

Mammographic screening: no reliable supporting evidence?

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Summary

Background Much medical and public confusion has resulted from a review in which the authors concluded that “there is no reliable evidence that screening for breast cancer reduces mortality.” However, the reviewers did not appreciate what we take to be the appropriate mortality-related measure of screening’s usefulness, namely the proportional reduction in case–fatality. Correspondingly, they did not estimate the magnitude of this measure. Whereas that review identified two trials as valid, we have focused on the one of these two that allowed for estimation of this measure.

Methods We studied the reduction in case–fatality rate in terms of the breast-cancer mortality ratio that pertains to deaths sufficiently distant in time from the onset of screening, since deaths prevented by early treatment will have occurred only after a suitable delay.

Findings The breast-cancer mortality of the screened women was lower than that of the control cohort from the 7th year after the onset of screening, and from years 8 to 11 (the last available), we found a substantial reduction in case–fatality rate.

Interpretation The improvement in case–fatality rate resulting from screening-based earlier interventions is apparent in a screening trial only after an appropriate delay. Allowing for this delay, we found reliable evidence of improvement in case–fatality rate of breast cancer from the only reported study that is valid and involves sufficiently long-term screening and follow-up.

<http://image.thelancet.com/extras/1093web.pdf>

Introduction

2 years ago, Gøtzsche and Olsen concluded from their review of published studies that “screening for breast cancer with mammography is unjustified”;¹ more recently, Olsen and Gøtzsche clarified this statement to have meant that “there is no reliable evidence that screening for breast cancer reduces mortality”;² adding that their subsequent review “confirmed and strengthened” their previous findings. A commentator on the paper shared the rephrased conclusion.³

This development has not gone unnoticed. An article in the *New York Times*⁴ headlined “Study sets off debates over mammograms” included the observation that many “experts and women’s health advocates... do not know what to think about the report.” The ensuing editorial,⁵ however, noted how “many experts believe that thorough analysis would once again endorse the value of mammography.” However, another article⁶ then appeared on the front page of the newspaper with a wider concern, this one under the headline “Questions grow over usefulness of some routine cancer tests.”

We accept the judgment of Gøtzsche and Olsen that, of the seven studies they considered, the most valid ones were the Malmö⁷ and Canadian^{8,9} trials. The Discussion section of the Malmö report includes this paragraph: “It is thus reasonable to assume that the effect of screening for breast cancer is delayed... . After a six year delay... our study showed a 30% reduction in mortality from breast cancer; when preliminary data from [another year of study] are included the reduction is 42%.”

That paragraph touches on something fundamental pertaining to screening for cancer and, thereby, to the assessment of its usefulness. Cancer—ie, malignant neoplasm—is malignant in the sense that its natural course is fatal, meaning that its case–fatality rate in the absence of curative treatment would be 100% if there were no role for other causes of death; if given the opportunity, it would kill each person having the disease. For breast cancer, with modern care in the absence of screening, the case–fatality rate is actually about 30%, indicating that the curability rate is about 70% since the role of competing causes of death is negligible. With screening, the idea is to achieve early diagnosis and, thereby, early treatment, which is presumed to be more commonly curative than later treatment in the absence of screening. The idea therefore is to reduce the case–fatality rate.

The paragraph cited above refers to the idea that, in instances in which screening-associated early treatment alone is curative and prevents death from that cancer, the death thereby averted would have occurred with considerable delay after the early diagnosis and its associated early treatment. That paragraph also refers to the research implication of this delay in regard to randomised controlled trials that compare screening with no screening: the reduced case–fatality rate presumed to prevail under screening results in fewer deaths from the cancer among the screened only after an appropriate delay, and not on entry into the trial; one needs to focus on deaths in the appropriate segment of follow-up—ie, not too soon after study entry and not too late after discontinuation of screening. The number of deaths

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divided by population-time in the appropriate time interval is the proper meaning of mortality (mortality rate) in this context.

Whereas Gøtzsche and Olsen did not examine the principle that any mortality benefit of screening-associated early intervention becomes apparent only after a delay of several years, we set out to examine the results of the Malmö study more closely from this vantage point. This assessment was possible because two requirements were met: the yearly numbers of deaths from breast cancer as of the time of study entry were reported for a sufficient number of years, and the screening was not discontinued prematurely. The Canadian trials did not meet these requirements.

Methods

Since the screened and control cohorts were of very similar sizes, we focused on the relative sizes of the yearly numbers of deaths from breast cancer in the two cohorts after entry into the study; and because the yearly numbers of breast-cancer deaths were small, we supplemented them with their corresponding 3-year moving averages, using the latter as the basis for addressing the mortality ratios specific to each of the successive years after entry into the trial. In the pattern of these rate ratios over time, our main interest was in the asymptote ($RR^* < 1$) that the mortality rate ratio approaches with increasing time since randomisation, since this is the fatality rate of interest and the complement of this ratio ($1 - RR^*$) is the proportion of breast-cancer deaths preventable by screening-associated early interventions but not by late interventions.

Our concern was to determine whether this asymptotic rate ratio, specific to deaths after a sufficient delay from the inception of screening, shows "reliable" (significant and valid) evidence of reduced mortality from breast cancer. If in a given interval there were d_1 deaths from breast cancer among the screened and d_0 deaths among the controls, $d_1 + d_0 = d$, then the point estimate of the rate ratio was d_1/d_0 and the Gaussian test statistic was $g = (d_1 - d/2)/(d/4)^{1/2}$. Like the Malmö investigators, we derived 95% CIs by the test-based method,¹⁰ raising the point estimate to the powers $1 \pm 1.96/g$.

Results

Table 1 shows, for successive years after entry into the Malmö study, the respective numbers of breast-cancer deaths in the screened and control cohorts, respectively, together with the corresponding mortality rate ratios. Initially, over the first 5 years since study entry, the numbers in the screened cohort exceeded those in the control cohort (16 vs 13); equivalence was reached in the

Year	Screened cohort		Control cohort		Rate ratio (95% CI)
	Actual number	Moving average	Actual number	Moving average	
1	0		0		
2	4	1.3	5	2.0	0.7
3	0	3.3	1	2.7	1.2
4	6	4.0	2	2.7	1.5
5	6	5.3	5	4.0	1.3
6	4	5.7	5	5.7	1.0
7	7	5.0	7	7.3	0.7 (0.36–1.31)
8	4	4.3	10	8.3	0.5 (0.27–1.00)*
9	2	2.7	8	6.3	0.4 (0.19–0.94)*
10	2	3.3	1	7.0	0.5 (0.23–0.99)*
11	6†		12†		

*Based on years 8–11, rate ratio point estimate is $14/31=0.45$ (95% CI 0.24–0.84). †Some of these deaths (from 1987) probably belong to year 10 or even to year 9.

Table 1: Number of breast-cancer deaths by year after entry into Malmö study for women 55–69 years of age at entry

Year	Screened cohort		Control cohort		Rate ratio (95% CI)
	Actual number	Moving average	Actual number	Moving average	
1	1		0		
2	0	1.3	1	0.3	4.0
3	3	1.3	0	0.7	2.0
4	1	3.0	1	1.0	3.0
5	5	3.7	2	2.0	1.8
6	5	4.0	3	3.7	1.1
7	2	4.3	6	4.0	1.1 (0.49–2.37)
8	6	4.3	3	4.7	0.9 (0.44–1.98)
9	5	3.7	5	3.0	1.2 (0.51–2.95)
10	0	1.7	1	4.0	0.4 (0.15–1.14)
11	0		6*		

*Some of these deaths probably belong to year 10 or even to year 9.

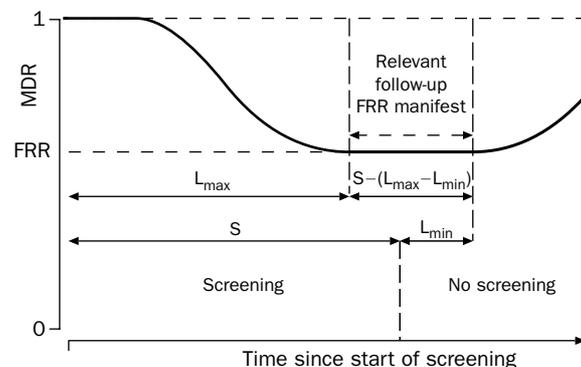
Table 2: Numbers of breast-cancer deaths by year after entry into Malmö study for women 45–57 years of age at entry

6th year; and from the 7th year onward, the deaths from breast cancer in the screened cohort were fewer than in the control cohort. On the basis of years 8–11, year 11 being the last one with information available, the point estimate for the rate ratio is $14/31=0.45$ (95% CI 0.24–0.84). Table 1 is specific to those who, at entry into the study, were 55 years of age or older.

The corresponding results for women 45–54 years of age at entry into the study are given in table 2. In years 1–5, the rate ratio was $10/4=2.5$ (95% CI 0.8–8.0); and in years 8–11 it was $11/15=0.7$ (0.3–1.6).

Discussion

In the Malmö study report, despite the Discussion paragraph cited here, the Abstract highlights the total numbers of breast-cancer deaths over almost the entire period (10 years) of screening and surveillance: "Altogether... 63 v 66 women died of breast cancer...", and the corresponding 10-year numbers are also given separately for women 55 years or older and for those younger than 55 years at entry into the study. For the older women, these numbers are given as "35 v 44; relative risk 0.79 (0.51 to 1.24)." And the conclusions in



Follow-up experience in a randomised controlled trial comparing screening for cancer with no screening in respect to cause-specific mortality: interrelations of parameters

At any given point in the follow-up there is a particular mortality density, MD, among the screened and the not screened; for an interval of t to $t+dt$, with dC cases expected in it, $MD = dC/Pdt$, where P is the size of the population. Contrasting the screened with the not screened, there is the corresponding mortality-density ratio, MDR. This ratio is depicted as a function of time since entry into the trial. The early excess mortality among the screened is not shown, since focus is on the intended result of reduced fatality rate, FR, quantified in terms of fatality-rate ratio, FRR. MDR coincides with FRR in a particular interval of follow-up time if the duration of screening, S , exceeds the difference between the maximum, L_{max} , and minimum, L_{min} , of the time lag from early diagnosis to the death prevented by early intervention but not by late intervention (ie, in the absence of screening).

the Abstract are that “invitations to mammographic screening may lead to reduced mortality from breast cancer, at least in women aged 55 and over.” Along the way, an allusion is made to the temporal pattern of cause-specific mortality, but with no indication that focus on this pattern is essential to any genuine understanding of the usefulness of the screening regimen under study.

The first review by Gøtzsche and Olsen quoted, from the Malmö study, only the overall result (63 *vs* 66) and its consequent “relative risk” and the associated 95% CI (0.96 [0.68–1.35]); and in their second review, this result was supplemented by the even more inclusive term, the all-cause mortality ratio (0.98 [0.93–1.04]). Moreover, because distinctions in terms other than “methodological quality” were not a concern of these authors, the overall Malmö result was pooled, in both reviews, with that of the Canadian study, despite very different regimens and durations of screening and follow-up. In particular, the Canadian follow-up stopped at the point at which the Malmö follow-up started to show fewer breast-cancer deaths among the screened, the Canadian screening having been continued for only 3–4 years after study entry. In Malmö, the screening continued throughout the 10–11 years of follow-up. If the duration of screening in a trial that compares screening with no screening (rather than early intervention with late intervention) is too short, nowhere in the follow-up time does the mortality ratio tend to decline all the way to the case–fatality ratio, which characterises early intervention relative to late intervention. For the fatality ratio to become fully apparent, in the appropriate interval of follow-up time, the duration of the screening must exceed the difference between the maximum and the minimum of the time lag from screening-associated early diagnosis to the death in the prevention of which early intervention is essential. The figure describes these parametric relations in more detail.

The delay principle above is not in dispute. Therefore, while we accept the reviewers’ conclusion^{1,2} that valid evidence derives mainly from the Malmö trial, we take our table 1 to give reliable evidence that, in women 55 years of age or older, mammographic screening is associated with reduced mortality from breast cancer after the necessary delay (during which somewhat increased mortality from treatment complications can be expected). Because screening was continued long enough in the Malmö study, the mortality ratio characterising late follow-up theoretically coincides with the ratio of case–fatality rates, screening versus no screening, or early intervention versus late intervention. So, were we to take the Malmö data quantitatively at face value (despite residual biases and imprecision), we would estimate that the Malmö screening—at intervals of 18–24 months, with incomplete (about 70%) adherence—resulted in a 55% (100%–45%) reduction in case-fatality rate and thereby, after the requisite delay, in cause-specific mortality in the older women.

In reviewing the published trials on breast-cancer

screening, Olsen and Gøtzsche were concerned with study quality in the sense of freedom from “the three most important sources of bias in randomised trials: suboptimum randomisation methods, lack of masking in outcome assessment, and exclusion after randomisation”;² and they were also concerned with comparability of the attribution of deaths to breast cancer. But nowhere did they address the quality issue of whether a study involved screening of sufficiently long duration and, especially, whether the investigators focused on deaths in the segment of follow-up in which long-term screening is associated with a meaningful reduction in breast-cancer mortality. Since their review lacked this focus, reliable evidence of the benefit of mammography in reducing case-fatality rate became obfuscated by mixing of irrelevant experience with the relevant experience.

This approach is ingrained in today’s orthodoxy surrounding trials on screening for cancer. We believe that the root problem with the present orthodoxy is the general focus on methodological design and the consequent general lack of attention to object design.¹¹ For the mammography trials and reviews, the object should have been designed to pertain to case–fatality rate and, specifically, the reduction in it resulting from the early interventions facilitated by screening-based early diagnoses.¹² Pursuit of reliable—ie, valid and statistically significant or precise—evidence in terms of a wrong measure of usefulness is not only useless; it misleads public policy and confuses the public and physicians.¹³

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