Breast Cancer Screening and Diagnosis

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Mammograms

- Screening Mammography
  - Asymptomatic women
  - ≥ 35 years
- Diagnostic Mammography
  - Breast Related Complaints
  - Palpable abnormalities, pain, suspicious nipple discharge
  - Personal history of breast cancer
  - Patients under screening age
  - Male patients

Regulation of Mammography

- 1985 Survey of US mammography facilities by FDA
  - 36% of facilities producing images of unacceptable quality
  - 15% of facilities utilizing general purpose x-ray equipment for mammography
- 1990 GAO survey
  - Many mammography facilities lacked adequate quality assurance programs
- 1992 Senate Committee on Labor and Human Resources
  - Hearings on quality issues in mammography

Regulation of Mammography

- Mammography Quality Standards Act of 1992
  - Annual inspections
  - Equipment
  - Image quality and quality assurance
  - Standards for interpreting physicians, technologists, physicists
  - Patient notification of results and image retention
**BI-RADS**

- Breast Imaging Reporting and Data System
  - Standardize reporting and facilitate outcomes monitoring
  - Assessment Categories

<table>
<thead>
<tr>
<th>BI-RADS 0</th>
<th>Assessment Incomplete</th>
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<tbody>
<tr>
<td>BI-RADS 1</td>
<td>Negative</td>
</tr>
<tr>
<td>BI-RADS 2</td>
<td>Benign Findings</td>
</tr>
<tr>
<td>BI-RADS 3</td>
<td>Probably Benign Findings</td>
</tr>
<tr>
<td>BI-RADS 4</td>
<td>Suspicious Abnormality</td>
</tr>
<tr>
<td>BI-RADS 5</td>
<td>Highly Suggestive of Malignancy</td>
</tr>
<tr>
<td>BI-RADS 6</td>
<td>Known Malignancy</td>
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**Female Cancer Estimates 2012 USA**

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Breast</td>
<td>232,340-Invasive 63,300-In-Situ</td>
<td>39,620</td>
</tr>
<tr>
<td>Colon</td>
<td>52,390</td>
<td>24,530</td>
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<tr>
<td>Cervical</td>
<td>12,340</td>
<td>4,030</td>
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<tr>
<td>Lung</td>
<td>110,110</td>
<td>72,220</td>
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<tr>
<td>Pancreas</td>
<td>22,480</td>
<td>18,980</td>
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</table>

**Breast Cancer in the United States**

- Most common cancer in women:
  - 1:8 by age 95
  - 20% in women <50 years of age
- Breast cancer incidence increasing
  - 1% per year
- Breast cancer death rate decreasing
  - 30% decrease since 1988

**Screening Mammography**

- Areas of Agreement
  - Screening mammography saves lives for women aged 39-69 based upon meta analysis of randomized controlled studies
  - Screening recommended for normal risk women aged 50-74
  - Screening mammography is an imperfect test
    - Limitations/Harms exist
    - Maximum benefit of 65% mortality reduction
    - Informed patient decision
Screening Mammography

• Effective
  – Scientific proof of benefit in decreasing breast cancer mortality
    • Death rate in US from breast cancer unchanged for 50 years prior to 1990
    • Mammographic screening begins in mid-1980’s
    • Increase in cancer incidence
    • 1990 decrease in death rate from breast cancer

• Available and Reproducible
  – Over 12,000 mammography units in U.S.

• Affordable
  – Still around $100 in most of U.S.

Screening Mammography Proof of Benefit

• Direct Proof of Benefit
  – Randomized Controlled Trials
    – Compare mortality of study group with control group
    – RCTs underestimate mortality benefit

• Indirect Proof of Benefit
  – Measure Surrogate End Points
    • Tumor size
    • Axillary lymph node involvement
    • Stage at diagnosis
      • Stage 0 or 1 breast cancer
    • Less morbidity from cancer treatment
      • Less extensive surgery
      • Less frequent radiation therapy
      • Less frequent chemotherapy
      • Less aggressive chemotherapy

Digital Mammography not included in RCTs or Modeling Data
DMIST Trial: 25-53% Improved Cancer Detection for Digital Mammography
-Dense Breasts
-Patients <50 years
**The Evidence for Screening**

- **HIP Trial (1963-1969)**
  - 62,000 women age 40-64 on entry
  - 31,000 women
  - Study group offered mammography and breast physical exam annually for 4 years
  - Attendance of study group first four screens
    - 67%, 54%, 50%, 46%
  - Demonstrated 30% statistically significant decrease in mortality

  - 5 randomized controlled trials
  - All 5 trials showed overall benefit
  - 2-county trial published in 1985
    - 31% statistically significant overall mortality reduction
  - Gothenburg RCT and Malmo RCT (1997)
    - Showed statistically significant mortality reductions of 44% and 36% for women aged 40-49

- **Review of screening outcomes in nine counties in Sweden**
  - January 2006
  - 45% of the Swedish population
  - Death rate in screened group decreased 44% since 1977
  - Results duplicated worldwide in organized screening programs
    - British Colombia
    - Holland
    - Australia
    - Norway
    - Nova Scotia

**Screening Guidelines**

- **ACS 1997**
  - Annual mammography beginning at age 40

- **USPSTF 2002**
  - Screening mammograms every 1-2 years beginning at age 40

- **ACS 2003**
  - Average risk women begin annual mammography at 40
  - Older women continue annual screening as long as in good health and candidate for treatment
  - Women at increased risk may benefit from additional screening strategies (Earlier initiation, MRI, US)

- **ACS 2007**
  - Annual supplemental screening breast MRI women with ≥ 20% lifetime risk of breast cancer
USPSTF 2009

- No mammography recommended for:
  - Women ages 40-49
  - Discussion with physician if high risk
  - Women over age 74
- Mammography recommended every two years for:
  - Women ages 50-74
- No breast self examination
- No clinical breast examination

USPSTF

- 17 experts on health care appointed by Agency of Health Care Quality and Research under Dept. of HHS
  - None with any expertise in diagnosing or treating breast cancer
  - Reviewed essentially the same data as in their review from 2002
    - Did not consider updated information of RCTs and screening data that was even more supportive of beginning screening at age 40

USPSTF 2009

- Evidence considered:
  - Randomized controlled trial data on screening mammography
    - CNBSS-1
    - AGE Trial
  - Harms of screening mammography
  - Age-specific screening results of BCSC
  - Modeling data from 20 different screening mammography regimens

USPSTF 2009

- Evidence not considered:
  - All peer reviewed studies assessing the benefit of screening mammography which were not RCTs
  - All service screening studies
  - All studies describing improvement in screening mammography since RCTs performed
  - All peer reviewed cost-benefit analyses of screening mammography
USPSTF

• Rationale for not screening women ages 40-49
  – Claim only a 15% mortality reduction
  – Claim 1904 women must be invited to screen to prevent one death
  – Harms of screening exceed the benefits of screening
    • False positives, anxiety, distress, radiation exposure, overdiagnosis of DCIS

Screening Women Aged 40-49

• No scientific basis for threshold of 50
  – No abrupt change in screening parameters at age 50
• Lowest possible mortality benefit used
  – RCTs and screening data show 30-48% mortality reduction
• Computer models favored over direct data

Screening Women Aged 40-49

• Breast Cancer is significant for women in their 40’s
  – 40% of all years lost to breast cancer are in women aged 40-49
• Harms of not screening
• No data to support only screening high-risk women
  – 80% of women diagnosed with breast cancers have no significant risk factors

Harms of Mammography Screening

• False-positives (recall, biopsy)
  – 5-15%
• Pain (breast compression)
  – 1-4%
• False-negatives
  – <1%
• Radiation oncogenesis
  – <<1%
• Overdiagnosis
• Anxiety
Harms of Mammography Screening

- Average years of annual screening for one occurrence (Age 40-79)
  - False positive biopsy
    - 149-233 years
    - 4.3-6.7 per 1000 screened
  - Additional imaging
    - 12-16 years
    - 64-84 per 1000 screened

Hendrick and Helvie, AJR 2011

Percentage mortality reduction from various screening strategies. Note that annual (A) screening from ages 40-84 years (A40-84, solid arrow) is estimated to have 71% greater mortality benefit than biennial (B) screening from ages 50-74 years (B50-74, dashed arrow). Number of mammograms shown on horizontal axis is per 1,000 women screened. Data shown are mean values of six models.

USPSTF

- Rationale for screening women aged 50-74 every two years
  - State that a large portion of the benefit of annual screening is maintained in biannual screening
  - Lose 15% of mortality benefit
  - State the harms are doubled by screening annually instead of biannually

USPSTF

- Rationale for no screening of women aged 75 and older
  - Claim there are no studies that show a statistically significant mortality reduction in this group
  - An otherwise healthy woman at age 75 may now live much longer
  - Decision to screen should be based on co-morbidity, not age alone
  - Most women in this group have fatty breasts
  - Cancers are the easiest to find at an early stage
### USPSTF Fallout

- 1 week later discovered at least 5 places in the original form of the U.S. Healthcare Reform Act that the government must accept and place into law USPSTF recommendations
  - A or B recommendations
  - Impact on coverage

### Current Screening Guidelines

- **Age 40 and older**
  - Annual mammograms
    - ACS, NCCN, ACOG, ACR
  - Every 1-2 years
    - NCI, HHS, FDA, AMA
- **Age 50-74**
  - Every 2 years
  - USPSTF(2009), ACP

### Evidence for Screening

- **September 2010**
  - SCRY study evaluated mortality rates in 40-49 age group in patients who underwent screening versus those not screened
    - Evaluated 600,000 women with average follow-up of 16 years
    - Statistically significant decrease in breast cancer mortality of those screened 29%

### USPSTF Fallout

- **December 2009**
  - Senate votes to amend health care bill to ensure routine mammogram insurance coverage to all women over 40
  - House votes 426-0 for resolution stating USPSTF guidelines not be used by insurers to deny screening mammogram coverage
- **New HHS Screening Guidelines**
  - New private health plans must cover evidence-based preventive services
    - Includes all services rated A or B by USPSTF
  - HHS specifically used USPSTF 2002 guidelines
  - 2009 guidelines labeled by HHS as “Not considered to be current”
### New data 2013

  - Invasive breast cancers diagnosed 1990-1997 followed through 2007
    - 609 confirmed breast cancer deaths
      - Median age at diagnosis 49
      - 29% among women screened
        » 19% detected on first screen
        » 10% interval cancers
      - 71% among unscreened women
        » 6% > 2 years
        » 65% never screened

### Current Screening Guidelines

- Average risk general population
  - Age 40
- BRCA gene mutation
  - Age 25-30 for carriers or untested relatives
- First degree relatives of women with premenopausal breast cancer or women with ≥ 20% lifetime risk based on family history
  - Age 25-30 or 10 years earlier than age of affected relatives
- Mantle radiation between ages 10 and 30
  - 8 years after radiation therapy but not before age 25
- Biopsy proven lobular neoplasia, atypical ductal hyperplasia, DCIS, or invasive carcinoma
  - Any age after diagnosis

### High Risk Patients

- ACS recommends annual supplemental breast MRI examination for patients with ≥ 20% lifetime risk of developing breast cancer
  - BRCA1/2 gene mutations
  - Untested first-degree relatives on carriers
  - Prior thoracic radiation therapy between ages 10 and 30
  - Genetic syndromes
    - Li-Fraumeni Syndrome
    - Cowden Syndrome
    - Bannayan-Ruvalcaba-Riley Syndrome

### Other factors

- Family history
- Prior biopsies showing hyperplasia, atypia, LCIS
- Prolonged estrogen exposures
High Risk Patients

- Models for determining risk
  - Gail Model
  - Claus Model
  - BRCAPRO
  - BOADICEA
  - Tyrer-Cuzick (IBIS)
  - http://www.ems-trials.org/riskevaluator/

Supplemental Screening
Supplemental Screening

- Breast Density Reporting Laws
  - Require facilities to report breast density in patient post-exam letter
    - Heterogeneously dense and extremely dense based on BI-RADS
      - 40% population
    - Some mandates include recommendation to discuss supplemental screening (US or MRI) with physician
  - Connecticut, Texas, Virginia, California, New York, Hawaii, Maryland, Tennessee, Nevada, Alabama, Oregon, North Carolina

ACRIN 6666 Trial

- 2,809 women (2004-2007)
  - At least heterogeneously dense breast tissue
  - Elevated risk for breast cancer
    - Personal or family history of breast cancer
    - Prior breast biopsy demonstrating atypia
    - BRCA 1/2 gene mutations
    - Prior chest radiation between ages 10 and 30
  - Evaluated screening whole breast ultrasound in conjunction with mammography
    - Additional supplemental MRI component

ACRIN 6666 Trial Table

<table>
<thead>
<tr>
<th>Modality</th>
<th>Cancer detection rate</th>
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<tbody>
<tr>
<td>Mammography</td>
<td>7.6 cancers per 1000 women</td>
</tr>
<tr>
<td>Mammography and US</td>
<td>11.8 cancers per 1000 women</td>
</tr>
<tr>
<td>Mammography and MRI</td>
<td>14.7 cancers per 1000 women</td>
</tr>
</tbody>
</table>

No additional benefit in combining mammography, US, and MRI. Cancers found were mostly <1cm and node negative.

ACRIN 6666 Trial

- Screening Whole Breast Ultrasound
  - BI-RADS 3
    - 19.5%
  - PPV of biopsy recommendation
    - Mammography alone
      - 29%
    - Mammography and screening ultrasound
      - 11%
  - Increased sensitivity with decreased specificity compared to mammography alone
Automated Whole Breast Ultrasound

- Alternative to manual handheld screening
- First system FDA approved in 2012 as adjunct to mammography
- Efficiently and quick scanning of both breasts
- Reproducible technique
- Drawbacks

Digital Breast Tomosynthesis

- FDA approved for diagnostic and screening mammography February 2011
- Three-dimensional derivative of digital mammography
- A series of individual low-dose images are obtained with the x-ray tube rotating over a limited arc above the compressed breast
- Data reconstructed using mathematical algorithms into a series of thin-sliced images
- High resolution 1mm thick slices
Digital Breast Tomosynthesis

- Anticipated benefits of DBT
  - Eliminates/reduces tissue superimposition
  - Screening recall reduction
  - Increased accuracy and PPV of mammography
  - Increased cancer detection
  - Increased visualization and characterization of masses and mass margins
  - Increased visualization of architectural distortion

Digital Breast Tomosynthesis

- Yale Study 2012
  - Compared screening recall rates
    - Standard 2D FFDM versus Standard 2D FFDM and DBT
    - 1800 patients
      - Recall rate 2D FFDM versus 2D FFDM and DBT
        - 11.9% versus 4.9%
        - 59% recall reduction

Digital Breast Tomosynthesis

- Issues to resolve
  - Population for use
  - Larger patients or patients with implants
  - Interpretation time
  - Radiation Dose
  - Technology cost and reimbursement

Digital Breast Tomosynthesis

- Oslo Prospective Screening Trial
  - 2 year long screening cycle
  - Women 50-69 invited to have FFDM+DBT
  - 12,631 examinations
  - 4 modes independently read
    - FFDM, FFDM+CAD, FFDM+DBT, Synthetic FFDM+DBT
  - 47% increase in detection of invasive cancers
  - 27% increase in all cancers
  - 15% decrease in false positives
### Digital Breast Tomosynthesis

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>mSV</th>
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<tbody>
<tr>
<td>Standard 2D FFDM</td>
<td>0.5</td>
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<tr>
<td>Standard 2D FFDM + 3D Tomosynthesis</td>
<td>1.0</td>
</tr>
<tr>
<td>Average Annual US Background Exposure</td>
<td>3.0</td>
</tr>
<tr>
<td>Average Annual Colorado Background Exposure</td>
<td>4.0</td>
</tr>
<tr>
<td>3D Tomosynthesis + Synthetic Composite 2D Views</td>
<td>0.5</td>
</tr>
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### Case 1 video

[Image of mammogram]

[Image of mammogram]
Case 2 video

Breast MRI

- Non-controversial indications
  - High-risk screening
  - Monitoring response to chemotherapy
  - Axillary node malignancy suspicious for breast primary with negative routine imaging
  - Evaluation of equivocal imaging findings after complete imaging evaluation
    • No definite target for image guided biopsy
  - Evaluation of clinically suspicious nipple discharge with negative routine imaging
  - Evaluation of silicone breast implant integrity
Breast MRI

• When is breast MRI not indicated?
  – Evaluation of imaging findings which can be targeted for biopsy
  – Evaluation of palpable findings with negative routine imaging
Breast MRI

- Controversial indications
  - Biopsy proven malignancy
  - Evaluating extent of disease
  - Evaluating the contralateral breast
    - Cancer staging and contralateral screening
      » More accurate than mammography and US in determining size/extent of cancer
      » MRI will detect additional areas of cancer in 10-37% (16% average)
      » Identifies occult contralateral cancers in approximately 4% of patients
  - No current evidence
    » Improved mortality
    » Improved prognosis
    » Improved surgical management

Molecular Breast Imaging

- Breast Specific Gamma Imaging (BSGI)/Scintimammography
  - Technetium 99m Sestamibi (Cardiolite)
  - Technetium 99m Tetrofosmin (Myoview)
- Positron Emission Mammography
  - F-18 Fluoro-deoxy-glucose
Molecular Breast Imaging

- Proposed indications
  - Radiodense breast tissue difficult to image
  - Evaluate suspected cancer recurrence
  - Evaluate extent of known cancer
  - Evaluate lesions for biopsy/treatment planning
  - Screening high risk patients
  - Evaluate palpable abnormalities not demonstrated on mammography or ultrasound
  - Additional evaluation when MRI unavailable or possible

- http://interactive.snm.org/docs/jnmt-1210b.pdf

Molecular Breast Imaging

- Advantages
  - Similar sensitivity and increased specificity relative to MRI
  - Similar positioning to mammography. Ease of interpretation.
  - Cost
  - Patient comfort

Molecular Breast Imaging

- Disadvantages
  - Ionizing radiation/radiation dose
  - Less supportive data
  - Not replacement for mammography

<table>
<thead>
<tr>
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<th>Mortality single exam age 40</th>
<th>Mortality single exam age 60</th>
<th>Mortality annual exams ages 40-80</th>
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<tbody>
<tr>
<td>Mammography</td>
<td>1.3</td>
<td>0.3</td>
<td>20</td>
</tr>
<tr>
<td>BSGI</td>
<td>33</td>
<td>27</td>
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<tr>
<td>PEM</td>
<td>31</td>
<td>26</td>
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</table>

- LAR-Lifetime attributable risk (per 100,000 studies)
Contrast Enhanced Mammography

- FDA approved device October 2011
  - Provides functional assessment of vascularity/neovascularity
  - Approved for use in patients when “Mammogram or ultrasound is inconclusive”
- Dual-Energy Technique
  - 20% increased radiation dose over standard mammography
- Drawbacks
  - Require intravenous contrast