Appropriate Intervals for Mammography for Breast Cancer Screening

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Disclosures

- None

Disclaimer:
- I won’t give you a definitive answer
Objectives

- Discuss methodology and results from the USPSTF recommendations
- Review new studies and how they support or oppose the above recommendations
- Discuss limitations and harms of mammogram screening
Mammograms

- Sensitivity: 77-95%
- Specificity: 94-97%
- Misses approximately 15% of cancers
  - Technical – may be improved by digital mammogram
  - Biology – aggressive fast growing cancers (ER-) – unlikely to benefit from aggressive screening strategies
Digital Mammography

All Women

Women with Dense Breasts

Women < 50 yrs

Pre or Perimenopausal Women

Pisano ET, NEJM, 2005;353:1773-1783
## Radiation Risk

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Radiation Dose (mSV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background (1 year)</td>
<td>3 mSV</td>
</tr>
<tr>
<td>Mammogram</td>
<td>0.13 mSV</td>
</tr>
<tr>
<td>Chest xray (PA and Lat)</td>
<td>0.06 mSV</td>
</tr>
<tr>
<td>CT Chest</td>
<td>8 mSV</td>
</tr>
<tr>
<td>CT Abdomen</td>
<td>10 mSV</td>
</tr>
<tr>
<td>Coronary Angio</td>
<td>4.6-15.8 mSV</td>
</tr>
<tr>
<td>Bone Scan</td>
<td>4.4 mSV</td>
</tr>
</tbody>
</table>

[Source](http://www.hps.org/hpspublications/articles/dosesfrommedicalradiation.html)
Imaging and Radiation Doses
Breast cancer Risk

- Lifetime Attributable Risk of Fatal Cancer per 100,000 people
  - Bilateral Mammogram yearly screening 1.3-1.7
    40-80 yrs
  - 1 Digital breast tomosynthesis yearly screening 1.3-2.6
    age 40 yrs
  - 1 Molecular breast imaging age 40 yrs 26-39
  - 1 PEM at age 40 yrs 31
  - 1 Pelvic, chest or abdominal CT 25-33

Hendricks RE, Radiology, 2010;257:1-7
Screening and Adjuvant Therapy Saves Lives
But......
Mammograms and Screening

- Over last 3 decades incidence of breast cancer has increased 40% via mammography
  - Diagnosis of early stage breast cancer has increased by 50-75%
  - But, only 8% drop in aggressive cancers
Mammogram and Stage

## Mammogram and Stage

**Table 1. Absolute Change in the Incidence of Stage-Specific Breast Cancer among Women 40 Years of Age or Older after the Introduction of Screening Mammography.**

| Variable                        | Annual Breast-Cancer Incidence | Women Affected over the Three Decades
decades† |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of cases per 100,000 women</td>
<td>Absolute Change</td>
</tr>
<tr>
<td>Increase in cases of early-stage breast cancer</td>
<td></td>
<td>estimated number of women</td>
</tr>
<tr>
<td>DCIS</td>
<td>7</td>
<td>56</td>
</tr>
<tr>
<td>Localized disease</td>
<td>105</td>
<td>178</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>234</td>
</tr>
<tr>
<td>Decrease in cases of late-stage breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional disease</td>
<td>85</td>
<td>78</td>
</tr>
<tr>
<td>Distant disease</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>94</td>
</tr>
</tbody>
</table>
Screening Mammogram: Recommendations
# Mammogram Recommendations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Cancer Society</td>
<td>Yearly beginning at 40</td>
</tr>
<tr>
<td>NCCN</td>
<td>Yearly beginning at 40</td>
</tr>
<tr>
<td>The American College of Obstetricians and Gynecologists</td>
<td>Yearly beginning at 40</td>
</tr>
<tr>
<td>American Medical Association</td>
<td>Yearly beginning at 40</td>
</tr>
<tr>
<td>American Society of Breast Surgeons</td>
<td>Yearly beginning at 40</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Yearly beginning at 40</td>
</tr>
</tbody>
</table>
USPSTF Recommendations

Recommendations are for the average women

- Excluded those at high risk for the development of breast cancer (BRCA mutation carriers or patients with previous chestwall irradiation)

Recommendations only for analog/film mammos

- Not enough data for digital mammos or MRI
USPSTF Recommendations

- Recommends against routine screening for women 40-49 years
  - Category C: There may be considerations that support providing the service in an individual patient. There is moderate-high certainty that the net benefit is small

- Recommends for biennial screening for women age 50-74 years
  - Category B: There is a high certainty that the net benefit is moderate to substantial

- Insufficient data for those ≥ 75 years
What is the US Preventive Services Task Force (USPSTF)

- Established in 1984
- Appointed by Agency for Healthcare Research and Quality (AHRQ)
- Not political
- Analysis started 2 years ago (finished now)
  - Spanned 2 administrations
- Update of 2002 results
What data was reviewed

- 7 randomized trials
  - Baseline study year
    - Varied
    - 1963-1991
  - Population screened
    - Varied
    - 39-74 years
    - ≥ 70 years least data
  - Number of participants
    - 21,195-106,956 Total: 308,735
  - Screening interval
    - Varied
    - 12-33 months

None evaluated digital mammos
Data Analyzed

- 2 of the trials, new from previous analysis
  - Age Trial specific to age 40-49
    - Important new contribution to the analysis
  - Swedish Two-County Trial
    - Only one that evaluates women 70-74
    - Limited small numbers
# Studies Evaluated

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline Year</th>
<th>Age (months)</th>
<th>Interval (months)</th>
<th>FU (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Insurance Plan of Greater NY, 1986</td>
<td>1963</td>
<td>40-64</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Stockholm, 2002</td>
<td>1981</td>
<td>40-64</td>
<td>24-28</td>
<td>11</td>
</tr>
<tr>
<td>Swedish Two-County Trial, 2002</td>
<td>1977</td>
<td>40-74</td>
<td>24-33</td>
<td>20</td>
</tr>
<tr>
<td>Age Trial, 2006</td>
<td>1991</td>
<td>39-41</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>
What data was reviewed

- Breast Cancer Surveillance Consortium (BCSC)
  - Collaborative network of 5 mammo registries
  - Sponsored by NIH
  - Data draws from community samples
  - Mix of analog/film and digital mammos
  - 600,830 women
  - 2000-2005
How Data Was Analyzed

- Meta-analysis of benefits and harms
- Modeling of benefits and harms (6 models used)
  - Assumption
    - Cumulative probability of developing breast cancer after age 40: 12-15%
    - Without screening risk of dying of breast cancer is 3%
    - 100% adherence to screening
    - Perfect treatment strategies
  - Evaluated
    - Initiation and cessation of screening
    - Screening interval
    - 20 screening strategies
Benefits

- Reduction in mortality
- Life-years gained
Harms

- False positive mammograms
  - Additional imaging
  - Negative biopsies
- Overdiagnosis
  - DCIS
  - Slow growing cancers that would never become clinically evident
- Evaluated but difficult to measure
  - Anxiety
Changes in 2009

- **40-49 year group**
  - No longer recommend screening mammogram
  - Not much different from 2002 guidelines
    - Very small benefit

- **50-70**
  - Confirmed biennial as good as annual

- **Extended screening to 74**
  - Previously no data in this age group
Benefits

- 15% reduction of breast cancer mortality 40-49 yr
  - But only 1 cancer death averted for every 1,904 women screened for 10 years
  - Same as the 50-59 yr group but more common a problem therefore mammo more effective

- Biggest benefit in the 60-69 yr group
  - Most common age group to develop breast cancer
## Risk Reduction for Screening Mammogram

<table>
<thead>
<tr>
<th>Age</th>
<th>Trials Included</th>
<th>RR for Breast Cancer Mortality (95% CI)</th>
<th>No. of Screening Mammos to Prevent 1 Cancer Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39-49 years</td>
<td>8</td>
<td>0.85 (0.75-0.96)</td>
<td>1904 (929-6378)</td>
</tr>
<tr>
<td>50-59 years</td>
<td>6</td>
<td>0.86 (0.75-0.96)</td>
<td>1339 (322-7455)</td>
</tr>
<tr>
<td>60-69 years</td>
<td>2</td>
<td>0.68 (0.54-0.87)</td>
<td>377 (230-1050)</td>
</tr>
<tr>
<td>70-74 years</td>
<td>1</td>
<td>1.12 (0.73-1.72)</td>
<td>Not available</td>
</tr>
</tbody>
</table>
## Breast Cancer Surveillance Consortium

### Table 2. Age-Specific Screening Results From the BCSC

<table>
<thead>
<tr>
<th>Screening Result</th>
<th>Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40-49 y</td>
</tr>
<tr>
<td>False-negative mammography result</td>
<td>1.0</td>
</tr>
<tr>
<td>False-positive mammography result</td>
<td>97.8</td>
</tr>
<tr>
<td>Additional Imaging</td>
<td>84.3</td>
</tr>
<tr>
<td>Biopsy</td>
<td>9.3</td>
</tr>
<tr>
<td>Screening-detected invasive cancer</td>
<td>1.8</td>
</tr>
<tr>
<td>Screening-detected DCIS</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### Yield of screening per screening round, n

<table>
<thead>
<tr>
<th>Patients undergoing mammography to diagnose 1 case of invasive breast cancer</th>
<th>556</th>
<th>294</th>
<th>200</th>
<th>154</th>
<th>143</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients undergoing additional imaging to diagnose 1 case of invasive breast cancer</td>
<td>47</td>
<td>22</td>
<td>14</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Patients undergoing biopsy to diagnose 1 case of invasive breast cancer</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Model Assessment

- Goal was to obtain a 10% reduction in breast cancer mortality
  - 3.0% to 2.7% (or 3 deaths averted per 1000)
- Found that the most efficient screening strategy biennial 50-74 years
  - No difference between annual or biennial
  - If extend screening from 69 to 79 years additional reduction of mortality of 7%
    - Not much differences between 69, 74, 79
  - If extend screening to 40 from 50 years additional reduction of mortality of 3%
Model Assessment

- More false negatives occur in strategies that include screening from 40-49 years.
- Risk of overdiagnosis increases with age.
- Biennial strategies decrease the risk of overdiagnosis by 50%.
Model Assessment
Efficiency

Most efficient
In all models
biennial
Screening in
60-69 years

When slope declines, efficiency is lost
Annual vs. Biennial Mammogram

The models predicted that biennial screening achieved an average of 81% of the benefits of annual screening, with individual model estimates ranging from 67% to 99%.
False Positives

- 0.9%-6.5% per screening
- 21-49% cumulative risk after 10 years
  - Up to 56% for 40-49 years
- Using the BCSC data
  - Common in all groups
  - Most common in 40-49 years
  - Rates of additional imaging higher in 40-49 years
  - For every breast cancer diagnosed in 40-49 years, 556 women have mammography, 47 have additional imaging, and 5 have biopsies
Effectiveness of Population-Based Service Screening With Mammography for Women Ages 40 to 49 Years

Evaluation of the Swedish Mammography Screening in Young Women (SCRY) Cohort

Barbro Numan Hellquist, MSc; Stephen W. Duffy, MSc; Shahin Abdsaleh, MD, PhD; Lena Björmelid, RN; Pál Bordás, MD; László Tabár, MD, PhD; Bedrich Viták, MD, PhD; Sophia Zackrisson, MD, PhD; Lennarth Nyström, PhD; and Håkan Jonsson, PhD

Cancer. 117(4):714-22, 2011
Methods

- 1986 Sweden issued guidelines regarding screening mammography
  - 40-54 years mammogram q 18 months
  - 55-74 years mammogram q 24 months

- Caveat: those counties that could not afford it were told to focus on women >50
  - More cosmopolitan better funded counties got screening mammogram for young age women
Methods

- Compare breast cancer death between the 2 groups
  - Excluded were patients who diagnosed with breast cancer before screening
Results

The estimated number of patients who need to undergo 6 episodes of mammogram screening to save 1 life is 1252 women.
Conclusions

- Mammography for women ages 40 to 49 revealed a reduction in breast cancer mortality.
- The reduction was estimated at 26% to 29%.
- Greater only when those women who actually attended screening were considered.
- Greater among women ages 45 to 49 years than among women ages 40 to 44 years.

Breast Cancer Mortality

Figure 2. This chart illustrates the crude cumulative breast cancer mortality per 100,000 person-years. Solid line indicates the study group; dashed line, control group.
Few differences in tumor characteristics between those patients who had a mammo \( \leq 12 \) mths \( (n=118) \) vs \( >12-24 \) mths \( (n=261) \)

- Mammo \( \leq 12 \) mths had
  - Higher incidence of Tis tumors (16% vs 9%)
  - Lower incidence of T1 tumors (67% vs 81%)
  - No difference in T2 or T3 tumor incidence

No difference in
- Mean tumor size
- Tumor markers
- Lymph node (LN) status
Screened patients were compared by presentation: mammo <24 mths (n=379, 64%) vs SBE/CBE and mammo ≤ 24 mths (n=209, 36%).

Presentation by SBE/CBE vs. mammo showed:
- Larger mean tumor size (2.4 vs 1.3 cm), p<0.0001
- Higher T stage, p<0.0001
- Higher grade p=0.01
- Higher incidence of ER- (29% vs 16%), p=0.0003
- Triple negative disease (21% vs 10%), p=0.0005
- LN+ (39% vs 17%), p<0.0001
- No difference between the groups Her2 status.
**Mammograms > 65 yrs: Annual vs Biennial**

<table>
<thead>
<tr>
<th>Age</th>
<th>Diagnosis</th>
<th>Charlson Score 0</th>
<th></th>
<th>Charlson Score &gt; 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 yr</td>
<td>2 yr</td>
<td>1 yr</td>
<td>2 yr</td>
</tr>
<tr>
<td>66-75</td>
<td>Invasive Ca</td>
<td>82%</td>
<td>80%</td>
<td>78%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>Advanced Stage</td>
<td>13%</td>
<td>11%</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Size &gt; 2 cm</td>
<td>18%</td>
<td>18%</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>LN+</td>
<td>21%</td>
<td>20%</td>
<td>24%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>False+ Recall</td>
<td>50%</td>
<td>30%</td>
<td>48%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>False+ Bx</td>
<td>10%</td>
<td>5%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>75-89</td>
<td>Invasive Ca</td>
<td>81%</td>
<td>85%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>Advanced Stage</td>
<td>9%</td>
<td>11%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Size &gt; 2 cm</td>
<td>16%</td>
<td>19%</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>LN+</td>
<td>16%</td>
<td>16%</td>
<td>17%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>False+ Recall</td>
<td>47%</td>
<td>26%</td>
<td>48%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>False+ Bx</td>
<td>9%</td>
<td>4%</td>
<td>11%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Braithewaite D, JNCI, 2013, online
Issues
Psychological Impact of a False Positive Mammogram

- 6 months after final diagnosis, women with false-positive findings reported changes in existential values and inner calmness as great as those reported by women with a diagnosis of breast cancer.
- 3 years after women with false-positive results consistently reported greater negative psychosocial consequences compared with women who had normal findings in all 12 psychosocial outcomes.
  - Sense of dejection, anxiety, negative impact on behavior, negative impact on sleep, breast exam, negative impact on sexuality, feel less attractive, keeping my mind off things, worries about breast cancer, inner calm, social network, and existential values.

Age and Mammograms

- Mammogram less effective 40-49 group
  - Lower incidence of cancer
  - Higher breast density lowers tumor delineation
  - Increased incidence of faster growing tumors

- Recent mathematical model demonstrated that poorer mammographic sensitivity was due to
  - Lower mammographic delectability 79%
  - Faster tumor doubling time 21%

Cancer Properties

- Slow growing tumors more common with advancing age
- In all randomized trials (screen vs no screen) ultimate number of cancers should be the same
  - More cases in the screened vs. not screened
    - Some cancers may not be clinically relevant
      - Not all DCIS progress to cancer
      - Estimates that at least 2 women are overdiagnosed vs. breast cancer death averted
Overdiagnosis

- Difficult to estimate
- Rates vary between 1%-30% (most likely 1-10%)

Welch HG, JNCI, 2010;102:605:613
## Cause of Death in Elderly Breast Cancer Patients

<table>
<thead>
<tr>
<th>Status</th>
<th>Age Group (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>67-69</td>
</tr>
<tr>
<td>Alive</td>
<td>75%</td>
</tr>
<tr>
<td>Death due to Breast Cancer</td>
<td>8%</td>
</tr>
<tr>
<td>Death due to other Causes</td>
<td>14%</td>
</tr>
<tr>
<td>Unknown</td>
<td>3%</td>
</tr>
<tr>
<td>Of those who died, % death due to breast cancer</td>
<td>32%</td>
</tr>
</tbody>
</table>

Cost of Screening - Medicare

- Screening plus work-up = $1.08 B
- Screening (including work-up) + treatment = $1.36 B
- 75 years or older
  - Screening plus work-up = $410 M
  - Screening (including work-up) + treatment = $498 M

Gross CP, JAMA Intern Med, 2013, online
High Risk
Screening for High Risk

Different criteria should be used for high risk patients (>20% lifetime risk of breast cancer)

- Mammograms start at 25 or 10 years before first breast cancer diagnosed in the family
- Mammograms performed yearly
- MRI added to screening
Screening Breast MRI

- Recommended (based on evidence/expert consensus) due to high risk (>20%)
  - Have a BRCA1/2 mutation
  - 1st degree relative with BRCA, but untested
  - >20% lifetime risk (by an appropriate risk-assessment model)
    - BRCAPRO, BOADICEA, Tyrer-Cuzick, Claus
  - RT to chest (10-30 yr dose>4Gy) before the age of 30
  - Have Li-Fraumeni syndrome, Cowden Syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or have of these syndromes in first-degree relatives
Screening Breast MRI

- Insufficient evidence for/against (moderate risk 15-20%)
  - LCIS/ALH
  - ADH
  - Heterogeneously/extremely dense breasts
  - Personal history of breast cancer (inv. or in situ)

- Not recommended
  - Lifetime risk <15%
Personal History of Breast Cancer or DCIS

- Yearly mammogram
- Q 6 month mammogram after BCT no longer recommended
Cases
Case #1

- 44 YOWF
  - Underwent yearly mammography
    - Switched from analog mammogram to digital mammography
    - New nodular density
  - New finding US ordered and mammogram spot compression views
    - US negative
    - Spot compressions persistent nodular density
    - $500
    - $300
    - $300
Case #1

- Stereotactic biopsy
  - Difficult to see
  - Biopsies taken of the entire tract
    - No clip left
  - Pathology: flat epithelial atypia
  - Pathology: negative
    - $3,500
    - $300
    - $3,000
    - $5,000
    - $300

- Breast MRI
  - Another enhancing nodule

- MRI guided biopsy
  - Pathology: negative
Case #1

- 6 month follow-up MRI
  - Negative
- Yearly screening digital mammo
  - Negative

Total cost
- $3,000
- $500
- $16,700

Anxiety Factor
- !!!!!!!!
Case #2

- 79 YOWF
  - Yearly mammo
    - Slowly increasing calcifications
    - Stereotactic biopsy
    - DCIS, grade 1 ER+/PR+
Case #2

PMH
- Mitral valve prolapse
- History of MI in 1968 and 1974
- Coronary artery disease
- Congestive heart failure
- Reactive airways disease
- Osteoporosis
- Hypertension
- Chronic angina
- Diastolic dysfunction
Case #2

- **Surgery**
  - Patient wanted bilateral mastectomies
    - Initially wanted reconstruction then decided against
  - Patient underwent bilateral mastectomies + SLN biopsy
    - Pathology: 1.2 cm intermediate grade DCIS, ER+, SLN-
Case #2

- Using adjuvant online 90% chance of dying within next 10 years of non-breast cancer causes
- If she had a < 1 cm ER+ breast ca, chance of dying of breast cancer 1%

- Did her surgery alter her survival?
Should one size fit all?
Conclusions

- Need to individualize to each patient
  - Balance risks and benefits
  - Listen to patient concerns
- Screening in older patients need to balance benefit of screening vs. risk of competing causes of mortality and risk of overdiagnosis
Conclusions

- Data supports biennial mammogram 50-74 years
  - Minimal change in survival
  - Decrease in false positive mammograms

- Limited data on 40-50 age group
  - Less risk of breast cancer
  - Higher risk of aggressive breast cancer
  - High false positive rates
Discussion

- Need to look at what is best for all our patients
  - Not one size should fit all
  - Limited healthcare dollars, need to put to best use
    - Screening women yearly from 40 onward costs $680,000 per quality-adjusted life-year vs. $35,000 using the new guidelines
- Put efforts into research to determine who needs more screening and who needs less
New Model of Care

Figure 1. Creating a New Risk–Benefit Model that Allows for Individualized Decision Making.

For most interventions, the current practice of seeking a single, universal threshold for intervention (Panel A) might be replaced by a model that allows for individualized decisions about whether to intervene on the basis of personal risk factors and preferences (Panel B).

Quanstrum KH, NEJM, 2010
Thank You

Questions?