New Evidence on the Value of Breast Cancer Screening

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Recent commentaries, systematic reviews, etc. have questioned the effectiveness of mammography, arguing that:

1. The benefit of mammography is modest.
2. Mammography only detects less aggressive cancers.
3. Advances in modern breast cancer treatments are steadily diminishing the importance of mammography.
Some Background---The Evolving Evidence for Mammography Screening from the Randomized Trials

Evaluation of Periodic Breast Cancer Screening With Mammography

Methodology and Early Observations
Sam Shapiro, Philip Straus, MD, and Louis Venet, MD

Cancer detection programs have for years emphasized the importance of early diagnosis in breast cancer. Proponents of periodic physical examinations have argued that this is the best way to detect breast cancer at an early stage, and recent studies have shown that mammography screening is effective in reducing breast cancer mortality.

Randomised controlled trial of mammographic screening women from age 40: results of screening in the first 10 years

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Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years

Anthony Wall, NSH

Screening with breast age 40

JAMA (The Journal of the American Medical Association)
RCTs of screening mammography:
Overall results show a 21% reduction in breast cancer mortality associated with an invitation to screening

Overall RR = 0.79 (95% CI: 0.73, 0.86)
Heterogeneity p = 0.3

What explains the different outcomes in the randomized trials of breast cancer screening?

- The RCT mortality outcomes range from a 36% mortality reduction to 6% excess mortality
- Little attention has been devoted to understanding these differences
- It is best to ask the simple, but most important question... How well did a trial perform in reducing the risk of being diagnosed with an advanced breast cancer?
Cumulative Mortality in the Breast Cancer RCTs by the RR of Being Diagnosed with an Advanced Breast Cancer

- Cumulative mortality outcomes reflect trial performance in reducing the risk of being diagnosed with an advanced breast cancer.
# Sensitivity Analysis of Various Scenarios by Attendance Rate & Sensitivity in Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Attendance</th>
<th>Sensitivity</th>
<th>RR for Advanced BC</th>
<th>Projected RR, BC Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>95%</td>
<td>0.67 (0.58, 0.76)</td>
<td>0.67 (0.58, 0.76)</td>
</tr>
<tr>
<td>60%</td>
<td>95%</td>
<td>0.78 (0.70, 0.86)</td>
<td>0.74 (0.67, 0.81)</td>
</tr>
<tr>
<td>30%</td>
<td>95%</td>
<td>0.89 (0.82, 0.96)</td>
<td>0.81 (0.76, 0.87)</td>
</tr>
<tr>
<td>90%</td>
<td>75%</td>
<td>0.79 (0.66, 0.93)</td>
<td>0.75 (0.65, 0.84)</td>
</tr>
<tr>
<td>60%</td>
<td>75%</td>
<td>0.86 (0.76, 0.96)</td>
<td>0.79 (0.72, 0.87)</td>
</tr>
<tr>
<td>30%</td>
<td>75%</td>
<td>0.93 (0.85, 0.86)</td>
<td>0.84 (0.78, 0.90)</td>
</tr>
<tr>
<td>90%</td>
<td>55%</td>
<td>0.93 (0.70, 1.01)</td>
<td>0.84 (0.72, 0.96)</td>
</tr>
<tr>
<td>60%</td>
<td>55%</td>
<td>0.95 (0.83, 1.10)</td>
<td>0.85 (0.77, 0.95)</td>
</tr>
<tr>
<td><strong>30%</strong></td>
<td><strong>55%</strong></td>
<td><strong>0.96 (0.89, 1.08)</strong></td>
<td><strong>0.87 (0.80, 0.94)</strong></td>
</tr>
</tbody>
</table>

High Attendance/High Sensitivity --- Shows a 33% reduction in breast cancer deaths

Low Attendance/Low Sensitivity --- Shows only a 13% reduction in breast cancer deaths

Chen TH, Medicine (Baltimore) 2017;96:e5684.
Background: It has been asserted that mammography screening preferentially benefits those with less aggressive cancers, with lesser or no impact on more rapidly progressing and therefore more life-threatening tumors.

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018
Questioning the Impact of Mammography on Reducing Deaths from Aggressive Cancers

Effect of Mammography Screening on Mortality by Histological Grade

• If screening does improve outcome in the more aggressive cancers, this will be reflected in a substantial effect of an invitation to screening on mortality from grade 3 cancer, by:

  – improving stage at diagnosis of such cancers, or
  – detecting these cancers before dedifferentiation, therefore preventing progression to grade 3
  – or both.
Swedish Two County Trial--Background and Methods

- 133,065 women ages 40-74 randomized to screening or usual care
- Screening phase = 7 years
- Screening interval
  - 40-49 = 24 months
  - 50-74 = 33 months
- Protocol
  - One view mammography, single reader
  - No physical exam
- 1st mortality results published in 1985
- 28 years of follow-up in this analysis
Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 1

• No significant difference is seen in between the ASP and PSP in the cumulative mortality of grade 1 tumors

• RR = 0.94, or a 6% mortality difference

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018
Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 2

Grade 2 tumors

- A statistically significant difference is seen between the ASP and PSP in the cumulative mortality of grade 2 tumors
- RR = 0.68, or a 32% mortality difference

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018
Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 3

Grade 3 tumors

- A statistically significant difference is seen between the ASP and PSP in the cumulative mortality of grade 3 tumors
- RR = 0.65, or a 35% mortality difference

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018
Summary

- Our results shows that *mammography screening prevents tumors from progressing to grade 3 and also detects grade 3 tumors at smaller sizes with lower rates of lymph node metastases*

- There was a 35% reduction in breast cancer mortality from grade 3 cancers in the ASP compared with the PSP, corresponding to 95 deaths prevented, *almost double the number of deaths prevented for grades 1 and 2 tumors combined*

- The assertion that mammography has little effect on the natural history of aggressive breast cancers is unfounded
What do we make of the lack of difference in the cumulative mortality for grade 1 tumors?

- The RRs of mortality from grade 1, 2, and 3 cancers were 0.94, 0.68, and 0.65
- The RRs of incidence of grade 1, 2, and 3 tumors were 1.33, 0.89, and 0.90
- Dividing RRs for mortality by those for incidence, we obtain 0.71, 0.76, and 0.72, very similar figures

This suggests that the lack of a mortality reduction in grade 1 tumors is driven by the increased incidence of these tumors, with a corresponding reduction in incidence of grade 2 and 3 cancers, and thus, the effect of screening on case fatality is similar for all grades.

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018
Screening Mammography — A Long Run for a Short Slide?
H. Gilbert Welch, M.D., M.P.H.

Thus, the increased awareness about the importance of promptly seeking care for overt breast abnormalities (there is no debate about diagnostic mammography) and the widespread use of adjuvant therapy have probably combined to make screening now less important.⁴,⁵
Women and their health care providers need a reliable answer to this important question: If a woman chooses to participate in regular mammography screening, then how much will this choice improve her chances of avoiding a death from breast cancer compared with women who choose not to participate?
The Incidence of Fatal Breast Cancer

• Using the incidence rates of fatal cancers within 10 & 20 years from diagnosis directly compares cancers diagnosed during the study period in women participating and not participating in mammography screening.

• Over a 58 year period, if treatment has reduced the importance of early detection, then it will be evident in differences in breast cancer death rates in exposed and unexposed women

• This method considerably reduces the risk of lead time bias given the long duration of follow-up, and length bias, given that the denominator is the population at risk
Methods

• We used registries for the study population, screening history, breast cancer incidence, and disease-specific death data in a defined population in Dalarna County, Sweden.

• We calculated (1) the annual incidence of breast cancer, and (2) the annual incidence of breast cancers that were fatal within 10 and within 11-20 years of diagnosis in women aged 40-69 who either participated or did not participate in mammography screening during a 39-year period (1977-2015).

• All patients were treated with stage-specific therapy according to the latest national guidelines, irrespective of the mode of detection.
Results

• Women who chose to participate in an organized breast cancer screening program had a 60% lower risk of dying from breast cancer within 10 years after diagnosis (RR=0.40, 95% CI 0.34 - 0.48) compared with corresponding risk of breast cancer death in non-participants.

• There was a 47% lower risk of dying from breast cancer within 20 years after diagnosis (RR=0.53, 95% CI 0.44 - 0.63) compared to the corresponding risks for the non-participants.
Cumulative incidence-based breast cancer mortality in the pre-screening period, and in the three screening periods by screening exposure.
Conclusion

• All breast cancer patients benefit from advances in breast cancer therapy

• *Women who have participated in mammography screening obtain a significantly greater benefit from the therapy available at the time of diagnosis than do women who have not participated.*
Early detection doesn’t matter???

Consider the consequences of early vs. advanced stage at diagnosis

- Increased probability of requiring mastectomy
- Near and long-term adverse effects of radiation therapy, adjuvant therapy, and chemotherapy
- Upper-body impairments
- Increased risk of lymphedema
- Increased risk of breast cancer death
Conclusion: Prevailing myths about mammography screening have been shown to unfounded

• Regular attendance in mammography screening:
  – Results in a significant decreases in death from breast cancer among the most aggressive cancers, and in fact, in all histologic grades
  – Insures a substantially greater benefit from the stage-specific therapy at the time of diagnosis compared with women who did not attend screening
The Swedish Two County Research Group

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Thank you