Review of Evidence on Breast Cancer Screening

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Cancer Conference
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I have no conflicts of interest.
2008: 182,460 invasive and 67,770 non-invasive cancers; 40,480 deaths

- Incidence increases with age
  - 40’s: 1 in 69 probability of developing breast cancer
  - 50’s: 1 in 38
  - 60’s: 1 in 27

- Incidence fell in 2003 and appears to be stable
- Mortality has decreased
NCI Statement on Breast Cancer Screening

NCI appreciates the U.S. Preventive Services Task Force's careful review and analysis of the evidence regarding breast cancer screening for women at average risk. The take-away message is that each woman needs to consider her individual benefits and risks and discuss them with her health care provider before making a decision on when to start screening mammography and how often to get one.


November 16, 2009
The United States Preventive Services Task Force (USPSTF) makes recommendations about preventive care services for patients without recognized signs or symptoms of the target condition. It bases its recommendations on a systematic review of the evidence of benefits and harms and an assessment of the net benefit of the service.

The USPSTF is an independent, voluntary body. The U.S. Congress mandates that the Agency for Health Care Research and Quality (AHRQ) support the operations of the USPSTF.
Commissioned Evidence Reviewed

- **USPSTF 2002**: Ann of Intern Med 137:344-346
  - Oregon Health & Science Center
    - Humphrey LL et al; Ann Intern Med 137:347-360

- **USPSTF 2009**: Ann of Intern Med 151:716-726
  - Oregon Evidence-based Practice Center
  - Oregon Health & Science Center
    - Nelson HD et al; Ann Intern Med 151:727-737
      - Two authors remain from 2002: Chan and Humphrey
  - Cancer Intervention and Surveillance Modeling Network (CISNET)
    - Mandelblatt JS et al; Ann Intern Med 151:738-747
Comparison of Grade B

Grade B 2002
The USPSTF recommends that clinicians routinely provide (the service) to eligible patients. The UPSTF found at least fair evidence that (the service) improves important health outcomes and concludes that the benefits outweigh the risks.

Grade B 2009
The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
Comparison of Grade C

Grade C 2002
The USPSTF makes no recommendation for or against routine provision of (the service). The USPSTF found at least fair evidence that (the service) can improve outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.

Grade C 2009
The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small.
Screening for Breast Cancer using Breast Examination Women Aged ≥ 40

- **2002: Grade B**
  The USPSTF recommends screening mammography, with or without clinical breast examination (CBE), every 1 to 2 years for women aged 40 and older.

- **2002: Grade I**
  CBE or BSE alone

- **2009: CBE Grade I**
  (insufficient evidence)
  No recommendation. Evidence of benefit is lacking.

- **2009: BSE Grade D**
  Adequate evidence suggests that BSE does not reduce breast cancer mortality.
## Shanghai RCT of BSE

<table>
<thead>
<tr>
<th>Type of Breast Lesion</th>
<th>Instruction Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologically confirmed carcinoma</td>
<td>857</td>
<td>890</td>
</tr>
<tr>
<td><em>In situ</em> (included in above)</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Benign Biopsies</td>
<td>2761</td>
<td>1505</td>
</tr>
</tbody>
</table>

Shanghai RCT of BSE


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Screening for Breast Cancer using Film Mammography Women Aged 40 - 49

- **2002: Grade B**
  
  The USPSTF recommends screening mammography, with or without clinical breast examination (CBE), every 1 to 2 years for women aged 40 and older.

- **2009: Grade C**
  
  Do not screen routinely, individualize decision to begin biennial screening according to patient’s context and values.
Screening for Breast Cancer using Film Mammography  
Women Aged 50 - 74

- 2002: Grade B
  The USPSTF recommends screening mammography, with or without clinical breast examination (CBE), every 1 to 2 years for women aged 40 and older.

- 2009: Grade B
  Screen every 2 years.
Screening for Breast Cancer using Film Mammography
Women Aged ≥ 75

- 2002: Grade B
  The USPSTF recommends screening mammography, with or without clinical breast examination (CBE), every 1 to 2 years for women aged 40 and older. *Evidence is generalizable to women aged 70 and older if their life expectancy is not compromised by co-morbid disease.*

- 2009: Grade I (insufficient evidence)
  No recommendation. Evidence of benefit is lacking.
Number Needed to Invite to Prevent 1 Breast Cancer Death

- 40 - 49 (1904)
- 50 - 59 (1339)
- 60 - 69 (377)
- 70 - 74 (500)
### USPSTF Meta-analysis 2009

<table>
<thead>
<tr>
<th>Study/Author, Year (Reference)</th>
<th>Relative Risk for Breast Cancer Mortality (95% CrI)</th>
<th>Events/Total, n/n</th>
<th>Screening</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIP/Habbema et al, 1986 (27)</td>
<td>0.78 (0.56–1.08)</td>
<td>64/13 740</td>
<td>82/13 740</td>
<td></td>
</tr>
<tr>
<td>Kopparberg*/Tabar et al, 1995 (31)</td>
<td>0.72 (0.38–1.37)</td>
<td>22/9582</td>
<td>16/5031</td>
<td></td>
</tr>
<tr>
<td>CNBSS-1/Miller et al, 2002 (28)</td>
<td>0.97 (0.74–1.27)</td>
<td>105/25 214</td>
<td>108/25 216</td>
<td></td>
</tr>
<tr>
<td>Malmö/Nyström et al, 2002 (26)</td>
<td>0.73 (0.51–1.04)</td>
<td>53/13 568</td>
<td>66/12 279</td>
<td></td>
</tr>
<tr>
<td>Stockholm/Nyström et al, 2002 (26)</td>
<td>1.47 (0.77–2.78)</td>
<td>34/14 303</td>
<td>13/8021</td>
<td></td>
</tr>
<tr>
<td>Östergötland*/Nyström et al, 2002 (26)</td>
<td>1.05 (0.64–1.73)</td>
<td>31/10 285</td>
<td>30/10 459</td>
<td></td>
</tr>
</tbody>
</table>

**Total**

- **Favors Screening**: 0.85 (0.75–0.96)
- **Final Events/Total**: 448/152 300 | 625/195 919
Age Trial
Moss et al  Lancet 2006;368:2053-60

- Enrolled women 39 – 41; randomized in 1:2 ratio
- Annual screening up to year of 48\textsuperscript{th} birthday; baseline with two-view mammography and then mediolateral oblique view
- Average follow-up 10.7 years; compliance 70%; contamination estimated as low
- Power
  - Sample size goal: 190,000 Power 80%; 5% significance level
  - Sample size attained 160,921 Revised power 72%
    - Three centers had to stop screening due to budgetary issues
  - Breast cancer mortality lower than expected in control group; revised power was 60% to detect a 20% mortality reduction
Breast Cancer Surveillance Consortium
Age-Specific Screening Results

<table>
<thead>
<tr>
<th>Outcomes per screening round (per 1000 screened)</th>
<th>40 - 49</th>
<th>50 - 59</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-negative</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>False-positive</td>
<td>97.8</td>
<td>86.6</td>
</tr>
<tr>
<td>Additional imaging</td>
<td>84.3</td>
<td>75.9</td>
</tr>
<tr>
<td>Biopsy</td>
<td>9.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Screening detected invasive cancer</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Screening-detected DCIS</td>
<td>0.8</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Another Harm Considered: Overdiagnosis

- **Definition:** Can occur when screening detects early-stage invasive breast cancer or DCIS in a woman, typically older, who is likely to die from another cause before the breast cancer would be clinically detected.

- **Rate Estimates:**
  - Moss from 5 RCTs 0.07 to 0.73/1000 women-years
  - Other studies rate ranges from 1 – 30% with most from 1 – 10%
Breast Cancer Initiative
Donald Berry PhD.
M.D. Anderson Cancer Center
Houston, TX

Berry et al. *NEJM* 2005;353:1784-1792

*JNCI* Monograph, summer 2006
Annual Incidence of Female Breast Cancer (1975-2004)

## Benefits and Harms
**Stanford model of different starting and stopping ages and intervals**

<table>
<thead>
<tr>
<th>Interval/Age</th>
<th>Deaths Averted</th>
<th>False Positives</th>
<th>Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 – 69</td>
<td>8.3</td>
<td>2250</td>
<td>158</td>
</tr>
<tr>
<td>50 – 69</td>
<td>7.3</td>
<td>1350</td>
<td>95</td>
</tr>
<tr>
<td>50 – 74</td>
<td>9.5</td>
<td>1570</td>
<td>110</td>
</tr>
<tr>
<td>Biannual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 – 74</td>
<td>7.5</td>
<td>940</td>
<td>66</td>
</tr>
</tbody>
</table>
“The Task Force considered both “mortality” and “life-years gained” outcomes. In this case, given that the age groups (40 to 49 and 50 to 59 years) are adjacent, the Task Force elected to emphasize the mortality outcomes from the modeling studies.”
Mortality compared to Life-Years
CISNET Stanford Model

C. Stanford University

Mortality Reduction, %

Gain in Lys per 1000 Women

Average Mammographies per 1000 Women, n

B50–69 B50–79 B50–74 B50–84 B40–84

A40–84

0 10 20 30 40

C. Stanford University

Average Mammographies per 1000 Women, n

B55–69 B50–69

B60–69

A40–84

A40–79

0 50 100 150 200 250
Number Needed to Invite to Prevent 1 Breast Cancer Death

- 40 - 49 (1904)
- 50 - 59 (1339)
- 60 - 69 (377)
- 70 - 74 (500)
Screening for Breast Cancer with other Imaging Modalities
Women Aged ≥ 40

- 2009 only: Grade I
  
  Evidence is lacking for benefits as substitute for film mammography; specifically no evidence on outcome of breast cancer mortality

  - Digital Mammography: for younger women and women with dense breast tissue, overall detection is somewhat better with digital mammography

  - MRI: contrast-enhanced MRI has been shown to detect more cases of cancer in very high-risk populations than does mammography
“Randomized clinical trials of film versus digital mammography among women with dense breast tissue, with sufficient follow-up to detect stage shifts (reductions of late-stage cancer) or decreased in clinical interval cases, would also be ethical and helpful.”

Individualization of Risk

- A scientific challenge of the post-genomic era to build upon the NCI Breast Cancer Risk Assessment Tool (BCRAT)
- Two potential new tools:
  - Mammographic density
  - Genome-wide association studies (GWAS)
Projected 5-year absolute risk of breast cancer from the new model with mammographic density (ordinate) plotted against the risk calculated with the National Cancer Institute's Breast Cancer Risk Tool (http://www.cancer.gov/bcrisktool/) (Gail Model 2)

Probability that a case patient has a risk greater than $t$, $[1-F_{D}(t)]$, plotted against the probability that a member of the general population has a risk greater than $t$, $[1-F_{r}(t)]$, as $t$ (not shown) varies from 0 to 1.
With gratitude to the many women who participated in the clinical trials that provided this important information.