Service screening with mammography of women aged 50–69 years in Sweden: effects on mortality from breast cancer

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Abstract

***Objectives*—To estimate the effect of the population based service screening programme in Sweden on mortality from breast cancer among women aged 50–69.**

***Setting*—In 1986, population based service screening with mammography started in Sweden, and by 1997 screening had been introduced in all counties. Half of the counties invite women from 40 years of age whereas women 50 and older are invited in the other counties. The upper age limit was either 69 or 74. Women in the age group 50–69 years are thus invited to screening in all counties.**

***Methods*—The counties which started with mammographic screening in 1986–87 constituted the study group and were compared with the counties which started in 1993 or later. In 1987 the mean number of women aged 50–69 was 161 986 and 98 608 in the study and control groups, respectively. Refined excess mortality (smoothed with the Lowess method) from breast cancer and refined cause specific mortality from breast cancer were used as effect measures. To adjust for geographical differences in mortality from breast cancer a reference period was used. Allowance was made for two potential biases: (*a*) inclusion bias implying the inclusion of cases diagnosed before invitation to screening in the first screening round, and (*b*) lead time bias.**

***Results*—After a mean follow up time of 10.6 years since the start of screening and a mean individual follow up time of 8.4 years, a non-significant reduction in refined excess mortality for breast cancer was estimated as relative risk (RR) 0.84 (95% confidence interval (95% CI) 0.67 to 1.05). After adjustment for inclusion and lead time biases the RR was 0.80 (20% reduction). Only 27% of the deaths from breast cancer in the total mortality for women aged 50–79 at death consisted of women aged 50–69 at diagnosis who were diagnosed after the start of screening. This figure has important implications for judgement of the impact of screening on age specific national breast cancer mortalities.**

***Conclusions*—A non-significant reduction in mortality from breast cancer was found in counties performing service screening with mammography in Sweden. Adjustment for possible biases changed the result towards a larger effect of screening. The results do not contradict the effects found in the Swedish randomised mammography trials.**

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Keywords: breast cancer; mortality; mammography screening; evaluation

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Randomised studies have shown that screening for breast cancer with mammography causes a reduction in mortality from breast cancer,[1 2] especially for women aged 50–69 at invitation to screening. Today nationwide service screening programmes have been initiated in Sweden, Finland, The Netherlands, the United Kingdom, and Luxembourg. Out of these, only the Finnish programme was designed to evaluate the impact on mortality from breast cancer at a later stage.[3] A few attempts have been made to estimate the effects of service screening in Sweden. Törnberg *et al*[4] compared mortality from breast cancer in counties where the randomised trials on mammographic screening were being conducted with mortality from breast cancer in all other counties. In the northernmost public health region the variation in mortality from breast cancer in counties which started screening early was compared with that of counties that started late,[5] and in the county of Uppsala the effect of screening on mortality from breast cancer was estimated by surrogate measures.[6]

When the first results from the two county study in Sweden were published,[1] the National Board of Health and Welfare issued guidelines for mammographic screening[7] recommending a lower age limit not below 40 years and not over 50 years, and an upper age limit not below 69 years. Consequently, the age group 50–69 years was covered in all counties where screening was introduced. Service screening started in Sweden in 1986 and by 1997 it had been introduced in all 25 counties.

The aim of the study was to estimate the effect of the population based service screening programme in Sweden on mortality from breast cancer among women aged 50–69. An evaluation of programmes inviting women of 40–49 to screening has previously been reported.[8]

Materials

There is no nationwide register in Sweden with data on individual screening history. Therefore characteristics of the screening programmes—for example, time of start, progression of

activities within the geographical areas, age groups invited, and intervals between screening rounds—were obtained from the screening centres through a questionnaire. For each breast cancer case, data on diagnosis and on death for those who had died were obtained from the nationwide Swedish Cancer Registry. Data on mortality from breast cancer aggregated by calendar year, county, and 5 year age groups were obtained from the Swedish Cause of Death Registry. Population data aggregated by calendar year, geographical area, and 5 year age groups were obtained from Statistics Sweden.

All organised mammographic screening in Sweden is population based. Some of the counties applied two or more screening programmes that differed in year of start and age limits. We therefore had to divide those counties into smaller geographical areas to obtain homogeneous units. The geographical areas where invitation to screening started in the mid-1980s constituted the study population, and the geographical areas which started screening in the mid-1990s formed the control population (table 1). The geographical distribution of the different areas is shown in figure 1. In 1987 the mean population of women aged 50–69 years was 161 986 in the study population and 98 608 in the control population. The weighted mean screening interval was 23 months.

We studied two periods, 1979–90 (reference period) and 1986–97 (study period). The time for start of screening in the study population varied between August 1986 and October 1987 (table 1) and the weighted mean was February 1987. The study population was defined as a cohort for each geographical area during the study period, and comprised all women aged 50–69 years in the calendar period from the month when the first invitation to screening was issued and 7 years thereafter (accrual period). The accrual periods for the geographical areas are given in table 2. For the reference period the corresponding cohorts were also defined with the same delays due to screening start in the respective geographical area. For the control population, cohorts were defined by women 50–69 years of age in the accrual periods 1980–6 and 1987–93, respectively, for the reference and the study periods. The cohorts in the reference period were followed almost up to the end of 1990 and the cohorts in the study period at most to the end of 1997 (table 2, fig 2). For geographical areas in the study group, start of follow up was defined as the month when invitation to screening started in the respective area. For all geographical areas the time for start of follow up was set at 0.

Due to lack of individual screening data we had to use aggregated data. We also had to make an approximation for time of start within the whole geographical area. However, for the breast cancer cases individual information was used about date, age, and residence at diagnosis of breast cancer, date of death, and cause of death. For the calculation of person-years, aggregated population data were used.

A breast cancer case was defined as a case of invasive breast cancer (site code=174 in the international classification of diseases, ICD-9, and histo-pathological code=096 according to WHO/HS/CAN/24.1) diagnosed at age 50–69 during the reference or the study period (fig 2). If a woman had two diagnoses of breast cancer in one of the periods, 1979–87 or 1986–94, the second cancer was excluded. A death from breast cancer was defined as a breast cancer case, defined as above, reported to the Cause of Death Registry not later than 31 December 1997, with breast cancer as the underlying cause of death.

Methods

Age specific mortality from breast cancer for the period 1971–97 was plotted for the study group and the control group. This was based on the total number of deaths from breast

Table 1 Female population 50–69 years old (1987), time of start of screening, years of follow up in the study, person-years, cumulative number of deaths, and refined mortalities (underlying cause of death) from breast cancer for the reference and the study period in the geographical areas

					Reference period			*Study period*		
Geographical area	*County, 1987*	*Mean population of women of 50–69, 1987 n*	*Start of screening month/year*	*Years of follow up*	*Person-years ×1000*	*Cumulative deaths from breast cancer n*	*Cumulative deaths from breast cancer n/100000*	*Person-years ×1000*	*Cumulative deaths from breast cancer n*	*Cumulative deaths from breast cancer n/100000*
Geographical areas with early start of invitation to screening (study areas):										
Eksjö/Nässjö*	Jönköping	13006	8/86	11	175	57	359	165	39	260
Kalmar*	Kalmar	26629	10/86	11	357	97	298	346	74	235
Västmanland*	Västmanland	28080	10/86	11	364	101	305	364	73	221
Bohus	Göteborgs and Bohus†	30297	11/86	11	383	92	264	405	96	261
Jönköping/Ryhov*	Jönköping	20728	4/87	10	247	80	324	243	53	218
Trelleborg*	Malmöhus‡	13444	4/87	10	156	43	276	167	43	258
Örebro*	Örebro	29802	10/87	10	364	99	272	346	73	211
Total		161986			2046	569	306	2036	451	244
Geographical areas with late start of invitation to screening (control areas):										
Värmland	Värmland	33021	4/93	11	437	122	307	419	103	270
Norra Älvsborg	Älvsborg†	17666	11/93	11	232	67	318	230	61	291
Västerbotten	Västerbotten	27049	2/95	11	348	94	297	348	96	304
Jämtland	Jämtland	15101	5/96	11	202	69	376	191	46	265
Gotland	Gotland	5771	5/97	11	77	17	244	76	12	174
Total		98608			1296	369	313	1265	318	277

*Lower age limit for invitation to screening is 40 years.
†Currently Västra Götaland.
‡Currently Skåne.

Table 2 Accrual periods and follow up for the study and the control group during the study and reference periods

		Reference period		Study period		
Geographical area	*County*	*Accrual*	*End of follow up month/year*	*Accrual*	*End of follow up month/year*	*Follow up time (y)*
Study areas:						
Eksjö/Nässjö*	Jönköping	8/79–7/86	7/90	8/86–7/93	7/97	11
Kalmar*	Kalmar	10/79–9/86	9/90	10/86–9/93	9/97	11
Västmanland*	Västmanland	10/79–9/86	9/90	10/86–9/93	9/97	11
Bohus	Göteborgs and Bohus†	11/79–10/86	10/90	11/86–10/93	10/97	11
Jönköping/Ryhov*	Jönköping	4/80–3/87	3/90	4/87–3/94	3/97	10
Trelleborg*	Malmöhus‡	4/80–3/87	3/90	4/87–3/94	3/97	10
Örebro*	Örebro	10/80–9/87	9/90	10/87–9/94	9/97	10
Control areas:						
All counties		1/80–12/86	12/90	1/87–12/93	12/97	11

*Lower age limit for invitation to screening is 40 years.
†Currently Västra götaland.
‡Currently Skåne.

cancer each year, referred to here as "total mortality from breast cancer". The mortality was also smoothed with the Lowess method.[9] The mortality from breast cancer for cases diagnosed after a certain time point and in a certain age group is referred to as "refined mortality from breast cancer".[5 10] By contrast with total mortality, refined mortality can naturally not be interpreted in the same way for different years of follow up.

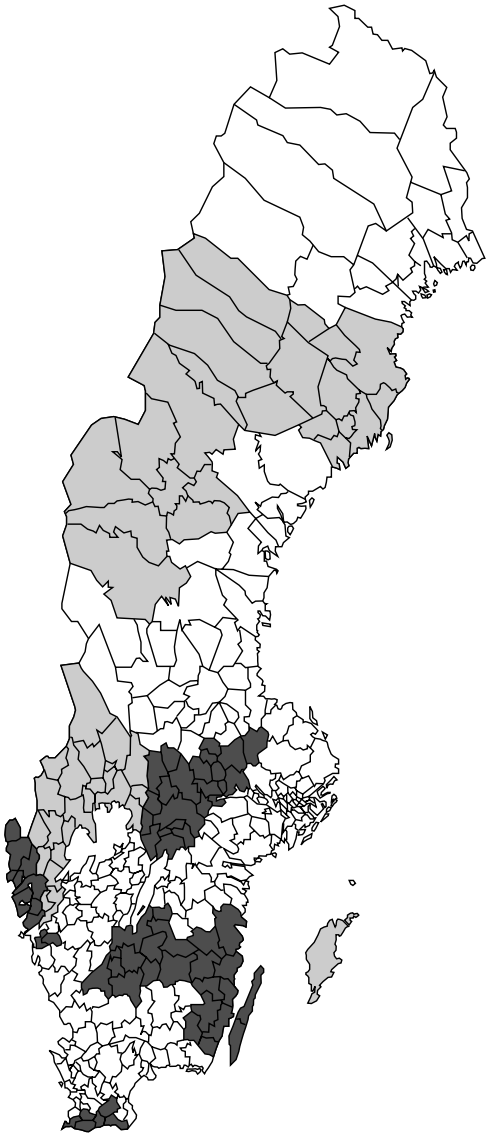

Figure 1 Municipalities in Sweden where invitation to screening for the age group 50–69 started in 1986–7 (dark grey) and in 1993–7 (light grey). Non-shaded areas refer to the counties not included in the study.

During the follow up, women were between 50 and 79 years of age. Particularly in older women, there may be some uncertainty about determination of the underlying cause of death. We therefore used two methods for determining mortality from breast cancer: excess mortality[5]; and breast cancer as the individual underlying cause of death.

Cumulative refined mortality from breast cancer/100 000 was computed with the mean number of person-years as denominator (person-years divided by years of follow up), and cumulative relative risks (RRs) were estimated. To adjust for possible geographical differences in mortality from breast cancer between the study group and the control group, the RR for the study period was divided by the RR for the reference period. This ratio is the RR due to invitation to screening assuming multiplicative effects between the groups and the periods. The adjustment also corrects for the slight difference in duration of follow up between the study group and the control group.

The refined mortality from breast cancer was also analysed with a multiplicative Poisson model with the number of breast cancer deaths (underlying cause of death) as dependent variable, and year of follow up, age during follow up (5 year classes), geographical area, and period as covariates, all categorical.[11] The excess mortality was analysed in the same way but here the dependent variable was the number of deaths among the cases of breast cancer (see appendix for more details). The screening effect was measured by a dummy variable set to 1 for the study group cohorts in the study period and 0 elsewhere. The logarithm of the number of person-years in each cell in the cohorts were taken as offset.

The statistical analyses were done with the program S-Plus.[12]

Some important biases may have been inherent in this observational study. These biases are (*a*) inclusion bias implying inclusion of cases in the study group diagnosed with

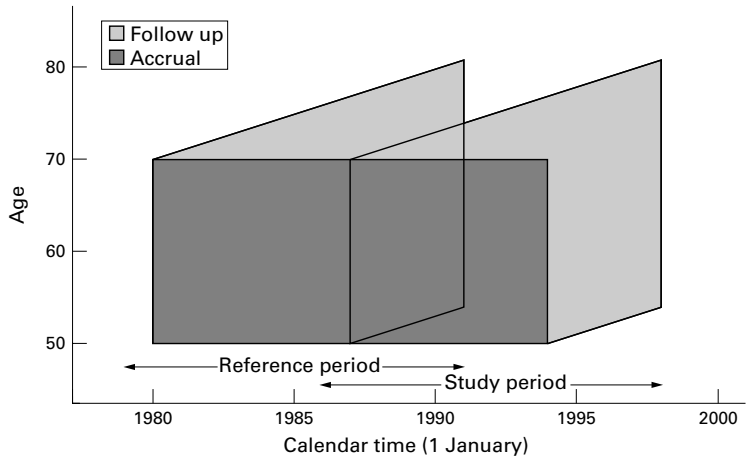

Figure 2 Example showing the inclusion (accrual) and follow up in the reference and the study periods for a cohort where invitation to screening started in January 1987. The study and reference periods are marked by arrows.

breast cancer before invitation within the first screening round, and (*b*) lead time bias.

INCLUSION BIAS

A potential bias which may lead to dilution of the results stems from difficulties at the beginning of the accrual period in defining the studied population, as it is necessary to wait until the first screening round is finished before all the women within a screening area have been invited. We included all incident cases of breast cancer after the start of invitation to screening within a geographical area, among which there were an unknown number of cases diagnosed before invitation to screening during the first round. This will of course lead to dilution of the potential benefits of screening, as several cases, not yet invited, were included in the screened population. The magnitude of this problem was estimated by a simulation using the fact that the weighted mean screening interval for the first round was 28 months. For a given 28 month calendar period we assumed a random time point for invitation of each woman with a diagnosis of breast cancer to be uniformly distributed over (0 to 28) months. Based on this sample, the cumulative mortality from breast cancer in the period was estimated for the women who were invited after diagnosis. This was replicated 200 times in each of the intervals from October 1981 to January 1984, and from February 1984 to May 1986, and the mean cumulative mortality from breast cancer was calculated. Breast cancer cases who lived in the same geographical areas as the combined study and control groups were used. This estimated mortality made it possible to calculate an expected number of deaths from breast cancer in the study cohorts among the cases diagnosed before they were invited for screening, and the calculation resulted in a figure of 118.1 (26% of the observed number of deaths (O) from breast cancer (underlying cause of death) in the study cohorts during the study period). If the adjusted RR is formulated as O/E, where E is the corresponding number expected without screening, we can perform a straightforward correction of the RR. The adjusted RR becomes

$$\frac{O-\psi}{\frac{O}{RR}-\psi}$$

where ψ is the expected number of deaths from breast cancer in women with a diagnosis of breast cancer before invitation to screening during the first screening round (28 months).

LEAD TIME BIAS

The purpose of mammographic screening is early detection of breast cancer. Therefore many cases of breast cancer in the study cohorts were probably diagnosed at an earlier time and at a lower age than corresponding cases in the control cohorts. If this also applies to women who died from breast cancer during the follow up, it might give rise to a lead time bias in this study. Age was defined at diagnosis in the present study. Thus, a woman in the group invited to screening may have been classified as belonging to the age group below 70 years whereas a corresponding woman in the control group might have been 70 years or more at diagnosis, even though she had an otherwise comparable cancer and died from it at the same time. At the lower age limit, lead time can also cause a bias in the opposite direction if women in the study cohorts below 50 years had been invited to screening.

To estimate the difference in lead time among women who died from breast cancer, we defined a group of women 45–60 years old at the start of screening who lived in the geographical areas where screening started in 1986–7. These are the same areas which were used as a base for the study population already mentioned. A corresponding group with a common start in February 1987 was defined in the geographical areas where screening started late (1993–7; the same areas which were used for the control population). The cohorts were followed up for 10 years. Mean survival in the two groups was derived for all women who were diagnosed with breast cancer and died from breast cancer during the follow up. If a woman had two diagnoses of breast cancer during the follow up, the second was omitted. In all geographical areas in the study group except for Bohus, women aged 40–49 were also invited to screening. Therefore Bohus was excluded from this computation. The mean survival times for the 249 and 238 women who died from breast cancer were estimated as 2.98 and 2.82 years, respectively, for the screening group and the group where screening started late. Hence the difference in mean survival time was 0.16 years. This difference was not significant (p=0.20 with the Wilcoxon's rank sum test). As it is possible that mammographic screening also can have caused prolonged survival among the women who died from breast cancer during the follow up the estimated mean lead time was at most 0.16 years. Assuming this estimate to be a constant difference in survival time between the study group and the control group among the women who died from breast cancer, a correction of the RR was made by excluding the cases in the study

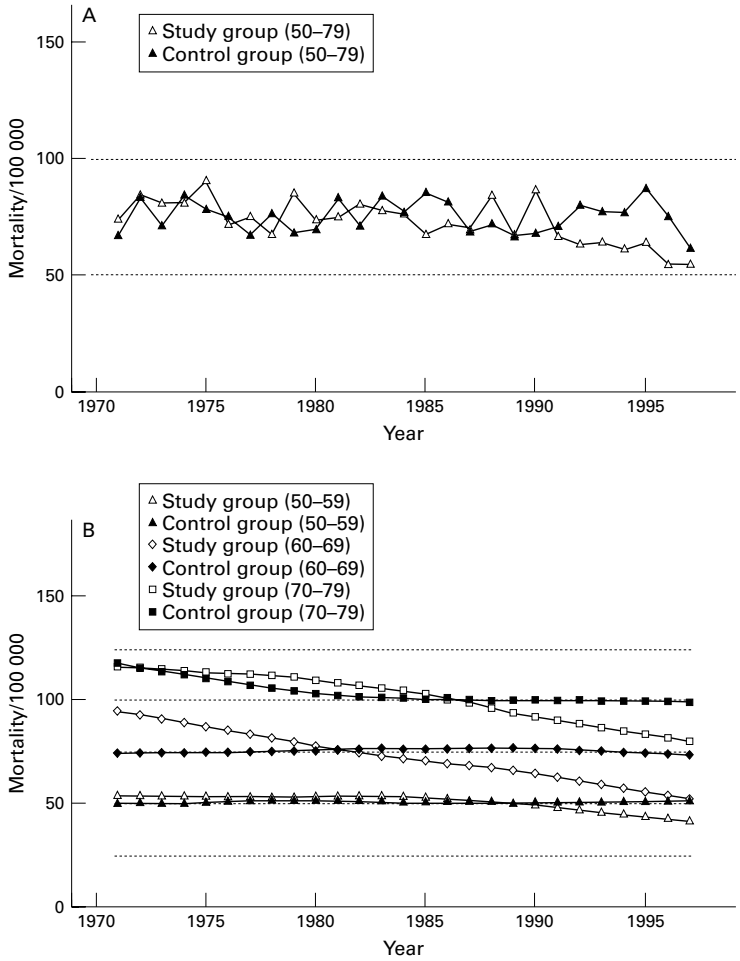

Figure 3 Annual mortality from breast cancer/100 000 (underlying cause of death) 1971–97 for women in the study and control groups. (A) Mortality from breast cancer for women 50–79 at death. (B) Curves for the age groups 50–59, 60–69, and 70–79 at death were smoothed with the Lowess method with fraction parameter 2/3.

cohorts who were diagnosed at the age of 69.84–70 years and died from breast cancer. We found two cases fulfilling this criterion. A correction in the opposite direction was made by adding women in the study group, except in Bohus where the lower age limit for invitation was 50 years, diagnosed at the age of 49.84–50 years. Here we found four cases who died from breast cancer. The total adjustment of the RR for possible lead time around the upper and lower limits of the RR should be an increase of (4–2)/451=0.4%.

As cases of breast cancer that occurred over 7 years were included and followed up for 10–11 years, there might be a lead time bias at the end of the accrual period (table 2). Women who died from breast cancer during the follow up might have been diagnosed earlier and therefore included in the screened cohorts, whereas a corresponding woman in the control cohorts might have been diagnosed after 7 years of accrual and therefore not included. Using the estimated difference in lead time of 0.16 years as already discussed, we found that there were two women in the study group who died from breast cancer more than 7 years after the start of screening and who were diagnosed 6.84–7.0 years after the start. This possible bias corresponds to a 2/451=0.4% reduction of the RR. Hence the impact of lead time bias seems to be small.

Table 3 Number of deaths, person-years and expected number of deaths among the cases of breast cancer and person-years in all women in the cohorts

		Breast cancer cases				*All women*
Group	*Period*	*Total deaths n*	*Person-years ×1000*	*Expected deaths n*	*Excess deaths n*	*Total person-years n×1000*
Study cohorts	Reference	728	11.1	126.7	601.3	2046
Control cohorts	Reference	452	7.2	90.6	361.4	1296
Study cohorts	Study	648	18.3	200.2	447.8	2036
Control cohorts	Study	397	7.3	83.0	314.0	1265

Results

TOTAL MORTALITY FROM BREAST CANCER

The total mortality from breast cancer/100 000 in Sweden in the age group 50–79 in 1975 and 1995 was 82 and 70, respectively. This corresponds to a yearly decrease of 0.8%. The annual age specific mortalities from breast cancer in the age group 50–79 for the study and the control groups during the period 1971–97 are shown in fig 3 A, and the corresponding smoothed curves for age groups 50–59, 60–69, and 70–79 are shown in fig 3 B. For the age groups 60–69 and 70–79, there seems to be a decreasing trend in mortality in the study group which is not found in the control group except for a decrease in the age group 70–79 between 1971 and 1980. For the control group the trend after 1980 seemed to have been constant. Among women of 50–59 the only change was a decrease in the study group after 1985.

REFINED MORTALITY FROM BREAST CANCER

The total mortality from breast cancer includes a number of breast cancer deaths in the study period due to cancer detected before the start of screening. To avoid including cases who were diagnosed to have breast cancer before the start of screening, the refined mortality from breast cancer was analysed. In the study period, the follow up started from the month of the start of invitation to screening in each study area, and from January 1987 for the control areas. The mean follow up time was 10.6 years (range 10–11) in the study areas and 11 years in the control areas. By definition, the mean follow up times were the same in the reference period.

During the study period 1986–97 there were 648 deaths among patients with breast cancer in the study cohorts and 397 deaths in the control cohorts (table 3). Based on the mortalities in the respective counties and the number of person-years among the breast cancer cases (a total of 18 250 in the study cohorts and 7282 in the control cohorts) the expected number of deaths was 200 and 83, respectively. This implies that the excess number of deaths were 448 and 314, respectively.

The cumulative excess mortality from breast cancer for the study and control groups in the two periods is given in figure 4. The cumulative excess mortality/100 000 from breast cancer at 11 years in the study period was 241.9 for the study group and 273.1 for the control group.

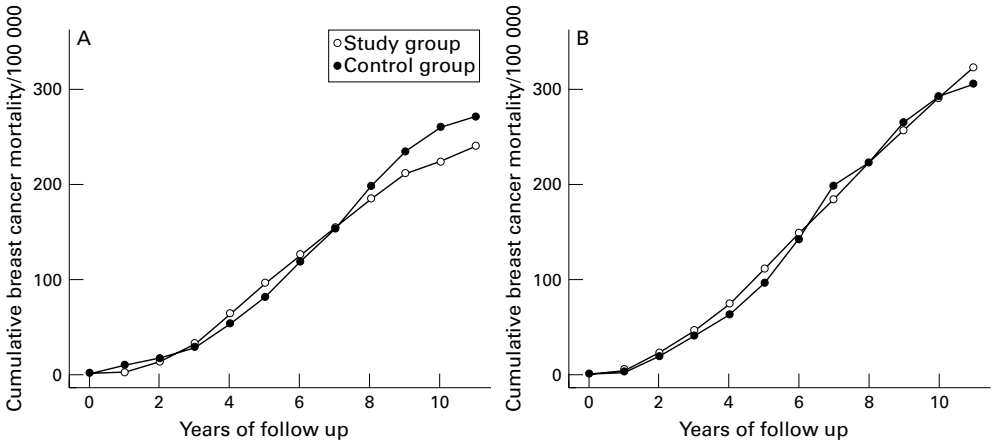

Figure 4 Cumulative number of deaths/100 000 from breast cancer (refined excess mortality) for women aged 50–69 at diagnosis for the study and the control populations by year since start of follow up. (A) Study period. (B) Reference period. The study population is adjusted to the delay of start of screening in the study period.

In the reference period the figures were 323.3 and 306.7, respectively. Thus the RR in the screening group adjusted for the reference period was 0.84 ((241.9/273.1)/(323.3/306.7)) (95% confidence interval (95% CI) 0.67 to 1.05).

The excess mortality data were fitted in a multiplicative Poisson model (table 4). Three covariates were found to be significant—namely, year of follow up ($p<0.001$), age ($p<0.001$), and period ($p<0.001$). The estimated RR in this model due to invitation to screening was 0.86 (95% CI 0.69 to 1.07).

During the study period 1986–97 there were 451 deaths from breast cancer (underlying cause of death) in the study cohorts and 318 in the control cohorts. The cumulative number of deaths from breast cancer and the cumulative mortality from breast cancer by geographical area and period are given in table 1. Due to the large variation in the estimates for each geographical area, only the aggregate measures for the study and control cohorts were used. The cumulative mortality from breast cancer for the study group and the control group in the two periods are given in figure 5. The

Table 4 Summary of fitting multiplicative Poisson models using excess mortality and underlying cause of death

Cause of death	*Model*	*Terms included in the model*	*Degrees of freedom*	*Deviance*	*Compared models*	*Difference in deviance*	*Difference in degrees of freedom*	*p Value*
Excess mortality		Null	1379	1876.1	—			
	1	Year of follow up	1369	1623.0	Null–1	253.2	10	<0.001
	2	1+ Age	1364	1421.6	1–2	201.4	5	<0.001
	3	2+ Period	1363	1410.7	2–3	10.9	1	<0.001
	4	3+ Geographical area	1352	1401.4	3–4	9.2	11	0.60
	5	4+ Screening	1351	1399.6	4–5	1.8	1	0.18
Underlying cause of death		Null	1379	1920.5	—			
	1	Year of follow up	1369	1611.7	Null–1	308.9	10	<0.001
	2	1+ Age	1364	1382.1	1–2	229.6	5	<0.001
	3	2+ Period	1363	1370.0	2–3	12.1	1	<0.001
	4	3+ Geographical area	1352	1359.6	3–4	10.3	11	0.50
	5	4+ Screening	1351	1358.6	4–5	1.0	1	0.32

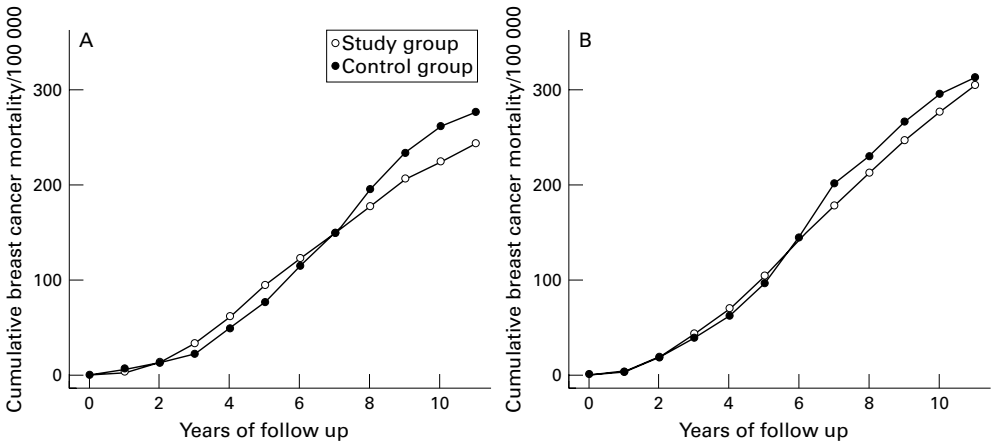

Figure 5 Cumulative number of deaths from breast cancer/100 000 (refined underlying cause of death) for women aged 50–69 at diagnosis for the study and control populations by year since the start of follow up. (A) Study period. (B) Reference period. The study population is adjusted to the delay in the start of screening in the study period.

Table 5 Cumulative number of deaths from breast cancer (underlying cause of death) in the refined mortality model compared with total mortality during the study period 1987–96/97

		Age at death (y)							
		Refined mortality				Total mortality			
Geographical area	Follow up (y)	50–59	60–69	70–79	50–79	50–59	60–69	70–79	50–79
Study cohorts:									
Eksjö/Nässjö	11	10	19	10	39	27	42	65	134
Kalmar	11	28	32	14	74	84	80	105	269
Västmanland	11	23	40	10	73	70	82	118	270
Bohus	11	28	54	14	96	95	127	136	358
Jönköping/ Ryhov	10	21	22	10	53	50	65	85	200
Trelleborg	10	15	20	8	43	37	45	57	139
Örebro	10	19	43	11	73	74	104	134	312
Subtotal		144	230	77	451	437	545	700	1682
Control cohorts:									
Värmland	11	29	56	18	103	79	136	165	380
N Älvsborg	11	17	37	7	61	53	77	87	217
Västerbotten	11	27	52	17	96	76	94	107	277
Jämtland	11	11	21	14	46	47	77	74	198
Gotland	11	4	6	2	12	12	16	33	61
Subtotal		88	172	58	318	267	400	466	1133
Total		232	402	135	769	704	945	1166	2815

Table 6 Summary of results on refined mortality from breast cancer

Model	RR	95% CI	Adjusted RR*
Cumulative excess mortality	0.84	0.67 to 1.05	0.80
Annual excess mortality, Poisson	0.86	0.69 to 1.07	0.82
Cumulative underlying cause of death	0.90	0.74 to 1.10	0.87
Annual underlying cause of death, Poisson	0.91	0.74 to 1.10	0.88

*RR adjusted for breast cancer cases diagnosed before invitation to screening.

cumulative mortality from breast cancer/ 100 000 at 11 years in the study period was 243.6 for the study group and 276.6 for the controls. In the reference period the figures were 305.9 and 313.2, respectively. Hence the adjusted RR in the screening group was 0.90 ((243.6/276.6)/(305.9/313.2)) and the 95% CI was 0.74 to 1.10.

These data were also analysed in a multiplicative Poisson model (table 4). Three covariates were found to be significant—namely, year of follow up ($p<0.001$), age ($p<0.001$), and period ($p<0.001$). The estimated RR in this model due to invitation to screening was 0.91 (95% CI 0.74 to 1.10).

For a comparison with the total mortality (fig 3 A and B), the cumulative number of deaths from breast cancer in the period 1987–96/97 for total and refined mortality are given in table 5. Out of the 1682 deaths comprising the total mortality from breast cancer for the age group 50–79 only 451 were included in the refined mortality model (27%).

Allowance for inclusion bias reduces the RR (excess mortality) from 0.84 to 0.80. A corresponding calculation for the results if the individual underlying cause of death were used would reduce the RR from 0.90 to 0.87 (table 6). Allowance for lead time bias did not change the results.

In conclusion, the results showed that with allowance for important biases, screening women aged 50–69 resulted in a 20% reduction of excess mortality from breast cancer.

Discussion

In a previous study, a 19% reduction in mortality from breast cancer associated with mammographic screening was estimated for women aged 50–74 by comparing data on mortality from breast cancer in counties that participated in the randomised trials with those that had not.[4] A study in England and Wales found a 12% reduction in total mortality from breast cancer in the age group 55–69 7 years after the start of screening.[13] In another study from England, mortality from breast cancer was compared with expected mortality.[14] After correction for effects of treatment, the direct reduction in mortality from screening was estimated to be 6%. In a Dutch study the nationwide breast cancer screening programme from 1990 to 1998 for women aged 50–69 was evaluated.[15] The mortality from breast cancer in 1998 was significantly lower than expected based on years without screening. In a study in Finland a rate ratio of 0.76 deaths from breast cancer for a screening programme on women aged 50–59 was obtained.[3] A study from northern Sweden[5] indicated a 33% reduction in excess mortality related to breast cancer in a service screened population compared with an unscreened population for women aged 50–69. However, in that study no reference period was used, and some of the reduction may thus be explained by differences in baseline mortality. To summarise, these studies showed a reduction in mortality comparable with the results from randomised studies of women aged 50 and above.

The present study had a mean follow up of 10.6 years after start of invitation to screening in women who were diagnosed with breast cancer at the age of 50–69. Although not significant, a reduction of 20% of mortality from breast cancer was estimated. Due to a mean screening interval of 28 months for the first round, the mean individual follow up since first invitation to screening was about 8.4 years. In the latest overview of all Swedish randomised studies, a significant reduction in mortality of 29% was evident after an individual follow up of 5–13 years.[2] The reduction after 8.4 years was estimated to be 25% (graphical reading).

To account for the difference between the present study and previous randomised studies, we found no obvious differences in quality indicators—such as rates of attendance, recall, cancer detection, and screening intervals—between service screening and the randomised trials.[16 17] There are, however some possible sources of bias, not mentioned before, that need to be taken into consideration.

The time trends in mortality from breast cancer differ between the study group and the control group during the reference period (fig 3 A and B). This is most pronounced in the age group 60–69, where the trend in the study group has been decreasing since 1971, although it was constant for the control group. We also looked at trends in refined mortality before the start of screening by comparing the cumulative mortality from breast cancer/ 100 000 (underlying cause of death) in the reference period defined in exactly the same way but with start of accrual 8 years earlier. The figures for the study group were 366 and 306 for the earlier and the reference periods,

respectively. For the control group the figures were 346 and 313. Hence there was a decrease of 60 for the study group and 33 for the control group over 8 years. We can only make assumptions about the trends after the start of screening in 1986. As the refined mortality from breast cancer follows the same trends as the total mortality from breast cancer, the observed reduction of refined mortality based on the underlying cause of death is most likely larger than what can be explained from mammographic screening only.

If opportunistic screening was carried out in the control group, there is a possibility that the observed reduction in mortality would have been diluted. However, opportunistic screening in Sweden occurs mainly in large cities. As there are no large cities included in the control group, any possible problem of dilution of this type would be minor.

There was a difference between the number of deaths from breast cancer (underlying cause of death) in the cohorts (refined mortality) and the total number of deaths from breast cancer for women of 50–79 at death (table 5). Only 27% of the deaths from breast cancer in the total mortality for women of 50–79 at death consisted of women aged 50–69 at diagnosis who were diagnosed after the start of screening—that is, cases included in the refined mortality model. The corresponding figures in the age groups 50–59, 60–69, and 70–79 were 33%, 43%, and 12%, respectively. This means that at least 73% of the deaths included in the total mortality from breast cancer in women of 50–79 at death were not relevant in evaluating the effects of screening at ages 50–69. Even if cases of breast cancer were included during the whole follow up time (11 years accrual time instead of 7 years), only 31% of the deaths in the total mortality for women of 50–79 at death consist of women who were aged 50–69 at diagnosis, and were diagnosed after the start of screening. Thus, total mortality from breast cancer does not illustrate the effect of screening, even after a decade of follow up.[18 19]

We have used two methods to estimate breast cancer mortality: excess mortality; and breast cancer as the underlying cause of death coded by the National Cause of Death Registry. With individual data, it can be difficult in many cases to decide whether breast cancer is an underlying or only a contributory cause of death. This decision becomes more complicated in older patients. Excess mortality compares observed and expected mortality among the patients with cancer. It is therefore possible to measure all mortality caused by breast cancer. The two methods were compared in a Swedish study.[20] The difference in RR increased over age but the RR was generally lower for excess mortality. In the age group 40–49 the difference was 1%, whereas in the age group 70–74 the difference was more than 20%. The difference in the age group 50–69 was 3%–4%. A contributory explanation for the differences could be the higher incidence of breast cancer in the study group due to screening. For some deceased cases a diagnosis of breast cancer may contribute to the decision of breast cancer as the underlying cause of death whereas in the absence of a diagnosis of breast cancer this would not have happened. Thus the RRs might be biased when comparing older women by underlying cause of death. In the current study the RR was 5%–6% lower when excess mortality was used.

To summarise, with a mean screening interval of 28 months and with a mean follow up of 10.6 years of the Swedish service screening programme, the reduction in excess mortality from breast cancer was estimated at 16%. When adjusting for biases due to inclusion of cases in the study cohorts diagnosed before invitation to screening, and lead time bias, the reduction increased to 20%. This reduction of mortality from breast cancer due to screening is in line with previous Swedish randomised studies.

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Appendix

The model of excess mortality used in this study is defined as follows. With categorical explanatory variables the data can be divided into several cells. The number of deaths among the cases of breast cancer in each cell X_i are assumed to be Poisson distributed with expected values $\mu_i=\lambda_i N_i+E_i$ where:

λ_i=excess mortality due to breast cancer in cell i

N_i=person-years in cell i in the cohorts

E_i=expected number of deaths among the cases of breast cancer in cell i based on the population mortality and the number of person-years among the cases of breast cancer.

As in the standard model with canonical link function we assume

$$\lambda_i = \exp\{\eta_i\} \text{ where } \eta_i = \exp\left(\sum_j z_{ij}\beta_j\right) \text{ and } z_{ij}$$

are the covariates.

To estimate the parameters $\{\beta_i\}_{j=1,2,\ldots,k}$ a GLM Poisson model[21] with individual link functions was used. In statistical software this model cannot generally be estimated with standard functions. However, with functions or macros it is possible to extend the standard procedures to include the excess mortality model. Examples are given on how to specify this excess mortality model in the programs S-plus and GLIM. As for the standard multiplicative Poisson model, $\log(N_i)$ is used as offset.

During the iterations it is possible that $\hat{u}_i-E_i\geq 0$ for some i which can cause problems. However, as we assume the excess mortality λ_i to be positive for all i we have $\mu_i-E_i>0$. This restriction was used in the fitting procedure in the link functions and the

$$\frac{\partial\eta}{\partial\mu}$$

functions.

The S-plus family object generator function[12] poem is used instead of the standard function Poisson. The input vector "e" is the vector of expected number of deaths among the cases of breast cancer (E_i).

```
poem <- function(e = stop("e must be specified"))
{
# This is a generator function for a family object
# To see a brief summary of the resulting family,
# evaluate the function, e.g. poem(), and let
# it print itself. To see individual components, either
# type poem()$link etc, or else assign it and look at
```

```
# the components.
li <- substitute(function(mu)
{
if(min(mu-e) <= 0) {
zero <-length(mu[(mu-e) <= 0])
warning(paste("mu-e<=0 in link in ", zero, " cases, replaced by 0.001"))
}
argument <- (mu - e) * ((mu - e) > 0) + 0.001 * ((mu - e) <= 0)
log(argument)
})
de <- substitute(function(mu)
{
if(min(mu - e) <= 0) {
zero <- length(mu[(mu - e) <= 0])
warning(paste("mu-e<=0 in deriv in ", zero, " cases, replaced by 0.001"))
}
argument <- (mu - e) * ((mu - e) > 0) + 0.001 * ((mu - e) <= 0)
1/argument
})
link <- list(name = paste("Log: log(mu-e)"), link = li, inverse = substitute(function(eta)
care.exp(eta) + e), deriv = de, initialize = glm.links[, "log"]$initialize)
make.family("Poisson", link, glm.variances(, "mu"))
}
```

These GLIM macros create a user defined model. E is the vector of E_i defined above.

```
$MAC M1 $CAL %FV=%EXP(%LP)+E $ENDMAC
$MAC M2 $CAL U=%FV-E
$CAL U2=%IF(%LE(U,0),0.001,U)
$CAL %DR=1/U2$ENDMAC
$MAC M3 $CAL %VA=%FV $ENDMAC
$MAC M4 $CAL %DI=2*(%YV*%LOG(%YV/%FV)-(%YV-%FV)) $ENDMAC
$OWN M1 M2 M3 M4
$CAL V=%YV-E$CAL V2=%IF(%LE(V,0),0.001,V)
$CAL %LP=%LOG(V2)
$SCALE 1$
```


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