

### The Mammography Controversy

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The appropriateness of screening mammography has emerged once again as a contentious issue. This report brings readers up-to-date with the latest developments in this long-running controversy.

#### BACKGROUND

Mammography has been evaluated in several large randomized screening trials beginning with the Health Insurance Plan trial in New York State, conducted in the 1960s [1]. The most recent trials were conducted in Canada in the 1980s [2, 3]. All of the other trials were conducted in Europe [4-8]. Results are summarized in Table 1. The early trials demonstrated consistent reductions in breast cancer mortality, and these led to the general acceptance of mammography as an

important public health intervention [9]. The issue became controversial with the publication of the Canadian study, which showed no benefit for mammography, and with the publication of consensus guidelines by the National Institutes of Health (NIH) that did not support screening for women under 50 years of age [10]. Many organizations have issued screening guidelines that recommend mammography at younger ages, including the U.S. Preventive Services Task Force [11], though other organizations support the NIH position of screening at age 50, notably the Canadian Task Force on Preventive Health Care [12].

Lack of uniformity of guidelines reflects the difficulties in drawing definitive conclusions from the data, and this, in turn, reflects the methodological and logistic challenges of

**Table 1.** Data from randomized mammography trials

Trial	n of subjects		Breast cancer deaths		Relative risk (95% CI) <sup>a</sup>	Total deaths from all causes
	Screen	Control	Screen	Control		
New York <sup>b</sup>	30,239	30,765	218	262	0.83 (0.70-1.00)	4,178
Swedish two-county	77,092	56,000	160	167	0.69 (0.55-0.88)	12,187
Malmo	21,088	21,195	63	66	0.96 (0.68-1.35)	3,586
Gothenburg	11,724	14,217	18	40	0.55 (0.31-0.96)	915
Edinburgh	23,226	21,904	68	76	0.83 (0.58-1.18)	2,764
Stockholm <sup>c</sup>	39,139	20,978	82	50	0.90 (0.63-1.28)	7,109
Canada (age 40-49)	25,214	25,216	29	18	1.36 (0.84-2.21)	315
Canada (age 50-59)	19,711	19,694	107	105	1.02 (0.78-1.33)	1,424

<sup>a</sup>95% confidence intervals: the range of values within which the relative risk can reasonably be expected to lie.

<sup>b</sup>Results for this study obtained from the Cochrane Library (mortality at 13 years).

<sup>c</sup>Results for this study obtained from the recent update of Swedish trials [16].

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evaluating cancer screening in randomized trials. These difficulties stem from the fact that the studies are conducted on healthy women, the vast majority of whom will not experience cancer. Of the small fraction of the participants who develop breast cancer, only a minority die from it. Table 1 shows the relatively small numbers of breast cancer deaths when compared with the huge numbers of participants. This table also shows the estimated reductions in breast cancer mortality in each of the trials. As an example, a relative risk of 0.69, as in the Swedish two-county study, corresponds to a 31% reduction in breast cancer mortality.

The degree to which mammography reduces mortality is an important aspect of the debate. Population screening is expensive, and some women who are screened inevitably receive a false-positive result, leading to unnecessary additional testing, including the chance of invasive surgical procedures. Therefore, in order for screening mammography to be viewed as cost effective by public health policymakers, the magnitude of its impact on mortality must be sufficient to offset the attendant costs and morbidities. This is the major reason why some organizations recommend screening for women over 50 years of age, but do not recommend it for younger women, since the trials show a smaller risk reduction in younger women, a population that has lower breast cancer incidence in the first place.

#### WHAT CAUSED THE NEW CONTROVERSY?

The current controversy arose with the publication in *The Lancet* of a new analysis of the data by two investigators at the Cochrane Center in Copenhagen, *Peter Gøtzsche* and *Ole Olsen* [13]. Although no new data were presented, the authors looked very critically at the individual trials and concluded that all but two of the trials were so flawed that the results were too unreliable to be used. The trials deemed flawed are the trials that demonstrated a benefit for mammography, while the two trials that were considered to be of acceptable quality, the studies in Malmo and Canada, showed little or no benefit (Table 1). It is of note that, in the older-aged portion of the Canadian study (age 50-59 years), the controls received screening with annual physical breast examinations. Although these have not been shown to be effective in reducing mortality, their use in the control group in this study may explain to some extent the lack of a positive effect of screening.

The *Gøtzsche* and *Olsen* study was sponsored by the Cochrane Collaboration, but it transpires that other members of the Cochrane Breast Cancer Group had disagreed with the conclusions published in *The Lancet*. Subsequently, *The Lancet* took the extremely unusual step of essentially republishing the study [14], this time only displaying the results from the two trials that showed no benefit for mammography,

and with a strongly supportive commentary from the editor [15]. The resulting firestorm of publicity led various organizations to reassert their existing guidelines, or in some cases, to change them.

#### IS THERE SUBSTANCE TO THE NEW CRITICISMS OF THE TRIALS?

The mammography trials are among the most thoroughly and repeatedly analyzed data-sets in the history of cancer research. The studies have methodological limitations, in part because of the tremendous logistical challenges involved in conducting trials of this nature. Recognizing this, the task before us is to make judgments about the strength of the evidence in the face of various challenges to the validity of the data. *Gøtzsche* and *Olsen* are highly critical of the trials on the basis of many issues, some of which reflect perceived inconsistencies, omissions, or ambiguities in the reporting of the results in the literature. They are especially critical of the randomization methods used. In some of the studies, the women were randomized in groups, defined by geographical region, and in some, all women in the population were allocated to the intervention (or not) depending on the precise day of the month on which they were born. These methods might seem peculiar when viewed from the perspective of randomized clinical trials in which individual patients are recruited and randomized to treatment. However, they were constructed in this way to address the practical challenges of investigations in whole populations. An inevitable consequence of this type of study design is that women with existing breast cancer are included in the study population, while in a conventional randomized trial using volunteers, such as the Canadian study, these women would not be eligible at the outset.

Among all of the issues raised, there are only two that rise to the level of having the potential to seriously undermine the overall conclusion that mammography is effective. The first issue is the exclusion of participants from the analyses of some of the studies for eligibility considerations. *Gøtzsche* and *Olsen* advocate the view that women were more likely to have been excluded as a result of a prior diagnosis of breast cancer if they were in the screened group, on the grounds that the identification of prior cancer was ascertained more assiduously among women screened than among controls. Since any breast cancer survivor has a significant chance of ultimately dying of breast cancer, differential rates of exclusions, if this occurred, could certainly bias the conclusions. However, *Gøtzsche* and *Olsen* provide no direct evidence that this was the case, although they report that there were substantially more exclusions in general in the screened groups in the Edinburgh and New York trials.

The second issue concerns the attribution of cause of death. In these trials, far more women die of causes other

than breast cancer than die of breast cancer (Table 1, last column). Although, in principle, any real reduction in breast cancer mortality should lead to a corresponding absolute reduction in overall mortality, the statistical variability in these other causes of death completely swamps the ability of the trials to reliably detect the impact of mammography on overall mortality. Consequently, investigators have counted only deaths due to breast cancer as the primary end point. This relies on the assumption that the attribution of breast cancer as the cause of death in individual women is accurate. *Gøtzsche* and *Olsen* believe that women who die subsequent to a screen-detected breast cancer are more likely to have their death misclassified as being due to a different cause than women who were not screened, and they fault several of the trials for failing to have the causes of death evaluated by experts who are “blinded” to the information on screening history. Again, it is difficult to judge whether this conjecture is simply a theoretical possibility or a genuine source of bias, since no data were presented that address the issue directly.

In summary, *Gøtzsche* and *Olsen* have asserted that all but two of the studies are flawed, but on close inspection, it is difficult to identify genuine substance in the criticisms. At best, the issues raised must be viewed speculatively as potential threats to the validity of the generally accepted

conclusion that mammography is effective in reducing breast cancer mortality.

### WHAT WILL HAPPEN NEXT?

The mammography trials have consumed enormous resources and have involved on the order of half a million women over the course of several decades. It is unlikely that a new study will be undertaken in the near future, and additional follow-up of the existing cohorts of participants is unlikely to provide data that will meaningfully improve the knowledge base. For the foreseeable future, policy decisions must be made on the basis of the existing data. The only critical new evidence that could emerge would be a more careful evaluation of women who were excluded from these analyses due to eligibility considerations, or a re-evaluation of cause-of-death assessments, and it is possible that the sponsors of the various trials will perform audits of this nature in response to the criticisms of *Gøtzsche* and *Olsen*. Indeed, the sponsors of the Swedish trials have already responded in some detail [16]. Whether these responses will alter the balance of evidence remains to be seen, but in the meantime, it would seem prudent to continue to advise women to follow the guideline that is most broadly accepted, namely the use of routine mammograms after age 50.

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