Detection and Significance of Small and Low Proliferation Breast Cancer

Solveig Hofvind, PhD[1,2] ; Gøril Knutsvik, MD, PhD[3,4]; Åsne Sørlien Holen, MSc[1];
Kaitlyn Tsuruda, MSc[1,5]; and Lars Andreas Akslen, MD, PhD[3,4*]

[1]Cancer Registry of Norway, Oslo, Norway
[2]Department of Life Sciences and Health, Oslo Metropolitan University, Oslo, Norway
[3]Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, Section for Pathology, University of Bergen, Bergen, Norway
[4]Department of Pathology, Haukeland University Hospital, Bergen, Norway
[5] Department of Biostatistics, Faculty of Medicine, University of Oslo, Oslo, Norway

*Corresponding author:
Lars A Akslen, MD PhD, Professor & Director
Centre for Cancer Biomarkers CCBIO
Department of Clinical Medicine, Section for Pathology
University of Bergen and Haukeland University Hospital
N-5021 Bergen, Norway
E-mail: lars.akslen@uib.no
Phone: +47 55973182

This is an accepted, peer reviewed postprint-version of the following published journal article:
Hofvind S, Knutsvik G, Holen ÅS, Tsuruda KM, Akslen LA. Detection and significance of small and low proliferation breast cancer. Journal of Medical Screening. 2022;29(1):32-37. DOI: https://doi.org/10.1177/09691413211023970

Abstract

OBJECTIVES: To determine the frequency and discuss possible implications of early breast cancer with particularly good prognosis and defined by tumor diameter and cell proliferation.

SETTING: Detection of small and slowly growing tumors presents a challenge in breast cancer management, due to the risk of over-treatment. Here, we attempted to define a group of such tumors by combining small diameter (≤10 mm, T1ab tumors) with low tumor cell proliferation (≤10% Ki67 expression rate). These tumors were termed small low proliferation cancers (SLPC).

METHODS: Two population-based cohorts were studied: a small research series (n=534), and a nation-wide registry-based series of prospectively collected routine data (n=8433). In the latter, we stratified by detection mode; screen-detected, interval, and breast cancers detected outside of screening. Patients were treated according to national guidelines at time of their diagnosis. For both cohorts, we compared tumor histopathology and risk of breast cancer death using a log-rank test for cases with SLPC versus non-SLPC.

RESULTS: In the research series (median follow-up 151 months), the frequency of SLPC was 10% (54/534), with one breast cancer death compared with 78 among the remaining 480 cases of non-SLPC (p=0.008). In the registry series (median follow-up 42 months), the frequency of SLPC was 10% (854/8433), with five deaths compared to 187 among the remaining 7579 cases (p=0.0004).

CONCLUSIONS: SLPC was associated with very low risk of breast cancer death. Prospective randomized trials are needed to clarify whether less aggressive treatment could be a safe option for women with such early breast cancers.

KEYWORDS: Early breast cancer, tumor diameter, tumor proliferation (Ki67), tumor stage, prognosis

INTRODUCTION

There are significant differences between breast cancer cases at diagnosis in terms of tumor diameter, histological grade, tumor stage, and molecular characteristics. Among the latter, hormone receptors and HER2 are routinely reported as a basis for molecular classification, while tumor cell proliferation by Ki67 expression is reported by most laboratories. Ki67 is closely related to tumor growth potential and is used to define Luminal B cases as a basis for treatment. Further, it is well known that tumor diameter and Ki67, and their combinations, are strong prognostic factors in breast cancer. Along with this, several reports have focused on how to define early breast cancer with excellent prognosis, in which the women might be treated less aggressively (1, 2). However, whether all subgroups of early breast cancer would need systemic treatment is not entirely clear (2). This is of particular interest in the setting of mammographic screening.

Here, we studied how routinely reported tumor characteristics may be used to define a subgroup of histologically confirmed breast cancer with particularly good prognosis, by combining tumor diameter and tumor proliferation rate (Ki67 expression). We termed this category "small low proliferation cancers" (SLPC). This approach should be interpreted as a search for markers that can be used to define a category of early and very slowly progressing tumors, by directly including a measure of the tumor's growth rate, and not only based on tumor diameter (pT). We comment on our results in the context of "prognostic stage groups" introduced by the recent TNM staging classification (8^{th} edition)(3), which combine anatomic and biomarker-based information.

MATERIALS AND METHODS

We defined SLPC as breast cancers with a maximum tumor diameter $\leq$10 mm (TNM category pT1ab tumors)(3) and tumor cell proliferation measured by immunohistochemical Ki67 protein expression of $\leq$10%. This Ki67 value is considered to indicate "clearly low" proliferation in the 2015 St. Gallen guidelines (4). Since 2012, there has been mandatory reporting of the proportion (%) of Ki67 positive tumor cells from breast cancer surgical specimens after immunohistochemistry based on standardized national guidelines in Norway.

Study Populations

We included two cohorts of women diagnosed with invasive breast cancer in this study (cohort I and II), both from BreastScreen Norway, a population-based screening program for breast cancer established in 1996 (5). The program invites women aged 50–69 to two-view biennial mammography.

Cohort I was a research cohort of 534 women who were screened with screen-film mammography in Hordaland county as a part of BreastScreen Norway during 1996–2003, and diagnosed with screen-detected or interval breast cancer (6). Hordaland county represents about 10% of BreastScreen Norway's target population (5). This part of the study was approved by the Western Regional Committee for Medical and Health Research Ethics, REC West (2014/1984).

Cohort II included all women targeted by BreastScreen Norway who were diagnosed with breast cancer during 2011–2016 after either full-field digital mammography screening, or mammography performed due to symptoms (n=10,621). Cases without complete data on tumor diameter and/or Ki67 (n=2188) were excluded, leaving 8433 cases for inclusion: 4913 were screen-detected breast cancers, 1525 interval cancers, and 1995 were diagnosed outside the screening program. The two latter groups represent cases of symptomatic breast cancer. Screen-detected cancer was defined as invasive breast cancer diagnosed after a recall due to abnormal mammographic findings. Interval breast cancer was defined as invasive cases diagnosed within 24 months of a negative screen or within 6-24 months of a false-positive screening result. Cases detected outside of screening were defined as invasive breast cancer diagnosed among non-attendees in the screening program or more than 24 months after the most recent screen in the program. The data protection official at the Cancer Registry of Norway approved this part of the study (2019/11324); the requirement to obtain informed consent was waived (7).

Data collection and study variables

Two breast radiologists read all the screening mammograms independently. Cases with a positive score by one or both readers are discussed at a consensus meeting where a decision is made whether to recall a woman. Consensus, as well as assessment of women with a positive screening examination and mammography due to clinical symptoms, takes place at multidisciplinary breast centers (5). Pathologists who work in close collaboration with the radiologists at the breast centers examine all breast biopsies and surgical specimens. The reporting routines in BreastScreen Norway are described in detail elsewhere (5). All women included in both cohorts were offered treatment based on national guidelines at the time of their diagnosis.

For cases in cohort I, the clinical information was carefully reviewed, and pathology data were included after re-examination of the slides, as previously reported (6). Briefly, tumor diameter and Ki67 protein expression were determined according to national guidelines. Tumor diameter (with microscopic extensions included) was determined by microscopy in 61% of the cases, by macroscopic examinations in 29%, and based on radiologic information in 10%. Ki67 was determined in "hot-spot" areas by

counting 500 tumor cells and by using an eye-piece graticule (x630 magnification). Thus, the Ki67 expression rate is the proportion (%) of tumor cell nuclei with positive staining for the Ki67 protein, indicating that these cells are dividing. These routines are identical to national guidelines and are also the basis for the registry data in cohort II (see below).

For cases in cohort II, data were extracted from the Cancer Registry of Norway where routine data on tumor diameter, Ki67 expression, and other characteristics of tumor histopathology are obtained from pathology reports. For cohort II, additional routine data on histologic type, histologic grade (using the Nottingham criteria), lymph node status and receptor status (estrogen receptor, ER; progesterone receptor, PR; human epidermal growth factor receptor 2, HER2) were obtained from the Cancer Registry based on pathology reports. Molecular subtypes of breast cancers (Luminal A, Luminal B HER2, Luminal B HER2+, Her2+, and Triple negative) were determined using the 2013 St. Gallen guidelines (8). Reporting to the Cancer Registry has been mandatory by law since 1953, and the registration of breast cancer cases is nearly 100% complete (9).

Statistical Analyses

The proportion of SLPC cases and disease specific survival were analyzed for both cohorts. The distribution of age and histopathologic characteristics, including grade, molecular breast cancer subtype, ER, PR, HER2, and lymph node status, was described for SLPC lesions and non-SLPC lesions for cohort II using proportions, and 95% confidence intervals (CI) were calculated using the Wilson score interval (10). We evaluated the association between five-year age groups and SLPC cases using a chi-squared test.

In both cohorts, we followed women from the date of diagnosis to death of breast cancer until December 31, 2011 (cohort I) and December 31, 2017 (cohort II); cases were censored at the time of death, or emigration. Kaplan-Meier survival estimates (cohort I) and Nelson-Aalen cumulative hazard estimates (cohort II) were used to describe the risk of breast cancer death. Differences between SLPC and other cancers were tested using the log-rank test for both cohorts. P-values less than 0.05 were considered statistically significant.

RESULTS

In both cohorts, the SLPC category represented 10% of all cases (cohort I: 54/534; cohort II: 854/8433). In cohort II, there was a higher proportion of SLPC among screen-detected cancers (12.9%; 632/4913, 95%CI: 12.0–13.8) than interval breast cancers (5.1%; 78/1525, 95%CI: 4.1–6.3) and those detected outside of screening (7.2%; 144/1995, 95%CI: 6.1–8.4) (**Table 1**). The proportion of SLPC cases

increased with increasing age (cohort II; p=0.0025 for the whole group). SLPC represented 36% of pT1ab cases.

SLPC lesions had favorable histopathologic characteristics compared to the remaining cases (**Table 2**). Briefly, histologic grade 3 tumors were observed in 1.4% of SLPC tumors (12/854, 95%CI: 0.8–2.5) compared with 26.9% of the other tumors (2026/7579, 95%CI: 25.9–27.9). Positive lymph nodes were found in 8.3% of the SLPC lesions (66/854, 95%CI: 6.5–10.3) compared with 30.3% among the other cancers (2200/7579, 95%CI: 29.3-31.4). The majority of SLPC lesions were classified as Luminal A (80.1%; 664/854, 95%CI: 77.2–82.7), compared to non-SLPC lesions (47.2%; 3464/7579; 95%CI: 46.0–48.3). A triple negative subtype was present in 0.8% of SLPC cases (7/854, 95%CI: 0.4–1.7) compared to 7.9% of other cancers (577/7579, 95%CI: 7.3–8.5).

Median follow-up time for cohort I was 12.5 years (range: 8.3–15.8), and 3.5 years (range: 0–7) for cohort II. One single breast cancer death (screen-detected, lymph node positive case) was observed among SLPC cases in cohort I (1/54 cases), compared with 78 deaths among the remaining cases (78/480, p=0.008, log-rank test; **Figure 1**). In cohort II, five breast cancer deaths were observed among SLPC cases (5/854) compared with 187 among the remaining cases (187/7579, p=0.0004, log-rank test; **Figure 2**). Among the five women in the SLPC group who died, three cases were screen-detected, and three were lymph node positive (two of which were screen-detected, and one was detected outside the screening program). In this cohort, the first breast cancer death in the SLPC group occurred nearly 2.5 years following diagnosis.

DISCUSSION

In this study, we attempted to define a subgroup of early breast cancers with particularly good prognosis, based on a combination of tumor diameter and Ki67 expression reflecting the growth rate. This would relate to the often-asked question on the nature of “small and slowly progressing breast cancers” and their optimal and safe treatment. Here, we found 10% of the women in both cohorts to be diagnosed with SLPC. Our findings indicate that Ki67 could potentially be used to further stratify T1ab tumors, which are already known to have an excellent prognosis (1, 2). This would represent an extension of the “prognostic stage group” concept introduced in the recent TNM staging classification (8^{th} edition), which combines anatomic and biomarker-based information (3). Although Hanrahan et al. (2007) and Ignatov et al. (2017) have reported a very high survival among T1ab patients, it is still not known whether subgroups within the T1ab spectrum could be safely treated without systemic therapy, for example among the HER2 positive or triple negative categories, given a proliferation rate of 10% or less (1, 2).

Our study defined tumors as “small low proliferation cancers” (SLPC) if they had a maximum tumor diameter ≤10 mm (TNM category pT1ab tumors) (3) and tumor cell proliferation (Ki67 expression) of ≤10%, a value termed as “clearly low” by the 2015 St. Gallen guidelines (4). We observed that these tumors made up 10% of both study cohorts. Thus, we found the same proportion of SLPC cases using data from a small research series, and using routinely and prospectively collected information from a nation-wide and registry-based series. In the small cohort, all data were re-examined and Ki67 expression was examined in a highly standardized manner for the purpose of this study. Notably, the readings were done by one breast pathologist. In the registry series, real-life routine data for tumor diameter and Ki67 were based on pathology reports collected from all laboratories. Ki67 data were based on identical protocols for how to determine the counts. Finding the same proportion of SLPC cases in both cohorts (10%) validates the robustness of our approach.

In this study, we were motivated to search for simple pathobiological markers that could be used to define very slowly progressing tumors in individual women. Such data can supplement the group-based epidemiologic approach of defining and evaluating early breast cancer. The overall prognosis of women with SLPC was very favorable when offered treatment according to national guidelines. We believe that the SLPC category may represent a subgroup of tumors where more limited treatment could be considered. However, since both cohorts in our study were offered treatment that adhered to national recommendations at the time of their diagnosis, prospective randomized trials are needed to provide additional evidence as to whether less treatment is safe and could be considered an appropriate option for these women.

The 8th edition of the TNM stage classification presents the concept of “prognostic stage groups”, in which tissue-based biomarkers such as hormone receptors and HER2 status can be added to traditional pathology information (3). Given the findings of our study, further sub-staging or stratification of the pT1 category that considers tumor cell proliferation (Ki67 expression) could be a potential extension of the prognostic stage group classification. Tumors could then be designated as pT1ab-Ki67-low (≤10%) or pT1ab-Ki67-high (>10%). However, additional evidence to validate the prognostic outcomes of these two groups would be needed.

Although SLPC lesions are small and have a very low tumor cell proliferation, there are still cases with tumor spread in terms of lymph node positivity. In our study, 7% of all screen-detected SLPC cases were lymph node positive at diagnosis, compared with 17% of symptomatic SLPC tumors. This indicates the complexity of developing precise markers for tumor progression at patient level. Importantly, we

think that node positive SLPC should be separated from node negative SLPC, which would be a natural consequence of integrated pTN-Ki67 “prognostic staging” of such lesions.

We used a threshold of ≤10 mm as the maximum tumor diameter criterion to define SLPC. We recently reported that breast pathologists in Norway demonstrate a tendency to round tumor diameters to the nearest 5 mm, which results in a relative excess of 10 mm cases reported to the Cancer Registry (11). We cannot exclude that such “rounding” is also present among Ki67 measurements. Inter-observer variation and the risk of misclassifications are well known in relation to pathology data and are continuously discussed. Here, two of the five SLPC deaths in cohort II were associated with cases that had a tumor diameter and/or Ki67 measurement of 10, although we have no information to conclude that these were misclassified.

The findings presented here highlight the diversity of breast tumors across detection modes. In relation to mammographic screening, the issues of defining over-detection at the patient level and over-treatment have been discussed and remain controversial (12-16). Women offered breast cancer screening should be given the opportunity to make an informed choice about participation. Insufficient knowledge about the factors influencing the progression of small and slowly growing tumors, and the extent of overdiagnosis at the group-level, makes this issue challenging and difficult (13, 16-18). In our study, the 10% of women diagnosed with SLPC may have benefitted less from the early detection associated with screening than the other 90% of women diagnosed with screen-detected breast cancer.

The analyses in our study used pooled information from women with screen-detected and symptomatic cancers and are subject to lead- and length time biases. Adjustments for lead-time are challenging given the limited number of cases with adequate follow-up time in cohort II. Although the short observation period is a limitation for the national cohort, the results appear to validate those from the research cohort regarding SLPC frequency. Further, all data presented are based on women diagnosed and treated for breast cancer according to national recommendations. Breast cancer death was thus highly influenced by the fact that the women were treated for their disease.

In conclusion, by combining routinely collected information on tumor diameter (≤10 mm) with tumor cell proliferation from Ki67 (≤10%), a subgroup of 10% of the breast cancers was defined in two independent cohorts. Our study indicates that this “rule of 10” might be useful to identify a group of slow-growing breast cancers with a particularly good prognosis. Prospective trial studies of women diagnosed with SLPC who undergo less aggressive treatment than is currently recommended might

clarify some of the remaining issues, relating to the complex relationships between treatment needed, risk of tumor recurrences, and patient quality of life.

Declaration of conflicting interests

The authors declares that there is no conflict of interest. All five authors work in different fields of BreastScreen Norway. SH has permanent employment as a researcher at the Cancer Registry of Norway independent of her position as the administrative leader of BreastScreen Norway.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the University of Bergen and the Research Council of Norway through its Centres of Excellence funding scheme (project number 223250), and through the Helse Vest Research Fund. Kaitlyn Tsuruda is a PhD student funded by the Dam Foundation via the Norwegian Breast Cancer Society (2018/FO201362).

Data Availability Statement

The dataset for Cohort I is not publicly available, but was obtained from the Cancer Registry of Norway under a specific ethical approval by the Regional Committee for Medical and Health Research Ethics in the Helse Vest, while Cohort II was approved by the data protection official at the Cancer Registry of Norway. Researchers with appropriate approvals can apply for Norwegian health registry data from https://helsedata.no/.

REFERENCES

1. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH, Rouzier R, Broglio KR, Hortobagyi GN, et al. Overall survival and cause-specific mortality of patients with stage T1a,bN0M0 breast carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(31):4952-60.
2. Ignatov T, Eggemann H, Burger E, Costa SD, Ignatov A. Management of small T1a/b breast cancer by tumor subtype. Breast Cancer Res Treat. 2017;163(1):111-8.
3. AJCC Cancer Staging Manual. Springer International Publishing. Eighth Edition. ISBN: 978-3-319-40617-6. 2017.
4. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(8):1533-46.
5. Hofvind S, Tsuruda K, Mangerud G, Ertzaas A, Holen Å, Pedersen K, et al. The Norwegian Breast Cancer Screening Program, 1996-2016: Celebrating 20 years of organised mammographic screening. In: Cancer in Norway 2016 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2017

6. Knutsvik G, Stefansson IM, Aziz S, Arnes J, Eide J, Collett K, et al. Evaluation of Ki67 expression across distinct categories of breast cancer specimens: a population-based study of matched surgical specimens, core needle biopsies and tissue microarrays. PLoS One. 2014;9(11):e112121.
7. Kreftregisterforskriften.https://lovdata.no/dokument/SF/forskrift/2001-12-21-1477. Lovdata. March 2021.
8. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Annals of oncology : official journal of the European Society for Medical Oncology. 2013;24(9):2206-23.
9. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. European journal of cancer (Oxford, England : 1990). 2009;45(7):1218-31.
10. Lydersen S FM, Laake P. Categorical data and contingency tables. In: Veierød MB, Lydersen S, Laake P, (eds) Medical statistics in clinical and epidemiological research. Gylendal Norsk Forlag, Oslo, pp 48-89. 2012.
11. Tsuruda KM, Hofvind S, Akslen LA, Hoff SR, Veierod MB. Terminal digit preference: a source of measurement error in breast cancer diameter reporting. Acta oncologica (Stockholm, Sweden). 2020;59(3):260-7.
12. Wallis MG. How do we manage overdiagnosis/overtreatment in breast screening? Clinical radiology. 2018;73(4):372-80.
13. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. British Journal Of Cancer. 2013;108:2205.
14. Duffy SW, Michalopoulos D, Sebuodegard S, Hofvind S. Trends in aggregate cancer incidence rates in relation to screening and possible overdiagnosis: a word of caution. Journal of medical screening. 2014;21(1):24-9.
15. Puliti D, Duffy SW, Miccinesi G, de Koning H, Lynge E, Zappa M, et al. Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. Journal of medical screening. 2012;19 Suppl 1:42-56.
16. Sardanelli F, Trimboli RM, Tot T. Expert Review of Breast Pathology in Borderline Lesions: A Chance to Reduce Overdiagnosis and Overtreatment? JAMA Oncol. 2018;4(10):1325-6.
17. Hersch J, Barratt A, Jansen J, Irwig L, McGeechan K, Jacklyn G, et al. Use of a decision aid including information on overdetection to support informed choice about breast cancer screening: a randomised controlled trial. Lancet (London, England). 2015;385(9978):1642-52.
18. Sasieni PD, Smith RA, Duffy SW. Informed decision-making and breast cancer screening. Journal of medical screening. 2015;22(4):165-7.

Table 1: Cohort II: Proportion of small low proliferation cancers (SLPC) among all women targeted by Breast Screen Norway during 2011–2016, stratified by mode of detection (screen-detected; interval; outside the screening program) and five-year age group.

Age group	Screen Detected n=4913			Interval n=1525			Outside Screening n=1995			Total* n=8433		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
50-55	103	2.1	(1.7-2.5)	12	0.8	(0.5-1.4)	44	2.2	(1.6-2.9)	159	1.9	(1.6-2.2)
55-59	133	2.7	(2.3-3.2)	17	1.1	(0.7-1.8)	20	1.0	(0.6-1.5)	170	2.0	(1.7-2.3)
60-64	168	3.4	(2.9-4.0)	24	1.6	(1.1-2.3)	24	1.2	(0.8-1.8)	216	2.6	(2.2-2.9)
65-71	228	4.7	(4.1-5.3)	25	1.6	(1.1-2.4)	56	2.8	(2.2-3.6)	309	3.7	(3.3-4.1)
Total	632	12.9	(12.0-13.8)	78	5.1	(4.1-6.3)	144	7.2	6.2-8.4)	854	10.1	(9.5-10.8)

*p for trend = 0.0025.

CI: confidence intervals; calculated using the Wilson score interval.

Table 2: Proportions and 95% confidence intervals (CI)* (unless otherwise specified) of histopathologic characteristics of invasive small low proliferation cancers (SLPC) (diameter ≤10 mm and Ki67 ≤10%) and other invasive breast cancers detected among women targeted by BreastScreen Norway during 2011–2016 (n=8433).

	SLPC		**Other invasive**		**Total**	
Histopathologic tumor	n=854		n=7579		n=8433	
characteristics	%	95% CI	%	95% CI	%	95% CI
Tumor diameter						
≤ 10 mm	100.0	-	19.7	(18.8–20.6)	27.8	(26.9–28.8)
10.01-20 mm	0	-	48.1	(47.0–49.2)	43.2	(42.2–44.3)
20.01-50 mm	0	-	30.1	(29.1–31.1)	27.0	(26.1–28.0)
>50 mm	0	-	2.1	(1.8–2.5)	1.9	(1.6–2.2)
Information not available		n=0		n=0		n=0
Histologic grade						
1	71.7	(68.6–74.7)	22.4	(21.5–23.3)	27.4	(26.4–28.3)
2	26.8	(24.0–29.9)	50.7	(49.6–51.9)	48.3	(47.2–49.4)
3	1.4	(0.8–2.5)	26.9	(25.9–27.9)	24.3	(23.4–25.2)
Information not available		n=8		n=43		n=51
Lymph node status						
Negative	91.8	(89.7–93.5)	69.7	(68.6–70.7)	71.9	(70.9–72.8)
Positive	8.2	(6.5–10.3)	30.3	(29.3–31.4)	28.1	(27.1–29.1)
Information not available		n=53		n=326		n=379
Estrogen receptor status						
Negative	1.4	(0.8–2.4)	11.4	(10.7–12.2)	10.4	(9.8–11.1)
Positive	98.6	(97.6–99.2)	88.6	(87.8–89.3)	89.6	(88.9–90.2)
Information not available		n=3		n=50		n=53
Progesterone receptor status						
Negative	18.9	(16.4–21.4)	29.6	(28.6–30.7)	28.5	(27.6–29.5)
Positive	81.1	(78.4–83.6)	70.4	(69.3–71.4)	71.5	(70.5–72.4)
Information not available		n=11		n=78		n=89
HER2† status						
Negative	98.0	(96.8–98.7)	88.2	(87.5–89.0)	89.2	(88.5–89.9)
Positive	2.0	(1.3–3.2)	11.8	(11.0–12.5)	10.8	(10.1–11.5)
Information not available		n=12		n=145		n=157
Molecular subtype						
Luminal A	80.1	(77.2–82.7)	47.2	(46.0–48.3)	50.5	(49.4–51.6)
Luminal B HER2-	17.0	(14.6–19.7)	33.4	(32.3–34.5)	31.7	(30.7–32.7)
Luminal B HER2+	1.7	(1.0–2.8)	8.4	(7.8–9.0)	7.7	(7.1–8.3)
HER2+**	0.4	(0.1–1.1)	3.2	(2.8–3.7)	2.9	(2.6–3.3)
Triple negative	0.8	(0.4–1.7)	7.9	(7.3–8.5)	7.1	(6.6–7.7)
Information not available		n=25		n=235		n=260

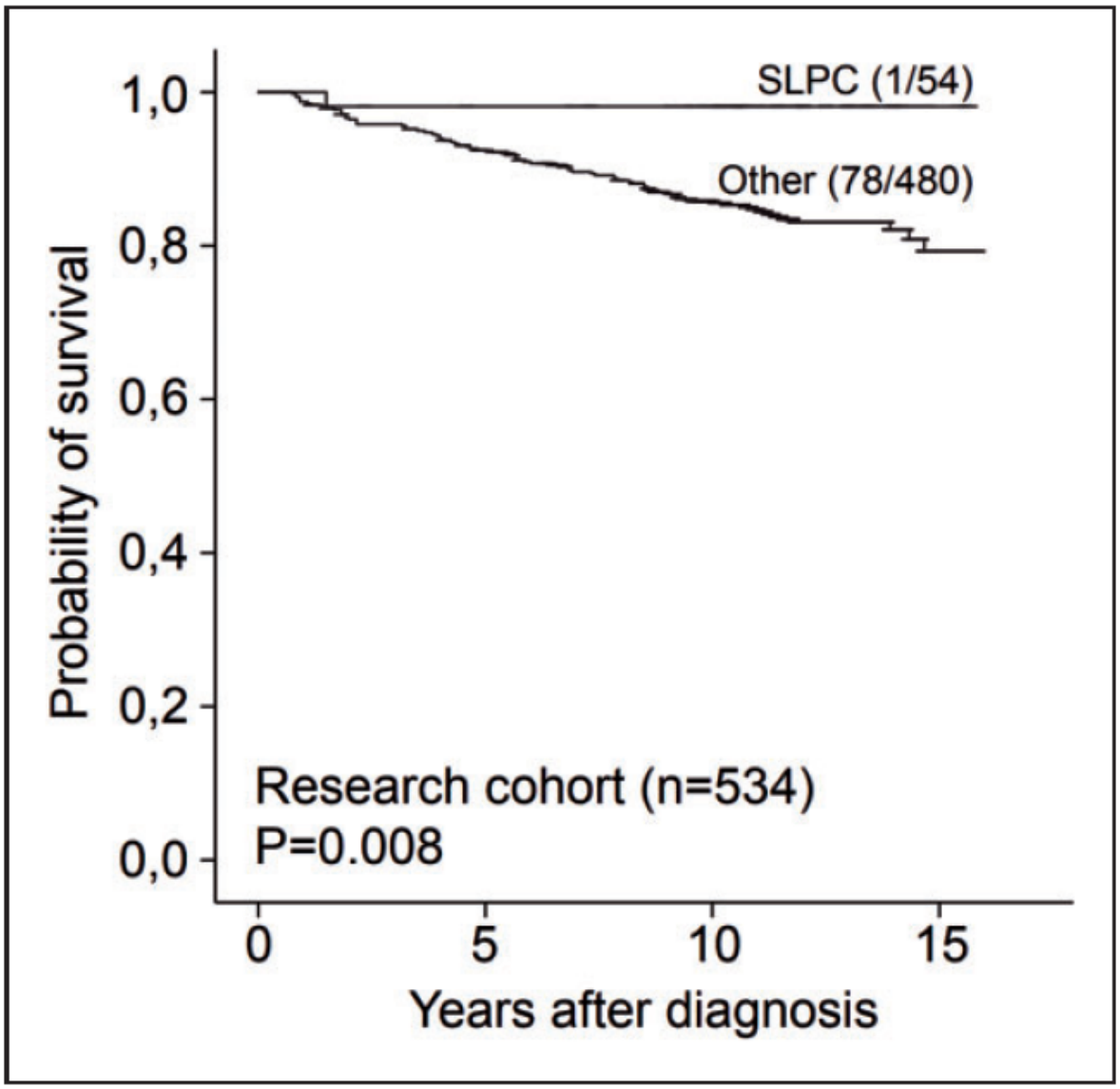
*Calculated using the Wilson score interval.

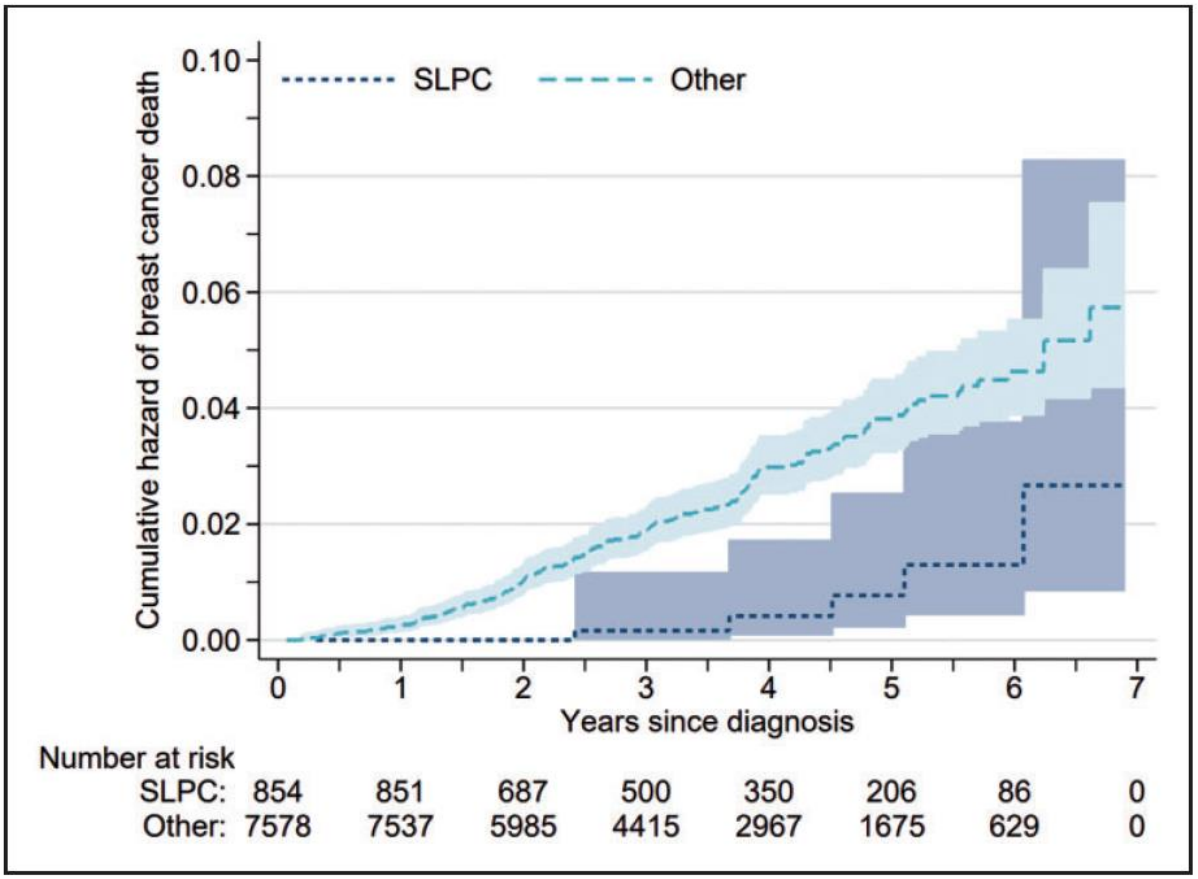
** Human epidermal growth factor receptor 2.

FIGURE LEGENDS

Figure 1: Kaplan-Meier estimates of breast-cancer specific survival using the log-rank test for small low proliferation cancers (SLPC) and all other invasive cancers among women targeted for screening in Hordaland, by BreastScreen Norway, during 1996–2003 (cohort I, n=534).

Figure 2: Nelson-Aalen cumulative hazard estimates of breast cancer death for small low proliferation cancers (SLPC) and all other invasive breast cancers among women targeted for screening by BreastScreen Norway during 2011–2016 (cohort II, n = 8433).




SLPC
Other
Cumulative hazard of breast cancer death
0.10
0.08
0.06
0.04
0.02
0.00
0
1
2
3
4
5
6
7
Years since diagnosis
Number at risk
SLPC: 854 851 687 500 350 206 86 0
Other: 7578 7537 5985 4415 2967 1675 629 0