THE STATE OF THE CONTROVERSY AND THE
UK INDEPENDENT BREAST SCREENING
REVIEW PANEL

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Member of the secretariat of the UK IBSR and Head of Statistical Information at Cancer Research UK
Contents

- Background to the review
- Controversy
- Mortality Benefit
- Overdiagnosis
- Other Harms
- Summary and Conclusions
- Panel Recommendations
Background

- Screening is effective if able to diagnose a cancer when more treatable – This is true for breast cancer

- 1986. Forrest Report
- 1988. NHS Breast Screening Programmes started

- subsequent large literature
- further trial results
- observational studies
- controversy
The Review

- Set up by Prof Sir Mike Richards (then National Cancer Director, England) and Dr Harpal Kumar (CEO, Cancer Research UK)
- Independent Panel with expertise in epidemiology, medical statistics, screening, breast cancer, patient views but
- No member had previously published on breast cancer screening
- A range of experts provided verbal and/or written evidence

- Aim - develop an up-to-date (2012) assessment of both the benefits and harms associated with population breast screening programmes.
The Panel

CHAIR: PROF SIR MICHAEL MARMOT,
   – Director of the Institute of Health Equity, University College London

PROF DOUG ALTMAN
   – Director of the Centre for Statistics in Medicine and Cancer Research UK Medical Statistics Group, University of Oxford

PROF DAVID CAMERON
   – Clinical Director of the Edinburgh Cancer Research Centre, and Professor of Oncology at Edinburgh University

PROF JOHN DEWAR
   – Consultant and Honorary Professor of Clinical Oncology at Ninewells Hospital, Dundee

PROF SIMON THOMPSON
   – Director of Research in Biostatistics at the University of Cambridge

MS MAGGIE WILCOX
   – Patient Advocate
The Controversy
The Controversy

Benefits:
Magnitude of the reduction in breast cancer mortality
Relevance of the original trials
Interpretation of observational data
Relevance with reduced mortality from changes in (adjuvant) treatment

Harms:
Overdiagnosis
DCIS
Psychological consequences of screening
Catering for the information needs of women called for screening
Mortality

- Consider effect on breast cancer mortality
- Not overall mortality since the studies are insufficiently powered to show an effect
- Not breast cancer survival since affected by lead time bias

- Evidence
  a. randomised controlled trials (RCTs)
  b. observational studies
Mortality - RCTs

- 11 trials (HIP, Malmo I & II, Swedish 2 county, Canada 1 & 2, Stockholm, Goteborg, UK Age and Edinburgh)
- All compared women invited to screening with controls, but otherwise varied
- Randomisation: only Edinburgh excluded because of significant imbalances
- Included all ages
- Cause of death important but not a reason to exclude any trials
Mortality - Meta-analysis

- Random effects not fixed effects
- Based on data in Cochrane Review
- 13 years of follow up
Mortality - Meta-analysis

- Overall relative risk (invited vs. controls) is 0.80 (95% CI 0.73-0.89)
  - Reduction in breast cancer mortality 20%
  - Some heterogeneity but not statistically significant
- Results not dissimilar to other meta-analyses
- Uncertainty
  - Statistical
  - Relevance of the data to current practice
- Other Methods
  - Generally found higher benefit, but have weaknesses in design
Mortality – Meta analysis

Table 2
Estimates of RR in a comparison of invited women versus control women in the trials of breast cancer screening

<table>
<thead>
<tr>
<th></th>
<th>Overall RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>This review</td>
<td>0.80 (0.73–0.89)</td>
</tr>
<tr>
<td>13-year follow-up in trials</td>
<td></td>
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<tr>
<td>reported in the Cochrane</td>
<td></td>
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<tr>
<td>Review random-effects</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<td>meta-analysis</td>
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</tbody>
</table>

Cochrane review

| Fixed-effect meta-analysis   | 0.81 (0.74–0.87)    |
| of the above trials          |                     |
| As above, but excluding     | 0.77 (0.69–0.86)    |
| women <50 years              |                     |

Trials considered adequately
randomised (Canada, Malmö, and
UK Age trial) had RR 0.90 (95% CI
0.79–1.02); trials deemed suboptimally
randomised gave RR 0.75
(0.67–0.83). As a compromise between
these two estimates, the authors
concluded that an RR of 0.85 was
plausible

US Task Force

| RR 0.86 (95% CI 0.75–0.99)   | 0.81                |
| for women aged 50–59 years   |                     |
| and RR 0.68 (0.54–0.87)      |                     |
| for those aged 60–69 years.  |                     |
| These estimates have an      |                     |
| inverse-variance weighted    |                     |
| average RR of 0.81           |                     |

Canadian Task Force

| Routinely screening for       | 0.79 (0.68–0.90)    |
| breast cancer with mammography|
| every 2–3 years for women     |                     |
| aged 50–69 years was rated    |                     |
| as a weak recommendation      |                     |
| based on moderate-quality     |                     |
| evidence according to GRADE  |                     |
| criteria11                    |                     |

Duffy et al, 2012

| Review of all trials and age | 0.79 (0.73–0.86)    |
| groups                      |                     |

RR=relative risk.
Mortality - Observational studies

1. Ecological – comparing areas or periods when screening was or wasn’t in place
   - Diverse findings
   - Many factors have changed substantially and The Panel felt that these studies could not allow for this

2. Case Control

3. Incidence based mortality
   - Generally showed more benefit than the trials but felt this may reflect residual bias. Are in the same direction as the trials.
Mortality – uncertainty around relative risk reduction

- External validity – do changes in treatment reduce relevance of screening?

- The panel felt effects of treatment and screening likely to be independent

- Effects of treatment would affect absolute benefit but not relative benefit of screening.
Mortality – Absolute benefit

- Estimates vary between one breast cancer death prevented for 100 women to 2000 women invited to screening.
- Number of “lives saved” (premature cancer deaths prevented)
  - Depends on underlying rate of BC death
  - Under 50 smaller gain as fewer deaths
- Panel assumed effect on mortality only seen ages 55-79 (i.e. 5-10 years after screening ages 50-69)
- Risk of death from breast cancer between ages 55-79 for a woman aged 50 is 1.70%
Mortality – Absolute benefit

- Without screening, 1.70% would be 2.13% \([2.13 \times 0.80 = 1.70]\) - difference is therefore 0.43%  
- 43 breast cancer deaths prevented for every 10,000 women invited to screening  
- One breast cancer death prevented for every 235 women invited  
- Figures have the same uncertainties as for the calculation of relative risk reduction
Back-extrapolation

- Take UK mortality data for the screening age women and “subtract” the 20% reduction in mortality.

Breast Cancer Mortality, UK, 1950 to 2010

Cumulative Risk

Cumulative Risk Without Screening

RR 0.8

2.13%

↓0.43%

1.7%
Overdiagnosis

- Definition:
  - Detection of cancers on screening that would not have been found were it not for the screening test

- Does it occur and if so, how common is it?
- Essentially occurs if woman dies before the end of the lead time for her cancer.

Panel decided to include invasive and DCIS since both treated.
Overdiagnosis

– Screening is expected to lead to earlier diagnosis
– This will cause a higher incidence in invited group compared to control in the short term
– Cessation of screening should lead a relative fall in incidence in the screened population compared to control (the “compensatory drop”)
– Once lead time of screening exhausted, incidence should be the same.
Estimating overdiagnosis

- Ideally compare group of women invited to screening for 20 years aged 50-70 with an exactly comparable (age, risk CA breast etc.) uninvited group
- Follow to death
- Any excess of breast cancers in the invited group would represent overdiagnosis
- Such a study does not exist
Overdiagnosis – estimate from RCT’s

- Need to follow up beyond screening
  - To allow for compensatory drop and lead time
- Lead time difficult to estimate
- Minimum 5-10 years follow up after end of screening

- Screening of the control group makes it difficult to estimate overdiagnosis since lose compensatory drop and the control group will include overdiagnosed cases.
Overdiagnosis – estimate from RCT’s

- Only 4 trials did not have screening of control group – HIP, Malmo, Canada 1 and 2
- HIP excluded by The Panel since difficult to obtain consistent figures and some included LCIS
Overdiagnosis – methods of calculating

- General agreement on the numerator
- Disagreement on the denominator – if a % what is it a % of?
- At least 10 different ways of estimating it.
- The Panel focussed on 4.
Overdiagnosis – methods of calculating

- Excess of cancers as a proportion of cancers diagnosed
- A. over whole follow up period in unscreened women
- B. over whole follow up period in women invited for screening
- C. during screening period in women invited for screening
- D. detected by screening in women invited for screening
<table>
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<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td>Malmö I 55-69</td>
<td>11.7% (82/698)</td>
<td>10.5% (82/780)</td>
<td>18.7% (82/438)</td>
<td>29.1% (82/282)</td>
</tr>
<tr>
<td>Canada 1</td>
<td>14.1% (82/581)</td>
<td>12.4% (82/663)</td>
<td>22.7% (82/361)</td>
<td>29.4% (82/279)</td>
</tr>
<tr>
<td>Canada 2</td>
<td>10.7% (67/626)</td>
<td>9.7% (67/693)</td>
<td>16.0% (67/420)</td>
<td>19.8% (67/338)</td>
</tr>
</tbody>
</table>
Overdiagnosis – estimate from RCTs

- The Panel thought that the most useful estimates are
- From a population perspective, the excess cancers as a proportion of all the cancers diagnosed from the start of screening to the end of follow up (method B)
  - RCT meta analysis 11%
- From the woman’s perspective, the excess cancers as a proportion of the cancers diagnosed during screening (method C)
  - RCT meta analysis 19%
- Both estimates are derived from limited data and share all the uncertainties of the mortality data.
Overdiagnosis – observational studies

1. Compare post-screening incidence breast cancer (BC) with extrapolation of pre-screening incidence: depends heavily on assumptions about likely incidence.

2. Compare incidence BC in screened and unscreened countries or within countries. Depend on allowing for differences and fully accounting for lead time.

Essentially - What would have happened if there had not been any screening....

- Family history, Age, Menopause, Diet, Exercise, Race, HRT, Etc......
Estimating overdiagnosis

Breast cancer age specific incidence rates, England 1975 to 2008

Figure 1 Breast cancer age specific incidence rates, England 1975 to 2008, age 50-64 with expected, observed and smoothed data
Assumptions

Same dataset can give different answers:
Overdiagnosis – Panel conclusion

- Overdiagnosis occurs.
  - **Difficult** to estimate its magnitude
  - Best estimate is from the RCTs without screening of the control group

- For UK women invited aged 50 for 20 years’ screening
  - Apply the 19% risk to the cumulative incidence of breast cancer (invasive and in-situ) in women aged 50-69 in UK
  - One in 77 women aged 50 invited to screening for 20 years would have an overdiagnosed cancer
  - Equivalent to a rate of 129/10,000 women invited.
  - ~1% risk for a woman entering UK screening
Ductal carcinoma in situ (DCIS)

- Found more commonly via screening compared with symptomatic practice
- Natural history difficult to define – need surgery to exclude invasive component
- Approx. 10% invasive relapse rate at 10 years in UK/ANZ DCIS trial if WLE only
- DCIS can relapse – will it progress within the lifetime of the woman?
Other harms

For example:

- Biopsy rate
- Complications of surgery, radiotherapy, chemotherapy
- Psychological harms

- All important but generally, magnitude agreed and risks outweighed by mortality benefit.
Main Conclusions

1. Breast screening extends lives

2. Overdiagnosis occurs
Benefit

Best estimate is a 20% reduction in breast cancer mortality
- One breast cancer death prevented for every 235 women invited to screening
- For the UK NHSBSP, estimate prevents about 1300 breast cancer deaths/year
- ~ 22,000 life-years saved
Overdiagnosis

Best estimate is
- 11% of cancers diagnosed during lifetime during and after screening
- 19% of cancers diagnosed during the screening period
Summary figures

- Panel’s review of the evidence
  - RCTs still relevant and best evidence
- For 10,000 women invited to screening for 20 yrs. from age 50 (to 70)
  - 681* cancers diagnosed
  - 129* of these represent overdiagnosis
  - 43* deaths from breast cancer prevented
  - If attend screening for 20 yrs, just over 1% chance of being diagnosed with an overdiagnosed cancer

*these figures are estimates with a large range of uncertainty
Recommendations

– Breast screening should continue

– Balance of benefits and harms should be communicated to all women invited for screening, so they can make an informed decision
Research Recommendations

- Support the ongoing meta-analysis of centrally collated individual patient data from all the trials
- Work to more accurately estimate and identify overdiagnosis
- DCIS – RCT’s and the Sloane Project
- Evaluate the cost effectiveness of the Screening Programme
Acknowledgments

– The Panel would like to thank
– All the experts who provided verbal and/or written evidence
– DH who funded the support for the review to occur
– CRUK for providing the staff to support the Panel’s work

– Thank you for listening