The benefits and harms of breast cancer screening

An assessment by the Independent UK Panel on Breast Cancer Screening

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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 treatment

Harms:
- Overdiagnosis

- DCIS
- Psychological consequences of screening
- Information given to women invited for screening

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The UK review

- Set up by Prof Sir Mike Richards (National Cancer Director, England) and Dr Harpal Kumar (CEO, Cancer Research UK)

- Independent Panel with expertise in epidemiology, medical statistics, breast cancer, patient views; but no member has previously published on breast cancer screening

- Panel: Sir Michael Marmot (chair), Douglas Altman, David Cameron, John Dewar, Simon Thompson, Maggie Wilcox

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The UK context

- 1986: Forrest Report
- 1988: UK Breast Screening Programmes started for women aged 50-64
- Later extended to ages 50-70
- Invitation to screening every three years

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Terms of reference

- "The overall aim of the review is to develop an up-to-date (2012) assessment of both the benefits and harms associated with the UK population breast screening programmes. This is a rigorous review of the evidence by an independent Panel; it is not a formal systematic review."

- Process:
  - Review of extensive published work
  - Verbal and written evidence from the main contributors to the debate
  - About 10 Panel meetings

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Effect on mortality

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

Consider
a. randomised controlled trials (RCTs)
b. observational studies
c. first relative risks, then absolute risks
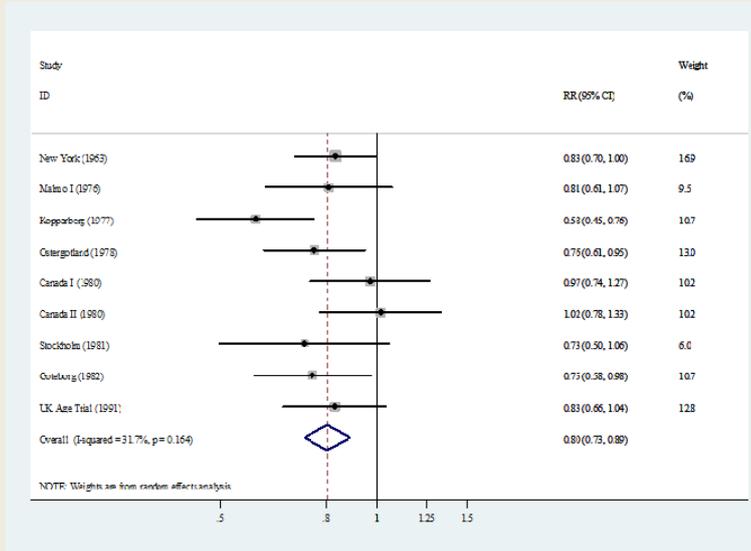
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11 RCTs

- All trials compared women invited to screening with controls
- Started between 1963 and 1991
- Heterogeneous: age, duration of screening, screening interval, number of views
- Subject to a number of concerns about potential biases

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11 RCTs – problematic issues

- Randomisation: individual / cluster / day of birth: only Edinburgh excluded
- Ascribing cause of death as breast cancer: locally / independent committee / national registry
- Controls were often screened at end of trial – after 4-10 years
- Little effect on mortality expected within first 5 years
- Considered 10-15 years follow-up as most relevant
- All age groups considered

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Breast cancer mortality – meta-analysis of relative risks
based on data in Cochrane Review, 13 years of follow-up
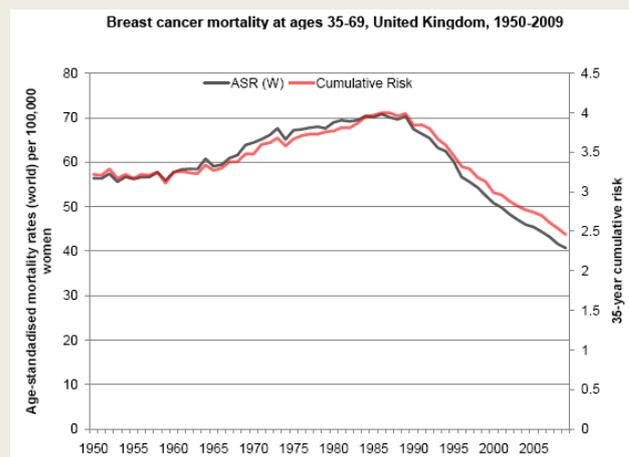

Breast cancer mortality – meta-analysis

- Overall relative risk (invited vs. controls) is 0.80 (95% CI 0.73 to 0.89)
- 20% reduction in breast cancer mortality
- Some heterogeneity
- Not dissimilar to other meta-analyses

- External biases
  - Screening frequency, screening duration, age group
  - Screening technology, current treatments
- How much uncertainty?
- More contemporary estimates of relative risk?

Breast cancer mortality: observational studies

- More recent
- More prone to internal biases
- More prone to publication bias

- Ecological studies – comparing areas or periods when screening was or was not in place.
- Case-control studies – comparing screening history between women dying of breast cancer and controls

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Breast cancer mortality: ecological studies

Breast cancer mortality at ages 35-69, United Kingdom, 1950-2009

Very diverse findings – treatment and services have changed substantially: estimating the (smaller) contribution of screening unreliable.

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Breast cancer mortality: examples of case-control studies

	Puliti 2008	Fielder 2004
Age group	50-74	50-74
Control matching	Age + residence	Age + GP practice
Unadjusted odds ratio	0.46 (0.38 to 0.56)	0.49 (0.36 to 0.66)
Self-selection adjustment	Women in non-screening areas	Women in same area prior to screening
Adjusted odds ratio	0.55 (0.36 to 0.85)	0.75 (0.49 to 1.14)

Generally showed more benefit than the trials but this may reflect residual bias. Results are in the same direction as the trials.

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Breast cancer mortality – absolute benefit

- Estimates vary between one breast cancer death prevented per 100 women screened to one prevented per 2000 women invited to screening
  - Extrapolation from individual trials
  - Absolute risks observed in trials

- Absolute benefit depends on age, duration of screening, length of follow-up

- Panel assumed effect on mortality only seen at ages 55-79 (i.e. 5-10 years after screening ages 50-69)

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Absolute benefit calculations

- Current risk of death from breast cancer between ages 55-79 for UK women aged 50 is 1.70%. This figure includes benefit of screening.
- Without screening, 1.70% would be 2.13% [2.13 x 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
- One breast cancer death prevented for every 180 women screened
- The UK screening programme prevents 1300 breast cancer deaths per year

- Figures have the same uncertainties as for the calculation of relative risk reduction

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Overdiagnosis

- Definition: Detection of cancers on screening that would not have been found in the woman's lifetime 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

- Neither a woman nor her doctor will ever know whether a breast cancer found represents overdiagnosis

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Overdiagnosis – compensatory drop
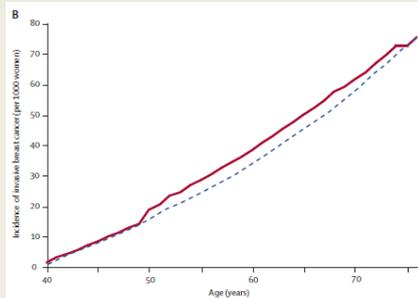
Full compensatory drop
= No overdiagnosis
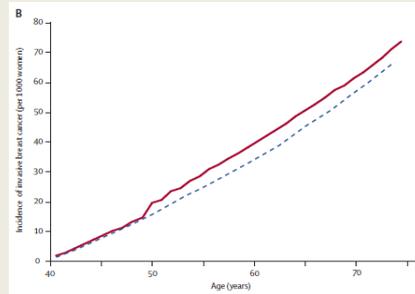
No compensatory drop
= Overdiagnosis

How to estimate overdiagnosis

- RCT of women invited to screening for 20 years aged 50-70 compared with an uninvited control group

- Follow-up to death

- Any excess of breast cancers in the invited group would represent overdiagnosis

- Such a study does not exist
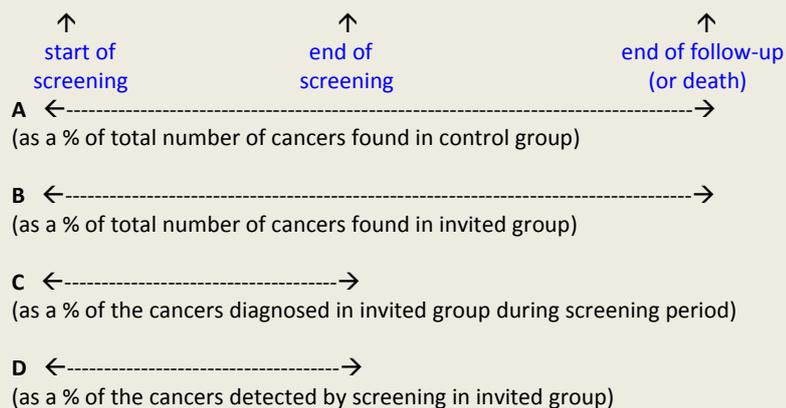
Overdiagnosis – estimate from RCTs

- Need to follow-up beyond screening period – minimum 5-10 years after end of screening
- Screening of the control group will lead to underestimate of overdiagnosis
- Only 3 trials did not have screening of control group – Malmo I, Canada I and II

Proportion of cancers that are overdiagnosed

- Agreement on the numerator
- No agreement on the denominator – a % of what?
- At least 10 different ways of estimating it

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Overdiagnosis – four denominators

↑   ↑   ↑
start of   end of   end of follow-up
screening   screening   (or death)

A ←--→
(as a % of total number of cancers found in control group)

B ←--→
(as a % of total number of cancers found in invited group)

C ←----------------------------------→
(as a % of the cancers diagnosed in invited group during screening period)

D ←----------------------------------→
(as a % of the cancers detected by screening in invited group)

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Overdiagnosis – estimate from RCTs

	A	B	C	D
Malmö I ages 55-69	11.7% (82/698)	10.5% (82/780)	18.7% (82/438)	29.1% (82/282)
Canada I	14.1% (82/581)	12.4% (82/663)	22.7% (82/361)	29.4% (82/279)
Canada II	10.7% (67/626)	9.7% (67/693)	16.0% (67/420)	19.8% (67/338)

Meta-analysis – overdiagnosis as a % of cancers diagnosed in the invited group during screening period
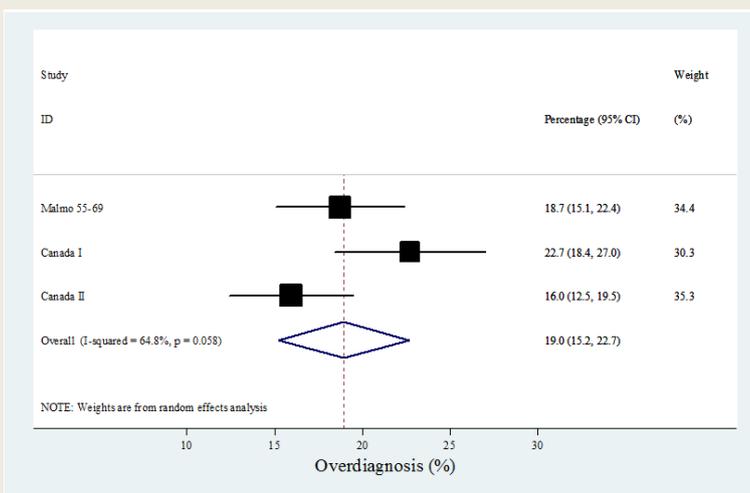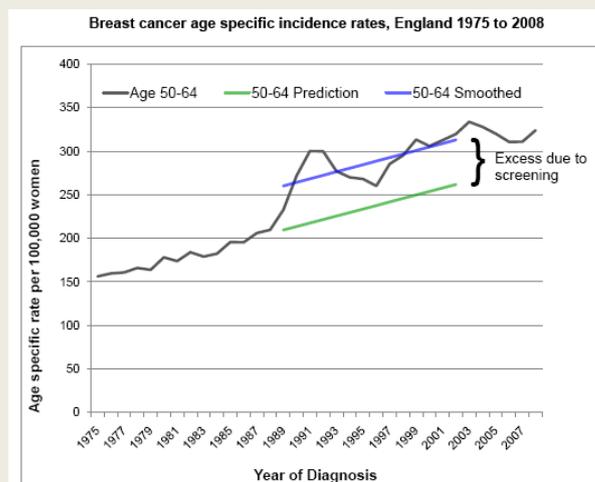
Overdiagnosis calculations

- Estimate that 19% of cancers diagnosed in invited women during the screening period are overdiagnosed
- Applying this to the current incidence of breast cancer (invasive and in-situ) in UK women aged 50-69, gives a risk of overdiagnosis of 129 per 10,000 women invited to screening

- One in 77 women aged 50 invited to screening for 20 years would have an overdiagnosed cancer
- 4000 breast cancers overdiagnosed per year in the UK through the screening programme

- Estimate is derived from limited data and shares similar uncertainties to the mortality data

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Overdiagnosis – time-trend studies

Compare post-screening incidence breast cancer with extrapolation of pre-screening incidence:

Breast cancer age specific incidence rates, England 1975 to 2008

— Age 50-64   — 50-64 Prediction   — 50-64 Smoothed

Age specific rate per 100,000 women

Excess due to screening

Year of Diagnosis

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Overdiagnosis – time-trend studies

Choice of assumptions:
- Pre-screening era (e.g. 1975-84, 1979-88)
- Screening era (e.g. 1989-2002, 1993-2004)
- Target screening age (e.g. 50-64, 50-69)
- Post-screening age group (e.g. 65-74, 70-79)
- Compensatory drop (rate ratio, absolute difference)
- Regression (linear for rates, Poisson for counts)

2250 models for England data
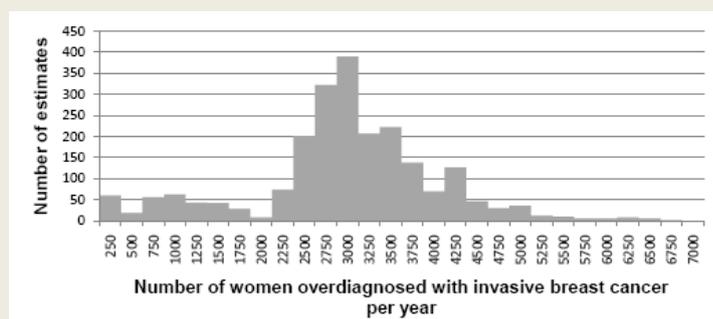
Other harms

For example:
- False positives
- Biopsy rate
- Complications of surgery, radiotherapy, chemotherapy
- Psychological effects

All important but magnitude generally agreed and mortality risks outweighed by survival benefit

Panel's main conclusions

1. Breast screening extends lives
2. The UK breast screening programmes should continue

3. Overdiagnosis occurs
4. Balance of benefits and harms should be communicated to all women invited for screening, so they can make an informed decision

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Balance of benefit and harm

Benefit: breast cancer deaths

- ~ 20% relative risk reduction
- Absolute risk reduction of ~ 0.43%
- One death prevented per ~ 235 women invited to screening
- ~ 1300 deaths prevented per year in UK

Harm: overdiagnosis of breast cancer

- ~ 19% of cancers diagnosed in women aged 50-69 represent overdiagnosis
- Absolute risk of ~ 1.3%
- One overdiagnosis per ~ 77 women invited to screening
- ~ 4000 overdiagnosed cancers per year in UK

For each death prevented, there are about 3 cases overdiagnosed

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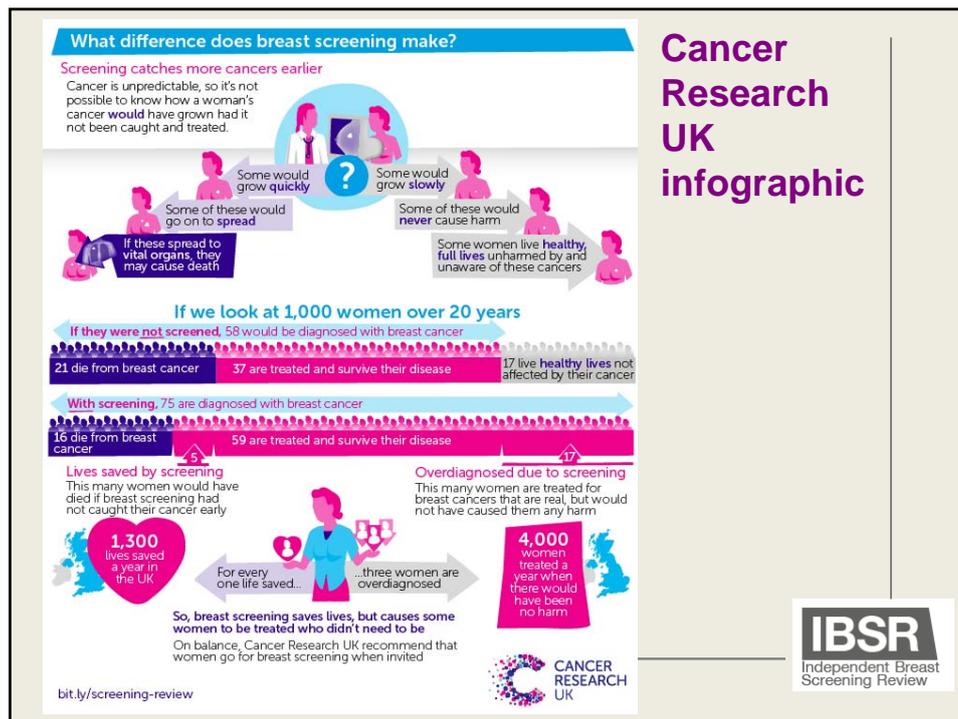
Panel's research recommendations

- Support the ongoing meta-analysis of centrally collated individual participant data from all the trials

- Work to more accurately estimate and identify overdiagnosis

- RCTs of treatment for screen-detected DCIS, and studies of its natural history

- Re-evaluate the cost-effectiveness of the UK screening programme

Acknowledgements

- Members of the Panel
- Experts who provided verbal and/or written evidence
- DH and CRUK who funded the support for the Review

Publications

1. Lancet article, www.thelancet.com 30 Oct 2012
2. Full report, www.cruk.org.uk/breastscreeningreview

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