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Article

Breast cancer mortality after implementation of organized population-based breast cancer screening in Norway

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Running head

Breast cancer mortality in women invited to mammographic screening

ABSTRACT

Background: We estimated breast cancer (BC) mortality reduction associated with invitations to a nation-wide population based screening program and changes in treatment, in Norway.

Material and methods: BreastScreen Norway started in 1996 and became nationwide in 2005. It invites women aged 50–69 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 (PY) in non-invited and invited periods. We created comparable periods for 1977–1995 (pre-screening window) by dividing the follow-up time for each woman into a pseudo-non-invited 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, counting BC deaths and person-years after screening-age only for women 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: There were 5818 BC deaths across 16,533,281 PY. Invitations to screening reduced BC mortality by 20% (HR: 0.80, 95%CI: 0.70-0.91) among women ≥50 years old and by 25% (HR: 0.75, 95%CI: 0.65-0.86) among screening-aged women. The treatment effect was 23% (HR: 0.77, 95%CI: 0.65-0.92) for women ≥50 years old, and 17% (HR: 0.83, 95%CI: 0.74-0.94) for screening-aged women.

Conclusion: We observed a similar reduction in BC mortality associated with invitations to screening and improvements in treatment among women ≥50 years old, during 1977–2014.

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), while 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 due to 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, since early detection and detection of small, low proliferation tumors, in combination with improved treatment, prolongs 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%–28% for invited versus non-invited 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.

In this study, we used nationwide individual-level data to estimate long-term BC mortality during the last two decades among women invited to the 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 50–69 years old during a given screening round (two year period). Due to the staggered rollout, cohorts offered screening differ slightly between counties. Moreover, some women can be 48 or 49 years old when they are invited to screening because they will turn 50 years old during the screening round. Similarly, women may be 50 during the screening round but not receive an invitation until they are 51. These women may receive their final (10^{th}) invitation to screening at age 71. During the first 20 years of the program, the attendance rate was 75% for each screening round, while 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, while 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, pre-screening and screening window

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

Women entered our study population on the date of either their 50th birthday, immigration between the ages of 50-69 (inclusive), or the window start (January 1, 1977 for the pre-screening window; January 1, 1996 for the screening window), whichever occurred last. The pre-screening window included women free from BC, born 1907–1945, while 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 pre-screening 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 1st 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 pre-screening window. To compare BC mortality before and after invitation to screening, we created a distribution of made-up invitations (pseudo-invitations) in the pre-screening window (1977-1995), to obtain a group of pseudo-invited and pseudo-non-invited women. These two groups mirrored the groups of invited and non-invited 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-non-invited, pseudo-invited, non-invited 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 2A and 2B**.

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

Statistical analyses

To compare BC mortality during the four periods (pseudo-non-invited, pseudo-invited, non-invited, 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 pre-screening window, following the same distribution as the true invitations in the screening window. For each combination of 5-years 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 pre-screening window. For example, if 3% of women aged 60–64 in January 1996 residing in county X were invited in March 1996, then 3% of women aged 60–64 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 non-invited and the pseudo-non-invited period (**Figure 2B)**. Women from the two periods were matched 1:1 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 non-invited and pseudo-non-invited women. However, in the evaluation model (see below), matched pairs could have different follow-up time 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 pre-screening period (1977–1995). Person-years previously used in the pseudo-non-invited period were no longer available. Using the same criteria applied to the (pseudo-)non-invited women, the (pseudo-)invited women were matched 1:1 and the longest follow-up time was censored to obtain equal follow-up within pairs. Given the matching approach and the censoring, we expected less women and follow-up time in the matching compared to 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 non-invited and pseudo-non-invited 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-non-invited versus non-invited as for

the pseudo-invited versus 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 non-invited period/mortality rate in the pseudo-non-invited 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 pre-screening or screening window, a covariate for invitation status, and an interaction term between the two, adjusting for county and age. To account for non-proportionality observed in the evaluation model, a time-dependent covariate for pre-screening 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-non-invited 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 all four periods **(Figure 1, Table 1)**. The observed BC mortality rates were 46.8 and 33.3/100,000 person-years for the pseudo-non-invited and non-invited periods and 49.6 and 29.5/100,000 person-years for the pseudo-invited and invited periods **(Table 1)**. The evaluation model included 5818 BC deaths and 16,533,281 person-years **(Figure 1 and Table 1)**. BC mortality rates were 35.0 and 23.4/100,000 person-years for the pseudo-non-invited and non-invited women, respectively, and 48.5 and 28.3/100,000 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 HR showed a 13% (HR: 0.87, 95%CI: 0.79-0.95) reduction in BC mortality due to invitations, 27% (HR: 0.73, 95%CI: 0.67-0.78) due to treatment **(Table 2)**. For the evaluation model, the adjusted HR showed a 20% (HR: 0.80, 95%CI: 0.70-0.91) reduction in BC mortality due to invitations, a 23% (HR: 0.77, 95%CI: 0.65-0.92) reduction due to treatment. For screening-aged women, the invitation effect was 25% (HR: 0.75, 95%CI: 0.65-0.86) and the treatment effect 17% (HR: 0.83, 95%CI: 0.74-0.94) for both the follow-up and the evaluation models..

The matching approach yielded results similar to those from the regression approach. 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 42.3/100,000 person-years in the pseudo-non-invited period and 30.5/100,000 person-years in the non-invited period, corresponding to a treatment effect of 28% (RR: 0.72, 95%CI: 0.66-0.78). BC mortality rates were 45.5/100,000 person-years in the pseudo-invited period and 28.7/100,000 person-years in the invited period, leading to an invitation effect of 13% (RRR=0.87 (i.e. 28.7/45.5)/(30.5/42.3), 95%CI: 0-79-0.97). In the evaluation model, BC mortality rates were 30.3 and 23.0/100,000 person-years in the pseudo-non-invited and non-invited period, respectively, corresponding to a treatment effect of 24% (RRR=0.86, 95%CI: 0.67-0.85). In the pseudo-invited and invited period, BC mortality rates were 44.6 and 27.9/100,000 person-years, respectively, giving an invitation effect of 18% (RRR=0.82 (i.e. (27.9/44.6)/(23.0/30.3), 95%CI: 0.72-0.94) . When limiting the analysis to women aged 50–69, the invitation effect was 26% (RRR=0.74, 95%CI: 0.63-0.87) and the treatment effect 17% (RR=0.83, 95%CI: 0.73-0.96) for both the follow-up and the evaluation models.

As a sensitivity analysis, we re-run the matching approach analysis 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 aged 50 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 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), while Olsen et al. reported a reduction of 7% and 11%, when using the follow-up and evaluation model, respectively (12). 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. on Norwegian data (7) 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 due to the 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 is 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 non-invited women and to separate the treatment from the invitation effect. Registry data is of high quality in Norway (21), which represent 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, while 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 exceeds that from all other published studies on BC mortality associated with screening in Norway (7, 12, 13), and also internationally.

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 is overestimated if the treatment effect increased more from the pseudo-invited to the invited periods than from the pseudo-non-invited to the non-invited 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, represent a limitation of our study. However, the follow-up time is the same for the invited and non-invited, 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 life style factors, in addition to constantly improved treatment, are all evidently of influence for both the incidence and mortality rates. These factors are challenging to measure and to control for in analyses, and are thus representing 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, due to 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, we observed a 20% reduction in BC mortality among invited women. An additional 23% reduction was observed in the study period 1977–2014, which we ascribe to improvements in BC awareness, treatment and care.

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Notes

No potential conflicts of interest reported. All authors are employed at the Cancer Registry of Norway and have fixed positions, independent of the screening program.

Author's contributions

Conception and design**:** All authors

Collection and assembly of data: Sofie Sebuødegård, Solveig Hofvind

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript**:** All authors

Accountable for all aspects of the work: All authors

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

Age (years)	Pre-screening window												Screening window											
	Pseudo-non-invited period						Pseudo-invited period						Non-invited period						Invited period					
	Women	BC cases*	BC death†	PY‡	BC IR§	BC MR‖	Women	BC cases*	BC death†	PY‡	BC IR§	BC MR‖	Women	BC cases*	BC death†	PY‡	BC IR§	BC MR‖	Women	BC cases*	BC death†	PY‡	BC IR§	BC MR‖
Follow-up model																								
50-69	858903	4106	611	2622979	156.5	23.3	669867	9762	1996	5383353	181.3	37.1	873559	5693	419	2426467	234.6	17.3	724392	22227	1376	6034640	368.3	22.8
50-79	858903	6465	1404	3586055	180.3	39.2	669867	13917	3305	7000497	198.8	47.2	873559	7745	865	3270017	236.8	26.5	724392	25778	2081	7395720	348.6	28.1
50-88¶	858903	7331	1817	3879620	189.0	46.8	669867	14456	3562	7177552	201.4	49.6	873559	8691	1200	3605980	241.0	33.3	724392	26235	2224	7540137	347.9	29.5
50-59	643336	2011	213	1437874	139.9	14.8	466872	3962	601	2487514	159.3	24.2	688536	3480	209	1530679	227.4	13.7	556964	10405	417	3006970	346.0	13.9
60-69	335001	2095	398	1185105	176.8	33.6	475471	5800	1395	2895839	200.3	48.2	278185	2213	210	895788	247.0	23.4	502112	11822	959	3027670	390.5	31.7
70-79	127123	2359	793	963076	244.9	82.3	279248	4155	1309	1617144	256.9	80.9	98278	2052	446	843550	243.3	52.9	242109	3551	705	1361080	260.9	51.8
80-88	69168	866	413	293565	295.0	140.7	60383	539	257	177055	304.4	145.2	70275	946	335	335963	281.6	99.7	50298	457	143	144417	316.4	99.0
Evaluation model																								
50-69	856524	4276	680	2698108	158.5	25.2	646726	9594	1977	5309629	180.7	37.2	873559	5693	419	2426514	234.6	17.3	724392	22227	1375	6034640	368.3	22.8
50-79	856524	4276	922	2703306	158.2	34.1	646726	9594	2573	5323550	180.2	48.3	873559	5693	556	2434053	233.9	22.8	724392	22227	1699	6067751	366.3	28.0
50-88¶	856524	4276	947	2704148	158.1	35.0	646726	9594	2582	5323998	180.2	48.5	873559	5693	571	2435582	233.7	23.4	724392	22227	1718	6069553	366.2	28.3
50-59	642183	2199	266	1514358	145.2	17.6	447296	3776	575	2411466	156.6	23.8	688536	3480	209	1530695	227.3	13.7	556964	10405	417	3006970	346.0	13.9
60-69	339963	2077	414	1183750	175.5	35.0	479435	5818	1402	2898163	200.7	48.4	278192	2213	210	895819	247.0	23.4	502112	11822	958	3027670	390.5	31.6
70-79	833	0	242	5198	0.0	4655.6	3403	0	596	13921	0	4281.3	904	0	137	7539	0.0	1817.2	7658	0	324	33111	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

* BC cases: Breast cancer cases (n)
† BC deaths: Breast cancer deaths (n)
‡ PY: Person-years
§ BC IR: Breast cancer incidence rate per 100 000 person years
‖ BC MR: 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 (95%CI) using regression and matching approaches for the follow-up and evaluation model, in the period 1977-2014

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

* HR: Hazard Ratio. HR from a flexible parametric survival model, adjusted for age and county of residence.
† RR: Rate Ratio: rate of breast cancer mortality in the non-invited period/rate of breast mortality in the pseudo-non-invited period.
‡ RRR: Ratio of Rate Ratios: (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 non-invited period/rate of breast cancer mortality in the pseudo-non-invited period).

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

Age (years)	Pre-screening window										Screening window									
	Pseudo-non-invited period					Pseudo-invited period					Non-invited period					Invited period				
	Women	BC cases*	BC deaths†	PY‡	BC MR§	Women	BC cases*	BC deaths†	PY‡	BC MR§	Women	BC cases*	BC deaths†	PY‡	BC MR§	Women	BC cases*	BC deaths†	PY‡	BC MR§
Follow-up model																				
50-69	756083	3282	446	2124809	21.0	618344	8721	1764	4868736	36.2	756083	5032	372	2124052	17.5	618344	18125	1090	4870447	22.4
50-79	756083	5000	1017	2821175	36.0	618344	11594	2638	5993831	44.0	756083	6731	735	2820748	26.1	618344	21023	1658	5993761	27.7
50-88†	756083	5526	1273	3006981	42.3	618344	11871	2768	6078157	45.5	756083	7266	918	3006981	30.5	618344	21287	1746	6078157	28.7
50-59	680064	1725	172	1270641	13.5	724234	3775	567	2378728	23.8	679814	2922	169	1271464	13.3	724805	8228	301	2380016	12.6
60-69	350121	1557	274	854168	32.1	677411	4946	1197	2490008	48.1	349605	2110	203	852588	23.8	676949	9897	789	2490431	31.7
70-79	161636	1718	571	696366	82.0	320157	2873	874	1125095	77.7	161451	1699	363	696696	52.1	319283	2898	568	1123314	50.6
80-88	62832	526	256	185806	137.8	38295	277	130	84326	154.2	62710	535	183	186233	98.3	38277	264	88	84396	104.3
Evaluation model																				
50-69	756083	3282	446	2124809	21.0	618344	8721	1764	4868736	36.2	756083	5032	372	2124052	17.5	618344	18125	1090	4870447	22.4
50-79	756083	3282	634	2128066	29.8	618344	8721	2170	4878347	44.5	756083	5032	483	2129205	22.7	618344	18125	1356	4897907	27.7
50-88†	756083	3282	644	2128504	30.3	618344	8721	2176	4878627	44.6	756083	5032	489	2130122	23.0	618344	18125	1367	4899009	27.9
50-59	680064	1725	172	1270641	13.5	724234	3775	567	2378728	23.8	679814	2922	169	1271464	13.3	724805	8228	301	2380016	12.6
60-69	350121	1557	274	854168	32.1	677411	4946	1197	2490008	48.1	349605	2110	203	852588	23.8	676949	9897	789	2490431	31.7
70-79	882	0	188	3257	5772.2	3327	0	406	9611	4224.3	1320	0	111	5153	2154.1	8950	0	266	27460	968.7
80-88	173	0	10	438	2285.6	151	0	6	280	2143.8	336	0	6	917	654.6	554	0	11	1102	997.9

* BC cases: Breast cancer cases (n)
† BC deaths: Breast cancer deaths (n)
‡ PY: Person-years
§ BC MR: Breast cancer mortality rate per 100 000 person years

Figure titles and legends

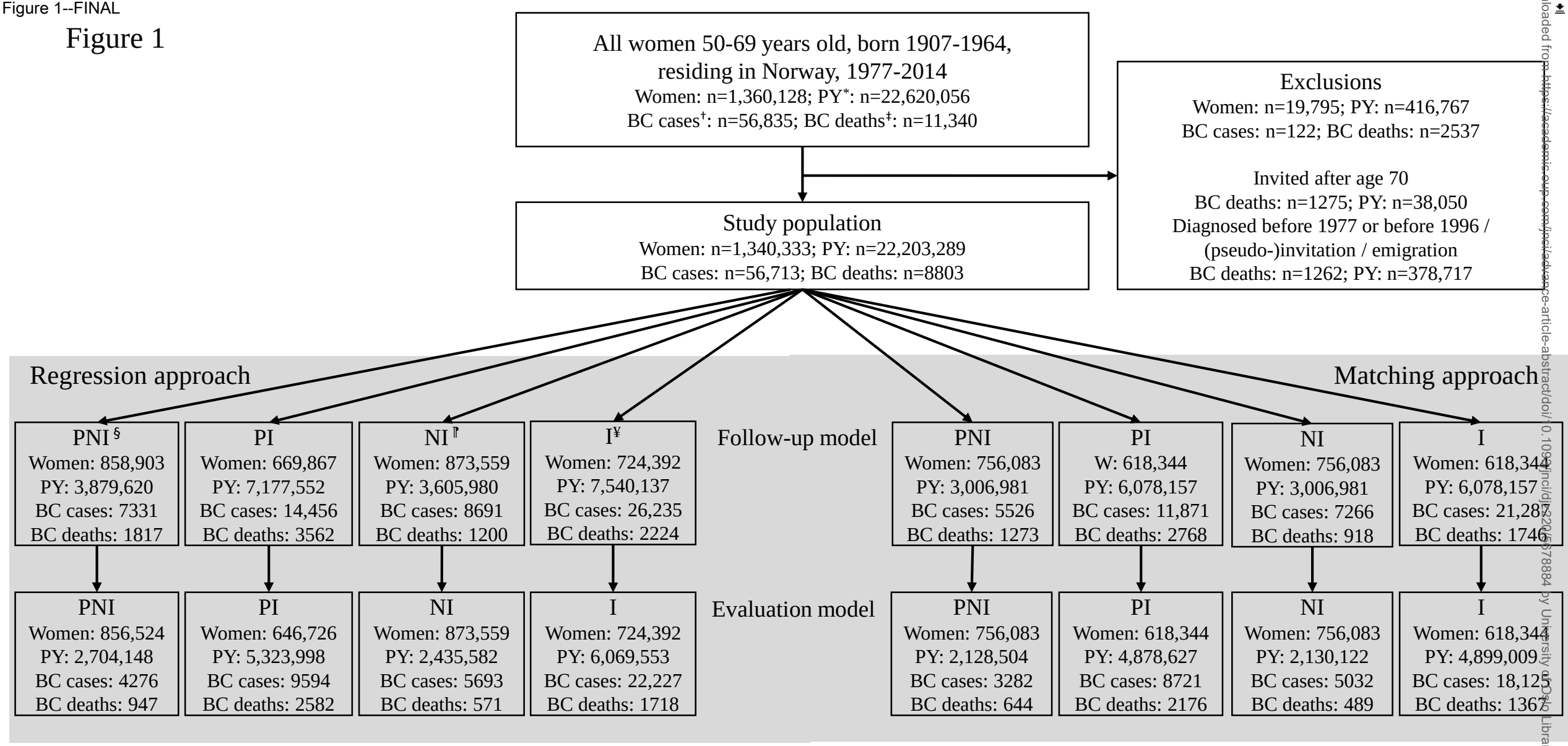
Figure 1: Women included in the study, and study outcome for the regression and matching approach using the follow-up and evaluation model.

Figure 2: Strategies for selecting invited women in the pre-screening window for the; Regression approach and Matching approach. Panel 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 pre-screening and screening window. We replicated the real invitation distribution in the screening window, as pseudo-invitations in the pre-screening window. Woman *x*, aged 50 and residing in county 3 in January 2002 was invited to screening and followed to end of follow-up. Woman *1*, aged 50 and residing in county 3 in January 1983 received a pseudo-invitation and was followed until end of follow-up. Woman y, aged 50 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 and residing in county 12 in January 1983 received a pseudo-invitation and was followed until she emigrated in 1994. Woman *4*, aged 57 and residing in county 10 in January 1996, was invited to screening in 2000 and followed throughout the screening window. Woman 3, aged 57 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 residing in county 10 in January 2008, was never invited and died of breast cancer in 2009. Woman 4, aged 50 and residing in county 10 in January 1989, was followed throughout the pre-screening window as pseudo-non-invited. **Panel 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 and residing in county 3 in January 1996, was matched to woman *1*, aged 61 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 pre-screening window to match the follow-up length of *y* (matched censoring). The same woman *y*, aged 67 at invitation in January 1983 was matched to woman *2* aged 67 at pseudo-invitation, residing in the same county as women 2. Woman *y* died of breast cancer; woman *2* was censored to match the follow-up length of *y*. Woman *x*, aged 56 and residing in county 10 at invitation in May 2003, was matched to woman *3*, aged 56 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 and residing in county 10 in January 1997 was matched to woman *3*, aged 50 and residing in county 10 in January 1978. Woman z emigrated; woman *3* was censored to match the follow-up length of woman *z*.

Figure 1--FINAL

Figure 1



*PY: person-years (n)
† BC cases: Breast cancer (n)
‡ BC deaths: Breast cancer deaths (n)
§ PNI: Pseudo-non-invited women (n)
PI: Pseudo-invited women (n)
‖ NI: Non-invited women (n)
¥ I: Invited women (n)

Figure 2

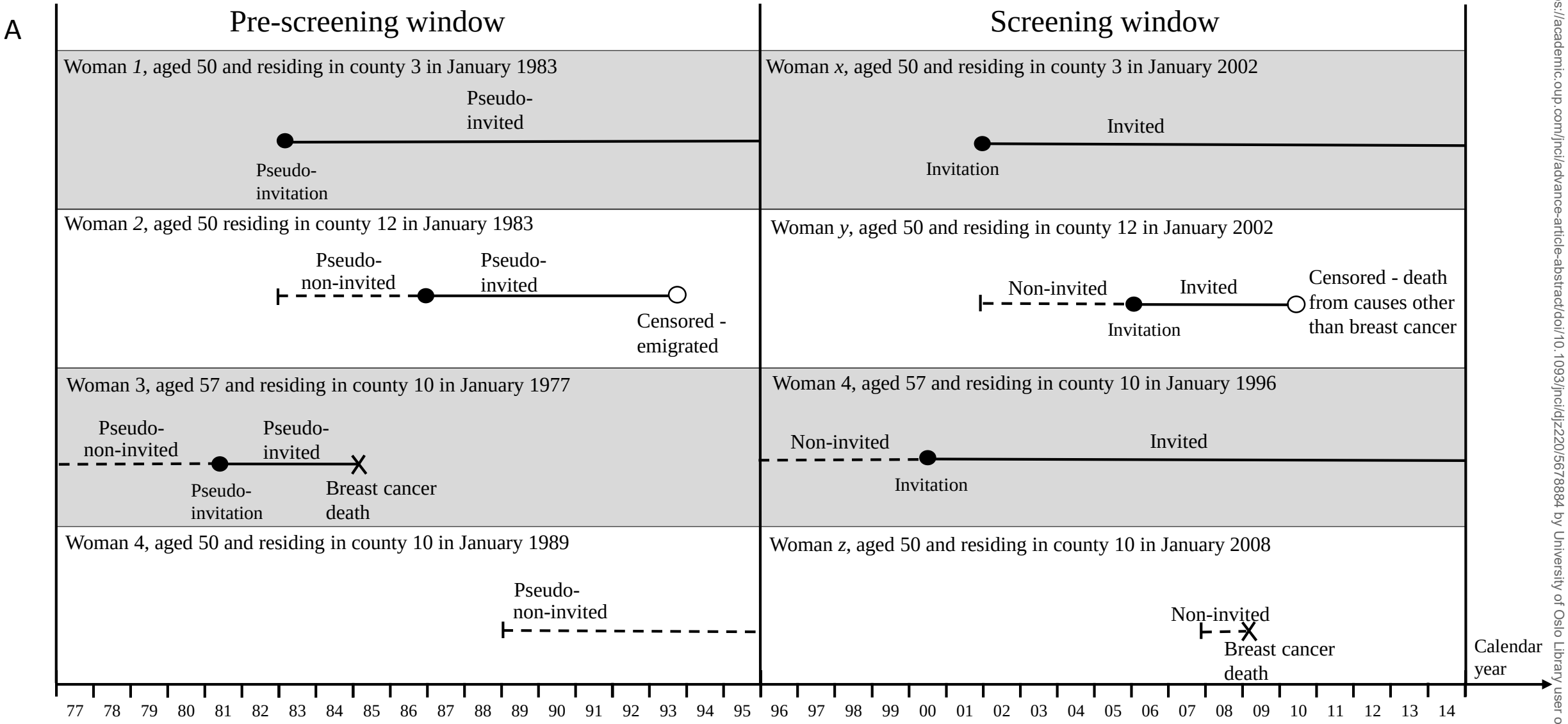


Figure 2