The Social Determinants of Cancer: A Challenge for Transdisciplinary Science

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UCSF
Research on Cancer Epidemiology: Risk Factors and Control in the Caribbean Basin
2.21.13
Outline

• Definitions
• Conceptual Frameworks
• Applications to Breast Cancer
• Frameworks for Social Determinants
• Challenges for Transdisciplinary Science
Population Health

• An approach to health that aims to improve the health of the entire population and to reduce health inequities among population groups. In order to reach these objectives, it looks at and acts upon the broad range of factors and conditions that have a strong influence on our health (e.g. income, education, environment, biology). Public Health Agency of Canada, 2005.
Transdisciplinary Science

- Transdisciplinary science involves the integration of theoretical and methodological perspectives drawn from different disciplines, for the purpose of generating novel conceptual and empirical analyses of a particular research topic (Rosenfield 1992).
Transdisciplinary Science

- **Multidisciplinary**: coordination of research among different disciplines, e.g. a multi-disciplinary P01 may be a coordinated effort to study a particular cancer issue although individual projects may be discipline-specific.
- **Interdisciplinary**: cooperation of different disciplines on issues that fall between disciplines.
- **Transdisciplinary**: collaborations in which exchanging information, altering discipline-specific approaches, sharing resources, and integrating different disciplines achieves a common scientific goal.
TDS requires a **common problem** and a **common understanding or conceptual model**.
THE CANCER CONTROL CONTINUUM

PREVENTION
- Tobacco control
- Diet
- Physical activity
- Sun exposure
- Virus exposure
- Alcohol use
- Chemoprevention

DETECTION
- Pap test
- Mammography
- FOBT
- Sigmoidoscopy
- PSA

FOCUS
DIAGNOSIS
- Informed decision-making

TREATMENT
- Health services
- and outcomes research

SURVIVORSHIP
- Coping
- Health promotion for survivors

CROSSCUTTING ISSUES
- Communications
- Surveillance
- Social Determinants of Health Disparities
- Genetic Testing
- Decision-Making
- Dissemination of Evidence-Based Interventions
- Quality of Cancer Care
- Epidemiology
- Measurement

Adapted from David B. Abrams, Brown University School of Medicine.
Social Determinants of Cancer

Social Determinants

Health Care System

Behavioral/Psychologic

Biologic

Pre-disease

Pre-clinical

Incidence

Morbidity & Survival

Mortality

Prevention

Early Detection & Diagnosis

Treatment

Quality of Life

Hiatt & Breen, AJPM 2007
Multiple Levels of Organization and Analysis
Social Determinants at play all along the Cancer Continuum interacting with other Levels of Analysis

- Prevention – tobacco use, culture and diet
- Detection – access, quality and acceptability
- Diagnosis – informed decisions based on SES, literacy and culture
- Treatment – comparative effectiveness & patient centered outcomes
- Survivorship – coping strategies
Bay Area Breast Cancer & the Environment Research Center

An example
Breast Cancer: The Challenge

- 226,870 estimated new cases in 2012
- 39,510 estimated deaths in 2012
- Now about 3.0 million survivors
- Still the most common cancer among women and the second leading cause of cancer mortality
# Selected Factors Known to Influence Breast Cancer Risk*

<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.
Usual Epidemiologic Approach

• Case – Control studies – recall bias
• Prospective cohort studies – lengthy and expensive
• Replication and validation
• Synthesis – meta-analysis or systematic reviews
Life-course Approach:
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
New 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
Puberty
Socioeconomic circumstances influence age at menarche
International Trends in Age at Menarche
Fig. 1 Secular trend of mean age at menarche for women born between 1920 and 1985

Prevalence of Menses by Age and Race

Herman-Giddens et al., Pediatrics, 1997
Prevalence of Breast Development at Tanner Stage 2 or Greater by Age and Race

Herman-Giddens et al., Pediatrics, 1997

Herman-Giddens et al., Pediatrics, 1997
Prevalence of Pubic Hair Development at Tanner Stage 2 or Greater by Age and Race

Herman-Giddens et al., Pediatrics, 1997
Trends in Pubertal Onset

• Downward age onset over last century.
• Decreasing trends in age at menarche and age at pubertal onset not parallel.
• Rapid change in the relationship of socioeconomic status (SES) and pubertal onset over last century.
Description of a Center

• Bay Area Breast Cancer and the Environment Research Center- funding started on 9/29/03

• Two primary research projects
  – Animal models of breast development - UCSF/LBNL
  – Epidemiologic cohort of adolescent girls – Kaiser

• Two cores
  – Community Outreach and Translational Core - MBCW
  – Administrative - UCSF
The Common Question or Problem

• 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?
Animal Models of Breast Development
Mammary Development

Dunbar et al. 1999

- e15: Mammary development at e15 stage.
- e18.5: Mammary development at e18.5 stage.
- 3 wks: Mammary development at 3 weeks.
- 4.5 wks: Mammary development at 4.5 weeks.
- 11 wks: Mammary development at 11 weeks.

- Nipple
- Lymph node
- Abdominal (#4) mammary gland
GFP-labeled mammary gland
Live Imaging of Sca-1-GFP in the Mammary Gland
Epidemiologic Cohort of Adolescent Girls
Epidemiologic Cohort
Specific Aims

• To examine several exposures and their effects on age at onset of various hallmarks of puberty and sexual maturation, including Tanner Stage for breast and pubic hair development, menarche, and on the time required to move through the pubertal transition.

• To collect biospecimens (blood, urine) to allow investigation of exposure effects of pubertal timing on hormone levels.
Study Design and Approach

• Recruit 400 7 yr old girls from Kaiser Permanente members in Marin, San Francisco and Alameda Counties.
• Only from those born in KP hospitals with birth records.
Cohort study of Young Girls’ Nutrition, Environment & Transitions

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

Girls born in & current members of KPNC, who live in Alameda, Marin or San Francisco Counties, by race/ethnicity, birth years 1996 & 1997

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>American Indian/Alaska Native</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>86</td>
<td>75</td>
<td>12</td>
<td>15</td>
<td>133</td>
<td>130</td>
<td>451</td>
<td>25.6</td>
</tr>
<tr>
<td>African American</td>
<td>124</td>
<td>130</td>
<td>4</td>
<td>1</td>
<td>38</td>
<td>34</td>
<td>331</td>
<td>18.8</td>
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<tr>
<td>Hispanic</td>
<td>101</td>
<td>98</td>
<td>15</td>
<td>15</td>
<td>49</td>
<td>65</td>
<td>343</td>
<td>19.4</td>
</tr>
<tr>
<td>White</td>
<td>108</td>
<td>103</td>
<td>100</td>
<td>103</td>
<td>95</td>
<td>99</td>
<td>608</td>
<td>34.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>0.7</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>429</td>
<td>421</td>
<td>134</td>
<td>134</td>
<td>316</td>
<td>330</td>
<td>1,764</td>
<td>100</td>
</tr>
</tbody>
</table>

* includes communities of Alameda, Albany, Berkeley, Emeryville, Oakland, & Piedmont
Outcomes of Interest

• Breast development (B2 – B5)
• Menarche
• Obesity
• Pubic hair development (PH2 – PH5)
• Tempo
Early Puberty

• Adolescent Health
  – Early sexual activity
  – Sexually transmitted infections
  – Early pregnancy
  – Depression

• Adult Health
  – Breast cancer (early age at menarche)
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
Exposures of Interest

• Developmental and lifestyle factors
  – Food intake
  – Physical activity
  – Growth patterns, birthweight, etc.

• Environmental exposures
  – Cigarette smoking, alcohol
  – Persistent organohalogen compounds
  – Less persistent Hormonally Active Agents

• Polymorphisms in relevant genes
Anthropometry & Tanner Staging

• Anthropometry
  – Annual standardized clinic measurement
  – Annual bioelectrical impedance analysis
  – Maternal or self report via questionnaire

• Tanner Staging
  – Annual standardized clinic measurement of breast and pubic hair development
  – Quarterly maternal (or self) assessment (?)
  – Data extracted from KP records
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
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
Psychosocial Factors

- Socioeconomic Status
- Family structure and function
- Depression, anxiety
- Mother’s depression
- Absent father
## 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>77</td>
<td>31 (28.7)</td>
<td>75</td>
<td>34 (31.2)</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>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>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>
## 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>
• 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.
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 (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 (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>$50-100,000</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>=$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>
SES – B2
Working DAG

Diagram showing relationships between SES, R/E, Site, BMI, and B2.
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.
Social Determinants in a Transdisciplinary Study of Puberty

• Race/ethnicity
• SES
• Geographic location/neighborhood
• Endocrine disrupting chemicals
• Family structure/stress
• BMI
• Molecular biology
• Genetics
Other Models

- Complex systems models
- Social networks
Causal thinking and complex system approaches in epidemiology

Sandro Galea,* Matthew Riddle and George A Kaplan

Identifying biological and behavioural causes of diseases has been one of the central concerns of epidemiology for the past half century. This has led to the development of increasingly sophisticated conceptual and analytical approaches focused on the isolation of single causes of disease states. However, the growing recognition that (i) factors at multiple levels, including biological, behavioural and group levels may influence health and disease, and (ii) that the interrelation among these factors often includes dynamic feedback and changes over time challenges this dominant epidemiological
Figure 5.4: The full obesity system map indicating the strength of the relationships between variables (see main text for discussion). A qualitative scale of 0–5 was used (a rating of 5 meaning that small changes in the tail variable lead to large changes in the head variable). Linkages were assigned a rating where possible or left ‘gray’ where there was no information (see key). Variables are represented by boxes, positive causal relationships are represented by solid arrows and negative relationships by dotted lines. The central engine is highlighted in orange at the centre of the map.
Breast Cancer Etiology as a Complex System
Expert committee on breast cancer (and complex systems modeling)

- Ana Diez-Roux, PhD - social epidemiologist, neighborhood
- Lawrence Kushi, ScD – nutritional epidemiologist
- Mark Moasser, MD - medical oncologist
- Travis Porco, PhD - mathematical modeler
- Zena Werb, PhD – cellular biologist, immunologist
- Gayle Windham, PhD – environmental and reproductive health
- Robert Hiatt, MD, PhD – cancer epidemiologist
- Dejana Braithwaite, PhD – cancer epidemiologist
- Galen Joseph, PhD – medical anthropologist
- Allan Balmain, PhD - geneticist
- David Rehkopf, ScD - social epidemiologist
- Janice Barlow, RN - community advocate
New Paradigm of Breast Cancer Causation and Prevention

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

Post Menopausal Breast Cancer Incidence

Strength of assoc (1 = strongest)

Quality of data (1 = strongest)

SOCIETAL/ CULTURAL

Country of Birth
Race/Ethnicity
Income
Education
Occupation

PHYSICAL/ CHEMICAL

Environmental tobacco
Endocrine disruptors (e.g., BPA, organochlorines)
LatITUDE

BIOLOGICAL

High penetrance genes: (e.g., BRCA1, BRCA2, TP53)
Low penetrance genes: (e.g., CASP8, 2a35, FGFR2)
Ancestry

BEHAVIORAL

Alcohol
Phytoestrogens (e.g., soy)
Physical activity
Tobacco use
Obesity

Breast feeding
HRT

Age at first birth, parity
Breast density
Height
Age at menopause
Immune function (inflammation)
Insulin resistance

Endogenous hormones (e.g., IGF, estradiol)
Age at menarche

Radiation/Medical imaging
Genotoxins
Vitamin D

References
Exit

Family History
Lifecourse Model

Radiation/Medical imaging

Age

Latitude

New Paradigm of Breast Cancer Causation and Prevention
The Spread of Obesity in a Large Social Network over 32 Years

Nicholas A. Christakis, M.D., Ph.D., M.P.H., and James H. Fowler, Ph.D.

What’s the **Point**? Transdisciplinary Science can lead to....

- More hassles
- Communications problems
- Different institutional and disciplinary cultures
- Members of collaborations may have different personal and institutional agendas
- Multiple IRBs and Administrative Offices
- Subcontracts
- Intellectual property
But...

• Collaborative, multi-center research can often accomplish objectives not possible in one center
• Required expertise cannot always be found in one institution
• Collaborators learn from one another
• Proposals are often stronger if based on partnerships
• Transdisciplinary science, by crossing disciplinary boundaries, is likely to generate questions not considered within a discipline
• Funding agencies may require collaboration
• It can be fun
Summary

• How social determinants play a role
• Transdisciplinary Science
• How one research project does it
• Thinking about new models