The Breast Cancer and Environment Research Centers: Experience and Plans

Institute of Medicine
Committee on Breast Cancer and the Environment
July 7, 2010
San Francisco, CA
Purpose of the Breast Cancer and Environment Research Centers

• Develop new scientific data on histology, pathology, cellular and subcellular changes in normal mammary gland tissue over the lifespan and compare with exposure-induced changes.

• Conduct a focused longitudinal study of the environmental and genetic determinants of puberty, focusing on the timing of breast development and age at menarche.

• Integrate results from biological, toxicologic, and epidemiologic studies from pertinent windows of exposure and development that may make the breast more susceptible to cancer to disseminate public health messages to young girls and women at risk.
A National Network

- A network of 4 collaborating research centers

- Supported by the NIEHS and NCI

  - UCSF Cancer Center - PI - Robert A. Hiatt, MD, PhD
  - University of Cincinnati - PI - Robert Bornschein, PhD
  - Fox Chase Cancer Center - PI - Jose Russo, MD
  - Michigan State University - Sandra Z. Haslam, PhD
Breast Cancer and the Environment Research Centers (BCERCs)
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
Bay Area Breast Cancer & Environment Research Center

PI: Robert A. Hiatt, MD, PhD, UCSF CCC

Project 1: Environmental Effects on the Molecular Architecture and Function of the Mammary Gland across the Lifespan.
PI: Zena Werb, PhD, UCSF

Project 2: Environmental and Genetic Determinants of Puberty
PI: Lawrence Kushi, ScD, KP/DOR

COTC: Community Outreach and Translation Core
PI: Janice Barlow, RN, Zero Breast Cancer
Project 1 - Biology of Mammary Gland Development
Project 1 - Specific Aims

Specific Aim 1: Determine the alterations in the mammary microenvironment and the mammary cells in normal and cancer prone mice in vivo during prenatal development, pubertal branching morphogenesis, pregnancy and aging.

Specific Aim 2: Determine the effects of exposure to prototypical environmental stressors during prenatal development, pubertal branching morphogenesis, pregnancy and aging on the mammary gland in normal and cancer prone mice in vivo.

Specific Aim 3: Determine the effects of environmental agents implicated from studies in Project 2 on regulating the mammary microenvironment of mammary cells during branching morphogenesis.

Specific Aim 4: Validate the animal experiments by determining how these environmental stressors affect human mammary epithelial cells in culture through the telomere crisis, comparing the critical endpoints derived from the animal.
Distinct mechanisms pattern the mammary gland

Adapted from Wiseman & Werb (2002) Science 296 1046
Mammary Development

- **3 wks**: Lymph node
- **5 wks**: Nipple
- **11 wks**: Duct development

**Mature Duct**

**Terminal End Bud**

- Luminal (Keratin 8/18)
- Myoepithelial (Keratin 5/14)

- Cap cells
- Body cells
Project 2- Environmental and Genetic Determinants of Puberty

CYGNET
Cohort Study of Young Girls’ Nutrition, Environment, and Transitions
Cohort study of Young Girls’ Nutrition, Environment & Transitions

A Project of the Bay Area Breast Cancer and the Environment Research Center
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
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
CYGNET Study Population

• Born in and currently a member of Kaiser Permanente

• Resident at birth and currently of Marin County, San Francisco, and selected East Bay communities (e.g., Richmond, El Cerrito, Berkeley, Oakland) in western Contra Costa and Alameda Counties

• Age 6 or 7 yrs at time of recruitment
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

• Demographics
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
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
Examples of Potential Environmental Factors to be Assayed in Biospecimens

- Phytoestrogens (e.g., genistein, daidzein, equol, enterolactone)
- Phthalates
- Alkyl phenols (e.g., bisphenol A)
- Organohalogen compounds (e.g., PBDEs, PCBs, pesticides)
- Heavy metals (e.g., Pb, Cd, Hg)
- PAHs (e.g., hydroxypyrene, PhiP)
- Cotinine
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
Possible Biologic Pathways

• Stem Cells
• Intrauterine programming and IGF-1
• Obesity/Physical activity - Energy Balance
• Gene-environment interactions
• Endocrine disruptors and other environmental factors
• Psychosocial environment
Baseline Date - Year 1
Breast Tanner Stage at age 7 Years by Race/Ethnicity in BCERC (n=926)

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Total</th>
<th>KPNC</th>
<th>CIN</th>
<th>MSSM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>N</td>
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<tr>
<td>Latina, Hispanic</td>
<td>256</td>
<td>11.0</td>
<td>12.5</td>
<td>15.8</td>
<td>35</td>
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<tr>
<td>Black, non-Hispanic</td>
<td>220</td>
<td>20.5</td>
<td>31.2</td>
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<tr>
<td>Asian</td>
<td>52</td>
<td>4.1</td>
<td>0.0</td>
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<tr>
<td>White, non-Hispanic</td>
<td>384</td>
<td>4.4</td>
<td>13.9</td>
<td>9.4</td>
<td>36</td>
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<tr>
<td>Other</td>
<td>14</td>
<td>0.0</td>
<td>9.1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Total N</td>
<td>926</td>
<td>432</td>
<td>303</td>
<td>191</td>
<td>124</td>
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<tr>
<td>Race/Ethnicity</td>
<td>&lt;85%</td>
<td>85-94%</td>
<td>&gt;=95%</td>
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<td></td>
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<tr>
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<td>-------</td>
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<td>-------</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>%</td>
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<td></td>
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<tr>
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<td>27</td>
<td>14.5</td>
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<td></td>
<td></td>
<td></td>
<td>17</td>
<td>9.1</td>
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<tr>
<td>Black, non-Hispanic</td>
<td>47</td>
<td>9</td>
<td>11.8</td>
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<td></td>
<td></td>
<td></td>
<td>20</td>
<td>26.3</td>
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</tr>
<tr>
<td>Asian</td>
<td>24</td>
<td>3</td>
<td>11.1</td>
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<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>Latina, Hispanic</td>
<td>66</td>
<td>21</td>
<td>18.6</td>
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<td>26</td>
<td>23.0</td>
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<td>3</td>
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<td></td>
<td>2</td>
<td>5.1</td>
<td></td>
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<tr>
<td>Other</td>
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<td>1</td>
<td>33.3</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>66.7</td>
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<tr>
<td>Total</td>
<td>313</td>
<td>64</td>
<td>14.4</td>
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<td></td>
<td>67</td>
<td>15.1</td>
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</table>

* Age-specific percentile based on CDC 2000 standards
Tanner Stage by Body Mass Index
(n=441 for B; n=426 for PH)

<table>
<thead>
<tr>
<th>Body Mass Index</th>
<th>B1</th>
<th>B2/3</th>
<th>PH1</th>
<th>PH2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>percentile*</td>
<td>N</td>
<td>N</td>
<td>%*</td>
<td>N</td>
</tr>
<tr>
<td>&lt;85</td>
<td>298</td>
<td>13</td>
<td>4.2</td>
<td>281</td>
</tr>
<tr>
<td>85-94</td>
<td>54</td>
<td>9</td>
<td>14.3</td>
<td>52</td>
</tr>
<tr>
<td>≥95</td>
<td>56</td>
<td>11</td>
<td>16.4</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>408</td>
<td>33</td>
<td>7.5</td>
<td>387</td>
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</tbody>
</table>

* Age-specific percentile based on CDC 2000 standards
† Row percent of those with Tanner Stage measurements for B or PH
Year 2
Pubertal Status at Year 2 visit by Race/Ethnicity \((n=386)\)

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>B1 &amp; PH1</th>
<th>≥B2 or ≥PH2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Latina, Hispanic</td>
<td>78</td>
<td>26</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Asian</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>139</td>
<td>28</td>
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<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>293</td>
<td>103</td>
</tr>
</tbody>
</table>

* Row percent for those with Tanner Stage measurements for B and PH
Year 3
Breast Tanner Stage at Year 3 visit
(8-10 yrs old, as of 8-10/08)

<table>
<thead>
<tr>
<th>Center</th>
<th>B1 N</th>
<th>B1 %</th>
<th>B2 N</th>
<th>B2 %</th>
<th>BMI &gt;85th</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York City (MSSM)</td>
<td>62</td>
<td>41</td>
<td>90</td>
<td>59</td>
<td>40%</td>
</tr>
<tr>
<td>Cincinnati (U of C)</td>
<td>115</td>
<td>50</td>
<td>114</td>
<td>50</td>
<td>30%</td>
</tr>
<tr>
<td>SF Bay Area (KPNC/UCSF)</td>
<td>226</td>
<td>61</td>
<td>147</td>
<td>39</td>
<td>29%</td>
</tr>
<tr>
<td>Total</td>
<td>403</td>
<td>53</td>
<td>351</td>
<td>46</td>
<td>33%</td>
</tr>
</tbody>
</table>
Selected Pubs


Youth, Environment & Neighborhood (YEN) Study

- Aims are to examine associations of body size and onset of puberty in girls from the CYGNET Study with:
  - Built environment characteristics assessed by neighborhood audits
  - Community-level development policies
- P.I.: Irene Yen, Ph.D., UCSF
- Funded by California Breast Cancer Research Program
Community Outreach and Translational Core (COTC)
Community Outreach and Translational Core Specific Aims

1. To facilitate communications and education about breast cancer and the environment for diverse community members.

2. To infuse the community perspective into the scientific process and translation of the work of the research teams’ efforts back to the community.

3. To maintain current and develop new collaborative partnerships in the San Francisco Bay Area.

4. To evaluate the success of COTC activities.
The Beginning: Four Centers, each with their own hypotheses
Fin