Integrating risk across the lifespan: the case of breast cancer prevention

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Conflict of interest

• I have no financial relationships to disclose

• I will not discuss off-label use and or investigational use in my presentation
Why are we not preventing breast cancer now?

Multiple barriers:
- Skepticism that cancer can be prevented
- Short term focus of cancer research
- Interventions deployed too late in life
- Research focused on treatment not prevention
- Debates among scientists
- Societal factors ignored
- Lack of transdisciplinary training
- Complexity of implementation

Colditz et al Sci Transl Med 2012: March 28
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Colditz et al Sci Transl Med 2012: March 28
Overcoming obstacles of skepticism and time frame

• Must counter skepticism that cancer can be prevented
  ▪ Goals of prevention: risk marker, premalignant lesion, invasive disease, death
  ▪ Avoid exposure vs. remove later in life
  ▪ Can we intervene if we don’t have the pathway defined?

• Take into account time frame of cancer development
Evidence that breast cancer is preventable

- Migrant studies
  - No US lifestyle
- Within country changes
  - Remove HRT, Korea rapid increase, etc
- RCTs of SERMs,
  - Tamoxifen, Raloxifene
- Bilateral oophorectomy for women with BRCA1/BRCA2
Birthplace and breast cancer incidence, SEER registry 1973-86

Stanford et al 1995

- White US
- Japanese
- Chinese
- Pilipino
Fig. 1. Trend toward earlier menarche in some European countries. (Sweden (□—□); Norway (■--■); Finland (●—●); Denmark (△—△); Holland (○••○); United Kingdom (▲—▲); United States (*). (From Tanner, 1978.)
Change in menarche, Korea

Cho Eur J Pediatr 2009
Trends in Fertility

Calendar year

Ito et al NEBR, 2008
Breast Cancer Incidence, Korea

1998 40, born 1958
2008 40, born 1968

Jung et al, J Breast Ca, 2011
RCT: Rates breast cancer P1 trial

Invasive

- Placebo
- Tamoxifen

P < .00001

Noninvasive

- Placebo
- Tamoxifen

P < .002

#Events Rate/1,000

- Placebo
- Tamoxifen

Fisher et al, 1998; 90:1371-88
Evidence that breast cancer is preventable

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• RCTs of SERMs,
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• Bilateral oophorectomy for women with BRCA1/BRCA2
  ▪ 10 studies, HR 0.49 (0.35, 0.64)
    Rebbeck JNCI 2009;101:80-7
## Summary of breast cancer prevention strategies

<table>
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<tr>
<th>Strategy</th>
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<td>Increase exercise</td>
<td>&lt;30 min/d</td>
<td>&gt;60%</td>
<td>Timing matters</td>
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* Loss after menopause based on Eliasson JAMA, 2006
Huge potential for cancer prevention

• More than half of cancer incidence and mortality could be prevented with what we know now.
• This applies to breast cancer as it does to other major malignancies
Time frame: Where is evidence for prevention in the development sequence of cancer?

- Majority of etiologic studies focus on lifestyle and drugs in proximate time before diagnosis
  - Epidemiology predominantly in postmenopausal women
  - Trials in high-risk women
Radiation

• Atomic bomb survivors, 70,165
• 40 year follow-up
• 1059 cases
• Linear increase with radiation dose
• Early age at exposure conveys substantially greater risk

Land et al  Radiation Research 2003
Breast cancer incidence

Globalcan 2008 incidence
Female cancer mortality by age

Cancer mortality England and Wales 1950 and 1951

Armitage and Doll, Br J Cancer 1954
Biology – association with age

- Armitage & Doll – increase with age – multistage model, BJC 1954
- Moolgavkar et al., 1981 JNCI evaluated data from Denmark, Japan, Iceland and the USA.
- The underlying effect of age is modulated by birth cohort
- Normalized incidence curves to age 40-44 in Connecticut
Moolgavkar et al JNCI 1979
If we conclude that attained age is marker of risk, then:

What does attained age mean?

• Accumulated exposure up to an age?
• Some other function of age?
• Menopause tells us “hormones” or accumulation through premenopausal years must be important
Attained age finding generates other key questions:

- Which lifestyle component to change?
- At what age?
- By how much?
- For how long?
- When will benefit be observed, and how long will benefit last?

See Colditz, Cancer Causes and Control 2010
Colditz and Taylor, Ann Rev Public Health 2010
Why are childhood and adolescence important?

• Risk accumulation from menarche to first birth and then to menopause
• Age at menarche has strong history of relation with breast cancer
• Dramatic changes with industrialization
  • Menarche reduced from 17 or 18 to 12 eliminating one third of growth and development period
• Growth and height are related to risk

Colditz and Frazier CEBP 1995
Height and relative risk of breast cancer incidence, Korea. 339,000 women, 10 yr

<table>
<thead>
<tr>
<th>Height Range</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;151 cm</td>
<td>1</td>
</tr>
<tr>
<td>151.1 - 155</td>
<td>1.24</td>
</tr>
<tr>
<td>155.1 - 158</td>
<td>1.4</td>
</tr>
<tr>
<td>158+</td>
<td>1.65</td>
</tr>
</tbody>
</table>

Sung J, et al AJE 2009
Growth curve of a girl, HLS
Peak height velocity = greatest growth in single year

Berkey et al, Cancer 1999
Peak height velocity

Berkey et al, Cancer 1999
Application: Nurses’ Health Study, then in adolescent cohort (GUTS)

- Higher peak height growth velocity (PHGV) associated with increased risk of pre and post menopausal breast cancer
- Highest vs. lowest quintile of PHGV; 8.9cm/yr vs. \(<7.6 \text{ cm/yr};
  - RR=1.31 premenopausal breast cancer
  - RR=1.40 postmenopausal breast cancer

- For Benign Breast Disease same range in PHGV gave RR = 2.10

Model of breast cancer evolution
Wellings-Jensen Model (JNCI 55:231, 1975)

- TDLU
- ADH
- DCIS
- LCIS
- ALH
- Invasion

↑ Growth

Δs Adhesion & Polarity

↑ Diversity

Time (decades)
Precursor lesions: benign breast disease (BBD)

RR = 1.8

= 3 to 5

London JAMA et al 1989
What predicts incidence of BBD?

NHSII – incident BBD (RO1-CA50385)

• Central pathology review
• Study of adolescent:
  ▪ diet
  ▪ physical activity
  ▪ body shape at ages 5 and 10
• GUTS, Growing Up Today Study
  ▪ Self-report benign breast disease confirmed by breast biopsy
Alcohol and BBD – GUTS data

- 6899 females, 9-15 in 1996
- 147 confirmed physician diagnosed benign breast disease
- Those who drank typically 3 to 5 days per week at increased risk (RR 2.99, 1.26-7.09)

Berkey et al, Pediatrics, 2010
Alcohol and incident proliferative BBD, NHSII

- Adolescent recall of high school diet
- Incident BBD – proliferative lesions on central pathology review
- 678 cases of proliferative BBD among 29,329 women followed over 10 years
- Alcohol intake directly related to subsequent risk of proliferative BBD

Liu et al – Pediatrics, in press, April 2012
## Alcohol intake, ages 18-22, incident proliferative BBD

<table>
<thead>
<tr>
<th>Alcohol intake (grams/day)</th>
<th>Cases</th>
<th>Person-yr</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>155</td>
<td>64,827</td>
<td>1.0 reference</td>
</tr>
<tr>
<td>0.1-4.9</td>
<td>193</td>
<td>78,365</td>
<td>1.11 (0.89, 1.38)</td>
</tr>
<tr>
<td>5.0-14.9</td>
<td>236</td>
<td>88,310</td>
<td>1.36 (1.09, 1.69)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>30</td>
<td>9519</td>
<td>1.35 (1.01, 1.81)</td>
</tr>
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$p, \text{trend} < 0.01$

Liu et al – Pediatrics, April 2012
Protein, fiber, and risk of BBD

• Previous retrospective evidence suggests vegetable fat inversely related to risk of proliferative BBD (Webb et al 2004)
  - Not confirmed in prospective analysis
• Evaluating sources of protein intake, we observe significant inverse relation for vegetable protein intake after onset of menses
• This finding significant among those with and without maternal history of breast cancer
Adolescent fiber & BBD: NHSII

Combined analysis

Prospective analysis

Su et al Cancer Causes Control 2010
Physical activity: What time period is important?

Total activity (MET-h/wk) during different ages and breast cancer

Maruti et al JNCI 2008 100:728-737
# Summary of evidence: Adolescent exposures and BBD

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>Relative Risk BBD</th>
</tr>
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<tbody>
<tr>
<td>Alcohol</td>
<td>↑</td>
</tr>
<tr>
<td>Peak Growth Velocity height</td>
<td>↑</td>
</tr>
<tr>
<td>Dairy</td>
<td>=</td>
</tr>
<tr>
<td>Fiber</td>
<td></td>
</tr>
<tr>
<td>Vegetable protein</td>
<td>↓</td>
</tr>
<tr>
<td>Family history</td>
<td>↓</td>
</tr>
<tr>
<td>Physical activity</td>
<td>↑</td>
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Understanding the accumulation of breast cancer risk: Pike model

- Factors associated with reduced risk of breast cancer were considered to lower the rate of breast tissue aging
  - Pike et. al., Nature 1983;303:767-70
- We translated this to mean the rate of cell division and accumulation of molecular damage on the pathway to breast cancer
Multiple birth model

Rosner, Colditz, Willett, Am J Epidemiology 1994;139:826
Multiple birth model

Rosner, Colditz, Willett, Am J Epidemiology 1994;139:826
Extensions to modeling

- Includes time from birth to menarche
- Allows the impact to the first birth to vary with age at first birth
- Fits log incidence (Poisson regression) model giving terms that are interpretable
- Contrast contribution of risk factors for receptor positive and negative breast cancer

Colditz and Rosner AJE 2000
Integrating exposures across lifecourse

• Our approach to incidence modeling is different from standard analytical approaches.

• Risk factors are assumed to have an effect on the rate of increase of breast cell proliferation.

• The cumulative number of breast cell divisions at age $t$ is a latent variable that is assumed to be proportional to incidence at age $t$. 
Interpretation

- The effect of most risk factors is cumulative over more than one year; although possibly differential in different periods of life
  - e.g., premenopause vs. postmenopause.
- This makes it more difficult to quantify associations of risk factors with disease.
- But our approach is more consistent with the evidence that tumors take many years to develop and are affected by risk factors early in life even when very few cases are present.
## Breast cancer prevention

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<td></td>
<td></td>
<td></td>
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<tr>
<td>Increase Activity</td>
<td>1-2 hrs / d</td>
<td>80%</td>
<td>25% ↓</td>
</tr>
<tr>
<td>Reduced alcohol</td>
<td>None, &lt;1/wk</td>
<td>?</td>
<td>0 to 40% ↓</td>
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<tr>
<td>Increase fiber/ (veg protein)?</td>
<td>30+ g/day</td>
<td>80%</td>
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Conclusions: breast cancer prevention

• Timing matters
• To maximize benefits we must focus on biologically relevant periods
• Untapped potential for adolescent diet and perhaps other strategies to counter adverse effect of alcohol
• We already have many tools for prevention that are not fully used
Breast Cancer Prevention

Biologic pathway
- Hormones + receptors

Lifestyle
- Diet, activity, weight gain

Policy
- Social environment
Why are we not preventing cancer now?

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Colditz et al Sci Transl Med 2012: March 28
How to move forward

- Design and fund research that is not chopped up, siloed
- TREC is one example (NCI U54)
- IOM report advocates for transdisciplinary science to bridge genes and environment among other challenges of integration
- “create incentives to promote transdisciplinary research” (NIH and universities)
  - IOM 2006
Our societal obligation

- As cancer prevention scientists, we must accept responsibility for breast cancer prevention.
- Prioritize studies that will identify key points for intervention to maximize prevention.
- Move beyond obstacles to implement prevention of breast cancer here and throughout the world.
Very long term prevention action:

“In the beginning of every enterprise we should know, as distinctly as possible, what we propose to do, and the means of doing it... We desire to lay the foundation and to mature some parts of the plan. Those who come after us must finish the work.”

William Greenleaf Eliot, co-founder
Washington University in St Louis
1854
Thank you

- Bernie Rosner & Cathy Berkey (statisticians)
- Stu Schnitt, Laura Collins, Jim Connolly, Craig Allred (pathologists)
- NHS investigators and trainees and participants
- American Cancer Society Clinical Research Professorship
- NCI & Breast Cancer Research Foundation for funding