“Life-course Epidemiology of Breast Cancer”

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UCSF
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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

Rate Per 100,000

Breast
Colon and rectum
Lung & bronchus
Uterine corpus
Non-Hodgkin lymphoma
Melanoma


*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Cancer Death Rates* Among Women, US, 1930-2006

*Age-adjusted to the 2000 US standard population.
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

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

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

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

Eaton SB et al, 1994
• These findings support a strong role of hormonal estrogens.
• And estrogen levels vary throughout life.
Estrogen levels throughout life

Most breast cancer studies
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

<table>
<thead>
<tr>
<th>Precanception</th>
<th>Childhood</th>
<th>Adulthood</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Childhood, Prepuberty</td>
<td>In utero / Perinatal</td>
<td>Puberty, Reproductive years (first full-term pregnancy), Menopause</td>
<td></td>
</tr>
</tbody>
</table>
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
Levels of Analysis

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

Pooled RR = 1.25 (1.14-1.37)

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

Birthweight & Age at Peak Growth & Breast Cancer

117,415 Women in Denmark, 1930-2001

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

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

*Overweight is defined as at or above the 95th percentile for body mass index by age and sex based on reference data.
Socioeconomic circumstances influence age at menarche

Mean age at menarche (yr)

- **China 1999**: 13.7
- **Senegal 1997**: 16.1
- **Cameron 1989**: 13.2 (well-off), 14.3 (underprivileged)
- **South Africa 1990**: 13.2 (well-off), 14.6 (underprivileged)
- **Venezuela 1991**: 12.3 (well-off), 12.9 (underprivileged)
- **Nigeria 1996**: 13.1
- **Guatemala 1995**: 13.8
- **Colombia 2001**: 13.4

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

% early menarche (<12 y)

Parental education

- college or more
- 1-3 y post high school
- high school or less

Black

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

Household income

% early menarche (<12 y)

$40,000+

$1,000-39,999

<9,999

Black

White
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

Pre-pubertal Adiposity

Physical Activity Level
Perinatal Factors
Diet
Environmental Agents

Psychosocial Factors

High BMI

“thelarche pathway”

Initial Breast Development

Earlier Menarche
Central Adiposity

Later Menarche
Central Adiposity

Low BMI

“adrenarche pathway”

Initial Pubic Hair Development

Psychosocial Factors

Environmental Agents

Breast CA Risk

Lifelong Estrogen Exposure

Geneic Polymorphisms

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

- Stage 1: Prepubertal
- Stage 2: Breast bud without areola or secondary mound
- Stage 3: Enlargement of the entire breast with or without areola or secondary mound
- Stage 4: Enlargement of the areola and papilla on a secondary mound
- Stage 5: Adult configuration of the breast with projections at the nipples

Linear Growth Velocity

Menarche

Pubic hair staging

Mean Age at Onset (years)
Tempo (Pace, B2 → Menarche)

B2
9 y 10 y

Menarche
12 y 13 y

Tempo
3 y
2 y
3 y

Age (years)
Results to Date
Breast Maturation Status, age 7 years

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

<table>
<thead>
<tr>
<th>Group</th>
<th>MSSM</th>
<th>Cincinnati</th>
<th>KPNC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B1</td>
<td>B2+ (%)</td>
<td>B1</td>
<td>B2+ (%)</td>
</tr>
<tr>
<td>Black</td>
<td>77</td>
<td>31 (28.7)</td>
<td>75</td>
<td>34 (31.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>117</td>
<td>25 (17.6)</td>
<td>10</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>0 (0.0)</td>
<td>40</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>White</td>
<td>184</td>
<td>29 (13.6)</td>
<td>179</td>
<td>13 (6.8)</td>
</tr>
</tbody>
</table>
Breast Maturation Status, age 8 years
*BCERP Puberty Studies, Biro et al., Pediatrics, 2010*

<table>
<thead>
<tr>
<th>Group</th>
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<th>KPNC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B1</td>
<td>B2+ (%)</td>
<td>B1</td>
<td>B2+ (%)</td>
</tr>
<tr>
<td>Black</td>
<td>83</td>
<td>11 (11.7)</td>
<td>54</td>
<td>58 (51.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>97</td>
<td>60 (38.2)</td>
<td>8</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>4  (0.0)</td>
<td>34</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>White</td>
<td>156</td>
<td>57 (26.7)</td>
<td>152</td>
<td>12 (7.3)</td>
</tr>
</tbody>
</table>
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*

<table>
<thead>
<tr>
<th>Income category</th>
<th>B2 onset All RR (95% CI)</th>
<th>PH2 onset - AA RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher income, ≥ $75,000/year</td>
<td>2.4 (1.2 – 4.9)</td>
<td>4.6 (1.6-12.7)</td>
</tr>
<tr>
<td>Lower income, &lt; $75,000/year</td>
<td>0.8 (0.5 – 1.2)</td>
<td>1.1 (.5-2.6)</td>
</tr>
</tbody>
</table>
FIN