Radiology

ORIGINAL RESEARCH • BREAST IMAGING

Beneficial Effect of Consecutive Screening Mammography Examinations on Mortality from Breast Cancer: A Prospective Study

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Background: Previously, the risk of death from breast cancer was analyzed for women participating versus those not participating in the last screening examination before breast cancer diagnosis. Consecutive attendance patterns may further refine estimates.

Purpose: To estimate the effect of participation in successive mammographic screening examinations on breast cancer mortality.

Materials and Methods: Participation data for Swedish women eligible for screening mammography in nine counties from 1992 to 2016 were linked with data from registries and regional cancer centers for breast cancer diagnosis, cause, and date of death (Uppsala University ethics committee registration number: 2017/147). Incidence-based breast cancer mortality was calculated by whether the women had participated in the most recent screening examination prior to diagnosis only (intermittent participants), the penultimate screening examination only (lapsed participants), both examinations (serial participants), or neither examination (serial nonparticipants). Rates were analyzed with Poisson regression. We also analyzed incidence of breast cancers proving fatal within 10 years.

Results: Data were available for a total average population of 549 091 women (average age, 58.9 years ± 6.7 [standard deviation]). The numbers of participants in the four groups were as follows: serial participants, 392 135; intermittent participants, 41 746; lapsed participants, 30 945; and serial nonparticipants, 84 265. Serial participants had a 49% lower risk of breast cancer mortality (relative risk [RR], 0.51; 95% CI: 0.48, 0.55; $P < .001$) and a 50% lower risk of death from breast cancer within 10 years of diagnosis (RR, 0.50; 95% CI: 0.46, 0.55; $P < .001$) than serial nonparticipants. Lapsed and intermittent participants had a smaller reduction. Serial participants had significantly lower risk of both outcomes than lapsed or intermittent participants. Analyses correcting for potential biases made little difference to the results.

Conclusion: Women participating in the last two breast cancer screening examinations prior to breast cancer diagnosis had the largest reduction in breast cancer death. Missing either one of the last two examinations conferred a significantly higher risk.

Online supplemental material is available for this article.

The effect of breast cancer screening on population-based breast cancer mortality does not appear immediately but takes years to accumulate. The protective effect remains for years after screening ceases, and there is evidence that there are clear benefits of repeated regular screening (1,2). It has been observed in the context of both randomized controlled trials and service screening that even women with symptomatic breast cancers who have recently participated in screening show a survival advantage over women with breast cancer who did not participate in screening (3,4). This advantage is partially accounted for by selection bias but was found to be largely due to finding the majority of invasive cancers earlier, especially the poorly differentiated tumors (5), when they are smaller and have less node positivity (3,4). It has also been noted that the subpopulation of women who decide not to attend screening has a substantially poorer outcome than an uninvited general population (3).

Abbreviation

RR = relative risk

Summary

Participation in the two most recent screening mammography appointments before a breast cancer diagnosis confers a significantly higher protection against breast cancer death than participation in neither or only one examination.

Key Results

- In a prospective study of 549 091 women eligible for screening mammography in nine Swedish counties between 1992 and 2016, women who attended screening mammography at either of their two last invitations before a breast cancer diagnosis had a significantly lower risk of breast cancer mortality compared with those who did not attend screening examinations; the greatest benefit (49% risk reduction) was seen in women who attended both screening appointments.
- The incidence of breast cancers that proved fatal within 10 years of diagnosis was 50% lower in women who had participated in both previous screening examinations than in those who did not attend either of their last screenings.
- Women who attended both previous screening examinations had a significant reduction in breast cancer mortality as compared with women who attended only one of the previous screenings.

The West Midlands Screening Histories Project observed better survival in symptomatic tumors in lapsed attenders (women whose most recent screening examination yielded negative results and was more than 3 years ago) than in women who never attended screening (6). Furthermore, case-control analyses of breast cancer mortality found that past screening participation was associated with a reduction in mortality, a reduction which declined with increasing time since the last screening examination (7). In a previous publication using the same database as in this study, a single class of nonparticipation (ie, those who did not attend their most recent scheduled screening examination prior to breast cancer diagnosis) was considered (8). We hypothesized that participation in serial screenings would confer a reduction in breast cancer mortality compared with irregular participation and that irregular participation would confer a reduction compared with serial nonparticipation. As consideration of serial patterns of participation may lead to improved accuracy of estimation of the effect of regular screening participation on patient outcomes and cast more light on the contribution of regularly attending screening examinations in reducing mortality from breast cancer, the purpose of this study was to estimate the effect of participation in successive mammographic screening examinations on breast cancer mortality.

Materials and Methods

The authors declare no conflict of interest. The population analyzed in this study partially (8–10) or completely (11) overlaps with that used in previous studies, but the current study examines participation data in greater detail, specifically studying the effect of serial participation on screening. The current study was approved by the ethics committee of Uppsala University (registration number 2017/147). Informed consent from study participants was not required due to the fact that the focus was on deceased women and the type of data collected. No personal identifiable data were collected from living participants. Data analyzed were provided by third parties. Requests for data should be directed to the providers indicated in the Acknowledgments.

General Methods

In this prospective analysis, breast cancer mortality data were provided by the Swedish Cause of Death Register of the Swedish National Board of Health and Welfare for nine counties: Stockholm, Dalarna, Värmland, Örebro, Västmanland, Gävleborg, Västernorrland, Västerbotten, and Norrbotten. Breast cancer incidence and tumor characteristics were obtained from the regional oncology centers of the Northern, Uppsala-Örebro, and Stockholm-Gotland health care regions and were then linked to population screening data on invitation to and participation in screening mammography, prospectively collected by Sectra Medical Systems, Linköping, Sweden.

According to national recommendations, women in Sweden are invited to screening with a letter including a prebooked appointment. During the study period, between 1992 and 2016, the policy was to screen women aged 40–54 years every 18 months and those aged 55–69 years every 24 months, although screening age ranges vary by county. Participation rates vary from around 70% in urban areas to 90% in more rural areas. More details on data collection, such as screening intervals by age and county, are given in a previous article analyzing the same database (11).

We defined four categories of screening participation before a breast cancer diagnosis: *(a)* serial participants, defined as women who participated in both of their last two scheduled screening examinations; *(b)* intermittent participants, defined as women who participated in their last scheduled screening examination but not the next-to-last one; *(c)* lapsed participants, defined as women who participated in their next-to-last scheduled screening examination but not the last one; and *(d)* serial nonparticipants, defined as women who did not participate in either of their last two scheduled screening examinations.

The primary end points of this study were to estimate the effect of these different participation patterns on mortality from breast cancer and on incidence of breast cancers proving fatal within 10 years after diagnosis. Additional analyses to correct for potential sources of bias from lead time or self-selection for screening (see Statistical Analysis section) were also performed.

Statistical Analysis

Statistical analyses were performed by a team of statistician-epidemiologists (G.H.H.J., M.M.S.K., and C.Y.H. with 1–10 years of experience; A.M.F.Y., S.Y.H.C., S.L.S.C., T.H.H.C., and S.W.D. with more than 20 years of experience). Cancer incidence was calculated up to 2 years after the last scheduled screening examination, so women were potentially aged up to 73 years at the time of their diagnosis. Breast cancer deaths were analyzed for cancers diagnosed after the commencement of the observation period in each county and in the relevant age range (40–73 years or 50–73 years), with no upper age limit for mortality.

Table 1: Counties Included in Analysis, with Screening Age Ranges, Periods of Observation, and Average Screening-eligible Population

County	Screening Age Range (y)	Period of Observation		Total Average Eligible Population
		Breast Cancer Mortality	Breast Cancer was Fatal within 10 Years	
Stockholm	50–69	1992–2016	1992–2007	202 021
Dalarna	40–69	1993–2016	1993–2007	52 721
Värmland	50–69	1993–2016	1993–2007	33 857
Örebro	50–69	1992–2016	1992–2007	32 031
Västmanland	40–69	1992–2016	1992–2007	48 019
Gävleborg	40–69	2001–2016	2001–2007	53 993
Västernorrland	40–69	1997–2016	1997–2007	47 386
Västerbotten	50–69	1997–2016	1997–2007	29 751
Norrbotten	40–69	1997–2016	1997–2007	49 312
Total	…	…	…	549 091

Rate data were analyzed with Poisson regression (12), producing relative risks (RRs) and 95% CIs for all nine counties combined. $P < .05$ was considered to indicate a significant difference. The two end points were analyzed according to the different participation groups and were offset by the person-years of observation.

Person-years were calculated separately for each end point. For each year of observation, person-years were calculated as the total observation time contributed by women still alive in that year and eligible or previously eligible for screening (in the 2 years before diagnosis). The incidence of breast cancers proving fatal within 10 years could be calculated only for those years for which we had more than 10 years of follow-up data. For this end point, the person-years were calculated using the number of women in the screening age range in each year of observation. Because these comparisons are contemporaneous with respect to time of diagnosis, there is no possibility of confounding with changes in therapeutic practice over time. However, we performed a number of subsidiary analyses, adjusting for other potential sources of bias, notably self-selection bias in comparison with serial nonparticipants, whereby those who choose not to undergo screening may be at different risk a priori from the general population in terms of socioeconomic status, health behavior, or comorbidities and lead time (ie, the amount of time by which a cancer diagnosis has been advanced by screening) bias (in the analysis of cancers proving fatal within 10 years after diagnosis).

Details on these adjustments are available in Appendix E1 (online) and in an earlier article analyzing data from the same population (11). Methodologic details of the correction for self-selection bias are given by Duffy et al (13). Analyses were performed with SAS software (version 9.4; SAS Institute).

Results

We evaluated data in a total average population of 549 091 women (average age, 58.9 years ± 6.7 [standard deviation]) over average observation periods of 22 years (maximum, 25 years) for mortality and 13 years (maximum 16 years) for breast cancers that were fatal within 10 years after diagnosis. Average numbers of women in the four groups were as follows: serial participants, 392 135; intermittent participants, 41 746; lapsed participants, 30 945; and serial nonparticipants, 84 265. Table 1 shows the counties included in this analysis, along with screening age ranges, periods of observation, and total average population of women eligible for screening mammography over the periods of observation. We also had individual-level data in a subgroup of 37 078 women with breast cancer in the same population.

We identified 3995 breast cancer deaths in the nine counties during the observation period. These are tabulated with person-years of follow-up according to county and participation status in Table 2. In addition, the table gives the RRs and 95% CIs on these for all counties combined. There was a 49% (100–19.6/38.2) reduction in mortality in serial participants compared with serial nonparticipants (RR = 0.51; 95% CI: 0.48, 0.55; $P < .001$). Lesser reductions of 33% (100–25.5/38.2) and 28% (100–27.7/38.2) were observed in intermittent (RR = 0.67; 95% CI: 0.59, 0.76; $P < .001$) and lapsed (RR = 0.72; 95% CI: 0.63, 0.83; $P < .001$) participants, respectively. There was a significant reduction in mortality in the serial participants compared with the intermittent participants (RR = 0.77; 95% CI: 0.69, 0.86; $P < .001$). There was also a significant reduction in mortality in the serial participants compared with the lapsed participants (RR = 0.70; 95% CI: 0.61, 0.80; $P < .001$). The mortality rate of intermittent participants did not differ significantly from that of lapsed participants (RR = 0.92; 95% CI: 0.78, 1.08; $P = .16$). Figure 1 shows the cumulative breast cancer mortality over time for each of the four different participation status groups for all counties combined.

A total of 2589 cancers proved fatal within 10 years. Table 3 shows the corresponding total numbers of fatal cancers and person-years of follow-up for all counties combined, with the RRs and 95% CIs. Women who attended both screenings (serial participants) showed a 50% (100–28.5/56.8) reduction in breast cancers that were fatal at 10 years (RR = 0.50; 95% CI: 0.46, 0.55; $P < .001$) compared with serial nonparticipants. Again, smaller reductions were observed for intermittent participants, who showed a 36% (100–36.4/56.8) reduction (RR = 0.64; 95% CI: 0.55, 0.75; $P < .001$), and lapsed participants, who had a 25%

Table 2: Breast Cancer Deaths, Person-Years of Observation, and Average Rates of Incidence-based Breast Cancer Mortality per 100 000 Person-Years by County and Participation Status

County and Parameter	Serial Participants	Intermittent Participants	Lapsed Participants	Serial Nonparticipants
Stockholm				
Breast cancer deaths	982	201	141	614
Person-years of follow-up	4 512 125	655 132	493 891	1 474 315
Mortality rate per 100 000 person-years	21.8	30.7	28.5	41.6
Dalarna				
Breast cancer deaths	214	17	30	59
Person-years of follow-up	1 250 696	99 479	76 824	124 707
Mortality rate per 100 000 person-years	17.1	17.1	39.1	47.3
Värmland				
Breast cancer deaths	172	22	10	67
Person-years of follow-up	877 085	70 745	44 875	149 086
Mortality rate per 100 000 person-years	19.6	31.1	22.3	44.9
Örebro				
Breast cancer deaths	215	13	21	55
Person-years of follow-up	930 499	94 313	55 351	177 609
Mortality rate per 100 000 person-years	23.1	13.8	37.9	31.0
Västmanland				
Breast cancer deaths	244	23	18	63
Person-years of follow-up	1 264 382	96 565	81 914	205 594
Mortality rate per 100 000 person-years	19.3	23.8	22.0	30.6
Gävleborg				
Breast cancer deaths	102	9	11	30
Person-years of follow-up	812 182	68 358	54 132	130 961
Mortality rate per 100 000 person-years	12.6	13.2	20.3	22.9
Västernorrland				
Breast cancer deaths	179	16	11	36
Person-years of follow-up	925 136	78 158	54 647	137 185
Mortality rate per 100 000 person-years	19.3	20.5	20.1	26.2
Västerbotten				
Breast cancer deaths	127	14	6	37
Person-years of follow-up	666 175	53 189	39 436	79 286
Mortality rate per 100 000 person-years	19.1	26.3	15.2	46.7
Norrbotten				
Breast cancer deaths	158	17	19	42
Person-years of follow-up	971 721	83 915	62 471	145 019
Mortality rate per 100 000 person-years	16.3	20.3	30.4	29.0
Total				
Breast cancer deaths	2393	332	267	1003
Person-years of follow-up	12 210 001	1 299 854	963 541	2 623 762
Mortality rate per 100 000 person-years	19.6	25.5	27.7	38.2
Relative risk	0.51 (0.48, 0.55)	0.67 (0.59, 0.76)	0.72 (0.63, 0.83)	1.00

Note.—Data in parentheses are 95% CIs.

reduction (100–42.4/56.8) (RR = 0.75; 95% CI: 0.63, 0.88; $P <$ .001). There was a significant reduction in breast cancers that were fatal at 10 years in serial participants compared with intermittent participants (RR = 0.78; 95% CI: 0.67, 0.90; $P <$ .001). There was also a significant reduction compared with lapsed participants (RR = 0.67; 95% CI: 0.57, 0.79; $P <$ .001). The rates did not differ significantly between intermittent and lapsed participants (RR = 0.86; 95% CI: 0.70, 1.06; P = .13). Figure 2 shows the cumulative incidence over time of breast cancers fatal within 10 years of diagnosis according to participation status.

After adjustment for potential self-selection bias, the reductions in breast cancer mortality when compared with serial nonparticipants were of similar magnitude to the unadjusted values for serial participants (RR, 0.55; 95% CI: 0.49, 0.62; $P <$ .001), intermittent participants (RR, 0.73; 95% CI: 0.61, 0.85; $P <$ .001), and lapsed participants (RR, 0.78; 95% CI: 0.66, 0.92; P = .003). After adjustment for potential self-selection bias and lead time, the reductions in incidence of breast cancers that were fatal within 10 years of diagnosis were as follows: RR of 0.56 (95% CI: 0.48, 0.64; $P <$ .001) for serial participants, RR of

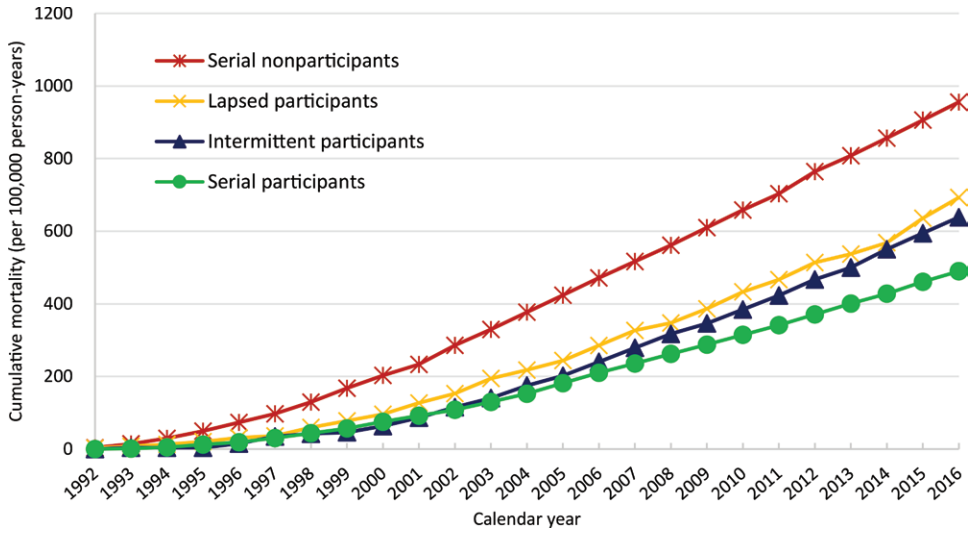

Figure 1: Graph shows cumulative mortality from breast cancer per 100 000 person-years in nine Swedish counties from 1992 to 2016 according to participation status: serial participants, who participated in both of the last two screenings; intermittent participants, who participated in only the most recent screening; lapsed participants, who participated in only the next-to-last screening; and nonparticipants, who participated in neither of the last two screenings. Serial participants experienced the lowest cumulative mortality from breast cancer as follow-up increased.

Table 3: Incidence Rates of Breast Cancers Proving Fatal within 10 Years according to Participation Status

Parameter	Serial Participants	Intermittent Participants	Lapsed Participants	Serial Nonparticipants
Breast cancers fatal within 10 years	1537	215	171	666
Person-years	5 389 083	590 461	403 147	1 172 783
Incidence rate per 100 000 person-years	28.5	36.4	42.4	56.8
Relative risk	0.50 (0.46, 0.55)	0.64 (0.55, 0.75)	0.75 (0.63, 0.88)	1.00

Note.—Data in parentheses are 95% CIs.

0.71 (95% CI: 0.58, 0.86; $P < .001$) for intermittent participants, and RR of 0.81 (95% CI: 0.66, 0.98; $P = .03$) for lapsed participants.

Discussion

To address the hypothesis that breast cancer mortality would differ between serial participants, intermittent participants, lapsed participants, and nonparticipants, we analyzed data on breast cancer mortality and incidence of subsequently fatal breast cancers between 1992 and 2016 in nine counties in Sweden, covering 549 091 women aged 40–69 years at the time of invitation to screening. We classified the population and the end points according to participation in the last two invitations to mammographic screening. We found substantial and significant reductions for both mortality from breast cancer (relative risk [RR], 0.51; 95% CI: 0.48, 0.55; $P < .001$) and incidence of breast cancers proving fatal within 10 years (RR, 0.50; 95% CI: 0.46, 0.55; $P < .001$) for women who had participated in both of their previous two screening examinations (serial participants) compared with women who did not attend either of their last two screening examinations (serial nonparticipants). Lesser but significant reductions were observed in intermittent participants who attended their most recent screening examination but not the one before and in lapsed participants who had attended their previous screening examination but not the most recent. When compared with intermittent participants, serial participants showed substantial and significant reductions in breast cancer mortality (RR, 0.77; 95% CI: 0.69, 0.86; $P < .001$) and in cancers proving fatal within 10 years (RR, 0.78; 95% CI: 0.67, 0.90; $P < .001$). Serial participants showed similarly significant but larger reductions compared with lapsed participants for both breast cancer mortality (RR, 0.70; 95% CI: 0.61, 0.80; $P < .001$) and incidence of cancer proving fatal within 10 years (RR, 0.67; 95% CI: 0.57, 0.79; $P < .001$).

A study analyzing the same database to compare the screening performance in the nine individual counties found the outcome of patients participating in screening to be very similar across all counties (9). However, the outcome of patients not participating in screening varied considerably among the counties. Failure to separate the outcome of nonparticipants from that of participants gives an erroneous perception of variability in services provided by the screening units. This similarity of outcomes in women participating in screening gives confidence in the combined results of the nine counties.

To our knowledge, only one other study has reported the association between different patterns of adherence to screening with risk of breast cancer mortality in a prospective analysis (14). In that study, Morrell et al defined regular screening

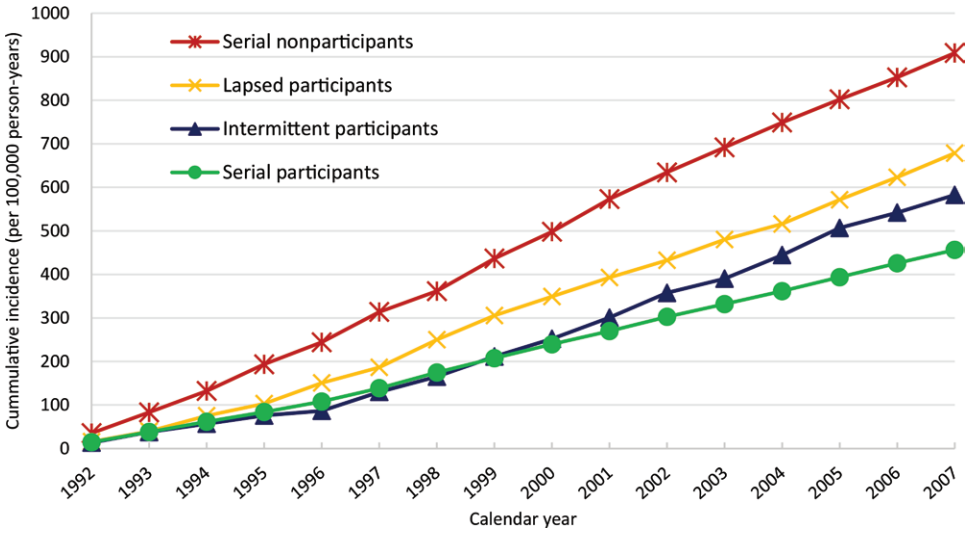

Figure 2: Graph shows cumulative incidence of breast cancers that were fatal within 10 years of diagnosis per 100 000 person-years in nine Swedish counties from 1992 to 2007 according to participation status: serial participants, who participated in both of the last two screens; intermittent participants, who participated in only the most recent screening; lapsed participants, who participated in only the next-to-last screening; and nonparticipants, who participated in neither of the last two screenings. Serial participants experienced the lowest cumulative incidence of fatal breast cancer within 10 years of diagnosis as follow-up increased.

as participants having been screened three times with a mean interval of 30 months or less, and similarly found a substantial benefit of regular adherence. There is also some evidence of an increased benefit with increased numbers of screening examinations attended in case control studies (7,15).

Previous studies relying on the same database have shown substantial reductions in breast cancer mortality and incidence of breast cancers fatal within 10 years of diagnosis with participation in screening (10,11). Our current study shows a greater mortality benefit for those attending two successive screening examinations than for those who attended only one examination. Further understanding of the cancers proving fatal despite attendance at screening and the use of modern therapeutic regimens is of great interest from a biologic, clinical, and screening organizational viewpoint. In previous studies, we used imaging biomarkers to identify subgroups of breast malignancies that are resistant to the benefits of both screening mammography and modern therapeutic regimens, such as small invasive carcinomas accompanied by casting-type calcifications, architectural distortion, or basal phenotype (16–18).

Women in this study were all cared for according to Swedish national guidelines for breast cancer. The guidelines consider stage, tumor grade, receptor status (including the human epidermal growth factor receptor type 2), proliferation, and patient age; detection mode is not a criterion for treatment recommendation.

This is an observational study. However, the data were prospectively collected, and assignment of participation status and characterization of outcome were independent of the research team. Also, adjustments were made for the main sources of potential biases (self-selection for screening and lead time). The results were only slightly changed with these adjustments, showing a significant reduction in risk of dying from breast cancer with screening participation and a greater reduction with greater adherence to the screening regimen. Some other limitations of this study were detailed in the previous article analyzing the same data set (11). These include data unavailability from private off-program facilities and the fact that population denominator data were supplied in tabular form. However, the population denominator data were supplied with sufficient granularity to have numbers in the appropriate age group according to serial screening status for each individual calendar year. Also, we did not have data on potential confounding factors. However, the large study population more than outweighs the absence of individual information on the population at risk. In addition, by using prior estimates, we were able to correct for self-selection bias potentially conferred by such confounders.

In conclusion, regular participation in screening mammography is necessary to optimize the reduction in risk of dying from breast cancer. Missing even one screening examination confers a significant increase in risk. This is an important message for women in the screening age groups, their referring physicians, and public health decision makers.

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