Molecular Breast Imaging: Unveiling the Reservoir of Hidden Cancers in Dense Breasts

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Disclosures

• None
Objectives

• Understand limitations of “sensitivity” in characterizing mammography’s performance

• Describe potential benefits and harms of Molecular Breast imaging and other supplemental screening options in women with dense breasts to enhance shared decision making
Annual screening mammography starting at age 40 reduces breast cancer mortality by 30%
Factors impeding further progress in screening

• Traditional measurement of mammography’s performance inflates its effectiveness
  • Sensitivity
  • Tumor size

• Requiring demonstration of a breast cancer mortality reduction means no other imaging modality can compete
ACCURACY OF MAMMOGRAMS

Mammography is good at finding breast cancer, especially in women ages 50 and older.

Overall, the sensitivity of mammography is about 87 percent [15]. This means mammography correctly identifies about 87 percent of women who truly have breast cancer.

Sensitivity is higher in women over 50 than in younger women [11]. It's also higher in women with fatty breasts compared to women with dense breasts [11].

Learn more about sensitivity.
Sensitivity, Specificity, and False negative rate for 1,682,504 Screening Mammography Examinations from 2007 - 2013 Based on BCSC data through 2013

<table>
<thead>
<tr>
<th>Performance Metric</th>
<th>All Screening Examinations</th>
</tr>
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<tr>
<td>Sensitivity</td>
<td>86.9%</td>
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### Performance Metric

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Size matters:
Probability of survival by tumor size

- 0 – 1 cm
- 1.1 – 2 cm
- 2.1 – 5 cm

Narod, Curr Onc, 2012
Benefit of detecting smaller tumors applies to node-positive and node-negative disease

Size distribution of invasive breast cancers in women undergoing screening mammography: Breast Cancer Surveillance Consortium

Tumor Growth

• Mean time for a breast tumor to grow from 10 mm to 20 mm = 1.7 years (even allowing for wide variance in individual tumor biology) (Weedon-Fekjaer et al. Breast Cancer Research Research 2008)

• What if we considered any tumor diagnosed at a size > 2 cm in a woman undergoing annual mammograms as a cancer UNDETECTED on prior mammography rather than a cancer detected on the current mammogram?

• How would that change our perception of mammography sensitivity?
What Mammography Studies Miss

Cancers found on mammography

Cancers that manifest before the study ends

The Invisible Reservoir
Breast Density

- Fat
- Ducts
- Lobules
Dense Breasts

• Increase odds of missed breast cancer by 9
  Ma et al; J Natl Cancer Inst 1992

• Increase risk of missed breast cancer by 15-fold in women 40-49
  Kerlikowske et al; NEJM 2007

• Explain 68% of mammography failure in women 40-49
  Buist et al; J Natl Cancer Inst 2004

• Explain 79% of poorer sensitivity in younger women
  Bailey S et al; J Natl Cancer Inst 2010
Tumors and breast density both appear white on mammography.

Mammograms from two different women
Both had 1 cm invasive ductal adenocarcinoma
BI-RADS® Breast Composition Categories
Used by Radiologists in Mammography Reports

Almost entirely fatty

Scattered areas of fibroglandular densities

Heterogeneously dense which *may* obscure small masses

Extremely dense which *lowers the sensitivity of mammography*
### Sensitivity of digital mammography in dense breasts

**Breast Cancer Surveillance Consortium**

Kerlikowske, Ann Intern Med, 2011; 155(8)

<table>
<thead>
<tr>
<th>By BI-RADS breast density</th>
<th>Cancer detection per 1000 examinations</th>
<th>Sensitivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost entirely fat</td>
<td>38 672</td>
<td>78.3 (59.4–89.9)</td>
</tr>
<tr>
<td>Scattered fibroglandular densities</td>
<td>211 535</td>
<td>86.6 (80.3–91.1)</td>
</tr>
<tr>
<td>Heterogeneously dense</td>
<td>206 609</td>
<td>82.1 (76.6–86.6)</td>
</tr>
<tr>
<td>Extremely dense</td>
<td>35 379</td>
<td>83.6 (69.7–91.9)</td>
</tr>
</tbody>
</table>
"A sensitivity of 48 percent for mammography in women with the densest breasts is unacceptable," Dr. Kolb said in a phone interview. "Screening ultrasound will find an enormous amount of cancer that would otherwise go undetected."
## Adding MRI in high-risk women

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Cancers per # Screened</th>
<th>Mammogram Sensitivity</th>
<th>MRI sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhl</td>
<td>2005</td>
<td>43/529</td>
<td>14/43 (33%)</td>
<td>39/43 (91%)</td>
</tr>
<tr>
<td>Warner</td>
<td>2004</td>
<td>22/236</td>
<td>8/22 (36%)</td>
<td>17/22 (77%)</td>
</tr>
<tr>
<td>Podo</td>
<td>2002</td>
<td>8/105</td>
<td>1/8 (13%)</td>
<td>8/8 (100%)</td>
</tr>
<tr>
<td>Tilanus-Linthorst</td>
<td>2000</td>
<td>3/109</td>
<td>0%</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>Morris</td>
<td>2003</td>
<td>14/367</td>
<td>-----</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Kriege</td>
<td>2004</td>
<td>45/1909</td>
<td>18/45 (40%)</td>
<td>32/45 (71%)</td>
</tr>
<tr>
<td>Lehman</td>
<td>2005</td>
<td>4/367</td>
<td>1/4 (25%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Leach</td>
<td>2005</td>
<td>33/649</td>
<td>14/35 (40%)</td>
<td>27/35 (77%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>172/4271</strong></td>
<td><strong>56/172 (33%)</strong></td>
<td><strong>144/172 (85%)</strong></td>
</tr>
</tbody>
</table>
X-rays preferentially detect more favorable cancers

Mammographic hallmarks of malignancy represent regressive changes (fibrosis, necrosis) caused by cell death
Functional screening with MRI overcomes these limitations

- MRI preferentially detects more aggressive cancers
- Gadolinium enhancement correlates with angiogenic and protease activity within tumors (*i.e.* tissue alterations that signify cell proliferation and metastatic growth) Kuhl, Radiology 2017 Feb 21:161444
Types of cancers detected by MRI vs. mammography (Sung et al Radiology 2016)
MRI: Why not for everyone?

- Screening beyond high-risk group limited:
  - Cost
  - Complexity of interpretation
  - Relatively high false positive rate
Optimal characteristics of a supplemental screening test for women with dense breasts

- High incremental cancer detection rate
- Low false positive rate
- Safe
- Affordable
Evolution of Molecular Breast Imaging (MBI)
Our First Patient

Old scintimammography system  1st MBI prototype
Molecular Breast Imaging

- FDA approved
- 2 high resolution gamma detectors
- Breast placed between detectors – gentle compression
- Injection of $^{99m}$Tc-sestamibi which is taken up by tumor cells regardless of surrounding density
- 8 images per study
Annual Background Radiation

- PET / CT Scan
- Myocardial Perfusion Scan
- CT Coronary Angiogram
- CT Urogram
- CT Abdomen / Pelvis
- Virtual Colonoscopy
- CT Screening Lung Cancer
- Coronary Calcium Score
- MBI (4 – 8 mCi Tc-99m sestamibi)
  - Mammogram + tomosynthesis
  - Breast Stereotactic Biopsy
  - Mammogram (screen / diagnostic)
- Chest X-ray
- Bone Densitometry

Lower annual limit for Radiation workers; AAPM guideline for single procedure

Note: Dose ranges vary by scanner, scan technique and protocol

Courtesy of Michael K O'Connor, Mayo Clinic
MBI Prospective Screening Data: Mayo Experience

- 2,587 women presenting for screening
- Dense breasts on prior mammogram
- Mammogram and MBI interpreted independently

Funded by Susan G. Komen for the Cure

Rhodes et al, Radiology 2011
Rhodes et al, AJR 2015
Mammographically occult invasive ductal carcinoma

Grade II Invasive Ductal Carcinoma, 1.9 cm
Mammographically occult invasive lobular carcinoma

Grade III Invasive Lobular Carcinoma, 3.6 cm; node positive
Mammographically occult invasive ductal carcinoma

Mammogram March 2010
Mammogram March 2011
MBI March 2011

Grade II Invasive Ductal Carcinoma, 4.1 cm
Mammographically occult tubular carcinoma

Grade I Tubular Carcinoma, 5 mm
MBI-occult small invasive ductal carcinoma

Grade II Invasive Ductal Carcinoma, 3 mm
Cancer detected by both modalities

Grade III Invasive Ductal Carcinoma, 2.2 cm
**MBI Prospective Screening Data: Mayo Experience**

<table>
<thead>
<tr>
<th></th>
<th>Number of cancers detected</th>
<th>Sensitivity</th>
<th>Cancers detected per 1,000 screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>8/32</td>
<td>25%</td>
<td>3.1</td>
</tr>
<tr>
<td>MBI</td>
<td>26/32</td>
<td>81%</td>
<td>10.1</td>
</tr>
<tr>
<td>Mammography + MBI</td>
<td>29/32</td>
<td>91%</td>
<td>11.3</td>
</tr>
</tbody>
</table>

**MBI-only detected cancers (22/32)**
- Median size 12mm (range 4-62mm)
- 17/22 (77%) invasive and 9/22 (41%) advanced

**Mammography-only detected cancers (3/32)**
- 3 mm invasive cancer and two ≤ 5 mm DCIS
• Incremental cancer detection rate: 7.7 per 1000
• Compared to 8.8 per 1000 in Mayo study
What is the Sensitivity of Mammography in the Dense Breast?
Depends on What You Measure it Against

Digital Mammography

Mammography Sensitivity (%)

<table>
<thead>
<tr>
<th>Source</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCSC Registry Data</td>
<td>87%</td>
</tr>
<tr>
<td>Rhodes <em>Radiology</em> 2011</td>
<td>27%</td>
</tr>
<tr>
<td>Berg <em>JAMA</em> 2012</td>
<td>31%</td>
</tr>
<tr>
<td>Kuhl <em>ASCO</em> 2015</td>
<td>21%</td>
</tr>
<tr>
<td>Rhodes <em>AJR</em> 2015</td>
<td>24%</td>
</tr>
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Comparing incremental invasive cancer detection rate

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Yield/1000 MMG alone</th>
<th>Yield/1000 Combined</th>
<th>Incremental cancer detection rate</th>
<th>Additional % yield over MMG alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomosynthesis (Friedewald)</td>
<td>2.9</td>
<td>4.1</td>
<td>1.2</td>
<td>41%</td>
</tr>
</tbody>
</table>
Breast-cancer screening with three-dimensional imaging finds more invasive cancers and yields fewer false alarms than standard digital mammograms alone, according to a new study in the Journal of the American Medical Association.

The study, funded largely by Hologic Inc., HOLX +6.38% which makes the 3D-imaging equipment, comes amid growing debate about how often women should be screened for breast cancer, when they should start and what technology is best in which cases.

In the JAMA study, researchers at 13 sites compared records of 281,187 women who had digital mammograms alone with 173,663 who had the 2-D and 3-D versions. Adding the 3-D imaging decreased the rate of recalls by about 10%—from 107 per 1,000 exams to 91 per 1,000.

At the same time, 3-D mammograms detected 41% more invasive cancers, finding 4.1 per 1,000 exams, compared with 2.9 per 1,000 for digital mammography alone.
## Comparing incremental invasive cancer detection rate

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<td>All densities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABUS (automated US) (Brem)</td>
<td>3.3</td>
<td>5.2</td>
<td>1.9</td>
<td>58%</td>
</tr>
<tr>
<td>Dense breasts only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US; tech performed (Berg)</td>
<td>NA</td>
<td>NA</td>
<td>2.2</td>
<td>NA</td>
</tr>
<tr>
<td>All densities; meta-analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBI (Rhodes)</td>
<td>1.9</td>
<td>8.8</td>
<td>6.9</td>
<td>363%</td>
</tr>
<tr>
<td>Dense breasts only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI (Kuhl)*</td>
<td>NA</td>
<td>NA</td>
<td>14.2</td>
<td>NA</td>
</tr>
<tr>
<td>All densities</td>
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* MRI (Kuhl) uses 1.5 Tesla imaging with contrast enhancement.
Comparing recall rates, biopsies, positive predictive value

<table>
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<tr>
<th>Imaging Modality</th>
<th>Recall rate (%) Combined</th>
<th>Biopsy rate Combined</th>
<th>PPV3(%) Cancers per biopsies Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomosynthesis (Friedewald) All densities</td>
<td>9.1</td>
<td>1.9* Biopsies increased significantly</td>
<td>29.2</td>
</tr>
<tr>
<td>US; tech performed (Berg) All densities; meta-analysis</td>
<td>13.2</td>
<td>4.5</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>MBI (Rhodes) Dense breasts only</strong></td>
<td><strong>17.6</strong></td>
<td><strong>4.2</strong></td>
<td><strong>28.4</strong></td>
</tr>
<tr>
<td>ABUS (automated US) (Brem) Dense breasts only</td>
<td>28.5</td>
<td>7.7</td>
<td>14.0</td>
</tr>
<tr>
<td>MRI (Berg) Dense breasts only; high-risk</td>
<td>31.2</td>
<td>9.6</td>
<td>25.4</td>
</tr>
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</table>
Chemotherapy given before surgery
Residual tumor size at time of surgery: 11 cm
Factors impeding further progress in screening

• Traditional measurement of mammography’s performance inflates its effectiveness
  • Sensitivity
  • Tumor size

• Requiring demonstration of a breast cancer mortality reduction means no other imaging modality can compete
“Follow-up of 20 years or more may be necessary to measure the full impact of breast cancer screening.”

(Webb, Cancer 2014; Tabar, Radiology 2011)
“Overall, many important questions remain about the potential role of breast density in individualizing screening approaches, and the current evidence is insufficient to recommend a specific screening strategy for women with increased breast density.”
Results

The literature search yielded 2067 unique citations; 128 full-text articles considered potentially relevant were reviewed to identify 24 unique studies meeting inclusion criteria. No studies addressed the effect of supplemental screening on breast cancer morbidity or mortality.
Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Services Task Force

Joy Melnikow, MD, MPH; Joshua J. Fenton, MD, MPH; Evelyn P. Whitlock, MD, MPH; Diana L. Miglioretti, PhD; Meghan S. Weyrich, MPH; Jamie H. Thompson, MPH; Kunal Shah

Increased breast density is not associated with higher breast cancer mortality among women with dense breasts diagnosed with breast cancer, after adjustment for stage and mode of detection (5).
What will it take to change the guidelines?

- Ongoing patient education and advocacy
- Endpoint other than mortality:
  - Reduction in advanced and interval cancers
Mammography has failed to reduce advanced cancer presentation


Most of this increase is DCIS
Supplemental screening must eliminate advanced and interval cancers

<table>
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<tr>
<th>Years</th>
<th>Rate per 100,000</th>
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<tbody>
<tr>
<td>2015</td>
<td>50</td>
</tr>
<tr>
<td>2016</td>
<td>55</td>
</tr>
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<td>2017</td>
<td>60</td>
</tr>
<tr>
<td>2018</td>
<td>65</td>
</tr>
<tr>
<td>2019</td>
<td>70</td>
</tr>
<tr>
<td>2020</td>
<td>75</td>
</tr>
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- Localized (breast only)
- Regional lymph nodes
- Distant metastases

**Initiate MBI screening**
What will it take to change the guidelines?

• Ongoing patient education and advocacy

• Endpoint other than mortality:
  • Reduction in advanced and interval cancers

• Robust, multi-center research
  • ACRIN Abbreviated MRI vs. DBT trial
  • Mayo Density MATTERS trial
    • 3000 women with dense breasts scheduled for screening DBT
    • Two consecutive years of imaging
MBI

Functional modality that unveils reservoir of cancers obscured by dense tissue on mammography

- Low cost (one-tenth the cost of MRI)
- Relatively high incremental cancer detection rate
- Relatively low false positive rate
- Low complexity of interpretation
MBI Team at Mayo Clinic

• Medical Physics
  • Carrie Hruska PhD
  • Michael O’Connor PhD

• Internal Medicine
  • Deb Rhodes MD

• Nuc Medicine Technicians
  • Tiffinee Swanson CNMT
  • Thuy Tran CNMT
  • Lacey Ellingson CNMT

• Radiology
  • Amy Conners MD
  • Katie Hunt MD
  • Dana Whaley MD
  • Shannon Zingula MD

• Patient Advocate
  • Linda Miller MD