

Environmental Exposures and the Onset of Puberty as a Window on Adult Breast Cancer

Robert A. Hiatt, MD, PhD
UCSF

Biobehavioral Contributions to Cancer Exposomes:
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Outline

- Conceptual frameworks
 - Life-course approach – “Windows of Susceptibility”
 - Complex Systems
- Breast Cancer and the Environment
- Puberty
- Findings
- Conclusions

Life-Course Approach to Breast Cancer Etiology

Transdisciplinary Science Conceptual Model for Breast Cancer

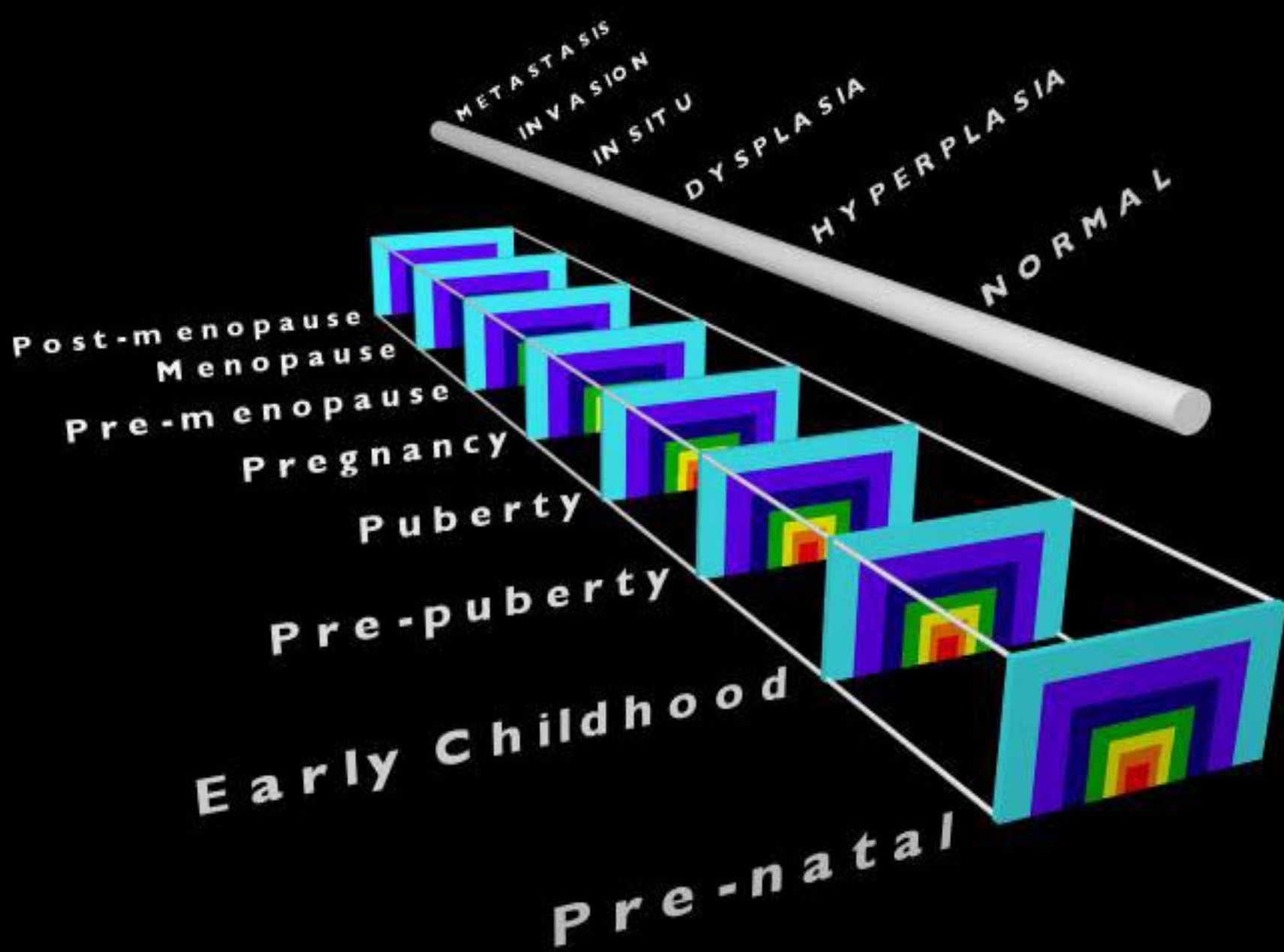
- Life-course approach
- Multiple levels of analysis (social ecologic model)
- Stages of carcinogenesis
- Must incorporate aims of constituent investigators and collaborators
- Demonstrate hypotheses
- Predictive value

Life-course Approach

- Pre-natal
- Early childhood
- Pre-puberty
- Pregnancy
- Pre-menopause
- Menopause
- Post-menopause

Levels of Analysis

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



Society/Region

Neighborhood / City

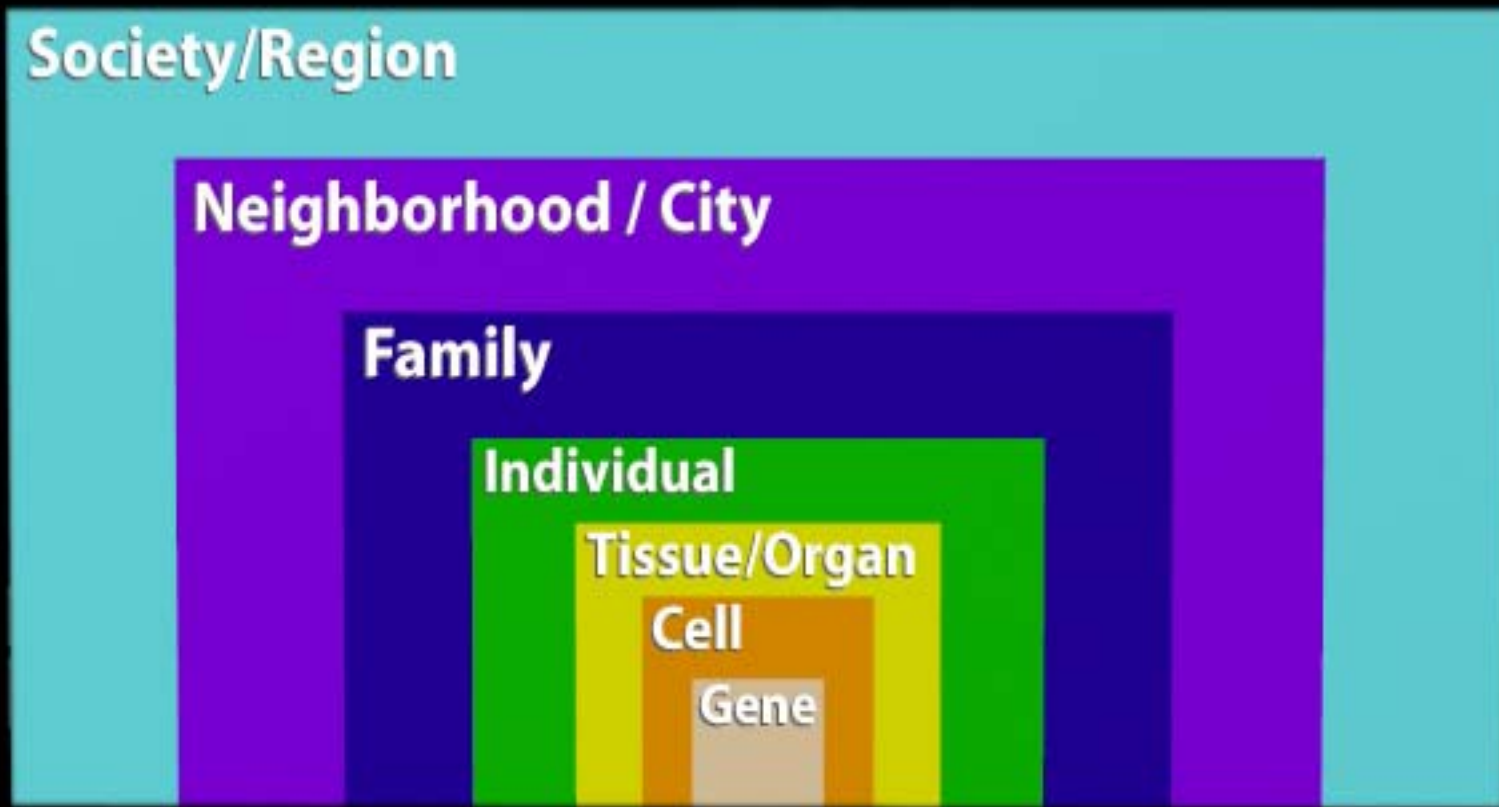
Family

Individual

Tissue/Organ

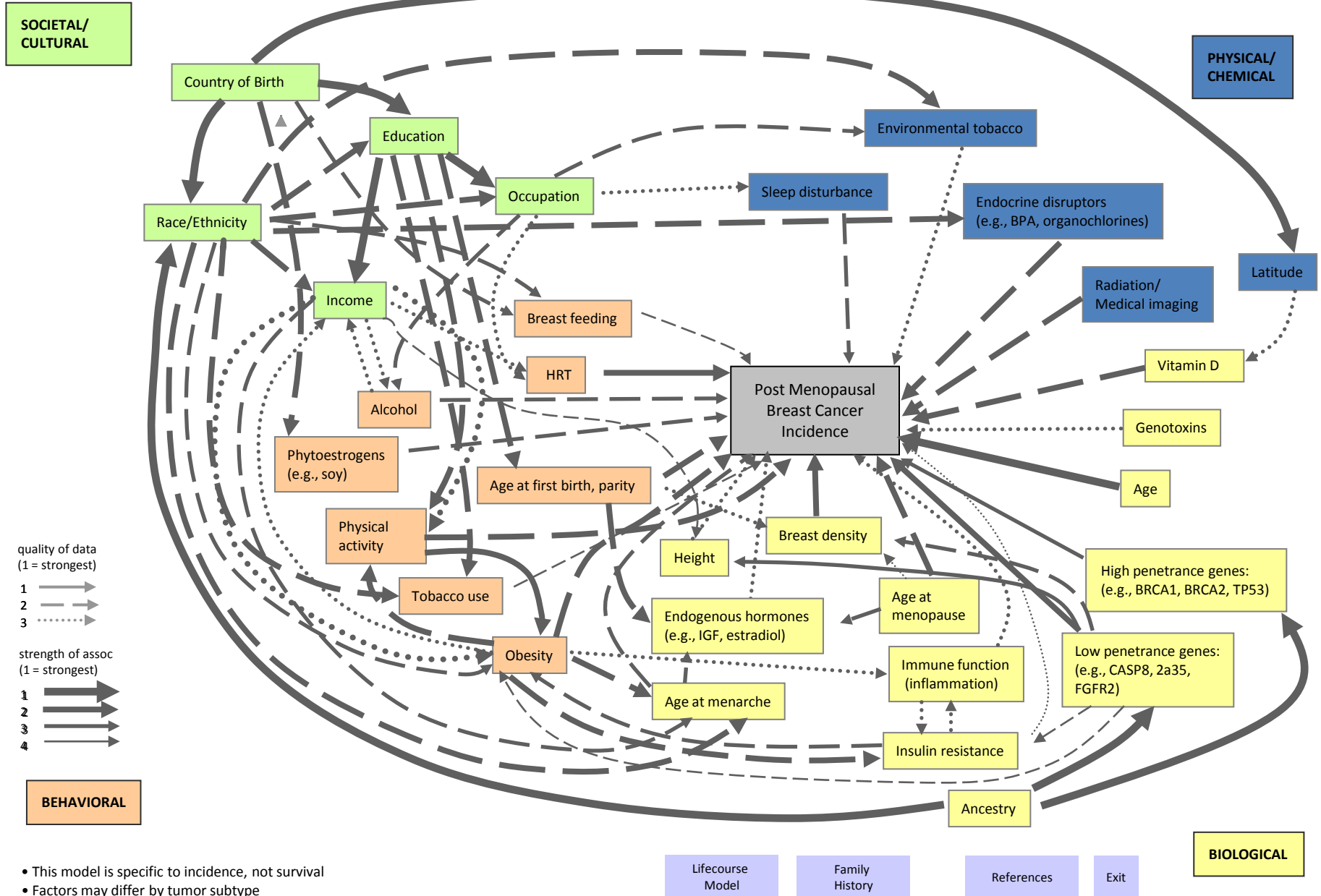
Cell

Gene



Breast Cancer Etiology as a Complex System

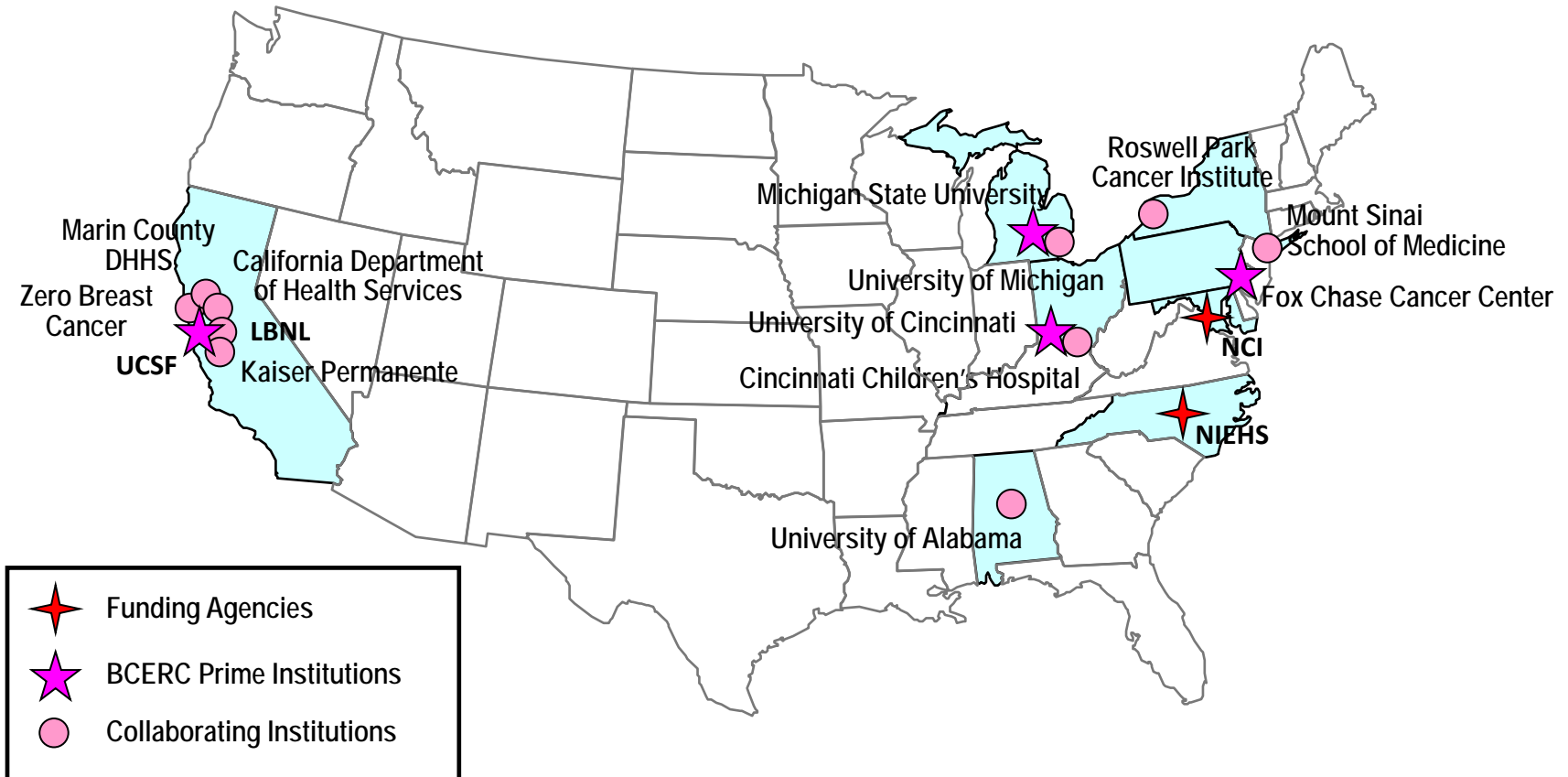
New Paradigm of Breast Cancer Causation and Prevention



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

The Breast Cancer and the Environment Research Centers

Breast Cancer and the Environment Research Centers (BCERCs)



Acknowledgements

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Common Goals

- to study the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer
- investigating mammary gland development in animals and young girls to determine vulnerability to environmental agents in the pre-pubertal period that may influence breast cancer development in adulthood

Transdisciplinary Science

- Pediatrics
- Endocrinology
- Epidemiology (social, environmental, nutritional, physical activity)
- Psychology
- Toxicology
- Geography
- Molecular biology
- Genetics

Aims of BCERC Epidemiology Studies

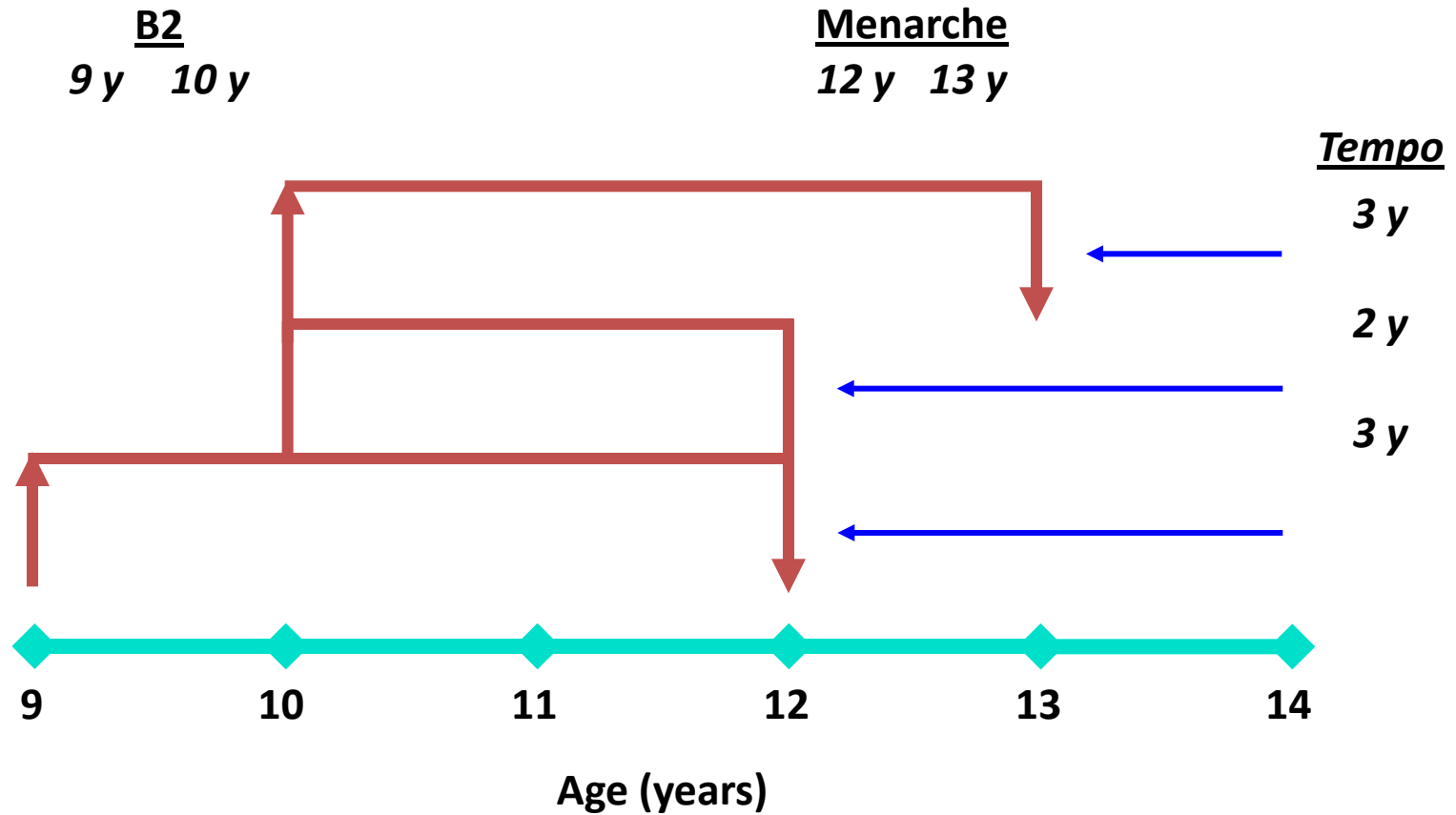
Examine predictors of age at onset of puberty, especially Tanner Stage for breast and pubic hair development, including:

- Developmental and lifestyle factors
 - Body size and anthropometry
 - Food and nutrition
 - Physical activity and energy expenditure
- Environmental factors
 - Psychosocial factors, social and built environment
 - Cigarette smoking, alcohol, medications
 - Persistent hormonally-active agents (e.g., PCB's, PBDE's)
 - Less persistent hormonally-active agents (e.g., phthalates)
- Genetic polymorphisms
 - Genes that may influence metabolism of exogenous exposures
 - Genes that may influence relevant hormonal pathways

BCERC Epidemiology Study Populations

- Healthy girls age 6-8 yrs at time of recruitment
- California:
 - Bay area KPNC members
 - Larry Kushi, PI, Division of Research, Kaiser Permanente Northern California
- Ohio:
 - Cincinnati-area school districts
 - Frank Biro, PI, Cincinnati Children's Hospital
- New York:
 - East Harlem neighborhood clinics
 - Mary Wolff, PI, Mount Sinai School of Medicine

Tempo (Pace, B2 → Menarche)



Methods

- Environmental exposures
 - cigarette exposure, home care products, use of personal care products, residential history, etc.
- Medical and related history
 - medication use, maternal age at menarche, family history of relevant diseases, etc.
- Psychosocial measures
 - familial stress, family structure
- Demographics

Methods

- Food intake
 - Quarterly 24-hour dietary recall
 - Supplemental interview on selected food exposures (high in phytoestrogens), organic food consumption, infant feeding practices
- Physical activity
 - Interview of mothers and girls on organized activities (sports, dance, etc.), passive activities (TV, computer use, etc.)
 - Pedometers worn for 1 week

Anthropometry & Tanner Staging

- Anthropometry
 - Annual standardized clinic measurement
 - Annual bioelectrical impedance analysis
 - Maternal or self report via questionnaire
 - Data extracted from KP records
- Tanner Staging
 - Annual standardized clinic measurement of breast and pubic hair development
 - Data extracted from KP records

Examples of **genes** of potential interest

- Steroid synthesis – *CYP11A*, *CYP17*, *CYP19*
- Sex hormone metabolism – *CYP1A1*, *CYP1B1*, *CYP3A4*
- FSH, LH, FSH receptor, Inhibin B
- Androgen metabolism – *AR*, *SRD5A2*
- Leptin, Leptin receptor

Psychosocial Factors

- Socioeconomic Status
- Family structure and function
- Depression, anxiety
- Mother's depression
- Absent father

Biospecimens

- Urine
 - Casual specimen at baseline, annual clinic visits
 - To assess exposure to selected environmental factors
- Blood
 - 20 ml collected at least once
 - genotyping
 - To assess exposure to selected environmental factors
- Saliva
 - if blood collection is refused or unsuccessful
 - genotyping

Puberty

The Common Question or Problem for BCERP

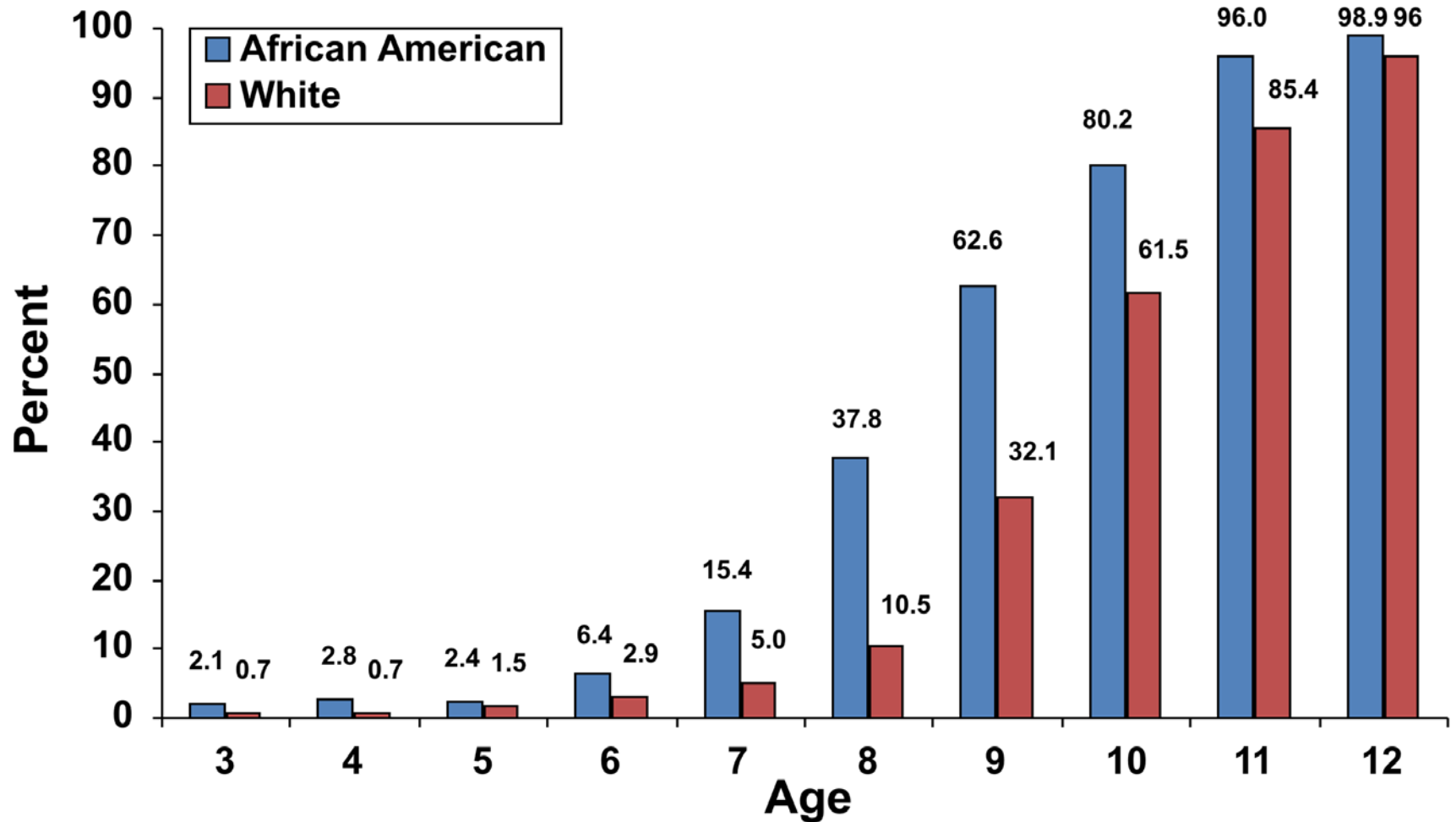
- What drives the onset of puberty and how might the period of puberty be a window of susceptibility on breast cancer development in adult life?

Early Puberty

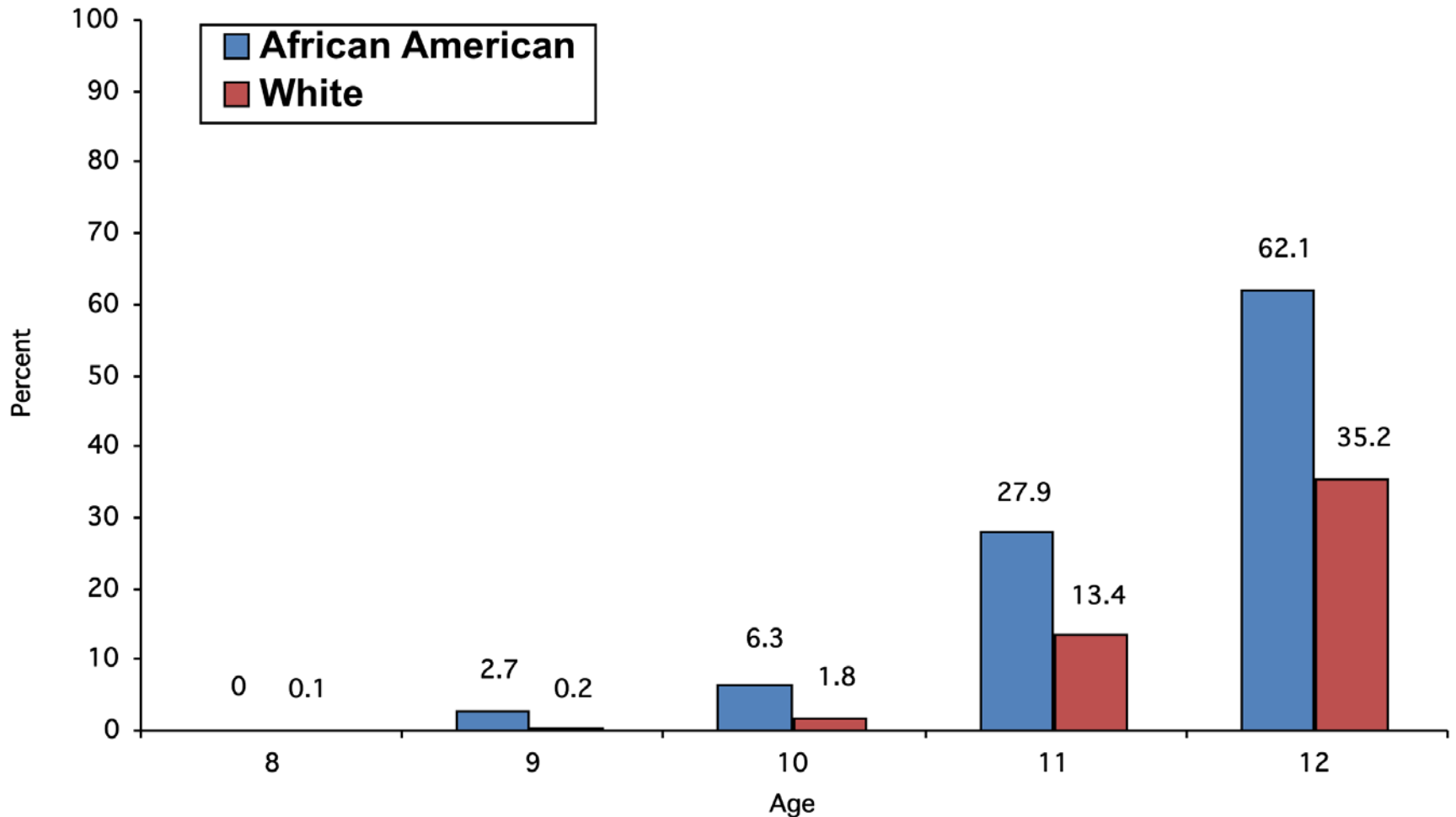
- Adolescent Health
 - Early sexual activity
 - Sexually transmitted infections
 - Early pregnancy
 - Depression
- Adult Health
 - Breast cancer (early age at menarche)

The Changing Age of Puberty Over Time

Prevalence of Breast Development at Tanner Stage 2 or Greater by Age and Race



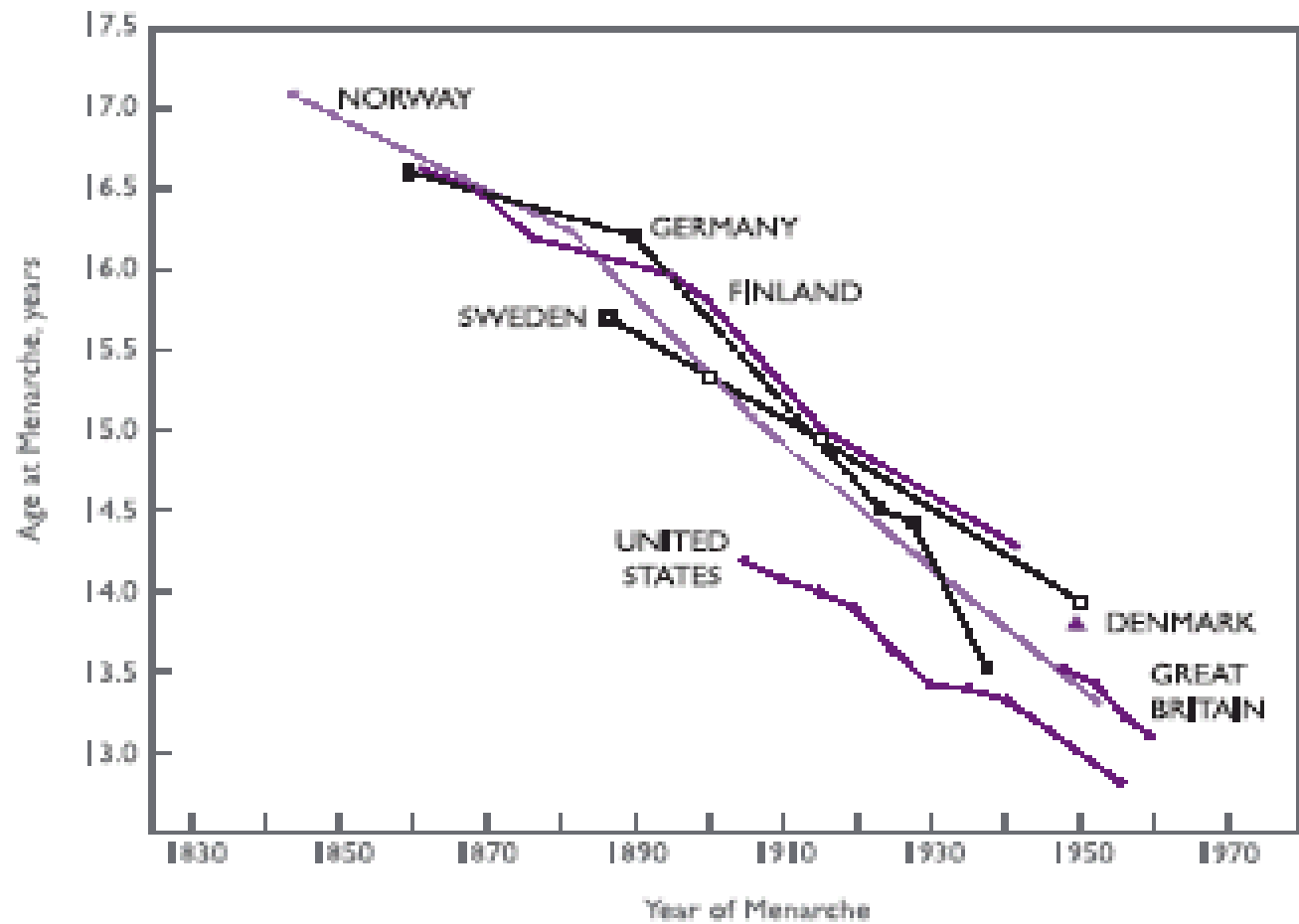
Prevalence of Menses by Age and Race



Herman-Giddens et al., Pediatrics, 1997

International Trends in Age at Menarche

Prevalence of menses by age and race (Tanner, 1962)



Korean example

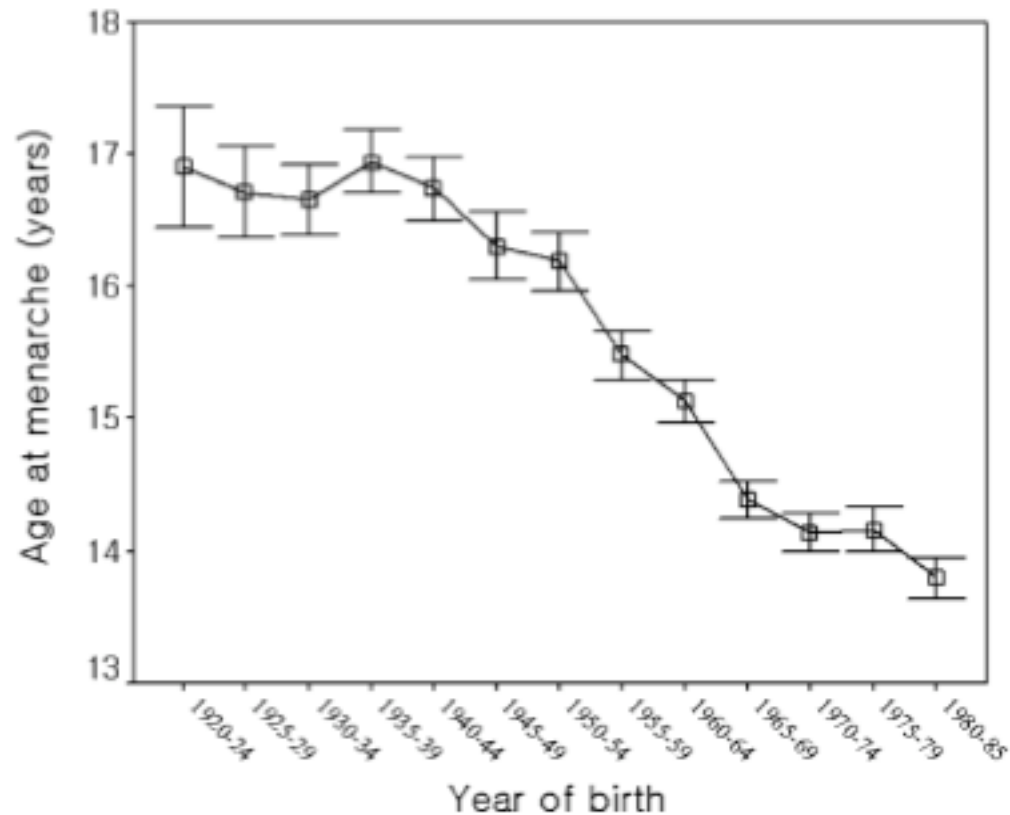


Fig. 1 Secular trend of mean age at menarche for women born between 1920 and 1985

Results to Date

Breast Maturation Status, age 7 years

BCERP Puberty Studies, Biro et al., Pediatrics, 2010

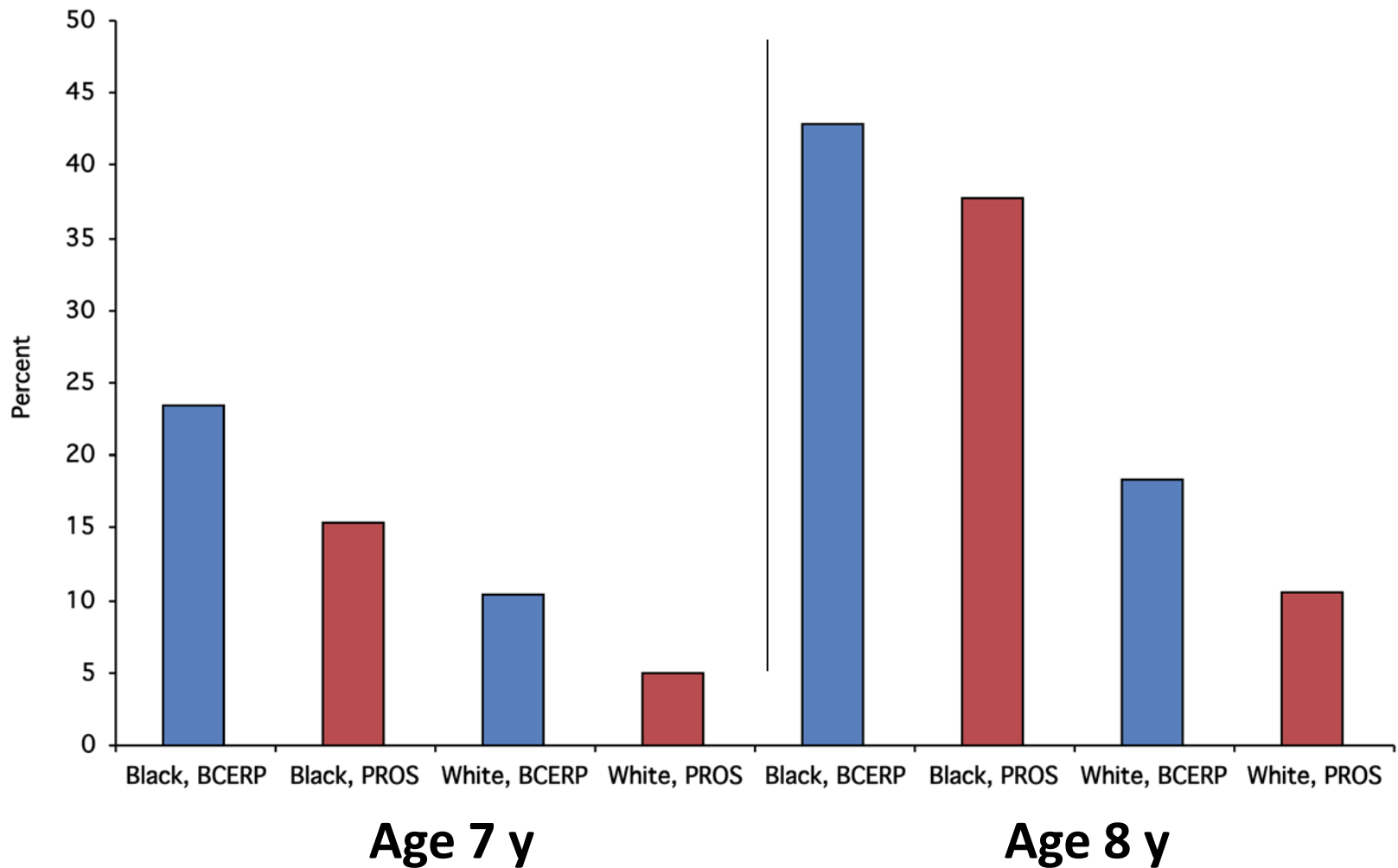
Group	New York City		Cincinnati		Bay Area		Total	
	B1	B2+ (%)	B1	B2+ (%)	B1	B2+ (%)	B1	B2+ (%)
Black	83	11 (11.7)	75	34 (31.3)	75	26 (25.7)	223	71 (24.1)*
Hispanic	117	25 (17.6)	10	1 (9.1)	79	10 (11.2)	206	36 (14.9)
Asian			4	0 (0.0)	40	1 (2.4)	44	1 (2.2)
White			184	29 (13.6)	179	13 (6.8)	363	42 (10.4)

Breast Maturation Status, age 8 years

BCERP Puberty Studies, Biro et al., Pediatrics, 2010

Group	New York City		Cincinnati		Bay Area		Total	
	B1	B2+ (%)	B1	B2+ (%)	B1	B2+ (%)	B1	B2+ (%)
Black	77	31 (28.7)	54	58 (51.8)	55	24 (30.4)	186	113(42.9)
Hispanic	97	60 (38.2)	8	4 (33.3)	78	18 (18.8)	283	82 (30.9)
Asian			4	0 (0.0)	34	6 (15.0)	38	6 (13.6)
White			156	57 (26.7)	152	12 (7.3)	308	69 (18.3)

Breast Development in the BCERP Puberty Studies (*Biro, 2010*) and PROS (*Herman-Giddens, 1997*)



Father absence and breast development

CYGNET Study, 2005 – 2008

Deardorff, et al., J Adol Health 2011

Income category	RR (95% CI)	p value
Higher income, ≥\$50,000/year	2.4 (1.2 – 4.9)	0.01
Lower income, <\$50,000/year	0.8 (0.5 – 1.2)	0.25

SES and B2

- High SES consistently associated with breast cancer incidence.
- Conventional explanation is that high SES associated with reproductive pattern and behaviors associated with higher risk of BC (e.g. early menarche, late first pregnancy or nulliparity, late menopause, use of HR, EtOH).
- Consistent with increased exposure to cyclical estrogen.

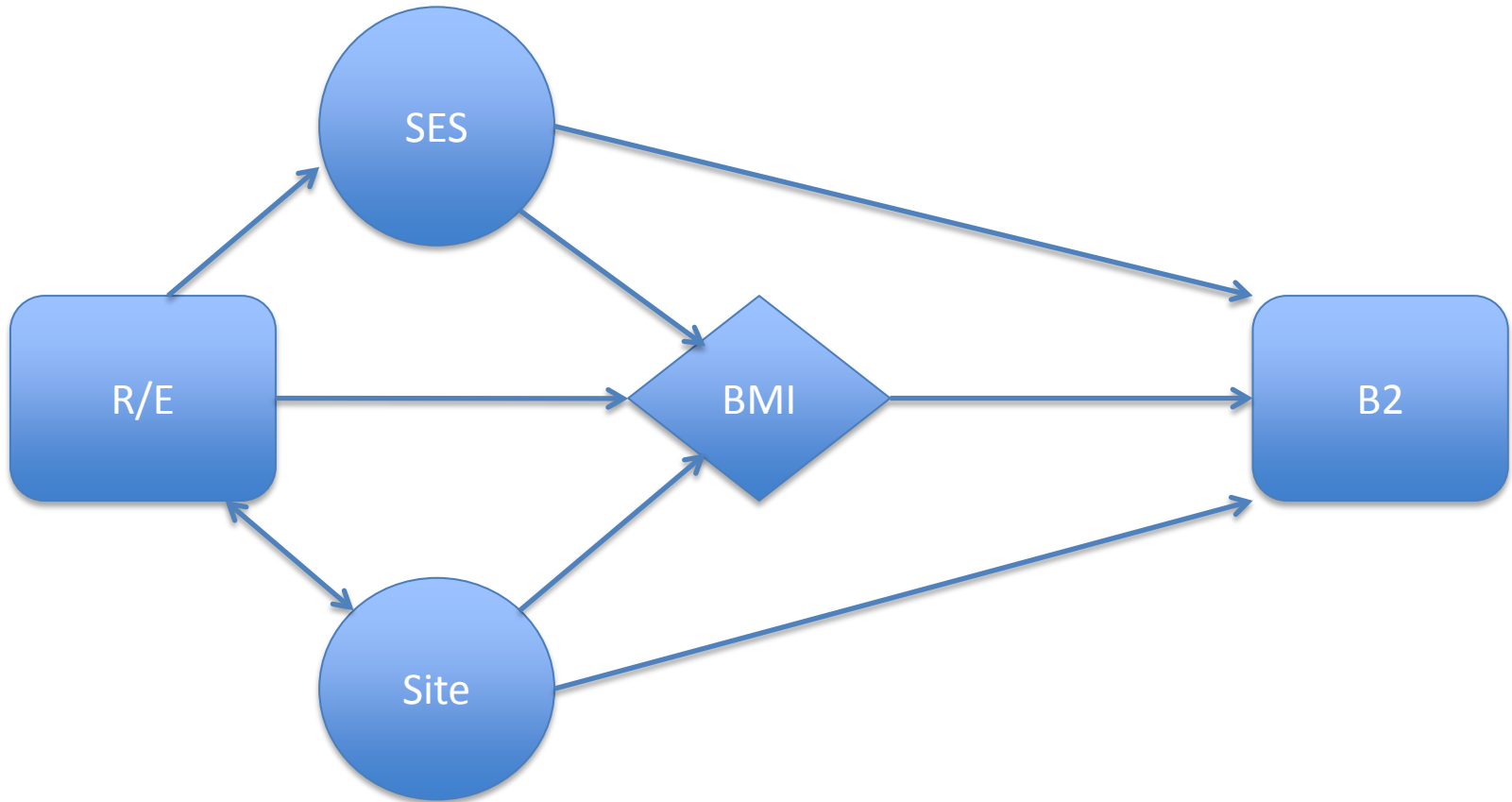
SES and B2

- Early menarche usually thought to be a risk factor because earlier exposure to cyclical estrogen.
- Age of menarche dropping in industrialized societies over last century.
- Age a pubertal onset (1-2 years before menarche) dropping in last 50 years.
- Better nutritional status thought to be main driver.

Research Questions

- What is the relationship between SES and pubertal onset?
- What are the mediators and moderators of this relationship?
- In particular, what is the role of BMI, race/ethnicity and geographic location?

SES – B2 Working DAG



Age and Race/Ethnicity BCERP (N = 1239)

	NYC (416)	Cincinnati Area (379)	San Francisco Bay Area (444)
Age – mean yrs	7.0	6.7	6.8
Race/ethnicity % (N)			
Black	40.1 (167)	33.5 (127)	21.9 (97)
Hispanic	59.9 (249)	4.0 (15)	24.3 (108)
Asian	0 (0)	1.3 (5)	11.7 (52)
White	0 (0)	61.2 (232)	42.1 (187)

SES (HH Income) and B2

Income HH	Ratio of Medians*	95% CI
< \$50,000	0.92	0.90 – 0.94
\$50-100,000	0.95	0.93 – 0.98
>=\$100,000		

*Ratio = ratio of medians. Effect size. Note that an 8% difference in median age at puberty (ratio of medians = 0.92) is equivalent to a 8 month difference in the onset of puberty.

SES (Education of Financial Provider) and B2

Education Level	Ratio of Medians	95% CI
<= HS Diploma	0.96	0.93 – 0.99
Some College/Vocational	0.95	0.92 – 0.98
Bachelor's Degree	0.97	0.94 – 1.00
>=Master's Degree	1.00	

BMI % and B2

BMI %	Ratio of Medians	95% CI
<50	1.19	1.16 – 1.21
50-85	1.12	1.09 – 1.14
>= 85	1.00	

Race/Ethnicity and B2

Race/Ethnicity	Ratio of Medians	95% CI
Black	0.91	0.89 – 0.94
Hispanic	0.96	0.94 – 0.99
Asian	1.06	1.01 -1.11
White	1.00	

Geographic Site and B2

City	Ratio of Medians	95% CI
Cincinnati Area	0.90	0.88 – 0.92
New York City	0.92	0.90 – 0.94
San Francisco Bay Area	1.00	

Tentative Conclusions on Influence of SES on Pubertal Onset

- SES is inversely related to onset of pubertal signs.
- The relationship is not strong but shows a consistent trend.
- The relationship is not influenced substantially by BMI%, race/ethnicity, or site of study each taken alone, but reduced to nonsignificance when all 3 factors are considered together.



Puberty, Breast Cancer, and the Environment



Take Away Points

- Example of transdisciplinary research approach to environmental influences on early development
- Decline in age of signs of pubertal onset
- Psychosocial factors in early development as a lens on cancer etiology

Fin

