Disease Screening:
Value vs. Jeopardy: Point-Counterpoint

Awbrey Glen Clubhouse
May 6, 2013
Objectives

Fathom concept of overdiagnosis created by screening

Appreciate potential magnitude of overdiagnosis as exemplified by screening mammography

Review requisites of successful disease screening

Review limitations of the NEJM report

Learn how to discuss the risks of overdiagnosis vs. benefits with patients and other medical professionals

Apply the Triple Aim of Berwick/St. Charles and the Oregon Health Plan to disease screening
Disclosures

Heather: Nothing to disclose
Cora: Nothing to disclose
Archie: Sigma-Tau Pharmaceuticals

Discussants

Heather West MD  Bend Memorial Clinic
Cora Calomeni, MD  St. Charles Cancer Center
Archie Bleyer, MD  St. Charles Quality Management
Who should undergo screening mammograms?

May 6, 2013

Dr. Heather West, Oncologist
Bend Memorial Clinic

Member, Community Breast Program at St Charles Cancer Center
Breast Screening

• Performed in women without signs or symptoms of breast cancer

• Dependent on patient age and underlying risk factors (medical/family history)

• Can include breast awareness, physical examination risk assessment and screening imaging (MMG, MRI)
### 2003 ACS Update-RCT Mortality

#### TABLE 2

Most Recently Published Results of the Breast Cancer Screening Trials on Breast Cancer Mortality Reduction With Invitation to Screening

<table>
<thead>
<tr>
<th>Study Age</th>
<th>Range</th>
<th>Percentage Mortality Reduction (95% CI†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIP</td>
<td>40 - 64</td>
<td>24 (7, 38)</td>
</tr>
<tr>
<td>Malmö</td>
<td>45 - 69</td>
<td>19 (-8, 39)</td>
</tr>
<tr>
<td>Two-County Trial, Sweden</td>
<td>40 - 74</td>
<td>32 (20, 41)</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>45 - 64</td>
<td>21 (-2, 40)</td>
</tr>
<tr>
<td>Stockholm</td>
<td>40 - 64</td>
<td>26 (-10, 50)</td>
</tr>
<tr>
<td>Canada NBSS-1</td>
<td>40 - 49</td>
<td>-3 (-26, 27)</td>
</tr>
<tr>
<td>Canada NBSS-2</td>
<td>50 - 59</td>
<td>-2 (-33, 22)</td>
</tr>
<tr>
<td>Gothenburg</td>
<td>39 - 59*</td>
<td>16 (-39, 49)</td>
</tr>
<tr>
<td><strong>All Trials Combined</strong></td>
<td><strong>39 - 74</strong></td>
<td><strong>24 (18, 30)</strong></td>
</tr>
</tbody>
</table>

CA Cancer J Clin 2003;53:141-169
# Summary of Guidelines: Ages 40-49

<table>
<thead>
<tr>
<th>Entity</th>
<th>Screening Recommended?</th>
<th>Frequency of Screening</th>
<th>RR of Breast Cancer (CI)</th>
<th>Number Needed to Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS/NCCN</td>
<td>Yes</td>
<td>Annual</td>
<td>0.76 (0.7-0.82)*</td>
<td>Not reported</td>
</tr>
<tr>
<td>USPSTF</td>
<td>No routine screening</td>
<td>N/A</td>
<td>0.85 (0.75-0.96)</td>
<td>1904</td>
</tr>
<tr>
<td>CTFPHC</td>
<td>No</td>
<td>N/A</td>
<td>0.85 (0.75-0.96)</td>
<td>2108</td>
</tr>
</tbody>
</table>

*Mortality reduction for all ages (39-74)

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Ann Int Med 2009;151:716-726

CA Cancer J Clin 2003;53:141-169

### Summary of Guidelines: Ages 50-69

<table>
<thead>
<tr>
<th>Entity</th>
<th>Screening Recommended?</th>
<th>Frequency of Screening</th>
<th>RR of Breast Cancer (CI)</th>
<th>Number Needed to Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS/NCCN</td>
<td>Yes</td>
<td>Annual</td>
<td>0.76 (0.7-0.82)*</td>
<td>Not reported</td>
</tr>
<tr>
<td>USPSTF</td>
<td>Yes</td>
<td>Every 2 years</td>
<td>0.86 (0.75-0.99)†</td>
<td>1339</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.68 (0.54-0.87)‡</td>
<td>377</td>
</tr>
<tr>
<td>CTFPHC</td>
<td>Yes</td>
<td>Every 2-3 years</td>
<td>0.79 (0.68-0.90)</td>
<td>910†</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>432‡</td>
</tr>
</tbody>
</table>

*Mortality reduction for all ages (39-74)
†Women 50-59
‡Women 60-69

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CA Cancer J Clin 2003;53:141-169
Ann Int Med 2009;151:716-726
## Summary of Guidelines: 70-74y

<table>
<thead>
<tr>
<th>Entity</th>
<th>Screening Recommended?</th>
<th>Frequency of Screening</th>
<th>RR of Breast Cancer (CI)</th>
<th>Number Needed to Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS/NCCN</td>
<td>Yes</td>
<td>Annual</td>
<td>0.76 (0.7-0.82)*</td>
<td>Not reported</td>
</tr>
<tr>
<td>USPSTF</td>
<td>Insufficient evidence (&gt;75y)</td>
<td>N/A</td>
<td>1.12 (0.73-1.72)</td>
<td>Not reported</td>
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<tr>
<td>CTFPHC</td>
<td>Yes</td>
<td>Every 2-3 years</td>
<td>0.68 (0.45-1.01)</td>
<td>451</td>
</tr>
</tbody>
</table>

*Mortality reduction for all ages (39-74)*

CA Cancer J Clin 2003;53:141-169
Ann Int Med 2009;151:716-726
2003 ACS Update: Risks of Screening

• False positives- benign biopsy, psychological distress
• Overtreatment of DCIS- invasive cancer developed subsequently in 50% of women in one study
• Not possible to distinguish between DCIS and invasive cancer or progressive versus non-progressive DCIS on imaging
USPSTF 2009 Update

• Potential harms of screening MMG
  – False positive results (lead to additional imaging, biopsy)
  – Psychosocial effects (anxiety, distress, usually transient)
  – Overdiagnosis (detecting invasive disease or DCIS in an older woman likely to die of another cause before breast cancer is detected, or DCIS in a young woman that never progresses to invasive cancer)

Ann Int Med 2009;151:716-726
How Much Breast Cancer Overdiagnosis is There?

Cora Calomeni MD
St. Charles Cancer Center
Euroscreens Working Group Results of Mammography Screening

- 25-31% Reduction in mortality from breast cancer in women invited to screening
- 38-48% Reduction in mortality in women actually screened.
- 6.5% risk of overdiagnosis for screened women.

- J Med Screen September 2012 vol.19 no. suppl 1 14-25
“Much of the current controversy on breast cancer screening is due to the use of inappropriate methodological approaches that are unable to capture the true effect of mammographic screening”

Broeders, et. al. J Med Screen September 2012 vol.19 no. suppl 1 14-25
• “Five studies found no to small effect of screening (0–12% relative risk reduction [RRR] in breast cancer mortality), 4 found a large effect (greater than 33% RRR), and 8 found a moderate effect (13% to 33% reduction).”

• “The authors found concerns about quality in all studies.”
Women’s views on overdiagnosis in breast cancer screening: a qualitative study

• Overdetection in numbers: 1–10% estimate and 50% estimate
• If overdetection were [10% or less / 50%], how would you feel about having screening?
• Does it make a difference to you whether overdetection is 1–10% or 30% or 50%?
• Is overdetection something that you would have liked to have known about before?
• There are different approaches to telling people about screening. Currently the main approach is to encourage people to be screened; another is to give people information about pros and cons and let them decide. Which approach would you prefer, and why?
  • Hersch, et. al., BMJ 2013;346:f158
Women’s views on overdiagnosis in breast cancer screening: a qualitative study

• Responses to overdiagnosis and the different estimates of its magnitude were diverse.
• The highest estimate (50%) made some women perceive a need for more careful personal decision making about screening.
• In contrast, the lower and intermediate estimates (1–10% and 30%) had limited impact on attitudes and intentions, with many women remaining committed to screening.
• The information raised concerns, not about whether to screen but whether to treat a screen detected cancer or consider alternative approaches (such as watchful waiting).

  » Hersch, et. al., BMJ 2013;346:f158
Breast Cancer Incidence Worldwide

Figure 4

Breast cancer incidence trends over time in selected cancer registries in Europe, the Americas and Asia: age-standardised rates (world population). Source: [2].
Gorini, Zappa, et. al.

Breast Cancer Survival by Subtype

Figure 1. Kaplan-Meier survival curve for breast cancer mortality.
Prerequisite Stage Shift for a Successful Cancer Screening Program

Advent of screening

Incidence

Early Stage Cancer

Late Stage Cancer

Reciprocal Stage Shift
Annual Incidence of Colorectal Carcinoma by Extent of Disease at Diagnosis, SEER9

Age 50+

Localized
Regional
Localized
Regional
Distant

Incidence per 100,000

Age <50
Unscreened

Regional
Localized
Distant
Annual Breast Cancer Incidence, Early- vs. Late-Stage Disease at Diagnosis

Age <40
unscreened

Incidence per 100,000

Early Stage
Late Stage

Screening Mammography Penetration, U.S.
Screening Mammography Penetration, U.S.

Number of Mammography Units in U.S.

% Screened (within 2 years)

Annual Breast Cancer Incidence, Early- vs. Late-Stage Disease at Diagnosis

Incidence per 100,000

Early Stage

Late Stage

Hormone Replacement Therapy (HRT)
Annual Breast Cancer Incidence, Early- vs. Late-Stage Disease at Diagnosis

Age 40+

Incidence per 100,000
Cumulative Number of Females Diagnosed with Early- and Late-Stage Breast Cancer since 1979, Age 40+, SEER9

“Best Guess“ Model
Background Increase = 0.25 %/Year

Number of Women Diagnosed with Breast Cancer

Early-Stage

Late-Stage

Overdiagnosis
1.37 M
Estimate
1.7 M as of 2013

Advent of screening mammography

Number of Females Diagnosed with Early- and Late-Stage Breast Cancer in 2008, Age 40+, SEER9

“Best Guess“ Model

Number of Women Diagnosed with Breast Cancer


Early-Stage

Late-Stage

Advent of screening mammography

Overdiagnosis 2008 Estimate 31% of all Women Diagnosed with Breast Cancer (all Stages)
<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Location</th>
<th>OD Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Zahl</td>
<td>Norway and Sweden</td>
<td>One-third</td>
</tr>
<tr>
<td>2006</td>
<td>Zackrisson</td>
<td>Malmö, Sweden</td>
<td>24%**</td>
</tr>
<tr>
<td>2008</td>
<td>Zahl PH, et al.</td>
<td>Four counties in Norway</td>
<td>22%</td>
</tr>
<tr>
<td>2009</td>
<td>Jørgensen KJ, et al.</td>
<td>Denmark</td>
<td>33%**</td>
</tr>
<tr>
<td>2010</td>
<td>Morrell S, et al.</td>
<td>New S. Wales, Australia</td>
<td>30-42%</td>
</tr>
<tr>
<td>2010</td>
<td>Martinez-Alonso M</td>
<td>Catalonia, Spain</td>
<td>47%</td>
</tr>
<tr>
<td>2012</td>
<td>Hellquist BN, et al.</td>
<td>Two counties in Sweden</td>
<td>5%</td>
</tr>
<tr>
<td>2012</td>
<td>Zahl PH, et al.</td>
<td>Seven counties in Norway</td>
<td>~75%</td>
</tr>
<tr>
<td>2012</td>
<td>Puliti D, et al.</td>
<td>Florence, Italy</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Mean 31.5%**

**of screen-detected cancers (other reports are of all breast cancer)**
Cumulative Number of Females Diagnosed with Breast Cancer, by Extent of Disease at Diagnosis since 1979, Age 40+, SEER9

“Best Guess”

Number of Women Diagnosed with Breast Cancer

- **Localized**: +928,000
- **DCIS**: +585,000
- **Distant**: 0 (no change)
- **Regional**: -208,000

Advent of screening mammography
Relative Survival of Females Diagnosed with Breast Cancer after Age 40 by Extent of Disease 2000-2009, SEER18

Survival of Females Diagnosed with Breast Cancer after Age 40 by Extent of Disease 2000-2009, SEER18
Among 66,500 females diagnosed since 1985 with DCIS, the relative survival rate has been >100%, with f/u to 24 years.

~2/3 of all breast cancer patients currently being diagnosed are “early stage”.

The graph shows the distribution of breast cancer stages: Localized (53%), Regional (23%), Distant (5%), LCIS (3%), and DCIS (16%).
Bottom Line

~2/3 of all breast cancer patients currently being diagnosed are “early stage”

~1/2 of early stage (DCIS+localized) would not progress to locoregional disease in the lifetime of those currently being diagnosed to have early stage and not treated.

Patients with metastatic disease at diagnosis account for 45% of breast cancer deaths and are not detected by screening mammography
Comparison of Old vs. 2009 USPSTF Guidelines

ACS, NCCN, ... 40+ Mammograms 30+ mSv

“as long as healthy”

35 40 45 50 55 60 65 70 75 80 85

USPSTF, 2009 13 Mammograms

Heidi Nelson, MD, MPH
OHSU

Pop Health Metrics 2011,9:16
The Treatment and Cost of Breast Cancer Overdiagnosis

- **mastectomy** or **lumpectomy + radiation**
- **anti-hormone therapy** for 5-10 years
- HER2/neu+: **trastuzumab** IV q 3 wks x 1 yr

Overtreatment treatments

- **Premature menopause**: supportive care
- **Osteopenia**: biphosphonate, etc.

Cost

- Physical, emotional, financial ...
Mortality Reduction in Women Diagnosed with Breast Cancer at Age 50-69 in 7 Countries

Lack of Correlation with Screening Mammography
% Females Age 50-69 Participated in Screening Mammography

Annual Age-Adjusted Breast Cancer Death Rate relative to 1980-1985

Autier P, et al, BMJ. 2011;343: d4411
^ Bleyer A. BMJ 2011; 343:d5630
* Ireland estimated from Autier’s starting dates
** Norway relative to 1986
The Big Squeeze
A Social and Political History
of the Controversial Mammogram

Handel Reynolds
Radiologist
MD
Atlanta

Aug 7, 2012
Cornell Press
Our Feel Good War on Breast Cancer

Peggy Orenstein
Diagnosis: Age 36
Screen Detected
now 52
Euroscreen Working Group
Self-appointed; mammographers

• 6.5% risk of overdiagnosis


• 25-31% ↓ in breast cancer mortality in women invited
• 38-48% ↓ in mortality in women actually screened

Cochrane Collaboration: case-control studies should not be used e.g., Malmo: ↓ in breast cancer mortality was 4%, when analyzed as a case-control study the ↓ in breast cancer mortality was 58%.

J Med Screen September 2012;19(suppl 1):14-25
Impact factor = 1.7

http://www.cochrane.dk/screening/EuroScreen-2012-critique.pdf
What Is the Risk of Overdiagnosis and What can We Do About It?

- Overdiagnosis is intrinsic to all effective screening programs.
- Present information is inadequate to accurately assess the risk.
- Women themselves must be informed of the risks as we know them, and make their own decisions.
- Continued monitoring of screening program results with appropriate statistical methodologies is important.
- Biomarker research is essential.
Where do we go now?

• Smarter tailoring of therapy based on the biology of tumors
• ?gene signatures on biopsy that may allow us to treat with hormonal therapy and/or monitor rather than proceed with treatment or more safely increase screening interval
• Think about cessation of screening age>75, depending on life expectancy
Perpetua Bay
Oregon ... Thank you

like the topic, is not black and white