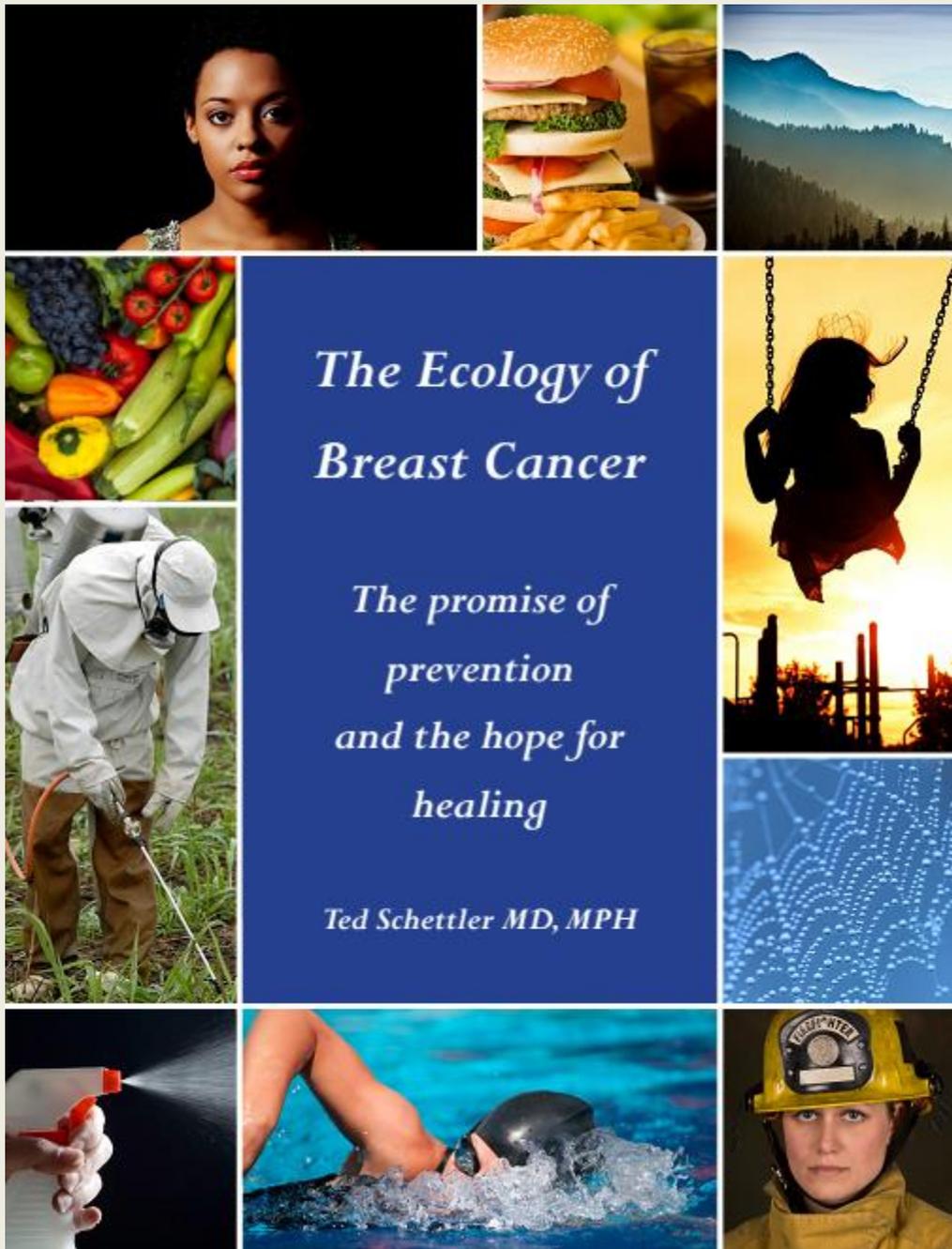


# The Ecology of Breast Cancer: Opportunities for Prevention

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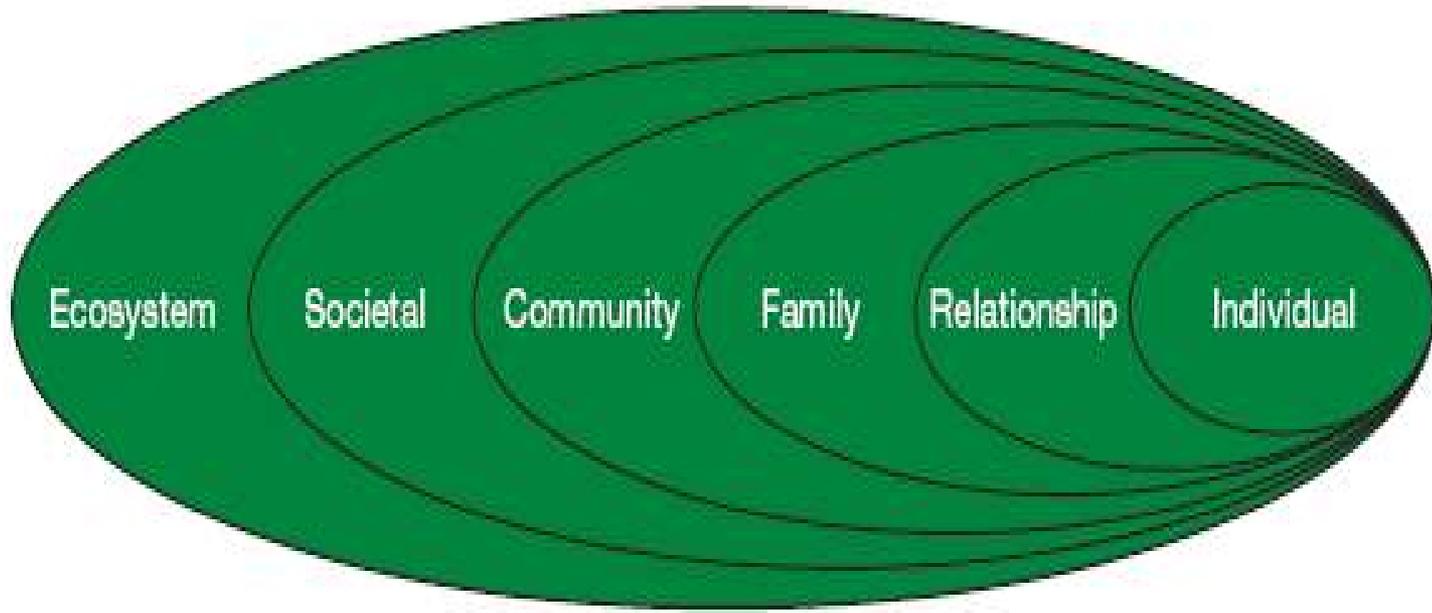
# Outline

- An ecologic framework for breast cancer
- Looking within the complexity
  - Generally-accepted risk factors
  - Diet, nutrition
  - Exercise, physical activity
  - Environmental chemicals
  - Vitamin D, the electromagnetic spectrum
  - Stress
- Putting it together: Designing for prevention

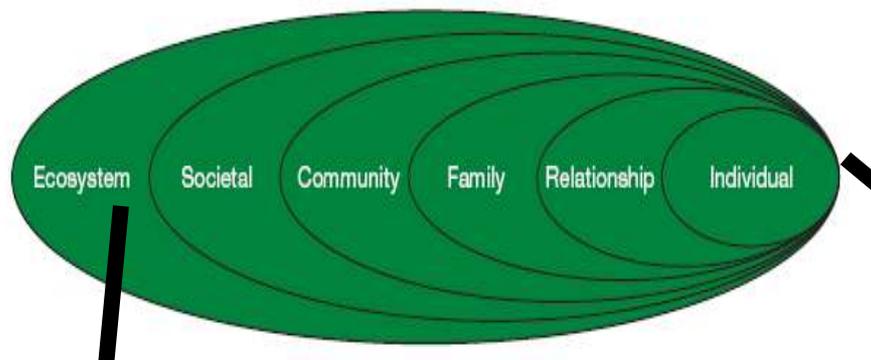
# Why an ecologic framework?

- Breast cancer is a systems problem requiring a systems response
- Multi-dimensional; multi-factorial
- Interactions and relationships are important
- History and time
  - What explains changing breast cancer incidence and patterns? Migration studies.
  - Early life events can influence vulnerability or resilience
- Lessons from the ecological sciences—shaping the terrain; altering system conditions

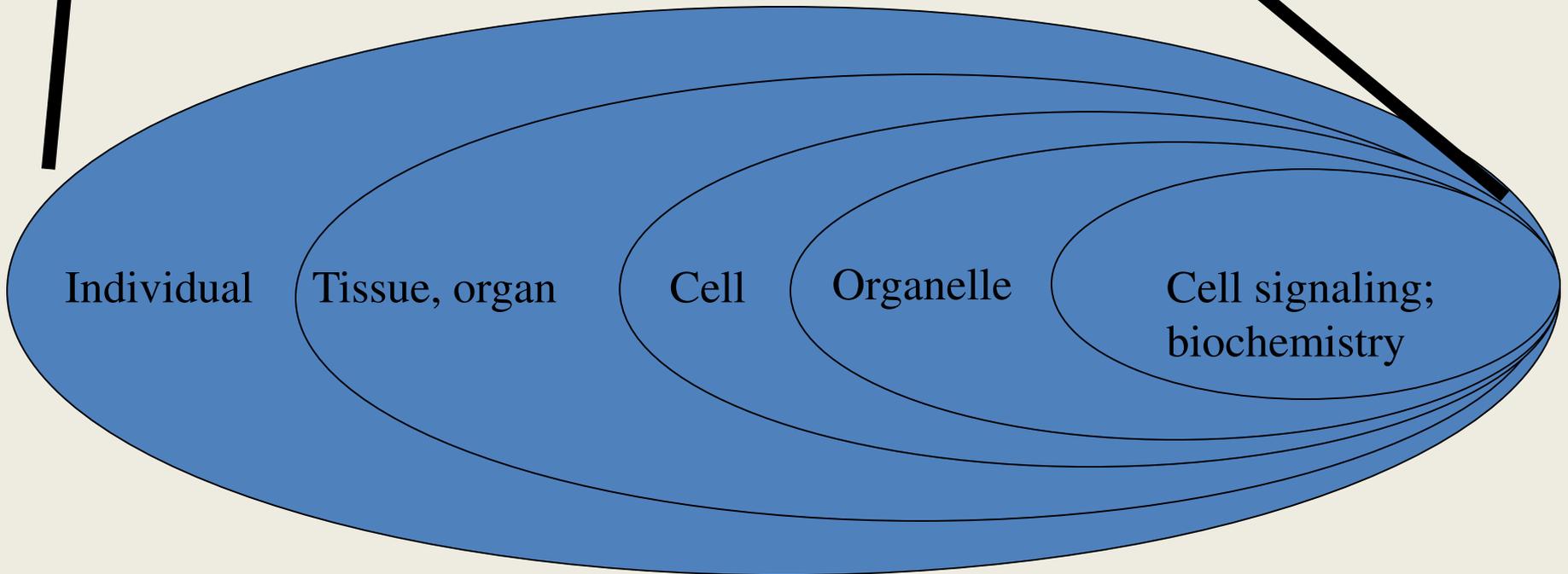
# Ecological (eco-social) framework



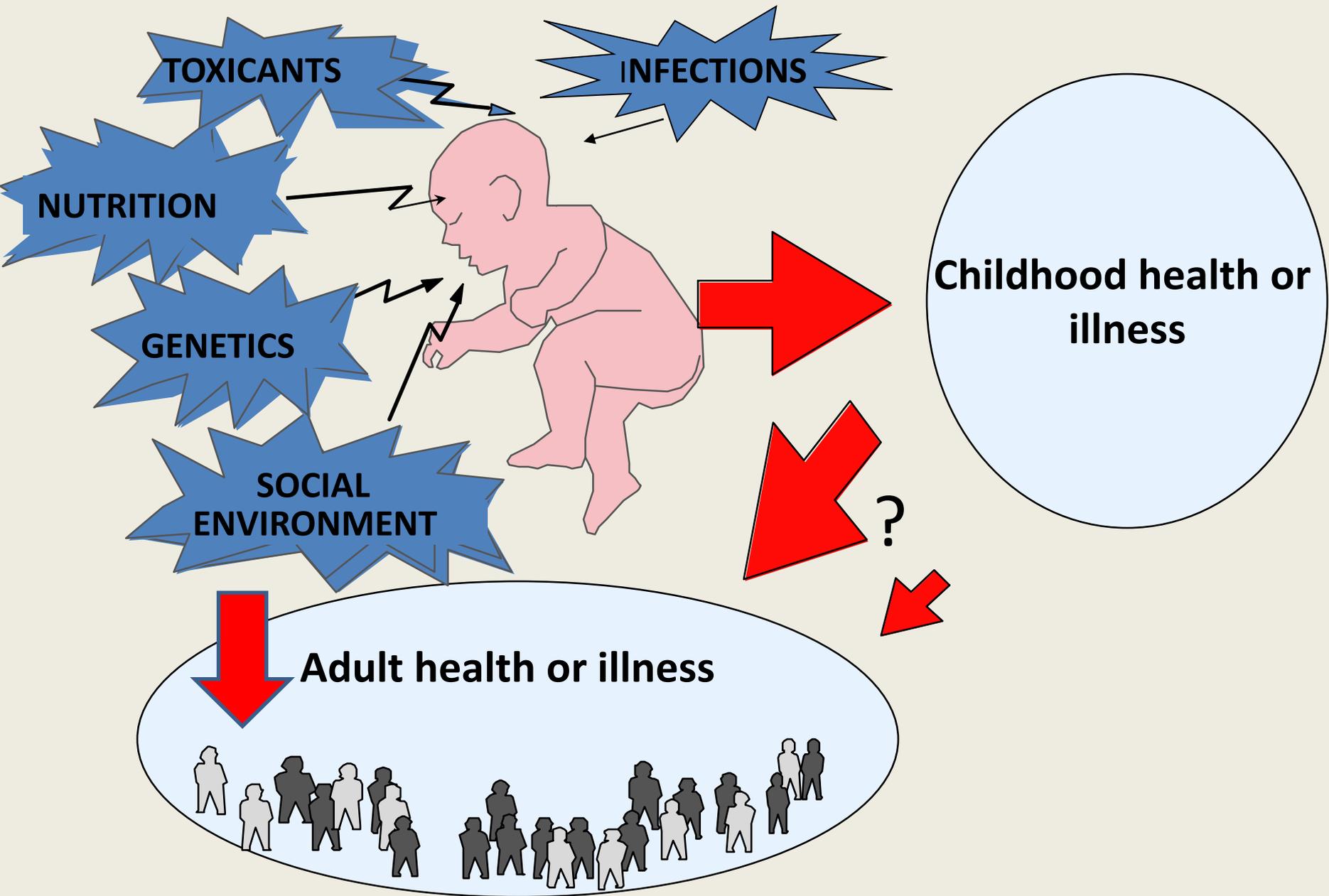
**Multi-level “nesting”**



The ecological  
framework:  
“environment getting  
under the skin”



# Life-course perspective



# Early life experiences; later life health

What determines these?



Diethylstilbestrol (DES) *in utero* associated with increased breast cancer risk  
Higher early life DDT exposures associated with higher breast cancer risk  
Severe childhood stress associated with increased breast cancer risk

# Rates and trends in breast cancer incidence and mortality

TABLE 3. Rates and Trends in Incidence and Mortality and Cause-Specific Survival for Female Breast Cancer by Race/Ethnicity

RACE/ETHNICITY	INCIDENCE		MORTALITY		5-YEAR CAUSE-SPECIFIC SURVIVAL
	RATE 2006-2010	AAPC <sup>a</sup> 2006-2010	RATE 2006-2010	AAPC <sup>a</sup> 2001-2010	RATE 2003-2009
Non-Hispanic White	127.3	0.1 <sup>b</sup>	22.7	-1.8 <sup>c</sup>	88.6
African American	118.4	0.2 <sup>c</sup>	30.8	-1.6 <sup>c</sup>	78.9
Asian American/Pacific Islander	84.7	0.0	11.5	-1.0 <sup>c</sup>	91.1
American Indian/Alaska Native	90.3	-0.3	15.5	-0.4	85.4
Hispanic/Latina	91.1	-0.6 <sup>c</sup>	14.8	-1.7 <sup>c</sup>	87.0

<sup>a</sup>AAPC indicates average annual percent change.

<sup>b</sup>AAPC is for white women and is not exclusive of Hispanic ethnicity.

<sup>c</sup>AAPC is significantly different from zero ( $P < .05$ ).

Sources: Incidence rates: Copeland et al.<sup>8</sup> AAPCs, mortality rates, and survival: Howlader et al.<sup>4</sup>

The female breast cancer incidence rate in Alaska Natives was **134.8/100,000** vs. **50.8/100,000** in the Southwest Indians (Arizona) from 1999–2004, the most recent complete data published. (Kaur, 2014)  
AI/AN women tend to be diagnosed at an earlier age than white women

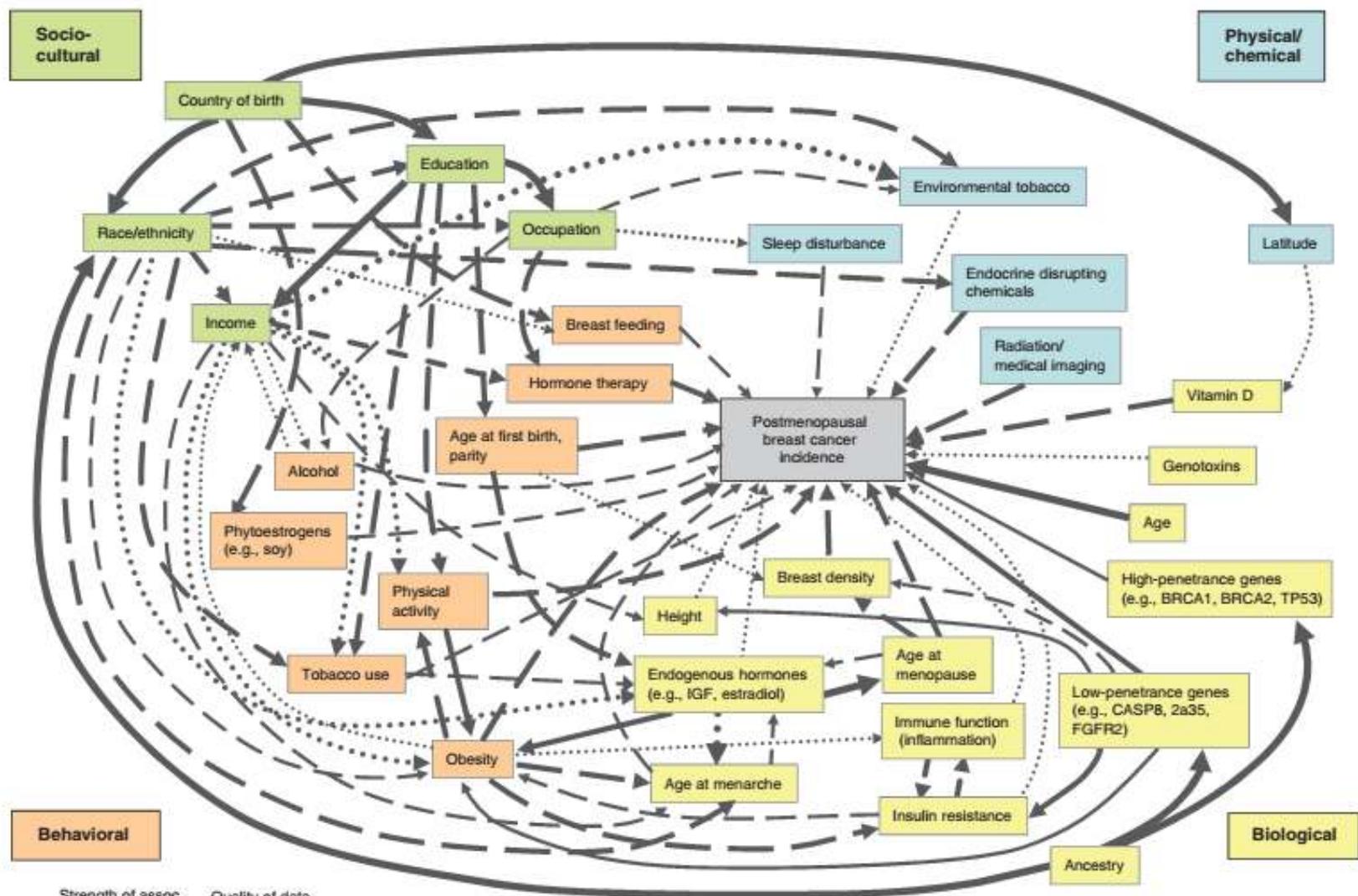
# Breast cancer prevention

- How do we frame this question?
- In individuals? At the population level?
- Prevention refers to strategies that lower risk
- Overall evidence points strongly to accumulation of risk through the life course, beginning during fetal development

# Well-established risk factors

- Family history
- Genetic: BRCA1/2; others
- Personal history of BC
- Dense breast tissue
- Benign breast disease\*
- Late age of first pregnancy; nulliparity (more cells at risk for longer time)
- Early age of puberty (higher estrogen levels later)\*
- Later age of menopause
- Chest radiation\*
- Recent oral contraceptive use
- Combination hormone replacement therapy
- Cigarette smoking
- Alcohol consumption
- Diet\*
- Exercise/physical activity\*
- Overweight/obesity\* (post-menopausal)

(\* potentially modifiable in childhood)



Strength of assoc. (1 = strongest)

Quality of data (1 = strongest)

1	→	1	→
2	- - -	2	- - -
3	⋯⋯⋯	3	⋯⋯⋯

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

# Why do this?

- **to acknowledge, communicate complexity**
  - The anatomy of a system map confirms the multi-level, **systemic nature of the problem**
  - It highlights the need for **broad and diversified efforts to study and change the dynamics of the system.**
- **to make sense of complexity.**
  - Constructing a model helps in understanding the system
  - Once the top-level architecture of a model is grasped, it becomes a filter for identifying relevant variables and an aid to thinking about the further study

# Why do this?

- **to support the development of strategies to study and intervene**
  - Study of a model suggests ways and places to intervene most effectively in the system.
  - These are: **leverage points, feedback loops, and causal cascades, among others**
  - Some uncertainty is inevitable within this complexity

# Diet and breast cancer

- Common limits of studies:
  - Until recently, most studies have focused on adult diet and risk; individual micro- or macro-nutrients
  - Dietary pattern analysis is relatively recent
  - Most epidemiologic studies have included large preponderance of white women
  - Most studies have failed to address exercise as a confounder or effect modifier
  - No studies in people have examined whether diet modifies the response to environmental chemicals (animal studies show an interaction)

# Dietary fat

- Higher amounts of saturated fat and trans fats modestly increase risk
- High omega 6/omega 3 FA ratio probably increases risk
- High dietary maternal omega 6s in pregnancy may also increase risk in offspring  
(higher estriol, testosterone levels)
- Substitution with omega 3s and olive oil is highly likely to be beneficial

# Fruits, vegetables—adult diet

- Higher intake associated with ↓ risk (~25%)
- Higher soy consumption ↓ risk; effect size larger in Asians than Westerners
- WHEL interventional study of women with BC, higher baseline levels of carotenoids associated with improved prognosis



# Dietary pattern

- Mediterranean dietary pattern ↓ risk
- PREDIMED: prospective; post-menopausal: Med diet + EVOO > 68% ↓ risk compared to control over 5 yr. followup
- “Westernized” dietary pattern generally associated with increased risk (variable effect size; differs among subtypes of cancer)



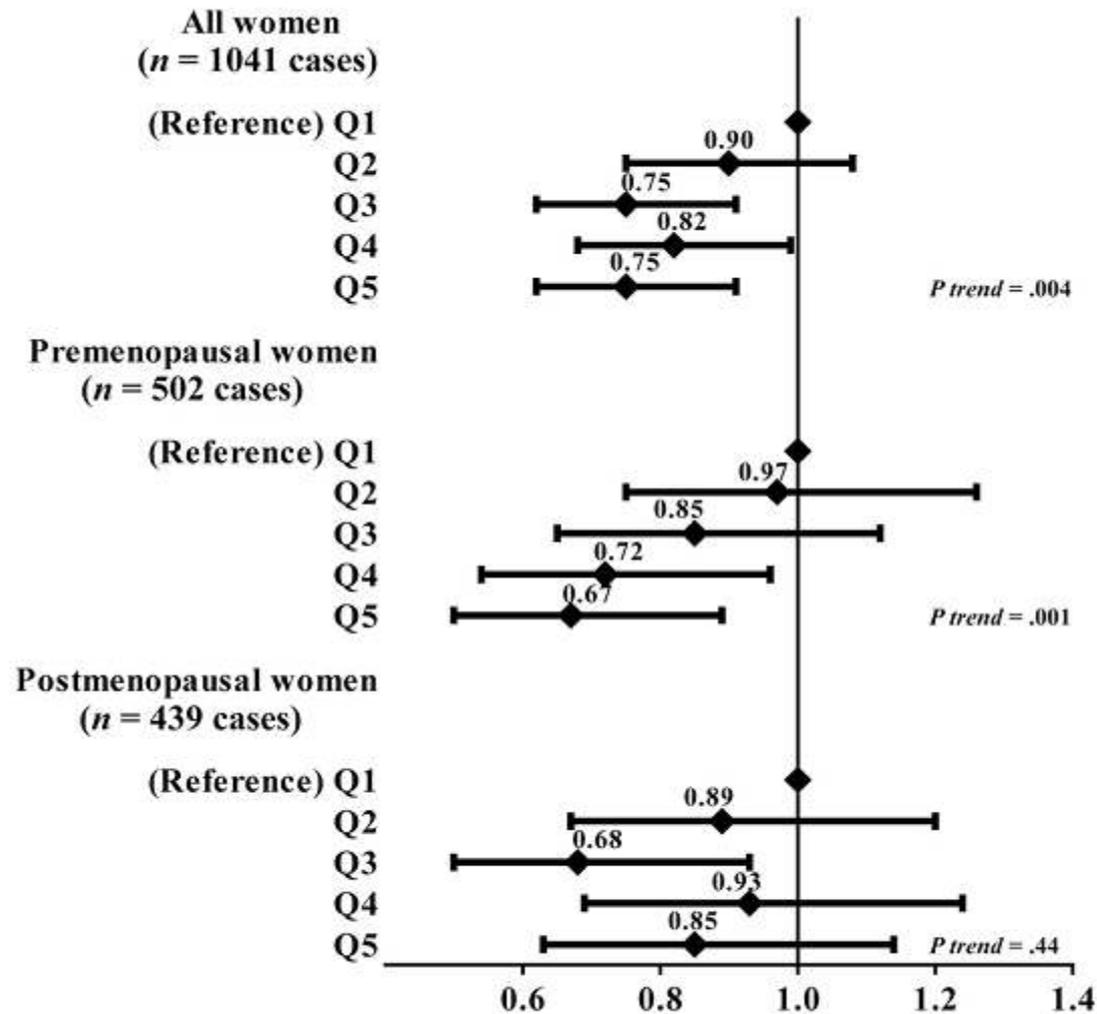
# Childhood, adolescent diet

- ↑ whole soy food in childhood and adolescence > ~50% ↓ breast cancer risk, mechanisms
- ↑ meat in adolescence > 22% ↑ breast cancer risk overall [pre- and post- menopausal (NHS II)]
- Substituting one serving/day of legumes for one serving/day of red meat was associated with a 15% lower risk among all women; 19% lower risk among premenopausal women

# Childhood, adolescent diet

- ↑ dietary vegetable protein, fat, nuts in girls 9-15 associated with ↓ risk of benign breast disease (BBD) at age 30 (Growing Up Today Study)
- ↑ milk associated with ↑ risk of BBD and more rapid height growth (Berkey, 2013)
- BBD and more rapid height growth velocity > ↑ risk of breast cancer
- Some evidence that ↑ childhood dietary meat and sugar sweetened beverages advances the age of puberty (newest, Jansen, 2016; GUTS)

# Dietary fiber adolescence; breast cancer risk; NHSII



**FIGURE 1**  
 Multivariable\* RR of BC (and 95% CI) associated with average intake of fiber in adolescence and early adulthood among women in the NHSII. Categories are quintiles of intake. Multivariable model

# Exercise, physical activity

- Evidence from more than 30 studies
- Typical 20-30% BC risk reduction with 4 hours per week moderate exercise
- Benefits for both pre- and post- menopausal women
- Adolescent exercise most strongly associated with decreased risk of pre-menopausal breast cancer
- Mechanisms: weight control, altered hormone and growth factor levels, modified gene expression
- Exercise after diagnosis and treatment improves quality of life; many studies show reduced risk of all-cause or BC-specific mortality

## Exercise, physical activity for cancer prevention

- 30-60 min. moderate-intensity exercise 5 days/wk; children and teens: 60 min daily
- Determinants of exercise levels:
  - Self-efficacy (confidence in ability): children, adolescents, and adults
  - Family and social support: particularly adolescents
  - Personal history of exercise; personal health; job strain; stress; overweight
  - Neighborhood safety, walkability, design, access to recreation facilities, transportation availability, aesthetics (adults)

# Environmental chemicals

- About 75 yrs. ago, dimethylbenzanthracene (DMBA) was first used to induce mammary gland cancer in lab rodents (Huggins)
- Study of chemicals in humans slow to develop
  - 1970-1980s: single-women hairdressers; PVC mfg; Swedish factory using an anti-rust oil; Canadian GE lamp mfg.—higher incidence/mortality from breast cancer
- Over 200 chemicals are mammary gland carcinogens in animal studies (Rudel, 2007)
- Increasing evidence in epidemiologic studies

# Environmental chemicals, pharmaceuticals

- Institute of Medicine (IOM) report (2011):
  - Sponsored by Komen; limited review
  - Strong evidence: HRT, current use of OCs, alcohol, tobacco smoke
  - Less strong but suggestive: other organic solvents, benzene, ethylene oxide, 1,3 butadiene, polycyclic aromatic hydrocarbons (PAHs)
  - Concerns but even more incomplete evidence: bisphenol A, cadmium, others

# Occupations and breast cancer

- History: single women hairdressers (UK 1960's); metal working; PVC plant (1977)
- Working Women and Breast Cancer
  - [www.breastcancerfund.org](http://www.breastcancerfund.org) (1.5-6 fold increased risk)
    - Nurses (shift work, light at night, chemicals)
    - Teachers
    - Professional women
    - Radiological technicians
    - Firefighters
    - Women working with chemicals
      - Plastics, rubber, solvents, pesticides, textiles

# Life-course approach

- Diethylstilbestrol (DES) *in utero* associated with increased risk of reproductive tract, breast cancers (~2 X higher risk BC after age 40)  
(Palmer, 2006)
- Higher early life exposure to DDT associated with increased risk of BC (3.7 X *in utero*, 5 X before age 14) (Cohn; EHP, 2007; JCEM, 2015)

# Endocrine disruptors and breast cancer

- Some chemicals can influence breast development, tissue architecture, gene expression after developmental exposures (rodents, primates)
  - DES, bisphenol A, perfluorinated cmpds, dioxin
- These changes can increase susceptibility to cancer in adulthood; e.g., BPA *in utero* increases susceptibility to DMBA-induced mammary cancer
- Atrazine and neonicotinoid pesticides promote aromatase production, activity (↑estrogen)

Caron-Beaudoin, 2016

# Vitamin D and breast cancer

- Animal and *in vitro* studies
  - low dietary levels increase mammary gland tumors after exposure to carcinogen
  - Vitamin D reduces aromatase levels, promotes cellular differentiation and apoptosis in breast tissue
- Most but not all studies find lower levels of vitamin D associated with higher risk of BC
- A prospective study in Bogota found low vitamin D levels predictive of early onset puberty

# Vitamin D

- Endocrine Society (>30 ng/mL 25(OH)D) and Institute of Medicine analysis (> 20 ng/mL) disagree on what constitutes an adequate level
- Inadequate levels of vitamin D are common
- American Academy of Pediatrics recommends that all breast-fed infants and formula-fed infants receive vitamin D supplement
- ACOG recommends testing women at risk of low vitamin D and supplementing as needed; large margin safety (IOM; adults up to 4000 IU D3 daily)

# Vitamin D levels Alaska

- Vitamin D insufficiency is common in Alaska, particularly during winter months
- Alaskan natives who eat a traditional diet are more likely to have adequate vitamin D levels year around
- Younger people who do not eat traditional diet more likely vitamin D insufficient (Fohner, 2016)

# Radiation, electromagnetic fields

- Ionizing radiation well-recognized risk factor for BC
- Radiofrequency radiation (cell phones) is not ionizing (does not break DNA bonds).
- IARC classifies RF radiation as “possibly carcinogenic in humans” —based on possible brain tumor risk.
- No studies of RF radiation from cell phones, towers, other wireless technologies) on breast cancer risk
- Anecdotal reports of breast cancer in women who carried cell phone in bras
- Quite easy to reduce exposures

# Designing for breast cancer prevention

# Intervening in the complexity

- Historical, life-course perspective
- Medical, behavioral interventions AND multi-level interventions; public health thinking
  - Opportunities: individual, family, community, society
  - Shift system dynamics (re-design the terrain)
  - Population-wide shifts more likely to be effective
  - Understanding cause-effect relationships will always be clouded by some degree of uncertainty
  - This should not be used as an excuse not to act, based on what we do know

# Combined risk factor reduction

- Post-menopausal
  - EPIC (European Investigation into Cancer and Nutrition); >200,000 women followed prospectively; median follow up 11 yrs.
  - 20-25% reduction in breast cancer incidence with highest scores on combinations of healthy lifestyles (diet, exercise, weight control, smoking, alcohol) (McKenzie, IJC, 2014)

# Combined interventions: women with breast cancer

- WHEL (Women's Healthy Eating and Living) study
  - Pre- and post-menopausal women (~3000)
  - Dietary intervention: plant-based & reduction in dietary fat
  - No effect on prognosis, but higher baseline carotenoids associated with delayed recurrence (average 7.3 yrs. follow up)
  - Over 10 yrs; higher fruit and vegetable consumption along with higher levels of exercise > reduced death rate by half (93% vs. 86% survival)
- [Three fairly large studies find no evidence of adverse effects of dietary soy on breast cancer prognosis and considerable evidence of a beneficial role]

# Who?

- Individuals
- Health care providers and institutions
- Public health professionals and organizations
- Governments, legislators
- Schools
- Workplace
- Farmers; farm and agricultural policy
- City planners

# Opportunities across the life-course: cancer prevention begins in the womb

- Diet, nutrition, the food system, food access; (emphasis on fruits, vegetables, nuts, legumes, whole grains, healthy fats); traditional foods?
- Breast feeding (good for mother and baby)
- Exercise, physical activity, built environment
- Optimize vitamin D levels (~30-50 ng/mL);  
—(AAP position)
- Avoid unnecessary radiation exposure
- Stress management; sleep; shift work

## Opportunities across the life-course: cancer prevention begins in the womb

- Reduction and elimination of exposure to hazardous chemicals potentially linked to BC; more than alcohol, tobacco, HRT
- Known carcinogens
- Endocrine disruptors—e.g. BPA (ACOG policy addresses BPA, pesticides)
- Investigate occupational exposures

# Endocrine disruptors: some sources

- Cosmetics  
(EWG database <http://www.ewg.org/skindeep/> )
- Other personal care products (e.g., parabens, triclosan)
- Bisphenol A: (linings of cans, thermal receipts, assorted plastics)
- Pesticides: food residues, home use, farm workers

# Design multi-dimensional strategies

- Health care providers
  - Counseling on diet, activity, weight gain/loss, vitamin D
  - Identify “higher risk” for other preventive interventions
    - Balance risks and benefits
  - Environmental assessment and interventions (home, hobbies, workplace, community)
- Governments: guidelines, regulations, labeling, research
  - facilitate lactation, physical activity, food, chemical policies
- Community/Schools
  - lactation, physical activity, healthy food access
- Research: impacts of chemicals during developmental windows of vulnerability

Thank you

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