
Executive Summary

In the autumn of 2001, the Cochrane Library and The Lancet published the results of a systematic review of randomised trials for early detection of breast cancer by mammography. The reviewers claimed that there was no reliable evidence to support the survival benefit of mammography screening. This has led to many discussions—both in scientific literature and in the lay press. The Dutch Minister of Health, Welfare and Sport requested from the President of the Health Council a rapid answer to the question of whether the outcome of the study, a so-called Cochrane review, nullifies the scientific basis of the current screening programme.

Service screening was gradually introduced, beginning in 1990. In 1999, the most recent year for which reports have been published, 744,000 women aged 50 – 75 years accepted the invitation to screening (78 per cent of those women invited). In 1996, when the screening programme had not yet covered the entire country, there were (according to the Dutch Cancer Registry) 4,400 women between the ages of 50 and 70 who were diagnosed with breast cancer. For half of these women the diagnosis was the result of screening. In 20 per cent of the cases this involved so-called interval cancer (breast cancer diagnosed in the time interval of two years between two successive screenings) and in almost 30 per cent of the cases it involved women who had never been screened. The President of the Health Council set up a committee that has compiled the present advisory report. As part of its work, the committee held a hearing that was attended by experts either involved in or opposed to screening, and re-examined the original studies.

The Cochrane review touches upon an important question: is breast-cancer mortality a valid endpoint for determining the efficacy of breast-cancer screening? This question is related to the ongoing debate on the design, analysis and methodological pitfalls of randomised trials of screening for (breast) cancer.

The Cochrane review is a systematic review (meta-analysis) of the results of published studies (randomised clinical trials or RCTs) into the benefit of population screening for breast cancer. The authors, two scientific staff members at the *Nordic Cochrane Centre* in Copenhagen, consider breast-cancer mortality to be an unreliable outcome. Of the seven eligible RCTs, they found that two were flawed; they were left out of consideration completely. Three of the RCTs were rated as having poor-quality data and the remaining two were rated as having medium-quality data.

The two RCTs of medium quality failed to find a statistically significant reduction in breast-cancer mortality in women who were offered screening. If the data from these two RCTs are combined with those from the RCTs for which the authors gave a quality rating of poor, then the results do, indeed, provide a statistically significant reduction. However, the authors consider breast-cancer mortality to be an unreliable outcome, biased in favour of screening.

On that basis, and assessed by overall (all-cause) mortality among the participants of the two medium-quality trials, they concluded that population screening has no survival benefit.

Furthermore, according to the version of the Cochrane review published by *The Lancet*, screening leads to increased use of aggressive treatment.

The committee endorses the quality criteria for the assessment of the eligible RCTs, but finds that they are inadequately specified and inconsistently applied. As a result, five of seven RCTs are left (completely or partially) outside the analysis and the trial results are weighted differently. Rather than keeping trials out of the analysis, the committee holds that it is better to use another method (sensitivity analysis) to investigate the effect of including or excluding data of lesser quality.

The committee agrees with the Danish scientists that the RCTs examined can be criticized in some respects, particularly in terms of randomisation. But, except for one trial, these shortcomings are not of a nature that renders unusable the published data. The committee does not find the reviewers' arguments convincing for scoring four of the RCTs much lower on methodological grounds than the two 'medium-quality' trials.

The committee considers as too extreme the conclusion that breast-cancer mortality is an unreliable outcome, biased in favour of screening. The Cochrane review

does indeed provide indications for possible sources of bias, but the authors do not provide evidence of important bias in favour of screening.

The committee does not agree with the conclusion that breast-cancer mortality as the primary endpoint must be replaced by overall mortality. They do, indeed, find that the use of breast-cancer mortality as the only outcome may cause one to overlook important harms (or benefits) of screening because of misclassification bias. Therefore, total cancer mortality, other important causes of death, and overall mortality must also be taken into consideration when interpreting the results of (breast-) cancer screening trials.

If screening has a beneficial effect on breast-cancer mortality, it should also be expected to have a (much smaller) beneficial effect on total cancer mortality and an (even smaller) effect on overall mortality. The reviewed RCTs were underpowered for detecting these small effects. Therefore, the requirement should not be that the small differences in question are statistically significant, but that they point in the right direction.

If data from all eligible trials (excluding Edinburgh) are taken into account for women older than 50 years, the relative risk for breast-cancer mortality is 0.72 (0.61 – 0.85) after 7 years, and 0.76 (0.67 – 0.85) after 13 years. In the same way, the relative risk for overall mortality is 0.97 (0.93 – 1.00) after 7 years, and 0.99 (0.97 – 1.02) after 13 years. The Cochrane review does not report the relative risk for total cancer mortality among women older than 50 years separately from that among younger women.

That the RCTs showed no clear reduction in total cancer mortality (all women > 40 years) may be explained by the fact that breast-cancer mortality made up a small proportion of total cancer mortality (11 per cent in the Swedish RCTs). That is much lower than among women of the same age in the general population (24 percent in the Netherlands). This difference arises because women who were diagnosed with breast cancer before randomisation are, rightly, subsequently excluded from analysis because they cannot benefit from screening.

The committee is aware that screening causes an increase in the number of diagnostic procedures. Screening can also lead to treatment among women who would never have known about their breast cancer if it were not for screening, because they would have died from something else before the disease became clinically manifest.

The Cochrane review also draws attention to the possibility of a screening-associated increase in mortality. The authors predict that overall, radiotherapy is harmful for women at low risk of local recurrence, such as those identified by screening. As shown in RCTs carried out before 1975, radiotherapy after

mastectomy results in an excess of cardiovascular deaths. However, this risk is likely to be much lower with modern radiotherapy techniques. No vascular morbidity and mortality have been seen in the medium term (median observation period 10 years) with these techniques.

Screening detects smaller tumours which have not so often spread to the lymph glands. This change in stage distribution means that it is increasingly possible to use less mutilating surgery for these women. Furthermore, they will not as often need adjuvant therapy and regional radiation is less frequently used. The safety and effectiveness of radiotherapy and adjuvant therapy following breast surgery should be monitored (also in the long term) by research and periodic meta-analyses.

The committee finds it of crucial importance that well-balanced, honest advice be provided to the women involved regarding the risks and benefits of population screening. They urge the Ministry of Health, Welfare and Sport and the Health Care Insurance Board's National Coordinating committee for Population Studies to give the necessary attention to this.

The committee sees no scientific basis, in the light of the Cochrane review, to conclude that population screening for breast cancer for women over the age of 50 has no survival benefit. However, it does not rule out the possibility that new evaluations might show that the effect of screening on breast-cancer mortality is lower than was expected in 1990.

The committee therefore instructs that research should be conducted into the causes of declining breast-cancer mortality in the Netherlands. This study, which is already being prepared, will link at the individual level cause-of-death records with screening records and data on treatment. A solution must quickly be found to the problem that women who do not take part in screening cannot give consent to cancer registration, which would provide relevant data for this research.

The Cochrane Breast Cancer Group and the editor of *The Lancet* have argued for a full, independent systematic review based on individual patient data (IPD). This so-called IPD meta-analysis should also include updated outcome data, and should be revised on a regular basis in the light of new data. The committee supports this recommendation.

It is advised that a broadly diverse committee from the Health Council provides advice (in due time, when adequate new data are available) about the balance of risks and benefits of population screening for breast cancer. Updating of an advisory report presented by the Council in 1987 is in any case opportune, because improvements made since then in therapy, early diagnosis, and screening mammography all play roles in decreasing mortality from breast cancer.