

The Benefits and Harms of Breast Cancer Screening:

An Independent Review

Authors:

**The Independent UK Panel on Breast Cancer
Screening**



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(England).**

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Members of the Independent UK Panel on Breast Cancer screening:

Chair: Professor Sir Michael G Marmot, professor of epidemiology and public health and director of the Institute of Health Equity at University College, London

Panel members:

- Professor **Douglas Altman**, director of the centre for statistics in medicine at the University of Oxford
- Professor **David Cameron**, professor of oncology and clinical director of the Edinburgh Cancer Research Centre
- Professor **John Dewar**, consultant and honorary professor of clinical oncology at Dundee University
- Professor **Simon Thompson**, director of research in biostatistics at the University of Cambridge
- **Maggie Wilcox**, patient advocate

Executive summary

Introduction

The Breast Cancer Screening Programmes in the UK currently invite women aged 50-70 years for screening mammography every three years. Since the screening programmes were established, there has been debate, at times sharply polarised, over the magnitude of their benefit and harm, and the balance between them. The expected major benefit is reduction in mortality from breast cancer. The major harm is overdiagnosis and its consequences; overdiagnosis refers to the detection of cancers on screening that would not have become clinically apparent in the woman's lifetime in the absence of screening.

Professor Sir Mike Richards, National Cancer Director, England, and Dr Harpal Kumar, Chief Executive Officer of Cancer Research UK, asked Professor Sir Michael Marmot to convene and chair an independent Panel to review the evidence on benefits and harms of breast screening in the context of the UK breast screening programmes. The Panel, authors of this report, reviewed the extensive literature and heard testimony from experts in the field who were the main contributors to the debate.

The nature of information communicated to the public, which too has sparked debate, was not part of the terms of reference of the Panel, which are listed in Appendix 1 of the full report.

Relative mortality benefit

The purpose of screening is to advance the time of diagnosis so that prognosis can be improved by earlier intervention. A consequence of earlier diagnosis is to increase the apparent incidence of breast cancer in a screened population and to extend the average time from diagnosis to death, even were screening to confer no benefit. The appropriate measure of benefit, therefore, is reduction in mortality from breast cancer in women offered screening compared to women not offered screening.

In the Panel's judgement the best evidence for the relative benefit of screening on mortality reduction comes from 11 randomised controlled trials (RCTs) of breast screening. Meta-analysis of these trials with 13 years of follow-up estimated a 20% reduction in breast cancer mortality in women invited for screening. The relative reduction in mortality will be higher for women actually attending screening but by how much is difficult to say because women who do not attend are likely to have a different background risk. Three types of uncertainty surround this estimate of 20% reduction in breast cancer mortality. The first is statistical: the 95% confidence interval around the relative risk reduction of 20% was 11% to 27%. The second is bias: there are a number of potential sources of distortion in the trials that have been

widely discussed in the literature ranging from sub-optimal randomisation to problems in adjudicating cause of death. The third is the relevance of these old trials to the current screening programmes. The Panel acknowledged these uncertainties, but concluded that a 20% reduction is still the most reasonable estimate of the effect of the current UK screening programmes on breast cancer mortality. Most other views of the RCTs have yielded similar estimates of relative benefit.

The randomised controlled trials were all conducted at least 20-30 years ago. More contemporary estimates of the benefit of breast cancer screening come from observational studies. The Panel reviewed three types of observational studies. The first were ecological studies comparing areas, or time periods, when screening programmes were and were not in place. These have generated diverse findings, partly because of the major advances in treatment of breast cancer, which have a demonstrably larger influence on mortality trends than does screening, and partly because of the difficulty of excluding imbalances in other factors that could affect breast cancer mortality. The Panel did not consider these studies helpful in estimating the effect of screening on mortality. The other two types of study, case-control studies and incidence-based mortality studies, showed breast screening to confer a greater benefit than did the trials. Although these studies, in general, attempted to control for non-comparability of screened and unscreened women, the Panel was concerned that residual bias could inflate the estimate of benefit. However, the Panel notes that these studies' findings are in the same direction as the trials.

Absolute mortality benefit

Estimates of absolute benefit of screening have varied from one breast cancer death avoided for 2000 women invited to screening to one avoided for about 100 women screened, about a twenty-fold difference. Major determinants of that large variation are the age of women screened and the durations of screening and follow-up. The age of the women invited is important, since mortality from breast cancer increases markedly with age. The Panel therefore applied the relative mortality reduction of 20% to achieve the observed cumulative absolute risk of breast cancer mortality over the ages 55-79 years for women in the UK – assuming that women who began screening at 50 would gain no benefit in the first five years, but that the mortality reduction would continue for 10 years after screening ended. This yielded the estimate that for every 235 women invited to screening one breast cancer death would be prevented; correspondingly 180 women would need to be screened to prevent one breast cancer death. Uncertainties in the figure of a 20% relative risk reduction would carry through to these estimates of absolute mortality benefit. Nonetheless the Panel's estimate of benefit is in the range of one breast cancer death prevented for approximately 250 women invited, rather than the range of one in 2000.

Overdiagnosis

The major harm of screening considered by the Panel was that of overdiagnosis. Given the definition of an overdiagnosed cancer, either invasive or non-invasive, as one diagnosed by screening that would not otherwise have come to attention in the woman's lifetime, there is need for long follow-up to assess the frequency of overdiagnosis. In the view of the Panel, some cancers detected by screening will be overdiagnosed, but the uncertainty surrounding the extent of overdiagnosis is greater than that for the estimate of mortality benefit because there are few sources of reliable data. The issue for the UK screening programmes is the magnitude of overdiagnosis in women who have been in a screening programme from age 50-70, then followed for the rest of their lives. There are no data to answer this question directly. Any estimate will therefore be, at best, provisional.

While the definition of an overdiagnosed case, and thus the numerator in a ratio, is clear, the choice of denominator has been the source of further variability in published estimates. Different studies have used: only the cancers found by screening; cancers found during the whole screening period, both screen detected and interval; cancers diagnosed during the screening period and for the remainder of the women's lifetime. The Panel focused on two estimates, the first from a population perspective using as the denominator the number of breast cancers, both invasive and ductal carcinoma in situ (DCIS), diagnosed throughout the rest of a woman's lifetime after the age that screening begins and the second from the perspective of a woman invited to screening using the total number of breast cancers diagnosed during the screening period as the denominator.

The Panel thought that the best evidence came from three RCTs that did not systematically screen the control group at the end of the screening period and followed these women for several more years. The frequency of overdiagnosis was of the order of 11% from a population perspective, and about 19% from the perspective of a woman invited to screening. Trials that included systematic screening of the control group at the end of the active part of the trial were not considered to provide informative estimates of the frequency of overdiagnosis.

Information from observational studies was also considered. One method that has been used is investigation of time trends in incidence rates of breast cancer for different age groups over the period that population screening was introduced. The published results of these studies varied greatly and have been interpreted as providing either reassurance or cause for alarm. So great was the variation in results, that the Panel conducted an exercise: by varying the assumptions and statistical methods underlying these studies, using the same datasets, estimates of overdiagnosis rates were found to vary across the range of 0% to 36% of invasive breast cancers diagnosed during the screening period. The Panel had no reason to

favour one set of estimates over another and concluded that this method could give no reliable estimate of the extent of overdiagnosis.

Were it possible to distinguish at screening those cancers that would not otherwise have come to attention from those that, untreated, would lead to death, the overdiagnosis problem could be much reduced, at least in terms of unnecessary worry and treatment. Currently this is not possible, so neither the woman nor her doctor can know whether a screen detected cancer is an “overdiagnosed” case or not. In particular, DCIS, most often diagnosed at screening, does not inevitably equate to “overdiagnosis” – screen detected DCIS, after wide local excision only, is associated with subsequent development of invasive breast cancer in 10% of women within 10 years.

The consequences of overdiagnosis matter: women are turned into patients unnecessarily, surgery and other forms of cancer treatment are undertaken, and quality of life and psychological well-being are adversely affected.

The balance of benefit and harm

The Panel estimates that an invitation to breast screening delivers about a 20% reduction in breast cancer mortality. For the UK screening programmes, this currently corresponds to about 1,300 deaths from breast cancer being prevented each year, or equivalently about 22,000 years of life being saved. However this benefit must be balanced against the harms of screening, especially the risk of overdiagnosis. In the Panel’s view, overdiagnosed cancers certainly occur, but the frequency in a screening programme of 20 years duration is unknown. Estimates from trials of shorter duration suggest overdiagnosis of about 11% as a proportion of breast cancer incidence during the screening period and for the remainder of the woman’s lifetime, or equivalently about 19% as a proportion of cancers diagnosed during the screening period. Any excess mortality stemming from the investigation and treatment of breast cancer is considered by the Panel to be small and considerably outweighed by the benefits of treatment. Some other harms, including increased anxiety and discomfort caused by screening, are also acknowledged.

Notionally, for 10,000 women invited to screening from age 50 for 20 years, it is estimated that 681 cancers (invasive and DCIS) will be diagnosed of which 129 will represent overdiagnosis (using the 19% estimate of overdiagnosis) and 43 deaths from breast cancer will be prevented.

Given that the treatment for breast cancer has improved, is screening no longer relevant? The Panel’s view is that the benefits of screening and those of better treatments are reasonably considered independent. Uncertainty about possible interaction between the benefits of screening and of contemporary treatments is not a reason for stopping breast screening.

The Panel was not asked to comment on costs, both of interventions and the consequences of overdiagnosis. With accurate figures an estimate of cost-benefit could be made and compared with other interventions but would be a significant piece of work in its own right.

An individual woman cannot know whether she is one of the number who will benefit or be harmed from screening. If she chooses to be screened it should be in the knowledge that she is accepting the chance of benefit, having her life extended, knowing that there is also a risk of overdiagnosis and unnecessary treatment. Similarly, a woman who declines the invitation to screening needs to recognise that she runs a slightly higher risk of dying from breast cancer.

Conclusions and recommendations

Breast screening extends lives. The Panel's review of the evidence on benefit – the older randomised controlled trials, and those more recent observational studies – points to a 20% reduction in mortality in women invited to screening. A great deal of uncertainty surrounds this estimate but it represents the Panel's overview of the evidence. This corresponds to one breast cancer death averted for every 235 women invited to screening for 20 years, and one death averted for every 180 women who attend screening.

The Panel's best estimate is that the breast screening programmes in the UK, inviting women aged 50-70 every three years, prevent about 1300 breast cancer deaths a year, a most welcome benefit to women and to the public health.

But there is a cost to women's well-being. In addition to extending some lives by early detection and treatment, mammographic screening detects cancers, proven to be cancers by pathological testing, that would not have come to clinical attention in the woman's life were it not for screening – overdiagnosis. The consequence of overdiagnosis is that women have their cancer treated by surgery, radiotherapy and medication, but neither the woman nor her doctor can know whether this particular cancer would be one that could possibly lead to death, or one that would have remained undetected for the rest of the woman's life.

The Panel sought to estimate the level of overdiagnosis in women screened for 20 years and followed to the end of their lives. Estimates of overdiagnosis abound, from close to zero to 50%, but there is a paucity of reliable data to answer this question. There has not even been agreement on how to measure overdiagnosis. Based on follow-up of three randomised controlled trials, the panel estimated that in women invited to screening, about 11% of the cancers diagnosed in their lifetime constitute overdiagnosis, and about 19% of the cancers diagnosed during the period that

women are actually in the screening programme. But, the Panel emphasises, these figures are the best estimates from a paucity of reliable data.

Putting together benefit and overdiagnosis from the above figures, the Panel estimates that for 10,000 UK women invited to screening from age 50 for 20 years, about 681 cancers will be found of which 129 will represent overdiagnosis, and 43 deaths from breast cancer will be prevented. In round terms, therefore, for each breast cancer death prevented about three overdiagnosed cases will be identified and treated. Of the approximately 307,000 women aged 50-52 who are invited to screening each year, just over 1% would have an overdiagnosed cancer during the next 20 years. Given the uncertainties around the estimates, the figures quoted give a spurious impression of accuracy.

The Panel concludes that the UK breast screening programmes confer significant benefit and should continue. The greater the proportion of women who accept the invitation to be screened, the greater is the benefit to the public health in terms of reduction in mortality from breast cancer. But for each woman the choice is clear: on the plus side screening confers a likely reduction in mortality from breast cancer because of early detection and treatment. On the negative side, is the knowledge that she has perhaps a 1% chance of having a cancer diagnosed, and treated with surgery and other modalities, that would never have caused problems had she not been screened.

Evidence from a focus group conducted by Cancer Research UK and attended by two panel members, and in line with previous similar studies, was that this was an offer many women will feel is worth accepting: the treatment of overdiagnosed cancer may cause suffering and anxiety but that suffering is worth the gain from the potential reduction in breast cancer mortality. Clear communication of these harms and benefits to women is of utmost importance and goes to the heart of how a modern health system should function. There is a body of knowledge on how women want information presented, and this should inform the design of information to the public.

