Original Article

Mammography Screening Reduces Rates of Advanced and Fatal Breast Cancers: Results in 549,091 Women

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BACKGROUND: It is of paramount importance to evaluate the impact of participation in organized mammography service screening independently from changes in breast cancer treatment. This can be done by measuring the incidence of fatal breast cancer, which is based on the date of diagnosis and not on the date of death. **METHODS:** Among 549,091 women, covering approximately 30% of the Swedish screening-eligible population, the authors calculated the incidence rates of 2473 breast cancers that were fatal within 10 years after diagnosis and the incidence rates of 9737 advanced breast cancers. Data regarding each breast cancer diagnosis and the cause and date of death of each breast cancer case were gathered from national Swedish registries. Tumor characteristics were collected from regional cancer centers. Aggregated data concerning invitation and participation were provided by Sectra Medical Systems AB. Incidence rates were analyzed using Poisson regression. **RESULTS:** Women who participated in mammography screening had a statistically significant 41% reduction in their risk of dying of breast cancer within 10 years (relative risk, 0.59; 95% CI, 0.51-0.68 [*P* < .001]) and a 25% reduction in the rate of advanced breast cancers (relative risk, 0.75; 95% CI, 0.66-0.84 [*P* < .001]). **CONCLUSIONS:** Substantial reductions in the incidence rate of breast cancers that were fatal within 10 years after diagnosis and in the advanced breast cancer rate were found in this contemporaneous comparison of women participating versus those not participating in screening. These benefits appeared to be independent of recent changes in treatment regimens. ***Cancer* 2020;126:2971-2979**. © 2020 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: breast cancer, fatality, mammography, mortality, screening.

INTRODUCTION

Randomized trials and incidence-based mortality studies of service screening programs have demonstrated a substantial reduction in breast cancer mortality associated with invitation to and participation in mammographic screening.[1-4] Measuring the effect of mammography screening on breast cancer mortality in observational studies suffers from a methodological challenge because the mortality data apply to cancers diagnosed and treated during many previous years, during which participation in screening and exposure to various therapies may be different from those prevailing in the year of death.

A recently described analytic strategy addresses this methodological problem by adopting a new endpoint: the incidence of breast cancer becoming fatal within 10 and 20 years after diagnosis.[5] In that analysis, the determinants of death from breast cancer, exposure to mammography screening and breast cancer treatment, belong to the same time period. This novel method also enabled the estimation of changes during discrete time periods in women participating or not participating in screening. A 60% lower incidence of breast cancer that was fatal within 10 years was observed in women participating in screening compared with women not participating in screening.

These results originated from a single county in Sweden.[5] We decided to extend this study to a larger population to determine whether we would observe a similar decrease in the incidence rate of breast cancers that were fatal within 10 years after diagnosis, as well as whether the incidence rate of advanced breast cancer in women participating in mammography screening also would be reduced.

The current study was performed using data from a population of greater than one-half million women aged 40 to 69 years. This population accounts for approximately 30% of the screening-eligible women in Sweden. Detailed annual data for each county are provided in Supporting Information Tables 1 and 2.

MATERIALS AND METHODS

We obtained data from the Swedish Cancer Register regarding breast cancer cases diagnosed in women who were eligible for screening and residing in 9 Swedish counties. The cause and date of death of each patient who died of breast cancer were collected from the Swedish Cause of Death Register of the Swedish National Board of Health and Welfare. Data were available for the following 9 Swedish counties (Fig. 1): Västmanland, Dalarna, Örebro, Gävleborg, Värmland, Västerbotten, Norrbotten, Västernorrland, and Stockholm, with the latter having substantial opportunistic screening activity.[6] In addition, we collected data regarding tumor characteristics from the clinical databases for breast cancer maintained by the regional cancer centers of the Northern, Uppsala-Örebro, and Stockholm-Gotland health care regions. Invasive breast cancer measuring >20 mm and/or with ≥4 metastatic axillary lymph nodes was defined as an advanced breast cancer for the purpose of the current study. This definition was used to circumvent differences in staging resulting from the introduction of the sentinel lymph node technique during

Figure 1. Map of Sweden showing the locations of the 9 counties (each indicated administratively in Sweden by one or two letters of the alphabet) involved in the current study.

the study period. Whereas previous staging would not label a cancer having a few malignant cells in a sentinel lymph node as lymph node–positive disease, changes in the registration rules for staging tumors having micrometastases in a lymph node caused these cases to become registered to a higher stage. The cancer data were linked to each woman's individual screening data regarding invitation and participation provided by Sectra Medical Systems AB (Linköping, Sweden), which maintains the information system for breast cancer screening in these 9 Swedish counties. Thus, we used a classification of individual screening status independent of the investigators and screening centers.

Breast cancer screening in Sweden is performed using 2-view mammography. The policy is to screen women aged 40 to 54 years every 18 months, and women aged 55 to 69 years every 24 months. However,

TABLE 1. Counties Included in the Current Analysis, With Screening Age Ranges, Periods of Observation, and Average Screening-Eligible Populations

County	Screening Age Range, Years	Period of Observation (Advanced Cancer Incidence)	Range of Observation, Years	Period of Observation (Incidence of Cancers That Were Fatal Within 10 Years)	Range of Observation, Years	Average Eligible Population
Stockholm	50-69	1992-2016	25	1992-2007	16	202,021
Dalarna	40-69	1993-2016	24	1993-2007	15	52,721
Värmland	50-69	1993-2016	24	1993-2007	15	33,857
Örebro	50-69	1992-2016	25	1992-2007	16	32,031
Västmanland	40-69	1992-2016	25	1992-2007	16	48,019
Gävleborg	40-69	2001-2016	16	2001-2007	7	53,993
Västernorrland	40-69	1997-2016	20	1997-2007	11	47,386
Västerbotten	50-69	1997-2016	20	1997-2007	11	29,751
Norrbotten	40-69	1997-2016	20	1997-2007	11	49,312

the age range at which to offer screening is a decision which was made at the county level. Accordingly, age ranges for screening varied by county, as did dates of available data. Table 1 shows the counties with screening age ranges, periods of observation, and the average number of women within the population who were eligible for screening. The average populations in Table 1 were estimated by retrieving the published population for the relevant county and age group in each year from national statistics and calculating the averages of these over the relevant period of observation. We had aggregated data for a population of 549,091 women who were eligible for screening, and individual-level data regarding 21,183 women with breast cancer and 2473 breast cancer deaths among these women. The average observation period was 13 years (range, 7-16 years) for measuring the incidence of breast cancer that was fatal within 10 years after diagnosis and 22 years (range, 16-25 years) for measuring the incidence of advanced breast cancer. Person-years for all breast cancers were calculated for women aged 40 to 69 years from the start of the study period until the date of diagnosis of breast cancer, attainment of age 69 years, death, or the end of the study period, whichever came first.

The Ethics Committee gave our research group permission to use individual-level data regarding breast cancer cases and aggregate data on >540,000 women included in this project. However, because all individual data in the screening registry were available to Sectra Medical Systems AB prior to providing us with the aggregated data, we requested that the breast cancer cases be removed from the aggregated data after the year of diagnosis. Thus, women with a breast cancer diagnosis did not contribute to the person-years in the years after the year of their diagnosis. The tabular aggregated data in the numerator and in the denominator, stratified by each county and year of diagnosis separately for participating and nonparticipating women, are provided in Supporting Tables 1 and 2. These totals constituted the person-years at risk.

To create a contemporaneous comparison between women participating and not participating in screening, and to adjust for changes in treatment regimens, we classified the population at risk (the denominator of our incidence calculations) for each year of observation according to each woman's current participation in screening. This was defined as follows: if a woman participated in her most recent scheduled screening mammogram, she was classified as participating in screening. Those not participating were classified as nonparticipants. This classification was made annually on the last day of each year.

Each case of breast cancer (the numerator of our incidence calculations) was classified only once, on the day of diagnosis, according to the participation status of the women diagnosed with breast cancer. Thus, breast cancers in participants were those diagnosed at the most recent screen plus cases not diagnosed at screening but detected in the interval after the screen and before the next scheduled screening examination (interval cancers). The breast cancers arising in women who did not participate in their most recent scheduled screening examination were considered as breast cancers occurring in nonparticipants.

The current study was approved by the Ethics Committee of Uppsala University (registration number 2017/147).

Statistical Analysis

Before any formal statistical inference, the cumulative incidence of advanced cancers and cancers that were fatal within 10 years was calculated by the accumulated annual rate of each outcome denoted as:

Cumulative incidence = $\sum d_i$, in which d_i is defined as the annual rate of the jth year (ie, the number of

relevant cases divided by the person-years at risk). These were plotted to describe the evolution of the screening effect on the 2 outcomes.

The effect size of reducing the number of advanced cancers and cancers that were fatal within 10 years as a result of breast cancer screening with mammography was estimated using the Poisson regression model, in which the counts of the 2 outcomes, assuming they followed the Poisson distribution[7] and offset by the person-year denominators, were regressed using a binary independent variable: whether or not to participate in screening.

The denominators were based on aggregate tabular data stratified by county, calendar year, and participation status, as noted above (see Supporting Tables 1 and 2). The data used for the analysis of the Poisson regression model suffice if we know the numerator as the number of breast cancers proven to be fatal within 10 years after diagnosis (counts) and the denominator as the underlying number of person-years. The tabular aggregated data in the numerator and in the denominator stratified by each county, year of diagnosis, and participation status as listed in Supporting Tables 1 and 2 basically are equivalent to information from 549,091 individuals.

Jonsson et al[8] estimated the average lead time of fatal cancers to be 0.29 years. Because the endpoint is the number of tumors proving fatal within 10 years, we therefore divided the person-years for the participants by a factor F, in which:

$$F = 1 + \frac{0.29}{10} = 1.029$$

This is equivalent to multiplying the estimated relative risk (RR) of cancers that were fatal within 10 years by 1.029. We further corrected the RR of dying of breast cancer within 10 years after diagnosis associated with participation in screening for self-selection bias using the method of Duffy et al,[9] using the estimate of an RR of 1.07 for breast cancer death unrelated to screening for nonattenders compared with an uninvited population.[10] Duffy et al[9] gave the estimate corrected for self-selection bias as:

$$RRc = p\psi Dr / \left(1 - \left(1 - p\right) Dr\right)$$

in which ψ is the RR uncorrected for self-selection, p is the proportion of people attending for screening (in this case, 0.8), and Dr is the RR of a person choosing not to be screened compared with an unscreened population (in this case, 1.07). Because lead time would

have a conservative influence, if any, on the incidence of invasive breast cancer measuring >20 mm and/or with ≥4 metastatic axillary lymph nodes, and because there is evidence that the self-selection bias that applies to mortality does not apply to the incidence of invasive breast cancer measuring >20 mm and/or with ≥4 metastatic axillary lymph nodes,[11] no correction was made to the RR for these breast cancers.
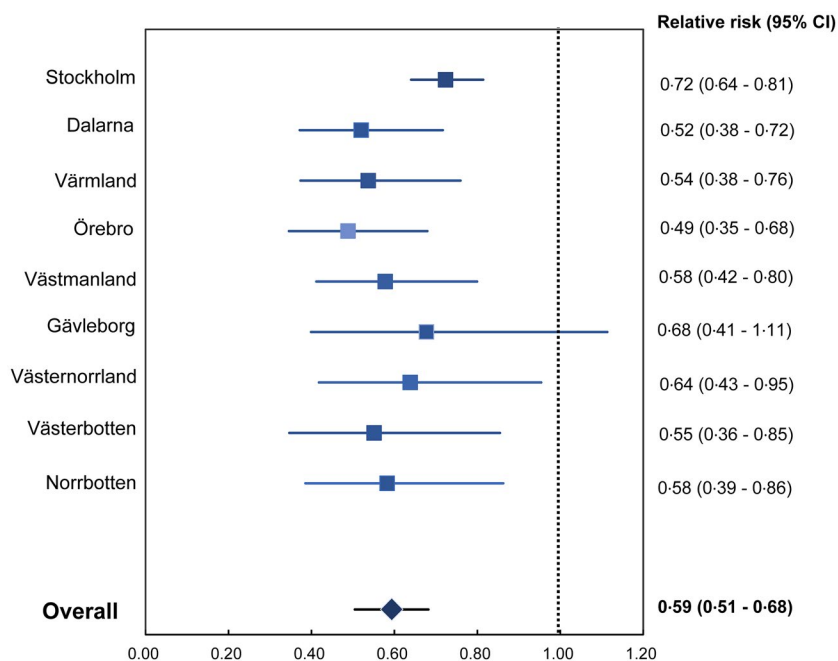
We combined the results from all 9 counties using a hierarchical Poisson regression model with random effects to capture the heterogeneity across counties (denoted by i) given each specific calendar year (denoted by j). The analytical framework was formed using a Bayesian-directed acyclic graphical model, as depicted in Supporting Figure 1. WinBugs 14 was used for all statistical analyses. The screening program is maintained by the Swedish taxpayer–funded general health insurance system organized on a county level. Virtually all breast cancer care is provided by this same system.

RESULTS

Table 2 shows the cumulative numbers and incidence rates of breast cancers that were fatal within 10 years after diagnosis and the corresponding person-years over the periods of observation for each county for women participating and not participating in screening. The corresponding RRs and the combined RR are shown in Figure 2. The heterogeneity across counties was found to be statistically significant ($P < .01$). As noted in Table 2, the variation among counties appeared to be due mainly to differences in the incidence of breast cancers that were fatal within 10 years among the nonparticipants, rather than to differences in outcome for those participating in screening. Figure 3 shows the cumulative incidence of breast cancers that were fatal within 10 years after diagnosis. The overall RR of breast cancers that were fatal within 10 years among women participating in screening was 0.59 (95% CI, 0.51-0.68; $P < .001$). After correction for potential lead time and self-selection, the conservative estimate of the reduction remained substantial at 34%, with an RR of 0.66 (95% CI, 0.55-0.79; $P < .001$). Table 3 shows the cumulative number of advanced breast cancers and corresponding person-years over the periods of observation for each county for women participating and not participating in screening. The corresponding RRs (with heterogeneity across counties; $P < .01$), with the RR for all counties combined, are shown in Figure 4. Figure 5 shows the cumulative incidence of advanced breast cancers over time. There was a statistically significant 25%

TABLE 2. Numbers and Incidence Rates of Breast Cancers That Were Fatal Within 10 Years After Diagnosis and the Corresponding Person-Years by County and Screening Participation

County	Nonparticipants in Screening			Participants in Screening		
	No. of Breast Cancers That Were Fatal Within 10 Years	No. of Person-Years	Incidence Rates of Breast Cancers That Were Fatal Within 10 Years per 100,000 Person-Years of Observation	No. of Breast Cancers That Were Fatal Within 10 Years	No. of Person-Years	Incidence Rates of Breast Cancers That Were Fatal Within 10 Years per 100,000 Person-Years of Observation
Stockholm	428	930,363	46.0	766	2,301,979	33.3
Dalarna	50	119,513	41.8	146	671,302	21.7
Värmland	43	78,004	55.1	125	42,291	29.6
Örebro	46	66,747	68.9	150	445,750	33.7
Västmanland	47	109,176	43.0	164	659,124	24.9
Gävleborg	20	61,280	32.6	70	316,670	22.1
Västernorrland	29	61,152	47.4	132	436,127	30.3
Västerbotten	26	68,791	37.8	86	412,903	20.8
Norrbotten	32	76,806	41.7	113	465,629	24.3
Total	721	1,571,832	45.9	1752	6,131,775	28.6

Figure 2. Meta-analysis of the relative risks of breast cancer that was fatal within 10 years after diagnosis.

reduction in the risk of advanced breast cancer in women participating in screening, with an RR of 0.75 (95% CI, 0.66-0.84; $P < .001$).

DISCUSSION

The major objective of the current study was to estimate the effect of participation in mammography screening on the incidence of advanced and fatal breast cancer compared with women who chose not to participate. The choice of whether or not to attend mammography screening becomes important in an era in which all women in a defined age cohort are invited to organized service screening, and programs are expected to describe the benefits and harms associated with participation. We analyzed data from a population of greater than one-half million women, which is nearly one-third of the women residing in Sweden who are eligible for mammography screening. The average observation time was 13 years for the incidence of breast cancer that was fatal within 10 years after diagnosis, and 22 years for the incidence
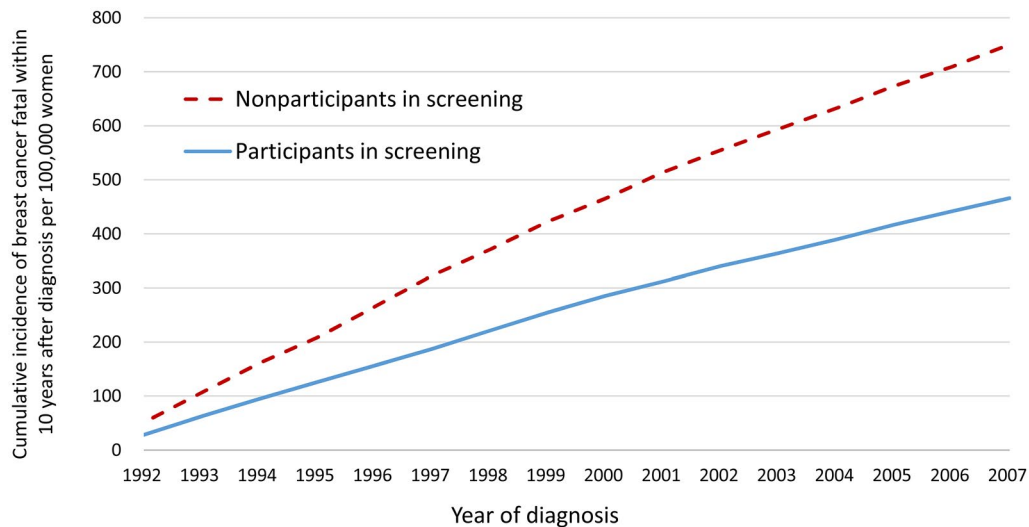
Figure 3. Cumulative incidence of breast cancer that was fatal within 10 years after diagnosis for all 9 counties combined.

TABLE 3. Numbers and Incidence Rates of Advanced Breast Cancers and Corresponding Person-Years by County and Screening Participation

County	Nonparticipants in Screening			Participants in Screening		
	No. of Advanced Breast Cancers	Person-Years	Incidence Rates of Advanced Breast Cancer per 100,000 Person-Years of Observation	No. of Advanced Breast Cancers	Person-Years	Incidence Rates of Advanced Breast Cancer per 100,000 Person-Years of Observation
Stockholm	1500	1,547,746	96.9	3481	3,901,832	89.2
Dalarna	140	205,865	68.0	559	1,081,399	51.7
Värmland	105	125,361	83.8	466	701,383	66.4
Örebro	112	121,884	91.9	408	712,327	57.3
Västmanland	183	183,648	99.6	663	1,030,628	64.3
Gävleborg	102	145,598	70.1	399	731,487	54.5
Västernorrland	102	117,573	86.8	445	811,036	54.9
Västerbotten	79	84,856	93.1	378	528,995	71.5
Norrbotten	113	147,752	76.5	502	839,575	59.8
Total	2436	2,680,283	90.9	7301	10,338,662	70.6

of advanced breast cancer. We found a 41% reduction (with a narrow 95% CI) in cancers that were fatal within 10 years after diagnosis among women who participated in screening and a 25% reduction in the incidence of advanced breast cancer (defined as invasive breast cancer measuring >20 mm and/or with ≥4 metastatic axillary lymph nodes). A conservative estimate adjusting for potential lead time and self-selection biases indicated a significant 34% reduction in cancers that were fatal within 10 years among screening participants.

To the best of our knowledge, the current study is only the second study to date to investigate the influence of mammography screening on the incidence of breast cancers subsequently proving to be fatal.[5] For the related question of

the effect of screening on incidence-based mortality, results inevitably vary,[3,12] but reviews have indicated that the body of evidence worldwide supports a substantial reduction in breast cancer mortality as a result of screening.[2,4] However, as noted above, the method used in the current study, namely using the incidence of cancers proving fatal within 10 years, more accurately connects outcome to exposure status at the time of diagnosis. Similarly, although results also vary with respect to the effect of screening on the incidence of advanced cancers,[13,14] reviews have indicated that the body of evidence supports a reduction in advanced stage disease with screening.[2,15] More specifically, the International Agency for Research on Cancer concluded that studies that compared screened with unscreened populations demonstrated
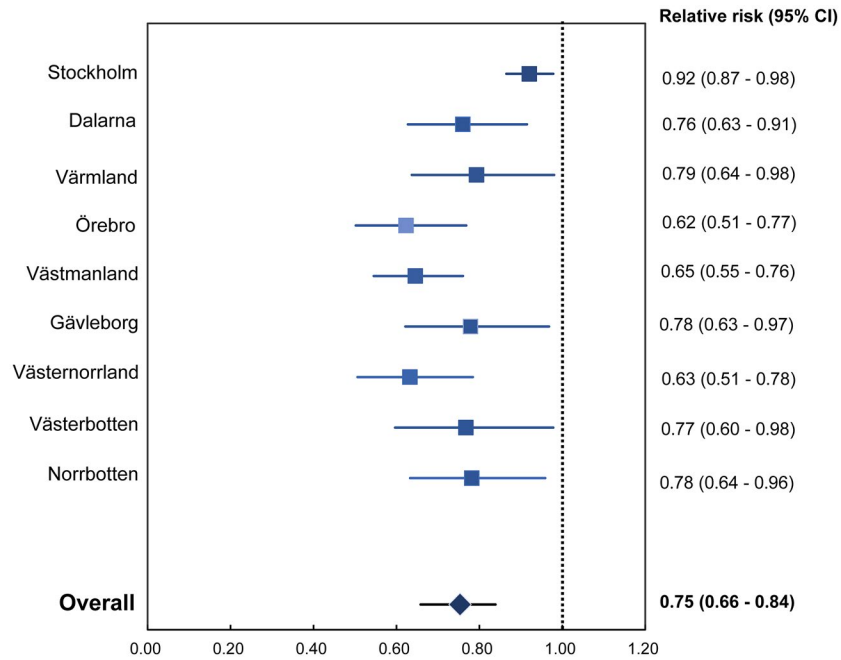
Relative risk (95% CI)

	Relative risk (95% CI)
Stockholm	0.92 (0.87 - 0.98)
Dalarna	0.76 (0.63 - 0.91)
Värmland	0.79 (0.64 - 0.98)
Örebro	0.62 (0.51 - 0.77)
Västmanland	0.65 (0.55 - 0.76)
Gävleborg	0.78 (0.63 - 0.97)
Västernorrland	0.63 (0.51 - 0.78)
Västerbotten	0.77 (0.60 - 0.98)
Norrbotten	0.78 (0.64 - 0.96)
Overall	**0.75 (0.66 - 0.84)**

Figure 4. Meta-analysis of the relative risks of advanced breast cancer.
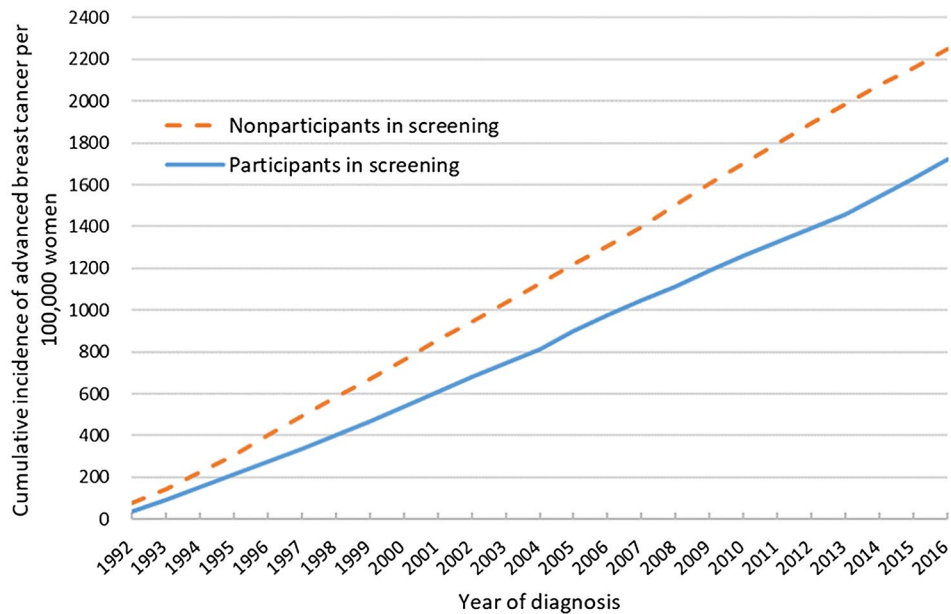
Figure 5. Cumulative incidence of advanced breast cancer for all 9 counties combined.

a substantial reduction in advanced cancer incidence, whereas those ecological studies that did not actually classify by screening exposure showed smaller effects.[2] The results of the current study, obtained from an average population of greater than one-half million women, confirmed the substantial effects of screening on both outcomes.

With the introduction of adjuvant breast cancer therapies, there has been speculation regarding the relative contribution of screening versus therapy to the observed reduction in breast cancer mortality, and whether the importance of early detection in reducing breast cancer deaths will diminish as newer therapies are introduced. To our knowledge, evidence to date with which to address this question has been elusive because mortality analyses consist of deaths from breast cancer diagnosed over many years, during which time adjuvant therapies and diagnostic imaging have been evolving. However, the methodology applied in the current study to measure the incidence of breast cancers that were fatal within 10 years after diagnosis overcomes this limitation because in each diagnosis year, patients with breast cancer who have participated and not participated in screening receive treatment according to the same protocols appropriate for their stage of disease at the time of diagnosis, regardless of detection mode. Thus, changes in therapy cannot account for the current study results. Our evaluation of outcomes demonstrated that women who attended screening, and typically had their breast cancer diagnosed at an earlier stage, benefited substantially more from the state-of-the-art therapy existing at the time of diagnosis and over the period of our analysis compared with women who did not attend screening. Detection at an earlier stage through participation in mammography screening confers a significant reduction in the risk of death from breast cancer in this era when modern adjuvant therapies are available. It also should be noted that these results are from contemporaneous comparisons between women participating and not participating in screening, and therefore are independent of changes in treatment over time. The findings of the current study are consistent with results from large current studies in the United Kingdom and the Netherlands.[16,17]

In addition to the contemporaneous comparison, the strengths of the current study included the large numbers and therefore the statistical precision of the overall results and the experience from a national screening service with long-term follow-up. Furthermore, data were collected from registries with high coverage and the outcomes both for deaths and later stage of cancer were assigned from sources independent of the screening centers or the research group. In addition, participation or nonparticipation in screening was assigned from an administrative system independent of the investigators. Women in Sweden receive therapy that is appropriate for their stage of disease at the time of diagnosis regardless of whether they participated in screening.

With regard to limitations, there were no data available regarding the extent of mammography screening offered by private facilities, an activity that is mostly restricted to the Stockholm region. Our denominator data were supplied to us in tabular form, which necessitated a loss of information regarding continuous time to events, replacing it with data aggregated into discrete years. However, with our large numbers, there still remained considerable statistical power for analysis. We did not have individual information regarding potential confounding factors, but prior estimates of the likely effect of these factors enabled us to correct for possible self-selection bias arising from such confounders.

These results from one-half million women with an independent classification of screening participation and breast cancer outcome, and taking into account the effects of new treatments, demonstrated that the results from the mammography screening trials can be attained in routine settings and over long-term periods, thus making routine mammography screening a reproducible service for reducing death from breast cancer. Furthermore, the results of the current study indicated the feasibility of collecting critical screening data on a national basis, thereby facilitating more detailed studies of screening performance over time. Such prospective data on a large scale will be important when evaluating new techniques implemented for screening purposes, for which long-term follow-up and large statistical precision will be critical.

The benefits of participating in mammography screening are truly substantial and save lives through early detection, lives that otherwise would have been lost under the prevailing therapy at the time of diagnosis.

CONFLICT OF INTEREST DISCLOSURES

László Tabár received personal fees from General Electric Healthcare for the preparation of automated breast ultrasound teaching cases as well as honoraria and travel costs to attend speaking engagements; personal fees from Mammography Education Inc in his capacity as president of the company, which organizes continuing medical education courses regarding breast imaging; and personal fees from Three Palm Software for consultation related to breast imaging interpretation, all for work performed outside of the current study. The authors do not consider these conflicts of interest but disclose them for completeness. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

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