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Breast Cancer Mortality After Implementation of Organized Population-Based Breast Cancer Screening in Norway

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Abstract

Background: We estimated breast cancer (BC) mortality reduction associated with invitations to a nationwide population-based screening program and with changes in treatment.
Materials and methods: BreastScreen Norway started in 1996 and became nationwide in 2005. It invites women aged 50–69 years to biennial mammographic screening. We retrieved individual-level data for 1 340 333 women from national registries. During 1996–2014 (screening window), women contributed person-years in noninvited and invited periods. We created comparable periods for 1977–1995 (prescreening window) by dividing the follow-up time for each woman into pseudo-noninvited and pseudo-invited periods. We estimated BC mortality for the four periods, using the so-called evaluation model: counting BC deaths in each period for all women diagnosed within the period and counting BC deaths and person-years after screening-age for those diagnosed within screening age. We used a multivariable flexible parametric survival model to estimate hazard ratio (HR) for the effect of invitation and improved treatment.
Results: Using the regression approach, we found 5818 BC deaths across 16 533 281 person-years. Invitations to screening reduced BC mortality by 20% (HR = 0.80, 95% confidence interval [CI] = 0.70 to 0.91) among women 50 years and older and by 25% (HR = 0.75, 95% CI = 0.65 to 0.86) among screening-aged women. The treatment effect was 23% (HR = 0.77, 95% CI = 0.65 to 0.92) for women 50 years and older and 17% (HR = 0.83, 95% CI = 0.74 to 0.94) for screening-aged women.
Conclusion: We observed a similar reduction in BC mortality associated with invitations to screening and improvements in treatment during 1977–2014, among women 50 years and older.

Mammographic screening aims to reduce breast cancer (BC) mortality by detecting the disease at an early stage. Review studies have confirmed the efficacy using results from randomized, controlled trials performed several decades ago (1–4). The trials reported a mortality reduction of about 20% among invited women (1–5), whereas screening programs yielded a higher reduction (2,4,6–8). Improvements in screening techniques and treatment after the trials likely contributed to the lower mortality observed in the programs. Estimating BC mortality associated with screening programs is challenging because of a lack of control groups and uncertainties around the contribution of improvements in BC awareness, treatment, and care (8–10).

Continuous evaluation of BC mortality is essential to ensure the quality of screening programs. This requires long follow-up, because early detection and detection of small, low-proliferation tumors, in combination with improved treatment, prolong survival (11). Various approaches have been used to evaluate BC mortality reduction following the implementation of organized BC screening in Norway, and estimates range from 7% to 28% for invited vs noninvited women (7,12,13). However, some of these studies were limited by short follow-up. A recent study using aggregated Norwegian data reported a 20% reduction in BC mortality after the implementation of organized screening but ascribed most of the effect to improved treatment (14). Importantly, none of these studies used individual-level data about screening history, BC diagnosis, or mortality from the periods before and after implementation of the screening program.

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In this study, we used nationwide individual-level data to estimate long-term BC mortality during the last two decades among women invited to a population-based screening program in Norway. Further, we estimated the reduction in BC mortality that was not attributable to invitation as a surrogate measure of the effect of improved treatment.

Material and Methods

BreastScreen Norway

BreastScreen Norway, the population-based screening program in Norway, was introduced in four counties in 1996 and became nationwide in 2005 after a staggered rollout (15). The screening program offers biennial two-view mammography to all women registered in the Population Registry who are aged 50–69 years during a given screening round (2-year period). Because of the staggered rollout, the screening cohorts differed slightly between counties. Moreover, some women can be aged 48 or 49 years when they are invited to screening because they will turn age 50 years during the screening round. Similarly, women may be age 50 years during the screening round but not receive an invitation until they are age 52 years. These women may receive their final (10th) invitation to screening at age 71 years. During the first 20 years of the program, the attendance rate was 75% for each screening round, and 84% of the invited women had attended at least once.

Data Extraction

We used the Population Registry in Norway to identify all women born after 1907 and residing in Norway between 1977 and 2014 (study period). We extracted individual-level data about immigration and emigration from the Population Registry, and information on cause and date of death was extracted from the Cause of Death Registry. Information about screening history and diagnosis was extracted from the Cancer Registry of Norway. Data were merged using the 11-digit personal identification number assigned to all residents. The regional committee for medical and health research ethics approved this study (REK 2013/795).

Study Population, Prescreening, and Screening Window

We divided the study period (1977–2014) into two: prescreening window (1977–1995) and screening window (1996–2014).

Women entered our study population either on the date of their 50th birthday, immigration between the ages of 50 and 69 years (inclusive), or the window start (January 1, 1977, for the prescreening window; January 1, 1996, for the screening window), whichever occurred last. The prescreening window included women free from BC, born 1907–1945, whereas the screening window included women free from BC, born 1926–1964 (Figure 1). We followed women for BC death until date of emigration, death from other causes, or end of follow-up (December 31, 1995, for the prescreening window; December 31, 2014, for the screening window), whichever occurred first. All dates were provided as month and year; the date of window start was assigned to the first day of the month, invitation to the 12th, screening examination to the 13th, diagnosis of BC to the 14th, emigration or death to the 15th, and end of follow-up to the 31st.

We classified the women as invited after receiving an invitation to participate in BreastScreen Norway, regardless of whether they participated. No women were invited during the prescreening window. To compare BC mortality in the prescreening and screening windows, we created a distribution of made-up invitations (pseudo-invitations) in the prescreening window (1977–1995) to obtain a group of pseudo-invited and pseudo-noninvited women. These two groups mirrored the groups of invited and noninvited women in the screening window (1996–2014). The term *period* was used for the individual woman's contribution of person-years in the four different groups (pseudo-noninvited, pseudo-invited, noninvited, and invited).

We used two independent approaches, regression and matching, to create the distribution of pseudo-invitations. This allowed the identification of possible discrepancies between outcomes from the two approaches or, in case of similar outcomes, proved the robustness of the estimates under investigation. The approaches are described below and in Figure 2, A and B.

The same women could be included in the (pseudo-)noninvited and in the (pseudo-)invited periods and in the prescreening and screening windows, contributing with person-years in different age spans. We excluded women invited before age 50 years and censored women invited after age 70 years.

Statistical Analyses

To compare BC mortality during the four periods (pseudo-noninvited, pseudo-invited, noninvited, and invited), two statisticians independently carried out the two approaches: the regression approach (by SS using STATA version 15.1, Stata Corp, TX) and the matching approach (by EB using SAS version 9.4, SAS Institute, Cary, NC).

In the regression approach, we randomly assigned pseudo-invitations during the prescreening window, following the same distribution as the true invitations in the screening window. For each combination of 5-year age groups, county, and time between January 1, 1996, and the date the women entered the period (5-year intervals), we replicated the invitation distribution in the prescreening window. For example, if 3% of women aged 60–64 years in January 1996 residing in county X were invited in March 1996, then 3% of women aged 60–64 years in January 1977 residing in county X were assigned a pseudo-invitation in March 1977 (Figure 2A).

In the matching approach, we first identified women who could contribute person-years to the noninvited and the pseudo-noninvited period (Figure 2B). Women from the two periods were matched 1 to 1 on county of residence, age when entering the study (± 1 year), and time between the window start date (January 1, 1977, or 1996) and the date the women entered the period (± 1 year). For all matched pairs, the longest follow-up time was censored so that both women were followed for the same time (16) to obtain comparable age distributions between noninvited and pseudo-noninvited women. However, in the evaluation model (see below), matched pairs could have different follow-up times if the follow-up exceeded the screening age for one of the women. We then identified invited women from the screening period (1996–2014) and women available for inclusion in the pseudo-invited prescreening period (1977–1995). Person-years previously used in the pseudo-noninvited period were no longer available. Using the same criteria applied to the (pseudo-)noninvited women, the (pseudo-)

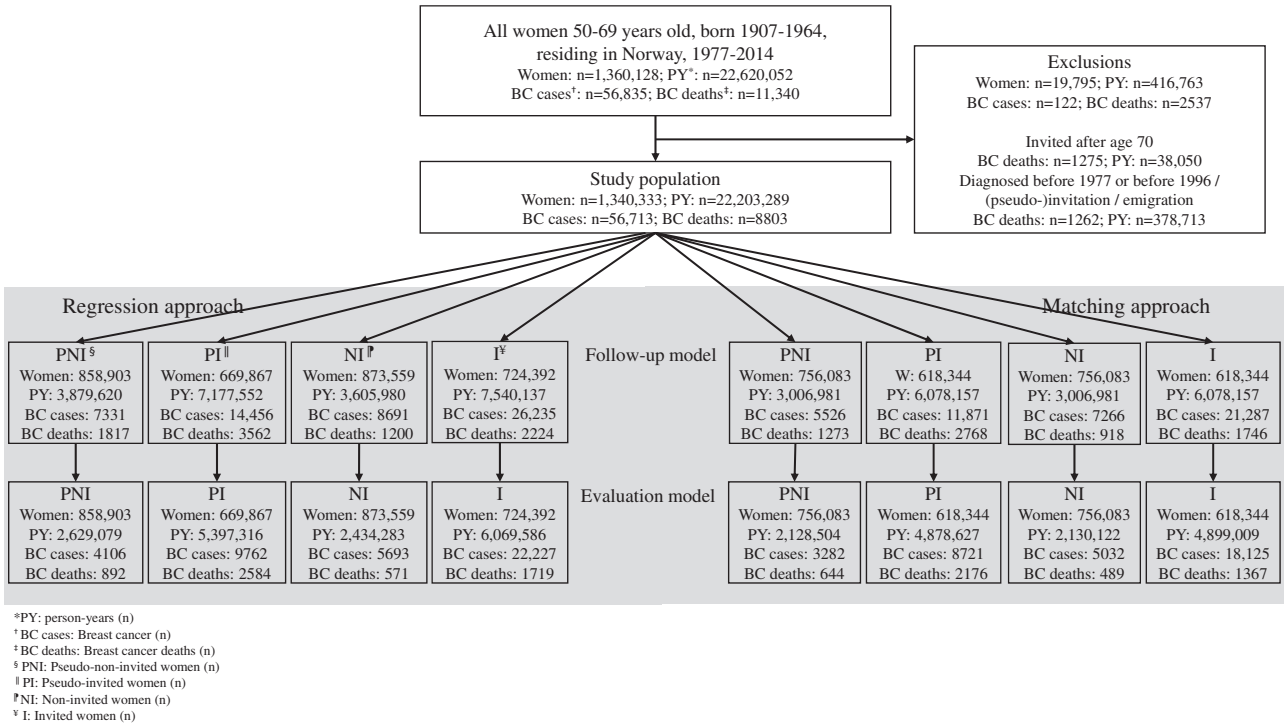

Figure 1. Women included in the study and study outcome for the regression and matching approach using the follow-up and evaluation model. BC = breast cancer; I = invited women; NI = noninvited women; PNI = pseudo-noninvited women; PI = pseudo-invited women; PY = person-years.

invited women were matched one to one and the longest follow-up time was censored to obtain equal follow-up within pairs. Given the matching design and the censoring, we expected less women and follow-up time in the matching compared with the regression approach.

For both the regression and matching approach, we used the follow-up and the evaluation model described by Nyström et al (17) to estimate BC mortality. The former counts BC deaths in each of the four periods for women diagnosed within the same period. The latter is similar but counts BC deaths and person-years only for women diagnosed within the screening age.

With the two approaches and the two models, we estimated BC mortality as the number of BC deaths divided by the number of person-years at risk in the four periods. The rate ratio (RR) of BC mortality between the noninvited and pseudo-noninvited women was interpreted as the change in BC mortality over time due to BC treatment, awareness, and care (treatment effect). This effect was assumed to be linear over time. The RR of BC mortality between the invited and pseudo-invited women was interpreted to include both the treatment effect and the effect of invitation to BreastScreen Norway (invitation effect). The treatment effect was assumed to be equally strong for the pseudo-noninvited vs noninvited as for the pseudo-invited vs the invited (linear assumption). Thus, in the matching approach, the invitation effect was expressed as a ratio of rate ratios (RRR) (mortality in the invited period/mortality rate in the pseudo-invited period)/(mortality rate in the noninvited period/mortality rate in the pseudo-noninvited period).

In the regression approach, we estimated the effect of being invited to BreastScreen Norway by fitting a flexible parametric survival model with a covariate for the prescreening or screening window, a covariate for invitation status, and an interaction term between the two, adjusting for county and age. To account for nonproportionality observed in the evaluation model, a time-dependent covariate for prescreening and screening window was included.

The interaction term is an estimate of the invitation effect; it represents the reduction in BC mortality in invited women adjusted for changes in BC mortality over time and for changes imposed by the study design (changes between pseudo-noninvited and pseudo-invited women).

Results

Using the regression approach and the follow-up model, we counted 8803 BC deaths and 22 203 289 person-years for women aged 50–88, in all four periods (Figure 1 and Table 1). The observed BC mortality rates were 46.8 and 33.3 per 100 000 person-years for the pseudo-noninvited and noninvited periods and 49.6 and 29.5 per 100 000 person-years for the pseudo-invited and invited periods (Table 1). The evaluation model included 5766 BC deaths and 16,530,264 person-years (Figure 1 and Table 1). BC mortality rates were 33.9 and 23.5 per 100 000 person-years for the pseudo-noninvited and noninvited women, respectively, and 47.9 and 28.3 per 100 000 person-years for the pseudo-invited and invited women, respectively (Table 1).

Using the regression approach and the follow-up model for all ages, the adjusted hazard ratio showed a 13% (HR = 0.87, 95% CI = 0.79 to 0.95) reduction in BC mortality due to invitations and 27% (HR = 0.73, 95% CI = 0.67 to 0.78) due to treatment (Table 2). For the evaluation model, the adjusted hazard ratio showed a 20% (HR = 0.80, 95% CI = 0.70 to 0.91) reduction in BC mortality due to invitations and a 23% (HR = 0.77, 95% CI = 0.65 to 0.92) reduction due to treatment. For screening-aged women, the invitation effect was 25% (HR = 0.75, 95% CI = 0.65 to 0.86) and the treatment effect 17% (HR = 0.83, 95% CI = 0.74 to 0.94) for both the follow-up and the evaluation models.

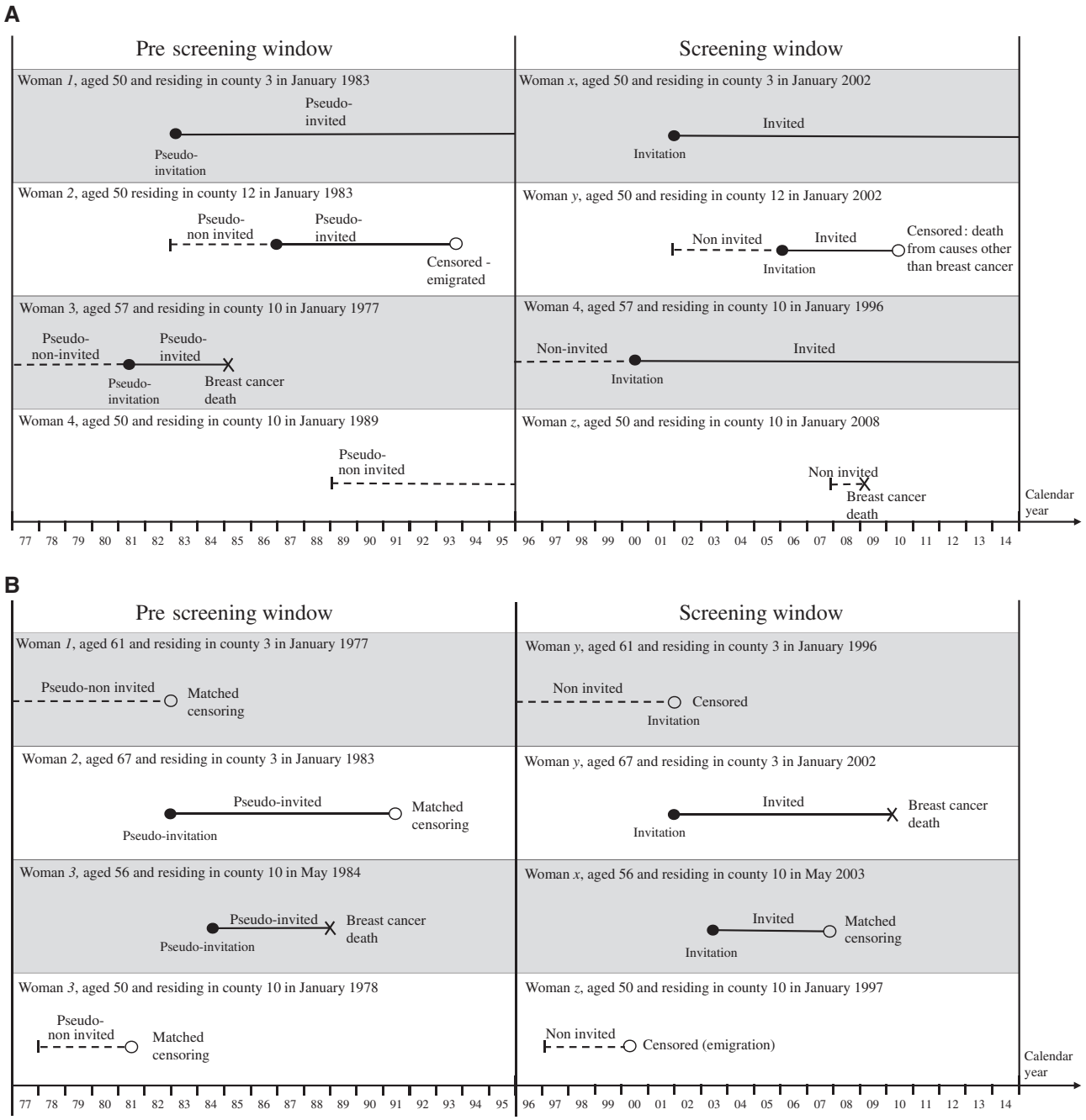

Figure 2. Strategies for selecting invited women in the prescreening window for the regression approach and matching approach. **A)** Regression approach: Seven hypothetical women exemplifying the regression approach: 1, 2, 3, 4, x, y, and z. Woman 4 contributed with women-years both in the prescreening and screening window. We replicated the real invitation distribution in the screening window, as pseudo-invitations in the prescreening window. Woman x, aged 50 years and residing in county 3 in January 2002, was invited to screening and followed to end of follow-up. Woman 1, aged 50 years and residing in county 3 in January 1983, received a pseudo-invitation and was followed until end of follow-up. Woman y, aged 50 years and residing in county 12 in January 2002, was invited to screening in January 2006 and died from pancreatic cancer in 2010. Woman 2, aged 50 years and residing in county 12 in January 1983, received a pseudo-invitation and was followed until she emigrated in 1994. Woman 4, aged 57 years and residing in county 10 in January 1996, was invited to screening in 2000 and followed throughout the screening window. Woman 3, aged 57 years and residing in county 10 in January 1977, received a pseudo-invitation in 1981 and died of breast cancer in 1985. Woman z, aged 50 years and residing in county 10 in January 2008, was never invited and died of breast cancer in 2009. Woman 4, aged 50 years and residing in county 10 in January 1989, was followed throughout the prescreening window as pseudo-noninvited. **B)** Matching approach: Six hypothetical women, 1, 2, 3, x, y, and z representing four matched pairs; woman 1 and y, 2 and y, 3 and x, and 3 and z. Woman y, aged 61 years and residing in county 3 in January 1996, was matched to woman 1, aged 61 years and residing in county 3 in January 1977. Woman y was censored on the date of screening invitation; woman 1 was censored at a corresponding date on the prescreening window to match the follow-up length of y (matched censoring). The same woman y, aged 67 years at invitation in January 1983 was matched to woman 2 aged 67 years at pseudo-invitation, residing in the same county as woman 2. Woman y died of breast cancer; woman 2 was censored to match the follow-up length of y. Woman x, aged 56 years and residing in county 10 at invitation in May 2003, was matched to woman 3, aged 56 years and residing in the same county as woman x in May 1984. Woman 3 died of breast cancer; woman x was censored to match the follow-up length of woman 3. Woman z, aged 50 years and residing in county 10 in January 1997, was matched to woman 3, aged 50 years and residing in county 10 in January 1978. Woman z emigrated; woman 3 was censored to match the follow-up length of woman z.

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Table 1. Number of women, breast cancer cases, deaths, person-years, breast cancer incidence, and mortality rates for pseudo-noninvited, pseudo-invited, noninvited, and invited women for the follow-up and evaluation model, in the period 1977–2014, using the regression approach

	Prescreening window												Screening window											
	Pseudo-noninvited period						Pseudo-invited period						Noninvited period						Invited period					
Age, y	No. Women	No. BC cases	No. BC death	PY	BC IR*	BC MR†	No. Women	No. BC cases	No. BC death	PY	BC IR*	BC MR†	No. Women	No. BC cases	No. BC death	PY	BC IR*	BC MR†	No. Women	No. BC cases	No. BC death	PY	BC IR*	BC MR†
Follow-up model																								
50–69	858 903	4106	611	2 622 979	156.5	23.3	669 867	9762	1996	5 383 353	181.3	37.1	873 559	5693	419	2 426 467	234.6	17.3	724 392	22 227	1376	6 034 640	368.3	22.8
50–79	858 903	6465	1404	3 586 055	180.3	39.2	669 867	13 917	3305	7 000 497	198.8	47.2	873 559	7745	865	3 270 017	236.8	26.5	724 392	25 778	2081	7 395 720	348.6	28.1
50–88‡	858 903	7331	1817	3 879 620	189.0	46.8	669 867	14 456	3562	7 177 552	201.4	49.6	873 559	8691	1200	3 605 980	241.0	33.3	724 392	26 235	2224	7 540 137	347.9	29.5
50–59	643 336	2011	213	1 437 874	139.9	14.8	466 872	3962	601	2 487 514	159.3	24.2	688 536	3480	209	1 530 679	227.4	13.7	556 964	10 405	417	3 006 970	346.0	13.9
60–69	335 001	2095	398	1 185 105	176.8	33.6	475 471	5800	1395	2 895 839	200.3	48.2	278 185	2213	210	895 788	247.0	23.4	502 112	11 822	959	3 027 670	390.5	31.7
70–79	127 123	2359	793	963 076	244.9	82.3	279 248	4155	1309	1 617 144	256.9	80.9	98 278	2052	446	843 550	243.3	52.9	242 109	3551	705	1 361 080	260.9	51.8
80–88	69 168	866	413	293 565	295.0	140.7	60 383	539	257	177 055	304.4	145.2	70 275	946	335	335 963	281.6	99.7	50 298	457	143	144 417	316.4	99.0
Evaluation model																								
50–69	856 524	4276	680	2 698 108	158.5	25.2	646 726	9594	1977	5 309 629	180.7	37.2	873 559	5693	419	2 426 514	234.6	17.3	724 392	22 227	1375	6 034 640	368.3	22.8
50–79	856 524	4276	922	2 703 306	158.2	34.1	646 726	9594	2573	5 323 550	180.2	48.3	873 559	5693	556	2 434 053	233.9	22.8	724 392	22 227	1699	6 067 751	366.3	28.0
50–88‡	856 524	4276	947	2 704 148	158.1	35.0	646 726	9594	2582	5 323 998	180.2	48.5	873 559	5693	571	2 435 582	233.7	23.4	724 392	22 227	1718	6 069 553	366.2	28.3
50–59	642 183	2199	266	1 514 358	145.2	17.6	447 296	3776	575	2 411 466	156.6	23.8	688 536	3480	209	1 530 695	227.3	13.7	556 964	10 405	417	3 006 970	346.0	13.9
60–69	339 963	2077	414	1 183 750	175.5	35.0	479 435	5818	1402	2 898 163	200.7	48.4	278 192	2213	210	895 819	247.0	23.4	502 112	11 822	958	3 027 670	390.5	31.6
70–79	833	0	242	5198	0.0	4655.6	3403	0	596	13 921	0	4281.3	904	0	137	7539	0.0	1817.2	7658	0	324	33 111	0.0	978.5
80–88	261	0	25	842	0.0	2969.1	250	0	9	448	0	2008.9	418	0	15	1529	0.0	981.0	747	0	19	1802	0.0	1054.4

*Breast cancer incidence rate per 100 000 person-years. BC = breast cancer; IR = incidence rate; MR = mortality rate; PY = person-years.
†Breast cancer mortality rate per 100 000 person-years.
‡All ages.

Table 2. Treatment and invitation effect on hazard ratio (HR), rate ratio (RR), and risk rate ratio (RRR) of breast cancer death with 95% confidence intervals (CI) using regression and matching approaches for the follow-up and evaluation model in the period 1977–2014

Effects	Follow-up model Estimate (95% CI)	Evaluation model Estimate (95% CI)
Regression approach		
All ages		
Treatment effect, HR*	0.73 (0.67 to 0.78)	0.77 (0.65 to 0.92)
Invitation effect, HR*	0.87 (0.79 to 0.95)	0.80 (0.70 to 0.91)
50–69 y		
Treatment effect, HR*	0.83 (0.74 to 0.94)	0.83 (0.74 to 0.94)
Invitation effect, HR*	0.75 (0.65 to 0.86)	0.75 (0.65 to 0.86)
Matching approach		
All ages		
Treatment effect, RR†	0.72 (0.66 to 0.78)	0.76 (0.67 to 0.85)
Invitation effect, RRR‡	0.87 (0.79 to 0.97)	0.82 (0.72 to 0.94)
50–69 y		
Treatment effect, RR†	0.83 (0.73 to 0.96)	0.83 (0.73 to 0.96)
Invitation effect, RRR‡	0.74 (0.63 to 0.87)	0.74 (0.63 to 0.87)

*HR from a flexible parametric survival model, adjusted for age and county of residence.

†Rate of breast cancer mortality in the noninvited period/rate of breast mortality in the pseudo-noninvited period.

‡RRR: (rate of breast cancer mortality in the invited period/rate of breast cancer mortality in the pseudo-invited period)/(rate of breast cancer mortality in the noninvited period/rate of breast cancer mortality in the pseudo-noninvited period).

The matching approach yielded results similar to those from the regression approach (Table 3). Overall, 6705 BC deaths and 18 170 276 person-years were recorded in the follow-up model (Figure 1 and Table 3). BC mortality rates were 42.3 per 100 000 person-years in the pseudo-noninvited period and 30.5 per 100 000 person-years in the noninvited period, corresponding to a treatment effect of 28% (RR = 0.72, 95% CI = 0.66 to 0.78). BC mortality rates were 45.5 per 100 000 person-years in the pseudo-invited period and 28.7 per 100 000 person-years in the invited period, leading to an invitation effect of 13% (RRR = 0.87 [ie, (28.7/45.5)/(30.5/42.3)], 95% CI = 0.79 to 0.97). In the evaluation model, BC mortality rates were 30.3 and 23.0 per 100 000 person-years in the pseudo-noninvited and noninvited period, respectively, corresponding to a treatment effect of 24% (RR = 0.76, 95% CI = 0.67 to 0.85). In the pseudo-invited and invited period, BC mortality rates were 44.6 and 27.9 per 100 000 person-years, respectively, giving an invitation effect of 18% (RRR = 0.82 [ie, (27.9/44.6)/(23.0/30.3)], 95% CI = 0.72 to 0.94). When limiting the analysis to women aged 50–69 years, the invitation effect was 26% (RRR = 0.74, 95% CI = 0.63 to 0.87) and the treatment effect 17% (RR = 0.83, 95% CI = 0.73 to 0.96) for both the follow-up and the evaluation models.

As a sensitivity analysis, we ran the matching approach analysis two other times by randomly selecting two different matched populations, and results did not change (data not shown).

Discussion

In this Norwegian population-based registry study using individual-level data from two time windows, 1977–1995 and 1996–2014, we estimated the invitation and treatment effect on BC mortality. For women 50 years and older, we found a 20% reduction in BC mortality due to invitations and an additional 23% reduction due to treatment.

The evaluation model includes only BC deaths among women diagnosed with BC when they were eligible for screening. Estimates of BC mortality reduction due to screening from a Danish population-based study based on individual-level data and the evaluation model were the same as those observed in our study (20%) (8). The follow-up model includes BC deaths among women diagnosed with BC also after screening age. Using this model, we observed an invitation effect of 13%; the Danish study observed an 11% reduction.

The follow-up model resulted in a diluted invitation effect due to the inclusion of BC deaths from women diagnosed after screening age. Longer follow-up of invited women, as was the case in our study, is expected to increase the proportion of old women and thereby increase the potential for dilution. It has been stated that the evaluation model should be used for internal comparison between study and control groups (8). We support this view when using an "intention-to-treat" approach (2,6). By design, when limiting the analysis to screening-aged women, we obtained the same results for the evaluation and follow-up models. The invitation effect on BC mortality among women 50–69 years was 25% with the regression approach and 26% by the matching approach.

Our estimates were higher than other studies from Norway: Kalager et al. reported a 10% reduction (13), whereas Olsen et al. (12) reported a reduction of 7% and 11%, when using the follow-up and evaluation model, respectively. Limited follow-up time is the likely cause for these low estimates. However, our effect was lower than the 28% reduction reported by Weedon-Fekjær et al. (7) on Norwegian data and the review of European service-screening programs (25% reduction for cohort studies and 31% for case-control studies) (6). These studies estimated a combined effect for invitation and treatment. We were able to separate these two effects, which is a substantial strength of our study.

The effect of treatment on disease-specific mortality has been debated during the last decade. It is claimed that the effect of organized screening is negligible because of improved treatment. Our results, based on data from the last two decades, showed that the invitation and treatment effects had similar magnitude, which is in keeping with findings from previous studies (18,19).

It is well known that individual-level data are essential to reach valid conclusions regarding mortality (2,8,20). To the best of our knowledge, this is the first study from Norway that used individual-level screening data during the time before and after BreastScreen Norway was implemented and included adequate follow-up time. Using individual-level data about invitations, BC diagnoses, and deaths, in combination with the time-window study design, enabled us to establish comparable controls for invited and noninvited women and to separate the treatment from the invitation effect. Registry data are of high quality in Norway (21), which represents a strength of the study. Another strength is the use of two approaches executed independently by two statisticians that yielded strikingly similar results, despite differences in sample sizes and methods. The regression approach included all women and adjusted for differences between the four periods, whereas the matching approach paired the women based on a set of covariates. Lastly, to the best of our knowledge, the number of women included in the study, BC cases and deaths, and follow-up time used in this study exceed that from all other published studies on BC mortality associated with screening in Norway (7,12,13), as well as internationally.

Table 3. Number of women, breast cancer cases, deaths, person-years, and breast cancer mortality rates for pseudo-noninvited, pseudo-invited, noninvited, and invited women for the follow-up and evaluation model in the period 1977–2014 using the matching approach

	Prescreening window										Screening window									
	Pseudo-noninvited period					Pseudo-invited period					Noninvited period					Invited period				
Age, y	No. Women	No. BC cases	No. BC deaths	PY	BCMR*	No. Women	No. BC cases	No. BC deaths	PY	BCMR*	No. Women	No. BC cases	BC deaths	PY	BCMR*	No. Women	No. BC cases	No. BC deaths	PY	BCMR*
Follow-up model																				
50–69	756 083	3282	446	2 124 809	21.0	618 344	8721	1764	4 868 736	36.2	756 083	5032	372	2 124 052	17.5	618 344	18 125	1090	4 870 447	22.4
50–79	756 083	5000	1017	2 821 175	36.0	618 344	11 594	2638	5 993 831	44.0	756 083	6731	735	2 820 748	26.1	618 344	21 023	1658	5 993 761	27.7
50–88†	756 083	5526	1273	3 006 981	42.3	618 344	11 871	2768	6 078 157	45.5	756 083	7266	918	3 006 981	30.5	618 344	21 287	1746	6 078 157	28.7
50–59	680 064	1725	172	1 270 641	13.5	724 234	3775	567	2 378 728	23.8	679 814	2922	169	1 271 464	13.3	724 805	8228	301	2 380 016	12.6
60–69	350 121	1557	274	854 168	32.1	677411	4946	1197	2 490 008	48.1	349 605	2110	203	852 588	23.8	676 949	9897	789	249 0431	31.7
70–79	161 636	1718	571	696 366	82.0	320 157	2873	874	1 125 095	77.7	161 451	1699	363	696 696	52.1	319 283	2898	568	1 123 314	50.6
80–88	62 832	526	256	185 806	137.8	38 295	277	130	84 326	154.2	62 710	535	183	186 233	98.3	38 277	264	88	84 396	104.3
Evaluation model																				
50–69	756 083	3282	446	2 124 809	21.0	618 344	8721	1764	4 868 736	36.2	756 083	5032	372	2 124 052	17.5	618 344	18125	1090	4 870 447	22.4
50–79	756 083	3282	634	2 128 066	29.8	618 344	8721	2170	4 878 347	44.5	756 083	5032	483	2 129 205	22.7	618 344	18 125	1356	4 897 907	27.7
50–88†	756 083	3282	644	2 128 504	30.3	618 344	8721	2176	4 878 627	44.6	756 083	5032	489	2 130 122	23.0	618 344	18 125	1367	4 899 009	27.9
50–59	680 064	1725	172	1 270 641	13.5	724 234	3775	567	2 378 728	23.8	679 814	2922	169	1 271 464	13.3	724 805	8228	301	2 380 016	12.6
60–69	350 121	1557	274	854 168	32.1	677 411	4946	1197	2 490 008	48.1	349 605	2110	203	852 588	23.8	676 949	9897	789	2 490 431	31.7
70–79	882	0	188	3257	5772.2	3327	0	406	9611	42 24.3	1320	0	111	5153	21 54.1	8950	0	266	27 460	968.7
80–88	173	0	10	438	2285.6	151	0	6	280	21 43.8	336	0	6	917	654.6	554	0	11	1102	997.9

*Breast cancer mortality rate per 100 000 person-years. BC = breast cancer; BCMR = breast cancer mortality rate; PY = person-years.
†All ages.

Our study period covered four decades and might include concerns regarding the use of historical control groups from so long ago. We assumed a linear increase in the treatment effect during the study period. Our estimate of the invitation effect is overestimated if the treatment effect increased more from the pseudo-invited to the invited periods than from the pseudo-noninvited to the noninvited periods. Moreover, linear assumption is a simplification of the real-life situation: improvements in BC treatment are likely to occur in leaps. BC treatment will probably continue to improve, and our study indicates that it has already exceeded the invitation effect. A lack of comparable control groups will present a challenge for future studies evaluating BC mortality associated with BreastScreen Norway. The relatively short follow-up time, given the early detection and improved treatment, represents a limitation of our study. However, the follow-up time is the same for the invited and noninvited in both models, and the results are thus comparable.

Evaluating BC mortality associated with screening programs is a challenging task (6,8–10). We identified an increase in BC incidence, which might be due to screening and diagnostic tools and detection of small, low-proliferation tumors. However, the potential "overdiagnosed" cases did not influence our results. Increased breast awareness, use of hormonal replacement treatment, and other changes in lifestyle factors, in addition to constantly improved treatment, are all evidently of influence for both incidence and mortality rates. These factors are challenging to measure and control for in analyses and thus represent a limitation of our study. We estimated the effect of being invited to a screening program. Evaluating the effect among participants (per protocol) is expected to show 10–15% higher BC mortality reduction (2,6). Other important considerations are the effect of BC mortality on overall mortality (1) and the validity of cause of death certificates over time (22,23). These potential confounders need to be further investigated. The benefit to harm ratio of BC screening is also an important evaluation metric. These aspects should be investigated in separate studies because of their complexity.

In summary, in our study based on 1 340 333 women invited to BreastScreen Norway, a biennial population-based screening program targeting women aged 50–69 years, we observed a 20% reduction in BC mortality among invited women. An additional 23% reduction was observed, which we ascribe to improvements in BC awareness, treatment, and care.

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All authors are responsible for the conception and design; data analysis and interpretation; manuscript writing; final approval of manuscript; and accountable for all aspects of the work. SS and SH are responsible for the collection and assembly of data.

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