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

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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

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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.

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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

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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

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The Review

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)

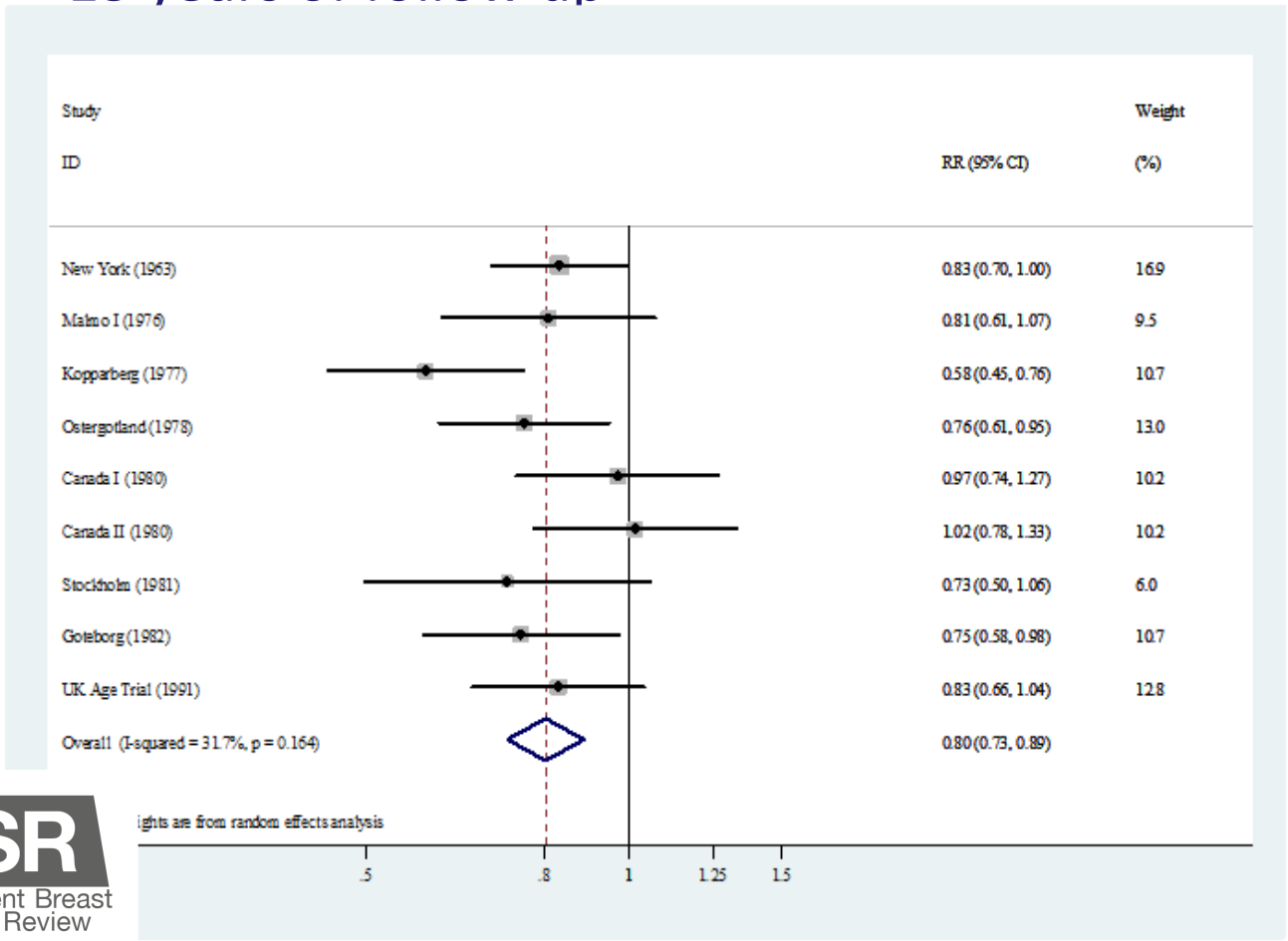
b. observational studies

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



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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

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Mortality – Meta analysis

Table 2

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

	Overall RR (95% CI)
This review	
13-year follow-up in trials reported in the Cochrane Review[5] random-effects meta-analysis	0·80 (0·73–0·89)
Cochrane review[5]	
Fixed-effect meta-analysis of the above trials	0·81 (0·74–0·87)
As above, but excluding women <50 years	0·77 (0·69–0·86)
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	0·85
US Task Force[9]	
RR 0·86 (95% CI 0·75–0·99) 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	0·81
Canadian Task Force[4]	
Routinely screening for 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 criteria[11]	0·79 (0·68–0·90)
Duffy et al, 2012[10]	
Review of all trials and age groups	0·79 (0·73–0·86)

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%
- This figure includes benefit of screening

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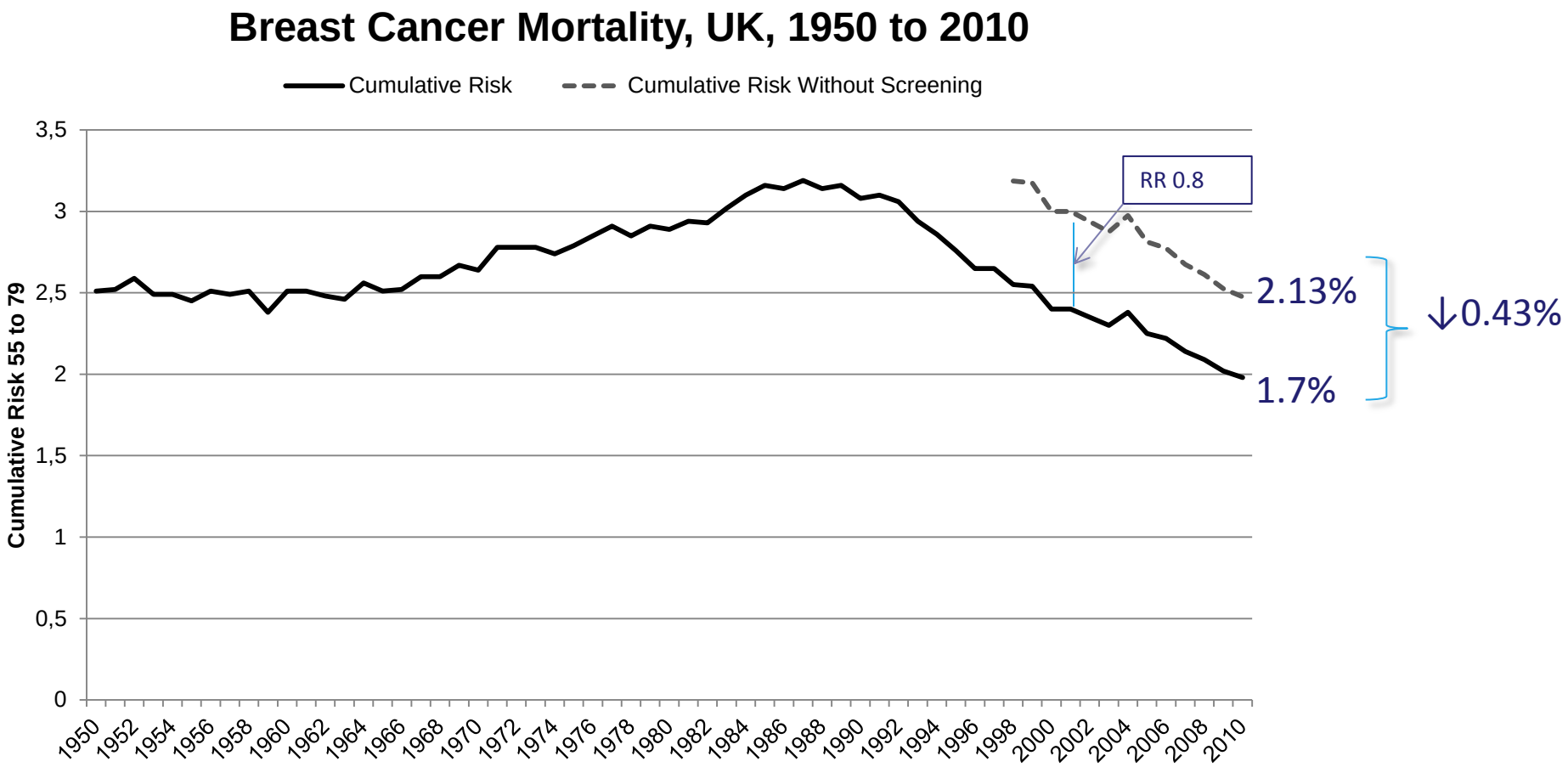
Mortality – Absolute benefit

- 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
- 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



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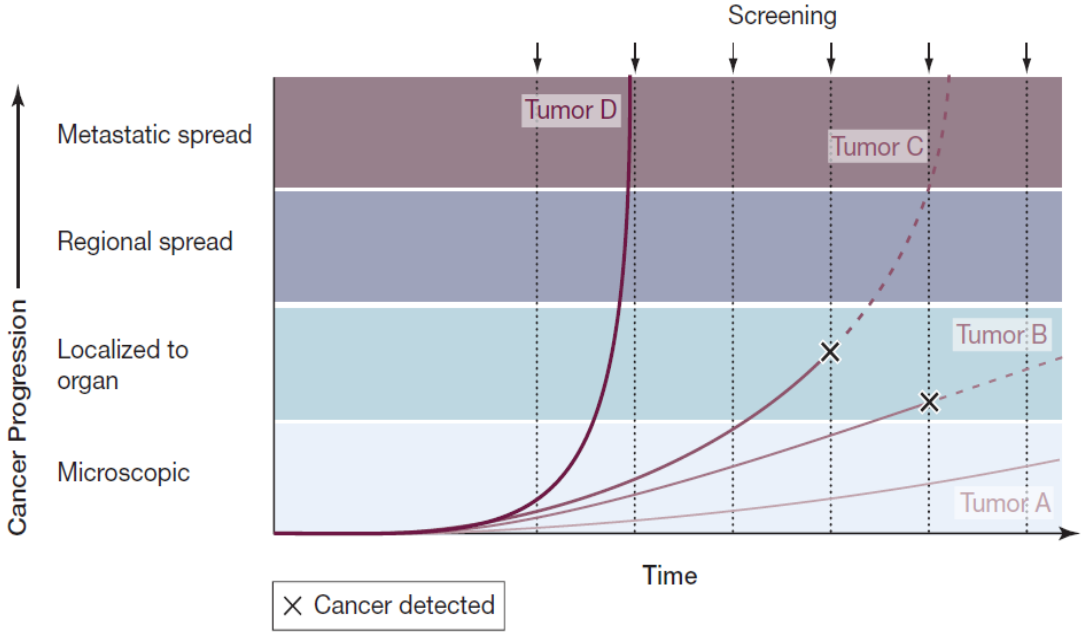
Overdiagnosis

- 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

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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

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Overdiagnosis – estimate from RCT's

	A	B	C	D
Malmö I 55-69	11.7% (82/698)	10.5% (82/780)	18.7% (82/438)	29.1% (82/282)
Canada 1	14.1% (82/581)	12.4% (82/663)	22.7% (82/361)	29.4% (82/279)
Canada 2	10.7% (67/626)	9.7% (67/693)	16.0% (67/420)	19.8% (67/338)

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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.

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Overdiagnosis – observational studies

- 1. Compare post-screening incidence breast cancer (BC) with extrapolation of pre-screening incidence: depends heavily 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……

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Estimating overdiagnosis

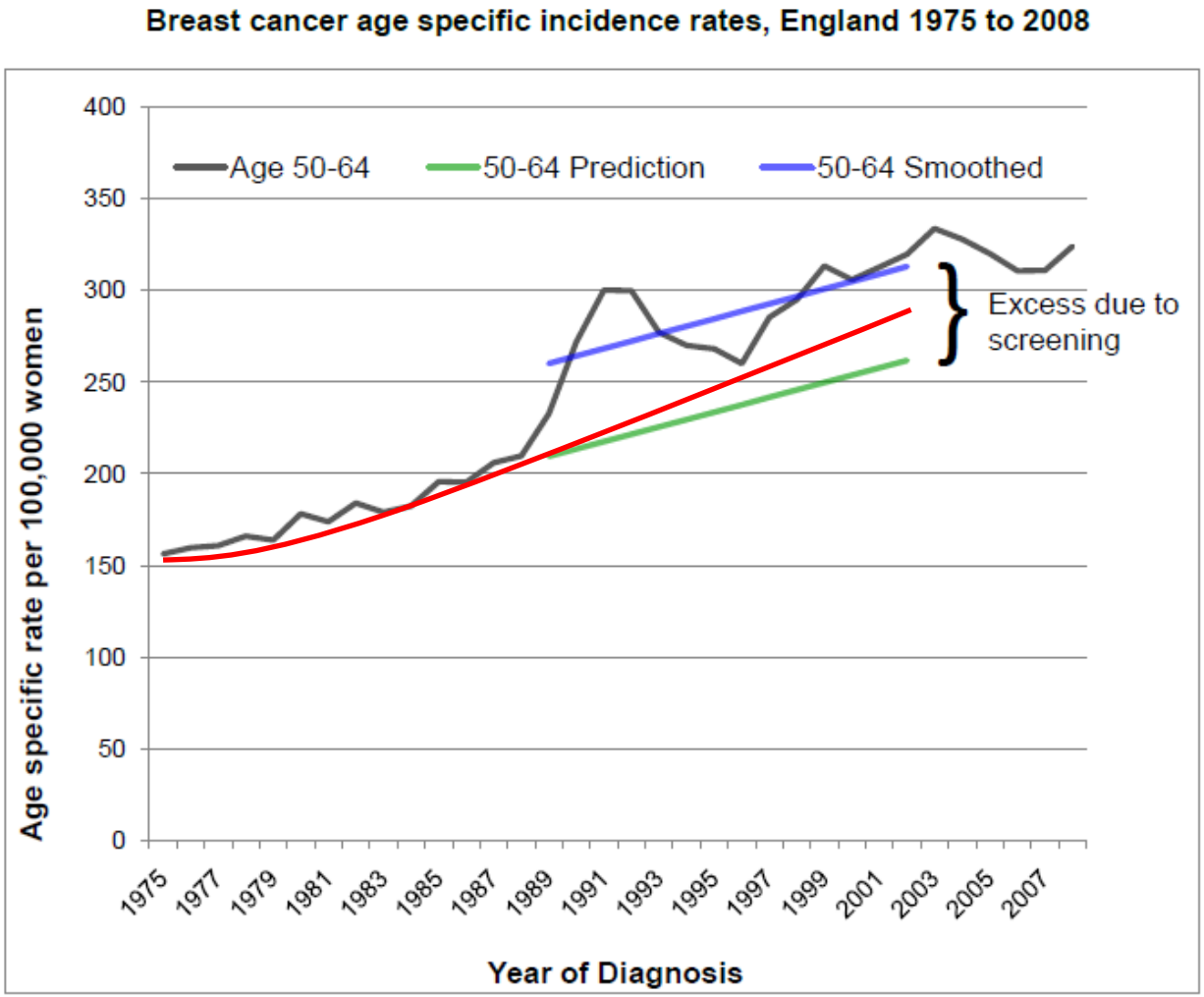

Figure 1 Breast cancer age specific incidence rates, England 1975 to 2008, age 50-64 with expected, observed and smoothed data

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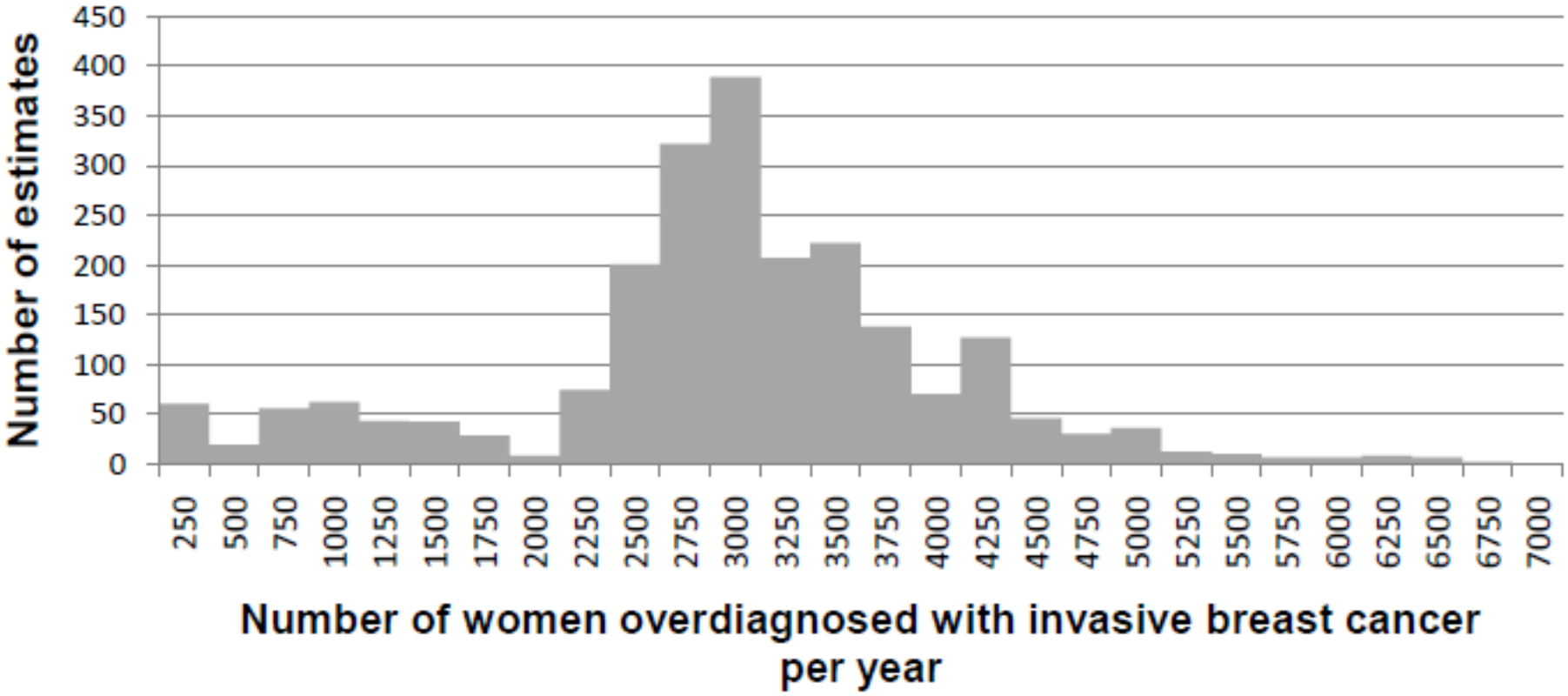
Assumptions

– Same dataset can give different answers:



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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?

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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

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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

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Overdiagnosis

Best estimate is

- 11% of cancers diagnosed during lifetime during and after screening
- 19% of cancers diagnosed during the screening period

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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

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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

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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

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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

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