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Mammography Screening and Breast Cancer Mortality in Sweden

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Background Swedish women aged 40–69 years were gradually offered regular mammography screening since 1974, and nationwide coverage was achieved in 1997. We hypothesized that this gradual implementation of breast cancer screening would be reflected in county-specific mortality patterns during the last 20 years.

Methods Using data from the Swedish Board of Health and Welfare from 1960 to 2009, we used joinpoint regression to analyze breast cancer mortality trends in women aged 40 years and older (1 286 000 women in 1995–1996). Poisson regression models were used to compare observed mortality trends with expected trends if screening had resulted in breast cancer mortality reductions of 10%, 20%, or 30% among women screened during 18 years of follow-up after the introduction of screening. All statistical tests were two-sided.

Results From 1972 to 2009, breast cancer mortality rates in Swedish women aged 40 years and older declined by 0.98% annually, from 68.4 to 42.8 per 100 000, and it continuously declined in 14 of the 21 Swedish counties. In three counties, breast cancer mortality declined sharply during or soon after the implementation of screening; in two counties, a steep decline started at least 5 years after screening was introduced; and in two counties, breast cancer mortality increased after screening started. In counties in which screening started in 1974–1978, mortality trends during the next 18 years were similar to those before screening started, and in counties in which screening started in 1986–1987, mortality increased by approximately 12% ($P = .007$) after the introduction of screening compared with previous trends. In counties in which screening started in 1987–1988 and in 1989–1990, mortality declined by approximately 5% ($P = .001$) and 8% ($P < .001$), respectively, after the introduction of screening.

Conclusion County-specific mortality statistics in Sweden are consistent with studies that have reported limited or no impact of screening on mortality from breast cancer.

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The Two-County Trials, which were conducted from 1977 to 1984 in Dalarna (formerly Kopparberg) and Östergötland counties in Sweden, showed that screening by two to four rounds of single-view mammography every 24–33 months could reduce breast cancer mortality by 31% in women who were aged 40–74 years at the initial invitation (1). By combining the results of other Swedish mammography trials conducted in Malmö (nine screening rounds), Stockholm (two screening rounds), and Göteborg (five screening rounds), it was subsequently concluded that a mortality reduction of 23% could be achieved among women aged 40–74 years (2).

In 1985, the Swedish Board of Health and Welfare recommended implementation of two-view mammography screening in all 21 Swedish counties. In 1990, 93% of women in the target age groups had been invited to screening, and nationwide coverage was achieved in 1997 (3). Currently, all Swedish women aged 50–69 years are invited to be screened, as well as all women aged 40–49 years in 11 of 21 counties, and all women aged 70–74 years in 10 of 21 counties (Table 1). About 75%–85% of eligible women attend screening regularly, and attendance is among the highest recorded in any country (3,4). Swedish women have attended many more screening rounds than the women who were allocated to the intervention groups of the Swedish randomized trials. Also, the two-view mammography protocol that is used in the national screening program is more sensitive than the single-view mammography protocol used in the Two-County (1) and Stockholm (5) trials and partly in the Malmö (6) and Göteborg (7) trials.

After the completion of the randomized screening trials, observational follow-up studies were conducted in various Swedish counties. Using incidence-based mortality and sophisticated statistical approaches (4,8–11), it has been concluded from those studies that breast cancer deaths decreased by 25%–50% among women who were diagnosed after the introduction of screening.

Table 1. Implementation of mammographic screening in Sweden*

County code†	County name	Subareas	Start of screening, year	Ages invited, y	Interval, mo	No. invited each year in 1995–1996	% Participation in 1995–1996
	Group 1 of counties (first invitation to screening in 1974–1978)		1976 ‡			201 600	
21	Gävleborg		1974	40–74	21	62 000	85
20	Dalarna (Kopparberg before 1998)		1977§	40–70	20–24	54 000	88
05	Östergötland		1978‖	40–74	18–24	85 600	80
	Group 2 of counties (most first invitations to screening in 1986–1987)		1986‡			291 000	
08	Kalmar		1986	40–74	24	50 000	85
19	Västmanland		1986	40–69	20–24	47 000	87
06	Jönköping		1986	40–74	22	62 000	86
12	Skåne		1986‡			132 000	
12		Malmö, municipality	1977¶	46–69	18–24	18 000	66
12		Malmöhus	1987	40–74	18–24	72 000	80
12		Ängelholm	1989	50–74	18–24	13 000	70
12		Kristianstad	1990	50–74	18–24	29 000	76
	Group 3 of counties (most first invitations to screening in 1987–1988)		1987‡			325 900	
14	Västra Götaland		1987‡			204 500	
14		Göteborg, municipality	1983#	50–74	18	60 000	70
14		Bohus	1986	50–74	24	37 000	90
14		Älvsborg, South	1988	40–74	24	55 000	84
14		Skaraborg	1989	50–69	24	31 500	87
14		Älvsborg, North	1993	40–74	24	21 000	83
18	Örebro		1987	40–74	18–24	47 000	83
03	Uppsala		1988	40–74	18–24	53 400	81
10	Blekinge		1988	45–69	18–24	21 000	87
	Group 4 of counties (most first invitations to screening in 1989–1990)		1989‡			415 500	
01	Stockholm		1989**	50–69	24	170 000	72
04	Södermanland (Sörmland)		1989	40–74	18–24	53 000	86
13	Halland		1989	50–74	21	31 000	84
25	Norrbotten		1989	40–74	18–24	55 000	82
07	Kronoberg		1990	50–69	18	18 500	75
22	Västernorrland		1990	40–74	21	55 000	89
17	Värmland		1993	50–69	18–24	33 000	83
	Group 5 of counties (first invitations to screening in 1995–1997)		1996‡			52 000††	
24	Västerbotten		1995	50–69	24	27 000	89
23	Jämtland		1996	50–69	20–24	15 000	91
09	Gotland		1997	40–69	18–20	10 000	89
	Total					1 286 000	

* Adapted from Olsson et al (3).

† Official administrative number of counties; see Figure 2 for geographical locations (there are no counties numbered 02, 11, 15, and 16).

‡ Average year of start in subareas in a county, or in counties included in the group, weighted for numbers of women invited in 1995–1996.

§ Screening started in 1977 as part of the Two-County trial, with invitation of two-thirds of the women aged 40–74 years. In 1986, screening was generalized to all women aged 40–70 years (1,2).

‖ Screening started in 1978 as part of the Two-County trial with invitation of half of the women aged 40–74 years. In 1985, screening was generalized to all women aged 40–70 years (1,2).

¶ Screening started in 1977 as part of the Malmö mammography screening trial that included 21 088 women in the intervention group and 21 195 women in the control group (6); these figures are greater than those included in the table from Olsson et al (3). Control women were first screened after September 1992 (22).

** Screening started in 1981 as part of the Stockholm mammography screening trial that included 60 261 women living in a part of the city. Control women were first screened after September 1985 (2,5).

Screening started as part of the Göteborg Breast Cancer Screening trial. Control women were first screened in 1988–1991 (2,7).

†† Invited later than 1996.

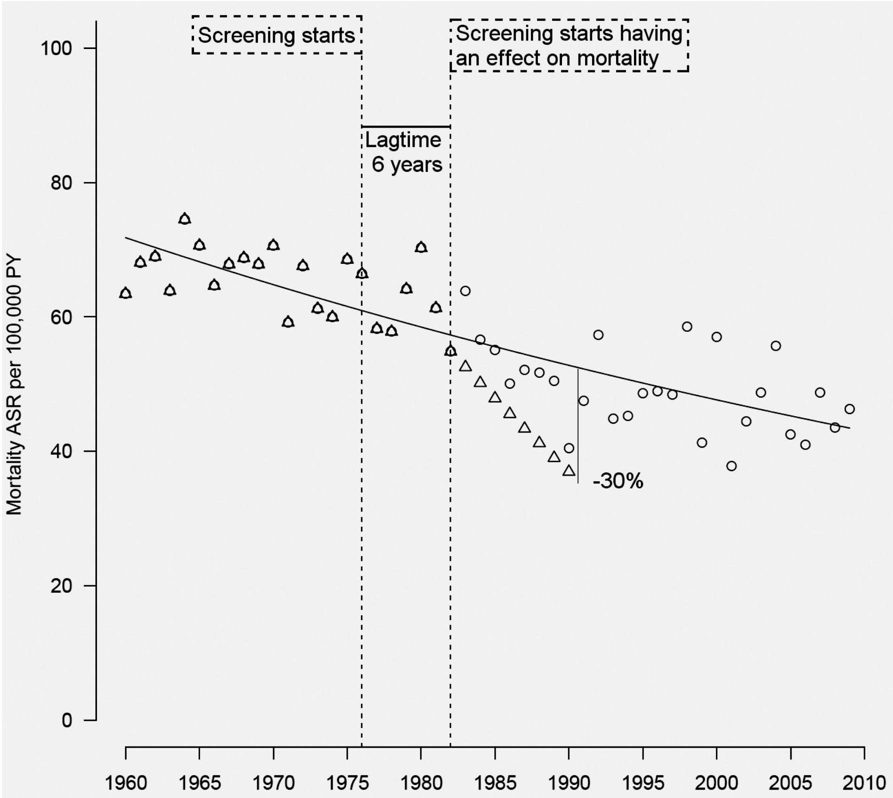

Figure 1. Observed breast cancer mortality rates in Group 1 of counties in Sweden and expected rates if a 30% mortality reduction had been obtained with screening (see text for explanations). The **open circles** represent the observed annual breast mortality rates per 100000 women aged 40 years and older; the **open triangles** represent the expected breast mortality rates per 100000 women aged 40 years and older.

We hypothesized that the impact of screening on breast cancer mortality would be reflected in mortality statistics in Sweden. By analyzing breast cancer mortality trends between the 21 counties, we expected that a mortality reduction would appear first in counties with early implementation of screening, with subsequent reductions in mortality following the gradual introduction of screening in other counties.

Methods

Data Sources

Breast cancer mortality data (ICD-10 code No. C50) and population data by county were provided by the Department of Statistics of the Swedish National Board of Health and Welfare. These data included county-specific deaths from breast cancer from January 1, 1960 to December 31, 2009 and the number of women in 5-year age groups in each county. Data on breast cancer incidence from January 1, 1960 to December 31, 2009 were extracted from the NordCan database (12).

Screening Data

Mammographic screening was gradually implemented in Swedish counties. The counties were categorized into five groups according to the year in which breast cancer screening programs were first implemented (Table 1): Group 1 (1974–1978), Gävleborg, Dalarna, Östergötland; Group 2 (1986–1987), Kalmar, Västmanland, Jönköping, Skåne; Group 3 (1987–1988), Västra Götaland, Örebro, Uppsala, Blekinge; Group 4 (1989–1990), Stockholm, Södermanland, Halland, Norrbotten, Kronoberg, Västernorrland, Värmland; Group 5 (1995–1997), Västerbotten, Jämtland, Gotland. The number of women in invited age groups has remained fairly stable across counties, following the natural population growth and aging, except for the most urban areas (Stockholm and Skåne) where the population has increased more rapidly than in other counties (13). In some counties, the time at which resident women were first invited to be screened was extended over several years, and for such counties, we used the average year when screening started weighted by the number of women who were invited to screening in 1995–1996 in each subarea (see Table 1).

Statistical Analysis

Breast cancer mortality rates of women who were aged 40 years and older in 1960–2009 were age-standardized by the direct method using the Standard European Population as the reference. All computations were done with R 2.13.0 (14).

We analyzed temporal trends in breast cancer mortality from 1960 to 2009 using joinpoint regression (15), which fits a straight line on a logarithmic scale to annual age-standardized trends in rates. While fitting the straight line, the joinpoint program uses permutation analysis to identify inflexions in trends with a statistical significance level of .05. We allowed up to two possible joinpoints during 1960–2009 and report the annual percentage change for each computed regression segment.

Models

We expected that reductions in breast cancer mortality in each group of counties would be temporally related to the time at which screening was implemented in that group of counties. We compared observed age-adjusted breast cancer mortality rates after screening was introduced in each group of counties (the Null Model) with a similar model including an additional variable indicating absence or presence of screening at age 40–74 years (the Screening Model) and with three theoretical scenarios in which breast cancer mortality was reduced by 10%, 20%, and 30% among women invited to be screened (10%, 20%, and 30% Models). In the theoretical models, we assumed that screening-associated inflexions in trends would become evident 6–10 years after screening was introduced, and that the full 10%, 20%, or 30% mortality reduction among women invited to screening would be reached 8 years after the appearance of the inflexion point.

We modeled the observed and hypothetical changes in trends using generalized linear models with a Poisson distribution, a log link, and the logarithms of year-specific population numbers as an offset variable. In the Null Model, the outcome was the age-adjusted observed number of deaths, and the independent variable was the calendar year. This model did not include a variable that could reflect changes in trends and, therefore, it was equivalent to a linear trend computed from the observed mortality trend, assuming no change over time. The Null Model had the form:

$$\text{Log (age-adjusted number of breast cancer deaths)} = \beta 0 + \beta 1 \times \text{(year) [offset = log (no. of women 40+)]}.$$

In the Screening Model, the outcome was the age-adjusted observed number of deaths, and the independent variables were calendar year and absence or presence of screening in a specific year. The screening variable may induce a change in trend if trends in mortality rates differ between years with and without screening.

In the 10%, 20%, and 30% Models, the outcomes were the hypothetical age-adjusted number of deaths under the 10%, 20%, and 30% mortality decrease scenarios, and the independent variables were calendar year and absence or presence of screening in a specific year.

The variable "calendar year" was centered. Its value was set to 0 for the year of screening start plus the lag-time of 6–10 years. Thus, under scenarios where mortality trends would start to decrease 6 years after screening had started, years before the year of start plus 6 years would take values −1, −2, −3, diminishing until 1960, and the years following the year of start plus 6 years would take increasing values +1, +2, +3, until 2009. In the Screening Model and the 10%, 20%, or 30% Models, the screening variable was coded 0 for years without screening, and +1, +2, +3, etc., for years with screening. The screening variable will induce a change in trends proportional to the differences in rates in years with screening and years without screening. The Screening Model, and the 10%, 20%, and 30% Models had the following form:

$$\text{Log (age-adjusted number of breast cancer deaths)} = \beta 0 + \beta 1 \times \text{(year)} + \beta 2 \times \text{(screening) [offset = log (no. of women 40+)]}.$$

We have provided a diagram to show how a theoretical 30% reduction scenario in breast cancer mortality after inception of invitations to screening would apply to county Group 1 (Figure 1). The continuous line is the observed mortality trend, assuming no changes in trend over time. If we assume that an inflexion in mortality due to screening would occur 6 years after screening started in 1976, the observed (circles) and expected (triangles) rates would be identical until 1982. If screening had resulted in a 30% decrease in mortality in women invited to screening, in addition to the secular downward trend represented by the continuous line, the 30% decrease should have been observable in 1990, that is, 8 years after the inflexion appeared. The open triangles between 1982 and 1990 represent the expected trend if a 30% reduction had occurred during the 8 years that followed the first 6 years after screening was introduced in 1976 (for the sake of clarity, expected trends for 10% and 20% reductions are not displayed).

Beta-Coefficients

The beta-coefficients $\beta 0$, $\beta 1$, and $\beta 2$ were calculated using the observed and theoretical annual 5-year age-group mortality data for each group of counties. For the observed mortality rates, we multiplied the age-standardized mortality rates of year i by the number of women aged 40 years and older residing in each group of counties in mid-year i. After that, we fitted the Null Model and the Screening Model to the observed data. To obtain the hypothetical number of breast cancer deaths at year i, we multiplied the hypothetical age-standardized mortality rates computed for year i by the number of women aged 40 years and older who were residents in the county groups at mid-year i.

We assessed possible changes in mortality trends after screening started by comparing the $\beta 2$ regression coefficient of the Screening Model with those of the 10%, 20%, and 30% Models. All statistical tests were two-sided. P values less than .05 were denoted as statistically significant, and associations were estimated with 95% confidence intervals.

Sensitivity Analyses

For both joinpoint and Poisson regression models, we performed sensitivity analyses by changing key parameters. First, we applied joinpoint regression on county group data, allowing zero to three and zero to four joinpoints. Second, for county Groups 1, 2, and 3, Poisson regressions from the Screening, 10%, 20%, and 30% Models were replicated, using the last year when screening started in each county group as the first year of screening. This analysis was equivalent to setting as the first year of screening the year when all eligible women had been invited to screening at least once. We did not perform this sensitivity analysis for county Group 4 because the majority of first invitations in these counties were sent out in 1989–1990.

Results

Mammographic screening was gradually implemented in five phases in Sweden (Table 1 and Figure 2). Efforts to screen the entire population of eligible women (1 286 000 women in 1995–1996) were initiated in 1974–1978 in Gävleborg county, where a demonstration project was started in 1974 (16), and in Dalarna and

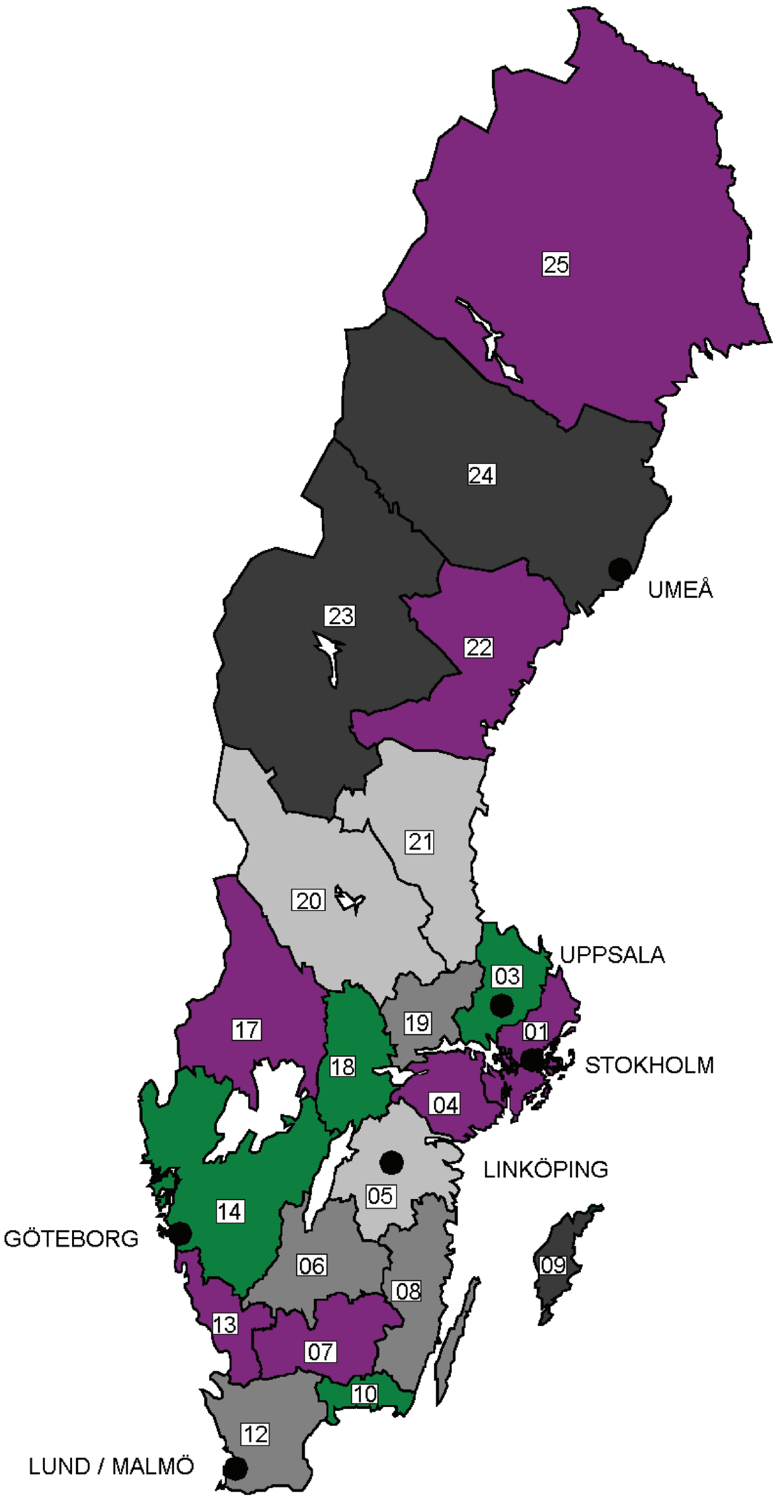

Figure 2. Map of Sweden with official county numbers. County names are listed by number in Table 1. Groups of counties are shaded according to the year when mammographic screening programs were implemented: Group 1 (1974–1978), Gävleborg, Dalarna, Östergötland in light gray; Group 2 (1986–1987), Kalmar, Västmanland, Jönköping, Skåne in medium gray; Group 3 (1987–1988), Västra Götaland, Örebro, Uppsala, Blekinge in green; Group 4 (1989–1990), Stockholm, Södermanland, Halland, Norrbotten, Kronoberg, Västernorrland, Värmland in violet; Group 5 (1995–1997), Västerbotten, Jämtland, Gotland in dark gray. The island of Öland near the south-east coast is part of Kalmar county. Areas in white are lakes.

Östergötland counties, where randomized trials were conducted (1) (Table 1). The national mammography screening program in Sweden officially started in 1986, and in 1986–1987, 1987–1988, and 1989–1990, the screening program rapidly expanded, with the addition of two groups of four counties each and then, an additional group of seven counties that included the nation's capital. In the counties of Skåne and Västra Götaland, eligible women were sent first invitations over the course of several years. The three remaining counties were added to the nationwide screening program in 1995–1997 such that breast cancer screening was in effect in all counties in Sweden by 1997.

We expected that the gradual implementation of screening in different counties would be associated with a gradual reduction in mortality that would culminate in the reductions predicted by previous randomized trials and observational studies (2–11). We also expected that reductions in mortality would be timed relative to the timing at which screening was introduced in each of the five groups of counties. For each group of counties (Table 1), we compared the observed age-adjusted breast cancer mortality rates after screening was introduced with three theoretical scenarios in which breast cancer mortality was reduced by 10%, 20%, and 30% among women who were invited to be screened at age 40–69 years. For county Group 5, mammographic screening had started late (1995–1997), and the population was too small to analyze in the same manner (only 4% of all women were invited to be screened in 1995–1996). In the theoretical scenarios, we hypothesized that inflexions in trends induced by screening would become evident 6–10 years after screening was introduced, and that a full mortality reduction (10%, 20%, or 30% among screened women) would be reached 8 years after the appearance of the inflexion point. The choice of 8 years was derived from the results of the Malmö trial, which is considered to be the most robust Swedish trial on methodological grounds (17,18). Thus, we suggested that within each group of counties, the full reduction in breast cancer mortality would be achieved between 14 and 18 years after the introduction of mammographic screening.

In Sweden as a whole, the annual breast cancer incidence rates increased by 1.09% from 1960 to 1986, followed by a steeper increase of 1.51% per year after screening had reached national coverage in 1997 (Figure 3). After 2004, incidence rates declined by 0.63% per year. Before 1972, breast cancer mortality was unstable with a period of decrease followed by a period of increase (Table 2 and Figure 3). From 1972 to 2009, breast cancer mortality rates in Swedish women aged 40 years and older declined by 0.98% annually, from 68.4 to 42.8 per 100 000, and no change in trend was detected by the joinpoint analysis.

We examined age-adjusted breast cancer mortality rates for each of the 21 Swedish counties, with periods of linear trends and years of inflexion identified by joinpoint analyses (Figure 4). In 14 of the 21 counties (Gävlegorg, Dalarna, Kalmar, Västmanland, Jönköping, Örebro, Uppsala, Blekinge, Södermanland, Norrbotten, Kronoberg, Västernorrland, Värmland, Gotland), mortality trends after the initial screening followed a pattern that was a continuation of the trends that were observed before screening began. A downward inflexion in mortality occurred during the implementation of the screening program in Västra Götaland. In two counties, downward inflexions occurred 5 years (Stockholm) and 11 years (Halland) after screening had started. In Östergötland county, there was a steep decrease in mortality 6 years after screening started, followed by an increase 5 years later, and in 2009, the mortality rates were close to the prescreening level. In Skåne county, the pronounced downward trend in mortality since 1960 ceased in 1989, during the implementation of the screening program, after which the rates have remained stable until 2009. In contrast to the rest of the country, in two sparsely populated counties (Västerbotten and Jämtland), continuous increases in breast cancer mortality were followed by mortality reductions that occurred immediately after screening started.

At the county group level, no change in trends occurred in Groups 1 and 2 (Table 2). In Groups 3 and 4, steeper downward trends were observed 2–4 years after screening implementation. In Group 4, trends started to sharply decline 1 year after screening implementation.

Allowing zero to three or zero to four joinpoints in the regression models for county groups did not change the results in Table 2. The only changes occurred in county Group 4 in which two additional inflexion years (1967 and 1972) were identified for zero to three joinpoints, and one additional joinpoint year (1962) for zero to four joinpoints (data not shown).

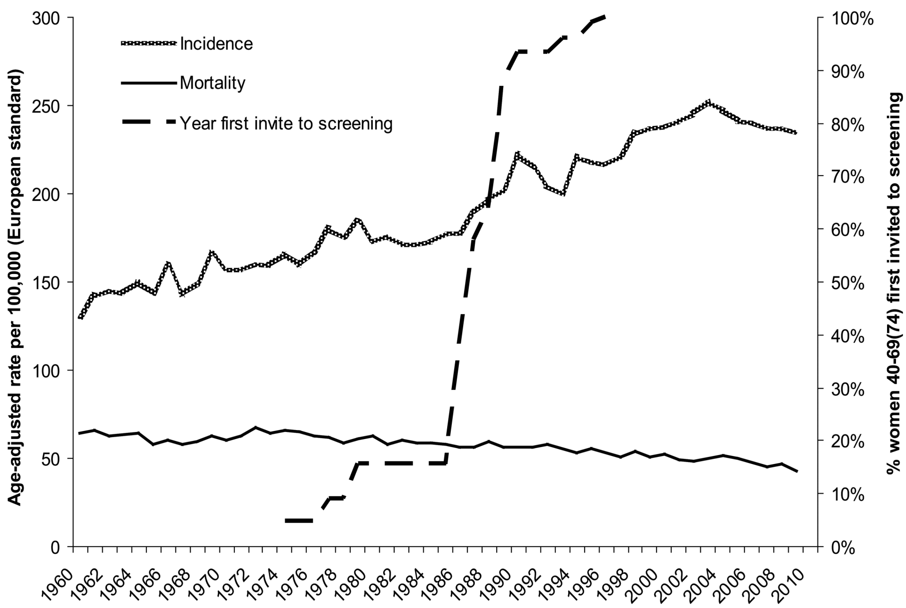

Figure 3. Age-adjusted breast cancer incidence and mortality in Swedish women aged 40 years and older in 1960–2009, and the cumulative proportion of women who received a first invitation to mammographic screening in 1974–1997.

Table 2. Annual percent changes with 95% confidence intervals in age-adjusted breast cancer mortality rates in Swedish women aged 40 years and older, 1960–2009*

			Trend 1		Trend 2 (if any)		Trend 3 (if any)	
	Code†	County	Period	Annual % change (95% CI)	Period	Annual % change (95% CI)	Period	Annual % change (95% CI)
	—	All of Sweden	1960–1967	−2.88 (−4.09 to −1.66)	1967–1972	1.83 (−1.18 to 4.94)	1972–2009	−0.98 (−1.08 to −0.87)
Group 1			1960–2009	−1.00 (−1.19 to −0.81)				
	21	Gävleborg	1960–2009	−0.79 (−1.08 to −0.51)				
	20	Dalarna	1960–2009	−1.47 (−1.84 to −1.10)				
	05	Östergötland	1960–1983	−0.40 (−1.25 to 0.46)	1983–1988	−6.88 (−18.29 to 6.14)	1988–2009	1.05 (0.03 to 2.09)
Group 2			1960–2009	−0.96 (−1.11 to −0.81)				
	08	Kalmar	1960–2009	−1.12 (−1.49 to −0.74)				
	19	Västmanland	1960–2009	−1.20 (−1.52 to −0.87)				
	06	Jönköping	1960–2009	−1.17 (−1.48 to −0.87)				
	12	Skåne	1960–1989	−1.30 (−1.96 to −0.90)	1989–2009	0.04 (−0.65 to 0.74)		
Group 3			1960–1992	−0.49 (−0.71 to −0.28)	1992–2009	−1.40 (−1.97 to −0.84)		
	14	Västra Götaland	1960–1991	−0.42 (−0.66 to −0.19)	1991–2009	−1.31 (−1.84 to −0.77)		
	18	Örebro	1960–2009	−0.78 (−1.13 to −0.42)				
	03	Uppsala	1960–2009	−0.96 (−1.10 to −0.52)				
	10	Blekinge	1960–2009	−0.76 (−1.17 to −0.36)				
Group 4			1960–1992	−0.43 (−0.68 to −0.19)	1992–2009	−1.74 (−2.36 to −1.12)		
	01	Stockholm	1960–1994	−0.54 (−0.88 to −0.20)	1994–2009	−2.06 (−3.14 to −0.96)		
	04	Södermanland	1960–2009	−0.78 (−1.09 to −0.47)				
	13	Halland	1960–1962	−18.09 (−43.95 to 19.71)	1962–2000	−0.27 (−0.7 to 0.15)	2000–2009	−3.80 (−6.95 to −0.54)
	25	Norrbotten	1960–2009	−0.39 (−0.76 to −0.01)				
	07	Kronoberg	1960–2009	−1.18 (−1.55 to −0.80)				
	22	Västernorrland	1960–2009	−0.48 (−0.93 to −0.03)				
	17	Värmland	1960–2009	−0.79 (−1.12 to −0.46)				
Group 5			1960–1998	0.33 (−0.08 to 0.75)	1998–2009	−4.54 (−7.20 to −1.80)		
	24	Västerbotten	1960–1998	0.38 (− 0.25 to 1.02)	1998–2009	−4.12 (−8.04 to −0.04)		
	23	Jämtland	1960–1998	0.78 (0.11 to 1.46)	1998–2009	−5.86 (−10.25 to −1.25)		
	09	Gotland	1960–2009	−0.78 (−1.44 to −0.10)				

* APC = annual percent change; CI = confidence interval.

† The "Code" is the official administrative number of a county (there are no counties numbered 02, 11, 15, or 16).

We graphed breast cancer mortality trends for four of the five groups of counties based on Poisson regression models for observed age-adjusted death rates (Null Model and Screening Model), and for the three hypothetical scenarios, that breast cancer screening had resulted in a 10%, 20%, or 30% reduction in mortality, assuming a lag time of 10 years from the start of screening until changes in trends (Figure 5). The β1-coefficients were statistically significantly negative for all five models (data not shown), reflecting statistically significant reductions in breast cancer mortality during the study period in each county group.

We next compared β2-coefficients associated with the screening variable for 6-, 8-, and 10-year lag times from the start of screening until an inflexion in trends was identified (Table 3). The Screening Model includes all years from 1960 to 2009 (Figure 5), whereas the three models for the theoretical scenarios do not include years after which the theoretical 10%, 20%, or 30% mortality reductions had been achieved. Because more years are included in the computation of the Screening Model than in the 10%, 20%, or 30% Models, the precision of the β2-coefficients for the Screening Model was greater than that of the models of the theoretical scenarios. Also, the P values of the β2-coefficients of the 10%, 20%, and 30% Models reflect that we made no assumptions about whether the theoretical trends in mortality after the end of the 12–18-year period would decrease further or stabilize. Of note, the β2-coefficients of the 10%, 20%, and 30% Models tended to decrease with observation time, which is a direct consequence of the continuous mortality reductions observed in the four county groups (Table 2).

The β2-coefficients in county Group 1 showed no statistically significant inflexion in mortality trends after screening was introduced. In county Group 2, the positive and statistically significant value of the β2-coefficients of the Screening Model ranged between the absolute values of the β2-coefficients of the 10% and 20% Models. Hence, the downward trend was statistically significantly less pronounced after than before screening was introduced, and we estimated that compared with rates in the prescreening period, mortality rates were increased by approximately 12% (=10%+10% × [(0.00921 − 0.00595)/(0.02021 − 0.00595)]; $P = .007$).

Statistically significantly negative β2-coefficients were observed in county Groups 3 and 4, respectively, indicating that inflexions in mortality trends took place after the introduction of screening. Compared with a scenario in which screening had not existed, we estimated the decrease in mortality to be approximately 5% (=10% × [0.01128/0.02119]) steeper in county Group 3 ($P = .001$) and 8% (=10% × [0.01906/0.02285]) steeper in county Group 4 ($P < .001$).

Using a lag time of 6 or 8 years from screening start until inflexion point did not appreciably affect the observed trends (Table 3).

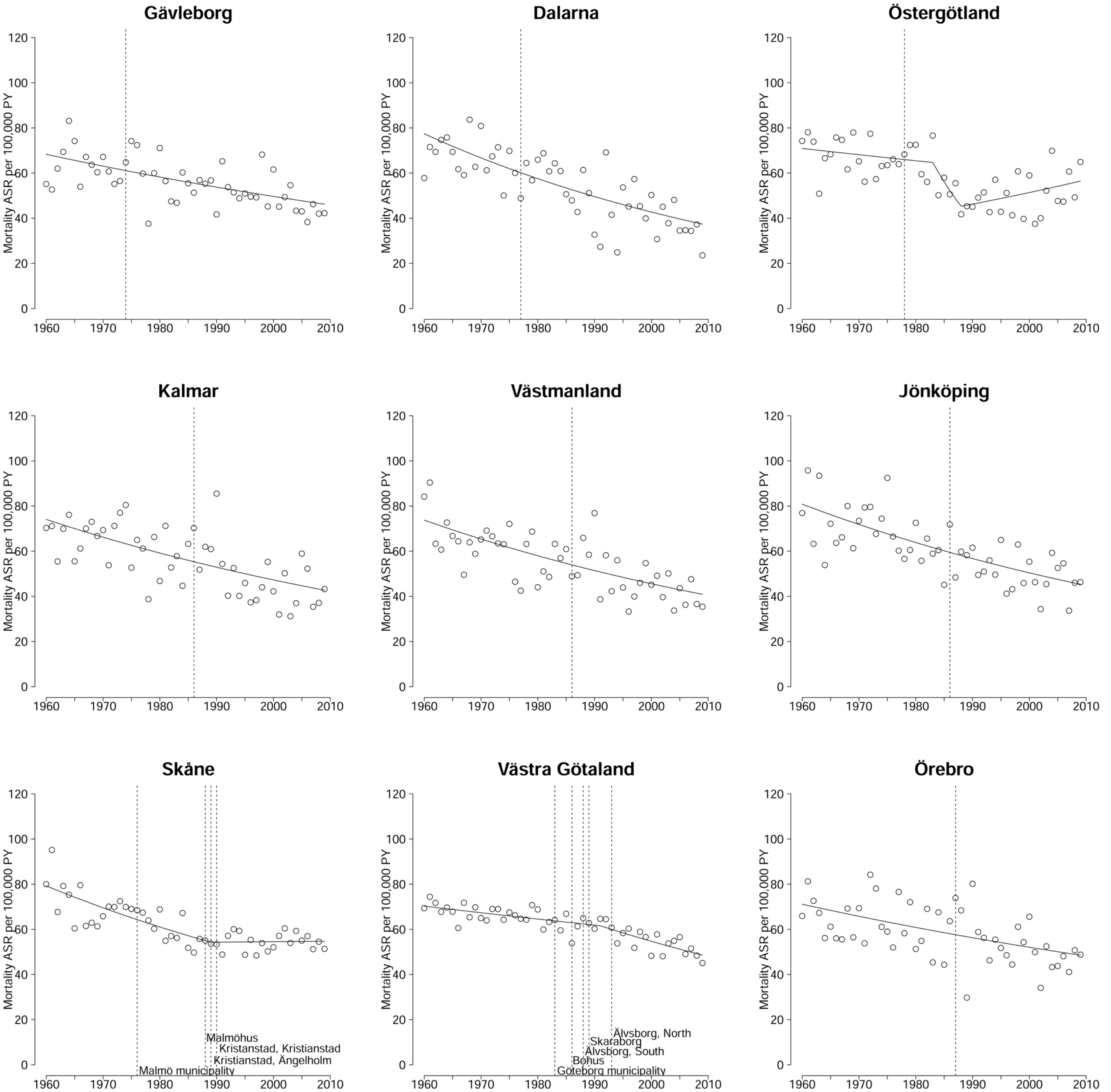

Figure 4. Age-adjusted breast cancer mortality rates in Swedish women aged 40 years and older in each of the 21 counties, 1960–2009. The **dots** represent annual rates and the **plain lines** the periods of linear trends identified by joinpoint analyses. The **vertical dashed line** is the year screening started.

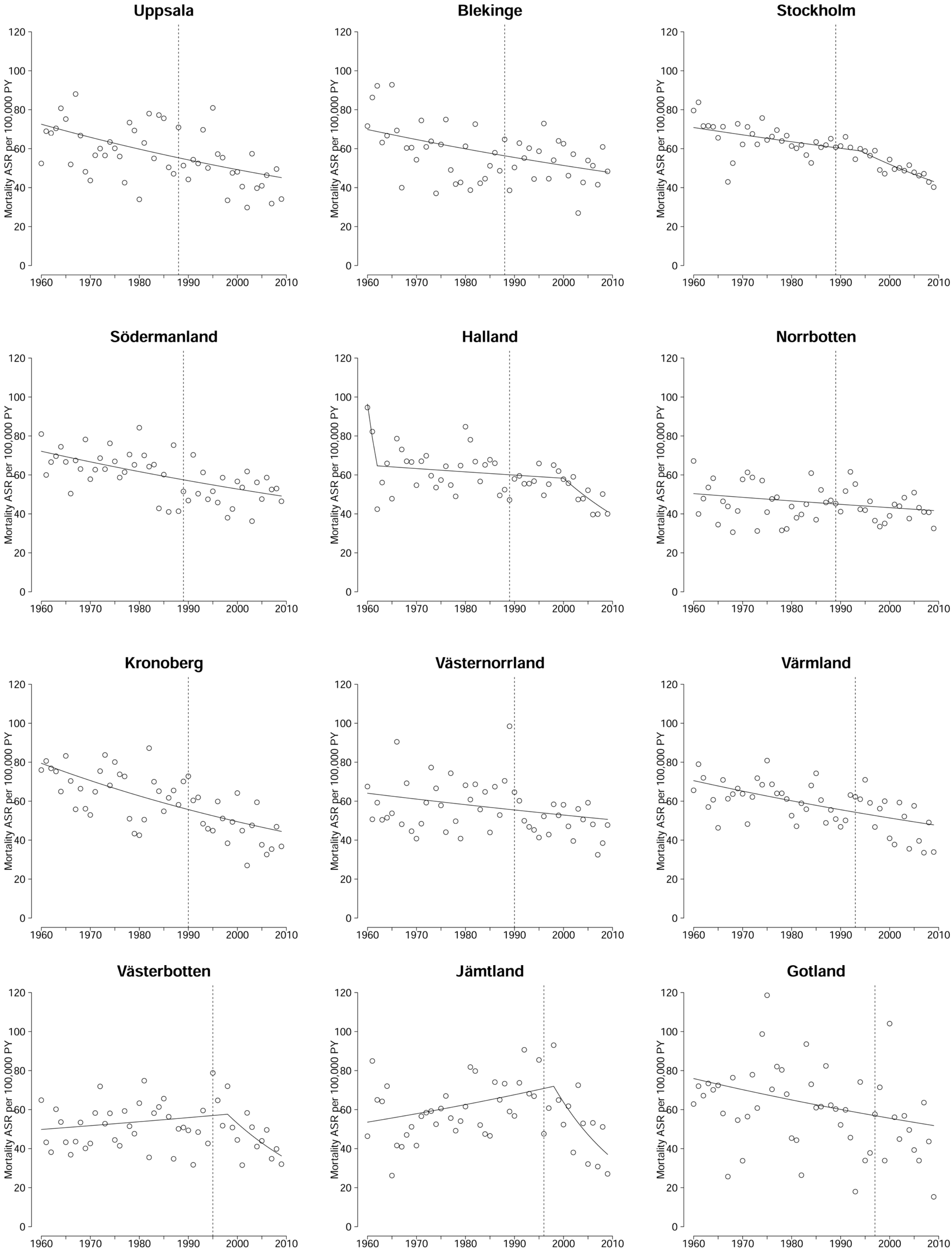

Figure 4. (Continued)

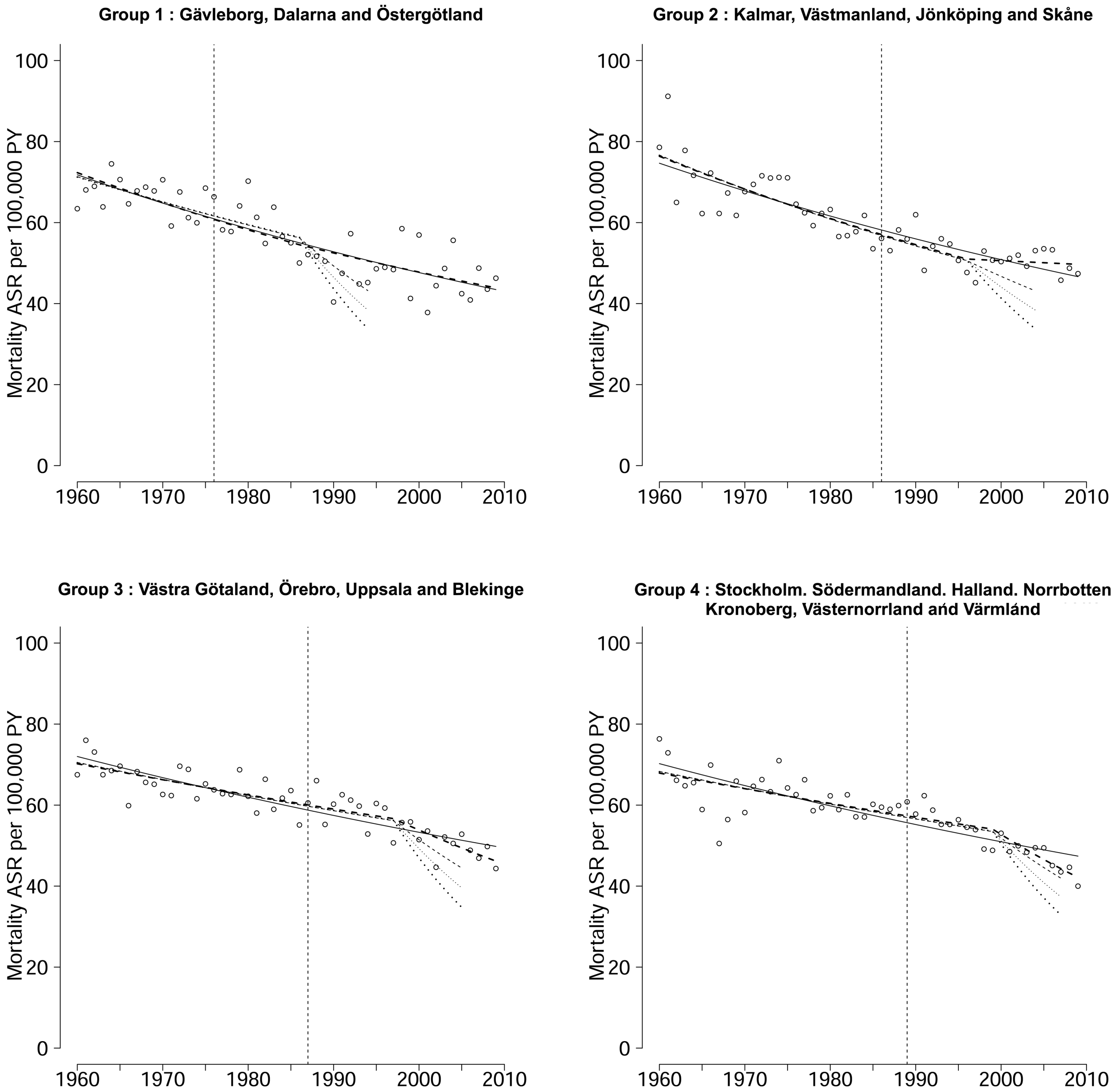

Figure 5. Trends derived from Poisson regression models for observed age-adjusted breast cancer death rates (Null Model and Screening Model) and for the three theoretical scenarios in which mammographic screening was expected to result in 10%, 20%, or 30% reductions in breast cancer mortality, considering a lag time of 10 years between the start of screening and changes in trends, and a further period of 8 years after the inflexion year for reaching the 10%, 20%, or 30% mortality reduction. The **open circles** represent the observed annual mortality rates per 100 000 persons, and the **vertical dashed line** represents the average year of screening start. **Continuous line**: Null Model; **thick dashed line**: Screening Model with inflexion point; **thin dashed line**: Model with screening-associated 10% reduced mortality; **thin dotted line**: Model with screening-associated 20% reduced mortality; **thick dotted line**: Model with screening-associated 30% reduced mortality.

In addition, setting the year when all eligible women had been invited at least once as the start of screening did not substantially change the results.

Discussion

Using official cause-specific mortality data from Sweden, we found that in most counties where screening was established before 1995, breast cancer mortality continued to decrease at a rate that was similar to the downward trend observed in the prescreening period. In two counties (Stockholm and Halland), the stronger mortality decrease that we observed could be compatible with an added effect of mammography screening. In Skåne county, mortality trends stabilized after screening was introduced, and in Östergötland county, the mortality tended to return to the levels observed before the start of screening.

Among the four groups of counties that we constructed, we observed no inflexion in the breast cancer mortality trend in county Group 1 after screening started, whereas in county Group 2, the observed trends were compatible with reductions in breast cancer mortality that were 12% less steep following the introduction of screening. In county Groups 3 and 4, the observed trends were

Table 3. Influence of mammography screening on breast cancer trends in groups of counties in Sweden compared with hypothetical changes in trends reflecting 10%, 20%, or 30% decreases in mortality after the start of screening*

		Time from screening start to change in trends								
		6 years		8 years		10 years			10 years	
County group (average year of screening start)	**Model**	**Estimate for $\beta 2$†**	**P for $\beta 2$‡**	**Estimate for $\beta 2$†**	**P for $\beta 2$‡**	**Estimate for $\beta 2$†**	**P for $\beta 2$‡**	**Sensitivity analysis: county group (last year of screening start)**	**Estimate for $\beta 2$†**	**P for $\beta 2$‡**
Group 1 (1976)								Group 1 (1985)		
	Screening Model	−0.00145	.671	−0.00011	.974	0.00143	.674		0.00552	.232
	Model 10%	−0.02624	.008	−0.02829	.003	−0.02246	.016		−0.00658	.454
	Model 20%	−0.04115	<.001	−0.04272	<.001	−0.03697	.001		−0.02038	.024
	Model 30%	−0.05751	<.001	−0.05917	<.001	−0.05332	<.001		−0.03609	.001
Group 2 (1986)								Group 2 (1990)		
	Screening Model	0.00671	.015	0.00763	.012	0.00921	.007		0.01128	.023
	Model 10%	−0.00735	.238	−0.00876	.153	−0.00595	.326		−0.00582	.327
	Model 20%	−0.02177	.001	−0.02305	.001	−0.02021	.001		−0.01990	.001
	Model 30%	−0.03737	<.001	−0.03880	<.001	−0.03599	<.001		−0.03559	<.001
Group 3 (1987)								Group 3 (1990)		
	Screening Model	−0.00951	<.001	−0.01044	<.001	−0.01128	.001		−0.01342	.005
	Model 10%	−0.02345	<.001	−0.02269	<.001	−0.02119	<.001		−0.02052	<.001
	Model 20%	−0.03811	<.001	−0.03694	<.001	−0.03576	<.001		−0.03499	<.001
	Model 30%	−0.05406	<.001	−0.05307	<.001	−0.05152	<.001		−0.05075	<.001
Group 4 (1989)								Group 4 §		
	Screening Model	−0.01523	<.001	−0.01678	<.001	−0.01906	<.001			
	Model 10%	−0.02707	<.001	−0.02614	<.001	−0.02285	<.001			
	Model 20%	−0.04166	<.001	−0.04064	<.001	−0.03736	<.001			
	Model 30%	−0.05779	<.001	−0.05677	<.001	−0.05328	<.001			

* In these models, the lag-time needed for observing a change in trend after the start of screening would be 6, 8, or 10 years and the full 10%, 20%, or 30% effect would be seen 8 years after the change in trend.

† The $\beta 2$ coefficient are derived from Poisson regression models and provide estimates of slopes of breast cancer mortality trends during the 8-year period following changes in trend possibly due screening that occurred 6, 8 or 10 years after screening start. For each group of counties, the Screening Model provides estimates for mortality trends actually observed, and estimates for Model 10%, 20% and 30% provide estimates for mortality trends if screening had contributed to 10%, 20% or 30% decrease in breast cancer mortality in the 8-year period following changes in trends.

‡ The two-sided P values are derived from the Poisson regression models and inform on the probability that $\beta 2$ coefficients would differ from zero.

§ For Group 4, the sensitivity analysis was not done because most of the screening program started in 1989–1990.

compatible with additional 5% and 8% reductions in breast cancer mortality following the introduction of screening compared with earlier trends. Thus, in the two groups of counties where screening started between 1974 and 1986, we found no evidence that mammography screening contributed to reductions in breast cancer mortality. In the two groups of counties where screening started between 1987 and 1989, mammography screening appeared to have contributed to a reduction in mortality, but the magnitude of the reduction was less than could be expected from the results of the randomized trials (1,2,5–7) and subsequent observational studies (4,8–11). The discrepancies between our results and those of randomized screening trials could be related to study design or could reflect a lower impact of screening on breast cancer mortality than that predicted by some of the trials.

To quantify and assess the direction of time trends, we applied joinpoint regression and Poisson regression analyses. Both approaches gave similar results, and sensitivity analyses with changes in key parameters did not substantially influence the results. A study in the United Kingdom related to effectiveness of cervical cancer screening used a similar methodology based on Poisson regression modeling and showed that reorganization of the screening service in 1988 was followed by steeper reductions in death rates (19). Nonetheless, for the interpretation of the results, several aspects should be considered.

It has been claimed that mammography screening is not likely to influence breast cancer mortality during the first years after screening introduction (20). Therefore, studies with short follow-up may not detect any effect on mortality. In Sweden, screening was fully implemented in county Group 1 in 1985, after the Two-County Trial was completed, and by 1990, 93% of Swedish women in targeted age groups had received their first invitation to the mammographic screening program. In the present analysis, we had mortality data until 2009, indicating a follow-up of 19–24 years for the various groups of counties. To the best of our knowledge, this is the longest observation period for which breast cancer mortality trends have been assessed after the introduction of a nationwide mammography screening program. Also, in the prediction models of breast cancer mortality, we applied lag times ranging from 6 to 10 years from the initiation of screening until changes in mortality rates could be attributed to the screening.

The cause-specific mortality data in the Swedish mammography randomized trials (21,22) were based on data from the Causes of Death Registry in Sweden. The World Health Organization considers cause-specific mortality data in Sweden to be of medium quality, similar to that in most European countries (23), but deaths caused by breast cancer may be more reliably reported than for many other cancers (21,24). Therefore, our results are not likely to be due to suboptimal reporting of breast cancer as a cause of death.

In Sweden, breast cancer mortality rates started to decrease in 1972, well before mammography screening was introduced. A similar long-lasting and steady decrease has not been observed elsewhere in Europe (25). Judged from the literature, no plausible explanation has been offered to provide an understanding of this special phenomenon in Sweden. Data on breast cancer management from the 1970s and 1980s are limited, but it has been suggested that special attention was given to breast cancer patients in Sweden (26). Thus, continuous but small improvements in the management of breast cancer could have resulted in the gradual reduction in mortality since the early 1970s (27), and the first regional management program recommending systemic therapy for stage I breast cancers was issued in 1983 (27). However, others claim that Sweden did not introduce adjuvant therapies particularly early (28). Modern mammography machines were first installed in Göteborg in 1968 (3), and it is possible that clinical mammography was used for screening purposes in certain areas before the national screening program was introduced. This reality was described in the Malmö trial, in which about 25% of the participants reported that they had received mammography between 1977 and 1989 (29); however, only 6% reported having had three or more mammographic examinations. Also, most of the screening in the form of clinical mammography was confined to the three largest urban areas (Stockholm, Göteborg, Malmö) (3). The mammography trial in Stockholm (1981–1986) did not report the proportion of women in the control group who received a mammography (5). Therefore, it is unlikely that mammographic examinations for screening purposes before 1988 contributed much to the steady decline in breast cancer mortality that started as early as in 1972 in Sweden.

In the absence of screening, the decrease in mortality observed since 1972 could have ceased by 1986 and been followed by stable rates or even an increase in mortality corresponding to the increase in incidence. However, this possibility is unlikely for a number of reasons: first, there was a consistent mortality decrease from 1972 to 1986, during a period in which incidence increased while mammography screening was rare (30). Second, between 1976 (the average year when screening started in county Group 1) and 1986–1990 (when screening started in county Groups 2, 3, and 4), there was no increase in mortality trends in counties from county Groups 1, 2, and 3 (Figure 4) that could have been the consequence of the absence of screening. Finally, as noticed by others (31), a strong increase in incidence has taken place in women aged 45–69 years after 1985, suggesting that mammography screening in itself increases the incidence, including the detection of many small tumors that may be clinically insignificant (ie, overdiagnosis) (32–34). Of note, the decrease in incidence after 2004 (Figure 3) was probably because of the discontinued use of hormone therapy (35).

Our study had the limitations of being observational in nature, and thus we were unable to consider the influence of risk factors for breast cancer death that could have masked the mortality effect of screening. For instance, overweight and obesity are associated with increased risk of dying from breast cancer (36,37), and the prevalence of obesity among adult women in Sweden nearly doubled from around 1980 until approximately 2000 (38). In Norway, there has been a similar increase in overweight and obesity (39), and the national breast screening program in Norway was launched about 12 years later than in Sweden. Changes in breast cancer mortality in Norway are similar to the changes in Sweden (40), suggesting that secular trends in overweight and obesity are not likely to mask the effect of mammography screening on breast cancer mortality. Nonetheless, the increasing prevalence of adiposity is likely to reduce the impact that screening, improved treatments, and greater efficiency of the health system may have on breast cancer mortality. It may be suggested that population mobility could have biased our results. However, it is not reasonable to assume that women who have received screening tend to have moved to counties where reception of screening is rare, whereas women who have not received screening are more likely to have remained in the same county. Also, attendance to screening has always been high in Sweden (3,4), suggesting little imbalance in the provision of screening between counties. In addition, about 75% of adults in Sweden live in the county where they were born (41).

It has been concluded from Swedish mammography trials and subsequent observational studies that mammography screening leads to a substantial reduction in breast cancer mortality. Therefore, it seems paradoxical that the downward trends in breast cancer mortality in Sweden have evolved practically as if screening had never existed. This observation is in sharp contrast with the experience with colorectal cancer. In the United States, the mortality decline for colorectal cancer has been stronger than that for breast cancer (42). The high prevalence of screening (endoscopy and fecal-occult-blood) in the United States (43) may be reflected in the dramatic decrease in advanced colorectal cancer that has occurred over the last 25 years (42). By contrast, a similar decrease in the occurrence of advanced breast cancer has not been noticed in areas with high prevalence of mammographic screening (44,45).

In conclusion, Swedish mortality statistics show little evidence that the decrease in breast cancer mortality corresponds to the results of mammography trials and observational studies conducted in Sweden. In fact, the Swedish breast cancer mortality statistics are consistent with studies that show limited or no impact of screening on mortality from breast cancer (40,46,47).

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Notes

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