	Total number of patients	Number positive for *BAT26* mutations in faecal DNA	Number negative for *BAT26* mutations in faecal DNA
No neoplasia	69	0	69
With adenoma	19	0	19
<1 cm	14	0	14
⩾1 cm	5	0	5
With cancer	46	17	29
Dukes' A	5	1	4
Dukes' B	22	11	11
Dukes' C	11	4	7
Dukes' D	8	1	7

Results of analysis of faecal DNA for *BAT26* alterations

Of 134 faecal DNA samples analysed, 17 were found to have *BAT26* alterations. Examples of the results from this assay are shown in the figure. All 17 faecal DNA samples yielding a positive *BAT26* test were subsequently found to have been derived from patients with colorectal cancer (table).

Among the cancer patients with proximal lesions, the clinical sensitivity of the *BAT26* faecal DNA test was 37% (17 of 46 [95% CI 23–52]), with no positives among 69 individuals with normal colonoscopies or among 19 individuals with adenomas. The specificity was therefore 100% (95% CI 95–100). None of the patients in our cohort had variant *BAT26* alleles in their germ line.[4]

To determine the concordance of *BAT26* alterations between faecal DNA and tumours, we microdissected neoplastic lesions from paraffin-embedded specimens of all 65 tumours (46 cancers plus 19 adenomas). DNA of adequate quality was recovered from 57 lesions, and 18 cases with *BAT26* alterations were seen, all among cancers. 17 of these 18 cases corresponded to those with positive faecal tests, and in each of these cases, the size of the *BAT26* alteration in tumour and faecal DNA was identical (figure).

The results recorded above have several important implications for faecal DNA testing. First, they provide compelling evidence that mutations in faeces can be used to identify patients with cancer. The fact that 17 of the 18 cases with *BAT26* mutations in their tumours gave rise to a positive faecal DNA test, coupled with the zero false-positive rate, was of particular note. Second, the results show that proximal cancers do not represent a barrier to faecal DNA analysis. Third, small samples of stool, rather than whole stools, could be analysed effectively, facilitating collection and storage of specimens for analysis. Finally, the proportion of mutant DNA molecules in faecal DNA ranged from 1·1% to 10·6%. Thus, techniques to assess faecal DNA mutations need be no more sensitive than this to detect most mutations. In the one sample that was a false negative, increasing the potential sensitivity five-fold by analysing an additional 2000 *BAT26* genes in faecal DNA did not result in detection of the mutation.

One practical application of these findings involves combination of *BAT26* with sigmoidoscopy. Cost-effectiveness modelling has indicated that sigmoidoscopy combined with unhydrated faecal occult blood tests can be more effective than colonoscopy for colorectal cancer screening.[1] The sensitivity of the *BAT26* assay is similar to that of the unrehydrated faecal occult blood tests but is more expensive. This cost disadvantage is counterbalanced by the fact that the *BAT26* test seems to be substantially more specific, thereby precluding the need for follow-up colonoscopies in many patients with false-positive faecal occult blood tests. Furthermore, the *BAT26* test does not require patients to change their dietary habits before testing, nor to provide several faecal samples, potentially increasing compliance. Prospective studies to validate the sensitivity and specificity in a screening context, and to compare efficacy and cost-effectiveness with other screening strategies, are justified by the results reported above.

Contributors

Giovanni Traverso, Kenneth W Kinzler, and Bert Vogelstein directed the molecular aspects of the paper, developed the digital BAT26 technology, and wrote the first draft of the paper. Giovanni Traverso also did the Digital BAT26 assays. Louise Olsson, Bernard Levin, and Constance Johnson directed the clinical aspects of the study, including the selection of patients and the collection of clinical samples. They also helped interpret the data and formulate the final paper. Anthony Shuber and Kevin Boynton purified the DNA from the faecal samples using hybrid capture, and participated in the interpretation of the data and the formulation of the final paper. Stanley R Hamilton assessed the histopathology of the studied tumors and helped formulate the final paper.

Conflict of interest statement

Under agreements between the Johns Hopkins University and Exact Sciences, Genzyme Molecular Oncology and Hoffmann-LaRoche, Kenneth W Kinzler and Bert Vogelstein are entitled to a share of the royalties received by the university on sales of products related to the use of stool DNA for cancer diagnosis. Kenneth Kinzler is a consultant to Genzyme and to Exact Sciences, and Bert Vogelstein has in the past consulted for Genzyme and Exact Sciences. Kenneth Kinzler and Bert Vogelstein also own stock in Exact Sciences, and the university, along with Kenneth Kinzler and Bert Vogelstein own stock in Genzyme, which are subject to certain restrictions under university policy. The terms of these arrangements are being managed by the university in accordance with its conflict of interest policies. Anthony Shuber and Kevin Boynton are employees of Exact Sciences and are stockholders in the company.

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Mammographic screening: no reliable supporting evidence?

Olli S Miettinen, Claudia I Henschke, Mark W Pasmantier, James P Smith, Daniel M Libby, David F Yankelevitz

Much confusion is being generated by the conclusion of a recent review that "there is no reliable evidence that screening for breast cancer reduces mortality." In that review, however, there was no appreciation of the appropriate mortality-related measure of screening's usefulness; and correspondingly, there was no estimation of the magnitude of this measure. We take this measure to be the proportional reduction in case-fatality rate, and studied its magnitude on the basis of the only valid and otherwise suitable trial. We found reliable evidence of fatality reduction, apparently substantial in magnitude.

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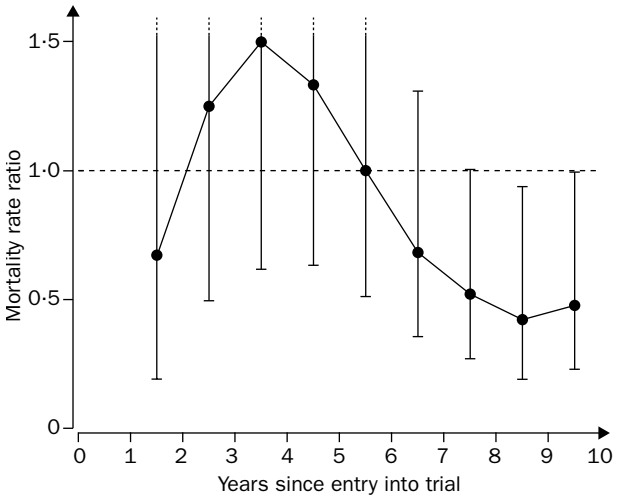
Cancer is malignant in the sense that its natural course is fatal, meaning that its case–fatality rate in the absence of curative treatment would be 100% if there were no role for other causes of death. Given the opportunity, it would kill every person with the disease. With screening, the idea is to achieve early diagnosis and, thereby, early treatment, which is presumed to be curative in more cases than later treatment. The idea, therefore, is to reduce the case–fatality rate. The authors of the Malmö study[1]—one of two accepted as valid by Olsen and Gøtzsche in their recent review[2]—refer to substantial reduction in breast-cancer mortality after a 6-year delay. They also mention that such a delay in the mortality gain is to be expected in randomised controlled trials that compare screening with no screening, since the reduced case–fatality rate presumed to be a consequence of screening tends to result in fewer deaths from the cancer only after a suitable delay. Analysis should therefore focus on deaths in the appropriate segment of follow-up—ie, not too early on study entry and not too late—after discontinuation of screening. Number of deaths divided by population-time in the appropriate time interval is the proper meaning of mortality (mortality rate) in this context.

Olsen and Gøtzsche did not address the case-fatality benefit of screening-associated early intervention, which, if it exists, becomes apparent only after a delay of several years. As a result, they concluded that "there is no reliable evidence that screening for breast cancer reduces mortality".[2] We set out to examine the results of the Malmö study more closely, allowing for the requisite delay. This analysis 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 figure shows, for successive years after entry into the Malmö study, the corresponding mortality rate ratios for women 55 years of age or older at study entry. During the first 5 years after study entry, the rates in the screened cohort exceeded those in the control cohort; identity was reached in the sixth year; and from the seventh year onward, the rates of death from breast cancer in the screened cohort were lower 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 0·45 (95% CI 0·24–0·84).

The abstract of the Malmö study report shows the total numbers of breast-cancer deaths during 10 years of screening and documentation after entry into the study. It gives overall numbers (63 in the screening group *vs* 66 in the control group) and numbers stratified according to age (at least 55 years or less than 55 years) at entry into the study. 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. Olsen and Gøtzsche refer only to the overall result (63 *vs* 66) and its associated "relative risk" and 95% CI (0·96 [0·68–1·35]), supplementing this information with the corresponding even more inclusive all-cause mortality ratio (0·98 [0·93–1·04]). Moreover, since they did not examine the studies for characteristics other than "methodological quality", they pooled the overall result from Malmö with that of a Canadian study,[3,4] despite very different regimens and durations of screening and follow-up.



Breast-cancer mortality ratio for women at least 55 years of age in the Malmö study
Shown are point estimates and 95% CI, based on the deaths in the year at issue together with those in the preceding and following years.

Screening in the Canadian study continued for only 3–4 years after study entry, and follow-up stopped at the point at which follow-up in the Malmö study started to show fewer breast-cancer deaths among those screened. In Malmö, the screening continued throughout the 10–11 years of follow-up. When the duration of screening in a trial that compares screening with no screening (rather than early intervention with late intervention) is too short, nowhere during follow-up does the mortality ratio 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, the duration of 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 delay principle addressed above is not in dispute. In its spirit, then, and also accepting Olsen and Gøtzsche's conclusion[2] that valid evidence derives mainly from the Malmö trial, we call attention to our figure. Screening in older women seems to have provided for a 100%–45%=55% reduction in case–fatality rate and thereby, after the requisite delay, in cause-specific mortality.

Contributors
O S Miettinen, C I Henschke, and D F Yankelevitz initiated the study, O S Miettinen did the analysis, and all authors participated in the writing and editing of the paper.

Conflict of interest statement
None declared.

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Mammographic screening: no reliable supporting evidence?

Olli S Miettinen, Claudia I Henschke, Mark W Pasmantier, James P Smith, Daniel M Libby, David F Yankelevitz

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.

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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 article[6] 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 Malmö[7] 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

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 $1\pm 1{\cdot}96/g$.

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 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.

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*		

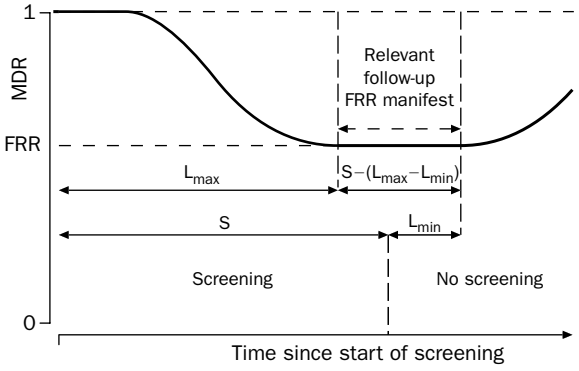
*Some of these deaths probably belong to year 10 or even to year 9.

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

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, $MD_t=dC/Pdt$, 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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