Breast screening:
a question of pros and cons
not right or wrong

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Decades after breast screening programmes first started, their value remains hotly disputed. Some lives are saved, but it's hard to tell how many. False-positives are a problem, but it's a risk some are happy to take. Women need to weigh up for themselves the pros and cons of attending screening – but they can only do so if they are given clear, unbiased information.

In June 2002, a Global Summit on Mammographic Screening was convened in Milan to examine the controversy created by a *Lancet* article and a Cochrane review, which suggested there was no evidence to support the efficacy of breast screening to reduce cancer deaths. The summit, chaired by Umberto Veronesi, was one of several groups looking again at the data on breast cancer screening, and the stir created by the Cochrane reviewers was by no means the first to ripple through the screening community.

But the conclusions from the summit and from many commentators afterwards were unequivocal – mammographic screening was effective. As Peter Boyle, now head of the International Agency for Research on Cancer (IARC), which re-examined the studies, wrote in an editorial in the *Annals of Oncology*, "Taking all the criticism into account, it was still possible to conclude that screening mammography reduced the mortality from breast cancer in women receiving an invitation to be screened in well-organised clinical trials: the reduction in breast cancer mortality appeared to be between 21% and 23% according to recent estimates. There were no grounds for stopping on-going screening programmes nor planned programmes."

The phrase most widely used was: "It's time to move on." But the Cochrane reviewers have continued to update their study and the latest version (published in 2006) still reaches more or less the same conclusion: "It is not clear whether screening does more good than harm." Given the Cochrane Collaboration is one of the most widely respected sources of systematic reviews, the controversy about mammographic screening is still very much an issue – as evidenced by a very public confrontation over an article withdrawn in 2006 from publication in the *European Journal of Cancer* that examined further (and criticised) the quality of data in one of the key screening trials, the Swedish two-county trial (the paper has since been published by the *Danish Medical Bulletin*).

Peter Gøtzsche and Ole Olsen (Margrethe Nielsen in the 2006 update) are the two Denmark-based Cochrane authors, and it is important to note that their review is only of randomised controlled trials that compared women invited to screening with non-invited controls, and that there are relatively few (seven met the inclusion criteria), and most were started some time ago (one as far back as 1963). There are many points made about methodological weaknesses, not surprisingly as trial methods have evolved for the better, but as Gøtzsche comments there are two key issues that stem from their analysis.

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Questionable data

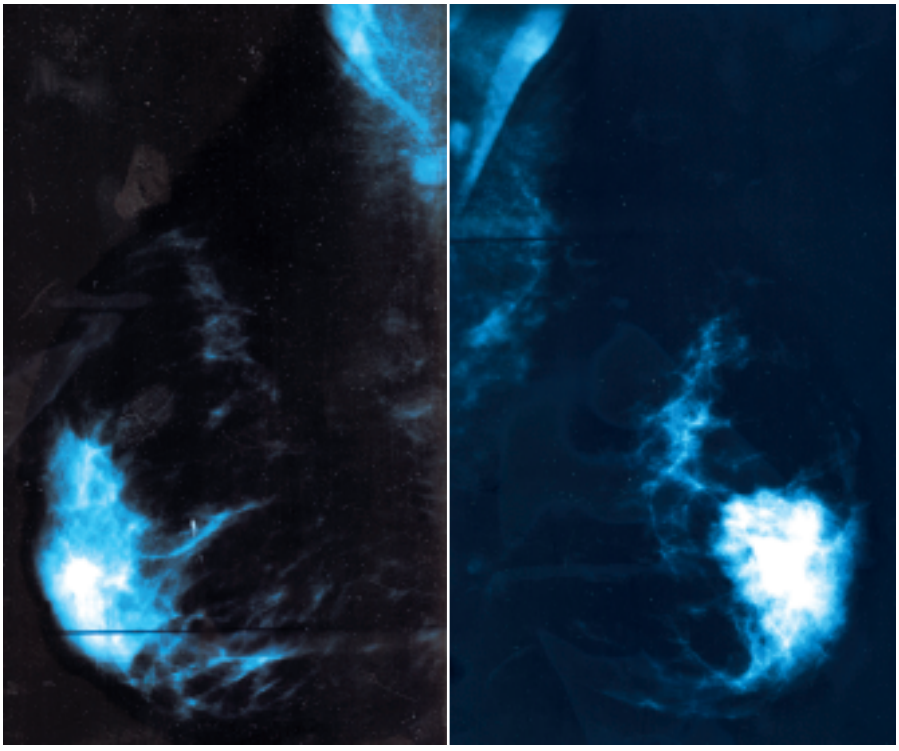
The first is that judging the main outcome target of the trials – assignment of death from breast cancer – is "unreliable and biased in favour of screening". The two best trials (in terms of the quality of randomisation) in fact showed no benefit. "Also, no mortality benefits were shown for overall mortality and all cancer mortality, which is interesting as misdiagnosis of death often concerns other cancers," says Gøtzsche. In other words, they called into question breast cancer mortality as an outcome.

The other big issue he raises is overdiagnosis. This applies especially to ductal carcinoma in situ (DCIS) – only detectable by conventional mammography or other techniques such as MRI – and also to slow-growing and benign cancers. Gøtzsche says he was surprised that the issue of overdiagnosis and overtreatment had not been more widely discussed before it was raised in his *Lancet* article, and notes that only half of detected DCIS progress to invasive cancer, and that inevitably there is unnecessary intervention.

"I'm still worried that it is not possible to see an effect on cancer mortality as such, but it would be unexpected if there was no effect at all measured by the trials. We do think there is a minor effect of screening. We don't know exactly how big it is, but we have come up with an estimate, a 15% relative risk reduction, which is close to the US Preventive Services Task Force estimate of 16%. So personally I think it is a realistic guess."

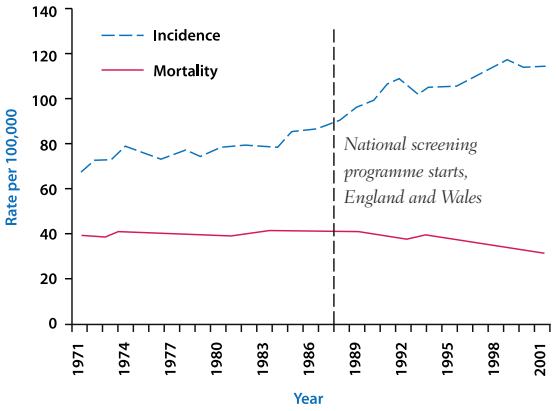
As Gøtzsche and Nielsen report, their 15% estimate translates into the estimate that for every 2,000 women invited for screening over 10 years, one will have her life prolonged but 10 healthy women will be unnecessarily diagnosed as cancer patients and treated unnecessarily. Gøtzsche qualifies the 15% figure by pointing out it is for all ages in the trials, not the higher-risk older groups, as the differences between the age groups were relatively minor. The US Taskforce found 'fair evidence' that mammography screening every 12–33 months significantly reduces mortality from breast cancer, especially in the 50–69 age group.

Most other reviewers, including the US Task Force and the IARC, consider that the quality of the trials has come in for unjustifiable criticism by the Cochrane reviewers, and there are many other types of study, such as national comparisons of age cohorts, that have added to the evidence base in favour of screening. The IARC's estimate of a 25% reduction in mortality in women first invited for screening between the ages of 50 and 69, based on an intention to treat analysis, implies a 35% reduction for women who are screened regularly, and is widely quoted.



Misleading. Mammography can be particularly unreliable for women with dense breast tissue. These images were not interpreted as suspicious, but cancer was detected by ultrasound three months later

MAKING SENSE OF THE STATISTICS



Following the introduction of the national screening programme in England and Wales, more women are being diagnosed with breast cancer but fewer are dying of it. Does this show that screening saves lives through earlier detection? Or is mammography simply identifying lesions that would never have gone on to become invasive cancers? And how much of the improvement in survival is due to the introduction of tamoxifen?

Source: UK National Statistics, 2005

What does seem to be emerging now is a stronger consensus that widespread screening for women in the 40–49 age range is not worthwhile, mainly as breast density creates a high false-positive rate and the mortality risk in this group is lower than for older women. This year, the American College of Physicians revised its recommendations from regular screening to advising women to talk to their doctors about whether a mammogram is suitable for them. In the UK, one of the few recent randomised trials, the 'Age' study, has recently reported no significant benefit for this younger age group (Gøtzsche describes this as a 'fine trial' and says it will be added to the Cochrane review). Sue Moss, who runs the UK Cancer Screening Evaluation Unit at the Institute of Cancer Research, says that follow-up with a better powered study will be done. Some countries and regions in countries, advocacy organisations such as the Susan G Komen for the Cure in the US, and bodies such as the American Cancer Society, continue to recommend regular screening from the age of 40.

More attention is now focused on the older, 50–70 years, age group. This is the target for the UK's NHS Breast Screening Programme, which has been screening 1.3 million women a year – about 75% of those invited – according to a 2006 report. This notes that for every 400 women screened regularly over 10 years, one fewer will die, and about 1,400 lives are being saved a year (and this is one of the main public messages of the programme). This is much higher than the Cochrane reviewers' estimate – about five times – and also shows the scale of the gap.

Stephen Duffy, professor of cancer screening at Queen Mary, University of London, and Cancer Research UK, says there are robust data to support the higher benefit. "From empirical data in both randomised trials and service screening programmes, our group has estimated that the benefit of being screened, as opposed to simply being invited to screening, was of the order of a 30–40% reduction in breast cancer mortality. This translates to one life saved per 400–500 women screened over 10 years. This bears out the estimates quoted for the UK programme."

The reasons for the much lower estimates of benefit quoted by others are, he adds, "reliance on guestimation based on personal judgements of the quality of the studies rather than the actual data, the confusion of invitation to screening with actually being screened [typically 25%–30% of those offered screening in the UK do not take it up], and the confusion of period of follow-up with period of screening." Duffy also considers the unreliability of mortality data to be a "red herring" and, as a researcher involved with the Swedish two-county trial and others since the late 1980s, can provide a battery of co-authored papers that address this and other issues such as overdiagnosis.

Practising radiologists tend to be much more circumspect (in part because they have been put on the defensive, considers Duffy). Robin Wilson, a consultant breast radiologist who chairs the NHS's screening radiology coordinating committee in the UK, and is also the screening representative of the European Society of Mastology, is if anything even more critical than Gøtzsche about the quality of the main screening trials. "The truth is the quality of the mammography in the New York trial [the oldest one] was awful, and there were all sorts of flaws in the data and designs of the studies," he says.

"What we do know is that breast cancer mortality has fallen by about 25% in the last 15 years, but of course you cannot attribute all that to screening. It is a combination of screening and better treatment, in particular the use of tamoxifen." A UK study reporting on a 21% reduction in death from breast cancer attributed 6.4% of the 21% to screening, the rest to better treatment and earlier diagnosis independent of screening. "Bear in mind this was

Some countries still recommend screening from age 40

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early on in the screening rollout, and we knew we were not seeing the full effect," says Moss.

Another factor in recent years is the impact of warnings about hormone replacement therapy (HRT) and its association with breast cancer. In the US, a study reported rising breast cancer incidence until the take up of mammography levelled off, and then a decline, with a big decrease in 2002–2003, which is probably attributable to less use of HRT. Attempts have also been made to distinguish between the effect of screening and adjuvant therapy on mortality – a US consortium came up with a wide range – the total mortality reduction contributed by screening varied from 28% to 65%, with adjuvant treatment contributing the rest.

Improving quality of care

For Wilson, the actual impact of screening on its own is of less importance than its contribution to the overall standard of care and treatment. "It is true that it does not save as many lives as we thought it would, but if you look at countries that have screening and compare them with those that don't, the standard of care is usually much higher in the former. In the UK it has helped improve care out of all recognition – and we also see big differences in standards between units that carry out screening and those that just offer symptomatic breast care."

Wilson notes that a revision to the NHS cancer strategy will recommend that symptomatic breast investigations should only be done in centres where screening is carried out. As he adds, there are only 105 screening centres in the UK, but some 3000 in France, which are mainly office-based units, where the only solution to keeping them going has been to send results to central locations for reading. If quality of screening is often raised as an issue in Europe, it is certainly a big problem in the US – as many as 40% of facilities there have been cited for violating federal rules, according to Madelon Finkel in her book *Understanding the Mammography Controversy*.

Jayant Vaidya, a consultant breast surgeon in Dundee, Scotland, who worked with one of screening's greatest critics, Michael Baum, reckons that we should be seeing a steeper mortality decline in the UK, thanks to its structured screening programme, than the US, where screening is "haphazard". "But the slope of decline is not very different," he says.

Early – or rather earlier – detection is the goal of breast screening, but it has led to a large increase in reported cancer incidence and problems with overdiagnosis and overtreatment. "By the time a mammogram detects a cancer it can be already half a centimetre in size and may have lived more than half its lifetime, and can have metastasised," says Vaidya. "Others won't be growing but we don't know which ones."

Treatment of DCIS – very rarely detected before mammography – is fraught with controversy. The US National Cancer Institute (NCI) simply notes: "DCIS can progress to become invasive cancer, but estimates of the likelihood of this vary widely." Vaidya points out that screening mammography does not seem to have reduced the incidence of invasive cancer. Moss says, however, "If you talk to pathologists they say most of the DCIS that gets picked up by screening is high grade."

False-positives

False-positive and overdiagnosis rates vary – they are high in the US, where there is a litigation culture, and of course mammograms also miss cancers. Misleading women about the accuracy of screening was the leading cause of medical negligence claims in the US, according to a 2006 book, *The Death of Mammography*, by Rene Jackson and Alberto Righi, which notes that 700 mammography facilities have shut in recent years. The NCI, in summarising harms of mammography in its Physician Data Query (PDQ) database, currently cites evidence that about a third of screen-detected cancers represent overdiagnosis, half of women screened annually for 10 years will have a false-positive (and a quarter will have biopsies), and 6%–46% of women with invasive cancer will have negative mammograms, especially younger women.

Says Duffy, "Our research on actual screening data arrives at lower estimates of overdiagnosis than those of some colleagues." Wilson considers the rate of overdiagnosis to be more like 9%–10%. "We don't know which ones are harmful, but if you say you have a 30% chance of developing a cancer that kills, very few people will take a risk and not have treatment. Further, very few women complain about being called back – obviously they are worried but they are mostly aware that one in nine of them will get breast cancer." He notes a study that

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shows that women will tolerate a high false-positive rate.

Both he and Gøtzsche agree that much more information about the balance between benefit and harm should be given to women. "We need to be much more honest about the downsides," says Wilson. Gøtzsche, with co-author Karsten Juhl Jorgensen, examined the content of invitations to public screening programmes in a 2006 *BMJ* paper, finding that while information about screening was often provided, it tended to mislead on benefits – such as giving relative, not absolute, risk reductions and not pointing out they apply only to the screening period and not to a lifetime. It was also unclear on the most important harms, with overdiagnosis and over-treatment not mentioned, and other harms "omitted or downplayed".

The important bond between doctor and patient is being bypassed by playing on fear of cancer and setting up appointments that imply a public duty to attend, says Gøtzsche. And of course women invited for screening are not patients – they are healthy citizens, at least for breast cancer. "This I think is the crux of the breast screening debate – the way it is being sold to the public is deeply unethical," he says. In short, Gøtzsche, who says he has received many personal attacks about his work, feels the tension between advocates and critics is still great, at least politically. As Duffy comments, "It is also sad to see the morale of the staff providing the service damaged by unduly pessimistic publications on the subject."

But has the debate moved on? The original *Lancet* paper by Gøtzsche and Olsen called mammography screening "unjustified". Now their message has moderated – it is "unclear". Most responsible advocates of screening are not making highly inflated claims, and warn against complacency in intervening with such large populations.

The uncertainty in this highly complex area is well reflected in most presentations, such as the NCI's PDQ guidelines (although the NCI itself recommends screening from age 40), and on breast charity websites, but it does have to be searched for. Indeed, another large US advocacy organisation, the National Breast Cancer Coalition (NBCC), considers that the "mortality reduction associated with mammography screening is modest, at best … NBCC believes that there is insufficient evidence to recommend for or against screening mammography in any age group of women." In the UK, there has been a move to promote all screening more by choice and informed consent than by herding people blindly in one direction.

Vaidya, who concurs with Wilson that screening has been pivotal to better organisation of cancer services, considers that it is not realistic to think that screening will be abandoned. The way forward, he believes, is through more research on new tools that can differentiate the harmful from the harmless.

That, at least, is something everyone can agree on.

Public duty or personal choice?