Current Status of Supplementary Screening With Breast Ultrasound

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Swedish Two-County Trial: Cumulative Breast Cancer Mortality

31% Mortality Reduction At 30 Years Follow-up

Demonstrated Benefits From Screening Mammography

- Swedish Two-County Randomized Trial:
  31% mortality reduction for ages 40-74
- Swedish 7 County Service Screening Study:
  45% mortality reduction in screenees

Tabar et al, Radiol 2011
Duffy et al, Cancer 2002
### Relative Likelihood of Interval Cancers

<table>
<thead>
<tr>
<th>Density</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>10-24%</td>
<td>2.1</td>
<td>(0.9 - 5.2)</td>
</tr>
<tr>
<td>25-49%</td>
<td>3.6</td>
<td>(1.5 - 8.7)</td>
</tr>
<tr>
<td>50-74%</td>
<td>5.6</td>
<td>(2.1 - 15.3)</td>
</tr>
<tr>
<td>≥ 75%</td>
<td>17.8</td>
<td>(4.8 - 65.9)</td>
</tr>
</tbody>
</table>

*p < .001*  

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**Can ultrasound find cancers missed by screening mammography?**

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**Breast Scanner developed in Australia, 1965**

*Courtesy, Jack Jellins Ph.D.*
Early Studies of Screening Ultrasound in 1980’s

- Inadequate detection of smaller cancers
- Excessive false positive biopsies
- Performance was time consuming
- Expensive

Improvements in Breast Ultrasound in 1990’s

- Better spatial resolution: 7.5 -10 MHz transducers
- Better contrast resolution
- Stavros criteria for interpretation

Cancers Detected by Ultrasound Alone In Dense Breasts: 6 Screening Series, 1995 - 2003

- 150 cancers / 42,838 exams
- 3.5 cancers / 1,000 exams
- 90% in dense breasts
- Mean tumor size of 0.9 – 1.1 cm
- All Stage 0 or Stage I
Increased Detection: Ultrasound and Mammography vs. Mammography Alone

<table>
<thead>
<tr>
<th>Study</th>
<th>Increased Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolb et al¹</td>
<td>42%</td>
</tr>
<tr>
<td>Buchberger et al²</td>
<td>37%</td>
</tr>
<tr>
<td>Leconte et al³</td>
<td>79%</td>
</tr>
</tbody>
</table>

¹Radiology 1998, 2002; ²AJR, 1999; ³AJR, 2003

False Positive Biopsies in Ultrasound Screening

- 2.5 x – 4.0 x higher than mammography
- Studies did not define biopsy criteria
- Higher false positive rates likely with ultrasound screening in community practice

Scientific Limitations of Screening Ultrasound Studies

- Non-blinded ultrasound interpretation
- Same radiologist read both modalities
- No documentation of technical quality or interpretive expertise
Multicenter Trial Protocol

- Independent interpretation of ultrasound and mammography
- Standardized ultrasound interpretive criteria
- High resolution ultrasound equipment
- Mammography and ultrasound technique monitored with quality control

Patients randomized to initial mammography or sonography
Ultrasound performed by radiologists
Radiologists:
  - received prior training in mammo and US interpretation
  - met interpretive performance standards prior to participation

High Risk Enrollment Requirements: At Least One of These Criteria

- BRCA-1 or 2 mutation
- Personal history of breast cancer
- Biopsy proven
  - Lobular carcinoma in situ (LCIS)
  - Atypical ductal hyperplasia (ADH)
  - Atypical lobular hyperplasia (ALH)
  - Atypical papillary lesion
- Prior radiation treatment of chest or axilla
- Gail of Claus model risk of \( \geq 25\% \)
Cancer Detection Rates at First Screening Round, ACRIN 6666 Trial:

Hand-held Ultrasound Screening of High Risk Women

• Mammography alone 7.6 / 1,000
• Mammography + US 11.8 / 1,000
• Supplementary yield for ultrasound 4.2 / 1,000
  or 55.3 % increase

Berg et al. JAMA 2008

Biopsy Positive Predictive Value at First Screening Round, ACRIN 6666 Trial:

Hand-held Ultrasound Screening of High Risk Women

• Mammography with Ultrasound correlation 22.6 %
• Ultrasound alone 8.9 %
• Mammography or Ultrasound 11.2 %

Berg et al. JAMA 2008

Results at Second and Third Screening Rounds: ACRIN 6666 Trial

• Supplementary yield of ultrasound = 3.7 cancers / 1,000 screens
• Biopsy PPV:
  Mammography alone = 38%
  Mammo + ultrasound = 16%

Berg et al., JAMA 2012; 307: 1394 - 1404
Limitations of Screening with Hand-held Ultrasound

- Exam time of 19 minutes (ACRIN Trial)
- Technique / Interpretation are linked and operator-dependent
- Need to document technologists’ skill for screening

Significance of Screening Ultrasound Performance Time

- Might lose money at screening mammography rates
- Low reimbursement might encourage excessively fast screening times
- Automated scanners might be the solution

Follow-Up of Sonographic vs Mammographic Probably Benign Lesions

- Sonographic follow-up is much more time consuming and operator dependant
Methods to Facilitate Follow-Up of Probably Benign Ultrasound Lesions

• Annual instead of 6 month follow-up
• Development of a high resolution, automated whole breast ultrasound scanner
Advantages of Coronal View

- New for breast ultrasound
- See slices of entire breast from skin to chest wall
- Tissue thickness reduced so better visualization

Invasive Ductal Carcinoma
Benign Fibroadenoma

Advantages of Automated Whole Breast Scanners
- Rapid acquisition time of 10 minutes
- Does not require physician performance
- Allows batch reading
- Can be integrated efficiently into breast center workflow

Interpretive Aspects of Automated Breast Ultrasound (ABUS)
- Suspicious findings may need hand-held confirmation and evaluation
- Hand-held transducer required for ultrasound-guided biopsy
- Some ABUS units have attached hand-held transducers
Automated Scanner with Handheld Capability

Increased Cancer Detection by Adding ABUS to DM For Screening Dense Breasts

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>DM + ABUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancers</td>
<td>31%</td>
<td>19 / 62</td>
</tr>
<tr>
<td>DCIS</td>
<td>6%</td>
<td>2 / 31</td>
</tr>
<tr>
<td>Invasive Cancers</td>
<td>55%</td>
<td>28 / 51</td>
</tr>
<tr>
<td>Stage 1A or 1B</td>
<td>54%</td>
<td>20 / 37</td>
</tr>
</tbody>
</table>

Brem RF, Tabar L, Duffy SW, et al. Radiology 2014 online

Effect of Adding ABUS to DM for Screening Dense Breasts

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<thead>
<tr>
<th></th>
<th>DM</th>
<th>DM + ABUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers/1000</td>
<td>5.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Recall Rate</td>
<td>15.0%</td>
<td>28.5%</td>
</tr>
<tr>
<td>PPV – 3 (False + Biopsy Rate)</td>
<td>14.0%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

Brem RF, Tabar L, Duffy SW. Radiology 2014 online
False Positive Biopsies in Ultrasound Screening

- Greater than with mammography
- Yet, US-guided core biopsy is:
  - Faster than stereotactic
  - Less invasive than excisional

Relative Advantages of Supplementary Screening Modalities

- Ultrasound vs MRI
  - Less expensive equipment
  - More easily available
  - Faster examination
  - No intravenous contrast
- MRI vs Ultrasound
  - More sensitive test
High Risk Triple Screening Studies with Mammography, Ultrasound, and MRI

Cancer Detection

Combined Mammo and Ultrasound 55%
Combined Mammo and MRI 93%


Current Screening Recommendations

- Mammography
  - Annually from age 40 for average risk women
  - May begin earlier for high risk women
- MRI
  - Annually if lifetime risk >20%
  - No recommendation for 15 – 20 % lifetime risk
  - No MRI if risk < 15%
- Ultrasound
  - Possibly for dense breasts

2010 ACR/SBI Guidelines for Screening Women with Dense Breasts as Only Risk Factor

- Addition of ultrasound to mammography may be useful
- Considerations include:
  - lack of reimbursement,
  - exam performance time,
  - high false positive biopsy rate,
  - insufficient personnel to perform and interpret studies
Preliminary Comparison of Automated Breast Ultrasound and Digital Breast Tomosynthesis for Supplementary Screening of Dense Breasts

<table>
<thead>
<tr>
<th></th>
<th>ABUS</th>
<th>DBT</th>
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</thead>
<tbody>
<tr>
<td>Early Detection Rate</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Ionizing Radiation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Recall Rule</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>False Positive Biopsy Rate</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>Dx Only</td>
<td>$60 Extra</td>
</tr>
</tbody>
</table>

Research Agenda for Screening Dense Breasts

• How to reduce false positive bx’s for masses detected by us alone
• Compare screening with ABUS vs. hand-held transducers: detection rates, cancer size, recall rates

Research Agenda for Screening Dense Breasts

• Which breast densities and age groups benefit most from tomosynthesis vs. 2D digital?
• Compare ABUS and tomosynthesis vs. tomosynthesis alone.