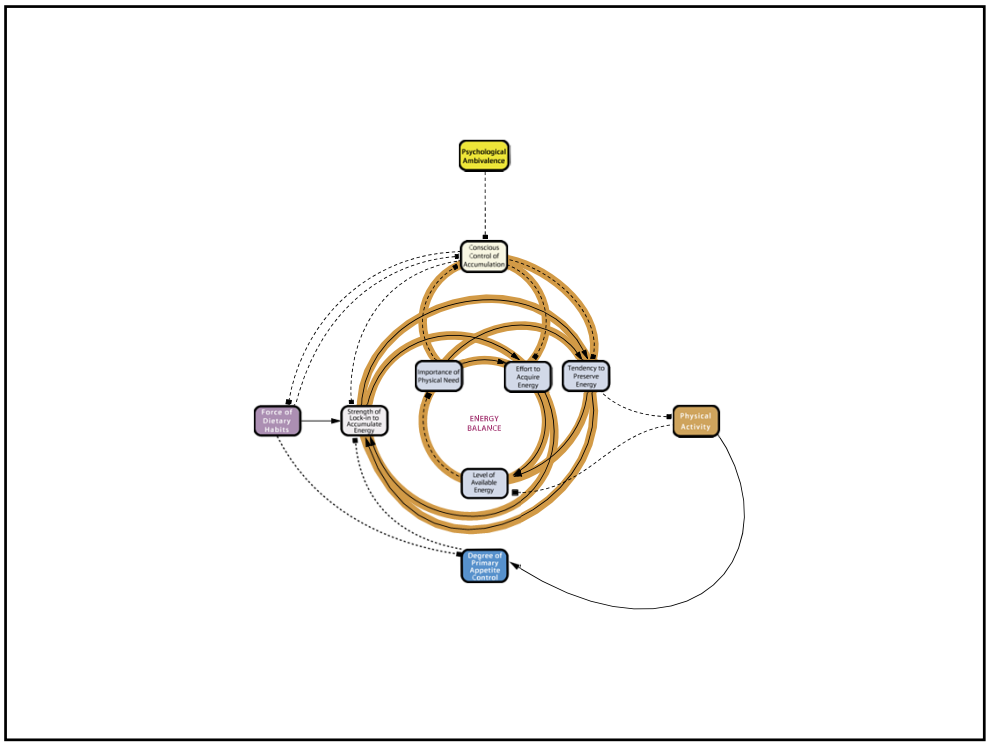
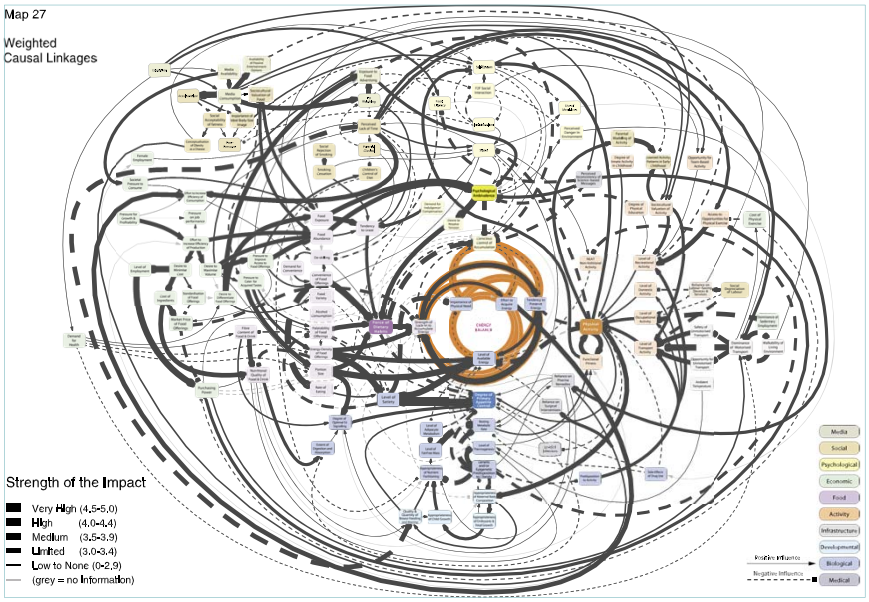


Figure 5.4: The full obesity system map indicating the strength of the relationships between variables (see main text for discussion).[17,18] A qualitative scale of 0-5 was used (a rating of 5 meaning that small changes in the tail variable lead to large changes in the head variable). Linkages were assigned a rating where possible or left 'grey' where there was no information (see key). Variables are represented by boxes, positive causal relationships are represented by solid arrows and negative relationships by dotted lines. The central engine is highlighted in orange at the centre of the map.



III. Creation of First Model

1. Bring together committee of experts on breast cancer and complex systems modeling
2. Three meetings over the course of 1 year
3. Iterative development of model of breast cancer causes
4. Feedback and input from external sources
5. Publication and dissemination
6. Adaptation of initial model

Expert Committee on Breast Cancer (and complex systems modeling)

Janice Barlow, RN - community advocate
Ana Diez-Roux, PhD - social epidemiologist, neighborhood
Lawrence Kushi, ScD – nutritional epidemiologist
Mark Moasser, MD - medical oncologist
Travis Porco, PhD - mathematical modeler
Zena Werb, PhD – cellular biologist, immunologist
Gayle Windham, PhD – environmental and reproductive health
Robert Hiatt, MD, PhD – cancer epidemiologist
Dejana Braithwaite, PhD – cancer epidemiologist
Galen Joseph, PhD – medical anthropologist
Allan Balmain, PhD - geneticist
David Rehkopf, ScD - social epidemiologist

Is This a New Prediction Model?

No. This is not intended to be a new prediction model like the Gail Model.

Then – what is it for? How does a prediction model differ from a model to understand the causes?

TABLE 2. RELATIVE RISK OF BREAST CANCER ACCORDING TO THE GAIL MODEL.*

RISK FACTOR	RELATIVE RISK
Category A	
Age at menarche	
≥14 yr	1.00
12–13 yr	1.10
<12 yr	1.21
Category B	
No. of breast biopsies and woman's age	
0	
Any age	1.00
1	
<50 yr	1.70
≥50 yr	1.27
≥2	
<50 yr	2.88
≥50 yr	1.62
Category C	
No. of 1st-degree relatives with breast cancer and woman's age at 1st live birth	
0	
<20 yr	1.00
20–24 yr	1.24
25–29 yr or nulliparous	1.55
≥30 yr	1.93
1	
<20 yr	2.61
20–24 yr	2.68
25–29 yr or nulliparous	2.76
≥30 yr	2.83
≥2	
<20 yr	6.80
20–24 yr	5.78
25–29 yr or nulliparous	4.91
≥30 yr	4.17

Characteristics of the Model

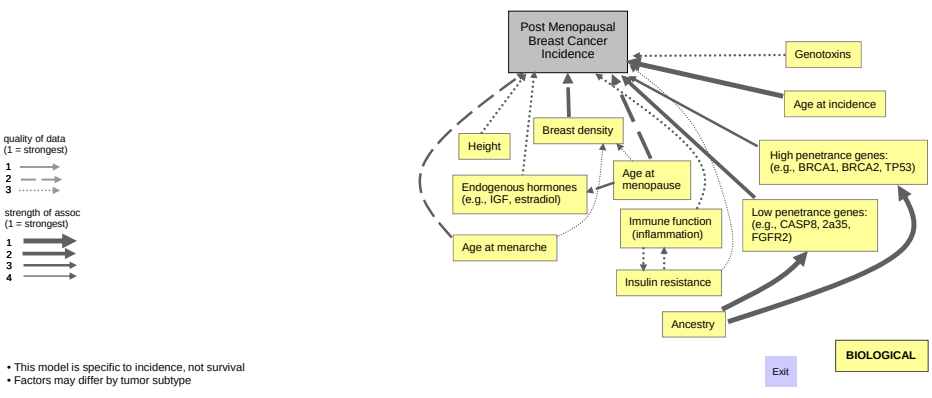
- Gail model as standard of comparison
- However, purpose of Gail model is for prediction, not for understanding causes
- Build on Gail model in three primary ways
  1. Include causes at multiple levels
  2. Attempt to capture the "black boxes" in the Gail model
  3. Include feedback & interrelation among individuals
- Limit to selected important factors
- Population rather than individual model

IV. Presentation of the Model

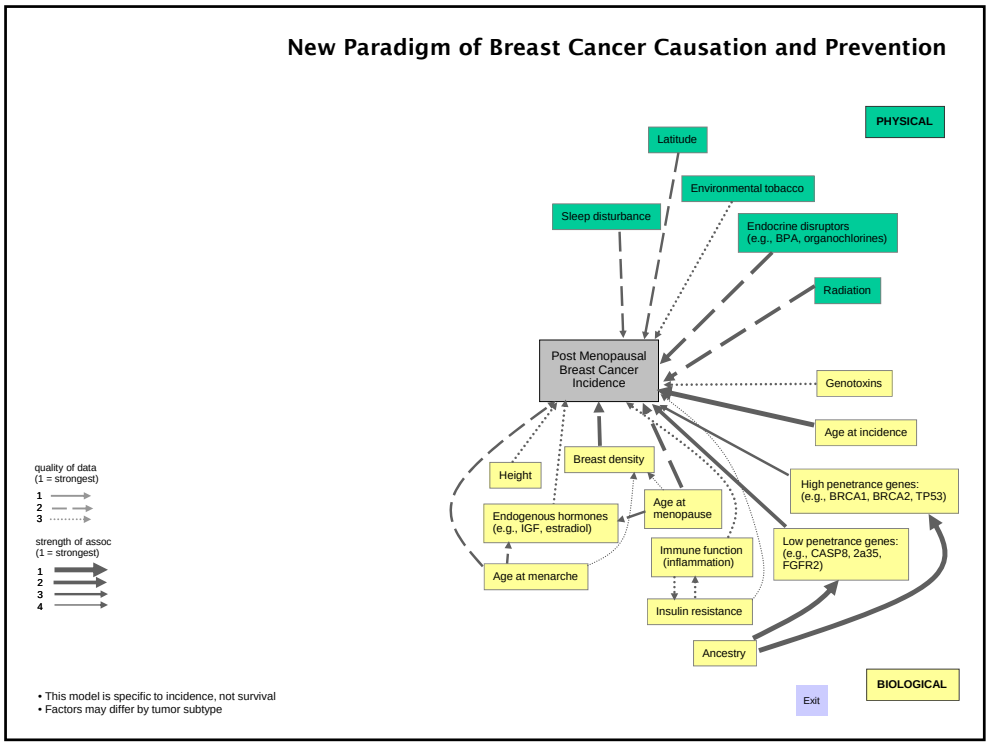
Obtained external comments on the overall model from potential model users.

We have developed both a print and online version.

New Paradigm of Breast Cancer Causation and Prevention



- This model is specific to incidence, not survival
- Factors may differ by tumor subtype


New Paradigm of Breast Cancer Causation and Prevention
PHYSICAL
Latitude
Environmental tobacco
Sleep disturbance
Endocrine disruptors (e.g., BPA, organochlorines)
Radiation
Post Menopausal Breast Cancer Incidence
Genotoxins
Age at incidence
Breast density
Height
High penetrance genes: (e.g., BRCA1, BRCA2, TP53)
Age at menopause
Endogenous hormones (e.g., IGF, estradiol)
Low penetrance genes: (e.g., CASP8, 2a35, FGFR2)
Immune function (inflammation)
Age at menarche
Insulin resistance
Ancestry
BIOLOGICAL
Exit
quality of data (1 = strongest)
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strength of assoc (1 = strongest)
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• This model is specific to incidence, not survival
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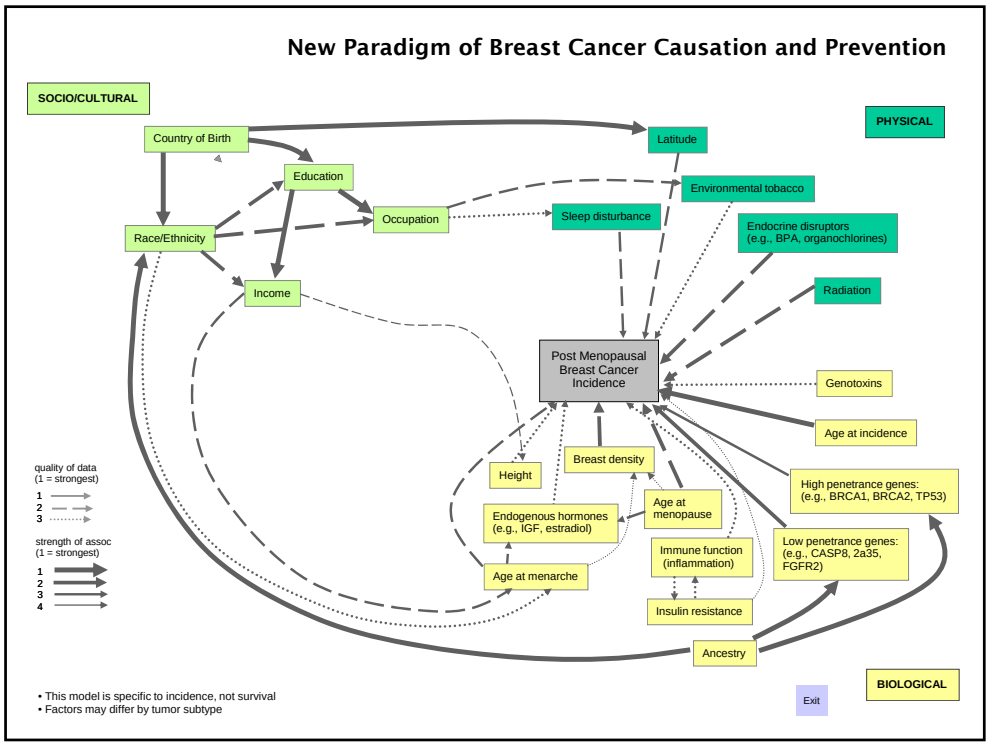
New Paradigm of Breast Cancer Causation and Prevention
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Country of Birth
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Income
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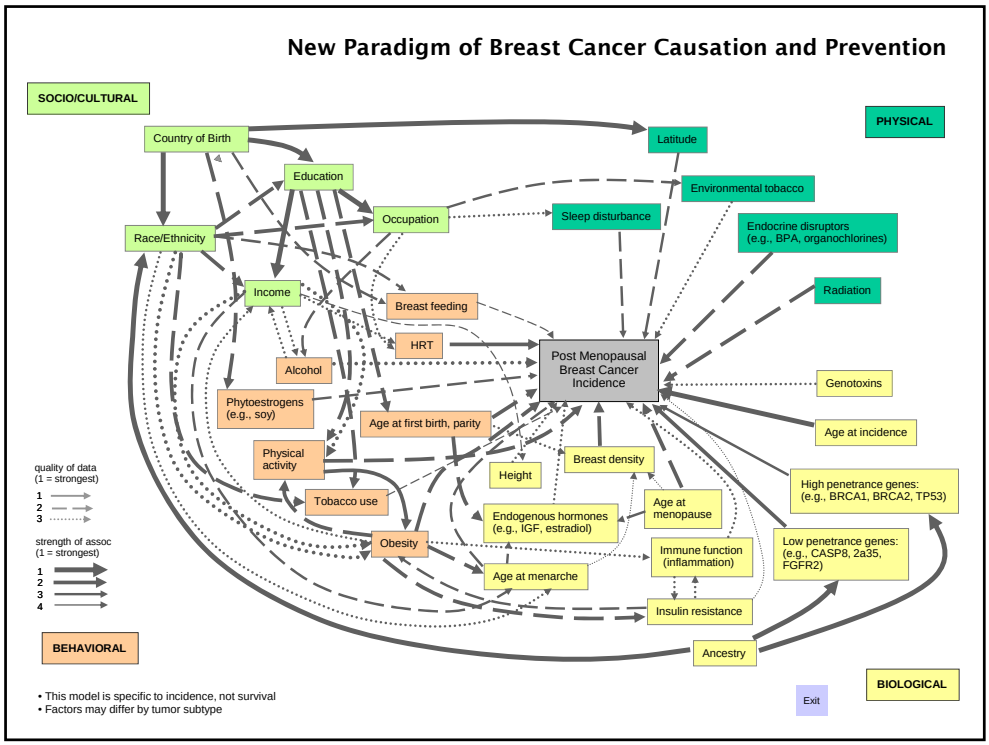
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HRT
Post Menopausal Breast Cancer Incidence
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Genotoxins
Phytoestrogens (e.g., soy)
Age at first birth, parity
Age at incidence
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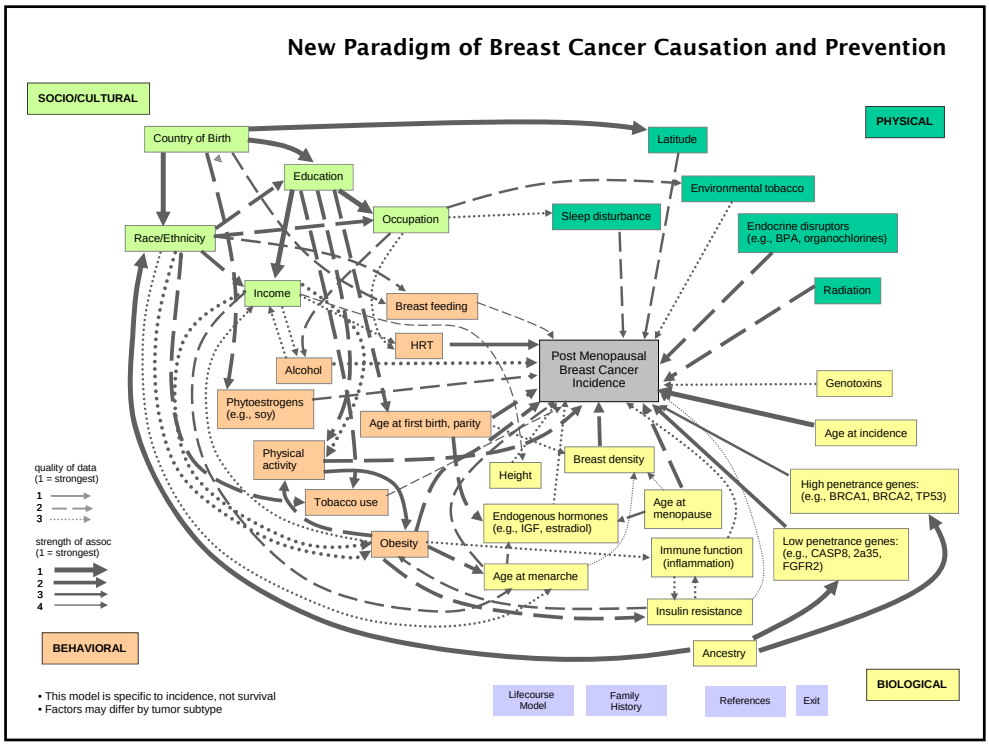
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Lifecourse Model
Family History
References
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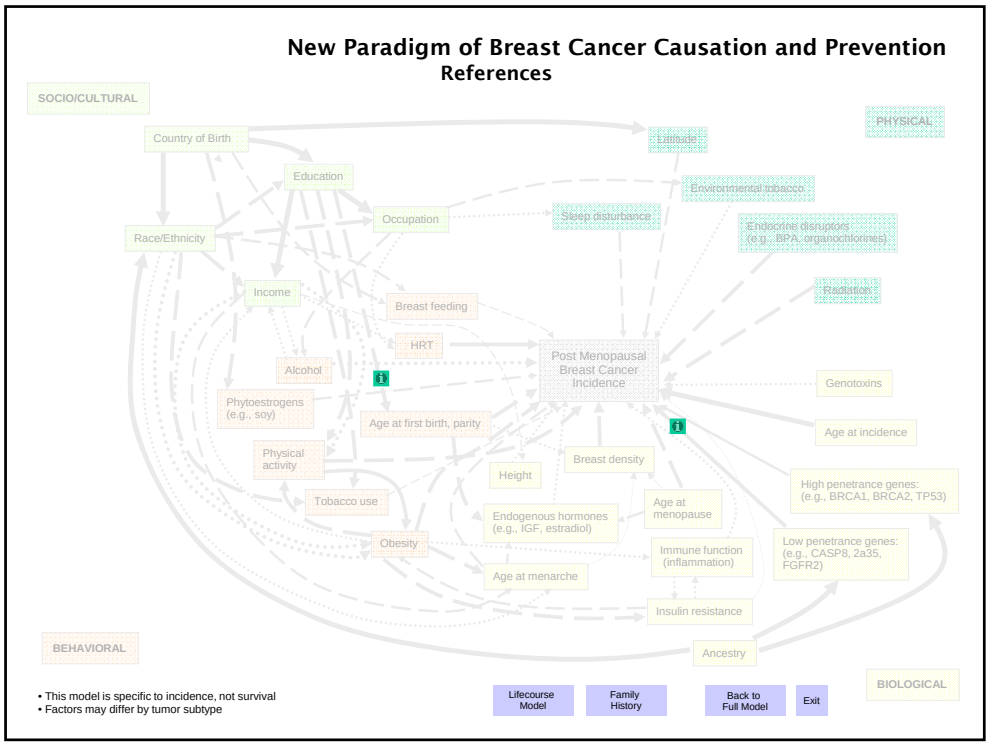
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Family History
Back to Full Model
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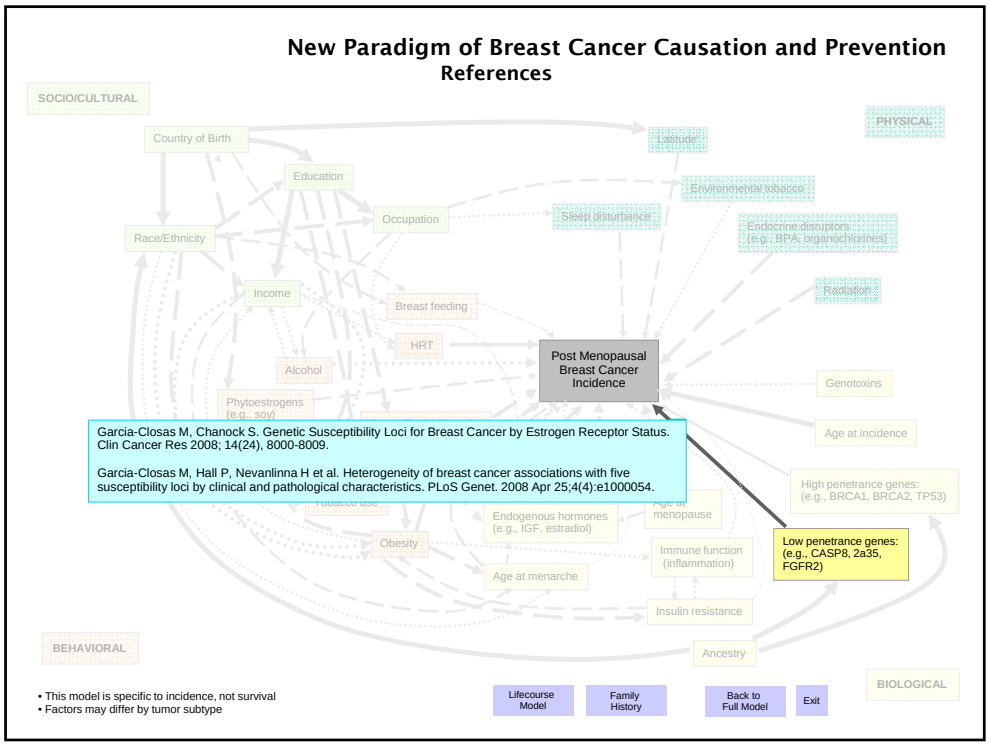
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Garcia-Closas M, Chanock S. Genetic Susceptibility Loci for Breast Cancer by Estrogen Receptor Status. Clin Cancer Res 2008; 14(24), 8000-8009.
Garcia-Closas M, Hall P, Nevanlinna H et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. PLoS Genet. 2008 Apr 25;4(4):e1000054.
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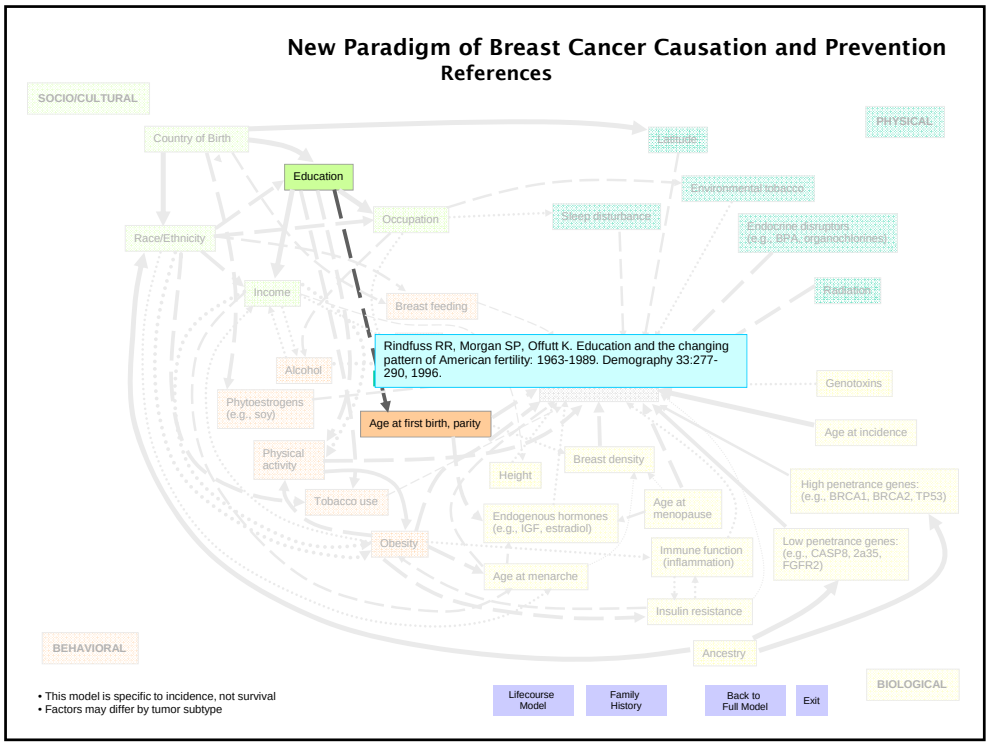
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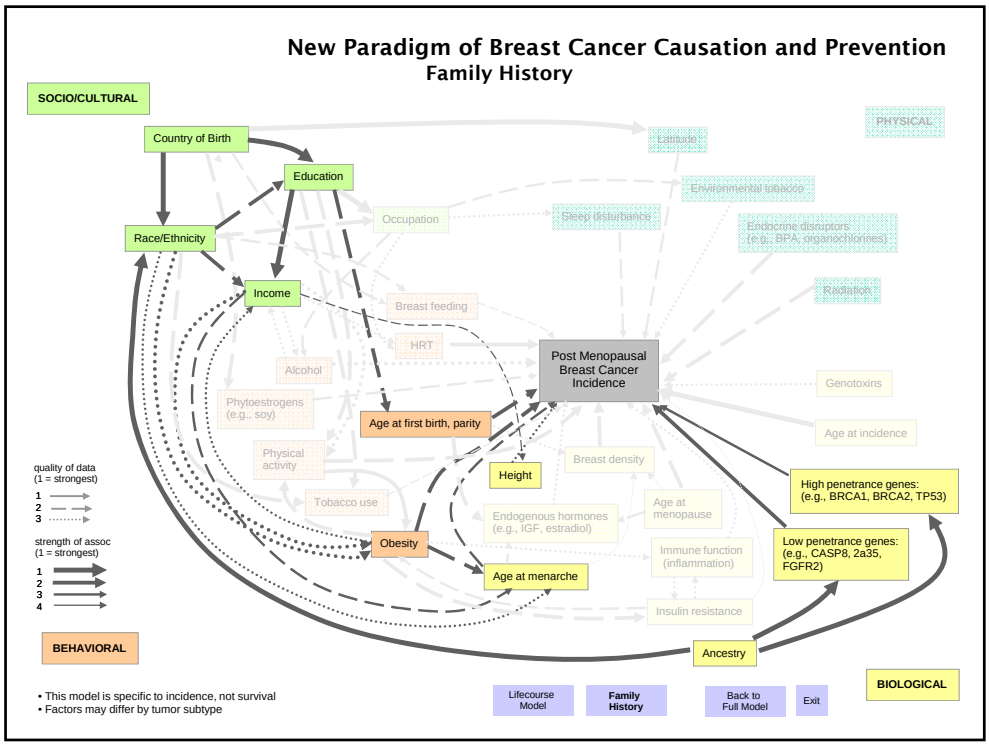
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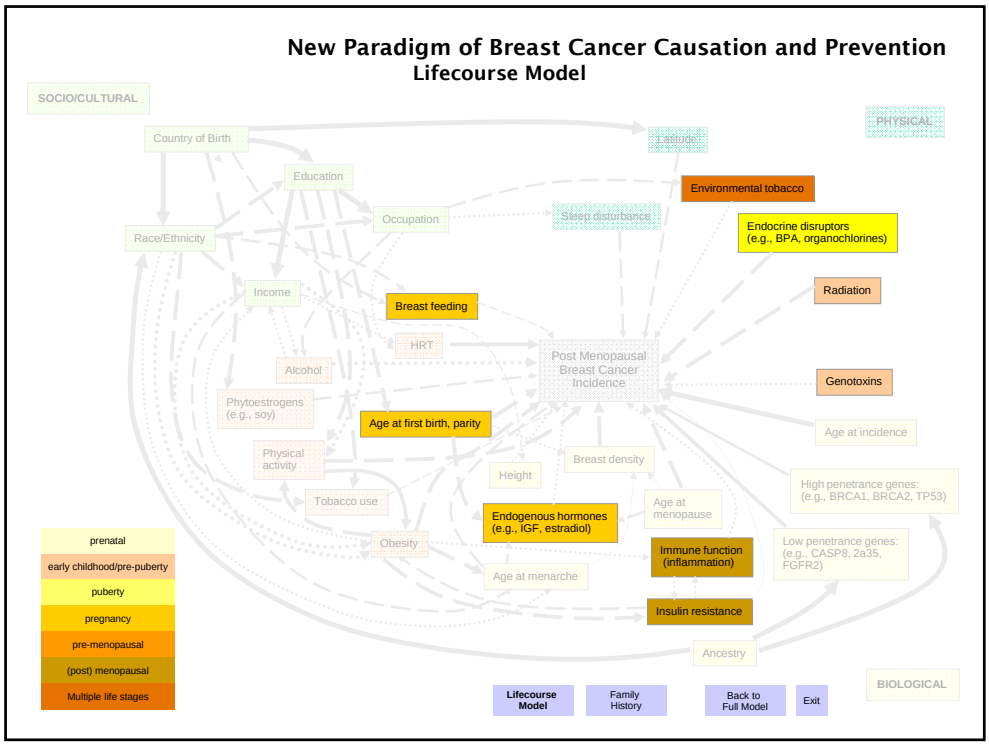

V. Results of Mathematical Model

Table 4. Rates of invasive postmenopausal breast cancer incidence with SDs by age category and race/ethnicity for risk factors in mathematical model for women ≥ 55 years of age and estimated impact of a change (degree change) at the population level of selected modifiable risk factors on incidence per 100,000 women by age at diagnosis and race/ethnic group, California, 2009

Predictive factor	Degree change	Total (White, Black, Latino)	SD	55–64 y	SD	65–74 y	SD	75+ y	SD	White	SD	Black	SD	Latina	SD
Total observed		379		314		451		423		430		379		254	
Total simulated		393.0	0.8	306.9	1.3	452.7	1.8	450.9	1.6	431.7	1.1	364.1	2.5	245.4	1.4
Excess BMI	50% decrease	384.4	0.8	300.4	1.2	442.6	1.7	440.9	1.5	423.3	1.0	349.4	2.4	238.3	1.4
	100% decrease	375.8	0.8	293.8	1.2	432.5	1.6	430.9	1.5	414.9	1.0	334.7	2.2	231.2	1.3
Alcohol consumption	25% decrease	391.9	0.8	305.9	1.3	451.4	1.7	449.7	1.6	430.5	1.0	363.5	2.5	244.3	1.4
	50% decrease	389.5	0.8	303.9	1.3	448.7	1.7	447.1	1.6	427.5	1.0	362.5	2.5	243.6	1.4
Tobacco use: % of	25% decrease	392.0	0.8	305.8	1.3	451.5	1.8	450.1	1.6	430.5	1.1	362.9	2.5	244.8	1.4
population	50% decrease	390.9	0.8	304.6	1.3	450.3	1.7	449.4	1.6	429.3	1.1	361.8	2.5	244.3	1.4
Age at menarche	1 y increase	377.4	0.8	294.3	1.2	434.5	1.7	433.5	1.5	415.3	1.0	346.9	2.4	233.5	1.4
	1.5 y increase	371.7	0.8	289.8	1.2	428.0	1.7	427.0	1.5	409.1	1.0	341.4	2.4	229.8	1.3
HT: % of population	50% decrease	288.3	0.7	225.2	1.1	332.1	1.6	330.7	1.4	316.7	1.0	267.1	2.3	180.0	1.3
	100% decrease	183.7	0.4	143.4	0.6	211.5	0.8	210.7	0.7	201.7	0.5	170.1	1.2	114.7	0.7

[1]Rates were simulated from 100,000 persons with 800 iterations, and were age adjusted to the 2,000 U.S. Standard Population (19 age groups - Census P25-1130: http://www.census.gov/prod/1/pop/p25-1130/p251130.pdf). The simulated incidence rates were from one parameter set using the average value in Table 3.

Results of Mathematical Model

Predictive Factor	Population	Rate (Age – adjusted)/ 100K
Total Stimulated Rate	All California women 19+	393
50% reduction in excess BMI	All California	384
100% reduction in excess BMI	All California	376
50% reduction in tobacco use	All California	288
50% reduction in alcohol use	All California	390
50% reduction in HT use	All California	288
1 yr decrease in menarache	All California	327
Total rate	75+ women	451
Total rate	White women	432
Total rate	Black	364
Total rate	Asian	245

For More Details…

Hiatt RA, Porco T, Liu F, Balke K, Balmain A, Barlow J, Braithwaite D, Diez-Roux A, Joseph G, Kushi L, Moasser M, Werb Z, Windham G, Rehkopf D. **A multi-level complex systems model of breast cancer incidence.** *Cancer Epidemiol Biomarkers Prev* 2014 Oct;23(10):2078-2092. PMID: 25017248.

Online Version on CBCRP Website

http://www.cbcrp.org/research-topics/causal-model.html

VI. Next Phase – Paradigm II

New 2-year grant from CBCRP to expand model to:

- Premenopausal women
- Include interactions – agent based model
- Integrate animal study results
- New expert team

Expert Committee for Paradigm II

Janice Barlow, RN – community advocate
Krisida Nishoka, LLD – breast cancer advocate
Travis Porco, PhD - mathematical modeler
Lee Worden, PhD – programmer/modeler
Robert Hiatt, MD, PhD – cancer epidemiologist
David Rehkopf, ScD - social epidemiologist
John Witte, PhD – genetic epidemiologist
Sue Fenton, PhD - environmental health biologist
Martyn Smith, PhD – toxicologist/molecular epidemiologist
Mellissa Troester, PhD – molecular epidemiologist/breast cancer
Sarah Gehlert, PhD – anthropologist/transdisciplinary science
Ross Hammond, PhD – complex systems modeler
George Kaplan, PhD – social epidemiologist
Tom McKone, PhD – environmental science/toxicologist
Natalie Engmann, MPH – epidemiology graduate student

Agent Based Model

- Woman is agent
- Population frame is California
- Lifecourse approach
- Building a simple model based on known risk factors and biology
- Key questions relate to:
  - Obesity
  - Environmental chemicals
  - Disparities

Finis