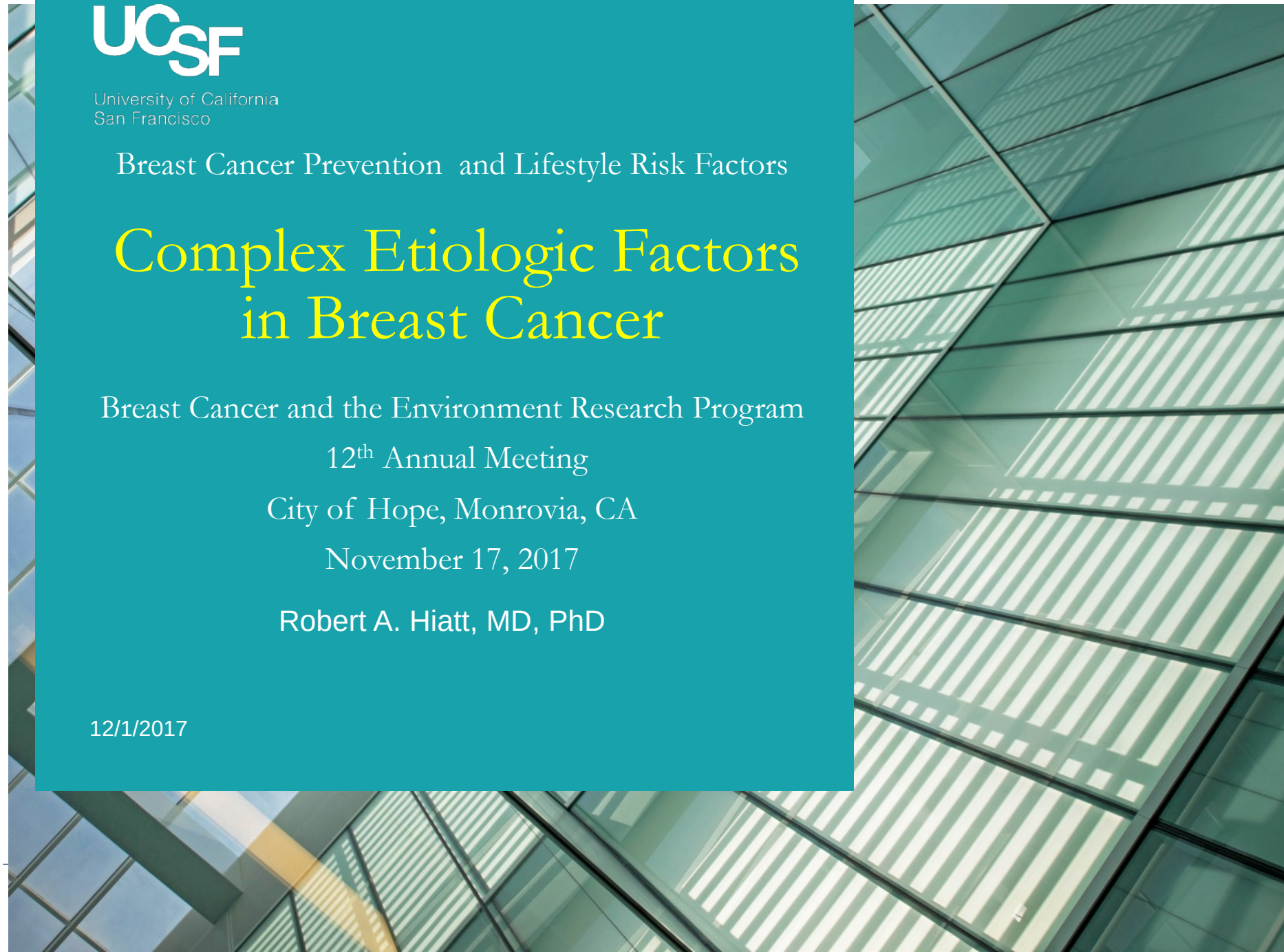


University of California
San Francisco

Breast Cancer Prevention and Lifestyle Risk Factors

Complex Etiologic Factors in Breast Cancer

Breast Cancer and the Environment Research Program

12th Annual Meeting

City of Hope, Monrovia, CA

November 17, 2017

Robert A. Hiatt, MD, PhD

12/1/2017

Motivation

- What is THE cause of breast cancer?
- A complex disease – multiple levels of determinants
- Multiple disciplines – sometimes siloed
- Lifecourse approach.
- “A New Paradigm for Breast Cancer Causation and Prevention” – California Breast Cancer Research Program

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

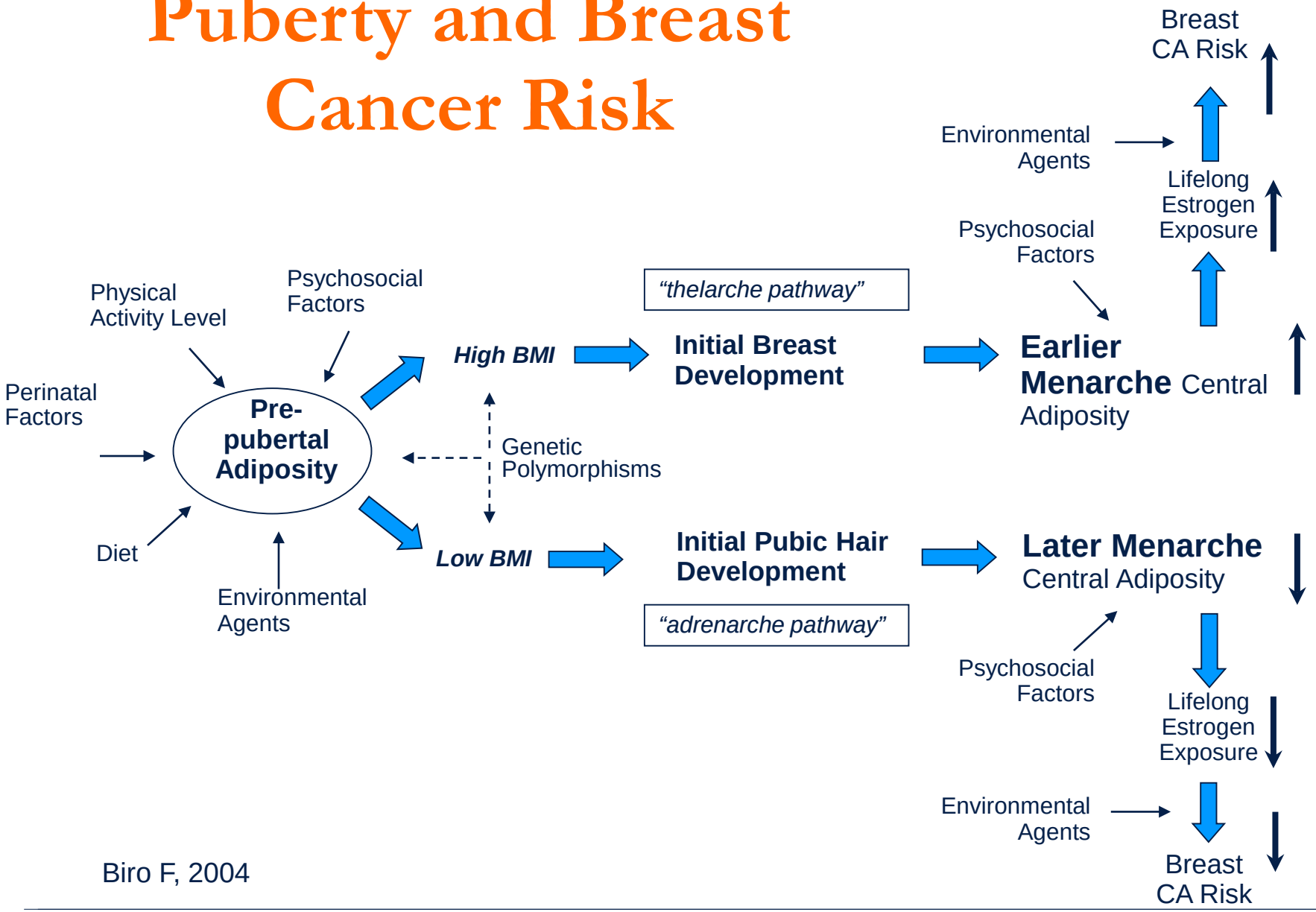
II. Background

- Lots of ways to create and use “models”:
- Different types of models:
  - Prediction models
  - Simulation models
  - Complex systems models
- Models can be:
  - Static or Dynamic
  - Stochastic or Deterministic
  - Time is Discrete or Continuous

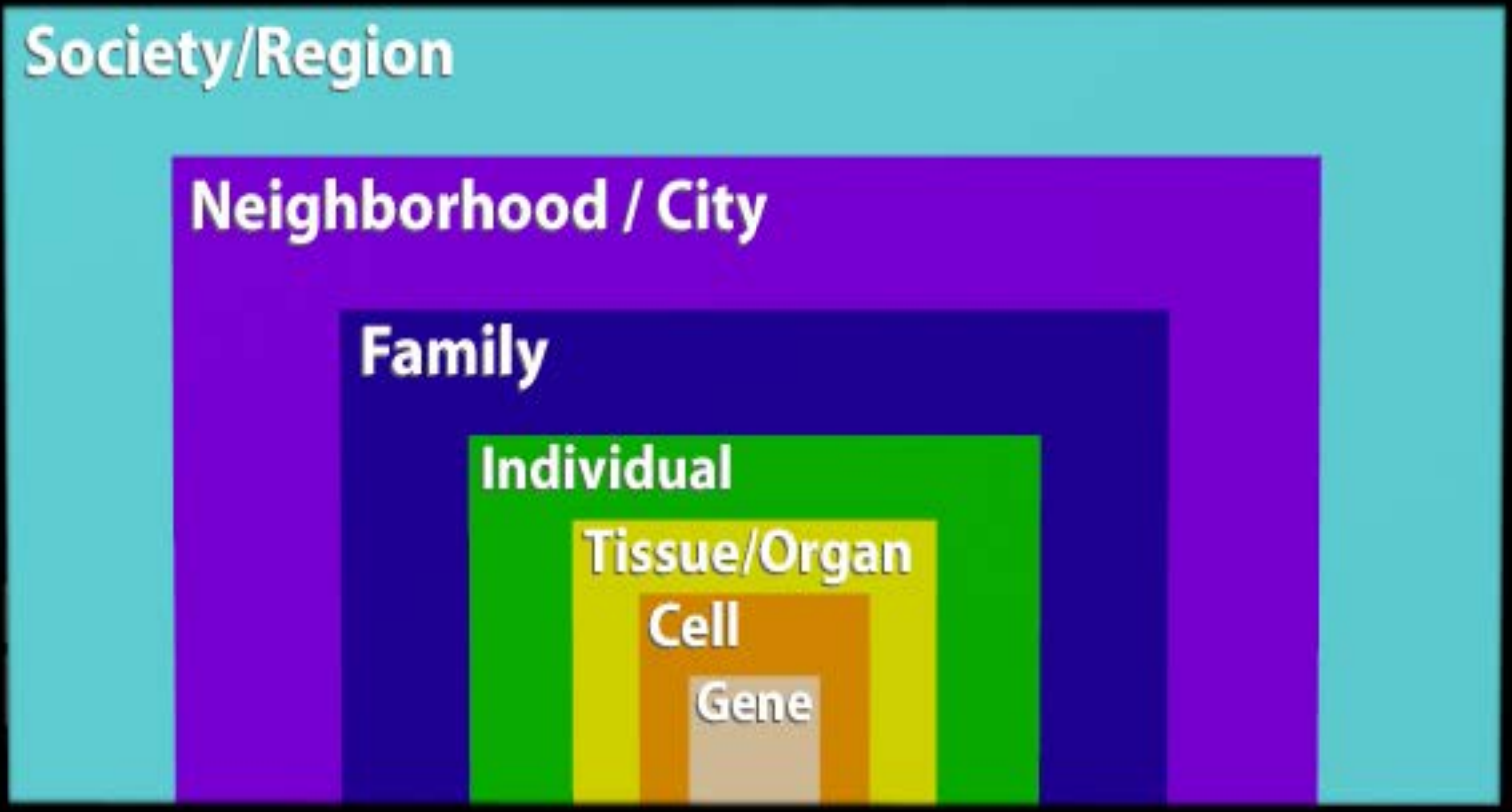
II. Background (2)

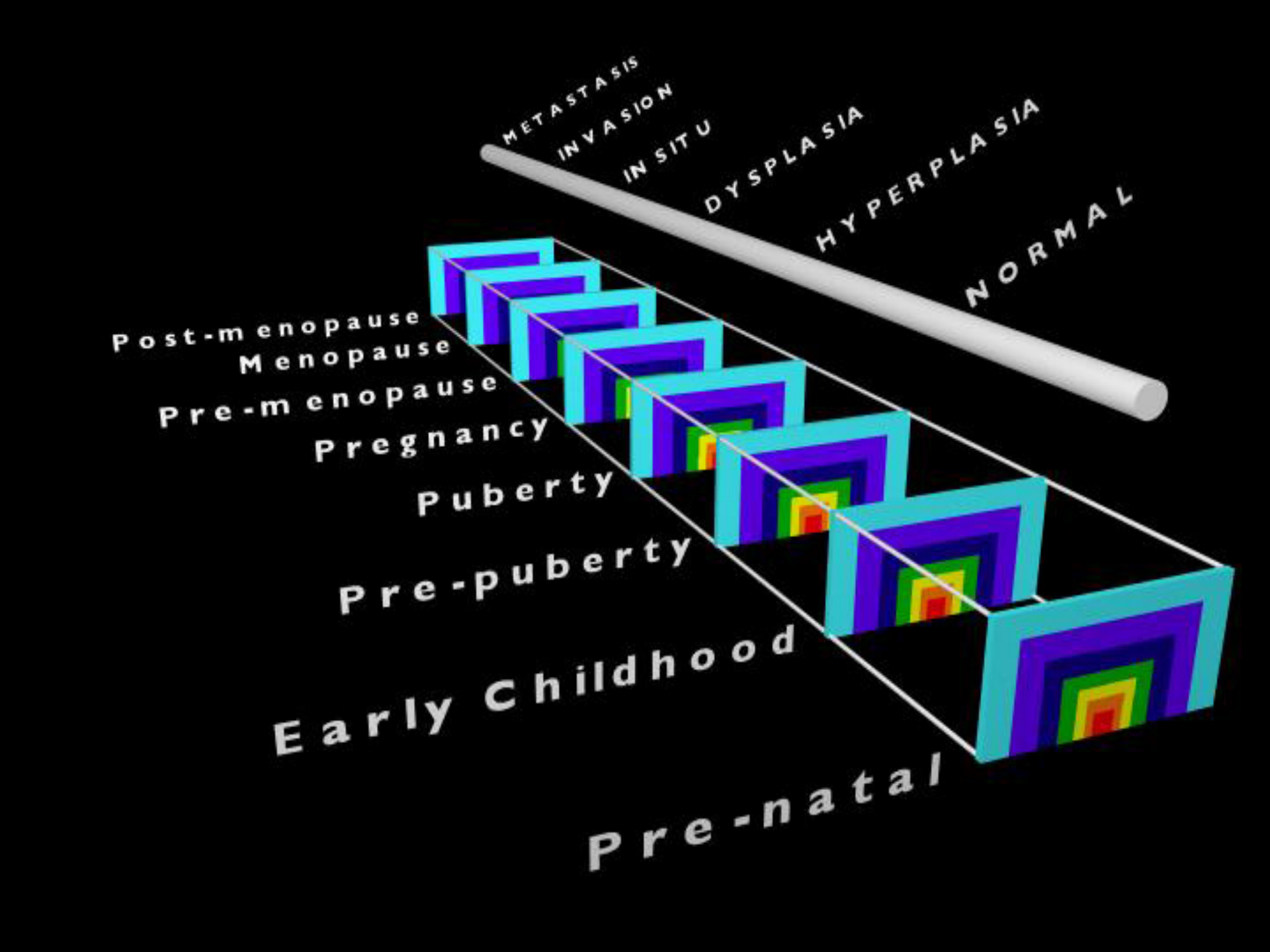
- Models can:
- Illustrate pathways
- Illustrate relationships and networks
- Identify gaps in knowledge
- Be useful in constructing causal relationships when no single database is available or possible to collect.
- But…
- They are only abstractions of reality

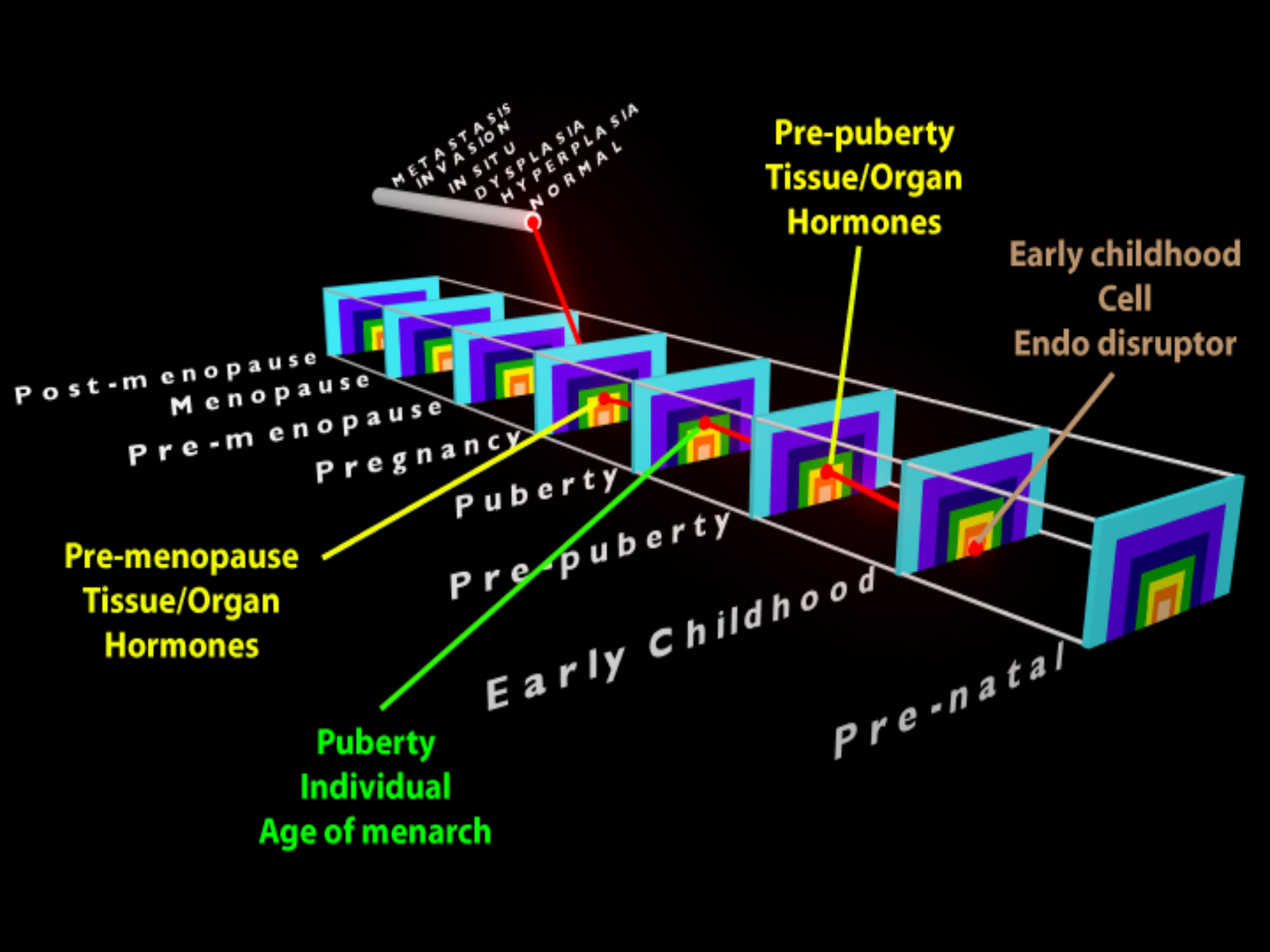
Puberty and Breast Cancer Risk



Biro F, 2004


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


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


METASTASIS
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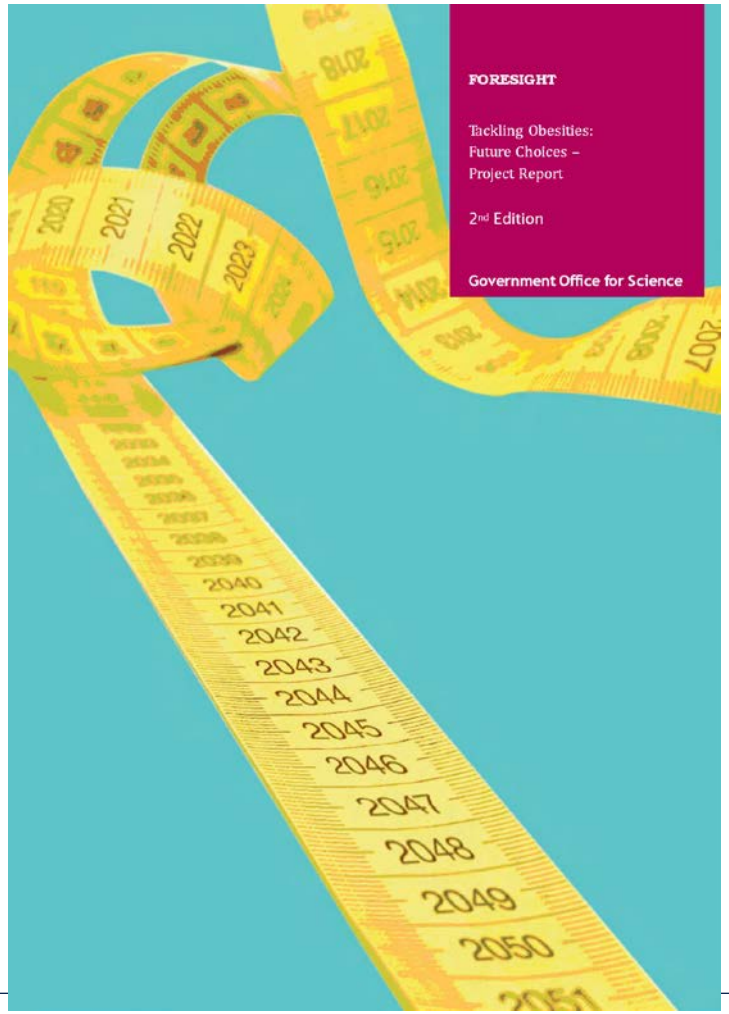
Hormones
Early childhood
Cell
Endo disruptor
Post-menopause
Menopause
Pre-menopause
Pregnancy
Puberty
Pre-puberty
Early Childhood
Pre-natal
Pre-menopause
Tissue/Organ
Hormones
Puberty
Individual
Age of menarch

Foresight UK



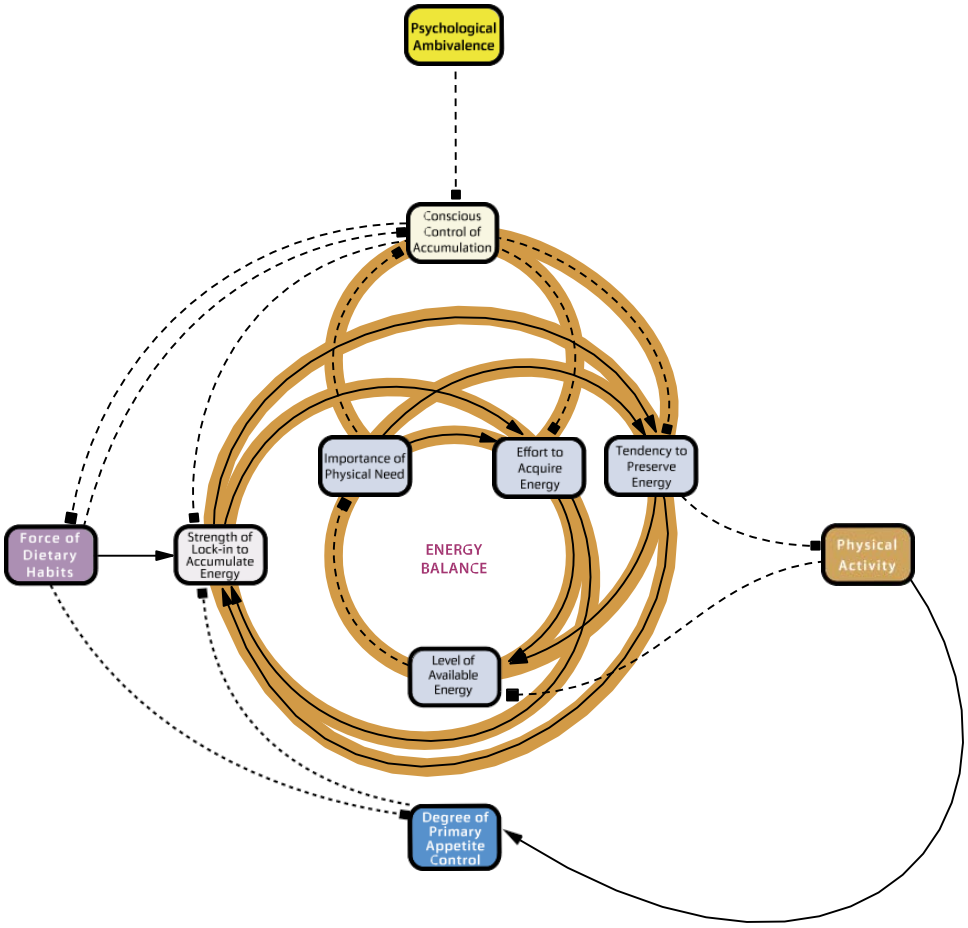

Psychological Ambivalence
Conscious Control of Accumulation
Importance of Physical Need
Effort to Acquire Energy
Tendency to Preserve Energy
Force of Dietary Habits
Strength of Lock-in to Accumulate Energy
ENERGY BALANCE
Physical Activity
Level of Available Energy
Degree of Primary Appetite Control

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. Brought together committee of experts on breast cancer and complex systems modeling
2. Three meetings over the course of 1 year
3. Iterative development of, first, a conceptual model of breast cancer causes, and then a quantitative model
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, which is useful in individual prediction of risk of breast cancer.

Rather, it focuses on understanding causation at the population level.

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

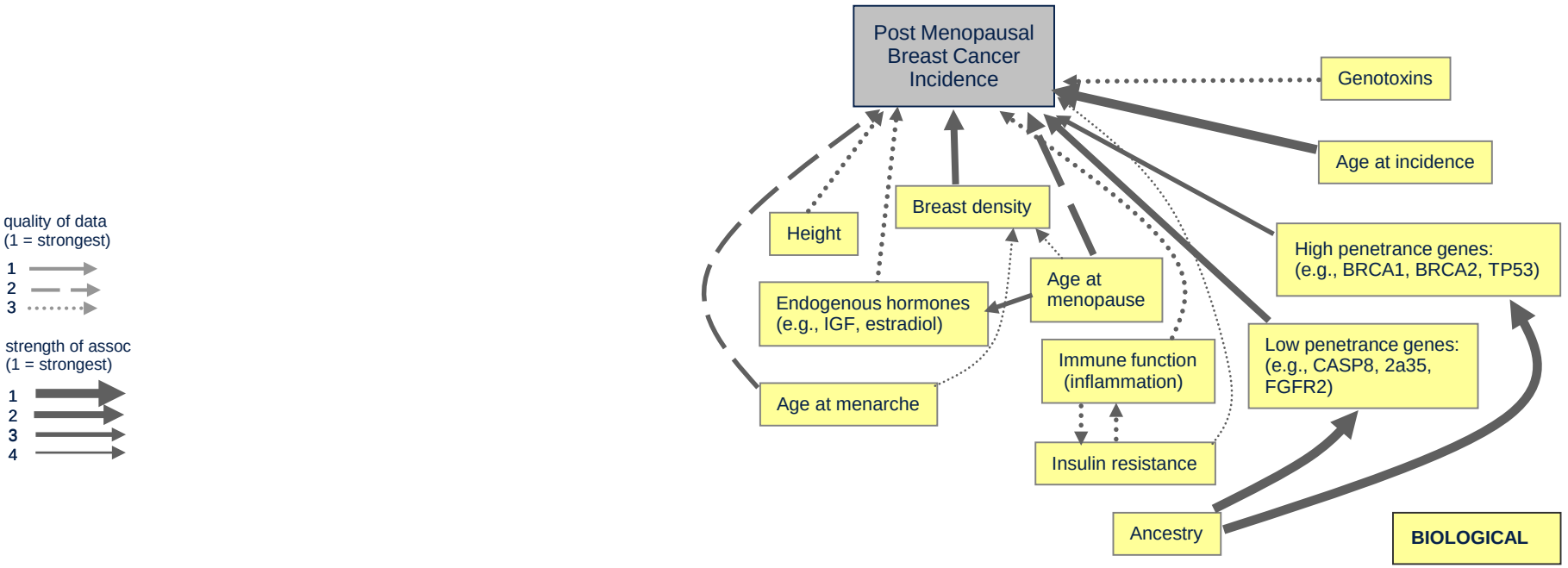
Sources of Data for Model

- California Census
- California Cancer Registry
- California Health Interview Survey
- NHANES
- Reviews of the literature

IV. Presentation of the Model

- Obtained external comments on the conceptual model from potential model users.
- We 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

Exit

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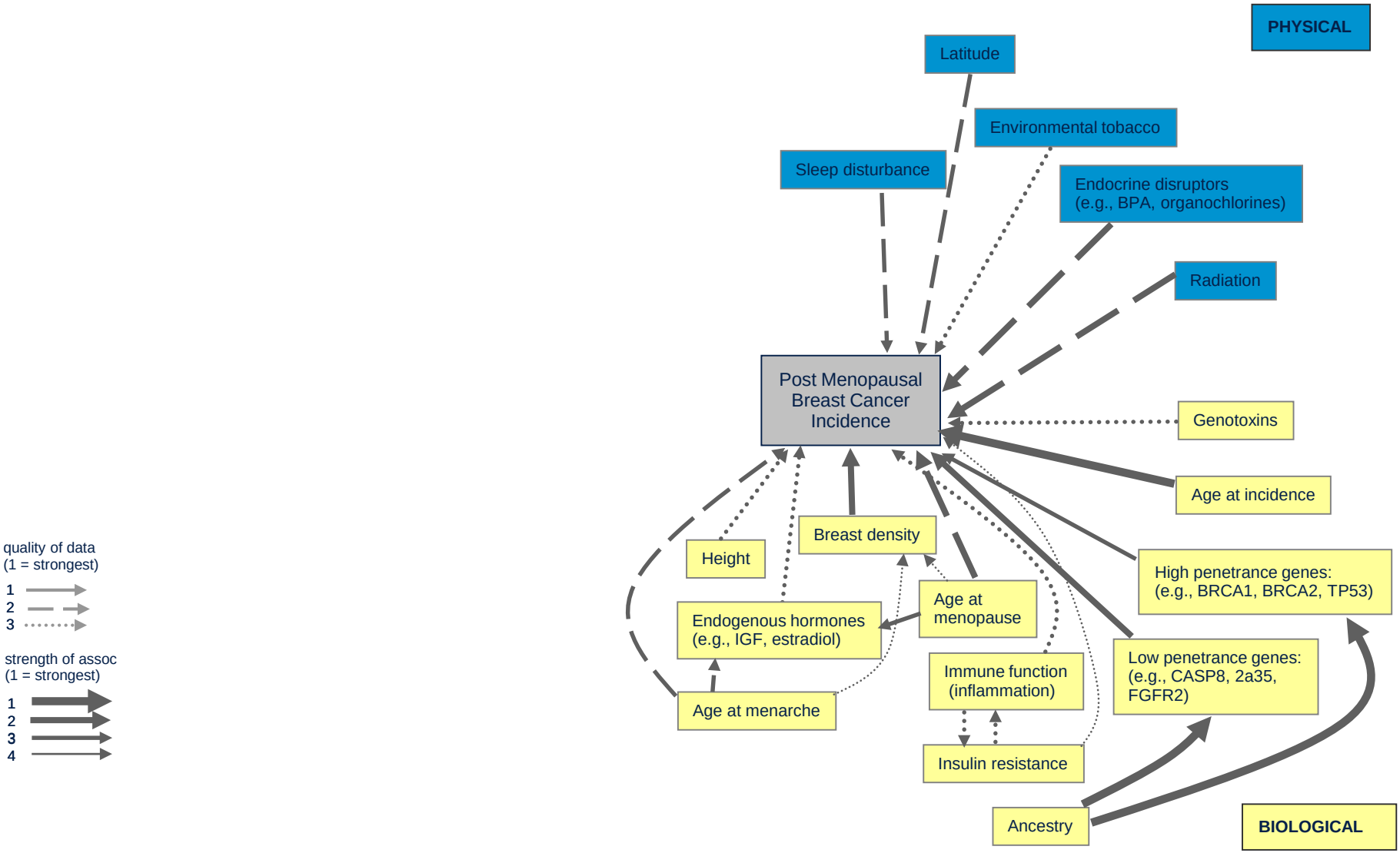
New Paradigm of Breast Cancer Causation and Prevention



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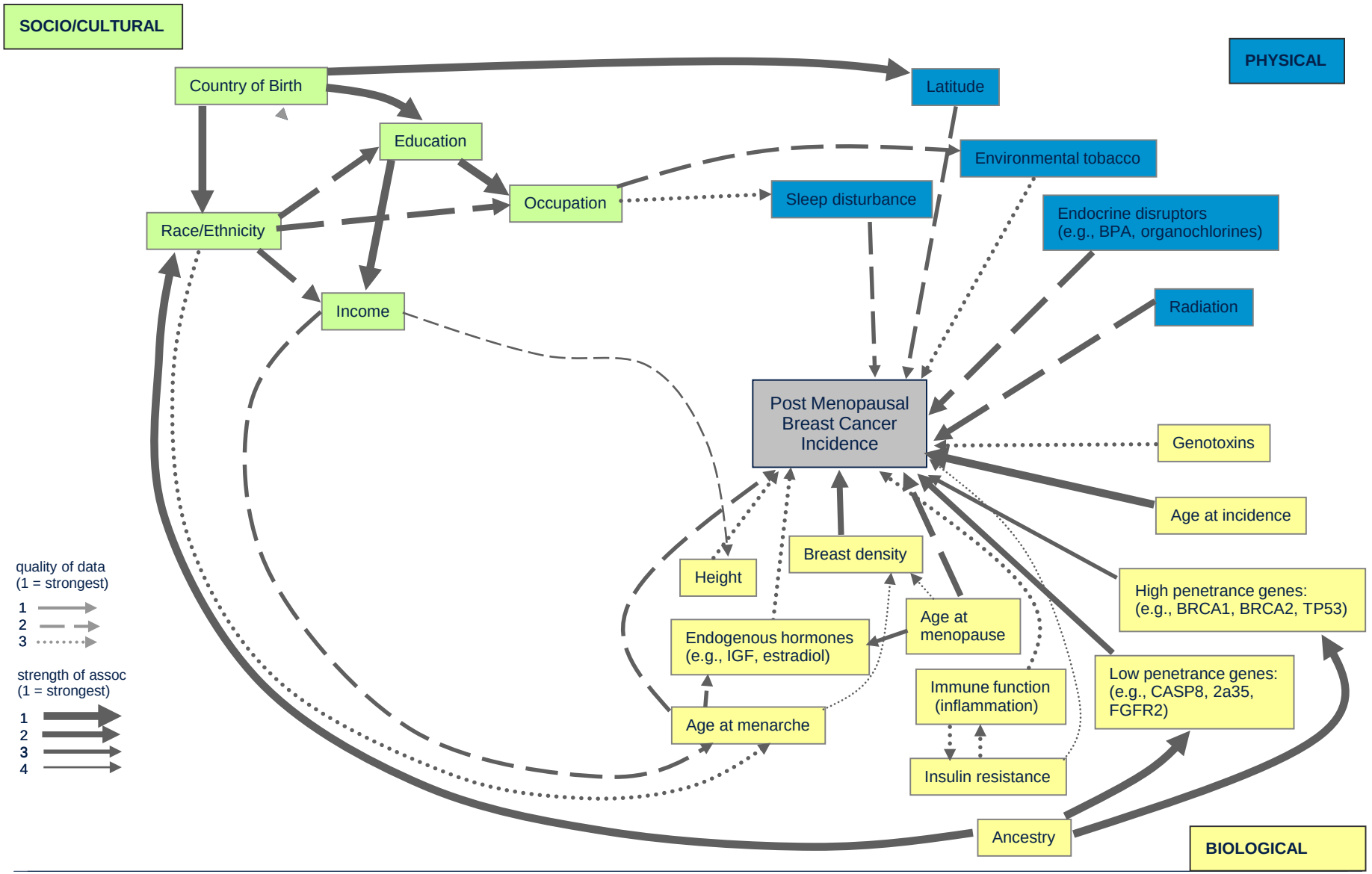
New Paradigm of Breast Cancer Causation and Prevention



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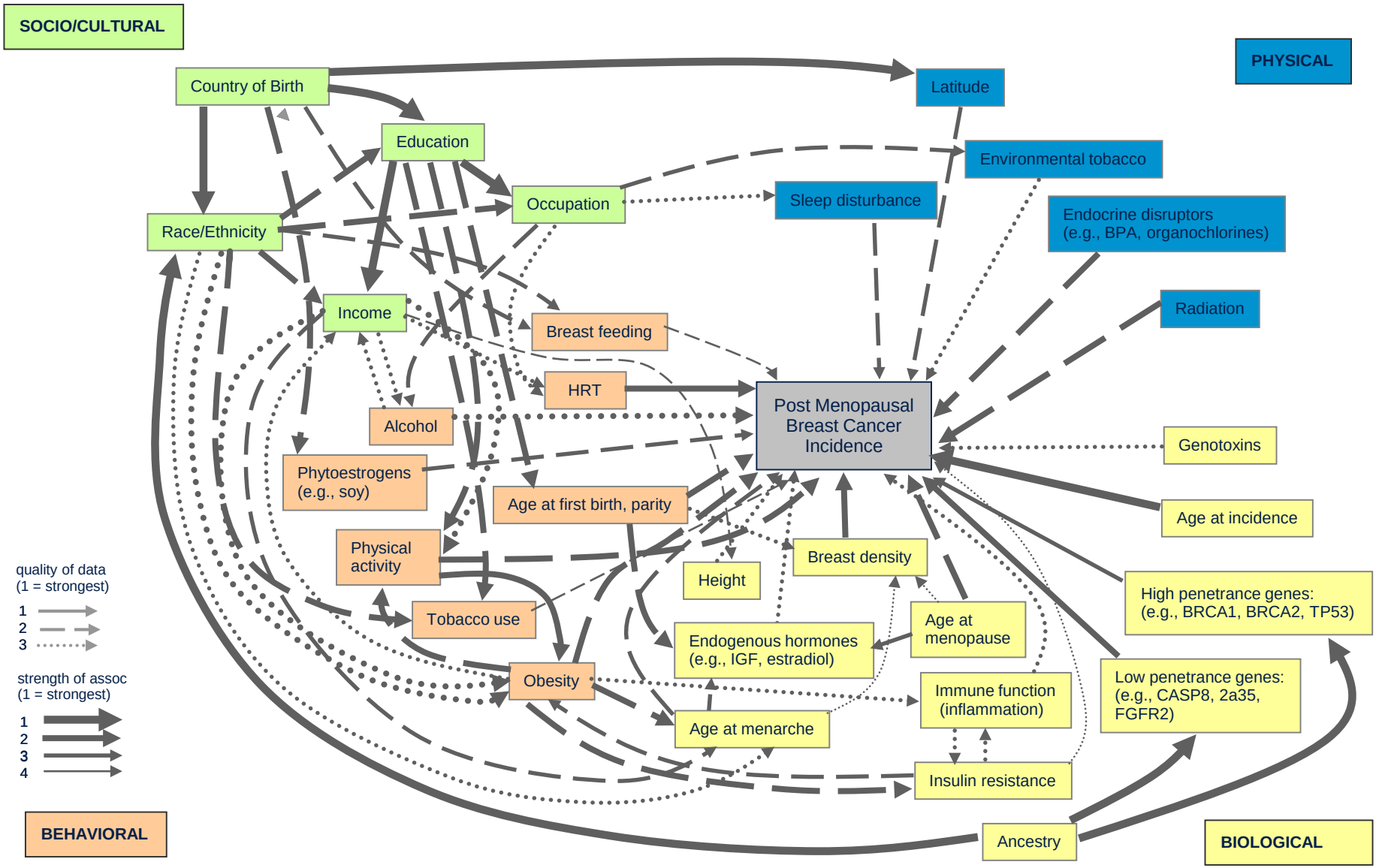
New Paradigm of Breast Cancer Causation and Prevention



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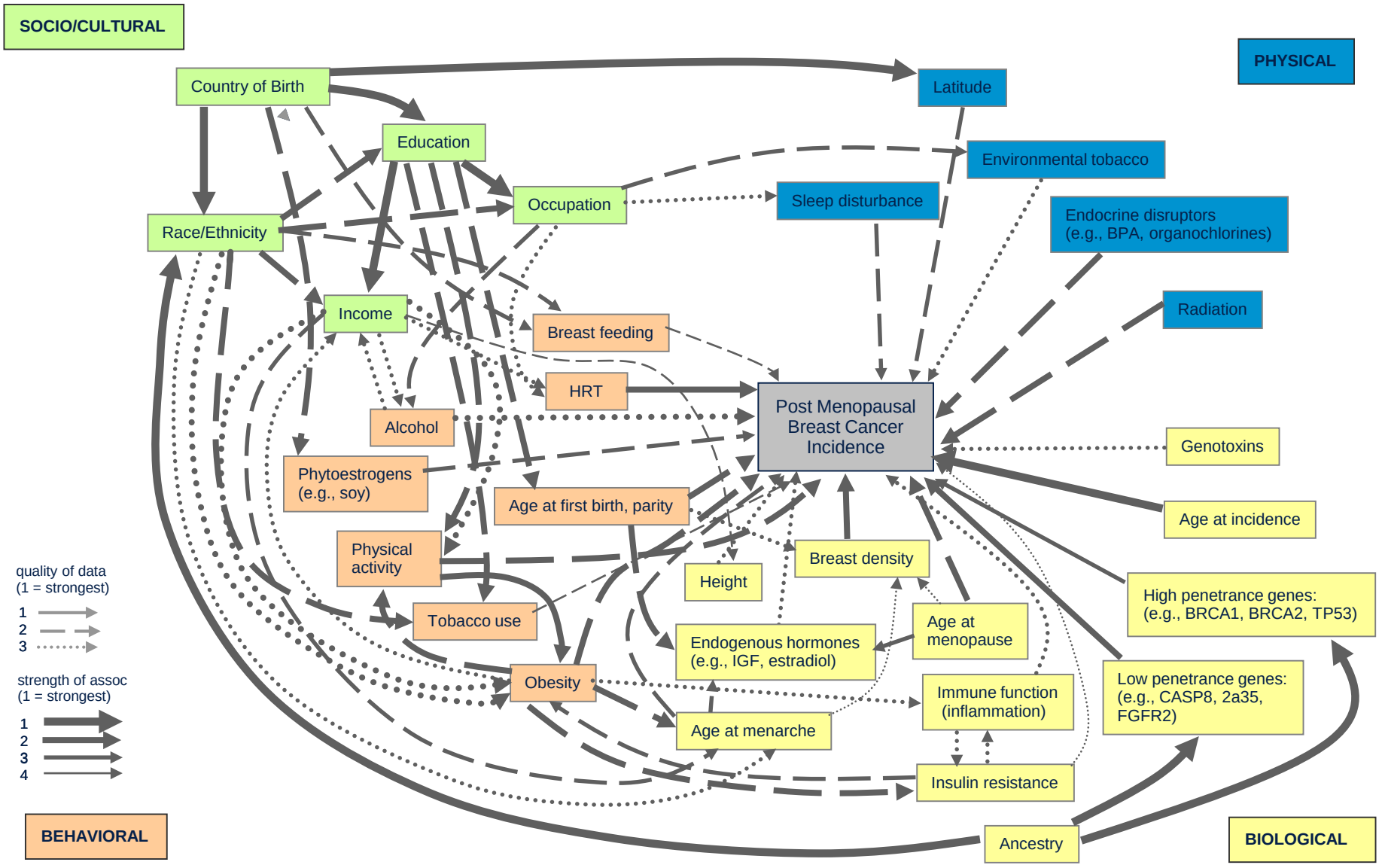
New Paradigm of Breast Cancer Causation and Prevention



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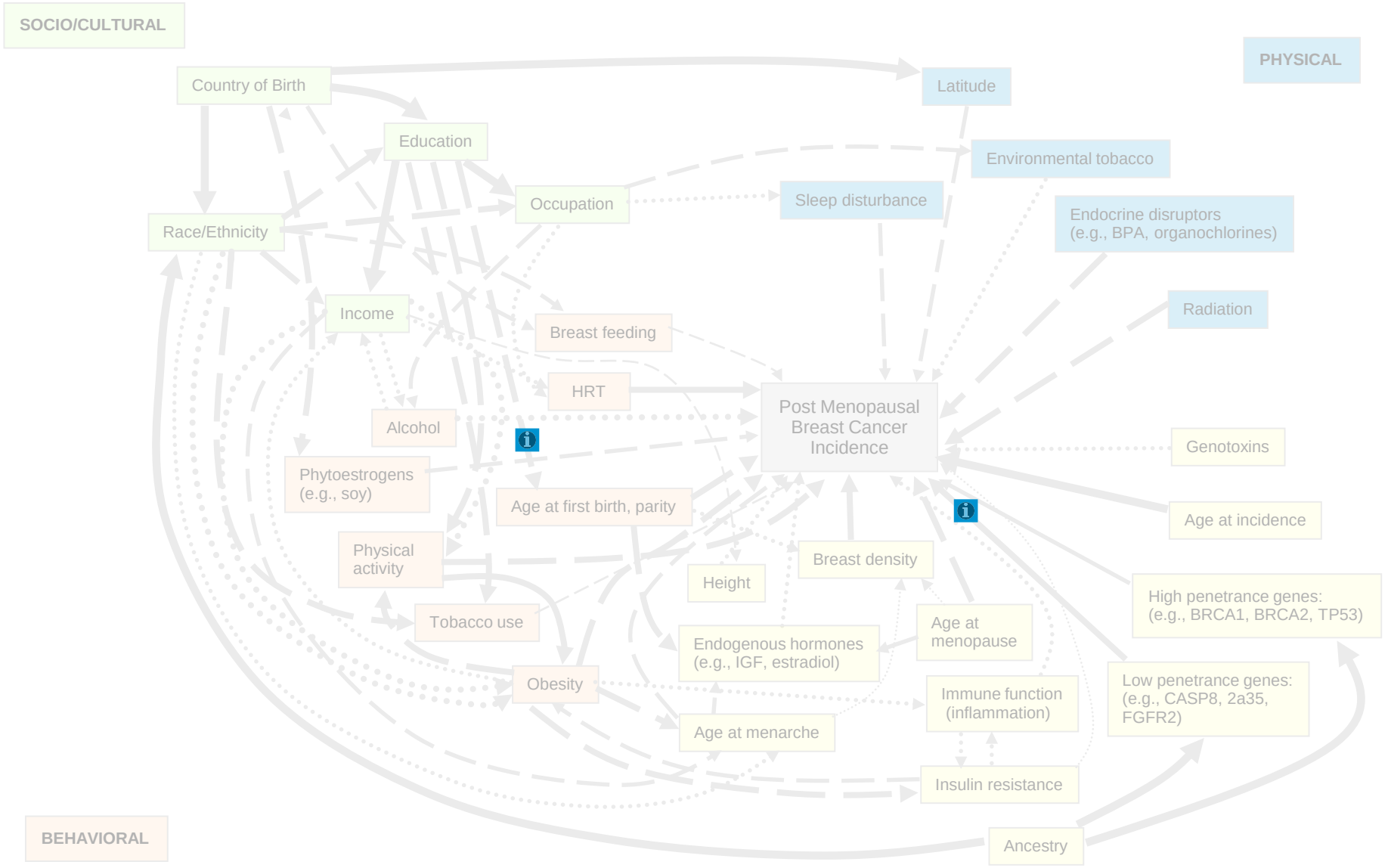
New Paradigm of Breast Cancer Causation and Prevention

References



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Lifecourse Model | Family History | Back to Full Model | Exit

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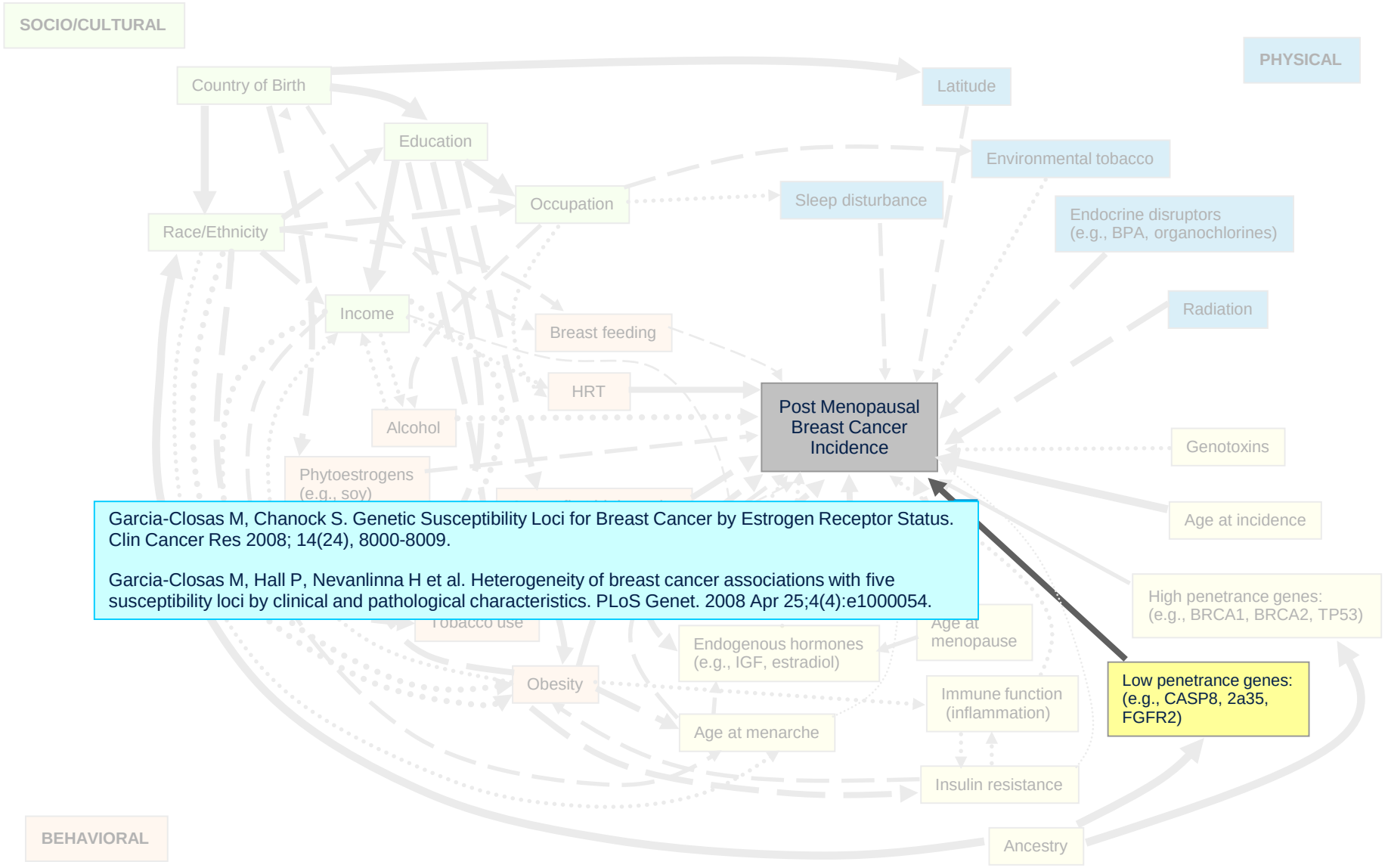
New Paradigm of Breast Cancer Causation and Prevention

References



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.

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

Lifecourse Model | Family History | Back to Full Model | Exit

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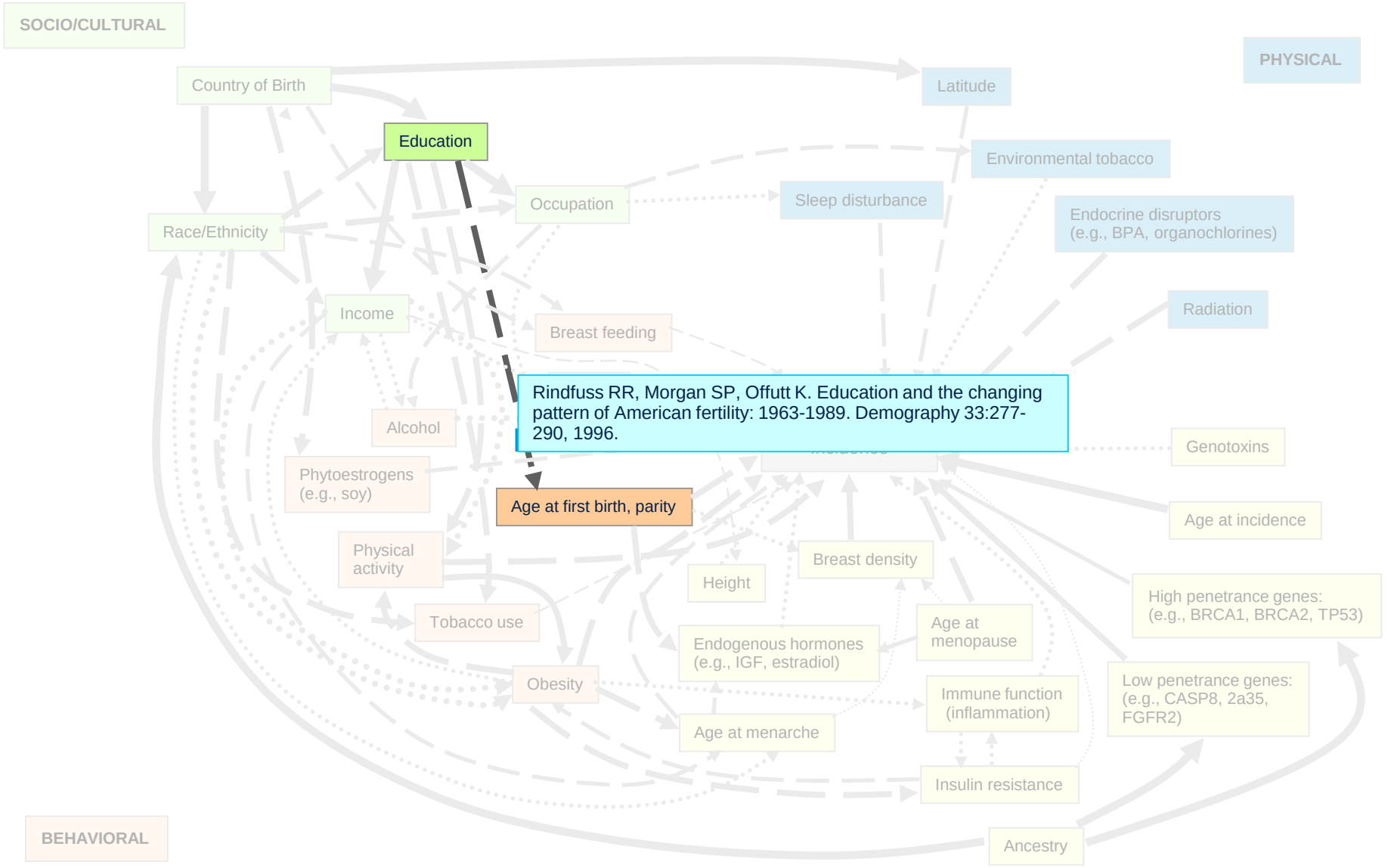
New Paradigm of Breast Cancer Causation and Prevention

References



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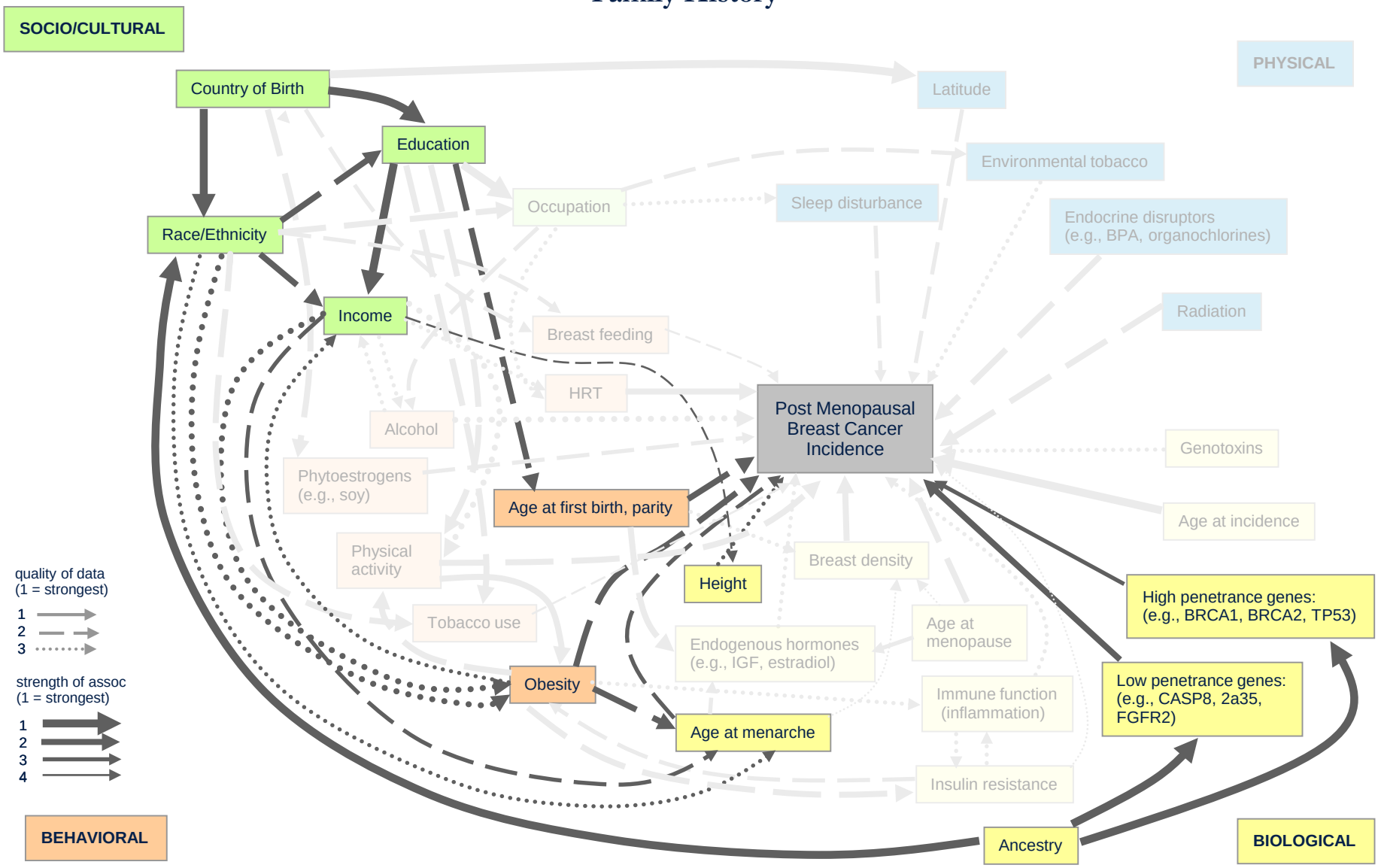
New Paradigm of Breast Cancer Causation and Prevention

Family History



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- Factors may differ by tumor subtype

Lifecourse Model | **Family History** | Back to Full Model | Exit

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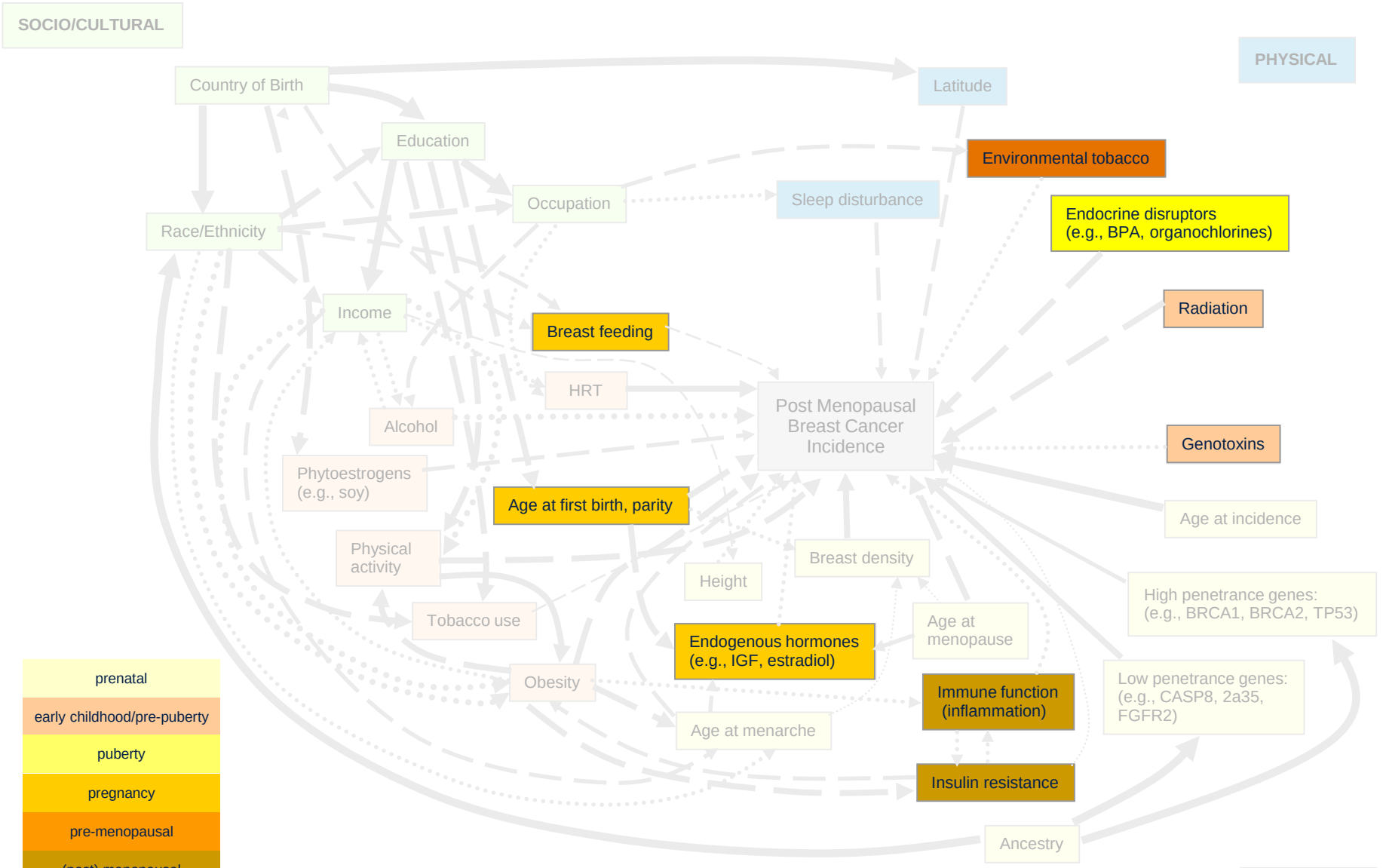
New Paradigm of Breast Cancer Causation and Prevention

Lifecourse Model



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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 population	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
	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.

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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	391
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;23:2078-2092. PMID: 25017248.

Online Version on CBCRP Website

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

A New Paradigm for Breast Cancer Causation and Prevention

“Paradigm II”

Paradigm II

2-year grant from CBCRP to expand model to:

- Update literature
- 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

Specific Aims

- 1. To enhance the current Conceptual Model with new up-to-date evidence acquired through a process of systematic review and a transparently clear process of selection for the variables included in the model.

- 2. To add premenopausal breast cancer to the current Conceptual Model that took only postmenopausal breast cancer as its outcome.

- 3. Develop a systematic process for incorporating factors demonstrated to contribute to mammary cancer in animal models into both the Conceptual and Mathematical Models.

- 4. Upon completion of Specific Aims 1-3, make the Paradigm model accessible to the public through a web-based application.

Agent Based Model

- Key questions to focus the model:
  - Obesity – What would be the impact on breast cancer incidence of a change in BMI at different stages of life (e.g. pre-puberty)?
  - Environmental chemicals – What is the potential impact of environmental chemical (e.g., endocrine disrupting chemicals) exposures on breast cancer incidence?
  - Disparities – What is the impact of changes in SES factors (e.g., income, wealth) on breast cancer incidence?

Model Development

- Goal is not to understand carcinogenesis, but the effects of external factors and how they map to biology.
- Model based on series of tissue transformations over the life course
- Rates of transformation, cell division and cell death/removal affected by individual characteristics

Model Development (2)

- Easy to make model more complex but we value staying “faithful to the data” which reduces complexity
- What are environmental/diet effect on tissue removal and at which times?
- Biology of aging and puberty needs to effect cell division rates and environmental exposures should effect transformation rates.

Model Development (3)

- Data on screening effects.
- Results of Fenton/EPA systematic review of chemical effects on breast.
- Social policy can effect traditionally non-modifiable factors (e.g., income)
- Causes of obesity may also independently cause cancer – how to disentangle
- Social networks and interactions – mechanism not clear- data on networks in short supply

Central Research Questions

- The effects of social policy on increasing or decreasing black-white disparities in breast cancer
- Effects of changes in obesity at different stages of life on breast cancer
- Effect of exposures to environmental toxins at different stages of life on breast cancer

- *All in progress…*

Finis