Breast Cancer Screening and Detection

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Topics for Today

• To understand screening and diagnostic modalities used for breast cancer detection
• To understand controversies regarding screening mammography
Breast Cancer Risk

- 207,090 new cases of breast cancer estimated in 2010
  - 39,840 cancer-related deaths
  - Accounts for 28% of all cancers in women

- Screening has improved earlier detection
  - Average US woman has 12.6% lifetime risk of breast cancer

Cancer Incidence Rates*

* Age adjusted to the 2000 U.S. standard population
Source: American Cancer Society, 2010
Cancer Death Rates*
Women, United States, 2005

* Age adjusted to the 2000 U.S. standard population
Source: American Cancer Society, 2010
Risk Factors

- **Major**
  - Age
  - Family history
    - *BRCA*
  - Prior breast cancer
  - Atypical ductal hyperplasia
  - LCIS
  - Ionizing radiation
    - Mantle radiation for Hodgkin’s disease

- **Minor**
  - Early age at menarche
  - Late age of menopause
    - 2.8%/year after the age of 50
  - Nulliparity
  - First child >30 years
  - Postmenopausal obesity
A Woman’s Chance for Breast Cancer as Determined by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>New cases/Decade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 30</td>
<td>1 out of 2,212</td>
</tr>
<tr>
<td>Age 40</td>
<td>1 out of 235</td>
</tr>
<tr>
<td>Age 50</td>
<td>1 out of 54</td>
</tr>
<tr>
<td>Age 60</td>
<td>1 out of 23</td>
</tr>
<tr>
<td>Age 70</td>
<td>1 out of 14</td>
</tr>
<tr>
<td>Age 80</td>
<td>1 out of 10</td>
</tr>
<tr>
<td>Ever</td>
<td>1 out of 8</td>
</tr>
</tbody>
</table>
Breast Cancer Screening

• Early detection is a key factor

• Components of screening:
  – BSE: breast self-examination
  – PE: physical examination by trained personnel
  – Mammography
Principles of Screening

Purpose of screening is to test a large defined population at an acceptable cost

- Disease should be important
- Disease must be able to be found when asymptomatic

- Treatment at earlier stages should offer better outcomes
  - Direct correlation between breast tumor size and mortality
  - Early treatment may be less treatment (e.g., omission of chemotherapy in small T1a breast cancers)

Smith et al. Diseases of the Breast, 2010
Guidelines for Screening

• Breast self exam starting at age 20
• Ages 20-39: physical exam every 1-3 years
• Age 40+: annual physical exam annual mammography

American Cancer Society, 2003
BSE (Breast Self-Examination)

- Widely promoted as a means of reducing breast cancer mortality
  - Little evidence to support its efficacy
- Only 2 randomized trials
  - WHO trial (Russia) 1985-1990
  - Shanghai trial 1989-1991
    - No routine mammography screening
- No significant difference in number of cancers
  - Increase biopsies in BSE group
  - Efficacy in conjunction with other screening modalities not addressed

Screening by Physical Examination

- No clinical trial comparing PE to no screening
  - PE arm often included in mammography screening trials
- Detects small numbers of cancers
  - Important in women who do not receive regular mammograms
  - Less than age 40
- Opportunity to discuss breast cancer risk and awareness
- In underdeveloped countries, interest in PE as screening
  - Mammography unaffordable or unavailable

Physicians’ Abilities To Detect Breast “Lump”

- Pennypacker silicone model
- 5 models with 18 lumps
  - size: 0.3, 0.5, 1.0 cm
  - hardness: 3 kinds
  - depth: medium or deep

JAMA, 1985; 253: 2224
Physicians’ Ability To Detect Breast “Lump”

- FACTORS NOT INFLUENCING DETECTION
  - Depth of lump in model
  - Specialty of physician
  - Level of training
  - Years of experience
  - Technique of search

- FACTORS INFLUENCING DETECTION
  - Size of lump
  - Hardness
  - Length of time used for search

JAMA, 1985; 253: 2224
Mammography Screening Guidelines
ACOG, ACS, ACR, NCI

- 40-50 years: every 1-2 years
  - ACS every year starting at age 40

- ≥50 years: every year
Major Controversies Concerning Screening Mammography

• Does Screening Reduce mortality?
• At what age should screening start and end?
• How often should women be screened?
• Does the benefit of screening outweigh the risks (or inconvenience) in all age groups
Most Recent Controversy
The US Preventive Task Force

- Searched Cochrane database and Medline for reported RCT for mammography screening as well as trials of screening MRI, CBE and BSE

- Purpose “net benefit”
  - effectiveness of mammography screening in women 40-49 and ≥70 yrs
  - effectiveness of clinical breast exam and BSE
  - determine the harms of screening

- Recommendations for general female population
  - not high risk groups

- Studies were considered and included in the meta-analysis on the basis of quality

# Randomized trials of screening mammography

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline Study Year</th>
<th>Age</th>
<th>Screening interval (mo)</th>
<th>Mortality Reduction (yrs of f/u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIP</td>
<td>1963</td>
<td>40-64</td>
<td>12</td>
<td>23% (18)</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>1979</td>
<td>45-64</td>
<td>24</td>
<td>29% (14)</td>
</tr>
<tr>
<td>Gothenburg</td>
<td>1982</td>
<td>39-59, 39-49</td>
<td>18</td>
<td>21% (11), 44% (11)</td>
</tr>
<tr>
<td>Stockholm</td>
<td>2002</td>
<td>40-64</td>
<td>24-28</td>
<td>26% (11)</td>
</tr>
<tr>
<td>Malmo</td>
<td>1976-1978</td>
<td>45-70</td>
<td>18-24</td>
<td>36% (20)</td>
</tr>
<tr>
<td>Swedish Two-County (2 trials)</td>
<td>1977</td>
<td>40-74</td>
<td>24-33</td>
<td>30% (20)</td>
</tr>
<tr>
<td>Age</td>
<td>1991</td>
<td>39-41</td>
<td>12</td>
<td>17% (11)</td>
</tr>
<tr>
<td>CNBSS-1,-2</td>
<td>1980</td>
<td>40-49, 50-</td>
<td>12</td>
<td>-7% (16)</td>
</tr>
</tbody>
</table>
USPSTF Recommendations 2009

1. Recommendation against routine screening mammography in women aged 40-49
2. Biennial screening mammography in women 50-74
3. Recommendation against teaching BSE
4. Current evidence is insufficient to assess benefits/harms of:
   - Screening in women age >75
   - CBE
   - Digital mammography/MRI
### Table 1. Pooled RRs for Breast Cancer Mortality From Mammography Screening Trials for All Ages

<table>
<thead>
<tr>
<th>Age</th>
<th>Trials Included, n</th>
<th>RR for Breast Cancer Mortality (95% CrI)</th>
<th>NNI to Prevent 1 Breast Cancer Death (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39–49 y</td>
<td>8*</td>
<td>0.85 (0.75–0.96)</td>
<td>1904 (929–6378)</td>
</tr>
<tr>
<td>50–59 y</td>
<td>6†</td>
<td>0.86 (0.75–0.99)</td>
<td>1339 (322–7455)</td>
</tr>
<tr>
<td>60–69 y</td>
<td>2‡</td>
<td>0.68 (0.54–0.87)</td>
<td>377 (230–1050)</td>
</tr>
<tr>
<td>70–74 y</td>
<td>1§</td>
<td>1.12 (0.73–1.72)</td>
<td>Not available</td>
</tr>
</tbody>
</table>

CrI = credible interval; NNI = number needed to invite to screening; RR = relative risk.

* Health Insurance Plan of Greater New York (27), Canadian National Breast Screening Study-1 (28), Stockholm (26), Malmö (26), Swedish Two-County trial (2 trials) (26, 31), Gothenburg trial (30), and Age trial (29).
† Canadian National Breast Screening Study-1 (28), Stockholm (26), Malmö (26), Swedish Two-County trial (2 trials) (26, 31), and Gothenburg trial (30).
‡ Malmö (26) and Swedish Two-County trial (Östergötland) (26).
§ Swedish Two-County trial (Östergötland) (26).

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Concerns with USPSTF Recommendations for Women Age 40-49

• USPSTF meta-analysis showed RR of breast cancer mortality decreased to 0.85 with screening, however
  – Magnitude of benefit may be underestimated
  – Screening interval of 2 years may be too long in younger women
    • Younger women have higher proportion of aggressive tumors – higher mortality
Biennial screening: USPSTF models
Costs of Screening

- Radiation exposure
- Pain during procedures
- Anxiety/distress
- False-positive, false-negative mammography results, additional imaging, biopsies
- Overdiagnosis

- False-Positive
  - 98/1000 screening rounds (age 40-49)
  - 1 cancer detected
    - 556 women have mammogram
    - 47 additional imaging
    - 5 biopsies
More Agreements than Disagreements

• Overall reduction in breast cancer mortality in women 40-74
• Failure of one third of American women to have screenings is a public health problem
• Mammography is an imperfect test
  • fail to detect many ER negative BC
  • false positives are common
• Mammography may lead to overdiagnosis
  • elderly
• Despite these limitations best breast cancer screening tool available for the general population
# What about Screening Under Age 40?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Screening Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of breast cancer or LCIS</td>
<td>Annually from diagnosis</td>
</tr>
<tr>
<td>First-degree relative with premenopausal breast cancer</td>
<td>10 years earlier than relative’s age at diagnosis: not younger than age 25</td>
</tr>
<tr>
<td>Hodgkin’s disease and mantle radiation</td>
<td>Initiate 8 years after radiation</td>
</tr>
<tr>
<td>BRCA 1, 2 carriers</td>
<td>Initiate age 25 to 35: depends on adequacy of first mammogram MRI</td>
</tr>
</tbody>
</table>
ACSM Guidelines For Cancer Screening With MRI As An Adjunct To Mammography

- Women with strong family history of breast and ovarian cancer
  - BRCA mutation carriers
- Radiation to chest wall as in Hodgkin’s disease
- Previous biopsies, LCIS or atypia

Screening Mammography

• Diagnostic mammography differs from screening mammography
  – Asymptomatic women
  – Detect clinically occult breast cancer

• Accuracy depends upon nature of breast
  – Could vary from 70-98% depending upon breast density
# Breast Composition

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Almost entirely fat</td>
</tr>
<tr>
<td>2</td>
<td>Scattered fibroglandular densities</td>
</tr>
<tr>
<td>3</td>
<td>Heterogeneously dense</td>
</tr>
<tr>
<td>4</td>
<td>Extremely dense</td>
</tr>
</tbody>
</table>
Breast Density

- Predominantly Fatty
- Dense
Mammographic Views

• 2 views of the breast
  – Craniocaudal view
  – Mediolateral oblique view
    • Pectoral muscle should be identified to level of nipple

• Breast compression
  – Eliminate motion and blurring
  – Uniform thickness
  – Minimize radiation dose
<table>
<thead>
<tr>
<th>BI-RADS™</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Need additional imaging evaluation – assessment incomplete</td>
</tr>
<tr>
<td>1</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Benign finding</td>
</tr>
<tr>
<td>3</td>
<td>Probably benign finding – short interval follow-up suggested</td>
</tr>
<tr>
<td>4*</td>
<td>Suspicious abnormality – biopsy should be considered</td>
</tr>
<tr>
<td>5</td>
<td>Highly suggestive of malignancy – appropriate action should be taken</td>
</tr>
<tr>
<td>6</td>
<td>Known biopsy; proven malignancy; appropriate action should be taken</td>
</tr>
</tbody>
</table>

Subdivision of Category 4 into 4a, 4b, and 4c, for probabilities for malignancy.
Short-term Follow-up for “Probably Benign” Lesions

• BI-RADS™ Category 3 lesions
  • single or multiple circumscribed masses
  • single or multiple groups of rounded or punctate calcifications
    – 0.5% to 2% frequency of carcinoma

• Short-interval follow-up mammography

BI-RADS™ Categories

- Useful predictors of malignancy
- Category 4: suspicious abnormality
  - 29% to 34% frequency of carcinoma
  - Subdivision into 4a, 4b, and 4c
- Category 5: highly suggestive of malignancy
  - 81% to 94% frequency of carcinoma
- Biopsy is generally recommended for BI-RADS™ 4 and 5
Screening Cost

• 2% will undergo surgical biopsy with first mammogram
  – 60-90% mammographically directed reveal benign disease
• Surgical procedures are the greatest cost of screening
• Mammography 1/3 of total cost
Yield of Nonpalpable Breast Cancer

- 20% of biopsies will be cancer
  - 50% DCIS
- 5-10 cancers per 1000 screened at start
- 2-3 cancers per 1000 screened afterward
Abnormal Mammogram Evaluation

• Additional mammographic views
  – same day
  – patient called back
• Other imaging modalities
  – ultrasound
  – MRI
Abnormal Findings: Calcifications

- Intermediate level of concern
  - amorphous / indistinct
    - “flake shaped”
    - small or hazy
- Higher probability of malignancy
  - pleomorphic
    - varying size and shape (<0.5 mm)
  - heterogeneous
    - granular
    - casting (fine / linear / branching)
    - discontinuous
Calcifications: Distribution

- Grouped or clustered
  - multiple in less than 2 cc of tissue
- Linear
- Segmental
  - suggests multifocal disease
- Regional
  - scattered in a large volume of tissue
- Diffuse / scattered
  - random arrangement
Palpable Mass: Mammography

• Negative mammogram should not delay further investigation of palpable mass

• Diagnostic uses
  – Survey remainder of breast
  – Screen contralateral breast
Diagnostic Methods

• Fine-needle aspiration (FNA)
  - Rapid, minimal discomfort, no incision complicating local therapy, immediate results
  - Cannot reliably distinguish in situ from invasive cancer
  - False-negatives
  - Requires skilled cytopathologist (sensitivity 80-95%)

• Core-needle biopsy
  - Rapid, minimal to moderate discomfort, no surgical incision
  - Interpreted by general pathologist
  - Some false-negatives
  - Sampling error with larger lesions
    (20 to 50% of Atypical Ductal Hyperplasia upstaged to DCIS)
Triple Diagnosis

• Examination
• Mammography
• FNAB

* If there is any discordance between these, excisional biopsy recommended
Other Screening Methods?

- Whole breast ultrasound
- Magnetic resonance imaging
- Full-field digital mammogram
Ultrasound Uses

• To evaluate a focal mass identified on a mammogram
• To evaluate a palpable lump
  – Distinguish a cyst or fluid-filled mass from a solid lesion
• To guide interventional procedures
Role of Ultrasound in Screening

- Poor use as screening tool
  - Cannot replace mammography
    - Microcalcifications
  - High false positive
    - May be too sensitive for detection of breast abnormalities that are benign

- Current studies evaluating use in patients with dense breasts on mammogram
  - Marked improvement in US technology
Screening With Combined Mammography Plus Ultrasound Compared With Mammography Alone
ACRIN Study

• 2700 high risk women
  – Mean age was 53
  – 53% had a personal hx of Breast cancer
  – 39 developed breast cancer in the 1 yr of follow up and one metastatic melanoma in lymph nodes

• Mammography alone detected 12 cancers
  mammography plus sono detected 31
  – sono alone detected 12
  – 9 detected by neither

• The diagnostic accuracy for mammography was 0.78 and increased to 0.91 (95% CI, 0.84-0.96) for mammography plus ultrasound ($P = .003$).

Summary of Performance Characteristics of Screening With Combined Mammography Plus Ultrasound Compared With Mammography Alone at the Participant Level

<table>
<thead>
<tr>
<th></th>
<th>Mammography Plus Ultrasound</th>
<th>Mammography Alone</th>
<th>Comparison of Mammography Plus Ultrasound vs Mammography Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yield per 1000</strong></td>
<td>31/2637</td>
<td>20/2637</td>
<td>Difference: 11.3 (4.6 to 11.7) P = 0.003, 7.6 (4.6 to 11.7)</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>31/40</td>
<td>20/40</td>
<td>-11.1 (4.6 to 11.7) P = 0.003</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>2322/2597</td>
<td>2481/2597</td>
<td>58.5 (9.5 to 45.5) P = 0.003</td>
</tr>
<tr>
<td><strong>Area under ROC curve</strong></td>
<td>99.81 (88.16 to 90.57)</td>
<td>95.53 (94.67 to 96.30)</td>
<td>-6.12 (-7.24 to -5) P = &lt;0.001</td>
</tr>
<tr>
<td><strong>Positive predictive value</strong></td>
<td>31/306</td>
<td>20/136</td>
<td>10.1 (7.0 to 14.1) P = 0.03</td>
</tr>
<tr>
<td><strong>Negative predictive value</strong></td>
<td>2322/2331</td>
<td>2481/2501</td>
<td>99.91 (99.27 to 99.82) P = 0.004</td>
</tr>
</tbody>
</table>

\(^{a}\) Estimates are rounded for presentation. For the comparison column, the counts are replaced by the metric of comparison. Calculations include 1 malignancy that was considered suspicious on mammography and was considered probably benign after integration with ultrasound and 1 malignancy that was not seen on initial imaging that was discovered to be metastasis (from prior primary in back) metastatic to axillary lymph nodes and diagnosed 205 days after study entry.

\(^{b}\) This table displays screening data. After complete diagnostic workup, results for mammography plus ultrasound are as follows: yield, 31 of 807 participants, 38.4 per 1000 (95\% CI, 26.2-54.1); sensitivity, 31 of 35 participants, 88.6\% (95\% CI, 73.3\% to 96.8\%); specificity, 550 of 772 participants, 71.2\% (95\% CI, 67.9\% to 74.4\%); PPV, 31 of 253 participants, 12.3\% (95\% CI, 6.5\% to 16.9\%); NPV, 550 of 554 participants, 99.3\% (95\% CI, 98.2\% to 99.8\%); area under curve, 99.81 (95\% CI, 98.77 to 99.51).

\(^{c}\) Testing H\(_0\): mammography plus ultrasound is equivalent to mammography alone.

\(^{d}\) Ultrasound results were included for completeness. The study was not designed to permit direct comparison of mammography with ultrasound alone. For one participant, the ultrasound alone interpretation was not available.

\(^{e}\) Odds ratios compare the odds of PPV or NPV for mammography plus ultrasound with the odds of PPV or NPV for mammography alone. The method of comparison is given by Leisinger et al.,\(^{2}\) which accounts for the paired design but does not readily permit the construction of a CI.

Berg, W. A. et al. JAMA 2008;299:2151-2163
MRI

- High sensitivity in diagnosis of breast cancer 86% to 100%
- Limitations
  - poor specificity 37% to 97%
  - expensive
  - requires intravenous contrast
  - technology for MRI-guided biopsy not widely available
  - Inconsistent interpretation between centers
MR Imaging of the Breast

• In the diagnostic setting
  – MRI has high (>90%) sensitivity for the visualization of invasive breast cancer
  – MRI can visualize DCIS
    • Sensitivity variable
  – MRI can detect mammogram, ultrasound, or physical exam occult breast cancer
    • Invasive and DCIS
Clinical Applications MRI

• Present uses
  – Implant rupture
  – Worrisome lumpectomy bed
    • Old scar/fibrosis vs tumor recurrence
  – In planning surgical treatment in women already diagnosed
    • Neoadjuvant chemo

• Screening for high-risk women
  – *BRCA* carriers
MRI Screening of Known or Suspected Carriers of *BRCA 1* and *BRCA 2*

- Reported breast cancer rate approximately 3-4% per year\(^1\)-\(^3\)
- 6% prevalence in mutation carriers\(^2\)
- 1/3-1/2 of cancers seen only on MRI\(^1\)-\(^2\)
- False positive rate 6-14%\(^2\)-\(^3\)

MRI: Breast Cancer Screening

- Patient with a strong family history of breast cancer
- Mammogram reveals dense breast
- MRI reveals two 7mm enhancing lesions in the superior lateral aspect of the left breast
  - Biopsy: invasive ductal carcinoma
MRI Screening in Mutation Carriers

• Now recommended on basis of
  – Higher sensitivity than mammography
  – High detection rates
  – Interval cancer risk with mammography-based screening

• Impact on stage at diagnosis, survival
  – Benefit not proven
Digital Mammography

• Image acquisition with digital detector instead of film

• Advantages
  – Reduced need for “call backs” and repeat imaging
    – Reduced dose of radiation
  – Digital image processing
    • Allows manipulation of image contrast
    • Subtle contrast differences enhanced

• Advantages (cont.)
  – Post-imaging processing
    • Image storage
  – CAD
  – Teleradiology

• Disadvantages
  – Lower spatial resolution
  – Cost
Film vs Digital

Film

Digital
Digital Mammography Trial

- 49,528 women in US and Canada
  - Screening film and digital mammography
    - 33 mammography sites
  - Breast cancer status based on biopsy within 15 months
- Results
  - Overall, diagnostic accuracy was similar
  - Digital better accuracy in women
    - Under 50
    - With extremely dense breasts
    - Premenopausal or perimenopausal

Emerging Technology: Breast Tomosynthesis

- Tomosynthesis is a 3-dimensional digital mammographic technique
- Detector remains stationary while the tube moves
- Acquires data through a series of 11 positions through a 50 degree arch
- Detector “reads out” the captured information to create an image

Park J M et al. Radiographics 2007;27:S231-S240
Breast Tomosynthesis

• Clinical Trials
  – increased lesion visibility
  – facilitation of margin analysis
  – reduction in call-back rate from screening
  – lesion location
  – Will require imagers to acquire experience in reading 3D
Summary

• The goal of breast cancer screening is early detection
• Mammography has significantly contributed to earlier diagnosis
• Increasing use of other modalities in breast imaging for screening, particularly for high risk women