Breast Density, Screening, and Prevention

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Outline

• Why is breast density so interesting to me?
• Factors that influence breast density
• BCERP project
• Tailoring screening based on density
• Summary: breast cancer prevention
Mammographic Breast Density: risk of breast cancer increases with density

Almost Entirely Fat \[ RR=1 \]
Scattered Densities \[ RR = 2.2 \]
Heterogeneously Dense \[ RR=2.8 \]
Extremely Dense \[ RR=3.9 \]


Breast density fundamentally changes how we can study breast cancer

- Very strong risk factor
- Measured in a standardized way
- Available for large groups of women – not just in research settings or among breast cancer patients
- “Intermediate marker” – a change in density reflects a change in breast cancer risk
- Many studies show how both density and breast cancer are related to the same risk factors

**Table 2. Age-specific Probability of Developing Invasive Breast Cancer for US Women**

<table>
<thead>
<tr>
<th>Current age</th>
<th>10-year probability:</th>
<th>or 1 in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.1%</td>
<td>1,567</td>
</tr>
<tr>
<td>30</td>
<td>0.5%</td>
<td>220</td>
</tr>
<tr>
<td>40</td>
<td>1.5%</td>
<td>68</td>
</tr>
<tr>
<td>50</td>
<td>2.3%</td>
<td>43</td>
</tr>
<tr>
<td>60</td>
<td>3.4%</td>
<td>29</td>
</tr>
<tr>
<td>70</td>
<td>3.9%</td>
<td>25</td>
</tr>
<tr>
<td><strong>Lifetime risk</strong></td>
<td><strong>12.4%</strong></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>

Note: Probability is among those free of cancer at beginning of age interval. Based on cases diagnosed 2012-2014. Percentages and “1 in” numbers may not be numerically equivalent due to rounding.

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Breast Cancer Risk Factors

• Increased risk
  ▪ Female sex
  ▪ Older age
  ▪ Family history of breast cancer
  ▪ Dense breasts
  ▪ Taller height
  ▪ Radiation
  ▪ Postmenopausal hormone use
  ▪ Later age at 1st birth
  ▪ Later age at menopause
  ▪ Alcohol consumption
  ▪ Obesity/weight gain

• Decreased risk
  ▪ Later age at first menstruation
  ▪ Full term pregnancies
  ▪ Breast feeding
  ▪ Physical activity
  ▪ Tamoxifen (anti-estrogen)

Estimating individual risk of breast cancer

BCSC Risk Calculator
https://tools.bcscc.org/bc5yearrisk/calculator.htm

Breast Cancer Risk Assessment Tool
Breast cancer risk factors are also related to breast density

- **Increased risk**
  - Female sex
  - Older age (↑)
  - Family history of breast cancer
  - Taller height
  - Radiation
  - Postmenopausal hormone use
  - Later age at 1st birth
  - Later age at menopause
  - Alcohol consumption
  - Obesity/weight gain (↑)

- **Decreased risk**
  - Later age at first menstruation
  - Full term pregnancies
  - Breast feeding
  - Physical activity
  - Tamoxifen (anti-estrogen)

Factors in **black** are related to breast cancer
Factors in **blue** are related to both breast cancer and breast density, in the same direction
**Red** arrows indicate that as age and obesity increase, breast cancer risk increases but density decreases

- About 28 million women aged 40-74 in the United States have dense breasts
  - 44% of the breast cancer screening population
- Density decreases with age

Data from the Breast Cancer Surveillance Consortium; Sprague et al., *JNCI* 2014
Puzzle: Breast cancer risk increases with age while density decreases

- Cumulative time living with dense breasts may be more important than density at a certain time point

Association or Causation?
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Breast Cancer and the Environment Research Program (BCERP)

• To focus science on the factors in our environment that may increase women’s risk of developing breast cancer

• To bring together laboratory scientists with clinical researchers and community partners to determine risk factors for breast cancer

• To study windows of time over a woman’s lifespan when she may be more vulnerable to environmental risks, or “Windows of Susceptibility”

➢ Visit www.bcerp.org
The “Environment”

ANY NON-INHERITED FACTOR

- **Lifestyle and behavioral factors:** physical activity, body weight, dietary foods and beverages
- **Menstrual and reproductive factors:** age of first menstruation, use of postmenopausal hormones
- **Chemical agents:** pesticides used to kill bugs, ingredients in cosmetics, materials in food containers
- **Physical agents:** radiation, metals, and chemicals
- **Social factors:** how the government regulates chemicals, where you live, access to fresh foods, and access to health care, etc

The Precautionary Principle

When an activity raises the threat of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.

In other words, “better safe than sorry”, “look before you leap”, “an ounce of prevention is worth a pound of cure”, etc.
Windows of Susceptibility (WOS)

Key Times of Hormone Changes and High Cellular Activity:

- Prenatal
- Puberty
- Pregnancy
- Menopause

Density provides a method for research across the lifespan, even during puberty

Approaches for evaluating breast density and other breast tissue features in BCERP

Mammography  Optical Spectroscopy  DXA
BCERP Research Projects

- Density and other breast tissue evaluated during puberty and menopausal transition, and in mother-daughter pairs
- Rodent experiments to examine the mechanisms by which chemical exposure at certain time points may cause mammary cancer

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Shared decision making for mammography

Benefits
Reduced morbidity and mortality from breast cancer

Harms
Inconvenience
Pain
Radiation
Anxiety
“Unnecessary” Biopsies
Over-diagnosis
Costs

1000 Screening Mammograms

Data from the Breast Cancer Surveillance Consortium
How can we optimize the benefit/harm balance of breast cancer screening?

• Who should get screened?

• How often?

• With which modality (or modalities)?
  ▪ Mammography
  ▪ MRI
  ▪ Ultrasound

Mammography screening for breast cancer has had a long history of debate

• Reasonable people disagree over interpretation of the same evidence
• “Strong political forces” are present

<table>
<thead>
<tr>
<th>Guideline</th>
<th>American Cancer Society</th>
<th>US Preventive Services Task Force</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-2003</td>
<td>40+ Yearly</td>
<td>2002: 40-70 Every 1-2 years</td>
</tr>
<tr>
<td>2003-2015</td>
<td>40+ Yearly, for as long as a woman is in good health</td>
<td>2009: 50-74 Biennial, &lt;50 Take patient context into account, 75+ Insufficient evidence</td>
</tr>
<tr>
<td>2015-present</td>
<td>45-54 Yearly 55+ Every 2 years, annual if they want, for as long as a woman is in good health with life expectancy ≥10 years</td>
<td>2016: 50-74 Biennial, &lt;50 Take patient context into account, 75+ Insufficient evidence</td>
</tr>
</tbody>
</table>
Sources of Evidence: Randomized Trials

Decreases or Increases Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York (1963)</td>
<td>0.83 (0.70-1.00)</td>
<td>16.9%</td>
</tr>
<tr>
<td>Malmö I (1976)</td>
<td>0.81 (0.61-1.07)</td>
<td>9.5%</td>
</tr>
<tr>
<td>Kopparberg (1977)</td>
<td>0.58 (0.45-0.76)</td>
<td>10.7%</td>
</tr>
<tr>
<td>Östergötland (1970)</td>
<td>0.76 (0.61-0.95)</td>
<td>13.0%</td>
</tr>
<tr>
<td>Canada I (1980)</td>
<td>0.97 (0.74-1.27)</td>
<td>10.2%</td>
</tr>
<tr>
<td>Canada II (1980)</td>
<td>1.02 (0.78-1.33)</td>
<td>10.2%</td>
</tr>
<tr>
<td>Stockholm (1981)</td>
<td>0.73 (0.50-1.06)</td>
<td>6.0%</td>
</tr>
<tr>
<td>Göteborg (1982)</td>
<td>0.75 (0.58-0.98)</td>
<td>10.7%</td>
</tr>
<tr>
<td>UK Age Trial (1991)</td>
<td>0.83 (0.66-1.04)</td>
<td>12.8%</td>
</tr>
<tr>
<td>Overall (I^2=31.7%, p=0.164)</td>
<td>0.80 (0.73-0.89)</td>
<td>Overall, mammography reduces risk of death from breast cancer by about 20%</td>
</tr>
</tbody>
</table>

Independent UK Panel on Breast Cancer Screening *Lancet* 2012

Conceptual view of computer models

- Common inputs
  - Background trends
  - Screening behavior
  - Diffusion of new treatments
  - Other common inputs

- Unique simulation or analytical model
  - 6 different breast cancer models
  - Breast cancer incidence & mortality
CISNET Analysis Conclusions

- Results consistent across 6 models
- Biennial strategies achieve good balance of benefits and harms
  - Modeling uniquely is able to assess screening intervals
- All models estimated some benefit for starting at age 40; benefits are generally small
  - Consistent with evidence review of trials

<table>
<thead>
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<th>IF GOAL</th>
<th>THEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 % mortality reduction per screen</td>
<td>50-79 every 2 years</td>
</tr>
<tr>
<td>2 Life years gained per screen</td>
<td>40-79 every 2 years</td>
</tr>
<tr>
<td>3 Maximum % mortality reduction</td>
<td>40-84 annually</td>
</tr>
<tr>
<td>4 Least false positives</td>
<td>Start later</td>
</tr>
<tr>
<td>5 Less detection of invasive tumors</td>
<td>Stop earlier</td>
</tr>
<tr>
<td>that would not become symptomatic</td>
<td></td>
</tr>
<tr>
<td>before death other causes</td>
<td></td>
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</tbody>
</table>

Breast density impairs mammography performance

“Sensitivity” is a measure of the probability that the mammogram finds a breast cancer if it is present

Sensitivity of mammography is better in women with fatty (less dense) breasts

Based on data from the Breast Cancer Surveillance Consortium
“Interval” cancers are more likely among women with dense breasts

Based on data from the Breast Cancer Surveillance Consortium

31 states have enacted breast density notification laws

Pink: Enacted Law
Red: Introduced Bill
Blue: Working on Bill
*Insurance coverage law
What to do?

- “...individuals with dense breasts should talk with their physicians about whether they would benefit from additional tests.”

- There is very limited evidence regarding the comparative effectiveness of supplemental screening strategies for women with dense breasts.
  - MRI? Prohibitively expensive to offer to 40% of population; also specificity concerns.
  - Ultrasound? Widely available but sensitivity (~55%) is modest and benign biopsy rate is high (6%).

Can we identify subsets of women with dense breasts who might benefit most from supplemental screening?

[Bar chart showing mammographic breast density and risk estimate]

Data from the Breast Cancer Surveillance Consortium
28 million women aged 40-74 have dense breasts.
7 million have combination of density and risk that result in interval cancer rate > 1 per 1000.

Based on data from the Breast Cancer Surveillance Consortium

Digital Breast Tomosynthesis (DBT, or 3D mammography)

- Multiple x-rays from multiple angles
  - 10 to 15 images over 10 to 20 seconds

- Trade offs
  - Increase invasive breast cancer detection
    - Especially in young women with dense breasts
  - Decrease recall rates
  - Possible increase in biopsies
  - Increased radiation exposure, especially if paired with digital mammography
    - “Synthetic” 2D image may replace mammography if concerns are alleviated about missing calcifications

- No clinical trial evidence yet, although a study is just getting started
Outline

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Conclusions

- Reasonable people can disagree on issues related to breast cancer screening and risks associated with environmental factors
- Know your (estimated) risk of breast cancer
- Reduce your risk of breast cancer
  - Follow physical activity recommendations – get those steps in!
  - Minimize alcohol
  - Avoid weight gain
  - Breastfeed your babies
  - These approaches also help reduce risk of other major health conditions
- Reasons for optimism
  - We are now having a more nuanced conversation
  - We’re making progress
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