# "Life-course Epidemiology of Breast Cancer"

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First Biannual International Evolution and Cancer Conference
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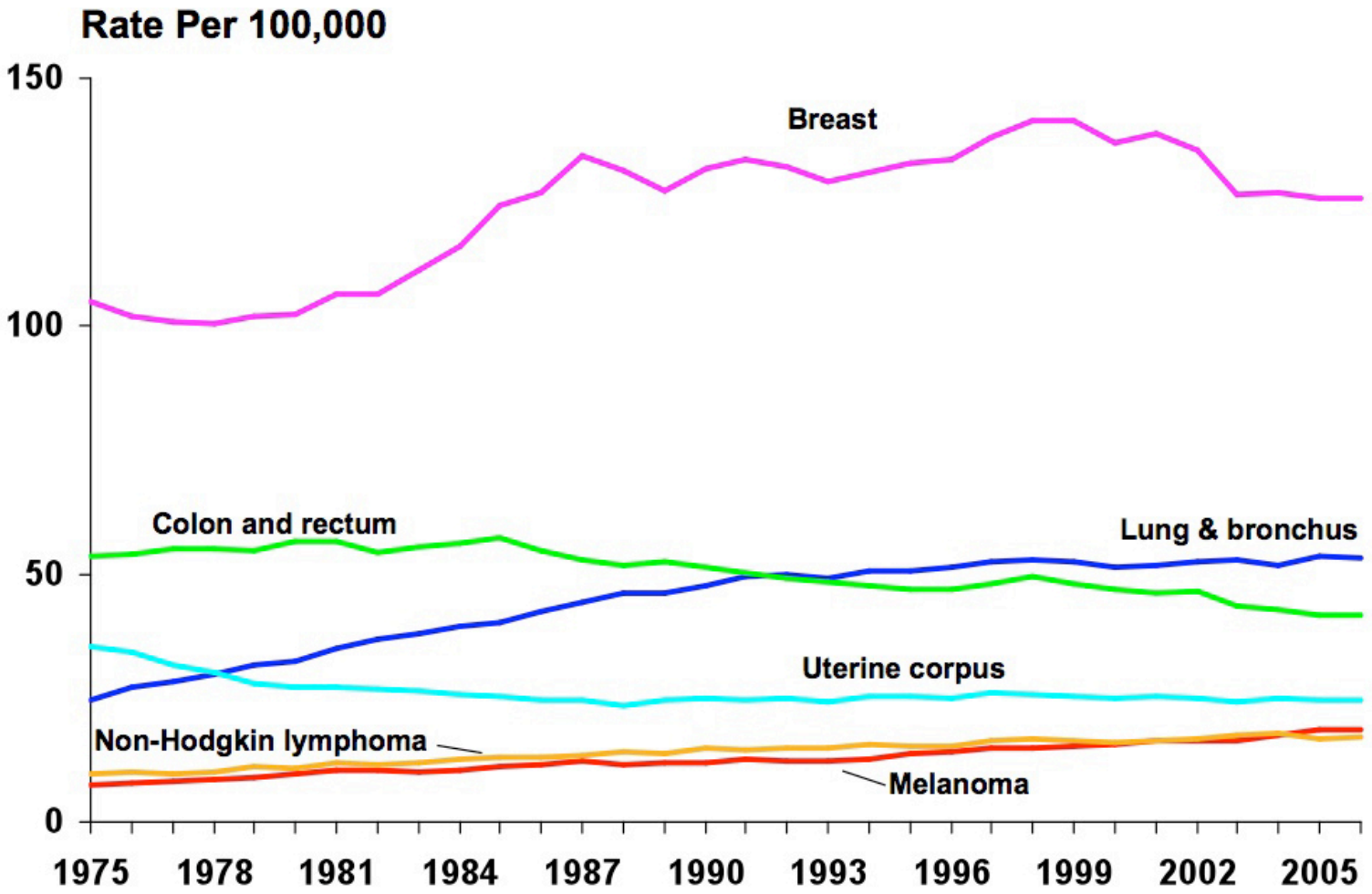
# Breast Cancer

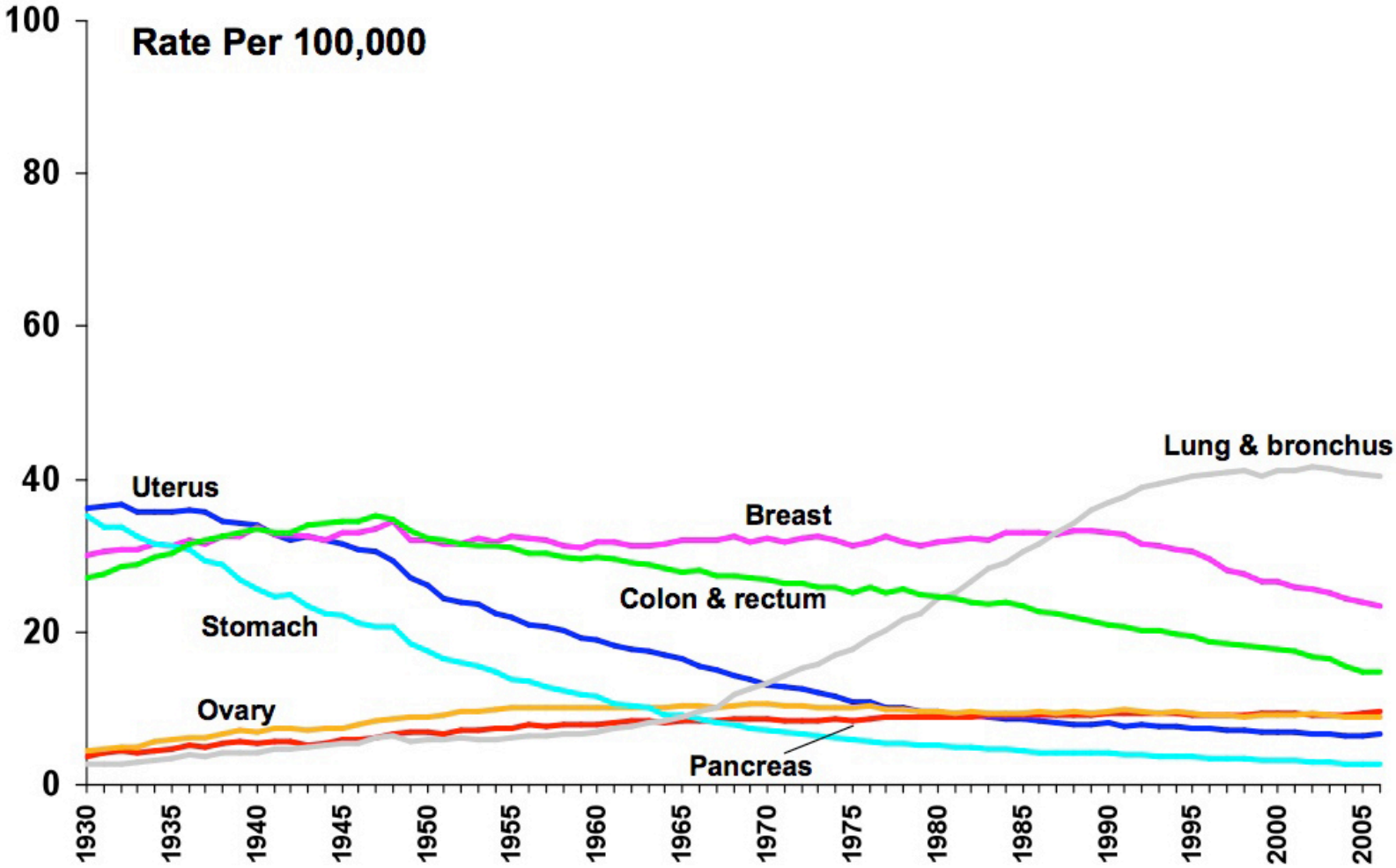
- Still the most common cancer among women
- Estimated 207,090 new cases in 2010
- Now the second leading cause of cancer death (after lung cancer)
- Estimated 39,840 deaths in 2010

# Cancer Incidence Rates* Among Women, US, 1975-2006




*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2006, National Cancer Institute, 2009.

# Cancer Death Rates* Among Women, US,1930-2006

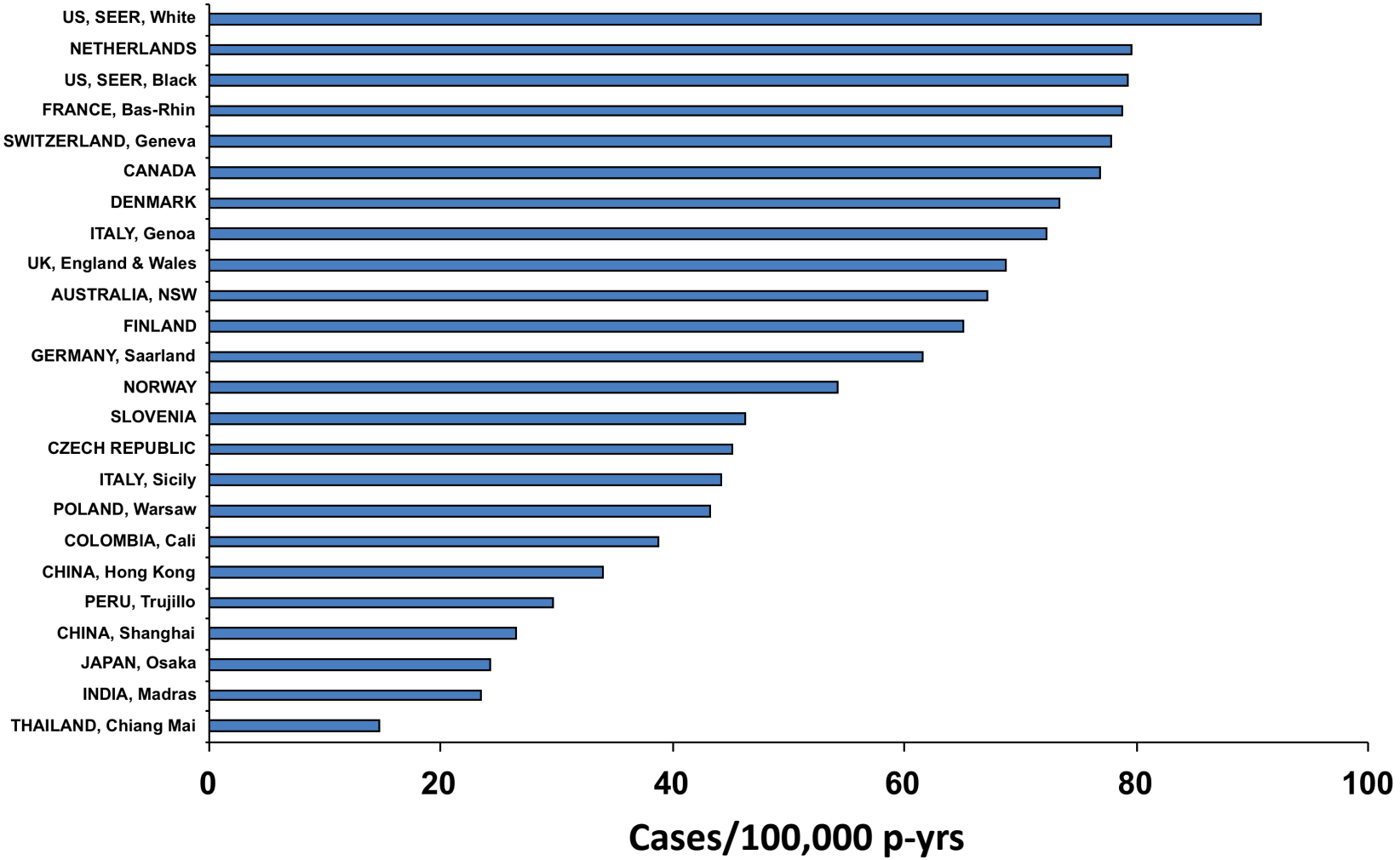



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Large (5-fold) international variation in breast cancer incidence rates.

# Female Breast Cancer Incidence Rates

*age-standardized rates, 1988-1992*

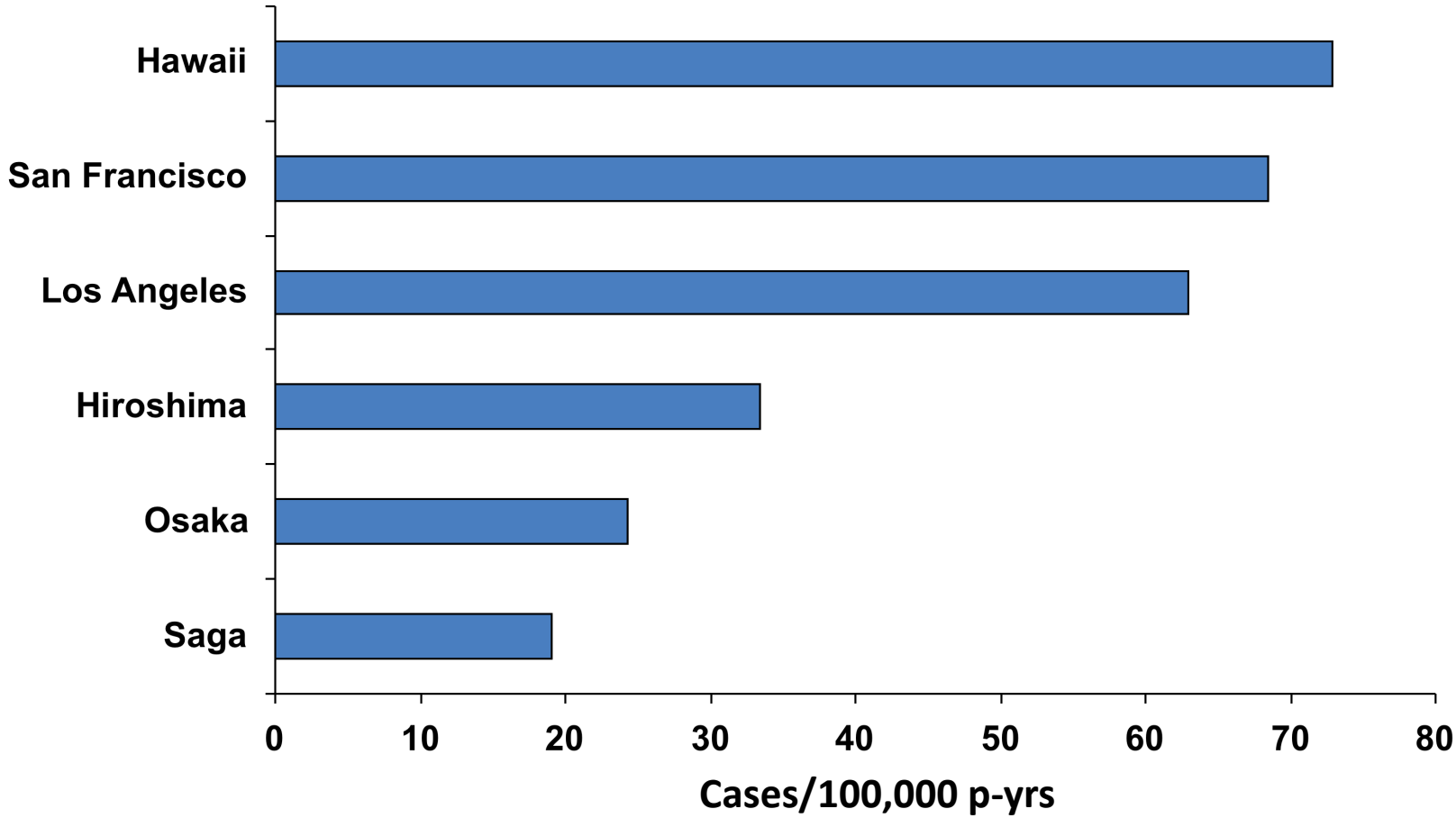



From Parkin, et al., IARC, 1997

Migrant studies indicate generationally rapid change and thus unlikely due to genetic mechanisms.

# Variation in Breast Cancer Rates, Japanese

*age-standardized incidence rates, 1988-1992*




From Parkin, et al., IARC, 1997

# What's the explanation?

Observations compatible with many hypotheses, but the two primary research directions have been directed at diet and reproductive practices.

# Selected Factors Known to Influence Breast Cancer

| Risk Factor | Comparison | RR | *95% CI* |
|---|---|---|---|
| Age at menarche | ≥15 vs. <12 y | 0.72 | *(0.62-0.82)* |
| Parity | ≥3 vs. none | 0.72 | *(0.61-0.86)* |
| Age at First Birth | >30 vs. ≤20 y | 1.46 | *(1.22-1.75)* |
| Education | >HS vs. <HS | 1.08 | *(0.90-1.29)* |
| BBD | Yes vs. No | 1.53 | *(1.41-1.65)* |
| Maternal History | Yes vs. No | 1.38 | *(1.14-1.67)* |
| Sister History | Yes vs. No | 1.47 | *(1.27-1.70)* |

From Hunter DJ, et al. Cancer Causes Control 1997;8:49-56. Analysis includes 322,647 women followed for 5-7 years, with 4,827 incident cases of breast cancer.

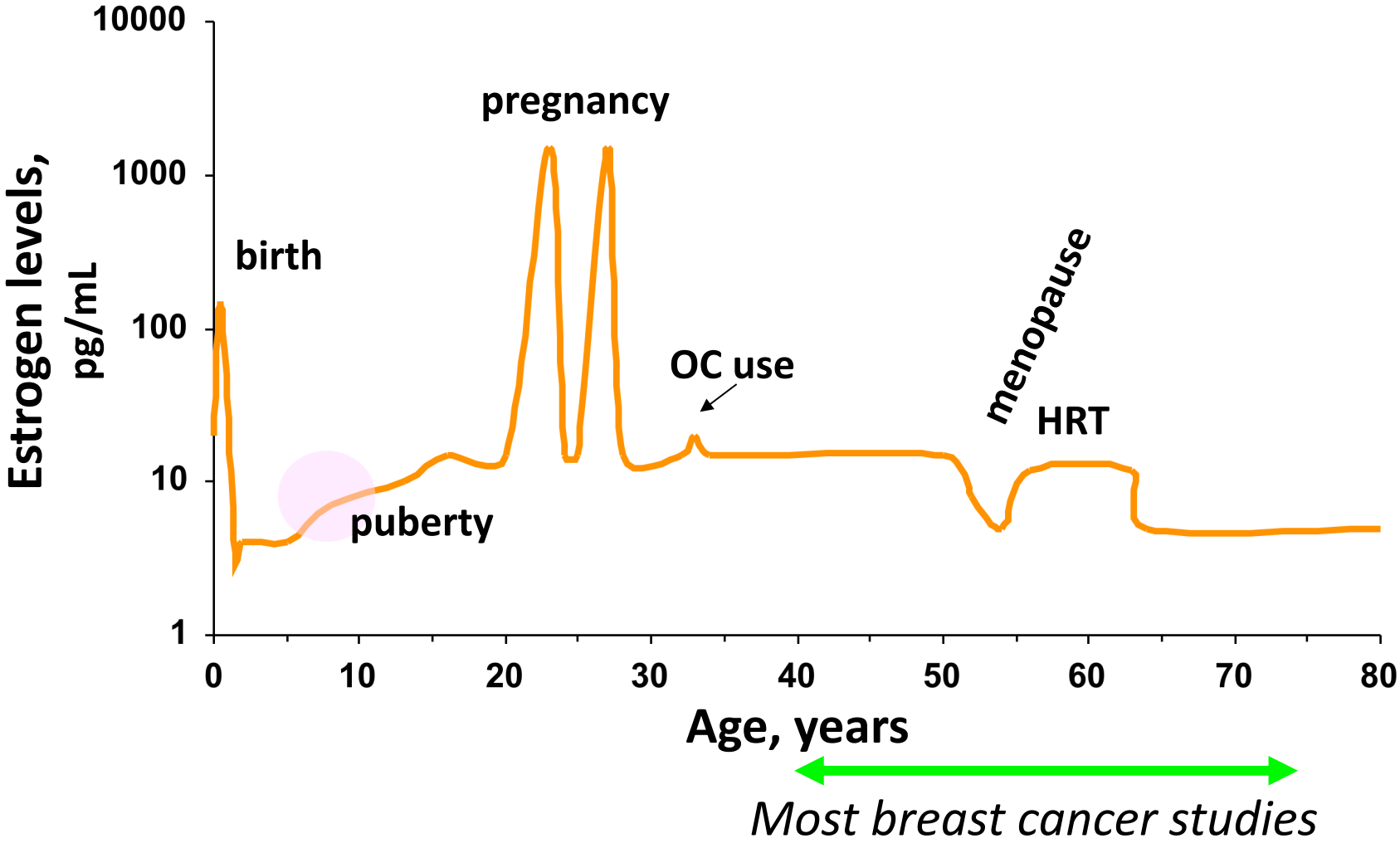
# Reproductive Experience and Risk of Breast Cancer

| | Hunter-gatherers | Americans |
|---|---|---|
| Age of menarche | 16.1 | 12.5 |
| Age at first birth | 19.5 | 24 (all), 26.5 (hi education) |
| Menarche to 1st birth | 3.4 | 11.5 (all), 14.0 (hi educ) |
| Duration of lactation/birth | 2.9 years | 3.0 months |
| Live births at age 50 | 5.9 | 1.8 |
| Age at menopause | 47 | 50.5 |
| Total # ovulations | 160 | 450 |

Eaton SB et al, 1994

- These finding support a strong role of hormonal estrogens.
- And estrogen levels vary throughout life.

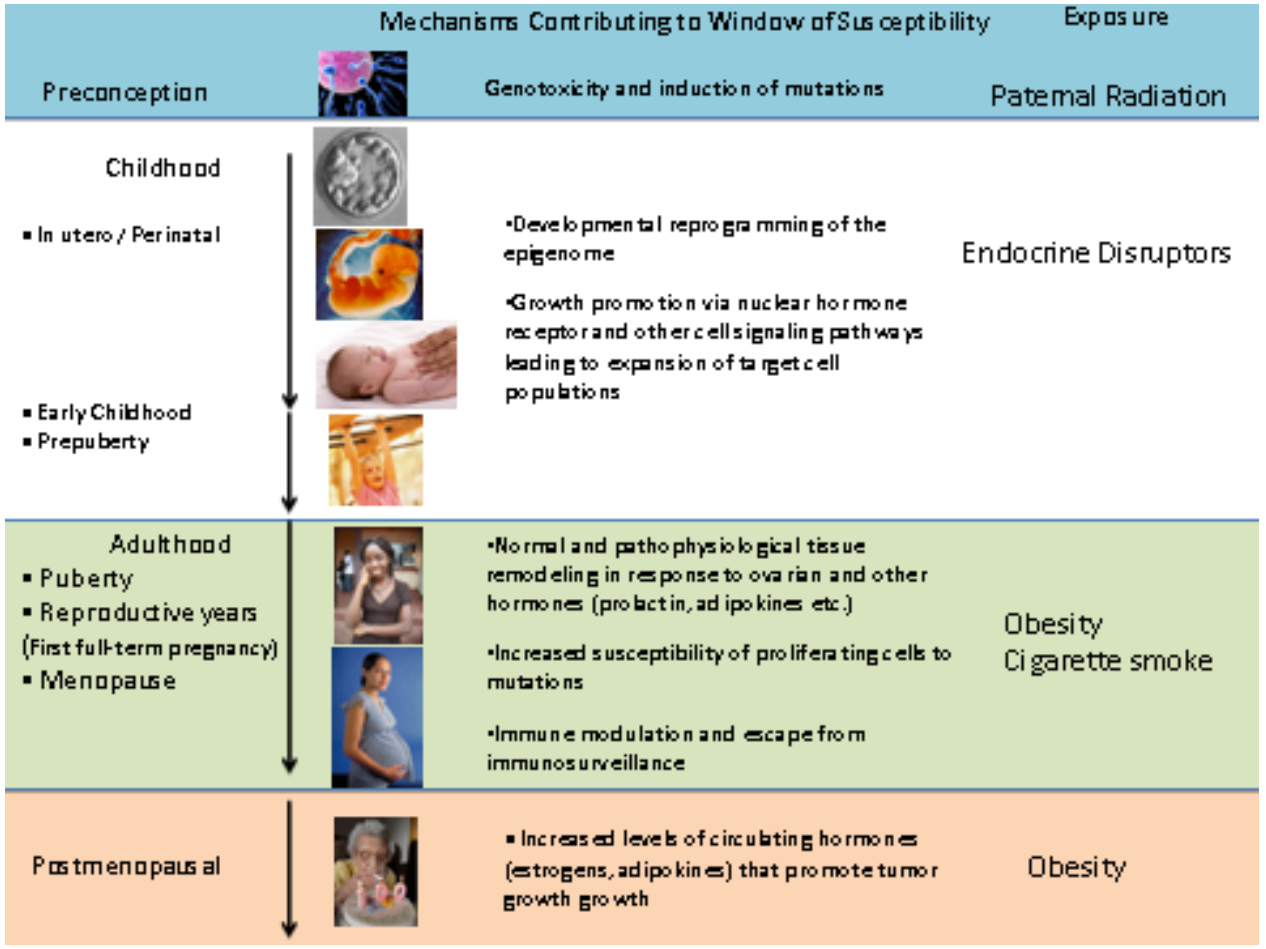
# Estrogen levels throughout life



# Seasons of Life & Breast Cancer Risk

- In utero: birthweight; in utero exposures?
- Infancy: infant feeding practices?
- Early childhood: growth patterns?
- Adolescence: earlier age at menarche increases risk
- Young adulthood: late age at first birth increases risk
- Childbearing years: greater parity decreases risk; breastfeeding decreases risk
- Menopausal transition: late menopause increases risk; use of HRT increases risk
- Postmenopausal years: lifetime body weight patterns influence risk

# Mechanisms at Life-course Stages

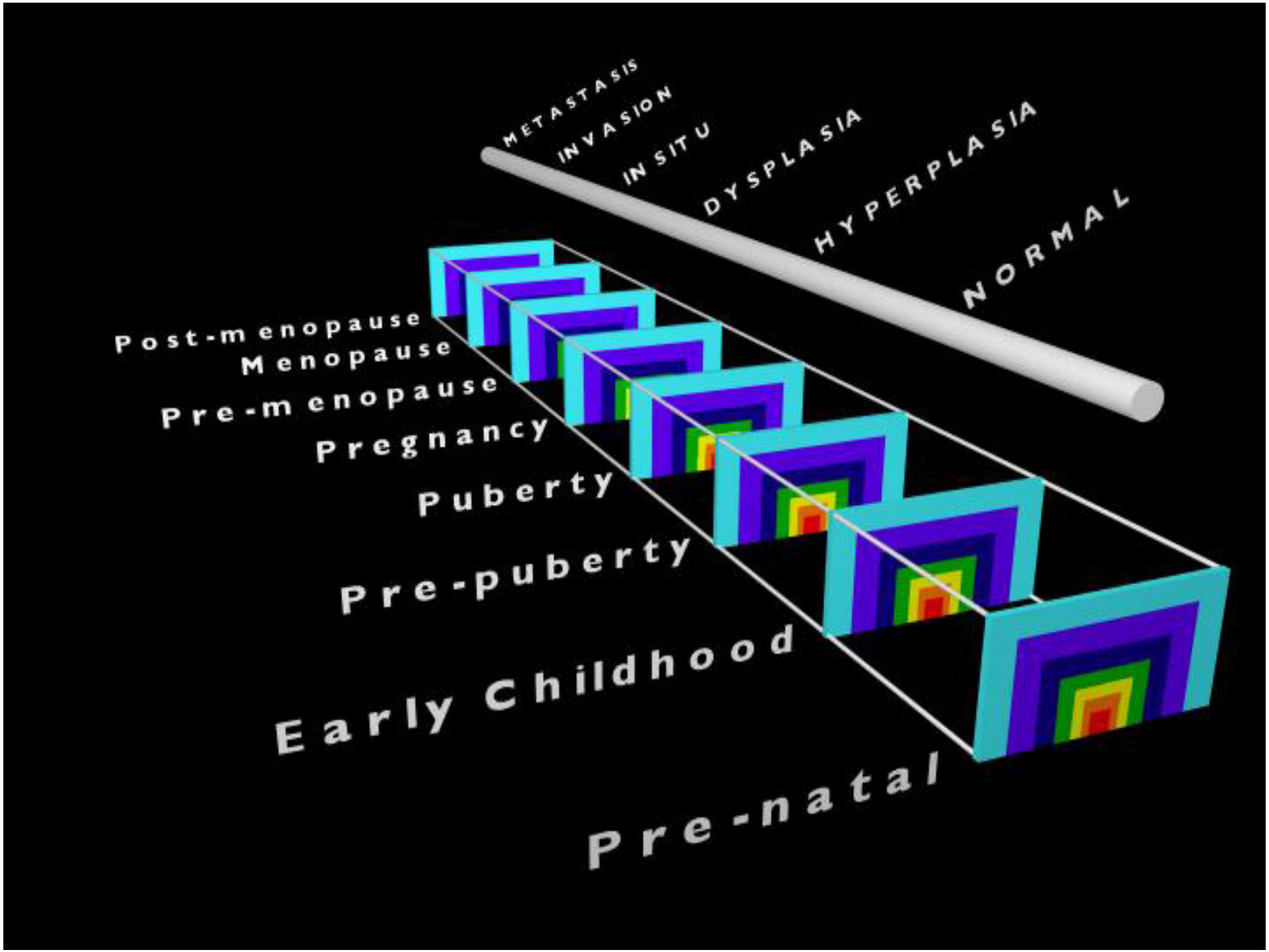


# Life-Course Approach

- Focus on early development
- Age at menarche an established risk factor
- Puberty a time of rapid breast development
- Changing age for initiation of puberty -likely due to environmental factors
- Intermediate outcomes available to study

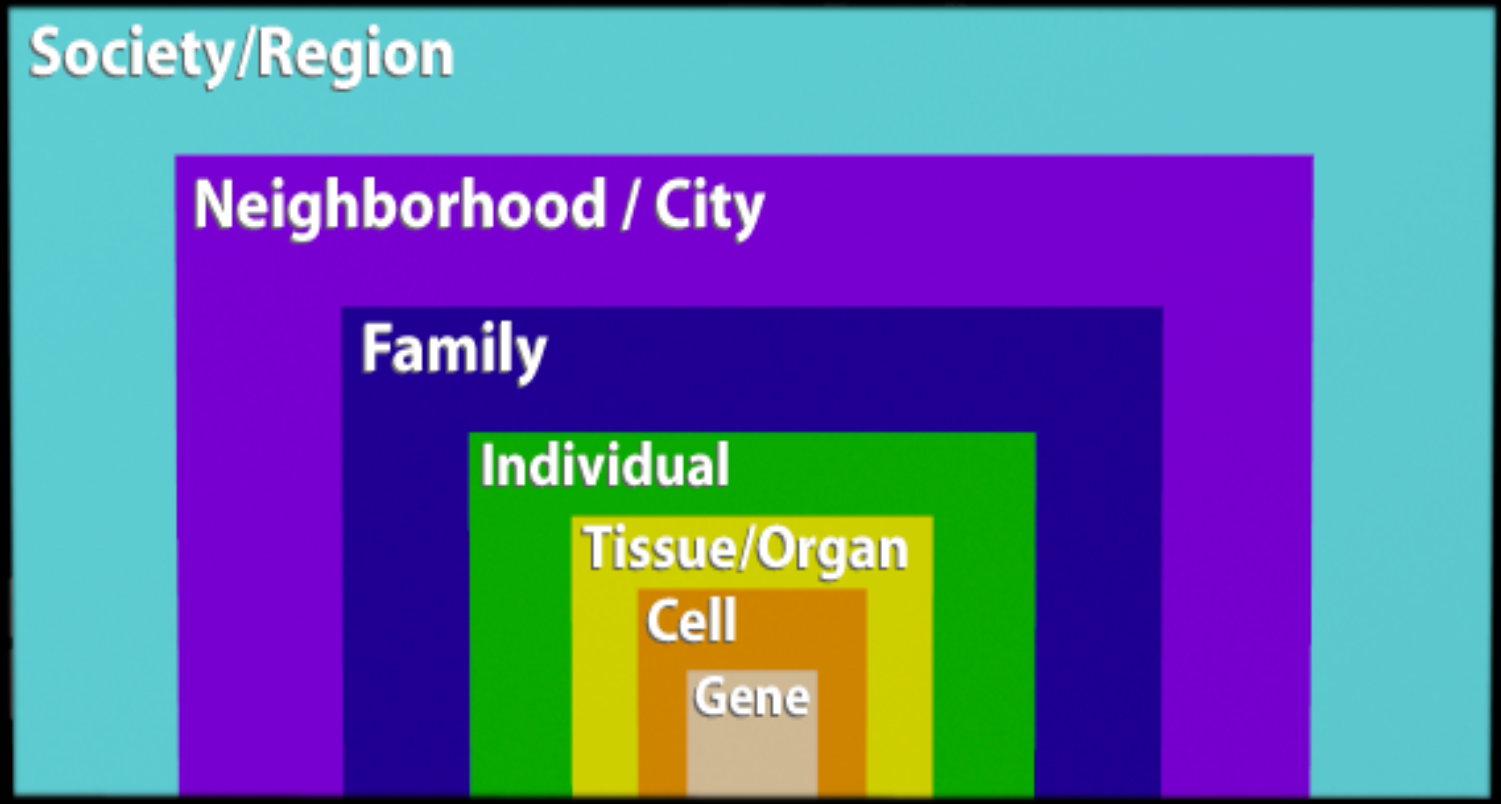
# Life-course Approach

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


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

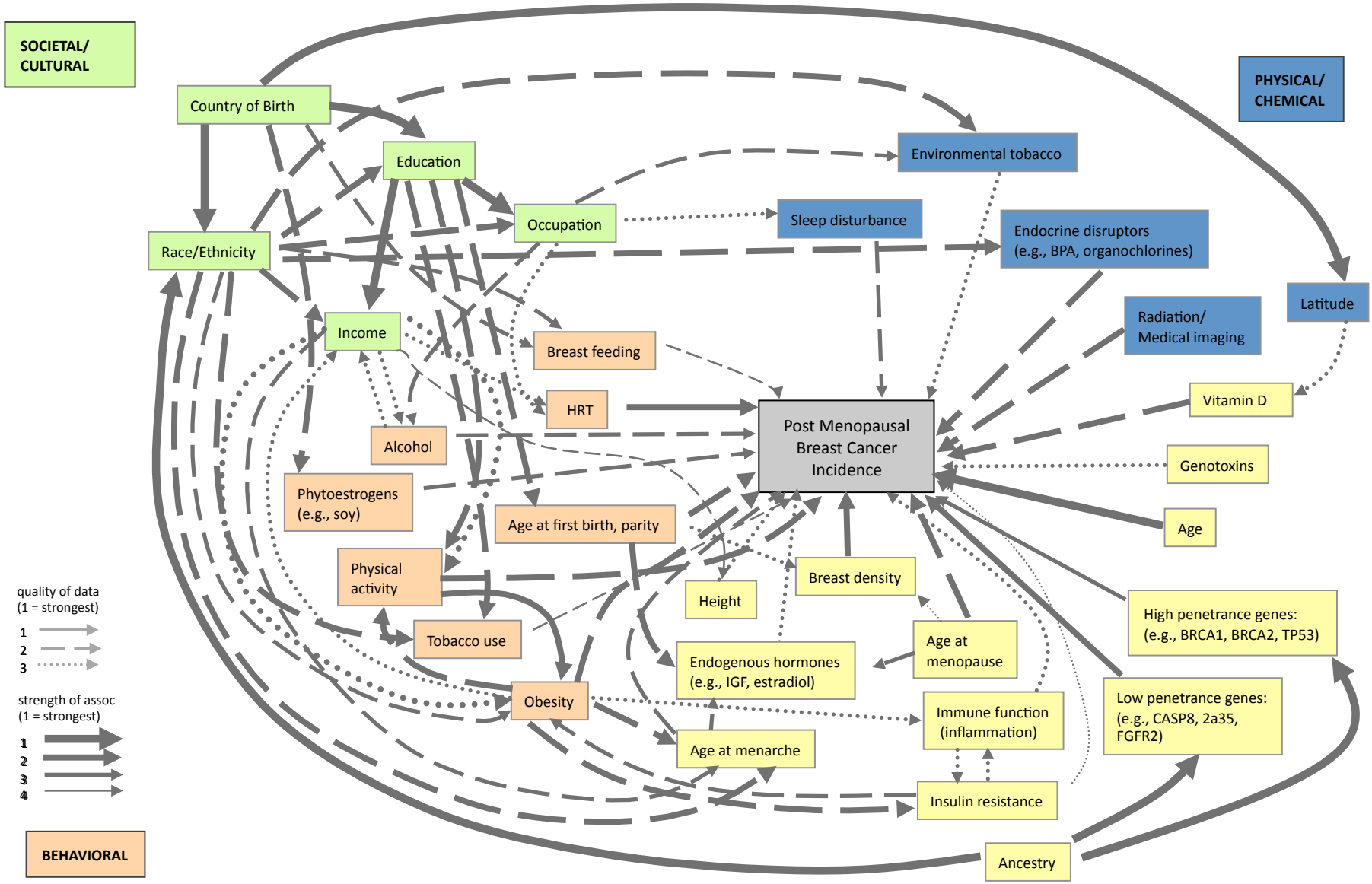
# Levels of Analysis

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


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

But life-course and multilevel causal factors and their interactions are complex….

# New Paradigm of Breast Cancer Causation and Prevention




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

# “Pre-conception”

- Earlier age at menarche associated with:
  - Maternal age a menarche
  - Maternal pre-pregnancy obesity
    - » Keim SA et al, 2009
  - Paternal influences

# *In Utero*

- DES exposure from mothers – elevated breast cancer risk
- Maternal weight gain

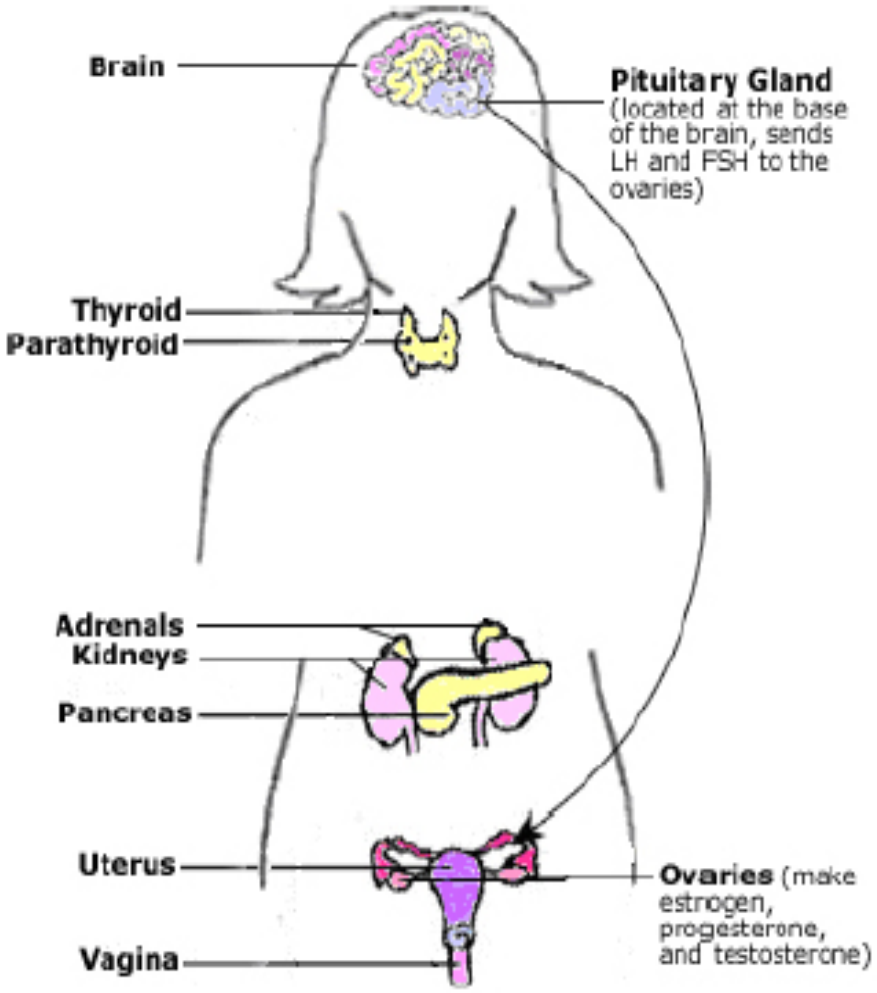
# Puberty

Reasons for interest as a window of susceptibility:

- Time of rapid development of both epithelial cells and stroma.
- Period of rapid growth in height.
- Age of menarche highly variable internationally
- Age of menarche dropping over last century with industrialization

# Puberty – The Hormonal Process

1. The brain's hypothalamus begins to release pulses of GnRH.
2. Cells in the anterior pituitary respond by secreting LH and FSH into the circulation.
3. The ovaries respond to the rising amounts of LH and FSH by growing and beginning to release estradiol.
4. Rising levels of estradiol produce the body changes of female puberty.



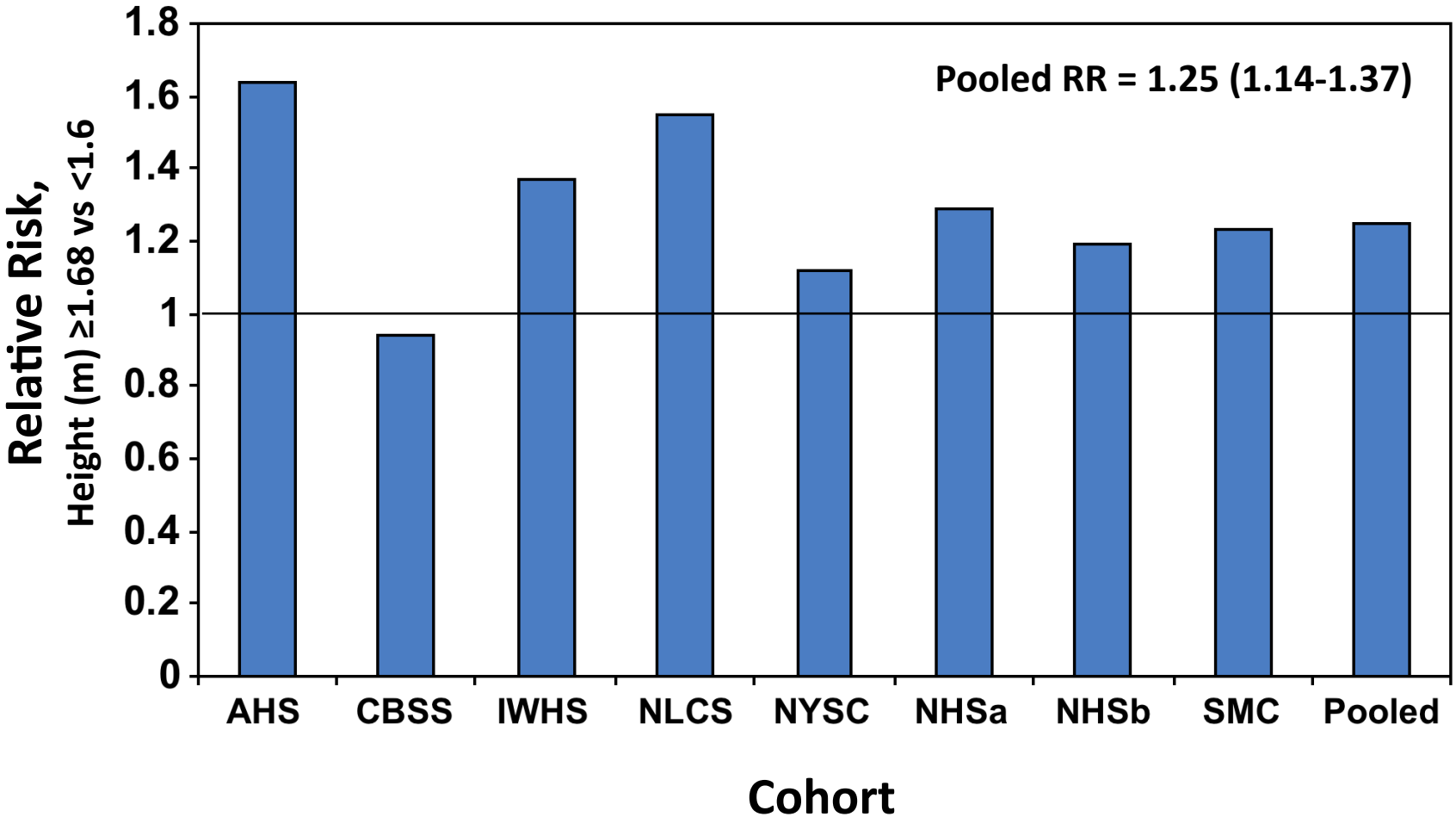
# Ionizing Radiation

Exposure of Japanese women to radiation following Hiroshima and Nagasaki led to increased rates of breast cancer in those exposed before age 14 years.

- Medical radiation for tuberculosis other conditions of the chest.

# Height & Breast Cancer

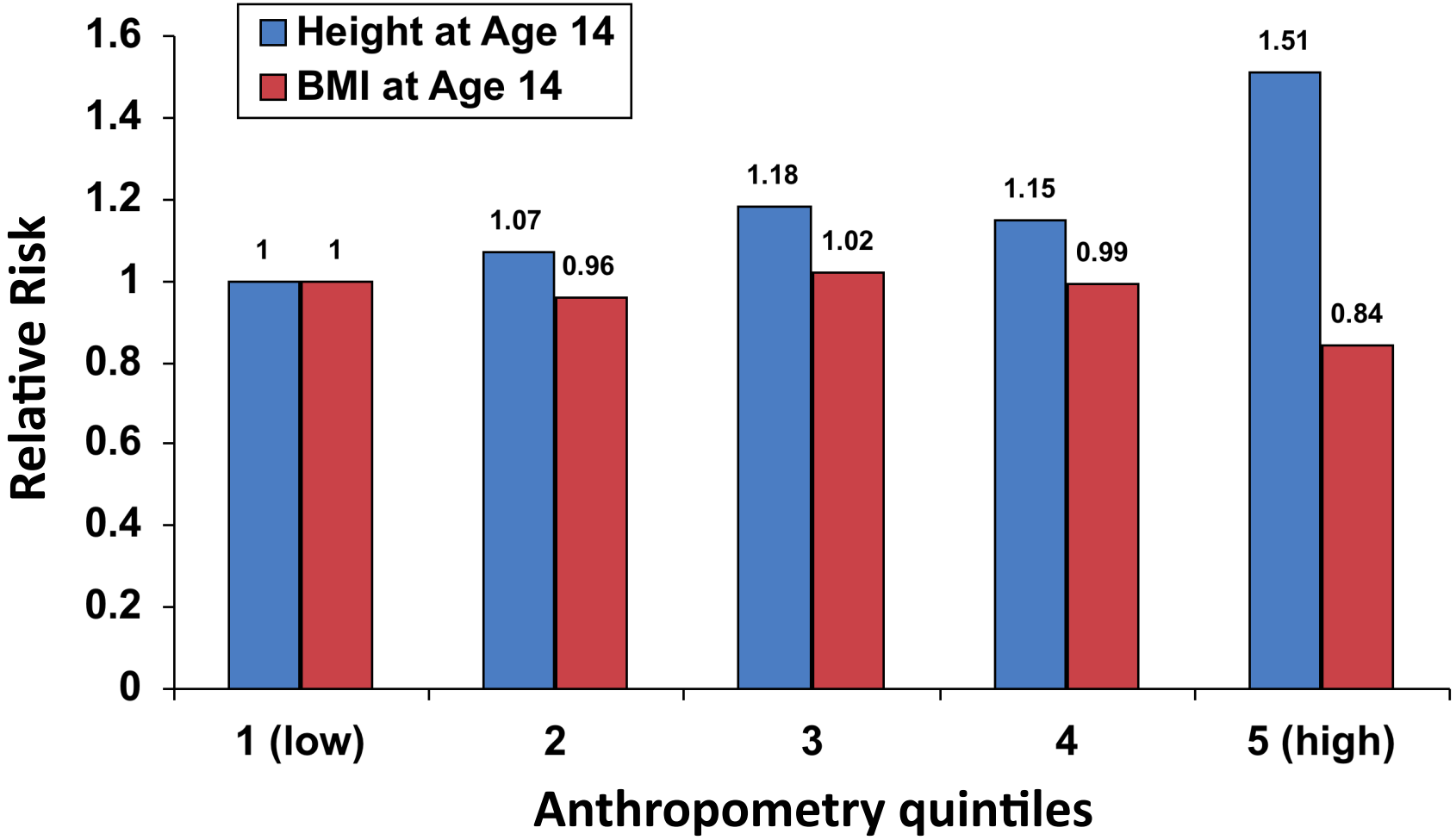
*Pooled Analysis, Cohort Studies of Diet & Breast Cancer*




from van den Brandt, et al., Am J Epidemiol, 2000

# Height & BMI at Age 14 y & Breast Cancer

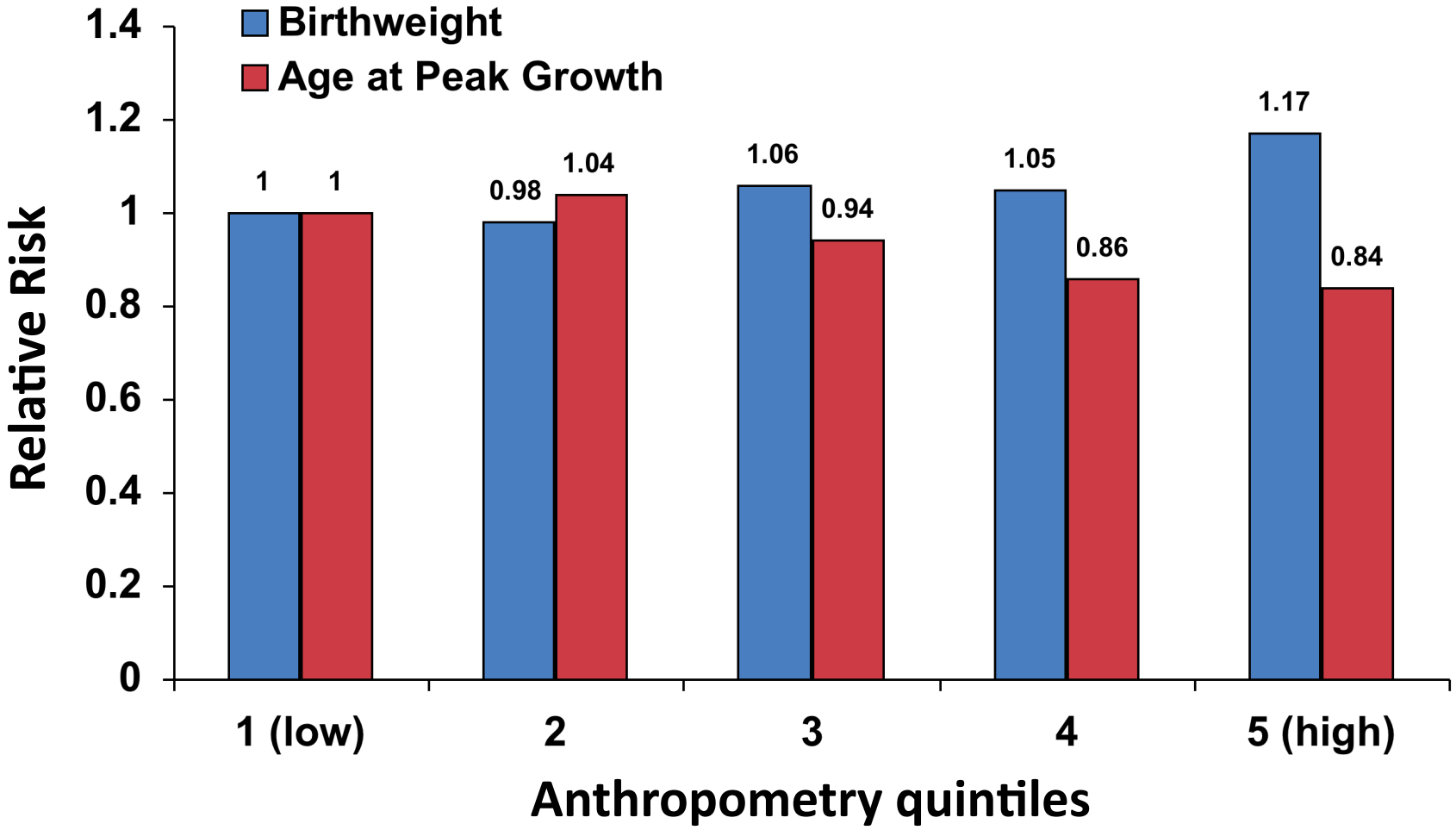
*117,415 Women in Denmark, 1930-2001*




Ahlgren, et al. N Engl J Med, 2004

# Birthweight & Age at Peak Growth & Breast Cancer

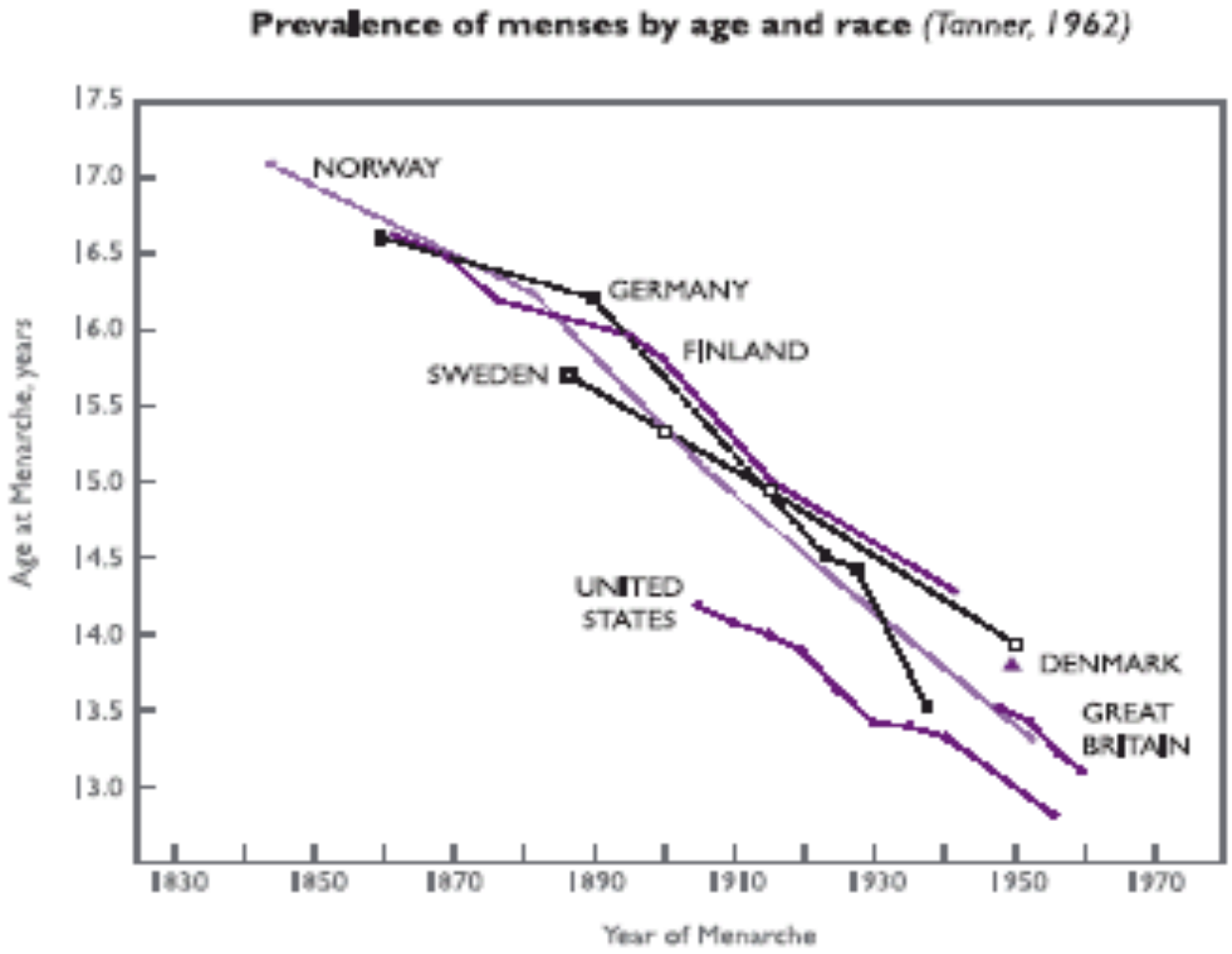
*117,415 Women in Denmark, 1930-2001*




Ahlgren, et al. N Engl J Med, 2004

# The Changing Age of Puberty Over Time

# International Trends in Age at Menarche



# Korean example

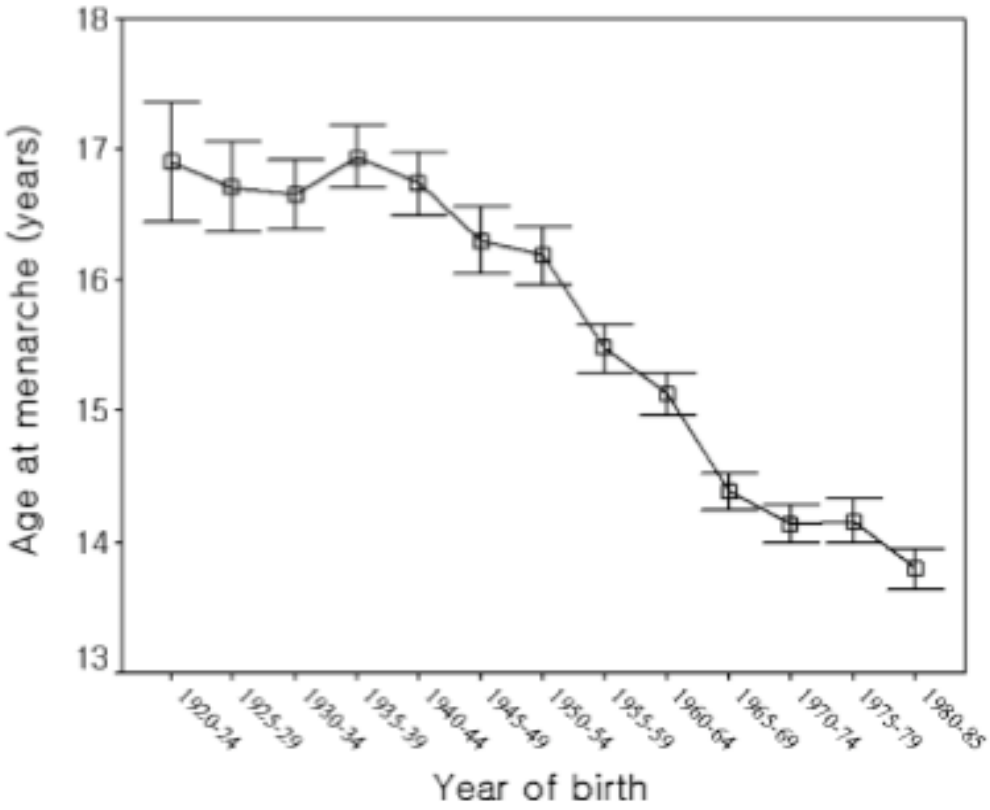
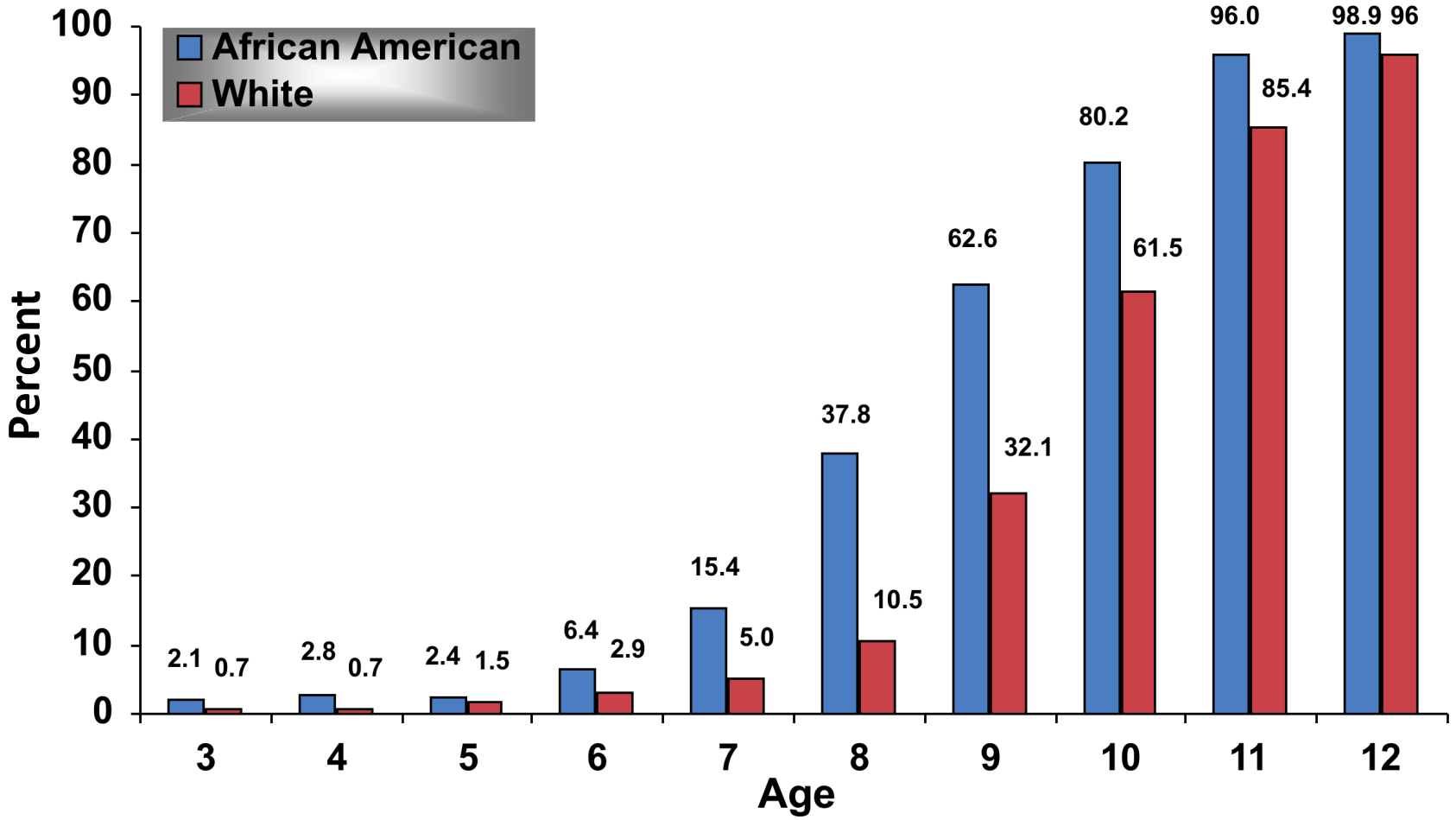



Fig. 1 Secular trend of mean age at menarche for women born between 1920 and 1985

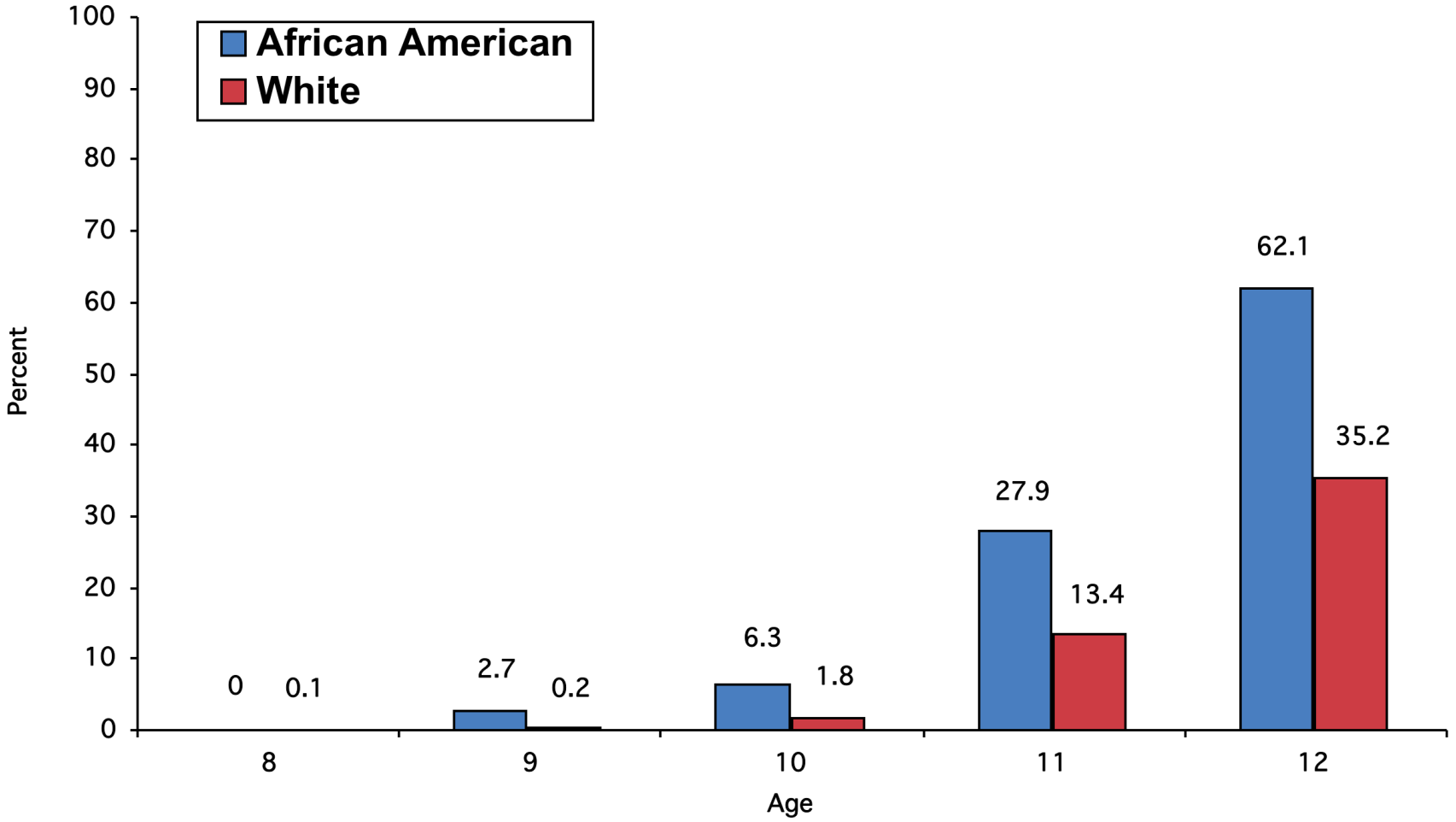
Cho GJ et al. Eur J Pediatrics 2010

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




Herman-Giddens et al., Pediatrics, 1997

# Prevalence of Menses by Age and Race



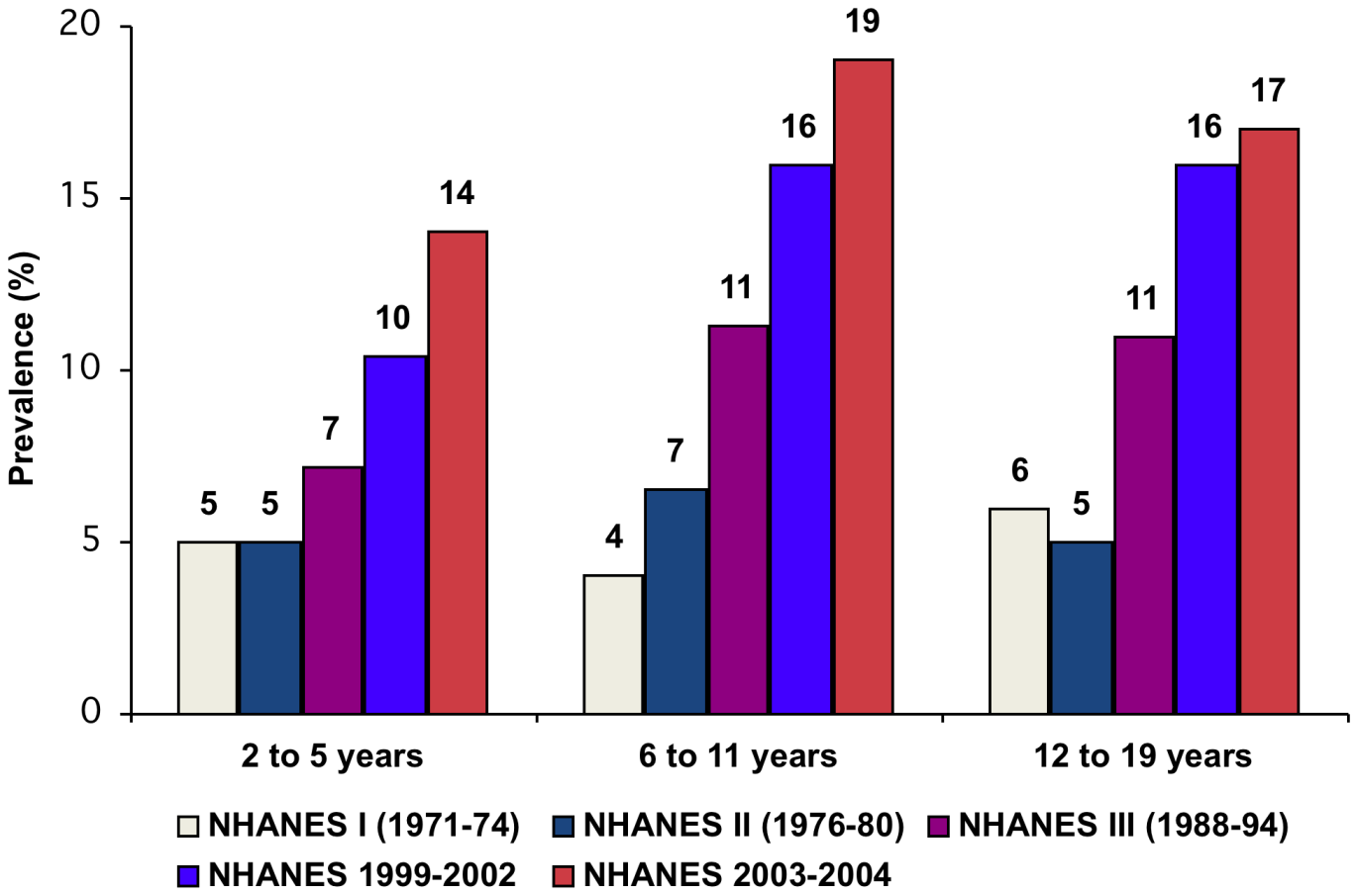

Herman-Giddens et al., Pediatrics, 1997

What might be the reasons for a decreasing age at pubertal onset?

# Possible Biologic Pathways

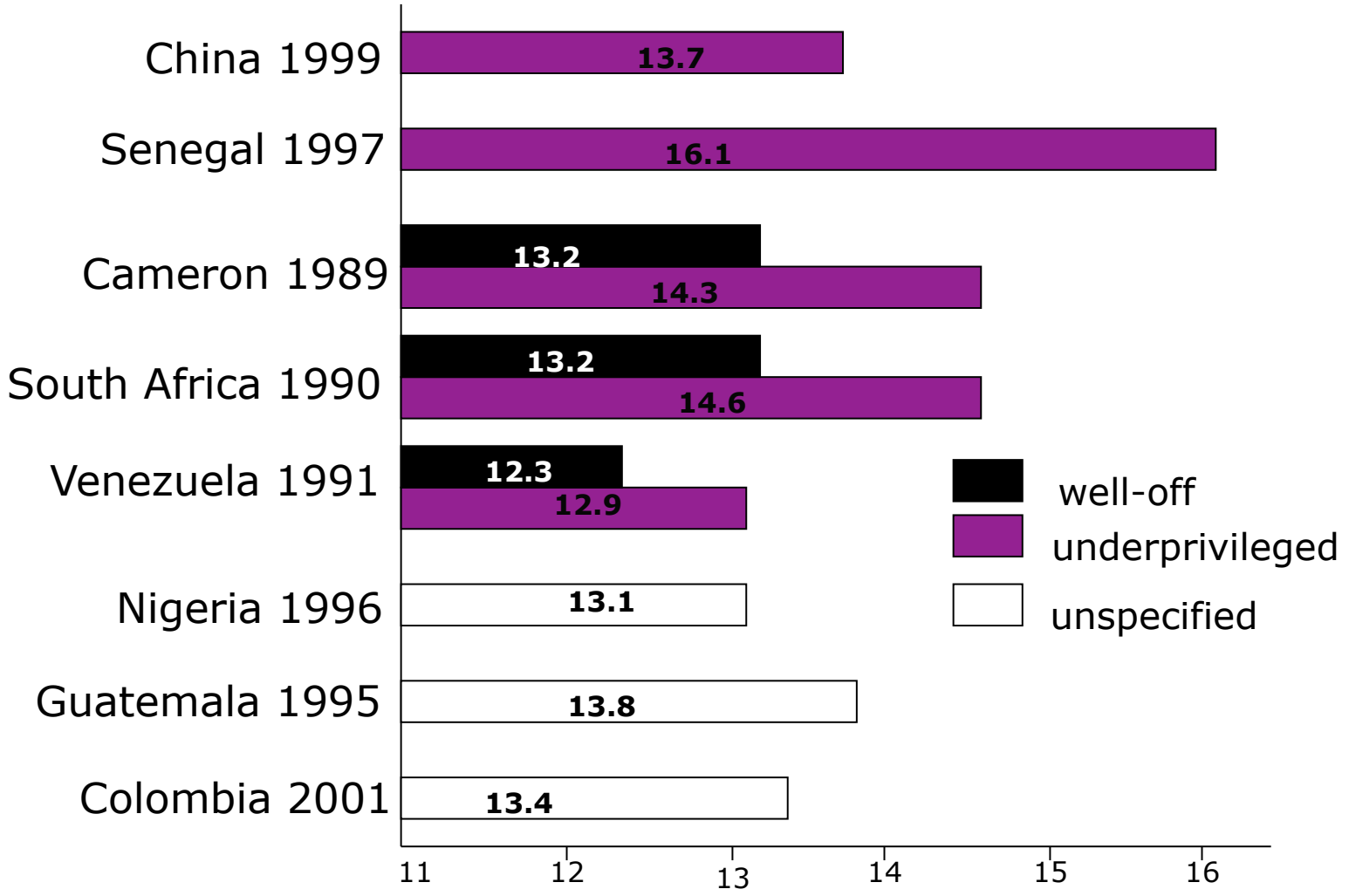
- Obesity/Physical activity - Energy Balance
- Intrauterine programming and IGF-1
- Stem Cells
- Gene-environment interactions
- Endocrine disruptors and other environmental factors
- Psychosocial environment

# Trends in Overweight* Prevalence (%), Children and Adolescents, by Age Group, US, 1971-2004



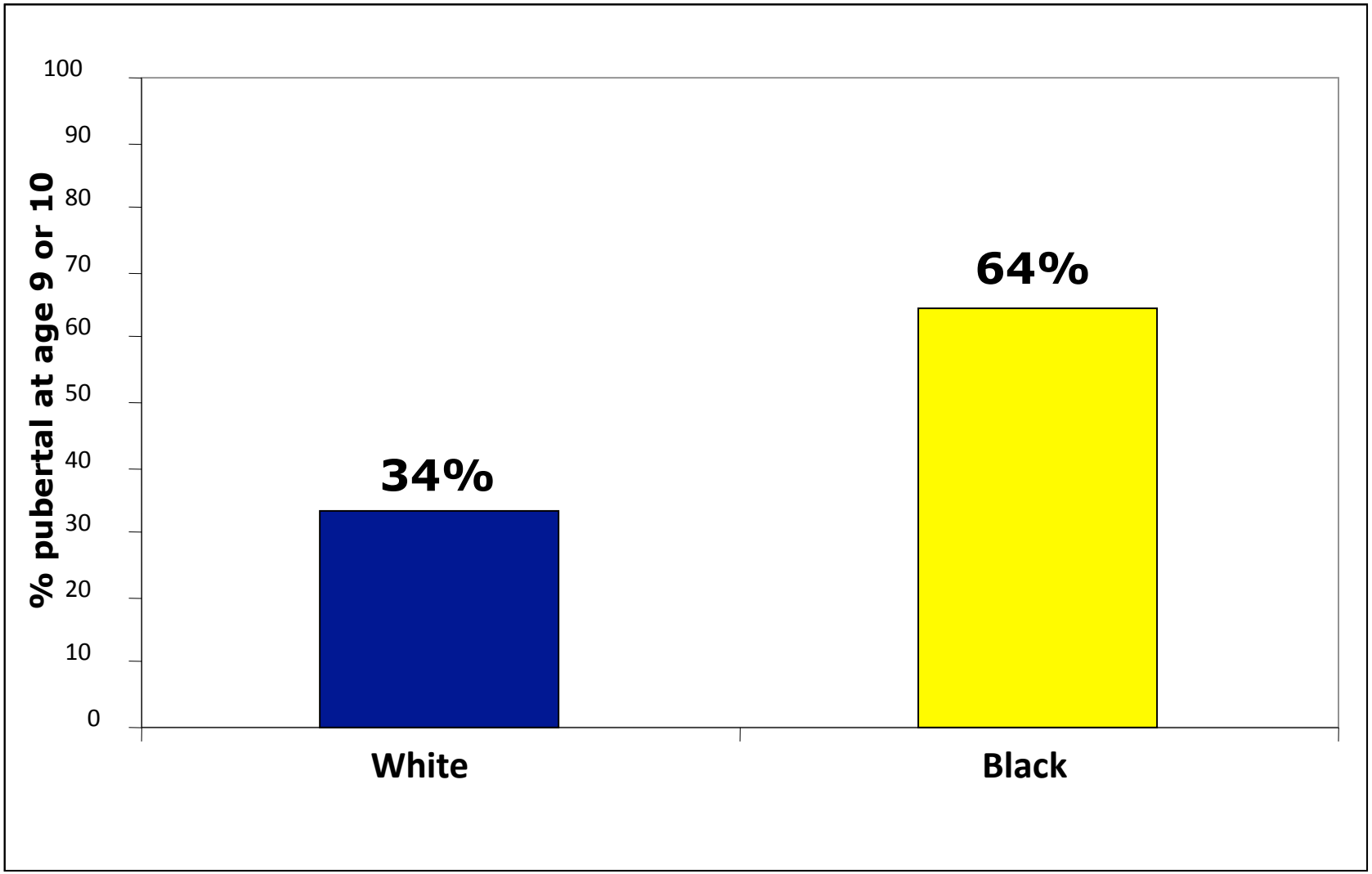

*Overweight is defined as at or above the 95th percentile for body mass index by age and sex based on reference data.
Source: National Health and Nutrition Examination Survey, 1971-1974, 1976-1980, 1988-1994, 1999-2002, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002, 2004. 2003-2004: Ogden CL, et al. Prevalence of Overweight and Obesity in the United States, 1999-2004. JAMA 2006; 295 (13): 1549-55.

# Socioeconomic circumstances influence age at menarche

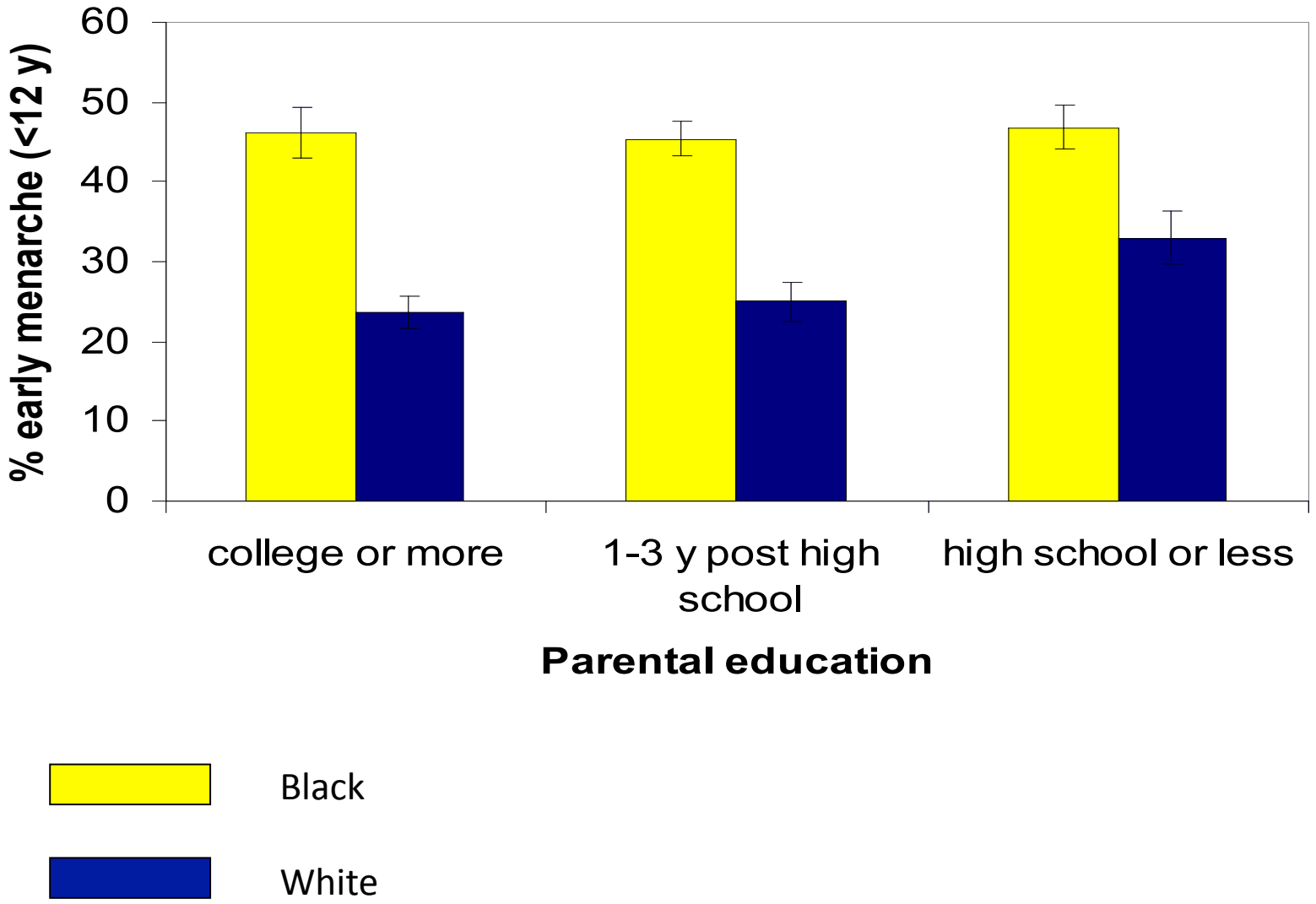



Parent et al.
Endocr Rev 2003

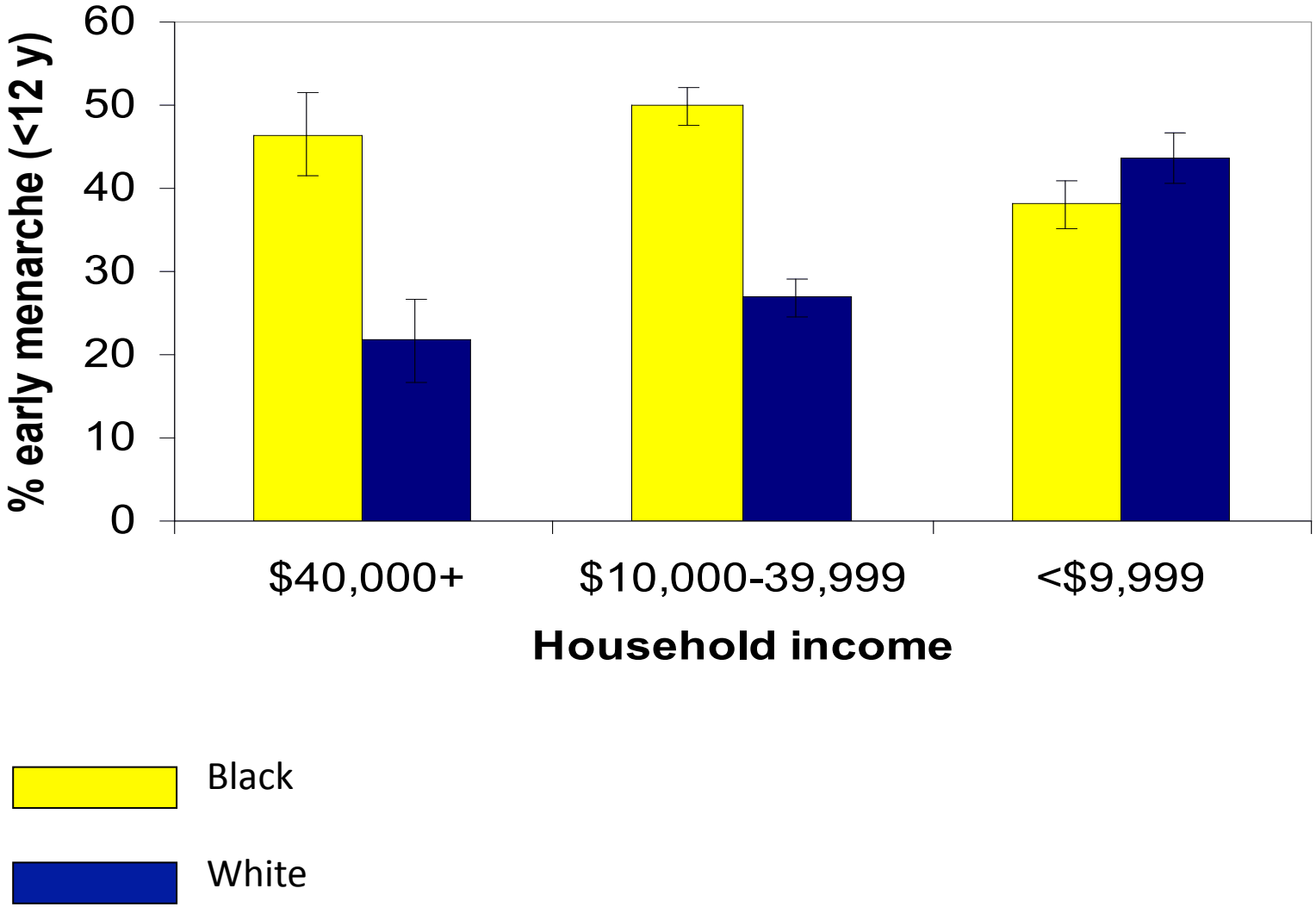
# Racial disparities in socioeconomic characteristics, adiposity and pubertal activation: NGHS



# Prevalence of Early Menarche Among White and Black Girls in the NGHS by Parental Education



# Prevalence of Early Menarche Among White and Black Girls in the NGHS by Household Income



**Adverse socioeconomic circumstances are associated with a greater risk of early menarche among white girls but not among black girls.**

***Among white girls*, a socioeconomic gradient was noted in the risk of early menarche, with decreasing income and education.**

*This association is modulated by adiposity.*

# Socioeconomic deprivation and puberty

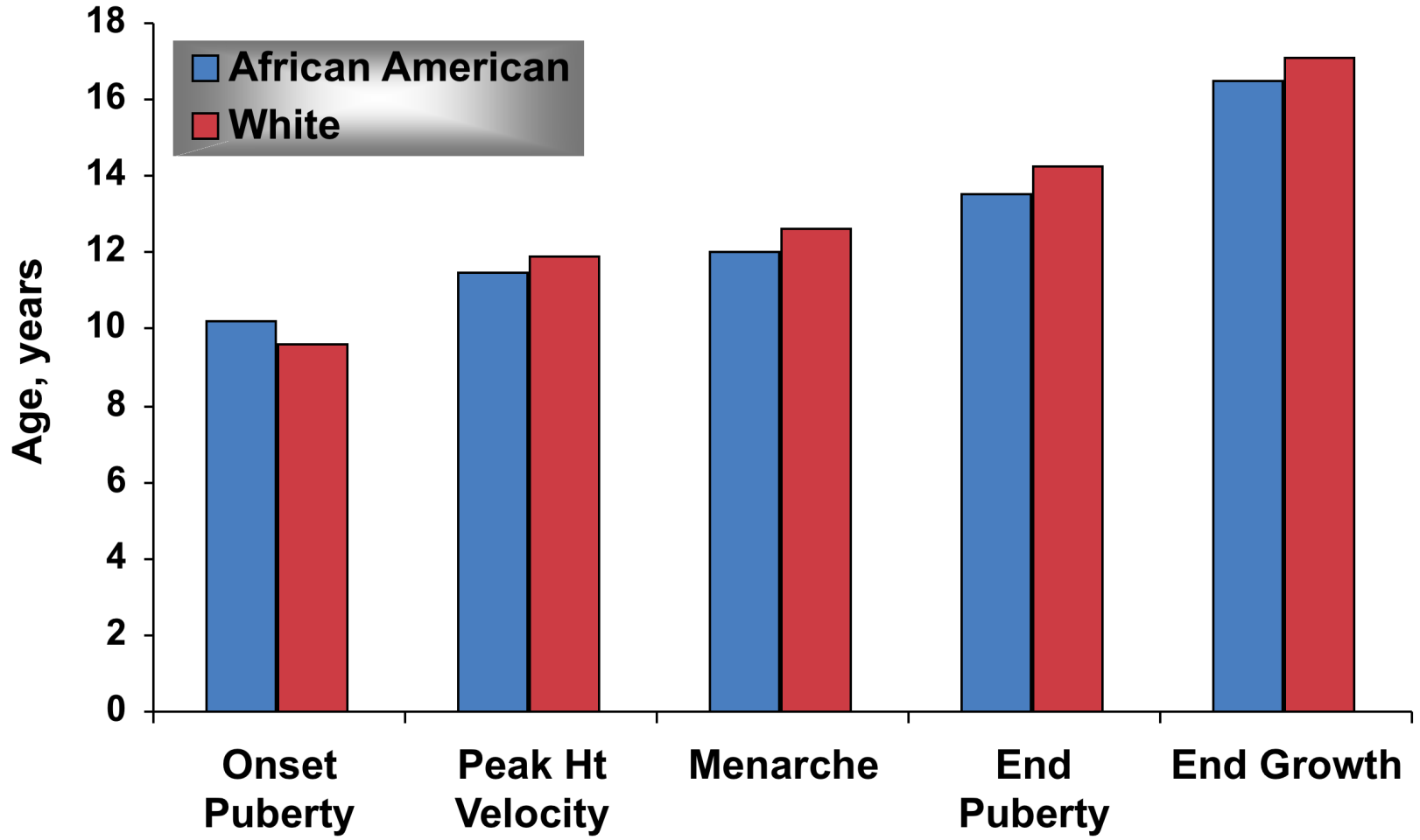
While later ages at menarche coincide with adverse socioeconomic circumstances in developing countries, perhaps as a consequence of poor diet, socioeconomic status has generally not been related to menarcheal timing in developed countries.

*However, a change may be underway in the United States, with lower socioeconomic status becoming linked to earlier pubertal timing in girls*.

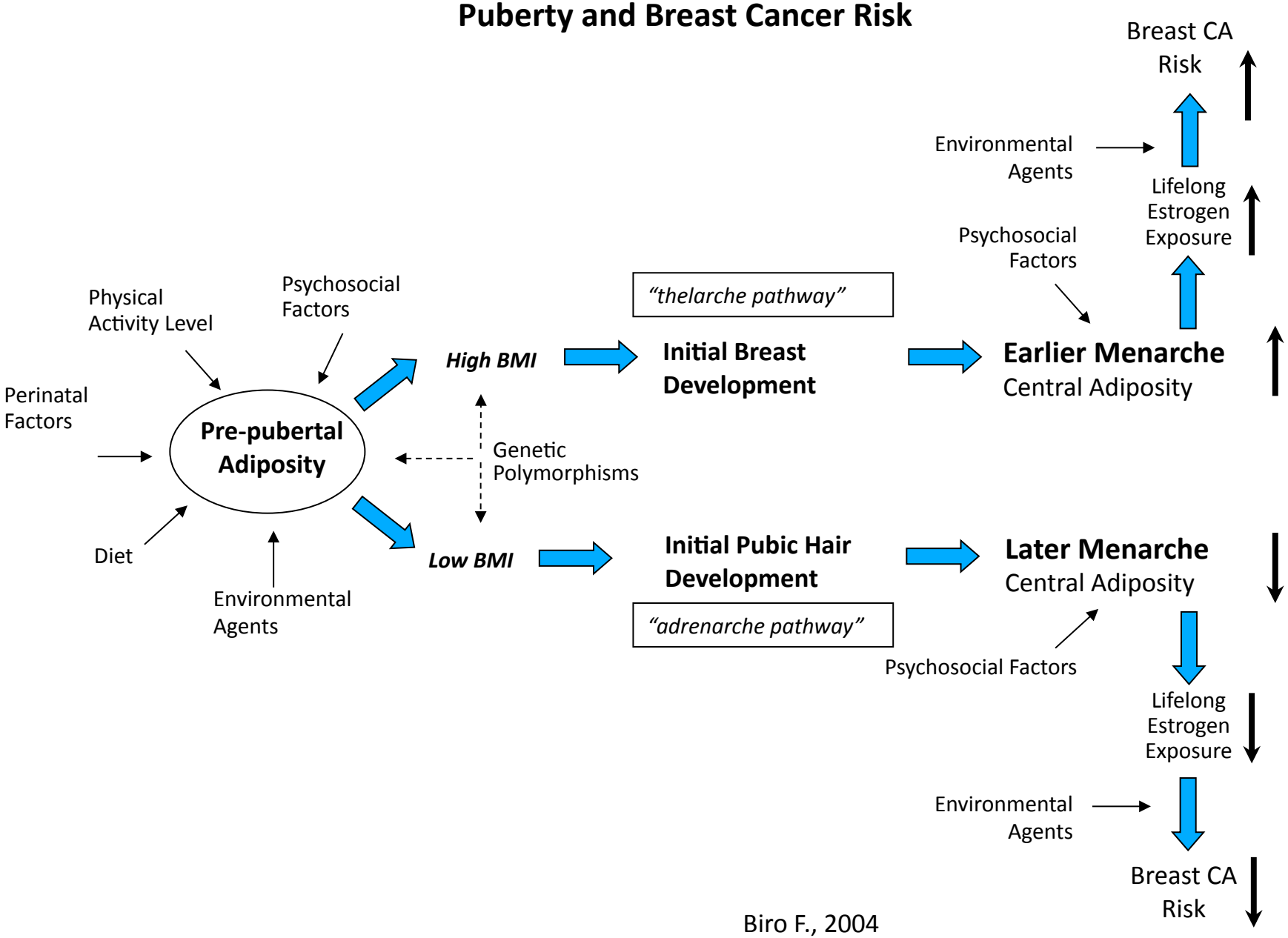
**This pattern of relationships, together with secular trends toward early puberty and higher BMI may herald a demographic shift in breast cancer risk.**

# Median Age at Maturation Milestones

*NHLBI Growth and Health Study, Biro et al., Pediatrics, 2006*



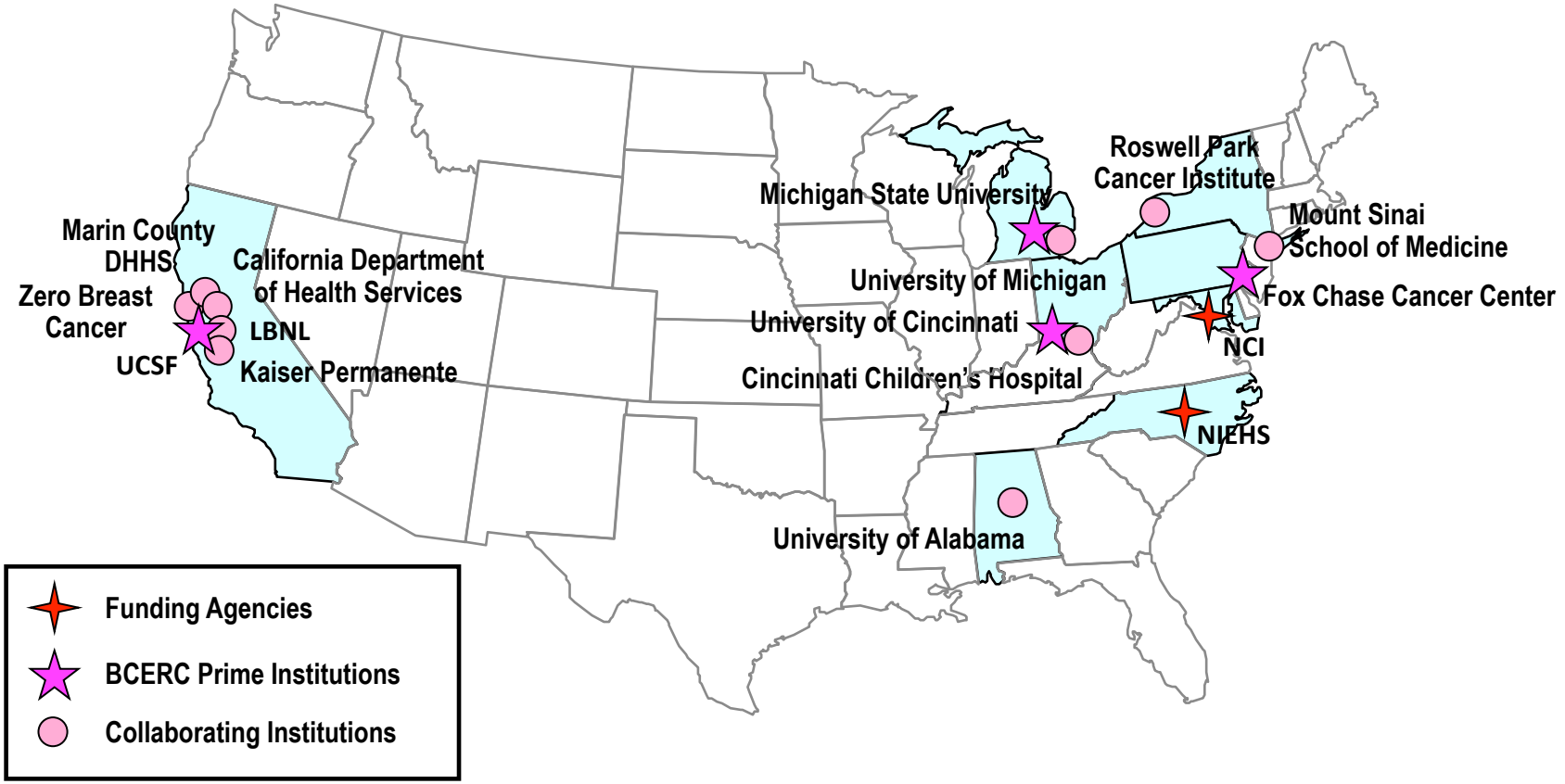
# Puberty and Breast Cancer Risk




Biro F., 2004

# The Breast Cancer and the Environment Research Centers

# Breast Cancer and the Environment Research Centers (BCERCs)



# 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

# 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

# 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, absent father
- Demographics
  - SES, race/ethnicity, residence, ancestry

# Anthropometry & Tanner Staging

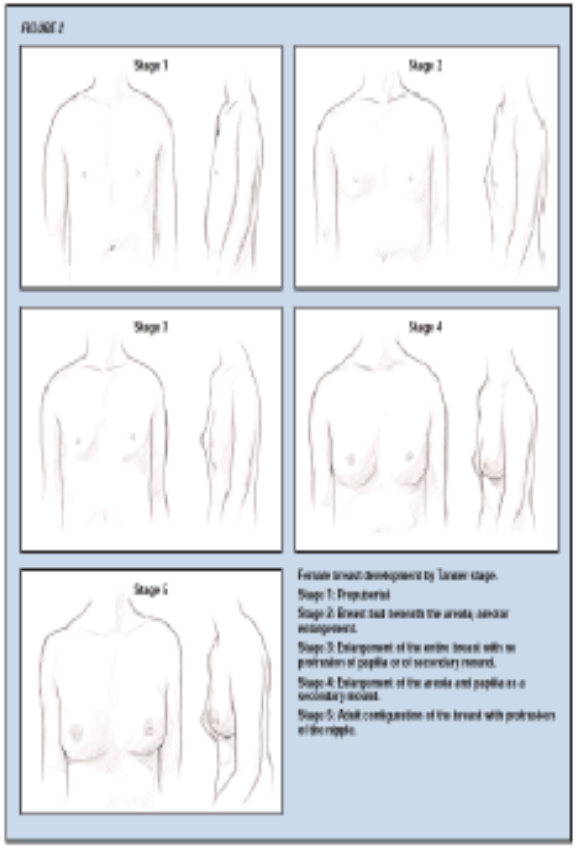
- Anthropometry
  - Annual standardized clinic measurement
  - Annual bioelectrical impedance analysis
  - Maternal or self report via questionnaire
  - Data extracted from KP records
- Tanner Staging
  - Annual standardized clinic measurement of breast and pubic hair development
  - Data extracted from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

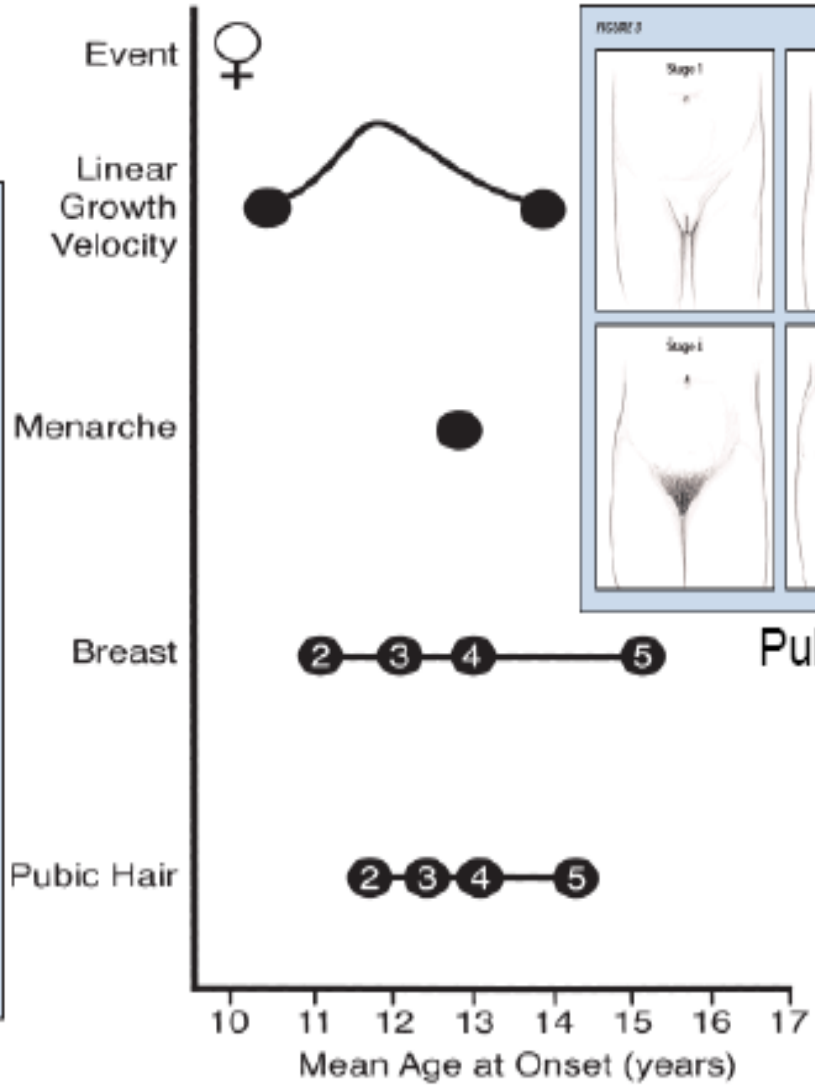
# Biospecimens

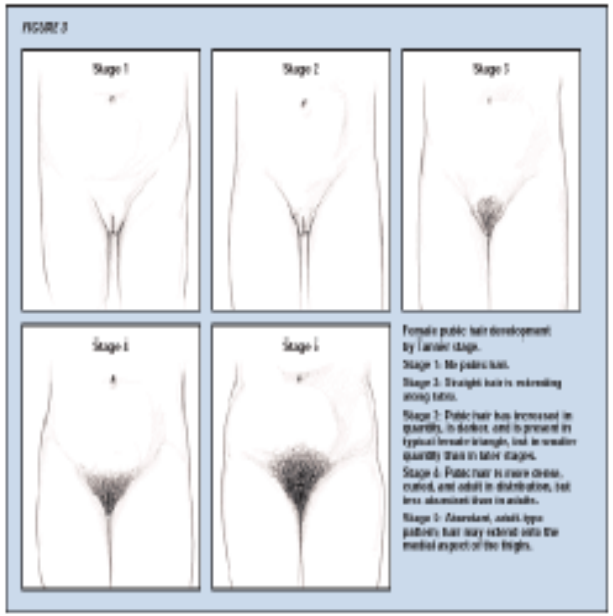
- Urine
  - Casual specimen at baseline, annual clinic visits
    - To assess exposure to selected environmental factors
- Blood
  - 20 ml collected at least once
    - genotyping
    - To assess exposure to selected environmental factors
- Saliva
  - if blood collection is refused or unsuccessful
 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

# Puberty – Tanner Staging

Breast staging

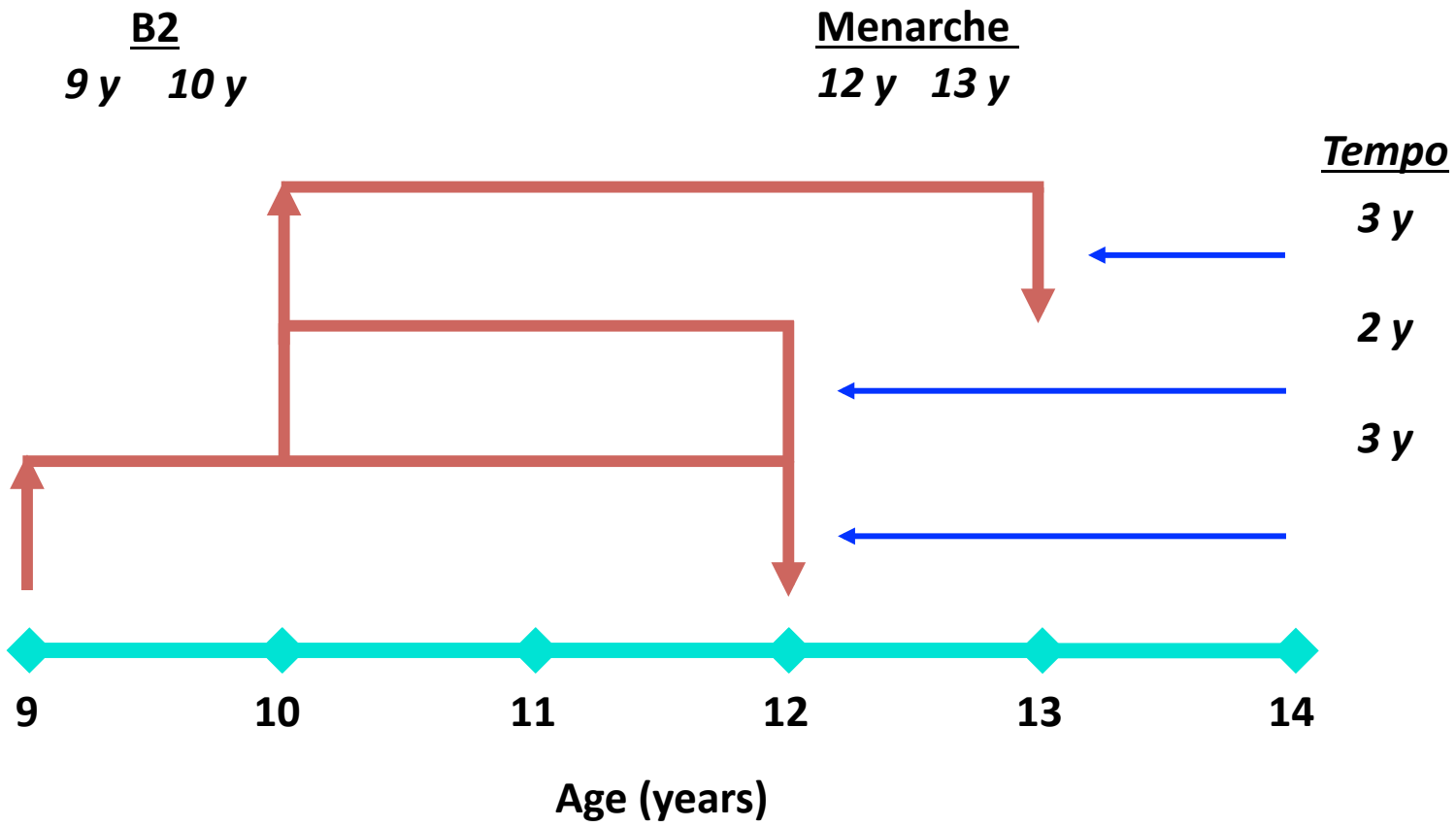




Pubic hair staging

# Tempo (Pace, B2 → Menarche)



# Results to Date

# Breast Maturation Status, age 7 years

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

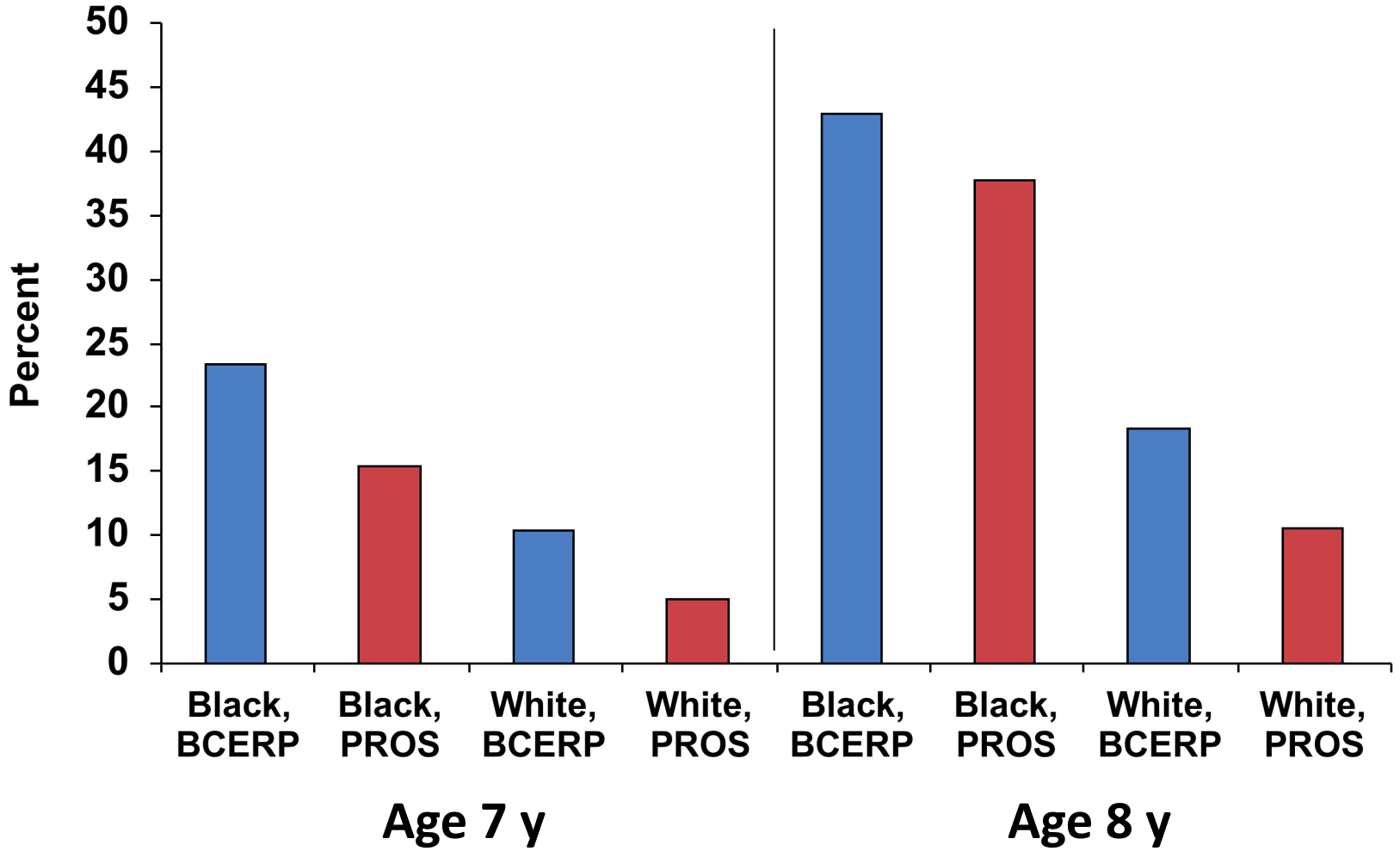
| Group | MSSM | | Cincinnati | | KPNC | | Total | |
|---|---|---|---|---|---|---|---|---|
| | B1 | B2+ (%) | B1 | B2+ (%) | B1 | B2+ (%) | B1 | B2+ (%) |
| Black | 77 | 31 (28.7) | 75 | 34 (31.3) | 75 | 26 (25.7) | 233 | 71 (23.4) |
| Hispanic | 117 | 25 (17.6) | 10 | 1 (9.1) | 79 | 10 (11.2) | 206 | 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 | MSSM | | Cincinnati | | KPNC | | Total | |
|---|---|---|---|---|---|---|---|---|
| | B1 | B2+ (%) | B1 | B2+ (%) | B1 | B2+ (%) | B1 | B2+ (%) |
| Black | 83 | 11 (11.7) | 54 | 58 (51.8) | 55 | 24 (30.4) | 109 | 82 (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 adjusted for BMI

*Deardorff, et al., J Adol Health 2011*

| Income category | B2 onset All RR (95% CI) | PH2 onset - AA RR (95% CI) |
|---|---|---|
| Higher income, ≥ $75,000/year | 2.4 (1.2 – 4.9) | 4.6(1.6-12.7) |
| Lower income, < $75,000/year | 0.8 (0.5 – 1.2) | 1.1(.5-2.6) |

# FIN

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