Breast Screening: risks if you do and risks if you don’t

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General principle

• There is often discussion of “benefits and harms” of breast screening

• This is a misnomer - no-one is guaranteed either

• As with all medical interventions, there are risks associated with complying and risks associated with not doing so

• The major ‘risk if you don’t’ is greater probability of death from breast cancer
RCTs of screening mammography:
Overall results in terms of breast cancer mortality

Overall RR = 0.80 (95% CI: 0.73, 0.87)
Insights from the Breast Cancer Screening Trials: How Screening Affects the Natural History of Breast Cancer and Implications for Evaluating Service Screening Programs
Positive randomised trial results

• The randomised trials show a 20% reduction in breast cancer mortality with the offer of screening
• They also show that the reduction in mortality corresponds to the reduction in advanced stage disease
• Since only 70% on average took up the offer, the effect of actually being screened is likely to be considerably greater
• So why the controversy?
Mortality benefit

• Different reviews quote different overall estimates of mortality benefit
• Relative reductions in mortality from 15% to 35% are quoted
  – Partly depends on whether the intervention is screening or invitation to screening
• Absolute benefits range from 1 life saved per 90 screened to 1 per 2000
Degree of consensus

• Surprisingly, this considerable range is largely artificial
  – Most estimates are consistent with each other
  – One notable exception

• High profile sources include the USPSTF, the UK review, the EUROSCREEN review of service screening in Europe and the Nordic Cochrane Review
### Quoted absolute benefits

<table>
<thead>
<tr>
<th>Source</th>
<th>No. needed to screen*</th>
<th>Follow-up period (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK review</td>
<td>179</td>
<td>20</td>
</tr>
<tr>
<td>USPSTF, depending on age</td>
<td>377-1904†</td>
<td>15</td>
</tr>
<tr>
<td>Nordic Cochrane Review</td>
<td>2000†</td>
<td>10</td>
</tr>
<tr>
<td>EUROSCREEN</td>
<td>90</td>
<td>30</td>
</tr>
</tbody>
</table>

*Number of women needed to screen for ten years to prevent one breast cancer death
†Number needed to invite to screening
RR from Nordic Cochrane Review

• Like everyone else, the NC Review obtained an approximate 20% reduction in breast cancer mortality from the data

• This pertains to invitation to screening

• On the basis of their opinion of the quality of the trials, they conjectured that 15% might be the true figure
Follow-up time

• If they had estimated the number needed to screen, their 2000 needed to invite would become 1400 needed to screen

• Another reason for the low estimated benefit is the restriction to ten years follow up, ie they estimate lives saved from ten years of screening DURING THAT TEN YEARS
Results from the Two-County trial

<table>
<thead>
<tr>
<th>Follow-up time</th>
<th>RR</th>
<th>Deaths prevented</th>
<th>Number needed to screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.74 (0.57-0.98)</td>
<td>71</td>
<td>922</td>
</tr>
<tr>
<td>15</td>
<td>0.70 (0.56-0.87)</td>
<td>124</td>
<td>526</td>
</tr>
<tr>
<td>20</td>
<td>0.70 (0.57-0.85)</td>
<td>141</td>
<td>464</td>
</tr>
<tr>
<td>25</td>
<td>0.70 (0.57-0.85)</td>
<td>150</td>
<td>436</td>
</tr>
<tr>
<td>29</td>
<td>0.69 (0.56-0.84)</td>
<td>158</td>
<td>414</td>
</tr>
</tbody>
</table>
Screening prevents deaths in the long rather than short term

- From seven years of screening, over a maximum of 29 years of follow-up, 158 deaths were prevented.
- More than half of those deaths prevented, 87 (55%), would have occurred after the first ten years.
Expressing review results relative to the same baseline

• The UK review of breast cancer screening expressed results as number needed to screen to prevent one breast cancer death
  – Screen for 20 years ages 50-69
  – Deaths prevented ages 55-79
  – UK population mortality

• What happens if we re-express all these review results in the same way?
Number needed to screen from age 50 to 69 to prevent one breast cancer death in ages 55-79, based on the UK population at ages 55-79

<table>
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<td>UK independent review</td>
<td>179</td>
</tr>
<tr>
<td>USPSTF</td>
<td>193</td>
</tr>
<tr>
<td>Nordic Cochrane review</td>
<td>257</td>
</tr>
<tr>
<td>EUROSCREEN</td>
<td>64-96</td>
</tr>
</tbody>
</table>

Only a fourfold difference, not a 20-fold
Do improvements in treatment make screening redundant?

- Do antiretroviral drugs make condoms redundant?
- Does screening make the treatment innovations redundant?
  - Diagnosis is antecedent to treatment
Survival by node status, 7209 breast cancer diagnosed since 1999

Kaplan-Meier survival estimates

- Analysis time
- Nodes = 0
- Nodes = 1
Symptomatic cancers only

Kaplan-Meier survival estimates

Analysis time

Nodes = 0

Nodes = 1
Screen-detected cancers only

Kaplan-Meier survival estimates

- Analysis time
- Nodes = 0
- Nodes = 1
Implications

• Despite treatment innovations, node positive disease still has poorer survival than node negative

• Thus there is still a benefit of early detection

• Both screening and the adjuvant therapies have been demonstrated in trials

• We should grow up and accept that both work

• While screening does prevent deaths from breast cancer, you have to wait for years to observe this
To summarise

- The major risk with not being screened is a higher chance of advanced stage disease and breast cancer death
- This remains the case in the epoch of adjuvant systemic therapy
Risks if you do -screening to diagnosis (first screen)

- 7 cancers
- 30 biopsies
- 80 recalled
- 1000 screened
Risks if you do -screening to diagnosis (later screens)

- 7 cancers
- 14 biopsies
- 30 recalled
- 1000 screened
Risks if you do- false positives

• There is a 7% chance of a false positive imaging result at first screen, and a 2% chance at each subsequent screen

• There is a 1-2% chance of a core biopsy for a lesion which is not cancer
Risks if you do- Overdiagnosis

- Remember definition: screen-detected cancer which would not have been diagnosed if screening had not taken place
- Usually estimated by comparing cumulative incidence in screened and unscreened populations
- Need to control for incidence trends independent of screening, and for lead time
- Use of RCT data would seem appropriate, but
  - Many trials screened the control group after a period
  - Follow-up of remaining trials probably not long enough
Range of overdiagnosis estimates from service screening
Estimates of overdiagnosis

• Estimates range from less than 5% to more than 50%
  – Less than one per life saved to 10 per life saved

• Those which fully adjust for lead time and underlying trends get estimates of 10% or less
  – 1 or less per life saved

• Whatever one’s personal opinion, we can find an estimate which contradicts it
Ductal carcinoma in situ

- There is concern that substantial numbers of DCIS cases diagnosed by screening would not have progressed to either symptoms or invasive cancer
Figure 1. Cumulative incidence of breast cancers in study and control groups of the Swedish Two-County Trial.

(a) Invasive Cancers

(b) In Situ Cancers

(c) All Cancers

Invasive deficit 1/1000

In situ excess 1/1000
DCIS

- Two trials found an excess of DCIS with screening, balanced by a deficit in invasive cancers
- In the UK programme, those units with high rates of DCIS at screening have lower invasive interval cancer rates
- Detection and treatment of DCIS does prevent some invasive breast cancers
Overdiagnosis and quality of life

• An overdiagnosed case is screen-detected by definition and cannot cause breast cancer death

• Overdiagnosed cases will be 100% screen detected and will be in situ or invasive localised, early stage disease

• In these cases, <5% receive mastectomy and <10% chemotherapy
  – (compared to around 30% generally)
Conclusions

• The implications of the reviews for absolute mortality reductions are not as different as first appears
• Screening saves substantial numbers of lives, even in the epoch of effective treatment
• There is no need to change practice, although there is always room for improvement
• Risks if you don’t have greater life-threatening and life-changing potential than risks if you do
Thank you