Fatal and non-fatal breast cancers in women targeted by BreastScreen Norway: a cohort study

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Abbreviations in order of appearance

DCIS	Ductal carcinoma in situ
TNM	Tumor-Node-Metastasis
ER	Estrogen receptor
PR	Progesterone receptor
CI	Confidence interval
SD	Standard deviation
SDC	Screen-detected cancer
IC	Interval cancer
OS	Outside screening
NST	No special type
HER2	Human epidermal growth factor receptor 2

Abstract

Background: Many breast cancer survivors experience anxiety related to dying from their disease even if it is detected at an early stage. We aimed to increase knowledge about fatal and non-fatal breast cancer by describing how histopathological tumour profiles and detection modes were associated with 10-year breast cancer-specific survival.

Methods: This cohort study included data from women targeted by BreastScreen Norway (aged 50-69) and diagnosed with invasive breast cancer during 1996-2011. Breast cancer was classified as fatal if causing death within 10 years after diagnosis and non-fatal otherwise. We described histopathologic characteristics of fatal and non-fatal cancers, stratified by mode of detection. Recursive partitioning identified subgroups with differing survival profiles.

Results: 6.3% of 9954 screen-detected cancers (SDC) were fatal, as were 17.4% of 3205 interval cancers (IC) and 20.9% of 3237 cancers detected outside BreastScreen Norway. 4-5 subgroups with differing survival profiles were identified within each detection mode. Women with lymph node negative SDC or grade 1-2, node negative IC without distant metastases had the highest 10-year survival (95-96%).

Conclusions: Two subgroups representing 53% of the cohort had excellent (95-96%) 10-year breast cancer-specific survival. Most women with SDC had excellent survival, as did nearly 40% of women diagnosed with IC.

Keywords: Mass screening; Cancer screening; Mammography; Breast cancer; Prognosis; Fatal outcome

Main text

Background

Breast cancer is the leading cause of cancer deaths in women worldwide.[1] Mammographic screening aims to reduce breast cancer mortality by detecting the disease at an early and curable stage. This effect is best documented for average-risk women aged 50–69, where those who attend organized screening have about 30% lower breast cancer mortality than those who do not attend.[2,3]

The association between prognostic histopathological factors and breast cancer mortality is well described, particularly in relation to stage and molecular subtypes.[4-6] Regarding the effect of screening on breast cancer mortality, observational studies often stratify analyses for “ever” versus “never” attenders or use an “intention to screen” approach based on whether a woman was invited to screening.[3,7] Less research has explored the effect of the women’s individual screening history and whether cancers were screen-detected, interval, or detected outside of a screening program.[8,9]

A 2021 meta-analysis reported that as many as 34% of women diagnosed with breast cancer – including those diagnosed as a direct result of screening – experience anxiety associated with their diagnosis, and as many as 39% experience symptoms of non-specific distress.[10] Increased knowledge about the histopathology and survival profiles associated with fatal versus non-fatal outcomes stratified by mode of detection can improve targeted information provided to women who are invited to organized screening. This could potentially reduce some of the psychological consequences of receiving a breast cancer diagnosis.

The aims of this population-based cohort study were to a) describe the histopathological tumour characteristics of fatal and non-fatal cancers and b) describe 10-year breast cancer-specific survival, stratified by mode of detection.

Methods

Study setting

BreastScreen Norway targets women aged 50–69 for biennial mammographic screening, based on national and international recommendations.[11-13] The program started in four counties in 1996 and became nationwide in 2005. As of 2023, the target group consists of roughly 650,000 women. The program is described in detail elsewhere.[14]

Study sample

This retrospective cohort study included all women in the target group of BreastScreen Norway diagnosed with invasive breast cancer after receiving at least one invitation to attend the program between January 1, 1996 and December 31, 2011. For women diagnosed with multiple primary breast cancers, we included their first cancer. For women with multifocal disease, the largest tumour was included. We excluded women who: were ≥72 years old at diagnosis; had a history of ductal carcinoma in situ (DCIS) or invasive breast cancer prior to their first invitation to BreastScreen Norway; were diagnosed at death; or participated in the Oslo age trial, which invited women aged 45–49 to mammographic screening.[15]

Data sources

Study data were obtained from the Cancer Registry of Norway. The Cancer Registry registers incidence and histopathology information about invasive breast cancer diagnoses in Norway for all women of all ages. Information about breast cancer diagnoses is nearly complete and over 99% of cases are morphologically verified.[16] The Cancer Registry administers BreastScreen Norway and therefore also captures information about screening invitations, attendance, and associated outcomes. The Norwegian Cause of Death Registry provides the Cancer Registry with information about date and cause of death.

Variables

We here defined breast cancer as invasive tumours. Cancer was described as “fatal” if it was listed as a woman’s cause of death within 10 years after her diagnosis. Mode of detection was categorized as screen-detected, interval, or outside the screening program. Screen-detected cancers were defined as those diagnosed within 6 months of a screening examination that led to a recall for further assessment. Interval cancers were those diagnosed within 24 months of a negative screening examination or 6–24 months after a screening examination with a false positive result. Cancers detected outside of screening were defined as those diagnosed among women who had not attended BreastScreen Norway in the 24 months prior to their diagnosis.

Person-level variables included age at and year of diagnosis, and birth country (Norway or other). For women with screen-detected cancer, attendance at the screening examination that led to their diagnosis was categorized as “prevalent screen”, “regular screen”, or “irregular screen”. Prevalent screens were defined as a woman’s first screening examination in BreastScreen Norway. Regular screens were those occurring within 24±6 months of the previous screening examination, and irregular screens were those performed >30 months after the previous screening examination.

Histopathologic variables included histologic type (invasive carcinoma of no special type, lobular, or other), histologic grade (1, 2, 3), and pathologic TNM categories described by the American Joint Committee on Cancer (pT-categories: T1a/b, T1c, T2, T3, T4; pN-categories: N0, N1, N2, N3; and pM categories: M0, M1).[4] Estrogen receptor (ER) and progesterone receptor (PR) status were also included and classified as positive, negative, or missing. Due to changes in national guidelines, ER status was recorded as positive if there was ≥10% ER expression (study start to Jan 2010) or ≥1% ER expression (Jan 2010 onwards).[4] PR status was recorded as positive if there was ≥10% PR expression (entire study period).

Statistical analysis

We described the variables outlined above using means and standard deviations for continuous variables, and frequencies and proportions for categorical variables. The proportion of fatal and non-fatal cancers within each mode of detection was presented for histopathological variables. Additionally, we evaluated the proportion of fatal and non-fatal cancers for various pT and pN combinations of non-metastatic screen-detected cancers. 95% confidence intervals (CIs) for proportions were calculated using the Wilson score interval.[17]

Defining subgroups with differing survival profiles

For each mode of detection, we used a recursive binary partitioning algorithm to create a tree diagram (survival tree) that identified patient and histopathological tumour characteristics that could be used to classify patients into subgroups with distinct 10-year breast cancer-specific survival profiles.

The recursive binary partitioning algorithm used information about 11 person and histopathological tumour characteristics ("input variables") to repeatedly split a group of women (parent group) into two subgroups (child groups) with more homogeneous survival outcomes than the initial (parent) group. The input variables are described later. All values for all input variables were candidates for creating each binary split. In this closed cohort study, women were followed from their breast cancer diagnosis until death from the disease. Their follow-up time was censored if they died from other causes or emigrated, or 10 years after diagnosis, whichever occurred first. Our approach assumed an exponential survival (i.e. constant hazard) model and variable/value selection was based on the likelihood ratio test for two variables with Poisson distributions.[18,19] This splitting process stopped when any resulting child group would include <30 women or when only marginal gains in survival homogeneity were obtained from creating additional splits. Although the outcome of interest was time to death from breast cancer, this approach did not explicitly consider the competing risk of death from other causes. The majority of women diagnosed with breast cancer in Norway

have a good overall prognosis and we assumed that any bias resulting from this approach would not substantially affect the results of the recursive partitioning algorithm.

Recursive binary partitioning can produce very large trees with many splits that can describe the survival of very specific groups but lack generalizability. Indeed, the aim of this descriptive study was to identify broad groups with differing survival profiles. Therefore, to prune potentially large trees, we used 10-fold cross-validation to select the minimum number of splits in our decision trees for which the cross-validated error was less than the minimum observed error plus the associated standard error.[20] The resulting survival trees outlined a simple set of classification rules to define subgroups of women with similar survival profiles.

The 11 input variables we considered were: year of diagnosis, age at diagnosis, birth country, attendance pattern (screen-detected cancers only), histopathological type and grade, T, N, and M categories, and ER and PR status. The levels and ranges for these variables are described in Table S1. Missing information for input variables (summarized in Tables 1 and 2) was handled automatically using surrogate splits where a suitable non-missing variable was used to classify an observation instead of the missing variable.[19,20] There was no missing information for the outcome of interest (survival).

Describing subgroups with differing survival profiles

Using the subgroups defined by the recursive binary partitioning algorithm and the same time-to-event data, we calculated women's 10-year breast cancer-specific survival as one minus the cumulative incidence of breast cancer-specific death. Corresponding 95% CIs were also presented. These results were presented graphically using survival curves that can be interpreted as the real-world proportion of women who did not die from their breast cancer.

Recursive partitioning was performed using R (v4.1.3) with the rpart (v4.1.19), and rpart.plot (v3.1.1) packages.[21-23] All other analyses were performed using Stata (v18.0); cumulative incidences were calculated using the stcompet package.[24]

Results

18,890 women were diagnosed with breast cancer after receiving at least one invitation to BreastScreen Norway between January 1, 1996 and December 31, 2011. After applying the exclusion criteria, 16,396 women were included in the study sample: 9954 (60.7%) with screen-detected cancer, 3205 (19.6%) with interval cancer, and 3237 (19.7%) with cancer detected outside of the screening program (Figure 1). Among screen-detected cancer, 6.3%

(n=630) were fatal, whereas 17.4% (n=559) of interval cancers, and 20.9% (n=675) of cancers detected outside of screening were fatal (Table 1).

The mean (SD) age at diagnosis was 60 (5.8) years and was similar across all modes of detection and for fatal and non-fatal cancers (Table 1). Overall, 95% of women in the cohort were born in Norway. The incremental roll-out of organized screening was reflected in an increasing number of cancers diagnosed later in the study period. Moreover, the proportion of fatal cancers was somewhat higher earlier in the study period versus later in the study period for all modes of detection (Table 1). The majority (64.3%) of screen-detected cancers were associated with regular screens and the proportion of fatal cancers was higher for prevalent screens (7.4%, n=238) than regular screens (5.7%, n=352).

Across all modes of detection, the proportion of fatal cancers increased among tumours with less favourable histopathology: increased tumour diameter, histopathologic grade, or lymph node involvement, and negative ER or PR receptor status (Table 2). The most pronounced difference in the proportions of fatal cancers was for women with versus without distant metastases at diagnosis, however only a small proportion of women were diagnosed with distant metastases (0.8% of screening-detected cancers, 4.2% of interval cancers, and 9.7% of cancers detected outside screening). Some of the lowest proportions of fatal cancers were observed among women with screen-detected cancers that were grade 1 (2.6% fatal), T1a/b (>0–10 mm; 2.2% fatal), or that were node negative (3.5% fatal; Table 2).

When evaluating the proportion of fatal screen-detected cancers among various combinations of pTNM-classifications and grade (Table S2), the highest proportions were observed among T1c or T2, node positive, and M0 cancers (10.7% among grade 1 or 2 cancers and 23.4% among grade 3 cancers). The lowest proportions of fatal screen-detected cancers were observed among T1a/b, N0, and M0 cancers (1.5% among grade 1 or 2 cancers and 3.5% among grade 3 cancers).

Survival

The 9954 women with screen-detected cancers contributed a total of 93,403 person-years to the analysis. The recursive partitioning algorithm identified four subgroups with distinct survival profiles among these women: node negative (SDC Subgroup 1); N1 and M0 (SDC Subgroup 2); N2 or N3, and M0 (SDC Subgroup 3); and node positive and M1 (SDC Subgroup 4; Figure 2A). The 10-year breast cancer survival was 96.3% (95%CI: 95.9 to 96.7) for women classified as belonging to SDC Subgroup 1; 89.3% (95%CI: 87.9 to 90.6) for SDC Subgroup 2; 72.6% (95%CI: 67.9 to 77.1) for SDC Subgroup 3; and 21.6% (95%CI: 12.6 to 35.6) for SDC Subgroup 4 (Figure 2B).

The 3205 women with interval cancer contributed a total of 27,623 person-years to the analysis. Five subgroups were identified by the recursive partitioning algorithm among women with interval cancer: grade 1 or 2, node negative and M0 (IC Subgroup 1); grade 3, node negative and M0 (IC Subgroup 2); N1 and M0 (IC Subgroup 3); N2 or N3, and M0 (IC Subgroup 4); and M1 (IC Subgroup 5; Figure 3A). IC Subgroups 2 and 3 had similar survival profiles and were therefore combined for the survival curves. The 10-year breast cancer survival for IC Subgroups 1, 2/3, 4, and 5 were: 94.9% (95%CI: 93.6 to 96.0); 82.7% (95% CI: 80.8 to 84.6%); 60.7% (95%CI: 55.3 to 66.2); and 19.2% (95%CI: 13.5 to 26.9) (Figure 3B). Survival estimates for each of the five subgroups are presented in the supplemental material (Figure S1).

The 3237 women with breast cancer detected outside of screening contributed 25,845 person-years to the analysis and four subgroups were identified for these women: T1 and M0 (OS Subgroup 1); T2 and M0 (OS Subgroup 2); T3 or T4, and M0 (OS Subgroup 3); and M1 (OS Subgroup 4; Figure 4A). The corresponding 10-year breast cancer survival for OS Subgroups 1 through 4 were 91.8% (95%CI: 90.5 to 93.1); 79.3% (95%CI: 76.8 to 81.7); 52.2% (95%CI: 44.9, 60.0); and 23.4% (95%CI: 19.1 to 28.5) (Figure 4B).

Discussion

This closed cohort study described the histopathology of 16,396 breast cancers diagnosed in women targeted by BreastScreen Norway and used recursive partitioning to identify survival profiles for subgroups of women attending and not attending the screening program. We found that 61% of cancers were screen-detected, 19% were interval cancers, and 20% were detected outside screening. Ten years after diagnosis, 6.3% of women with screen-detected cancers had died from breast cancer, compared to 17.4% of those with interval cancer and 20.9% of women with cancer detected outside screening.

Univariable analyses revealed a higher proportion of fatal cancers among prevalent screen-detected cancers than “subsequent regular” screen-detected cancers (7.4% vs 5.7%, respectively). Although the relative risk between these groups is roughly 30%, the risk difference is small (1.7 percentage points). The proportion of fatal cancer was particularly low for women with histologic grade 1, T1a/b, or node negative screen-detected cancers. The recursive partitioning algorithm identified that women with node negative screen-detected cancer had excellent 10-year breast cancer-specific survival (96%). This group represented 76% of women with screen-detected cancer. Women with interval cancer whose disease was histologic grade 1 or 2, node negative, and did not present with distant metastases also had excellent 10-year breast cancer-specific survival (95%); this group represented 38% of

women diagnosed with interval cancer. Combined, these groups represented 53% of the cohort, suggesting that many women diagnosed with breast cancer had an excellent prognosis when offered the best available treatment according to national guidelines.

Across all modes of detection, the proportion of fatal cancers increased with increasing histologic grade, tumour diameter, and lymph node involvement. The highest proportion of fatal cancers was observed among women with distant metastases at diagnosis, and all subgroups with distant metastases at diagnosis had <25% 10-year breast cancer-specific survival. However, the proportion of women with distant metastases at diagnosis was low, particularly for women with screen-detected cancers.

The variables selected by the recursive partitioning algorithm to define women with differing survival profiles are well-established prognostic factors for breast cancer, underlining the validity of the approach used.[2,4,25] Nonetheless, the present approach did not select T-category to define prognostic subgroups for women with screen-detected or interval cancer. This does not imply that tumour diameter is not an important prognostic factor – the opposite is well-established.[2,4,25] It rather implies that T-category did not provide more information about 10-year breast cancer-specific survival than lymph node involvement/histologic grade for the women with screen-detected/interval cancers included in our cohort. Indeed, nodal status and grade have been shown to be stronger prognostic factors than tumour diameter in the Nottingham Prognostic Index and univariate analyses in our study showed a larger difference in the proportion of fatal cancers across N-categories than across T-categories for these modes of detection.[25]

This closed cohort study used 10-year breast cancer-specific survival to evaluate non-fatal and fatal cases. Using an open cohort with longer follow-up and more contemporary cases may have improved external validity, but the closed cohort design helped ensure that the proportion of non-fatal cancers generally mirrored the 10-year breast cancer-specific survival. This improves the interpretability and face validity of the results produced by the recursive partitioning algorithm, which we consider important since this data-driven approach is novel in descriptive epidemiology. A limitation of using single trees, such as those presented in our study, is that small changes in the data used to create the trees can lead to different variables included in the final models. This instability is inherent to the recursive partitioning method and is the “cost” of the intuitive output that trees offer.[26] More advanced methods called “ensemble methods” can reduce this instability but offer less intuitive interpretation than single trees.[20,26] Our descriptive study prioritized the simple interpretation of single trees, but future research may consider using ensemble methods such as random forests to evaluate whether a more advanced approach may be suitable for predicting survival

outcomes for individuals. Such research could also include information from a more contemporary cohort where not all women have 10 years of follow-up.

Another limitation of this study is the absence of data on human epidermal growth factor receptor 2 (HER2) status and tumor cell proliferation (by Ki67), since this information is largely missing in the Cancer Registry of Norway's databases for cases diagnosed ≤2009. Such data may be useful for further stratification of survival groups for women with screen-detected breast cancer, particularly ER-positive cases.[6] Indeed, HER2 and Ki67 are currently used as surrogate markers for molecular breast cancer subtypes, which are known to have different survival profiles, and HER2 is also used to define the AJCC prognostic stage groups.[4,6,27] The focus of the current study was on women's prognosis at diagnosis. Information on treatment was not included and this is a limitation since survival is influenced by treatment, however treatment is determined by tumour histopathology and not explicitly by mode of detection. In terms of external validity, women diagnosed after 2011 would have increased access to neoadjuvant therapy and newer therapies such as immunotherapy than women included in this study.[28] Moreover, breast cancer morality in Norway has continued to decrease over time and, therefore, the breast cancer-specific survival estimates we presented are likely to be conservative estimates for patients diagnosed today.[29] Nonetheless, as noted above, the variables selected by the recursive partitioning algorithm are well-established prognostic factors for breast cancer and have been shown to be relevant for modern cohorts.[6]

Lastly, we didn't have information on whether an interval cancer or cancer detected outside of screening was asymptomatic. Opportunistic screen-detected cancers likely have a prognosis similar to screen-detected cancers in BreastScreen Norway but were classified as interval cancers or cancers detected outside screening in our study because reporting information about opportunistic (private) screening is not mandatory in Norway and this information was unavailable for our study. The proportion of fatal cancers among symptomatic interval cases and tumours detected outside of screening is therefore likely somewhat higher than we observed.

A strength of our study is the use of recursive partitioning: this relatively simple algorithm evaluated many linear combinations of patient and histopathologic variables against breast cancer survival to produce simple and applicable tree diagrams describing survival-based subgroups. We used survival curves to further describe the profiles of the subgroups identified by the algorithm; this presentation is familiar to researchers and clinicians and supports the validity of our results. Presenting 10-year breast cancer-specific survival adjusted for the competing risk of death from other causes represents another strength of our study because it represents the real-world proportion of women who survived their breast

cancer. (It should be noted, however, that some women who survived their breast cancer will have died of other causes during the follow-up period.) On the other hand, the often-used Kaplan-Meier estimate of breast cancer-specific survival is biased in the presence of competing risks.[30-33] In this context, the Kaplan-Meier method would have estimated the probability of surviving from breast cancer in a hypothetical world where it is not possible to die from other causes (so-called net survival).[33] Although such hypothetical estimates can be useful for making comparisons over time or between countries, real-world estimates are most relevant for communicating with patients.

Conclusion

Our cohort study included data from women diagnosed with breast cancer in 2011 and earlier and considered person and tumour characteristics to define subgroups with differing survival profiles, stratified by mode of detection. Only tumour characteristics (grade, tumour diameter, lymph node involvement, and distant metastasis at diagnosis) were ultimately selected to describe these subgroups. Approximately half of women were classified into subgroups with excellent (95–96%) 10-year breast cancer-specific survival. The proportion of fatal breast cancer ten years after diagnosis was 6.3% among women with screen-detected cancers, versus 17.4% among women with interval cancer and 20.9% among women with cancer detected outside screening. The results of our study are descriptive, but clinicians may use them to inform and potentially reassure women diagnosed with breast cancer about 10-year outcomes.

Additional information

Acknowledgements

The authors would like to thank Luca Pestarino for sharing his insights on recursive partitioning.

Author contributions

Conceptualization: SH, SRH, LAA
Methodology: SH, SRH, LAA, KMT
Software: KMT
Validation: KMT, SH, SRH, LAA
Formal analysis: KMT
Investigation: all authors

Resources: SH
Data curation: KMT, SH
Writing – original draft preparation: KMT, SH, SRH
Writing – review and editing: KMT, SH, SRH, LAA
Visualization: KMT
Supervision: not relevant
Project administration: SH
Funding acquisition: not relevant

Ethics approval and consent to participate

This study has been reviewed by the privacy ombudsman at the Oslo University Hospital (PVO 20/12601) and was performed in accordance with the Declaration of Helsinki. It has legal basis in accordance with Articles 6 (1) (e) and 9 (2) (j) of the GDPR. The data was disclosed with legal basis in the Cancer Registry Regulations section 3-1 and the Personal Health Data Filing System Act section 19 a to 19 h.

Data availability statement

The data underlying this article cannot be shared publicly due to patient privacy. The data can be shared for research purposes on request to the Cancer Registry of Norway's data delivery unit via Helsedata.no (https://helsedata.no/).

Competing interests

SH is the head of BreastScreen Norway. The other authors declare no competing interests.

Funding information

The author(s) received no specific funding for this work.

Disclaimer

Data from the Cancer Registry of Norway (CRN) have been used in this publication. The authors are solely responsible for the interpretation and presentation of the results in this paper.

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Figures

Figure 1: Number of women included and excluded in this study. Women were excluded sequentially using the given criteria.

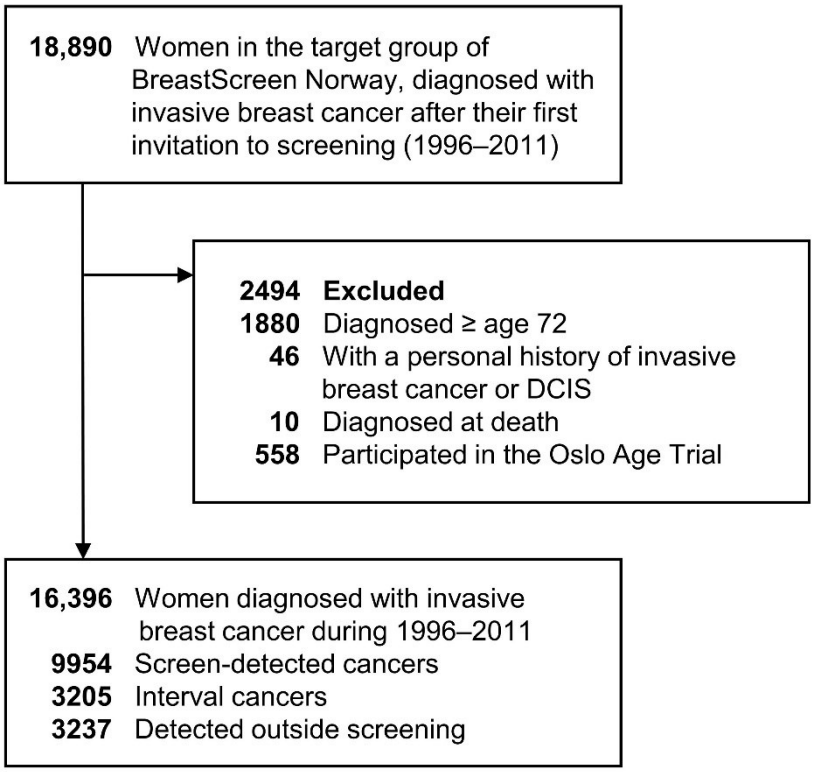


Figure 2: (A) Breast cancer-specific survival tree for women diagnosed with screen-detected cancer through BreastScreen Norway, % indicates the proportion of women who died of breast cancer within each subgroup **(B)** 10-year breast cancer-specific survival, stratified using the subgroups created by the survival tree.

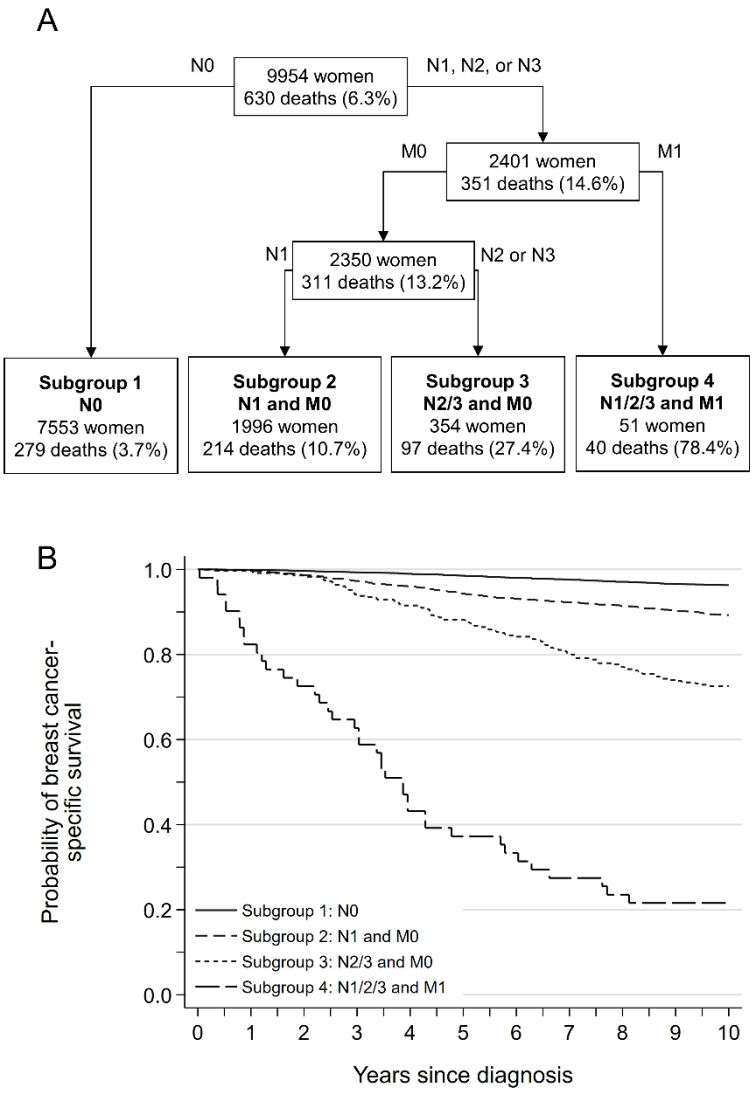


Figure 3: (A) Breast cancer-specific survival tree for women diagnosed with interval cancer through BreastScreen Norway, % indicates the proportion of women who died of breast cancer within each subgroup **(B)** 10-year breast cancer-specific survival, stratified using the subgroups created by the survival tree.

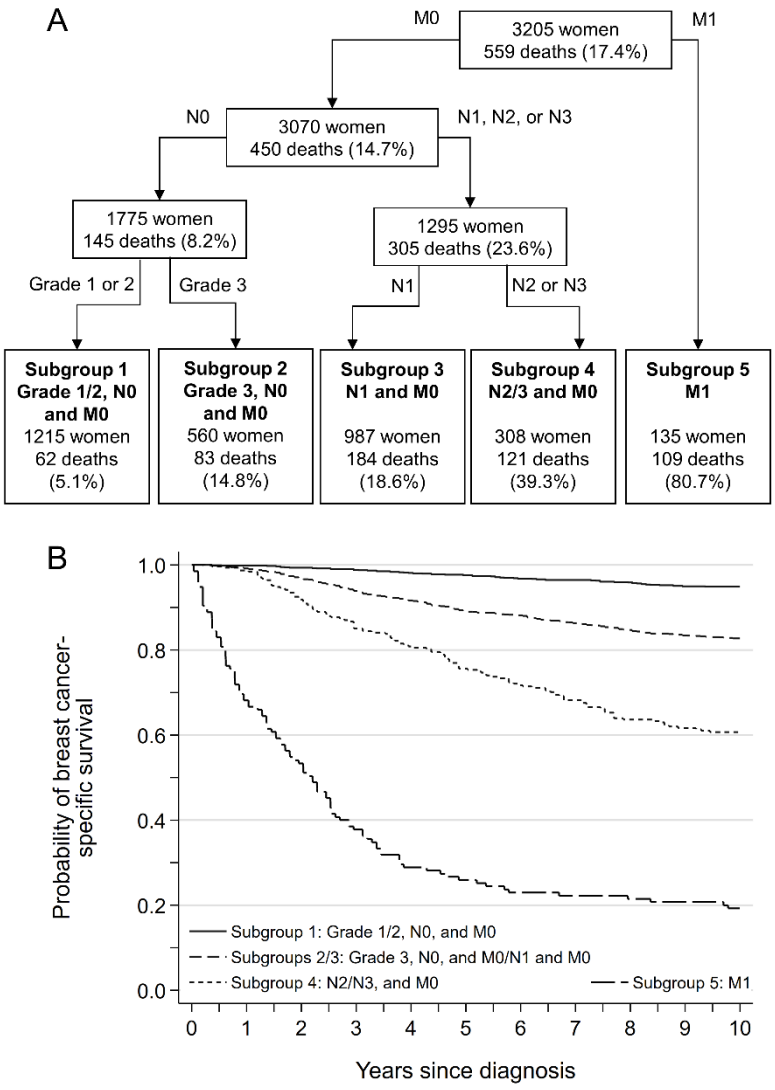
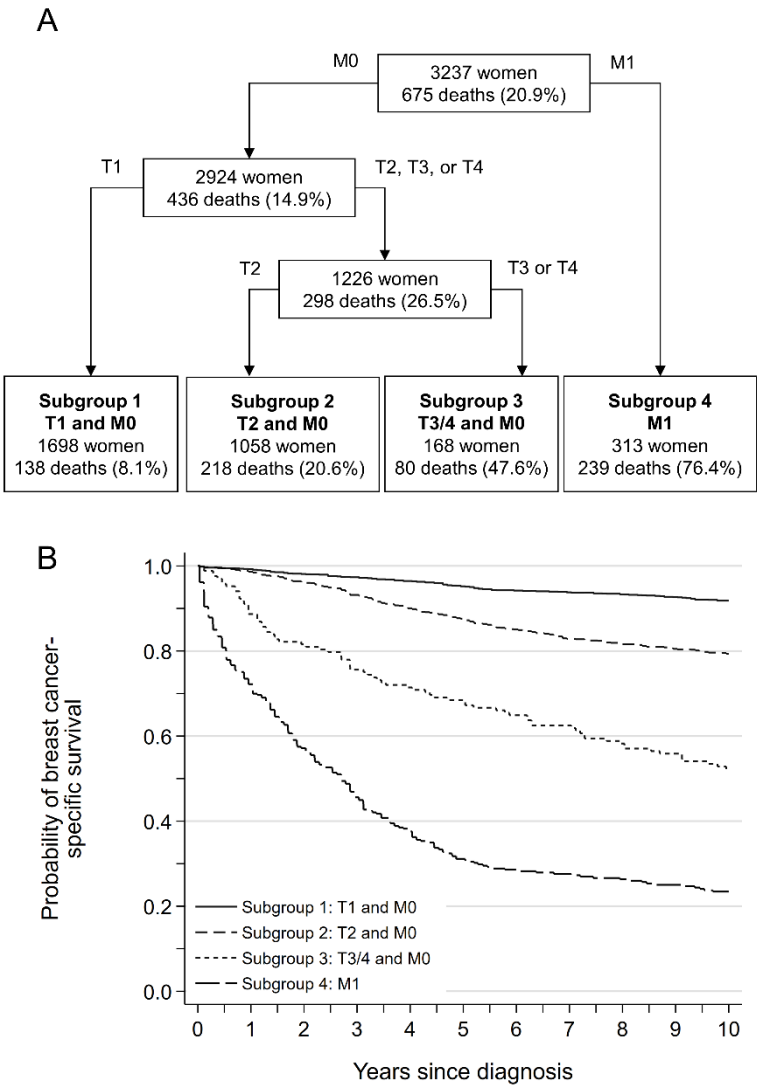


Figure 4: (A) Breast cancer-specific survival tree for women diagnosed outside of BreastScreen Norway, % indicates the proportion of women who died of breast cancer within each subgroup **(B)** 10-year breast cancer-specific survival, stratified using the subgroups defined by the survival tree.



Tables

Table 1: Patient characteristics of 16,396 women in the target group of BreastScreen Norway and diagnosed with breast cancer during 1996–2011, stratified by mode of detection and whether the cancer was fatal or non-fatal within 10 years of diagnosis.

	Screen-detected cancers		**Interval**		**Outside screening**		**Total**	
	Fatal	**Non-fatal**	**Fatal**	**Non-fatal**	**Fatal**	**Non-fatal**	**Fatal**	**Non-fatal**
	n = 630 (6.3%)	n = 9324 (93.7%)	n = 559 (17.4%)	n = 2646 (82.6%)	n = 675 (20.9%)	n = 2562 (79.1%)	n = 1864 (11.4%)	n = 14,532 (88.6%)
Age at diagnosis (years), Mean (SD)	60.2 (5.6)	60.1 (5.7)	59.9 (5.4)	60.0 (5.6)	61.6 (6.2)	61.1 (6.2)	60.6 (5.8)	60.3 (5.8)
Age at diagnosis (years), [range]	[49, 71]	[49, 71]	[50, 71]	[49, 71]	[49, 71]	[48, 71]	[49, 71]	[48, 71]
Birthplace, n (%)								
Norway	602 (6.3)	8895 (93.7)	529 (17.3)	2520 (82.7)	630 (20.7)	2419 (79.3)	1761 (11.3)	13,834 (88.7)
Other	21 (6.1)	322 (93.9)	24 (22.6)	82 (77.4)	34 (22.5)	117 (77.5)	79 (13.2)	521 (86.8)
Unknown	7 (6.1)	107 (93.9)	6 (12.0)	44 (88.0)	11 (29.7)	26 (70.3)	24 (11.9)	177 (88.1)
Year of diagnosis, n (%)								
1996–1999	112 (9.7)	1040 (90.3)	56 (19.6)	229 (80.4)	52 (20.1)	207 (79.9)	220 (13.0)	1476 (87.0)
2000–2004	226 (7.1)	2941 (92.9)	189 (20.7)	723 (79.3)	200 (22.1)	703 (77.9)	615 (12.3)	4367 (87.7)
2005–2009	218 (5.5)	3710 (94.5)	253 (17.8)	1170 (82.2)	300 (21.4)	1102 (78.6)	771 (11.4)	5982 (88.6)
2010–2011	74 (4.3)	1633 (95.7)	61 (10.4)	524 (89.6)	123 (18.3)	550 (81.7)	258 (8.7)	2707 (91.3)
Attendance prior to diagnosis, n (%)								
Prevalent screen[a]	238 (7.4)	2995 (92.6)	-	-	-	-	238 (7.4)	2995 (92.6)
Regular screen[b]	352 (5.7)	5789 (94.3)	-	-	-	-	352 (5.7)	5789 (94.3)
Irregular screen[c]	40 (6.9)	540 (93.1)	-	-	-	-	40 (6.9)	540 (93.1)

[a] Prevalent, first screening examination in BreastScreen Norway

[b] Regular screening examinations performed within 24±6 months of the previous screen

[c] Irregular screening examinations performed more than 30 months after the previous screen

Table 2: Histopathology of breast cancers among 16,396 women in the target group of BreastScreen Norway and diagnosed with breast cancer during 1996–2011, stratified by mode of detection and whether the cancer was fatal or non-fatal within 10 years of diagnosis. Proportions with 95% confidence intervals, CIs, calculated using the Wilson score interval.

	Screen-detected cancers				Interval				Outside screening			
	Fatal		Non-fatal		Fatal		Non-fatal		Fatal		Non-fatal	
	n = 630 (6.3%)		n = 9324 (93.7%)		n = 559 (17.4%)		n = 2646 (82.6%)		n = 675 (20.9%)		n = 2562 (79.1%)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Histologic type												
Invasive NST[a]	561	6.6 (6.1, 7.2)	7904	93.4 (92.8, 93.9)	465	17.8 (16.4, 19.3)	2144	82.2 (80.7, 83.6)	560	21.5 (19.9, 23.1)	2050	78.5 (76.9, 80.1)
Lobular	61	6.2 (4.8, 7.9)	927	93.8 (92.1, 95.2)	80	19.2 (15.7, 23.3)	336	80.8 (76.7, 84.3)	75	21.0 (17.1, 25.5)	282	79.0 (74.5, 82.9)
Other	8	1.6 (0.8, 3.1)	493	98.4 (96.9, 99.2)	14	7.8 (4.7, 12.6)	166	92.2 (87.4, 95.3)	15	9.9 (6.1, 15.6)	137	90.1 (84.4, 93.9)
Not available	0	-	0	-	0	-	0	-	25	-	93	-
Histologic grade												
1	87	2.6 (2.1, 3.2)	3207	97.4 (96.8, 97.9)	26	4.7 (3.2, 6.7)	532	95.3 (93.3, 96.8)	30	5.7 (4.0, 8.0)	498	94.3 (92.0, 96.0)
2	293	6.3 (5.6, 7.0)	4349	93.7 (93.0, 94.4)	230	16.0 (14.2, 18.0)	1207	84.0 (82.0, 85.8)	230	16.9 (15.0, 19.0)	1130	83.1 (81.0, 85.0)
3	233	13.1 (11.6, 14.8)	1540	86.9 (85.2, 88.4)	266	24.7 (22.2, 27.4)	811	75.3 (72.6, 77.8)	248	28.4 (25.5, 31.5)	626	71.6 (68.5, 74.5)
Not available	17	-	228	-	37	-	96	-	167	-	308	-
pT-category												
T1a/b: > 0–10 mm	81	2.2 (1.8, 2.8)	3529	97.8 (97.2, 98.2)	30	6.3 (4.5, 8.9)	444	93.7 (91.1, 95.5)	19	4.1 (2.7, 6.3)	442	95.9 (93.7, 97.3)
T1c: 11–20 mm	239	5.5 (4.8, 6.2)	4134	94.5 (93.8, 95.2)	123	10.5 (8.9, 12.4)	1047	89.5 (87.6, 91.1)	75	7.8 (6.2, 9.6)	890	92.2 (90.4, 93.8)
T2: 21–50 mm	229	14.4 (12.7, 16.2)	1364	85.6 (83.8, 87.3)	205	19.6 (17.3, 22.1)	840	80.4 (77.9, 82.7)	178	20.3 (17.7, 23.1)	700	79.7 (76.9, 82.3)
T3: > 50 mm	47	21.1 (16.2, 26.9)	176	78.9 (73.1, 83.8)	116	34.8 (29.9, 40.1)	217	65.2 (59.9, 70.1)	44	57.1 (46.0, 67.6)	33	42.9 (32.4, 54.0)
T4: Direct extension to the chest wall	13	23.6 (14.4, 36.3)	42	76.4 (63.7, 85.6)	23	44.2 (31.6, 57.7)	29	55.8 (42.3, 68.4)	96	60.8 (53.0, 68.0)	62	39.2 (32.0, 47.0)
Not available	21	-	79	-	62	-	69	-	263	-	435	-
pN-category												
pN0	257	3.5 (3.1, 3.9)	7094	96.5 (96.1, 96.9)	151	8.7 (7.4, 10.1)	1590	91.3 (89.9, 92.6)	112	7.5 (6.3, 8.9)	1385	92.5 (91.1, 93.7)
pN1	232	11.5 (10.2, 13.0)	1787	88.5 (87.0, 89.8)	218	21.6 (19.2, 24.3)	790	78.4 (75.7, 80.8)	356	30.7 (28.1, 33.4)	804	69.3 (66.6, 71.9)
pN2	62	23.6 (18.8, 29.1)	201	76.4 (70.9, 81.2)	84	37.8 (31.7, 44.4)	138	62.2 (55.6, 68.3)	24	35.8 (25.4, 47.8)	43	64.2 (52.2, 74.6)
pN3	52	47.3 (38.2, 56.5)	58	52.7 (43.5, 61.8)	54	50.9 (41.6, 60.3)	52	49.1 (39.7, 58.4)	14	35.9 (22.7, 51.6)	55	64.1 (48.4, 77.3)
Not available	27	-	184	-	52	-	76	-	169	-	305	-

PM-category												
M0	542	5.8 (5.4, 6.3)	8752	94.2 (93.7, 94.6)	421	14.6 (13.4, 15.9)	2463	85.4 (84.1, 86.6)	378	14.1 (12.9, 15.5)	2998	85.9 (84.5, 87.1)
M1	54	71.1 (61.0, 80.0)	22	28.9 (20.0, 40.0)	109	80.7 (73.5, 86.5)	26	19.3 (13.5, 26.7)	239	76.4 (71.3, 80.7)	74	23.6 (19.3, 28.7)
Not available	34	-	550	-	29	-	157	-	58	-	190	-
ER[b] status												
Positive	449	5.4 (5.0, 5.9)	7831	94.6 (94.1, 95.0)	319	14.1 (12.7, 15.5)	1951	85.9 (84.5, 87.3)	135	17.1 (14.7, 19.9)	653	82.9 (80.1, 85.3)
Negative	148	13.5 (11.6, 15.6)	949	86.5 (84.4, 88.4)	207	27.3 (24.2, 30.5)	552	72.7 (69.5, 75.8)	45	23.8 (18.3, 30.4)	144	76.2 (69.6, 81.7)
Not available	33	-	544	-	33	-	143	-	495	-	1765	-
PR[c] status												
Positive	320	4.9 (4.4, 5.5)	6166	95.1 (94.5, 95.6)	222	13.0 (11.5, 14.7)	1480	87.0 (85.3, 88.5)	91	15.1 (12.5, 18.2)	511	84.9 (81.8, 87.5)
Negative	272	9.7 (8.7, 10.9)	2521	90.3 (89.1, 91.3)	300	23.1 (20.9, 25.5)	996	76.9 (74.5, 79.1)	85	23.4 (19.4, 27.0)	278	76.6 (72.0, 80.6)
Not available	38	-	637	-	37	-	170	-	499	-	1773	-

[a] Invasive carcinoma of no special type

[b] Estrogen Receptor

[c] Progesterone Receptor

Supplementary material

Table S1: Candidate variables for recursive partitioning analysis

Variable	Type	Range/levels
Patient characteristics		
Year of diagnosis	Continuous	1996–2011
Age at diagnosis	Continuous	48–71
Birth country	Categorical	Norway, Other
Attendance prior to diagnosis	Categorical	Prevalent, Regular, Irregular, Outside screening
Tumour characteristics		
Histologic type	Categorical	Invasive carcinoma of no special type, Lobular, Other
Histologic grade	Categorical	1, 2, 3
pT	Categorical	T1a/b, T1c, T2, T3, T4
pN	Categorical	N0, N1, N2, N3
pM	Categorical	M0, M1
ER status	Categorical	Before January 2010: Negative (<10%), Positive (≥10%) January 2010 onwards: Negative (<1%), Positive (≥1%)
PR status	Categorical	Negative (<1%), Positive (≥10%)

Table S2: Proportion of patients diagnosed with screen-detected cancers through BreastScreen Norway during 1996–2011 that were fatal or non-fatal after 10 years of follow-up, stratified by various pTNM-classifications and grade. Frequencies and proportions with 95% confidence intervals, CIs, calculated using the Wilson score interval.

	Fatal		Non-fatal	
	n	**% (95% CI)**	**n**	**% (95% CI)**
T1a/b, N0, M0				
Grade 1 or 2	38	1.5 (1.1, 2.1)	2485	98.5 (97.9, 98.9)
Grade 3	13	3.5 (2.0, 5.8)	362	96.5 (94.2, 98.0)
T1a/b, N1/2/3, M0				
Grade 1 or 2	11	4.4 (2.5, 7.7)	238	95.6 (92.3, 97.5)
Grade 3	4	6.7 (2.6, 15.9)	56	93.3 (84.1, 97.4)
T1c or T2, N0, M0				
Grade 1 or 2	108	3.5 (2.9, 4.3)	2939	96.5 (95.7, 97.1)
Grade 3	65	9.1 (7.2, 11.4)	649	90.9 (88.6, 92.8)
T1c or T2, N1/2/3, M0				
Grade 1 or 2	149	10.7 (9.2, 12.4)	1247	89.3 (87.6, 90.8)
Grade 3	100	23.4 (19.6, 27.6)	328	76.6 (72.4, 80.4)

T1a/b: ≤10 mm
T1c: >10 to ≤20 mm
T2: >20 to ≤50 mm
N0: no axillary lymph node involvement
N1/2/3: ≥1 positive axillary lymph nodes
M0/M1: without/with distant metastasis at diagnosis

Figure S1: 10-year breast cancer-specific survival for interval cancer, stratified using the five subgroups created by the survival tree: grade 1 or 2, node negative and M0 (IC Subgroup 1); grade 3, node negative and M0 (IC Subgroup 2); N1 and M0 (IC Subgroup 3); N2 or N3, and M0 (IC Subgroup 4); and M1 (IC Subgroup 5; Figure 3A). The 10-year breast cancer survival with 95% confidence intervals for IC Subgroups 1 through 5 were: 94.9% (95%CI: 93.6 to 96.0); 85.2% (95%CI: 82.1 to 88.0); 81.3% (95%CI: 78.8 to 83.7); 60.7% (95%CI: 55.3 to 66.2); and 19.2% (95%CI: 13.5 to 26.9).