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

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UCSF

Biobehavioral Contributions to Cancer Exposomes: Toward Precision Medicine
American Psychosomatic Society
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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
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

- Kaiser Permanente
  - Lawrence Kushi, ScD
  - Louise Greenspan, MD
- Mt. Sinai School of Medicine
  - Mary Wolff, PhD
  - Susan Teitelbaum, PhD
  - Maida Galvez, MD
- Univ of Cincinnati/Cincinnati Children’s Hospital
  - Frank Biro, MD
  - Susan Pinney, PhD
- California Department of Public Health
  - Gayle Windham, PhD
- UC Berkeley
  - Julie Deardorff, PhD
- UC Davis
  - Susan Stewart, PhD
- UC San Francisco
  - Dejana Braithwaite, PhD
  - Irene Yen, PhD
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)

B2
9 y  10 y

Menarche
12 y  13 y

Tempo
3 y
2 y
3 y

Age (years)
9  10  11  12  13  14
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

Herman-Giddens et al., Pediatrics, 1997
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*

<table>
<thead>
<tr>
<th>Group</th>
<th>New York City</th>
<th>Cincinnati</th>
<th>Bay Area</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>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>
<th>New York City</th>
<th>Cincinnati</th>
<th>Bay Area</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>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>4</td>
<td>0 (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

*CYGNET Study, 2005 – 2008*

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

<table>
<thead>
<tr>
<th>Income category</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher income, ≥$50,000/year</td>
<td>2.4 (1.2 – 4.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lower income, &lt;$50,000/year</td>
<td>0.8 (0.5 – 1.2)</td>
<td>0.25</td>
</tr>
</tbody>
</table>
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

Diagram with nodes labeled SES, R/E, Site, BMI, and B2 connected by directional arrows.
## Age and Race/Ethnicity

**BCERP (N = 1239)**

<table>
<thead>
<tr>
<th></th>
<th>NYC (416)</th>
<th>Cincinnati Area (379)</th>
<th>San Francisco Bay Area (444)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – mean yrs</strong></td>
<td>7.0</td>
<td>6.7</td>
<td>6.8</td>
</tr>
<tr>
<td><strong>Race/ethnicity % (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>40.1 (167)</td>
<td>33.5 (127)</td>
<td>21.9 (97)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>59.9 (249)</td>
<td>4.0 (15)</td>
<td>24.3 (108)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1.3 (5)</td>
<td>11.7 (52)</td>
</tr>
<tr>
<td>White</td>
<td>0 (0)</td>
<td>61.2 (232)</td>
<td>42.1 (187)</td>
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</table>
SES (HH Income) and B2

<table>
<thead>
<tr>
<th>Income HH</th>
<th>Ratio of Medians*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; $50,000</td>
<td>0.92</td>
<td>0.90 – 0.94</td>
</tr>
<tr>
<td>$50-100,000</td>
<td>0.95</td>
<td>0.93 – 0.98</td>
</tr>
<tr>
<td>&gt;=$100,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Education Level</th>
<th>Ratio of Medians</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= HS Diploma</td>
<td>0.96</td>
<td>0.93 – 0.99</td>
</tr>
<tr>
<td>Some College/Vocational</td>
<td>0.95</td>
<td>0.92 – 0.98</td>
</tr>
<tr>
<td>Bachelor's Degree</td>
<td>0.97</td>
<td>0.94 – 1.00</td>
</tr>
<tr>
<td>&gt;=Master’s Degree</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>
### BMI % and B2

<table>
<thead>
<tr>
<th>BMI %</th>
<th>Ratio of Medians</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>1.19</td>
<td>1.16 – 1.21</td>
</tr>
<tr>
<td>50-85</td>
<td>1.12</td>
<td>1.09 – 1.14</td>
</tr>
<tr>
<td>&gt;= 85</td>
<td>1.00</td>
<td></td>
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</tbody>
</table>
# Race/Ethnicity and B2

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Ratio of Medians</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>0.91</td>
<td>0.89 – 0.94</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.96</td>
<td>0.94 – 0.99</td>
</tr>
<tr>
<td>Asian</td>
<td>1.06</td>
<td>1.01 – 1.11</td>
</tr>
<tr>
<td>White</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>
### Geographic Site and B2

<table>
<thead>
<tr>
<th>City</th>
<th>Ratio of Medians</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cincinnati Area</td>
<td>0.90</td>
<td>0.88 – 0.92</td>
</tr>
<tr>
<td>New York City</td>
<td>0.92</td>
<td>0.90 – 0.94</td>
</tr>
<tr>
<td>San Francisco Bay Area</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>
## SES (Income) and B2 Adjusted Models

### Ratio of Medians

<table>
<thead>
<tr>
<th>Income HH</th>
<th>BMI%</th>
<th>R/E</th>
<th>Site</th>
<th>BMI%, R/E</th>
<th>BMI%, Site</th>
<th>R/E, Site</th>
<th>BMI%, R/E, Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;$50,000</td>
<td>0.94</td>
<td>0.96</td>
<td>0.94</td>
<td>0.96</td>
<td>0.95</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>$50-100,00</td>
<td>0.96</td>
<td>0.97</td>
<td>0.96</td>
<td>0.97</td>
<td>0.97</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>&gt;=$100,000</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
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.
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