Outline

- Screening mammography based on age
  - When to start
  - How often to screen
  - When to stop
- Risk-based screening
- Screening women with dense breasts
- Screening women with breast MRI
- Evaluation of breast pain
- Screening women with breast implants

Women at average breast cancer risk

- Do not have
  - Personal history of breast cancer
  - Previously diagnosed high-risk breast lesion
  - Any genetic mutation known to increase the risk for breast cancer
  - History of exposure to radiation to the chest in childhood
When to start mammography screening and how often

- ACR, SBI -- *annual* starting at 40
- ACOG, ACS, USPSTF, ACP -- discuss 40s, offer based on value of benefit vs. harm, *biennial or 1-2 years*
- ACS -- *annual* 45-54, *biennial* starting at 55
- USPSTF, AAFP, WHO, ACOG, ACP – *biennial* starting at age 50
- European countries and Canada start age 50, *biennial*; Canada *q2-3*; United Kingdom *q3*

Do the benefits of screening outweigh the harms?

**Benefit**
Reduced breast cancer mortality

**Harm**
False-positives
Benign biopsies
Overdiagnosis
### Meta-analyses of screening mammography trials -- film

<table>
<thead>
<tr>
<th>Age</th>
<th>RR (95% CI)</th>
<th>NNS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>39-49</td>
<td>0.92 (0.75-1.02)</td>
<td>3333</td>
</tr>
<tr>
<td>50-59</td>
<td>0.86 (0.68-0.97)</td>
<td>1300</td>
</tr>
<tr>
<td>60-69</td>
<td>0.64 (0.45-0.92)</td>
<td>470</td>
</tr>
<tr>
<td>70-74</td>
<td>0.80 (0.51-1.28)</td>
<td>800</td>
</tr>
</tbody>
</table>

All cause mortality

|  | 0.99 (0.97-1.002) |

*NNumber women screened for 10 years to avert a breast cancer death

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### Advanced disease reduced in screened women ages ≥50

**Definition of Advanced Cancer**

- Stage III or greater
- Size ≥50 mm
- Size ≥40 mm
- Size ≥50 mm

**Events/Screening Group, n/N**

- Stage III or greater: 20/13,740
- Size ≥50 mm: 14/19,844
- Size ≥40 mm: 26/25,214
- Size ≥50 mm: 33/53,890

**Events/Control Group, n/N**

- Stage III or greater: 23/13,740
- Size ≥50 mm: 7/15,604
- Size ≥40 mm: 22/25,216
- Size ≥50 mm: 77/106,971

**Relative Risk (95% CI)**

- Stage III or greater: 0.87 (0.48-1.58)
- Size ≥50 mm: 1.57 (0.63-3.90)
- Size ≥40 mm: 1.18 (0.67-2.08)
- Size ≥50 mm: 0.85 (0.57-1.28)

---

ACS rationale for starting screening at age 45

- Observational studies – 20-40% reduction in breast cancer mortality
- Breast cancer mortality similar 45 vs. 50
  - 40-44 -- 13.2 per 100,000
  - 45-49 -- 20.6 per 100,000
  - 50-54 -- 30.8 per 100,000
  - 55-59 -- 41.3 per 100,000

Oeffinger et al, Jama, 2015

BCSC outcomes per 10,000 digital screens

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–74</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positives (false alarms)</td>
<td>1,212</td>
<td>932</td>
<td>808</td>
<td>696</td>
</tr>
<tr>
<td>No. biopsies per invasive breast cancer diagnosed</td>
<td>100</td>
<td>60</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>False-negatives (missed cancers)</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>22</td>
<td>35</td>
<td>58</td>
<td>72</td>
</tr>
<tr>
<td>DCIS</td>
<td>16</td>
<td>18</td>
<td>21</td>
<td>23</td>
</tr>
</tbody>
</table>

Overdiagnosis & overtreatment from screening mammography

- Cases not clinically detected in the absence of screening because of lack of progression or death from other causes
  - Canadian National Breast Screening Studies
    - 22% of invasive cancers
    - 37% invasive + DCIS
  - CISNET
    - 12% of detected cases
  - UK independent panel
    - 19% of detected cases


Model estimates of *digital* screening mammogram effectiveness by interval

<table>
<thead>
<tr>
<th>Age &amp; Interval</th>
<th>Deaths* averted</th>
<th>Benign biopsy*</th>
<th>False-negative*</th>
<th>Overdiagnosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-74 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>9</td>
<td>228</td>
<td>1,798</td>
<td>25</td>
</tr>
<tr>
<td>2 y</td>
<td>7</td>
<td>146</td>
<td>953</td>
<td>19</td>
</tr>
<tr>
<td>40-49 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>1.3</td>
<td>99</td>
<td>1,143</td>
<td>5</td>
</tr>
<tr>
<td>2 y</td>
<td>1.0</td>
<td>58</td>
<td>576</td>
<td>2</td>
</tr>
</tbody>
</table>

*per 1,000 women screened over screening period

### Risk of late stage disease with 2 vs. 1 year screening interval

<table>
<thead>
<tr>
<th>Factor</th>
<th>Advanced stage†</th>
<th>Tumor &gt;15mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>+17%</td>
<td>+10%</td>
</tr>
<tr>
<td>50-59</td>
<td>-2%</td>
<td>+9%</td>
</tr>
<tr>
<td>60-69</td>
<td>-1%</td>
<td>+13%</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>+28%*</td>
<td>+21%*</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>-5%</td>
<td>+11%*</td>
</tr>
</tbody>
</table>

†Stage IIB or higher  
*P< 0.05

White, JNCI, 2004; Hubbard, Ann Intern Med, 2011; Miglioretti, Jama Oncol, 2015

### Lifetime risk of breast cancer death

<table>
<thead>
<tr>
<th>Risk %</th>
<th>Deaths averted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2.70</td>
</tr>
<tr>
<td>50-74 biennial</td>
<td>2.00</td>
</tr>
<tr>
<td>40-74 biennial</td>
<td>1.88</td>
</tr>
<tr>
<td>45-49 annual, 50-74 biennial</td>
<td>1.90</td>
</tr>
</tbody>
</table>

0.47 (−0.14-1.09) deaths averted per 1,000 women 40-49 - Age trial

†per 1,000 women screened

Improving benefit-harm ratio with risk-based screening

- Screening most efficient if strategy based on risk
  - Target fixed number of women at high risk
  - Decreases harms for low risk women
  - Decreases costs
- Breast cancer risk used to determine
  - When to start screening
  - Screening frequency
  - Supplemental imaging

Screening & treatment reduce breast cancer mortality – 2000-2012

<table>
<thead>
<tr>
<th></th>
<th>% Absolute mortality reduction</th>
<th>2000</th>
<th>2012</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>37*</td>
<td>49*</td>
<td>+12</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td>16</td>
<td>18</td>
<td>+2</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>21</td>
<td>31</td>
<td>+10</td>
</tr>
</tbody>
</table>

Of 12% mortality reduction -- 17% from screening & 83% from treatment

*Relative to breast cancer mortality without screening or treatment

Plevritis et al, JAMA, 2018
BCSC model ONLINE includes strong & prevalent risk factors

https://tools.bcsc-scc.org/BC5yearRisk/calculator.htm

Breast Imaging Reporting and Data System (BI-RADS)

Almost entirely fat 12%
Scattered fibroglandular densities 41%
Heterogeneously dense 39%
Extremely dense 8%

Common risk factors account for breast cancers

![Graph showing population attributable risk percentages for various risk factors.]

**Combined PAR = 43%**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dense breasts</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>BMI</td>
<td>3%</td>
<td>16%</td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>History of breast biopsy</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Nulliparous or age at first live birth &gt;30 years</td>
<td>9%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Engmann and Kerlikowske, et al., *Jama Oncol*, 2017

5-year risk (%) for 45-49y women

<table>
<thead>
<tr>
<th>Density</th>
<th>BCSC 5-yr risk</th>
<th>No Family Hx</th>
<th>Family Hx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No bx</td>
<td>Bx</td>
<td>No bx</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td>a</td>
<td>.4</td>
<td>.3</td>
<td>.5</td>
</tr>
<tr>
<td>b</td>
<td>0.8</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>c</td>
<td>1.2</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td>d</td>
<td>1.6</td>
<td>1.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Average 5-year risk >1.3% for 50-year-old – 16% of women 40-49

5-year risk (%) for 50-54y women

<table>
<thead>
<tr>
<th>Density</th>
<th>BCSC 5-yr risk</th>
<th>No Family Hx</th>
<th>Family Hx</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>.5</td>
<td>.4</td>
<td>.7</td>
</tr>
<tr>
<td>b</td>
<td>1.0</td>
<td>0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>c</td>
<td>1.6</td>
<td>1.3</td>
<td>2.2</td>
</tr>
<tr>
<td>d</td>
<td>2.1</td>
<td>1.7</td>
<td>2.8</td>
</tr>
</tbody>
</table>

32% of 50 year old women average risk less than average risk 40-year old

Tice, Ann Intern Med, 2008; Tice, JCO, 2015

Deaths averted vary by risk if screen women 50-74 biennial

Deaths averted per 1000 women

- Almost entirely fat
- Scattered densities
- Heterogeneously dense
- Extremely dense

Deaths averted vary by risk if screen women 50-74 triennial

Fewer false-positives (21-23%), benign biopsies (13-17%), overdiagnosis (8%-20%)

Deaths averted per 1000 women

Almost entirely fat
Scattered densities
Heterogeneously dense
Extremely dense


Deaths averted vary by risk if screen women 50-74 annual

More deaths averted with annual screening among women at high breast cancer risk

Deaths averted per 1000 women

Almost entirely fat
Scattered densities
Heterogeneously dense
Extremely dense

Breast Cancer Risk Factors

RR= 1.3
- >25g alcohol/day
- Postmenopausal HT
- Nulliparous or age first birth ≥30
- Body mass index >30 kg/m²
- First-degree relative with breast cancer
- Hx of breast biopsy

RR= 2.0
- Two first-degree relatives with breast cancer
- History of proliferative disease without atypia

RR= 4.0
- LCIS or ADH


When to stop screening mammography

- ACR, SBI -- if life expectancy <5-7 years
- ACS -- if life expectancy <10 years
- ACOG – to age 75, shared decision-making
- USPSTF, WHO, AAFP, ACP – age 75
- Most European countries and Canada stop at age 70-75
Breast cancer incidence decreases with advanced age

Demb, JNCI, 2019

75-84 yo 10-year breast cancer risk 3.6%; non-breast cancer death 36%; breast cancer death 0.29%

Breast cancer deaths averted per 1000 women screened

Lee, BMJ, 2013
New federal law for breast density notification - 2019

47% of women have dense breasts (heterogeneously or extremely dense)

High breast density masks interval invasive tumors

<table>
<thead>
<tr>
<th>BI-RADS Density</th>
<th>Screen-detected*</th>
<th>Interval cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1.8</td>
<td>0.21</td>
</tr>
<tr>
<td>b</td>
<td>3.3</td>
<td>0.38</td>
</tr>
<tr>
<td>c</td>
<td>4.8</td>
<td>0.84</td>
</tr>
<tr>
<td>d</td>
<td>5.1</td>
<td>1.11</td>
</tr>
</tbody>
</table>

64% of interval cancers in women with BI-RADS c or d

*per 1,000 women 40-74 screened


Half of women with dense breasts have low 5-year risk

50% of women with dense breasts have low to average risk

**BCSC 5-year risk %**

- Low: 0-1
  - Almost entirely fat: 67
  - Scattered densities: 38
  - Hetero. Dense: 23
  - Extremely dense: 19
- Average: >1-1.66
  - Almost entirely fat: 23
  - Scattered densities: 30
  - Hetero. Dense: 28
  - Extremely dense: 34
- Intermediate: 1.67-2.49
  - Almost entirely fat: 9
  - Scattered densities: 21
  - Hetero. Dense: 29
  - Extremely dense: 22
- High: >2.5
  - Almost entirely fat: 1
  - Scattered densities: 11
  - Hetero. Dense: 20
  - Extremely dense: 25

**High risk, high density – interval cancer rate >1 per 1000 exams**

24% of women with dense breasts at high risk of missed cancer

<table>
<thead>
<tr>
<th>BCSC 5-year risk %</th>
<th>Almost entirely fat</th>
<th>Scattered densities</th>
<th>Hetero. dense</th>
<th>Extremely dense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low: 0-1</td>
<td>0.14</td>
<td>0.21</td>
<td>0.63</td>
<td>0.72</td>
</tr>
<tr>
<td>Average: &gt;1-1.66</td>
<td>0.31</td>
<td>0.38</td>
<td>0.58</td>
<td>0.89</td>
</tr>
<tr>
<td>Intermediate: 1.67-2.49</td>
<td>0.48</td>
<td>0.43</td>
<td>0.83</td>
<td>1.17</td>
</tr>
<tr>
<td>High: &gt;2.5%</td>
<td>N/A</td>
<td>0.90</td>
<td>1.48</td>
<td>1.62</td>
</tr>
</tbody>
</table>


---

**High density and risk – rate of advanced rate elevated**

27% of women with dense breasts at high risk of advanced cancer

<table>
<thead>
<tr>
<th>Advanced cancer stage IIB or higher rate per 1000 screens</th>
<th>Almost entirely fat</th>
<th>Scattered densities</th>
<th>Heterogeneously dense</th>
<th>Extremely dense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 0-1</td>
<td>0.13</td>
<td>0.26</td>
<td>0.31</td>
<td>0.17</td>
</tr>
<tr>
<td>Average &gt;1 -1.66</td>
<td>0.17</td>
<td>0.31</td>
<td>0.35</td>
<td>0.61</td>
</tr>
<tr>
<td>Intermediate 1.67-2.49</td>
<td>0.41</td>
<td>0.6</td>
<td>0.56</td>
<td>0.68</td>
</tr>
<tr>
<td>High &gt;2.5%</td>
<td>0.41</td>
<td>0.6</td>
<td>1.08</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Kerlikowske, *JAMA Intern Med*, 2019
Alternative imaging strategies for women with dense breasts

- Change screening frequency
- Tomosynthesis or DBT (3D)
- Supplemental screening ultrasound -- hand held; whole breast
- Supplemental breast MRI

Odds of advanced stage with 2 vs. 1yr screening interval

<table>
<thead>
<tr>
<th>Age group</th>
<th>Heterogeneously dense</th>
<th>Extremely dense</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>1.32 (0.93-1.88)</td>
<td>1.89 (1.06-3.39)</td>
</tr>
<tr>
<td>50-74</td>
<td></td>
<td><strong>Dense</strong></td>
</tr>
<tr>
<td>No HT</td>
<td>1.21 (0.92-1.61)</td>
<td></td>
</tr>
<tr>
<td>E+P</td>
<td>1.56 (0.88-2.80)</td>
<td></td>
</tr>
<tr>
<td>E only</td>
<td>1.19 (0.66-2.13)</td>
<td></td>
</tr>
</tbody>
</table>

Cancer detection by extent of density for digital vs. DBT

<table>
<thead>
<tr>
<th></th>
<th>Digital</th>
<th>Digital + DBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exams</td>
<td>278,906</td>
<td>173,414</td>
</tr>
<tr>
<td>Invasive cancer rate*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dense</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Dense</td>
<td>2.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Recall rate*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dense</td>
<td>90</td>
<td>79</td>
</tr>
<tr>
<td>Dense</td>
<td>127</td>
<td>109</td>
</tr>
</tbody>
</table>

*per 1,000 exams, P< 0.001

*Biopsy rate: 18.1 vs. 19.3


J-START ultrasound trial

- Randomized trial of average-risk women age 40-49 years
- Annual digital mammography + screening ultrasound vs. annual digital mammography
- Outcome = interval cancer
- 18 interval cancers in intervention group vs. 35 in control group
  - Rate of 0.5 per 1000 vs. 0.97 per 1000

MRI in women with dense breasts

- Randomized trial of women with extremely dense breasts
- Biennial MRI vs. biennial mammography
- Age 50-75 years (mean 54 years)
- 59% participation (N=4756)
- Negative mammogram
- Outcome = interval cancer

Preliminary results; significant reduction in rate of interval cancers in the MRI group

de Lange, Clinical Radiology, 2018

Supplemental breast imaging

<table>
<thead>
<tr>
<th>Test</th>
<th>Incremental breast cancer detection per 1,000 exams</th>
<th>Biopsy rate per 1,000 exams</th>
<th>Radiation dose (location)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital mammography</td>
<td>NA</td>
<td>22</td>
<td>0.5 mSv (breast)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>2 to 4</td>
<td>50 to 57</td>
<td>None</td>
</tr>
<tr>
<td>Digital breast tomosynthesis</td>
<td>1 to 2</td>
<td>28</td>
<td>1.0 mSv (breast)</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>10 to 16</td>
<td>44</td>
<td>None</td>
</tr>
<tr>
<td>Molecular breast imaging</td>
<td>8 to 9</td>
<td>32 to 37</td>
<td>2.4 mSv (whole body)</td>
</tr>
</tbody>
</table>

Kerlikowske, Jama, 2019
### Cost-effectiveness of mammography + MRI in BRCA1/2 mutation carriers

<table>
<thead>
<tr>
<th></th>
<th>Mortality reduction</th>
<th>Deaths averted*</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Mammography</td>
<td>16.4%</td>
<td>87</td>
<td>$16,751</td>
</tr>
<tr>
<td>MRI</td>
<td>17.8%</td>
<td>95</td>
<td>$206,384</td>
</tr>
<tr>
<td>Mammography + MRI</td>
<td>22.3%</td>
<td>118</td>
<td>$69,125</td>
</tr>
</tbody>
</table>

*per 1000 women diagnosed with breast cancer

Lee, *Radiology*, 2010

### MRI + mammography in other intermediate/high-risk women

- TP53, PTEN, STK11, CDH1 mutation carrier
- ATM, PALB2, or CHEK2 mutation carrier with positive family history of breast cancer
- Women with a history of mantle radiation between ages 10–30 years

Esserman, *NPJ Breast Cancer*, 2017
Women with history of early-stage breast cancer

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mammography</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy rate*</td>
<td>24</td>
<td>57</td>
</tr>
<tr>
<td>Cancer yield%</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>High-risk benign lesions†</td>
<td>52</td>
<td>75</td>
</tr>
</tbody>
</table>

2-fold higher biopsy rates with MRI, with lower cancer yield and no difference in interval cancer rate

*Per 1,000 screening episodes
†ADH, LCIS


Risk of breast cancer with breast pain <1%

Imaging not needed
- Bilateral, non-focal
- Cyclic
- Age <40

Consider diagnostic mammography
- Non-cyclic
- Unilateral, focal, persistent
- Age ≥40

Breast implants decrease detection on mammograms

- Order displacement views
- Lower mammography sensitivity compared to women without implants
- Type and location of implant similar impact on mammography detection
- More likely to undergo excisional biopsy vs. core biopsy


Primary prevention of breast cancer matters

- Maintain ideal body weight
- Alcohol in moderation
- Exercise regularly
- Limit postmenopausal E+P hormone therapy to 5 years or less
Summary

- Offer biennial screening ages 50-74 or 13 mammograms in a woman’s lifetime
  - Consider triennial screening if low density & low to average risk
  - Consider annual screening if high density & risk
  - Stop screening before 74 for women with moderate to severe comorbidities
- Consider biennial screening age 40-49 if 5-year breast cancer risk >1.3%, i.e., average-risk of fifty year old woman

Summary

- Digital mammography for most women, consider DBT if heterogeneously dense breasts
- Women with dense breasts at high risk of advanced breast cancer, consider supplemental screening ultrasound or MRI
- BRCA1 and 2 mutation carriers -- breast MRI and annual mammogram
- History of breast cancer -- annual mammogram
- Breast pain rarely requires breast imaging
- Displacement views for women with implants
Thank you