Update: Breast Cancer Screening

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Objectives:

• Review current recommendations for breast cancer screening
• Describe harms and benefits of different methods of breast cancer screening
• Discuss current recommendations for use of mammography, ultrasonography, MRI, clinical breast examination for women at average and high risk for developing breast cancer.

Common Types of Cancers

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Cases 2015</th>
<th>Deaths 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>231,040</td>
<td>48,230</td>
</tr>
<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>221,290</td>
<td>196,940</td>
</tr>
<tr>
<td>3. Prostate Cancer</td>
<td>235,880</td>
<td>272,940</td>
</tr>
<tr>
<td>4. Colon and Rectal Cancer</td>
<td>132,790</td>
<td>40,270</td>
</tr>
<tr>
<td>5. Bladder Cancer</td>
<td>74,039</td>
<td>10,039</td>
</tr>
<tr>
<td>6. Melanoma of the Skin</td>
<td>72,670</td>
<td>9,910</td>
</tr>
<tr>
<td>7. Non-invasive Tumors</td>
<td>71,859</td>
<td>19,740</td>
</tr>
<tr>
<td>8. Thyroid Cancer</td>
<td>62,459</td>
<td>1,859</td>
</tr>
<tr>
<td>10. Endometrial Cancer</td>
<td>54,070</td>
<td>10,170</td>
</tr>
</tbody>
</table>

In 2015, it is estimated that there will be 231,840 new cases of female breast cancer and an estimated 40,290 people will die of this disease.

Female Breast Cancer Statistics


Screening

• Aim: Reduce morbidity and mortality associated with breast cancer in asymptomatic women.
• Key: Provide early access to effective diagnostic and treatment services.
• Maintain balance between benefits and harms.

Screening

• Standard Mammography
  • Standard mammography (2D)
  • Digital breast tomosynthesis (DBT, 3D)
• Clinical breast examination
  • Visual inspection and palpation
• Self breast examination
Supplemental Screening

• In addition to mammography
• For a select population of patients
  • Elevated lifetime risk of developing breast cancer
    • >20-25%
  • Whole breast ultrasound
    • Automated breast US (ABUS)
    • Handheld breast US (HHUS)
  • Dense breasts

Breast cancer Screening

Women at Average risk

• No personal history of breast cancer, atypical ductal hyperplasia or lobular carcinoma in situ
• No significant family history of breast cancer
• Absolute lifetime risk 12.7%

Women at Average or Low Risk
### Breast Cancer Screening Recommendations of Selected Organizations

<table>
<thead>
<tr>
<th>Procedure</th>
<th>NCCN 2015</th>
<th>ACOG</th>
<th>ASCC</th>
<th>ACS</th>
<th>USPSTF</th>
<th>AGS/AGECNS</th>
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<tbody>
<tr>
<td>Mammography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 40-44, annual</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age &gt;44, annual screening</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Age &gt;50, interval 1-2 y</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Age 50-74, biennial</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient evidence to support screening over age 75</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clinical Breast Examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age 19 and older</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age &gt;25 &lt;40 q 1-3 y</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient evidence</td>
<td></td>
<td>X</td>
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<tr>
<td>Not recommended</td>
<td></td>
<td>X</td>
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<tr>
<td>Breast Self-Awareness</td>
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<tr>
<td>Recommended</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Insufficient evidence</td>
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<tr>
<td>Not recommended</td>
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### 2015 Updated Breast Screening Guidelines

**American Cancer Society**

**U.S. Preventive Services Task Force**

### 2015 Guideline Update from ACS

- Outcomes considered:
  - Mortality
  - Life expectancy
  - False positive findings
  - Overdiagnosis
  - Overtreatment
  - Quality of life
Mammography Debate

- Mammographic screening is effective in reducing mortality from breast cancer.
- Issue not whether mammography is effective, but whether the false positive rate and false negative rates can be reduced.
- Debate continues about the absolute size of the mortality benefit conferred and the concomitant risks associated with screening.
RCTs of screening mammography

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Breast Cancer Mortality Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>McArdle et al. (1985)</strong></td>
<td>0.921</td>
</tr>
<tr>
<td><strong>Narens et al. (1978)</strong></td>
<td>0.886</td>
</tr>
<tr>
<td><strong>Tollefsen et al. (1975)</strong></td>
<td>0.908</td>
</tr>
<tr>
<td><strong>Tomasso-Maltrano et al. (1975)</strong></td>
<td>0.896</td>
</tr>
<tr>
<td><strong>Telford et al. (1967)</strong></td>
<td>0.907</td>
</tr>
<tr>
<td><strong>Tocci et al. (1984)</strong></td>
<td>0.900</td>
</tr>
<tr>
<td><strong>Todt et al. (1980)</strong></td>
<td>0.900</td>
</tr>
<tr>
<td><strong>Scheurer et al. (1991)</strong></td>
<td>0.900</td>
</tr>
<tr>
<td><strong>Green et al. (1964)</strong></td>
<td>0.900</td>
</tr>
</tbody>
</table>


Benefit of Breast Cancer Screening

Table 1. Distribution of cancer stages (American Joint Committee on Cancer) in screened and never-screened women

<table>
<thead>
<tr>
<th>Stage</th>
<th>Screened (%)</th>
<th>Unscreened (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>62</td>
<td>39</td>
</tr>
<tr>
<td>II</td>
<td>30</td>
<td>46</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>0.3</td>
<td>7</td>
</tr>
</tbody>
</table>


Benefits of Early Detection

- Compared to detection by palpation, cancers diagnosed by mammography are usually:
  - Smaller
  - Less likely to have metastasis
  - More likely to be treated with breast conservation surgery and less likely to require adjunct chemotherapy
  - Decreased morbidity associated with treatment
Limitations of mammography

• False Positive
  • Superimposed breast tissue can mimic appearance of malignancy, leading to callbacks
• False Negative
  • Overlapping dense fibroglandular tissue within the breast decreases visibility of malignant lesions
  • 15% - 30% of cancers are not detected by standard screening depending on age and breast density

False Positive Result

• Definition
  • A mammogram is interpreted as abnormal in a woman who does not have cancer
• 7-10% women will be recalled
  • Vast majority will be resolved
• Less than 2% of women will undergo a minimal invasive needle biopsy
  • % of the women biopsied will have benign findings
  • Anxiety and worry do not impact follow-up imaging.

False Negative

• Mammographically occult cancer
• Masked by dense breast tissue
• Poor technique
• Oversight
• Reader variability
Breast Density

- Overall sensitivity 85%, dense breasts decrease sensitivity to 68%

![Breast density images]

Changes in Screening technology

ACRIN DMIST

- Film-screen mammography
- Full-field digital mammography (FFDM)
- Found increased sensitivity of FFDM in breast cancer detection in women with dense breast tissue, peri- and pre-menopausal women and in women <50 years old.
- No change in sensitivity of FFDM vs film screen in older post-menopausal women or women with fatty breast tissue.
Digital Breast Tomosynthesis (3D Mammography)

- Developed to allow for the detection of lesions that had been obscured by overlapping breast tissue.
- X-ray mammography technique in which tomographic images of the breast are reconstructed from multiple low-dose projection images acquired by moving the x-ray tube in an arc over a limited angular range.
- Breast compression and projections obtained (CC, MLO) are similar to conventional mammography.
- Radiation dose can be greater than 2D mammography alone; but well within maximum dose guidelines specified by the ACR.

Digital Breast Tomosynthesis (3D Mammography)

- Studies have demonstrated:
  - Decrease recall rates of 15-20%
  - Increase cancer detection
  - Improved lesion visibility in terms of size and classification
  - Increase detection of architectural distortion
  - Friedewald et al. in a multicenter analysis demonstrated that combined 2D and 3D mammography increased rates of invasive cancer detection from 27-51%
Automated Whole-Breast Ultrasound

• Extremely dense breasts associated with 4 to 6 times higher risk of breast cancer
• 2012 several states adopted mandatory breast density notification laws
• FDA approved AWBUS for use in screening for breast cancer as a adjunct to mammography.
• Studies demonstrate ability to detect mammographically occult lesions less than 1cm.
• Positive predictive value for biopsy is lower (7% to 21%) with mammogram + ABUS versus mammography alone.
ABUS

- Easily tolerated by the patient
- Mild compression
- No radiation
- Helpful in women with heterogeneously dense or extremely dense glandular tissue

Debated issues in screening mammography
Ideal Screening Age: 40-49

- Starting screening at age 40 results in greatest mortality reduction by 30%.
- Analysis by Hendrick and Helvie (2011) demonstrated annual screening at age 40 saves 6,500 more women's lives each year in the U.S., then biennial screening starting at age 50.
- Webb, et al. (2014) reported among 609 women who died of breast cancer between 1990 to 1999, 71% of women were unscreened and 29% were screened.

Oeffinger, KC et al, JAMA 2015, 314(15)

Relationship between mammography screening to mortality reduction in women aged 40-49 years.

Ideal Screening Age: 74+

- No randomized prospective trials included women older than 74 years of age.
- 26% of breast cancer deaths are in women over the age 75 and yet 50% of women over age 80 are expected to live another 10 years.
- Breast cancer incidence increases with age and mammographic sensitivity is higher in older women.
- Decision to stop screening should be based on individual woman’s life expectancy and co-morbidities not age alone.

Oeffinger, KC etal, JAMA 2015, 314(15)
Over diagnosis

• Issue of screen detected breast cancer, that might not become clinically apparent during the lifetime of the patient.
• Or, a tumor is detected early and the woman dies of another cause before breast cancer symptoms develop.
• Greatest harm is overtreatment; therefore goal should be not be less diagnosis but better treatment decision tools.
• Over diagnosis likely 1 to 10%.
• RCTs- Using advanced imaging and molecular markers.
  + Questions: No treatment? Or Less treatment?

Clinical Breast Exam

• Purpose:
  + Detect breast cancer in asymptomatic women
  + Evaluate breast symptoms
• Effectiveness is dependent on technique and time spent on the exam.
• Reported sensitivity 98% specificity 48%.
• Studies demonstrated when mammography is combined with CBE, 2%-6% more breast cancers are detected as compared to mammography alone.
• CBE helps to direct the evaluation of the mammogram.

Before abandoning CBE consider:

• Mammographically screened women still present with significant incidence of symptomatic breast cancer.
• Studies demonstrate that older women who do not participate in mammography screening, present with locally advanced disease.
• Younger women are more frequently diagnosed more aggressive breast cancer which often presents with a palpable mass.
Breast Self Exam

- 2003 ACS did not recommend BSE due to absence of evidence of improved outcomes associated with self-examination.
- 2015 ACS no change to recommendation
- Trials conducted in Russia and China suggested increase in need for biopsies with no improvement in mortality.
- Retrospective study in US, demonstrated no improvement in detection of breast cancer when women with average risk were taught BSE.
- “Breast self-awareness” recommended.

BSE

- **Potential Benefits**
  - Women gain a sense of control over their health
  - Women become more comfortable with their breasts
  - Simple, noninvasive test
  - Some breast cancers have been detected with BSE
  - Increased awareness of breast changes

- **Potential Harms**
  - Increased number of healthcare visits
  - Increase the number of benign breast biopsies
  - Increased healthcare costs
  - Increased levels of cancer related anxiety
  - No change in mortality from breast cancer with detection from BSE

Breast cancer Screening for women with high Risk
When to start mammography:

• BRCA1/2 mutation, untested relatives who are proved to have BRCA mutations
  • Yearly starting age 30 (not before age 25)
• ≥ 20% lifetime risk
  • Yearly starting by age 30 (not before age 25), or 10 years earlier than the age of diagnosis of the youngest affected relative
• History of mantle radiation between ages of 10-30
  • Yearly starting 8 years after radiation therapy but not before age 25
• History of LCIS, ADH, DCIS, invasive breast cancer
  • Yearly from time of diagnosis, regardless of age

2007 ACS Consensus Panel

Breast Screening in High Risk Women

• Overall Sensitivity
  • Breast MR 71% to 100%
  • Mammography 16% to 40%
  • U/S 26-40%
• No cancer detected by U/S not seen by MRI
• Mammography detects some cancer not detected by MRI
  • Mostly DCIS
Breast MRI

- Specificity lower than that of mammography
- Call back rates 8% to 17%
- Biopsy rates 3% to 15%
- Requires injection of intravenous gadolinium
- Expensive averaging 5-10 times cost of mammogram
- A nonsignificant increase in general anxiety and breast cancer–related anxiety.

Breast Cancer Risk Assessment Models

- Familial Breast Cancer Risk Assessment
  - Claus Tables
  - Gail Model
- BRCA Probability Models
  - BRCAPRO
  - Tyrer-Cuzick Model (IBIS Breast Cancer Risk Evaluation Tool)
  - BOADICEA

Annual breast MRI recommended for:

- BRCA 1 or 2
- Other genetic mutation carriers (CDH1, STK11/LKB1, P53, PTEN)
- Pedigree suggestive of or known genetic predisposition.
- Lifetime risk >20% based on models largely dependent on family history
- Prior thoracic RT for patients younger than 30y, screening begins
Screening Ultrasound

- Not currently recommended for high-risk breast cancer screening.
- Across studies, combined sensitivity of mammography+ ultrasound was only 52% vs 92.7% mammography + MRI in high risk women.
- Recommended in high risk women who cannot tolerate MRI or are allergic to contrast.

Intermediate-Risk Women

- Includes:
  - Women with personal history of breast cancer
  - LCIS
  - ADH or ALH
  - Dense breasts
  - Lifetime risk of 15% to 20%

Intermediate-Risk Women

- Currently no data for or against use of supplemental MRI screening.
- In women with dense breast there is a role for whole breast screening ultrasound.
Personalized Risk Counseling

• Recommendations:
  • Age to begin screening
  • Supplemental breast imaging
  • Determine which patients should undergo genetic testing
  • Chemoprevention
  • Preventative surgery

In Summary:

• Breast cancer screening is associated with decreased morbidity and mortality.
• Beginning annual screening at age 40 saves the most lives.
• CBE and Breast self awareness enhance screening.
• Supplemental MRI screening for women at high risk can help detect breast cancer early in young women.