Swedish Two-County Trial: Impact of Mammographic Screening on Breast Cancer Mortality during 3 Decades[1]

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Purpose: To estimate the long-term (29-year) effect of mammographic screening on breast cancer mortality in terms of both relative and absolute effects.

Materials and Methods: This study was carried out under the auspices of the Swedish National Board of Health and Welfare. The board determined that, because randomization was at a community level and was to invitation to screening, informed verbal consent could be given by the participants when they attended the screening examination. A total of 133 065 women aged 40–74 years residing in two Swedish counties were randomized into a group invited to mammographic screening and a control group receiving usual care. Case status and cause of death were determined by the local trial end point committees and, independently, by an external committee. Mortality analysis was performed by using negative binomial regression.

Results: There was a highly significant reduction in breast cancer mortality in women invited to screening according to both local end point committee data (relative risk [RR] = 0.69; 95% confidence interval: 0.56, 0.84; $P < .0001$) and consensus data (RR = 0.73; 95% confidence interval: 0.59, 0.89; $P = .002$). At 29 years of follow-up, the number of women needed to undergo screening for 7 years to prevent one breast cancer death was 414 according to local data and 519 according to consensus data. Most prevented breast cancer deaths would have occurred (in the absence of screening) after the first 10 years of follow-up.

Conclusion: Invitation to mammographic screening results in a highly significant decrease in breast cancer–specific mortality. Evaluation of the full impact of screening, in particular estimates of absolute benefit and number needed to screen, requires follow-up times exceeding 20 years because the observed number of breast cancer deaths prevented increases with increasing time of follow-up.

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The Swedish Two-County Trial of mammographic screening was the first breast screening trial to show a reduction in breast cancer mortality from screening with mammography alone, finding a 30% reduction in breast cancer mortality among 40–74-year-old women invited to screening (1). Regular updates of the trial data have shown that the relative effect of invitation to screening on breast cancer mortality has remained stable over extensive follow-up (2–4). The absolute benefit in terms of lives saved, however, has increased with longer follow-up times (2,5,6). Because breast screening prevents deaths in the medium to long term, rather than in the immediate future, long-term follow-up (at least 15 years) is required to estimate the absolute number of breast cancer deaths prevented (6).

The purpose of this study was to estimate the long-term (29-year) effect of mammographic screening on breast cancer mortality in terms of both the relative and absolute effects.

Materials and Methods

The design of the Swedish Two-County Study has been described previously (1,7). Briefly, the female population aged 40–74 years in two counties—Dalarna (then called Kopparberg) and Östergötland—was divided into 45 geographic clusters. These clusters were randomized within 19 socioeconomically homogeneous strata into either the active study population (ASP), which was invited to undergo one-view screening mammography, or the control group, the passive study population (PSP), which received usual care. The ASP/PSP randomization ratio was approximately 1:1 in Östergötland and 2:1 in Dalarna. After exclusion of women with previously diagnosed breast cancer, there were 77 080 women in the ASP and 55 985 in the PSP. The trial began in 1977 in Dalarna and in 1978 in Östergötland. The trial was gradually built up by successively randomizing the matched ASP and PSP geographic clusters step-by-step during a 31-month period in Dalarna and during a 34-month-period in Östergötland (8).

The screening phase of the trial lasted approximately 7 years. Women aged 40–49 years at randomization were invited to screening every 24 months on average, and women aged 50–74 years were invited to screening every 33 months on average. The screening method was one-view screen-film mammography with single reading—without physical examination. In Dalarna, screening ceased in women aged 70–74 years after the second round of invitations, although cancers diagnosed thereafter and breast cancer deaths from these cases were still included in the results. The screening phase of the trial ended with the PSP cluster in each matching ASP-PSP pair being invited to screening in the same order as their initiation into the trial (8). The first mortality results of the trial were published in 1985 (1), showing a significant 30% reduction in mortality from breast cancer among women invited to screening. Breast cancer mortality among all cancer cases diagnosed in the ASP (cancers detected during screening, cancers diagnosed in the interval between screening examinations, and cancers diagnosed among nonattenders [subjects who failed to attend one or more screening examinations]) was compared with breast cancer mortality among cases diagnosed in the PSP (symptomatic cancers and those detected at the closure screening examination) during the trial period (1). Although all women in the trial have been followed up to calculate the person-years at risk, the breast cancer deaths reported pertain to follow-up of women with cancers diagnosed during the screening phase of the trial. Follow-up was to December 31, 2005, in Dalarna and to December 31, 2006, in Östergötland (ie, 28 and 29 years after the start of the trial).

The county councils appointed local trial end point committees consisting of physicians (chiefs of the departments of mammography, surgery, and pathology and, in Östergötland, the chief of oncology). Case status and cause of death were determined by these committees after detailed review of patient records and autopsy data (where the latter were available). The cause of death was determined according to strict guidelines (2). In 1987, the Swedish Cancer Society set up an overview committee to review all of the randomized mammography trials in Sweden, including the Dalarna-Östergötland trial. The overview committee performed two overviews by collecting data from all four Swedish mammography trials (9,10). Although the first overview used an end

Advances in Knowledge

- The results of this study show that the relative benefit in breast cancer mortality from mammographic screening remains steady up to 29 years after the inception of screening.
- The absolute number of breast cancer deaths prevented increases with follow-up time.
- Screening 300 women for 10 years prevents one death from breast cancer.
- Long-term observation (at least 20 years) is required to obtain an accurate estimate of the absolute benefit of breast cancer screening.

Implication for Patient Care

- Screening results in a highly significant decrease in breast cancer–specific mortality.

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Abbreviations:
ASP = active study population
PSP = passive study population
RR = relative risk

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See also the articles by Jørgensen et al and Kopans et al in this issue.

point committee similar to the ones used in this trial (consisting of a radiologist, a surgeon, a breast pathologist, and an oncologist—experts in the diagnosis and treatment of breast cancer), the second overview relied on data from the national registry, and, in each instance, the overview committee used slightly different inclusion and/or exclusion criteria. These differences resulted in differences in the numbers of cases and deaths in subsequent reports. In an effort to reconcile these differences, a third independent overview committee was established by the Swedish Cancer Society to develop a consensus breast cancer case status and cause of death (11). Results from the original Dalarna-Östergötland trial end point committee and the third overview committee are presented herein.

This study was carried out under the auspices of the Swedish National Board of Health and Welfare. The board determined that, because randomization was at a community level and was to invitation to screening, informed verbal consent could be given by the participants when they attended the screening examination.

Mortality analysis was performed by using negative binomial regression, yielding conservative standard error estimates, and significance testing to account for additional uncertainty introduced by the cluster randomization (12). Relative risks (RRs) of breast cancer death and 95% confidence intervals were calculated and analyzed according to intention to treat (ie, breast cancer deaths in the ASP and PSP were compared independent of screening status). We converted these estimates to absolute numbers of breast cancer deaths prevented and calculated numbers needed to screen for different follow-up times, taking into account the different sizes of the ASP and PSP (5). A computer package (Stata, version 10.1; Stata, College Station, Tex) was used for statistical analysis.

Results

Table 1 shows the number of tumors diagnosed during the screening phase of the trial along with breast cancer deaths from these tumors over a maximum follow-up of 29 years by using the local end point committee data. In the ASP, a minority of tumors ($n = 498$, 35%) were symptomatic; however, these cancers contributed to the majority of breast cancer deaths ($n = 186$, 53%). There were 351 breast cancer deaths among the 77 080 subjects in the ASP group and 367 deaths among the 55 985 subjects in the PSP group. The corresponding results obtained with use of the case status and death end points from the consensus with the Swedish overview committee are shown in Table 2. The numbers of cases and deaths differed only slightly (<10%) from those obtained by the local end point committee. There were 339 breast cancer deaths in each group according to the consensus determination.

Figure 1 shows the cumulative breast cancer mortality in the ASP and PSP groups according to the local end point

Table 1

Local Trial End Point Committee Data: Breast Cancer Cases and Deaths during 29 Years of Follow-up

Group	No. of Subjects	No. of Subjects Who Died from Breast Cancer
ASP		
All detected cancers	1426	351
Cancers detected before first screening examination	28 (2)	9 (3)
Cancers detected at first screening examination	427 (30)	81 (23)
Cancers detected at second (or later) screening examination	501 (35)	84 (24)
Cancers detected between screening examinations	300 (21)	91 (26)
Cancers detected in nonattenders	140 (10)	77 (22)
Cancers detected after screening stopped*	30 (2)	9 (2)
PSP		
All detected cancers	1042	367
Cancers detected before screening examination	755 (72)	332 (90)
Cancers detected at first screening examination	287 (28)	35 (10)

Note.—Numbers in parentheses are percentages.

* In subjects at least 70 years old.

Table 2

Swedish Overview Committee Consensus Data: Breast Cancer Cases and Deaths during 29 Years of Follow-up

Group	No. of Subjects	No. of Subjects Who Died from Breast Cancer
ASP		
All detected cancers	1439	339
Cancers detected before first screening examination	30 (2)	12 (4)
Cancers detected at first screening examination	430 (30)	76 (22)
Cancers detected at second (or later) screening examination	503 (35)	81 (24)
Cancers detected between screening examinations	298 (21)	89 (26)
Cancers detected in nonattenders	148 (10)	71 (21)
Cancers detected after screening stopped*	30 (2)	10 (3)
PSP		
All detected cancers	1049	339
Cancers detected before screening examination	764 (73)	308 (91)
Cancers detected at first screening examination	285 (27)	31 (9)

Note.—Numbers in parentheses are percentages.

* In subjects at least 70 years old.

Figure 1

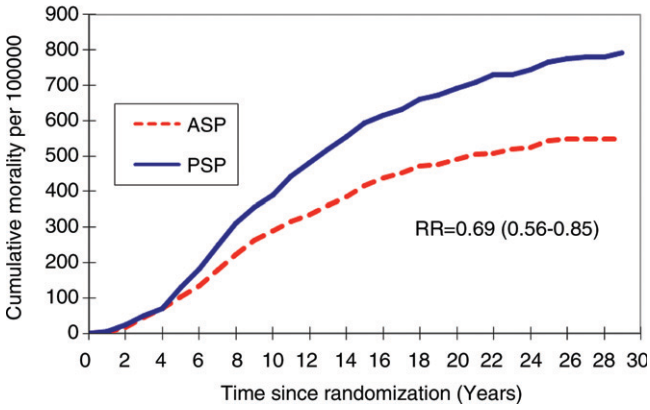

Figure 1: Graph shows cumulative mortality from breast cancer according to study group, as determined with local end point committee data.

Figure 2

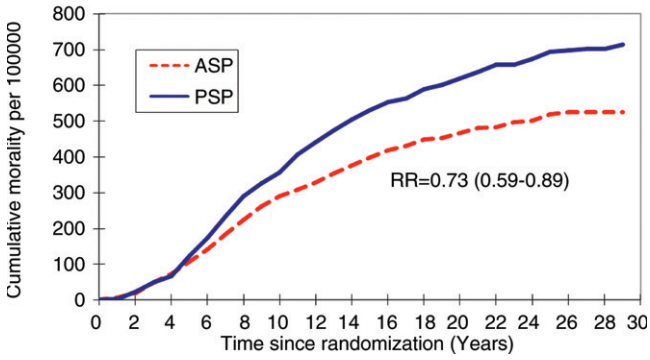

Figure 2: Graph shows cumulative mortality from breast cancer according to study group, as determined with Swedish overview committee consensus data.

committees. There were 351 breast cancer deaths in the ASP group and 367 deaths in the PSP group by the end of follow-up. Taking into account the different sizes of the ASP and PSP groups, there was a highly significant reduction in breast cancer mortality in the population invited to screening (RR = 0.69; 95% confidence interval: 0.56, 0.84; $P <$ .0001). Taking the years of life saved as the area between the curves, this gives 42 years of life saved per 1000 women invited to screening. Figure 2 shows the corresponding results obtained with data from the Swedish overview consensus. A lesser but still highly significant reduction in mortality was observed with the consensus data (RR = 0.73; 95% confidence interval: 0.59, 0.89; P = .002). The estimated years of life saved from the consensus data was 34 per 1000 women invited to screening.

Table 3 shows the absolute numbers of deaths prevented and the estimated numbers of women needed to screen during the 7 years of screening to save one life, calculated for various periods of follow-up, by using the local end point committee data. Note that of the 158 breast cancer deaths prevented over the 29 years, only 71 (45%) of these were observed during the first 10 years. Most prevented breast cancer deaths would have occurred, in the absence of screening, after the first 10 years of follow-up, that is, more than 3 years after closure of the screening phase of the trial. The attendance rate at screening was 85% (65 518 of 77 080 subjects). An average of 65 518 women participated in each round of mammographic screening, resulting in a total of 211 303 examinations (5). Thus, the number of women needed to screen for a period of 7 years to prevent one breast cancer death (as calculated at 29-year follow-up) was 414 (65 518 ÷ 158). There were 1334 mammographic screening examinations per death avoided. Table 4 shows the corresponding results from the consensus data. There were 126 breast cancer deaths prevented in follow-up to 29 years. Again, most deaths were prevented after the first 10 years of follow-up. To prevent one breast cancer death, the corresponding estimates from these data were as follows: 519 women need to be screened for 7 years, 400 need to be screened for 10 years, and 1677 mammographic examinations need to be performed.

Discussion

The Swedish Two-County Trial has the longest follow-up of any breast screening trial, with a maximum 29-year follow-up for breast cancer mortality. The original report documented a 30% reduction in breast cancer mortality with invitation to screening according to the cause of death determination by the local end point committee (1). This result has persisted throughout the long follow-up period. After a comprehensive review in collaboration with the Swedish Cancer Society's independent overview investigators, a consensus end point gave a smaller but still substantial and highly significant reduction in breast cancer mortality. The current results confirm the original findings of the trial and are consistent with those from the most recent meta-analysis (13).

The trial has also demonstrated a substantial absolute reduction in mortality from breast cancer. At 29-year follow-up, 34 or 42 years of life were saved per 1000 women screened over a 7-year period, depending on whether the local or consensus cause of death end point was used. One breast cancer death was prevented for each 414 women (local committee data) or 519 women (consensus data) screened for 7 years. Had the screening continued for 10 years, with the same benefit per screening episode, the absolute benefit would have been higher, with approximately 300 women needed to screen to save one life.

The absolute benefit corresponds to one life saved for 1334 (local committee data) or 1677 (consensus data) mammographic screening examinations. This in turn would mean that for 1000 women screened every 2 years from ages 40 through 69 years, between eight and 11 breast cancer deaths would be prevented. In the United Kingdom National Breast Screening Program, for every 1000 women attending three yearly screenings from ages 47 to 73 years (nine screening episodes), five to seven breast cancer deaths would be prevented. The relative

Table 3

Local End Point Committee Data: Breast Cancer Deaths Avoided and Number of Women Needed to Screen for 7 Years to Prevent One Death according to Follow-up Time

Time between Randomization and Follow-up (y)	RR*	Deaths from Breast Cancer in ASP Group	Expected Deaths in ASP Group*	Deaths Prevented in ASP Group	No. of Women Needed to Screen†
10	0.74 (0.57, 0.98)	206	277	71	922 (515, 4410)
15	0.70 (0.56, 0.87)	284	408	124	526 (351, 1055)
20	0.70 (0.57, 0.85)	324	465	141	464 (316, 871)
25	0.70 (0.57, 0.85)	347	497	150	436 (297, 815)
29	0.69 (0.56, 0.84)	351	509	158	414 (286, 748)

* Expected deaths if the ASP had the same mortality rate as the PSP, calculated by dividing the observed deaths by the RR (eg, at 10 years, 206/0.7435 = 277 expected deaths).

† Numbers in parentheses are 95% confidence intervals.

Table 4

Swedish Overview Committee Consensus Data: Breast Cancer Deaths Avoided and Number of Women Needed to Screen for 7 Years to Prevent One Death according to Follow-up Time

Time between Randomization and Follow-up (y)	RR*	Deaths from Breast Cancer in ASP Group	Expected Deaths in ASP Group*	Deaths Prevented in ASP Group	No. of Women Needed to Screen†
10	0.80 (0.62, 1.05)	207	257	50	1303 (621, 13169)
15	0.73 (0.59, 0.92)	274	373	99	663 (412, 1695)
20	0.73 (0.60, 0.90)	311	425	114	577 (370, 1315)
25	0.73 (0.60, 0.90)	335	457	122	539 (346, 1217)
29	0.73 (0.59, 0.89)	339	465	126	519 (336, 1144)

* Expected deaths if the ASP had the same mortality rate as the PSP, calculated by dividing the observed deaths by the RR (eg, at 10 years, 207/0.8046 = 257 expected deaths).

† Numbers in parentheses are 95% confidence intervals.

benefit is an underestimate of the true effect of screening due to nonattendance in the ASP and contamination with screening in the PSP. The absolute estimate is unaffected by the former but will be slightly conservative owing to the latter.

Most of the prevented breast cancer deaths were those that would have occurred more than 10 years after inception of screening. This has two major implications: *(a)* Because of the varying growth rates of breast cancers, some remain asymptomatic for several years and would take some years after symptoms appear to lead to death, and *(b)* as in other primary and secondary prevention activities, long-term follow-up is necessary for considerably more than 10 years to estimate the absolute effect on clinical outcome.

It is also worth considering the absolute numbers of lives saved per screening-detected case. With use of the local committee end point, 17% of screening-detected cases (158 from Table 3 divided by 427 + 501 from Table 1) resulted in the prevention of one breast cancer death. The corresponding figure from the consensus end point was 14%. These empirical estimates from a randomized controlled trial refute assertions of 5% based on modeling of assumed benefits calculated from much shorter follow-up than ours, unexplained assumptions of very high levels of overdiagnosis, and estimation of screening performance from nonexperimental data (14).

The reduction in breast cancer mortality is also consistent with previously reported reductions in the incidence of advanced disease, whether defined as TNM stage II or worse, pathologic size larger than 20 mm, or node-positive cancer (1,3). The reductions in mortality observed in the breast screening trials closely followed the reductions in the incidence of node-positive disease (15).

The major human costs of mammographic screening are the radiation exposure, the physical and psychologic effects of further investigation of suspicious mammographic findings in women who are ultimately found not to have breast cancer, and overdiagnosis. The radiation dose in this trial was considerably less than that in most modern programs owing to the use of single-view mammography (7). Call-back rates in the Two-County Trial were 5.0% at prevalent screening and 2.5% at incident screening (7). The number of overdiagnosed cases in this study has been estimated as less than half the number of breast cancer deaths prevented and, thus, is a small fraction of all cases (6).

In this trial, we used single-view mammography and a 24–33-month interval between screening examinations. After the trial was closed, practice changed to two-view mammography. Two-view mammography and a shorter (usually annual) interval represent the standard in the United States. There is good reason to

believe that had two-view mammography and a shorter interval been used in our trial, the impact on breast cancer mortality would have been even greater. Studies about mean sojourn time (tumor progression rates according to age and histologic type), double reading, and the value of two-view versus single-view mammography have resulted in the acceptance of two views, 1–2-year intervals, and double reading as current standards of practice in most programs. In addition, the technical aspects of the screening in this study pertained to the era in which it took place, the late 1970s and early 1980s. Consequently, they differ from those prevailing now. Screen-film mammography has been largely replaced by digital methodology, which also represents improved technology. The application of the multimodality approach to screening is currently under investigation (16).

Cluster randomization introduces additional uncertainty to results. As noted earlier, we analyzed the data by using a conservative method to reflect this possibility. Previous detailed analyses taking account of prior within-cluster breast cancer mortality and allowing variation among clusters yielded the same results (17,18).

Questions concerning the trial design and the determination of cause of death (19,20) have been thoroughly addressed by the trial investigators and by independent reviewers (11,17,21). Recently, a full review of case status and cause of death determination, investigating all differences between the trial end point committee and the Swedish overview, was carried out in collaboration with the overview investigators (10); the trial data were found to be reliable (11).

In conclusion, the results of the Swedish Two-County Trial of mammographic screening are qualitatively the same at 29-year follow-up as when they were first published: A substantial and significant reduction in breast cancer mortality was associated with an invitation to screening. In quantitative terms, the absolute number of prevented breast cancer deaths observed increases with increasing time of follow-up. Depending on the case status and cause of death source used, at 29 years of follow-up there was one death prevented for every 414 or 519 women screened for a 7-year period.

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