Reduction in Breast Cancer Mortality from the Organised Service Screening with Mammography: 2. Validation with Alternative Analytic Methods

The Swedish Organised Service Screening Evaluation Group

Abstract

Background: **In our companion article, incidence-based mortality analysis of data from breast cancer screening programs in 13 areas in Sweden indicated a 40% to 45% reduction in incidence-based breast cancer mortality among women actually screened. In this article, we apply new analytic methods for the evaluation of breast cancer mortality, using all breast cancer deaths in the period under study.**

Methods: **Data were available from 13 areas on breast cancer mortality by year of diagnosis, year of death, and screening exposure. The period of study varied by area, the overall range of year of diagnosis being 1968 to 2001. We had data on 6,231 deaths and an average population of 555,676 women ages 40 to 69 years. Analysis of the effect of being screened was conducted using an alternative statistical analysis applied to all breast cancer deaths in the period of study, in addition to the incidence-based mortality analysis in our companion article. Data were analyzed using Poisson regression and adjusted for self-selection bias, contemporaneous changes in incidence, and changes in mortality independent of screening.**

Results: **Using all deaths in the period of observation, a significant 42% reduction in breast cancer mortality was observed, adjusting for contemporaneous changes independent of screening [relative risk (RR), 0.58; 95% confidence interval (95% CI), 0.53-0.62]. After further adjustment for self-selection bias, the mortality reduction was 39% (RR, 0.61; 95% CI, 0.55-0.68), also highly significant.**

Conclusions: **These results indicate a reduction in breast cancer mortality of 39% in association with screening, after adjustment for contemporaneous changes and self-selection bias. These results confirm previous conclusions arrived at using incidence-based mortality analyses.** (Cancer Epidemiol Biomarkers Prev 2006;15(1):52–6)

Introduction

Our companion article (1) analyses incidence-based mortality from breast cancer, comparing deaths from breast cancers diagnosed in the prescreening epochs in 13 Swedish areas with deaths from breast cancers diagnosed in the corresponding screening epochs. The results include a 43% reduction in breast cancer mortality associated with being screened, after adjustment for self-selection for screening, and a 27% reduction associated with the policy of offering screening. This is consistent with evidence from the randomized trials of breast cancer screening (2, 3).

Incidence-based mortality has been used before for evaluation of breast screening in Sweden, Italy, and Finland (4-6). As noted in our companion article, the use of incidence-based mortality has been criticized (7, 8), and although the objections have been shown to be mistaken (9), it is clearly desirable to use all information available on breast cancer mortality and not to discard potentially useful data. In this article, therefore, we develop a method of analysis that uses all deaths from all tumors diagnosed throughout the total period of observation. We apply the method to all breast cancer deaths in both epochs in the 13 Swedish areas in our companion article. In this analysis, we also aim to take account of changes in incidence and fatality of breast cancers taking place during the period of study independently of screening and to adjust for self-selection bias.

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Materials and Methods

Data Available. We studied breast cancer mortality data from 13 areas in Sweden, after excluding one county, previously included in our seven-county analysis (5), and two newly participating counties, with <10 years of screening activity. For this purpose, Stockholm, the capital city, is treated as five areas, as it has five large populations served by five screening units. The 13 areas are listed in Table 1, with the period of study, age range invited for screening, number of breast cancer deaths during the period, and average population for each area. The periods studied are mostly approximately divided equally between the prescreening and screening epoch. See our companion article for more details. For some counties, the years available are slightly different from our companion article. This is because extra years can be used because there is no longer the requirement to have equal prescreening and screening epochs (1) or because for some counties, individual year of diagnosis and death were not available in digital form throughout the prescreening epoch.

We used data on deaths in women ages 40 to 69 or 50 to 69 years, depending on the age at starting screening in the various areas. Some counties also offered screening to women ages 70 to 74 years, but we restricted this analysis to women ages <70 years. Breast cancer diagnoses, including both invasive and ductal carcinoma *in situ*, were obtained from the Swedish Cancer Registry, backed up by the Regional Oncological Centres. If a woman had more than one breast cancer, the earlier diagnosis was used. Breast cancer deaths were obtained from the National Cause of Death Register, including only those with breast cancer as the underlying cause of death. All reporting of mortality below refers to mortality from breast cancer as underlying cause.

The size of the female populations by year and county in the age ranges offered screening were provided by Statistics Sweden. The screening centers provided data on the screening exposure for women who died of breast cancer

Table 1. Periods studied, average populations and age groups invited to screening

Area	Period studied	Breast cancer deaths	Average population	Age group invited
Dalarna	1968-2000	810	51,118	40-69
Gävleborg	1968-2001	840	52,807	40-69
Örebro	1979-2001	424	48,502	40-69
Norrbotten	1976-2001	419	46,016	40-69
Västernorrland	1974-2001	638	47,633	40-69
Södersjukhuset*	1977-2000	593	48,561	50-69
Uppsala	1985-2001	250	45,259	40-69
Västmanland	1979-2001	352	46,115	40-69
Södermanland	1979-2000	384	45,445	40-69
Skärholmen*	1977-2000	445	34,515	50-69
Danderyd Hospital*	1977-2000	411	30,526	50-69
Karolinska Hospital*	1977-2000	301	28,001	50-69
Sankt Göran Hospital*	1979-2000	364	31,179	50-69
Overall	—	6,231	555,677	—

NOTE: Dates for Örebro refer to epoch of diagnosis. Each epoch had an additional follow-up of 5 years for mortality. For explanation, see Materials and Methods.
*Stockholm centers.

and of the population, enabling us to calculate deaths and person-years in each calendar year by screening exposure. For each year, the percentage exposed to screening rather than invited was calculated, and the person-years of observation were divided into exposed and unexposed using that percentage. Cancer cases exposed to screening are defined as those attending their last scheduled screening appointment before diagnosis.

The total population studied averaged 555,677. There was a total of 6,231 breast cancer deaths available for analysis.

Statistical Analysis. For this analysis, Poisson regression was used (10), and for each year in the period of observation, we counted all breast cancer deaths, with no exclusions based on year of diagnosis. We estimated the effect of exposure status without misclassification by linking each death to time of and exposure status at diagnosis. The basic log-linear model was as follows:

$$\ln(M_{ids}) = \ln(PY_{ids}) + xi + \alpha + \beta s + \gamma i + \delta(d - i - c) \qquad (A)$$

where i = year of diagnosis, d = year of death, s = screening exposure (0 = unexposed, 1 = exposed), and c is a correction for lead time. It should be noted that in the prescreening epoch, for the most part, $s = 0$ throughout. The variable β is the log relative risk associated with screening exposure; γ is the change in potential fatality with time due to other innovations independent of screening, such as the increase in adjuvant therapy at the end of the 1980s. The term δ is estimated in the regression analysis and represents the change in hazard of death from breast cancer as time elapses since diagnosis. The term x is the trend of change in incidence with time. The value x was estimated within each area from a separate log-linear regression of incidence on year, but using only the prescreening years or unexposed subjects in the screening years for its estimation, to avoid overadjustment due to the screening-induced changes in age-specific incidence (i.e., incidence increases due to lead time). The resulting estimate of the trend in incidence with time was then included in the mortality model above as a constant.

The proportion of the exposed cases that were screen-detected will have artificially increased time from diagnosis due to lead time. This is the reason for the correction c in the term for elapsed time since diagnosis. To estimate c, we first calculated the expected additional follow-up time due to lead time in a screen-detected case. If t (= d-i) is the nominal follow-up time, the lead time l is assumed to be exponential with mean $1/\lambda$ and u is the extra time conferred by lead time (l). The extra time u will be l if $l \leq t$ and will be t if $l > t$. Thus, c, the estimate of additional follow-up time gained, is estimated as follows:

$$E(u) = tP(l > t) + \int_0^t \frac{v\lambda e^{-\lambda v} dv}{(1 - e^{-\lambda t})} P(l \leq t)$$

After integration by parts, we have

$$E(u) = \frac{(1 - e^{-\lambda t})}{\lambda} \qquad (B)$$

Finally, we calculate $c = E(u) \times P_s$ among the exposed, where P_s is the estimated proportion of breast cancer death cases that are screen detected among the exposed. This is because it only applies to screen-detected cases. This was estimated as 0.45 using the data from the study group of the Swedish Two-County Trial (2). By definition, $c = 0$ among the nonexposed. The rate of progression λ was also estimated using Markov process models and maximum likelihood estimation from the Swedish Two-County Trial (2) data as 0.28 for age groups 40 upwards, and 0.25 for age groups 50 upwards, for counties that initially offered screening to women ages ≥40 or ≥50 years. This is because rates of progression from preclinical to clinical disease are faster in younger disease cases.

To calculate the person-years, we start with the exposure-specific population at year i, P_{is}. By year $i + 1$, the population will have aged, and ~1% will have been lost by attrition for reasons, including migration, administrative losses, and all-cause mortality (chiefly the last). At year $i + 2$, 1% of the remaining 99% will have been lost, and so on. Thus, for a given single year of diagnosis i and a given single year of death d, the person-years is

$$PY_{ids} = P_{is}(0.99)^{d-i} \qquad (C)$$

A worked example for Norrbotten county is given in the results section below.

This analysis gives the mortality reductions associated with screening, after adjusting for the trends in mortality and incidence independent of screening. As in our companion article, results were combined for all counties by inverse variance weighed average in the logarithmic scale. After estimating the overall screening effect for all counties combined, we applied a correction for self-selection bias, resulting in an estimate of the effect of screening among those actually exposed to screening rather than the effect of simply being invited (11). We used the relative risk (RR) corresponding to the estimate of Cuzick et al. (12), which is

analogous to the causal risk difference estimate of Baker et al. (13). The correction was made after combining area results, to avoid further complexity of the area level analysis. Because most of the unexposed are actually uninvited, we amend the method of Duffy et al. to estimate the effect of actually being screened to the following formula:

$$RR_2 = \frac{pRR}{(1-(1-p)D_r)}$$

where RR is the uncorrected relative risk; RR_2 is the corrected relative risk; p is the average proportion of attenders in the screening epoch; and D_r is the relative risk of breast cancer mortality in the nonattenders compared with an uninvited population.

Results

Worked Example. To carry out the mortality analysis, we must first estimate x, the trend in incidence with time. Table 2 shows the incidence data by year in Norrbotten county, during the prescreening epoch. Poisson regression of year on incidence gives a trend in the logarithmic scale of $x = 0.0205$, an estimated increase in incidence of 2% per year.

Table 3 shows breast cancer deaths by year of diagnosis and exposure status, with the person-years calculated by summing the quantities in Eq. C over the years between diagnosis and death. To carry out the Poisson regression, we must also calculate a follow-up time for corrected for lead time in the exposed women. The corrected follow-up time in the unexposed is simply the year of death minus the year of diagnosis. In the exposed, for example, for the exposed cases with diagnosis in 1993 and death in 1999, we substitute $\lambda = 0.28$ and $t = 6$ in Eq. B, giving $E(u) = 2.91$ years. The corrected follow-up time for these cases would be

$$6 - 2.91 \times 0.45 = 4.69$$

To estimate the regression coefficients in Eq. A, we therefore fit a Poisson regression with number of deaths for each year of diagnosis and death as the y variable, and with the logarithm of the person years added to 0.0205 times year of diagnosis as the offset. The regression terms would be the corrected follow-up time, the year of diagnosis and exposure status. In the case of Norrbotten, this gives the results in Table 4. The relative risk associated with exposure to screening is therefore $\exp(-0.41) = 0.66$. The trend with year of diagnosis indicates a 2% reduction in fatality per year, and the corrected follow-up variable indicates that risk of death from the disease decreases with time elapsed since diagnosis by around 10% per year.

Table 2. Breast cancer incidence by year in the Norrbotten area, in the prescreening epoch, 1976-1988

Year	Breast cancers	Population	Rate/1,000
1976	34	42,916	0.79
1977	49	43,069	1.14
1978	40	43,229	0.93
1979	47	43,359	1.08
1980	63	43,532	1.45
1981	46	43,707	1.05
1982	56	43,790	1.28
1983	50	43,875	1.14
1984	49	44,077	1.11
1985	57	44,380	1.28
1986	43	44,802	0.96
1987	67	45,280	1.48
1988	55	45,841	1.20

Table 3. Breast cancer deaths and person-years in Norrbotten by year of diagnosis and exposure to screening

Year of diagnosis	Unexposed		Exposed	
	Deaths	Person-years	Deaths	Person-years
1976	15	986,776	0	0
1977	26	956,792	0	0
1978	23	926,384	0	0
1979	15	894,757	0	0
1980	28	863,435	0	0
1981	22	831,513	0	0
1982	27	797,275	0	0
1983	23	762,574	0	0
1984	22	729,303	0	0
1985	20	696,906	0	0
1986	19	665,386	0	0
1987	21	633,542	0	0
1988	20	601,568	0	0
1989	19	540,525	1	28,226
1990	16	357,774	8	174,305
1991	5	136,802	13	355,671
1992	2	75,289	6	377,048
1993	0	60,615	14	351,295
1994	3	59,576	4	310,744
1995	1	49,994	17	277,262
1996	2	42,531	9	241,147
1997	1	33,147	2	205,801
1998	0	22,882	4	169,573
1999	3	21,691	1	123,482
2000	2	11,847	5	85,498
2001*	—	—	—	—

*No tumors diagnosed in 2001 resulted in death in the same year.

Analysis of All 13 Areas. Table 5 shows the relevant results of the incidence and mortality Poisson regressions for all 13 areas studied. The exposure log relative risks were transformed to the relative risks shown in Fig. 1. When results were combined, there was a significant 42% reduction in mortality associated with screening (RR, 0.58; 95% confidence interval, 0.53-0.62), adjusting for changes in incidence and mortality due to other factors than screening. To adjust for self-selection bias, we used the facts that the relative risk for breast cancer death in nonattenders was estimated to be 1.17, and the average attendance for incidence screens in the 13 areas was 78% (1). After adjustment for self-selection bias, there was a 39% mortality reduction with exposure to screening (RR, 0.61; 95% confidence interval, 0.55-0.68), still highly significant. Figure 2 shows the annual changes in log fatality.

Discussion

Our results showed a significant 42% reduction (RR, 0.58; 95% confidence interval, 0.53-0.62) in mortality from breast cancer in screened women, taking into account changes in incidence and fatality occurring independently of screening. After adjustment for self-selection bias, the mortality reduction for women actually screened was 39% (RR, 0.61; 95% confidence interval, 0.55-0.68). This is consistent with our previous results, showing a 39% reduction after adjustment for self-selection bias alone (5). These results are consistent with those in our

Table 4. Results of the Poisson regression for Norrbotten county

Regression variable	Estimate (95% confidence interval)	Significance (P)
Exposure	−0.41 (−0.74 to −0.07)	0.015
Year of diagnosis	−0.02 (−0.04 to 0.00)	0.029
Corrected follow-up time	−0.11 (−0.14 to −0.09)	<0.001

Table 5. Results of Poisson regression on incidence and mortality in the 13 areas studied

Area	Incidence trend	Fatality trend	SE (fatality trend)	Exposure log RR	SE (log RR)
Dalarna	0.0179	−0.02	0.006	−0.79	0.10
Gävleborg	0.0108	−0.01	0.006	−0.53	0.11
Örebro	−0.0195	0.02	0.011	−0.39	0.14
Norrbotten	0.0205	−0.02	0.011	−0.41	0.17
Västernorrland	−0.0050	−0.01	0.008	−0.24	0.15
Södersjukhuset	0.0151	−0.03	0.009	−0.54	0.15
Uppsala	0.0212	−0.04	0.020	−0.43	0.16
Västmanland	0.0129	0.02	0.013	−0.88	0.16
Södermanland	0.0393	−0.03	0.013	−0.74	0.17
Skärholmen	−0.0047	−0.01	0.010	−0.43	0.17
Danderyd Hospital	0.0035	−0.001	0.018	−0.54	0.17
Karolinska Hospital	−0.0014	−0.002	0.012	−0.58	0.19
Sankt Göran Hospital	−0.0119	0.002	0.012	−0.34	0.19

companion article (1), although slightly more conservative due to explicitly taking account of contemporaneous changes in incidence and fatality in the present model.

The results of the analysis can be used to further illustrate effects of screening and other changes over time on fatality of diagnosed breast cancers. The overall, self-selection–adjusted relative risk associated with screening was 0.61, and the trend in risk of death with year of diagnosis, adjusting for the increasing incidence rates, was a 1% reduction per year, a regression coefficient of −0.01on the log relative risk (Fig. 1). For example, a woman not exposed to screening and diagnosed with breast cancer in 1995 has a relative risk of dying of breast cancer compared with an unexposed woman diagnosed in 1985 of

$$\mathrm{RR} = \exp(-0.01 \times 10) = 0.90,$$

or a 10% lower risk of dying of breast cancer. A woman exposed to screening and diagnosed in 1995, has a relative risk of dying of breast cancer of

$$\mathrm{RR} = \exp(-0.01 \times 10 + \log(0.61)) = 0.55,$$

or a 45% lower risk of dying of breast cancer. Thus, although risk of dying from breast cancer reduced over time for all women, probably due to improvements in therapy and more favorable stage characteristics at diagnosis as a consequence of increasing awareness, for those exposed to screening, the estimated mortality reduction was considerably greater.

Our correction for lead time may be an overcorrection, in that we used the estimated lead time of all screen-detected cases, which may be greater than that of cases who die of breast cancer (14). There are arguments in favor of and against using the lead time estimate for all screen-detected cases. Accordingly, we carried out a sensitivity analysis, applying no correction whatever (equivalent to a correction for a lead time of 0). This made only a 1% difference to the estimated relative risks associated with exposure to screening.

In conclusion, our results show a significant and substantial 42% reduction in breast cancer mortality with exposure to service screening with mammography in 13 Swedish counties, adjusting for self-selection bias and contemporaneous changes in incidence and fatality occurring independently of screening. The analysis used all breast cancer deaths in the period of study, as has been recommended in the past. This is consistent with previous results and confirms the results from our companion article.

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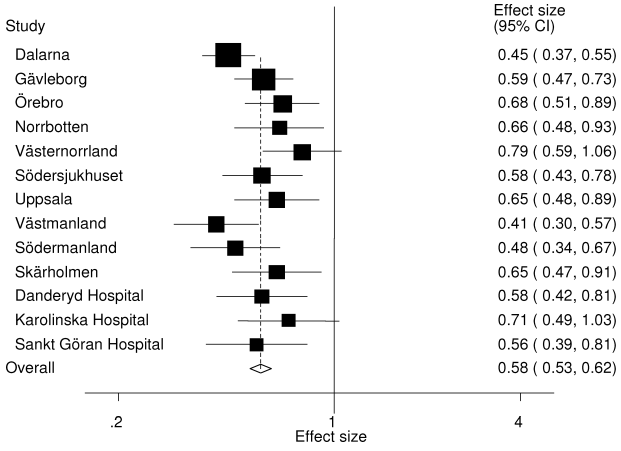

Figure 1. RR of breast cancer mortality for screened compared with unscreened women, adjusting for changes in incidence and fatality occurring independently of screening and for lead time–corrected follow-up time.

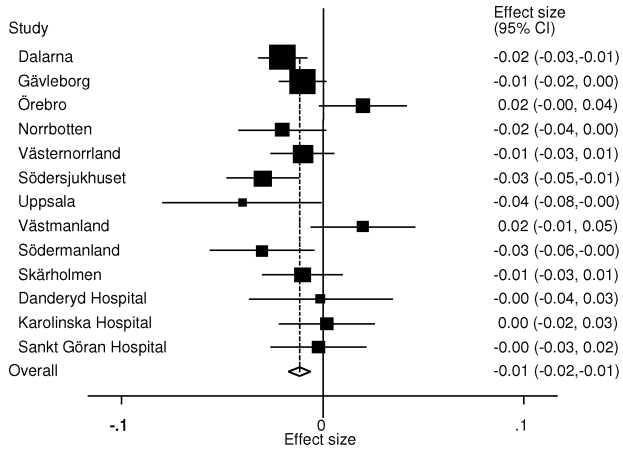

Figure 2. Annual change in log fatality, adjusting for contemporaneous changes in incidence, corrected follow-up time, and the effect of screening.

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