Screening Options in Dense Breasts

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Associate Professor of Radiology
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Dense Breasted Women

- Decreased sensitivity of mammography from 84% down to 25-50%
- Increased Tumor size and worsened prognosis is associated with increased breast density
- Independent risk factor for breast cancer

## Risk Categories

<table>
<thead>
<tr>
<th><strong>Personal (RR1.2-2.0)</strong></th>
<th><strong>Breast Related (RR2.0-4.0)</strong></th>
<th><strong>Genetic (life time risk 40-70%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age at menarche</td>
<td>Biopsy with ADH, ALH, LCIS</td>
<td>BRCA 1 or 2</td>
</tr>
<tr>
<td>Older age at menopause</td>
<td>Radiation Therapy to the Chest</td>
<td>Li-Fraumeni syndrome</td>
</tr>
<tr>
<td>Nulliparity</td>
<td></td>
<td>Cowden Syndrome</td>
</tr>
<tr>
<td>Late parity</td>
<td>- Dense breast tissue on mammogram</td>
<td>Bannayan-Riley-Ruvalcaba Syndrome</td>
</tr>
<tr>
<td>Menopausal Hormone Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Biopsy with ADH, ALH, LCIS
- Radiation Therapy to the Chest
- Dense breast tissue on mammogram
Screening Options

• Mammography
• Digital Breast Tomosynthesis
• Screening Breast Ultrasound
• MRI
• Molecular Breast Imaging
• Contrast Enhanced Mammography
Mammography

• The only test proven to decrease mortality from breast cancer
• Decreased sensitivity and specificity in women with radiographic dense breast tissue
• Overlapping tissue may hide or mimic breast cancer
Does the woman have at least a 10-year life expectancy?

Yes

Is the woman under the age of 75?

Yes

Is the woman at high risk for breast cancer according to accepted models based on family history, pathogenic BRCA or other mutation, or did she have prior chest radiation therapy before age 30?

Yes

Recommend annual contrast-enhanced MRI beginning at age 25-30 with mammography beginning by age 50 if patient can tolerate MRI. If MRI cannot be performed, then recommend annual ultrasound in addition to mammography if breasts are dense.

No

Obtain baseline mammogram.

Is the woman age 40 or older?

Yes

Does the woman have heterogeneously or extremely dense breasts on the mammography report?

Yes

Recommend annual screening mammography (with tomosynthesis if available). Include annual clinical breast examination.

No

Recommend annual digital mammography (with tomosynthesis if available) and consider adding screening ultrasound (especially if breasts are extremely dense) if patient accepts the potential for false positives. Include annual clinical breast examination.

No

Recommend annual or biennial mammography (with tomosynthesis if available) supplemented by clinical breast examination.

No

Recommend clinical breast exam every 2-3 years, then screening mammography beginning at age 40.

A See also DenseBreast-info.org (Technology tab Table: Summary of Cancer Detection Rates for Commonly Available Breast Screening Tests).

B See DenseBreast-info.org (with Care Provider tab / Risk Models).
Digital Breast Tomosynthesis: the next generation of mammography

• Eliminates overlap of tissue
• Increases cancer detection
• Decreases call back rates
# DBT clinical studies

<table>
<thead>
<tr>
<th>Study</th>
<th># pts</th>
<th>Type of study</th>
<th>CBR reduction</th>
<th>P value</th>
<th>CDR increase</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STORM Italian</td>
<td>7,292</td>
<td>Prospective Double read</td>
<td>17.2%</td>
<td>( p &lt; 0.01 )</td>
<td>53% all Ca 48% invasive</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Oslo Norway</td>
<td>12,631</td>
<td>Prospective Double read</td>
<td>15%</td>
<td>( p &lt; 0.001 )</td>
<td>31% all Ca 45% invasive</td>
<td>( p = 0.001 ) ( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Rose, 2014 USA</td>
<td>21,756</td>
<td>Retrospective Double read</td>
<td>37%</td>
<td>( p &lt; 0.001 )</td>
<td>54% all Ca 66% invasive</td>
<td>( p &lt; 0.001 ) ( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Yale USA</td>
<td>6,100</td>
<td>Retrospective Single read</td>
<td>30%</td>
<td>( p &lt; 0.001 )</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td>JAMA multisite USA</td>
<td>454,850</td>
<td>Retrospective Single read</td>
<td>15%</td>
<td>( p &lt; 0.001 )</td>
<td>29% all Ca 41% invasive</td>
<td>( p &lt; 0.001 ) ( p &lt; 0.001 )</td>
</tr>
</tbody>
</table>
### CDR increases 3D/2D vs 2D

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative to 2D</th>
<th>Absolute increase/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skaane</td>
<td>27%</td>
<td>1.9</td>
</tr>
<tr>
<td>Haas</td>
<td>9.5%</td>
<td>0.5</td>
</tr>
<tr>
<td>Ciatto</td>
<td>57%</td>
<td>2.7</td>
</tr>
<tr>
<td>Freidewald</td>
<td>29%</td>
<td>1.2</td>
</tr>
<tr>
<td>Greenberg</td>
<td>43.8%</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Breast Cancer Screening Using DBT and DM in Dense and Non-dense Breasts

- 452,320 exams:
  - 278,906 DM
  - 173,414 DM + DBT
- Recall Rates, CDR, invasive CDR and PPV of recall
From: Breast Cancer Screening Using Tomosynthesis and Digital Mammography in Dense and Nondense Breasts


<table>
<thead>
<tr>
<th>Table. Model-Adjusted Rates and Positive Predictive Values for Screening Examinations vs Breast Density Among US Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Density</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>No. of screens (%)</td>
</tr>
<tr>
<td>Digital mammography</td>
</tr>
<tr>
<td>Digital mammography + tomosynthesis</td>
</tr>
<tr>
<td><strong>Model-Adjusted Rates</strong></td>
</tr>
<tr>
<td>Recalls per 1000 screens, estimate (95% CI) [No. of screens]</td>
</tr>
<tr>
<td>Digital mammography</td>
</tr>
<tr>
<td>Digital mammography + tomosynthesis</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
</tr>
<tr>
<td>P value</td>
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<tr>
<td><strong>Cancers per 1000 screens, estimate (95% CI) [No. of screens]</strong></td>
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<tr>
<td>Difference (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td><strong>Invasive cancers per 1000 screens, estimate (95% CI) [No. of screens]</strong></td>
</tr>
<tr>
<td>Digital mammography</td>
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<tr>
<td>Digital mammography + tomosynthesis</td>
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<tr>
<td>Difference (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td><strong>Positive predictive value for recall, % (95% CI)</strong></td>
</tr>
<tr>
<td>Digital mammography</td>
</tr>
<tr>
<td>Digital mammography + tomosynthesis</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
</tr>
<tr>
<td>P value</td>
</tr>
</tbody>
</table>

*Model estimates were used to estimate rates with screening mammography (digital mammography and digital mammography + tomosynthesis) as a fixed effect and site as a random effect. Additive models used SAS PROC MIXED (SAS Institute), version 9.3.

Cancer detection rate (prop of screening examinations with screen-detected breast cancer).

Invasive cancer detection rate (prop of screening examinations with screen-detected invasive breast cancer).

Recall rate (prop of screening examinations requiring additional imaging based on screening examination result).

Positive predictive value for recall (prop of recalls after screening subsequently diagnosed with breast cancer).
Screening Breast Ultrasound
Screening US ACRIN 6666

- 2662 high risk women underwent 7473 mammogram and US screenings over 3 years (limited number had additional MRI in year 3)
- 110 women had 111 cancers
  - 33 mamm only
  - 32 US only
  - 26 both
  - 9 by MRI only (after mamm and US were -)
  - 11 were not detected by imaging
Screening US ACRIN 6666

- US supplemental cancer yield = 3.7/1000
- 92% invasive, 89% node negative cancers
- US PPV3=8%
- MRI supplemental cancer yield = 14.7/1000
Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts
Scheel, J, Lee, J Sprague B, Lee C, Lehman C.
AJOG January 2015

- **Biopsy Rates (On top of mamm bx’s of 10.2/1,000)**
  - HHUS ranged from 25-107/1,000 (median of 56) (~5X that of mamms)
  - ABUS (only one study recorded data) 11.7/1,000

- **Additional Cancer detection**
  - HHUS ranged from 0.3-6.8/1,000 (median of 4.2/1,000)
  - ABUS was 3.6/1,000 in one study
  - Median rate overall is 4.2 cancers /1,000 women
Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts
Scheel, J, Lee, J Sprague B, Lee C, Lehman C.
AJOG January 2015

- Connecticut experience (3 studies, all retrospective)
- Technologists perform the study
- Additional Biopsies
  - 32.8 -71.0/1,000
- Additional Cancers
  - 1.8-4.6/1,000 (probably closer to 2 when accounting for # of pts in each study)
Italy ASTOUND Trial: Comparing screening breast US and DBT

• 3,231 Screening 2D Mammography negative patients with dense breasts
• All had supplemental DBT and screening US
• 24 additional BCs were detected (23 invasive) (7.1/1,000)
  • 13 detected by DBT (+ 4.0/1,000 cancers)
  • 23 detected by US (+ 7.1/1,000 cancers)
• FP recall and RP biopsy did not differ between DBT and US

ASTOUND Trial: Comparing screening breast US and DBT

- Conclusion: adjunct screening with DBT detected more than 50% of the additional breast cancers in these dense breasted women and could be the primary screening modality.

Molecular Breast Imaging
How does Molecular Breast Imaging (MBI) Work?

- Patient receives a low dose injection of a radiotracer (Tc-99m Sestamibi) by IV
- The tracer preferentially accumulates in cancer cells and is not influenced by breast density
- The breast is lightly immobilized between 2 digital gamma cameras, only light pain-free compression is necessary (1/4 of the pressure used in mammography)
- Imaging starts ~5 minutes post injection. Acquire CC and MLO views of each breast for 10 minutes per view
MBI Reduced Radiation Dose for Supplemental Screening in Mammographically Dense Breasts
Rhodes D AJR 2015;204:241-251

- 1585 asymptomatic women with dense breasts
- MBI and mammogram with 300-MBq $^{99m}$Tc-sestamibi (effective dose of 2.4 mSv)
- CDR, Sensitivity, Specificity, PPV$_3$
MBI Reduced Radiation Dose for Supplemental Screening in Mammographically Dense Breasts
Rhodes D AJR 2015;204:241-251

• 21 Cancer total
  • 2 mammography only
  • 14 MBI only
    • 11 invasive median size 0.9mm
      • 9 were node negative
      • 2 were bilateral
  • 3 by both
  • 2 by neither
MBI Reduced Radiation Dose for Supplemental Screening in Mammographically Dense Breasts
Rhodes D AJR 2015;204:241-251

• Supplemental cancer detection rate of 8.8/1,000
• For combination of DM + MBI:
  • Sensitivity = 91%
  • Specificity = 83%
• Recall rate increased from 11% to 17.6% (p<0.001)
• Biopsy rate increased from 1.3% to 4.2% (p<0.01)
Abbreviated MRI
Abbreviated Breast MRI

- Prospective observational reader study in 443 women (mild to moderate increase risk)
- All pts had negative or benign DM, 427 had dense breasts and neg US
- 606 screening MRIs
- MRI was 3 min
- MIP, one pre and one post contrast, subtraction images
- Avg reading time < 1min (MIP read first)
Abbreviated Breast MRI

- Cancer detection: 11 Cancers (4 DCIS, 7 invasive, T1N0)
- Additional cancer yield of 18.2/1,000
- NPV 90.8%
- Sensitivity 94.3%
- PPV 24%
Cancers detected by MRI

- Effective in vivo biomarker for disease activity or tumor biology
- Locally increased vessel density, increased vessel permeability and permeability of the ductal basal membrane
- Detection is based on pathophysiological changes: cancer proliferation, infiltrative growth and metastasis
MRI detected cancers

- Prognostically important disease
- Higher nuclear grade
- High Ki-67 values
Abbreviated MRI Protocols: Wave of the Future for Breast Cancer Screening
Chloe M. Chhor¹ and Cecilia L. Mercado¹

TABLE 2: Selected Results from Six Studies of Abbreviated MRI Protocols

<table>
<thead>
<tr>
<th>Reference</th>
<th>Acquisition Time (min)</th>
<th>Average Interpretation Time (s)</th>
<th>No. of Cancers</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohl et al. [17]</td>
<td>17</td>
<td>3</td>
<td>28 (2.8 MIP only)</td>
<td>11</td>
<td>100</td>
<td>100 (99.9 MIP only)</td>
<td>93.9</td>
</tr>
<tr>
<td>Mango et al. [18]</td>
<td>30–40</td>
<td>16–15</td>
<td>44</td>
<td>100</td>
<td>–</td>
<td>95 (93 MIP only)</td>
<td>–</td>
</tr>
<tr>
<td>Grimm et al. [19]</td>
<td>20</td>
<td>11, 13²</td>
<td>177</td>
<td>12</td>
<td>95</td>
<td>86, 89³</td>
<td>–</td>
</tr>
<tr>
<td>Harvey et al. [20]</td>
<td>23.2</td>
<td>4.4</td>
<td>385.8</td>
<td>7</td>
<td>52</td>
<td>52, 45²</td>
<td>–</td>
</tr>
<tr>
<td>Heacock et al. [21]</td>
<td>35³</td>
<td>12³</td>
<td>25³</td>
<td>107</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mocchetta et al. [22]</td>
<td>16</td>
<td>10</td>
<td>360</td>
<td>69</td>
<td>92</td>
<td>99</td>
<td>98</td>
</tr>
</tbody>
</table>

Note—Dash (–) indicates no data available. MIP = maximum intensity projection.
²Two of three protocols.
³Average.
⁴Total average for three readers.
Ultra Fast MRI sequences

• Periphery of the k-space is heavily undersampled
• Data from the different k-space samplings are shared to increase spatial resolution
• Center of k-space is used to measure image contrast, so the rate of enhancement can be measured
TWIST: Time-resolved angiography with stochastic trajectory

• Diagnostic spatial resolution for morphologic evaluation while inflow of contrast is captured for kinetic information
• Kinetic curves are acquired immediately after contrast admin (4.32 sec per time point)
• Only information from the early contrast phase is obtained, determining maximum slope
A novel approach to contrast-enhanced breast magnetic resonance imaging for screening: high-resolution ultrafast dynamic imaging.

FIGURE 2. Schematic drawing of the breast MRI scan protocol: The TWIST acquisitions allow evaluation of the contrast inflow in the lesion, whereas the VIBE acquisitions are used for 3 time point analysis, creating the classic contrast enhancement versus time curve.
A novel approach to contrast-enhanced breast magnetic resonance imaging for screening: high-resolution ultrafast dynamic imaging.

Determining Maximum Slope (MS)

FIGURE 3. Determining the MS. A tangent is drawn along the steepest part of the curve. The slope of the tangent is calculated by dividing the relative enhancement over time.

Maximum slope, three types:
Type 1: low risk for cancer <15% chance of cancer
Type 2: intermediate risk >15% and <85% chance of cancer
Type 3: high risk >85% chance of cancer
A novel approach to contrast-enhanced breast magnetic resonance imaging for screening: high-resolution ultrafast dynamic imaging.

• 166 patients with 199 lesions
• All lesions were visible on both the TWIST and standard series. Maximum slope allows discrimination between benign and malignant disease with high accuracy (area under the curve, 0.829).
• One pre and 19 post contrast scans
• Maximum slope, three types:
  • Type 1 low risk for cancer <15% chance of cancer
  • Type 2 intermediate risk >15% and <85% chance of cancer
  • Type 3 high risk >85% chance of cancer
A novel approach to contrast-enhanced breast magnetic resonance imaging for screening: high-resolution ultrafast dynamic imaging.

• Ultrafast dynamic breast MRI allows detection of breast lesions and classification with high accuracy using MS. This allows substantial shortening of scan protocols and hence reduces imaging costs, which is beneficial especially for screening.
ECOG-ACRIN Study: EA1141

• Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women with Dense Breasts

• The purpose of this study is to evaluate a low-cost abbreviated breast MRI (AB-MR) protocol as a supplemental screening method to mammographic screening (DBT) in women with dense breasts.
ECOG-ACRIN Study : EA1141
Comparing DBT to Aabbreviated MRI

• Cancer rate
• Types and biology of cancers detected
• If abbreviated MRI proves to detect significantly high-grade cancers than mammography while reducing interval cancers, future studies may be indicated to evaluate AB-MRI as a stand-alone screening modality to replace mammography
• Detection of biologically significant tumors at a smaller size and earlier stage will lead to an overall reduction in surgical and adjuvant therapies and their associated morbidities
ECOG-ACRIN Study : EA1141

• Compare CDR
• Compare PPV3, CBR, Cat3 rates on initial and 1 year follow up
• Compare sensitivity and specificity
• Compare short-term quality of life related to testing
• Compare willingness to return for testing
• Compare tumor biologies
• Estimate incident cancer rate during 3 years following year one
Contrast Enhanced Mammography
<table>
<thead>
<tr>
<th>Modality</th>
<th>CDR/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital Mammography</td>
<td>2-7</td>
</tr>
<tr>
<td>DBT</td>
<td>+0.5-2.7</td>
</tr>
<tr>
<td>Screening US</td>
<td>+1.8-4.6</td>
</tr>
<tr>
<td>MBI</td>
<td>+8.8</td>
</tr>
<tr>
<td>Abbreviated MRI</td>
<td>+18.1</td>
</tr>
</tbody>
</table>