Updates and Controversies in Breast Cancer Screening

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Disclosure information: Update in Breast Cancer Screening
Karla Kerlikowske, MD

- Grant/Research support from: National Cancer Institute

- and -

- Primary care physician at San Francisco VA
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 -- *annual* starting at 40
- ACOG, ACS, USPSTF, ACP -- discuss 40s, offer screening 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 -- *biennial* starting at age 50; Canada q2-3; UK q3


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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)

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

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

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


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 (ductal carcinoma in situ or low grade invasive cancer) 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
  - UK independent panel
    - 19% of detected cases

CISNET models

Common inputs
- Background Trends – SEER
- Screening - BCSC
- Treatment -- RCT
- Other common inputs

Unique simulation or analytical model
- 6 different breast cancer models

Outputs
- BC incidence, mortality, life years gained (LYG), false positives

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-positive*</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></th>
<th>Advanced stage†</th>
<th>Tumor &gt;15mm</th>
</tr>
</thead>
<tbody>
<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></th>
<th>Risk %</th>
<th>Deaths averted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2.70</td>
<td></td>
</tr>
<tr>
<td>50-74 biennial</td>
<td>2.00</td>
<td>7</td>
</tr>
<tr>
<td>40-74 biennial</td>
<td>1.88</td>
<td>8</td>
</tr>
<tr>
<td>45-49 annual, 50-74 biennial</td>
<td>1.90</td>
<td>8</td>
</tr>
</tbody>
</table>

†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

BCSC Risk Calculator
FREE iPhone & iPad app

Tice J, et al., JCO, 2015
Breast Imaging Reporting and Data System (BI-RADS)

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

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


Common risk factors account for breast cancers

Combined PAR = 43%

Premenopausal
Postmenopausal

Engmann and Kerlikowske, et al., Jama Oncol, 2017
Breast cancer risk assessment models

**General**
- Breast cancer risk assessment tool
- BCSC
- Tyrer-Cuzick*

**Family risk**
- BRCAPro – BRCA carrier
- BOADICEA* – BRCA carrier + ovarian cancer
- Tyrer-Cuzick* – 10y – BRCA carrier

*includes breast density measure

McCarthy, JNCI, 2019

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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></td>
<td>No bx</td>
<td>Bx</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

Tice et al, Ann Intern Med, 2008; Tice et al, JCO, 2015
### 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></td>
<td>BCSC</td>
<td>No bx</td>
<td>Bx</td>
</tr>
<tr>
<td>No bx</td>
<td>Bx</td>
<td></td>
<td></td>
</tr>
<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: RR = 4.0, 4.1
- Scattered densities: RR = 4.0, 5.1
- Heterogeneously dense: RR = 4.0, 6.5
- Extremely dense: RR = 4.0, 10.8

Triennial screening for low density and average risk

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

Deaths averted per 1000 women

Almost entirely fat   Scattered densities   Heterogeneously dense   Extremely dense

1.0  1.3  2.0  2.0
4.4  5.1  7.2  11.5
4.8  6.0  8.3  12.4
5.1  6.2  8.4  12.0


Annual screening if high risk regardless of breast density

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

Deaths averted per 1000 women

Almost entirely fat   Scattered densities   Heterogeneously dense   Extremely dense

1.0  1.3  2.0  2.0
4.7  6.9  8.7  10.4
8.4  10.4  13.3  21.1
8.9  10.9  17.7  28.8

Breast Cancer Risk Factors

**RR= 1.3-1.9**
- >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


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When to stop screening mammography

- ACR -- 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 deaths averted per 1000 women screened

Lee, BMJ, 2013; Demb, JNCI, 2019

New federal law for breast density notification - 2019

Low density for BI-RADS a and b
High density for BI-RADS c and d
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

Kerlikowske, Ann Intern Med, 2015
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>

Kerlikowske, Ann Intern Med, 2015

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>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>0.13</td>
<td>0.26</td>
<td>0.31</td>
</tr>
<tr>
<td>Average &gt;1 -1.66</td>
<td>0.17</td>
<td>0.31</td>
<td>0.35</td>
</tr>
<tr>
<td>Intermediate 1.67-2.49</td>
<td>0.41</td>
<td>0.6</td>
<td>0.56</td>
</tr>
<tr>
<td>High &gt;2.5</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>
</tbody>
</table>

Higher advanced stage with biennial vs. annual screening in extremely dense group

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

• Decrease recall and increase cancer detection -- mostly density b and c
• No difference in interval cancer rate overall or by breast density category

*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

- RCT of women with extremely dense breasts
- Age 50-75 years (mean 54 years)
- 59% participation (N=4756)
- Negative mammogram
- Biennial MRI vs. biennial mammography
- Outcome= 2.5 vs. 5.0 interval cancer/1000 screens – node positive rate no different
- False-positive rate MRI group 79.8/1000 screens

de Lange, *Clinical Radiology*, 2018; Bakker, *NEJM*, 2019

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>Clinical</th>
<th>Mortality reduction</th>
<th>Deaths averted*</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>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

41

42
Consider referral to genetic testing

- Breast cancer before age 50
- Bilateral breast cancer
- >2 premenopausal breast cancer
- >3 family members, >1 premenopausal breast cancer
- Ovarian cancer + premenopausal breast cancer
- Ovarian cancer + 2 breast cancers
- >2 Ovarian cancer
- Male breast cancer + female breast cancer or ovarian cancer

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>

*Per 1,000 screening episodes
†ADH, LCIS

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

Buist, JAMA Intern Med, 2018; Wernli, Radiology, 2019
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

Jokich, J Am Coll Radiol, 2017

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

Miglioretti, JAMA, 2004; Sosin, Plast Reconstr Surg, 2018
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
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

Thank you