Update: Breast Cancer Screening

Anna C Purdy, NP
Department of Surgery
Division of Surgical Oncology
Medical College of Wisconsin
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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.
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

**Number of New Cases and Deaths per 100,000:** The number of new cases of female breast cancer was 124.8 per 100,000 women per year. The number of deaths was 21.9 per 100,000 women per year. These rates are age-adjusted and based on 2008–2012 cases and deaths.

**Lifetime Risk of Developing Cancer:** Approximately 12.3 percent of women will be diagnosed with female breast cancer at some point during their lifetime, based on 2010–2012 data.

**Prevalence of This Cancer:** In 2012, there were an estimated 2,975,314 women living with female breast cancer in the United States.

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
  • MRI
    • Elevated lifetime risk of developing breast cancer
    • > 20-25%
  • Whole breast ultrasound
    • Automated breast US (ABUS)
    • Hand held breast US (HHUS)
    • Dense breasts
Breast cancer Screening
Women at Average risk
Women at Average or Low 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%
# Breast Cancer Screening Recommendations of Selected Organizations

<table>
<thead>
<tr>
<th>Mammography</th>
<th>NCCN 2015</th>
<th>ACOG</th>
<th>ASBS</th>
<th>ACS</th>
<th>USPSTF</th>
<th>ACR/SBI</th>
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<tr>
<td>Age 40 or older, annual</td>
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<td></td>
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<td>Age &gt;40 - 44, annual (Shared decision making)</td>
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<th>Clinical Breast Examination</th>
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<th>ACS</th>
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2015
Updated Breast Screening Guidelines
2015 Guideline Update from ACS

- Outcomes considered:
  - Mortality
  - Life expectancy
  - False positive findings
  - Over-diagnosis
  - Overtreatment
  - Quality of life
### Table. ACS and USPSTF 2015 Breast Cancer Screening Guidelines

<table>
<thead>
<tr>
<th>Mammography Screening Parameter</th>
<th>Recommendation</th>
<th>ACS</th>
<th>USPSTF</th>
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<tbody>
<tr>
<td>Starting age, y</td>
<td>45</td>
<td>50</td>
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<tr>
<td>Screening frequency</td>
<td>Annually to age 54 years, then biennially</td>
<td></td>
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<tr>
<td>Stopping age, y</td>
<td>As long as healthy and with life expectancy of at least 10 years</td>
<td>75</td>
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<td>Total lifetime mammograms if screening continued to age 74 years, No.</td>
<td>20</td>
<td>13</td>
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<tr>
<td>Lifetime risk of dying from breast cancer, %</td>
<td>1.8-1.9(^a)</td>
<td>2.0(^a)</td>
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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.
Trends in Cancer Death Rates* Among Women, US, 1930-2011

*Age-adjusted to the 2000 US standard population
†Uterus includes uterine corpus and uterine cervix combined.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2014.
RCTs of screening mammography

Glasziou, P., Houssami, N. Prevention Medicine 2011;53(3):100-102
Benefit of Breast Cancer Screening

<table>
<thead>
<tr>
<th>Stage</th>
<th>Screened (%)</th>
<th>Unscreened (%)</th>
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<tr>
<td>I</td>
<td>62</td>
<td>39</td>
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<tr>
<td>II</td>
<td>30</td>
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<td>III</td>
<td>8</td>
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<tr>
<td>IV</td>
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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
  • ¾ 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%
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.
Figure 1: Tomosynthesis Can Reduce or Eliminate Tissue Overlap

With tomosynthesis imaging, images acquired from different angles separate structures at differing heights. Conventional mammography would acquire only the central image.
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.
Figure 1. Breast Cancer Burden by Age at Diagnosis for the Period 2007-2011

A. Distribution of breast cancer cases by age at diagnosis

B. Distribution of breast cancer deaths by age at diagnosis

C. Distribution of person-years of life lost due to breast cancer by age at diagnosis

A. Age distribution of invasive female breast cancer cases (n = 292,369). Source: Surveillance, Epidemiology, and End Results (SEER) 18 registries.

B. Distribution of breast cancer deaths by age at diagnosis (n = 16,789), with patients followed up for 20 years after diagnosis. Source: SEER 9 registries.

C. Distribution of person-years of life lost (PYLL) due to breast cancer by age at diagnosis (total = 326,560), with patients followed up for 20 years after diagnosis. Source: SEER 9 registries. The PYLL is based on the 2011 US Female Life Table.28

Oeffinger, KC et al, JAMA 2015, 314(15)
Relationship between mammography screening to mortality reduction in women aged 40-49 years.

Figure 6: Relapse-free survival after diagnosis according to detection method (n = 1583).

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.
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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 then 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
American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography
Debbie Saslow, Carla Boetes, Wylie Burke, Steven Harms, Martin O. Leach, Constance D. Lehman, Elizabeth Morris, Etta Pisano, Mitchell Schnall, Stephen Sener, Robert A. Smith, Ellen Warner, Martin Yaffe, Kimberly S. Andrews, Christy A. Russell and for the American Cancer Society Breast Cancer Advisory Group
CA Cancer J Clin 2007;57;75-89
Breast Screening in High Risk Women

• Overall Sensitivity
  • Breast MRI 71% to 100%
  • Mammography 16% to 40%
  • U/S 16-40%
• 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.