




# Risk of Breast Cancer by Prior Screening Results Among Women Participating in BreastScreen Norway

Marie Lilleborge, PhD <sup>1</sup>; Ragnhild S. Falk, PhD<sup>2</sup>; Hege Russnes, MD, PhD<sup>3</sup>; Torill Sauer, MD, PhD<sup>4,5</sup>; Giske Ursin, MD, PhD<sup>1,6,7</sup>; and Solveig Hofvind, PhD<sup>1,8</sup>

**BACKGROUND:** A premalignant lesion in the breast is associated with an increased risk of breast cancer. The aim of this article was to identify women with an increased risk of breast cancer based on prior screening results (PSRs). **METHODS:** This registry-based cohort study followed women who participated in the organized breast cancer screening program in Norway, BreastScreen Norway, in 1995-2016. Incidence rates and incidence rate ratios were used to estimate absolute and relative risks of breast cancer associated with PSRs. Histopathological characteristics of subsequent breast cancers were presented by PSRs. **RESULTS:** This study included 762,643 women with up to 21 years of follow-up. In comparison with negatively screened women, increased incidence rate ratios of 1.8, 2.0, 2.9, and 3.8 were observed after negative additional imaging, for benign biopsy, for hyperplasia with atypia, and for carcinoma in situ, respectively. Subsequent breast cancers did not differ in tumor diameter or histological grade, whereas the proportion of lymph node-positive breast cancers decreased as the presumed malignancy potential of PSRs increased. **CONCLUSIONS:** The risk of subsequent breast cancer increased with the presumed malignancy potential of PSRs, whereas the tumor characteristics of subsequent cancers did not differ except for the lymph node status. Women with screen-detected benign lesions or hyperplasia with atypia might benefit from more frequent screening. *Cancer* 2019;125:3330-3337. © 2019 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

**KEYWORDS:** breast cancer, breast carcinoma in situ, breast diseases, early detection of cancer, mammography, risk assessment, screening.

## INTRODUCTION

Mammographic screening is aimed at reducing the mortality from breast cancer by detecting tumors at an early stage. However, the increased breast cancer incidence, particularly after the implementation of screening programs, has raised questions about overdiagnosis and subsequent overtreatment.<sup>1,2</sup> *Overdiagnosis* refers to the detection of slowly growing or dormant tumors that would not have presented clinically or symptomatically during a woman's lifetime.<sup>3</sup> There are currently no distinct criteria or sets of markers to differentiate between nonprogressive and progressive lesions. It is assumed that some of the women diagnosed with ductal carcinoma in situ (DCIS) or breast cancer are overtreated, and this is considered a substantial harm of mammographic screening.

Studies have shown that women with a prior diagnosis of a premalignant breast lesion have an increased risk of breast cancer.<sup>4-8</sup> Studies, including data from Norway, have recently confirmed these findings in women participating in organized screening.<sup>9-12</sup> However, to our knowledge, no studies have analyzed long-term risk estimates of subsequent breast cancer among women who have been screened negative and among women with benign and premalignant lesions in the same population during the same period. In our study, the phrase *screened negative* should not be confused with the collective term *normal screen* because women with negative recalls resolved after additional imaging are analyzed separately. Furthermore, the histopathological characteristics of the subsequent breast cancers are compared by the same categories of prior screening results (PSRs). Our study will form the basis of several Norwegian multidisciplinary studies of premalignant lesions and their characteristics related to progression.

**Corresponding author:** Marie Lilleborge, PhD, Cancer Registry of Norway, Oslo University Hospital, Post Box 5313 Majorstuen, 0304 Oslo, Norway; marie.lilleborge@krefregisteret.no

<sup>1</sup>Cancer Registry of Norway, Oslo University Hospital, Oslo, Norway; <sup>2</sup>Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway; <sup>3</sup>Institute for Cancer Research, Oslo University Hospital, Oslo, Norway; <sup>4</sup>Department of Pathology, Akershus University Hospital, Lorenskog, Norway; <sup>5</sup>Institute of Clinical Medicine, University of Oslo, Lorenskog, Norway; <sup>6</sup>Institute for Basic Medical Sciences, University of Oslo, Oslo, Norway; <sup>7</sup>Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; <sup>8</sup>Department of Life Sciences and Health, Oslo Metropolitan University, Oslo, Norway

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Information about the results of screening and recalls, including the histological types of all premalignant lesions, has been collected for all participants in BreastScreen Norway since the program started in 1995.<sup>13</sup> In addition, the Cancer Registry Regulation ensures the reporting of all cancer cases to the Cancer Registry of Norway.<sup>14</sup> This allows us to follow a screened woman for breast cancer regardless of her screening adherence and eventual moves from one county to another. The aim of this study was to estimate the long-term risk of breast cancer by PSRs among women participating in BreastScreen Norway.

## MATERIALS AND METHODS

BreastScreen Norway is administered by the Cancer Registry of Norway and has been described in detail elsewhere.<sup>13</sup> In short, this population-based screening program started in 1995 and became nationwide by 2005. The program serves approximately 650,000 women, who are offered 2-view digital mammographic screening every 2 years. The program targets women born in birth cohorts corresponding to the ages of 50 to 69 years at the start-up of the screening rounds. The participation rate for each screening round is approximately 75%, whereas 84% of invited women attended at least once during the study period (1995-2016). The program includes independent double reading, which means that 2 radiologists independently read and assign a numerical score of 1 to 5 to the screening mammograms of the left and right breasts to indicate the level of suspicion for malignancy. If one radiologist or both radiologists indicate suspicion of a benign or malignant lesion, a consensus or arbitration meeting is used to determine whether to call the woman back for further assessment (recall) because of the mammographic findings. Approximately 3% to 4% are recalled; the recall includes additional imaging (mammography, ultrasound, and magnetic resonance imaging) with or without needle biopsy. Needle biopsy is performed in approximately 40% of recalled women, and approximately 50% of the women who undergo biopsy are diagnosed with DCIS or breast cancer.<sup>13</sup> In this study, the term *breast cancer* refers to invasive breast cancer (*International Classification of Diseases, Tenth Revision* code C50).<sup>15</sup>

The results of screening and radiological procedures for assessments were reported electronically. Pathology reports describing the results of needle biopsies (cytological or histological) were sent to the Cancer Registry of Norway electronically or on paper forms. We received information about benign outcomes, hyperplasia with atypia, and lobular carcinoma in situ as a result of screening, whereas information about DCIS and breast cancer was available regardless of the detection mode. If several

forms were used for reporting the histological type of the same lesion within a period of 6 months (the diagnosis period), we used the report describing the most aberrant type of lesion. We received information about histopathological tumor characteristics (tumor diameter, histological grade, lymph node status, progesterone receptor status, and estrogen receptor status) and the treatment of breast cancer from the Cancer Registry.

BreastScreen Norway used Systematized Nomenclature of Medicine codes to classify benign and premalignant lesions, whereas malignant cases were reported according to the *International Classification of Diseases, Tenth Revision*.

The detection mode was defined as screen-detected (breast cancer diagnosed after a recall), interval breast cancer (breast cancer diagnosed within 24 months of a negative screen or within 6-24 months after a false-positive screening result), or detected outside the screening program (breast cancer diagnosed more than 24 months after the most recent previous screen).

The regional ethics committee approved the study, which was based on indirectly identifiable data about women who had attended at least 1 screening examination in BreastScreen Norway during the study period (1995-2016).

### Study Population

We received data for approximately 767,572 women with no prior diagnosis of DCIS or breast cancer before their first attendance in BreastScreen Norway and with at least 6 months of follow-up after their first screening from the Cancer Registry of Norway. We excluded 4929 women on the basis of the results of their first screening (4153 with breast cancer, 749 with inconclusive histology results, and 27 with another type of cancer located in the breast; see Supporting Table 1 for a list of corresponding Systematized Nomenclature of Medicine morphology codes), and this resulted in a study population of 762,643 women and 3,170,081 screening examinations.

We classified the follow-up time of each woman in 5 groups according to her PSR. Depending on her screening history, 1 woman could contribute with woman-years in several PSR groups during the study period (Table 1).

The order of the groups (Table 1), as indicated by their numbering, refers to the increasing presumed malignancy potential.

### Statistical Analysis

We followed the women longitudinally from first attendance in BreastScreen Norway until the diagnosis

**TABLE 1.** A Screened Woman Contributes Woman-Years to 1 or More Prior Screening Result Groups According to Her Screening History

	Contribution of Woman-Years per Screened Woman
1. Screened negative	Followed from the first negative screen until the first positive screen and/or the diagnosis of carcinoma in situ (LCIS or DCIS) or breast cancer
2. Negative after additional imaging	Followed from the first screen resulting in a recall for further assessment, which was concluded to be normal after additional imaging only, until the diagnosis of carcinoma in situ or breast cancer
3. Benign	Followed from the first screen resulting in needle biopsy with a benign result <sup>a</sup> until the diagnosis of carcinoma in situ or breast cancer
4. Atypia	Followed from the first screen resulting in needle biopsy with hyperplasia with atypia <sup>a</sup> until the diagnosis of carcinoma in situ or breast cancer or the end of follow-up
5. In situ	Followed from the first screen resulting in a diagnosis of carcinoma in situ <sup>a</sup> until the diagnosis of breast cancer

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ. The numbering of the groups follows the direction of increasing presumed malignancy potential.

<sup>a</sup>For a complete list of Systematized Nomenclature of Medicine morphology codes, see Supporting Table 1.

of breast cancer independently of the detection mode. Women were censored at the end of follow-up, that is, at the end of 2016, at the age of 80 years, or at the diagnosis of another type of cancer located in the breast (for the morphology codes, see Supporting Table 1).

We used individual-level data on attendance in the program to assign each woman's follow-up time to PSR groups (Fig. 1). We applied a 6-month diagnosis period, from which the most aberrant histology was used for analysis. The first 6 months after a positive screen resulting in a PSR group move was contributed only to the prior group as a result of the diagnosis period. Similarly, we excluded the initial 6 months after each woman's first screen. Women could contribute follow-up time to only 1 PSR group, as indicated by the result of their first screen, from the first screen until breast cancer or the end of follow-up (women 1-3 in Fig. 1) if no move occurred. Women whose first screen was negative and who later experienced a positive screening result contributed follow-up time to the group of negatively screened women from the first (negative) screen to the first positive screen, and follow-up time after the positive screen was contributed to the corresponding PSR group (women 4-8 in Fig. 1). A woman with a history of more than 1 positive screen moved to a different PSR group if the result of the subsequent positive screen had a higher presumed malignancy potential than the prior one (women 7-10 in Fig. 1). More specifically, woman 7 in Figure 1

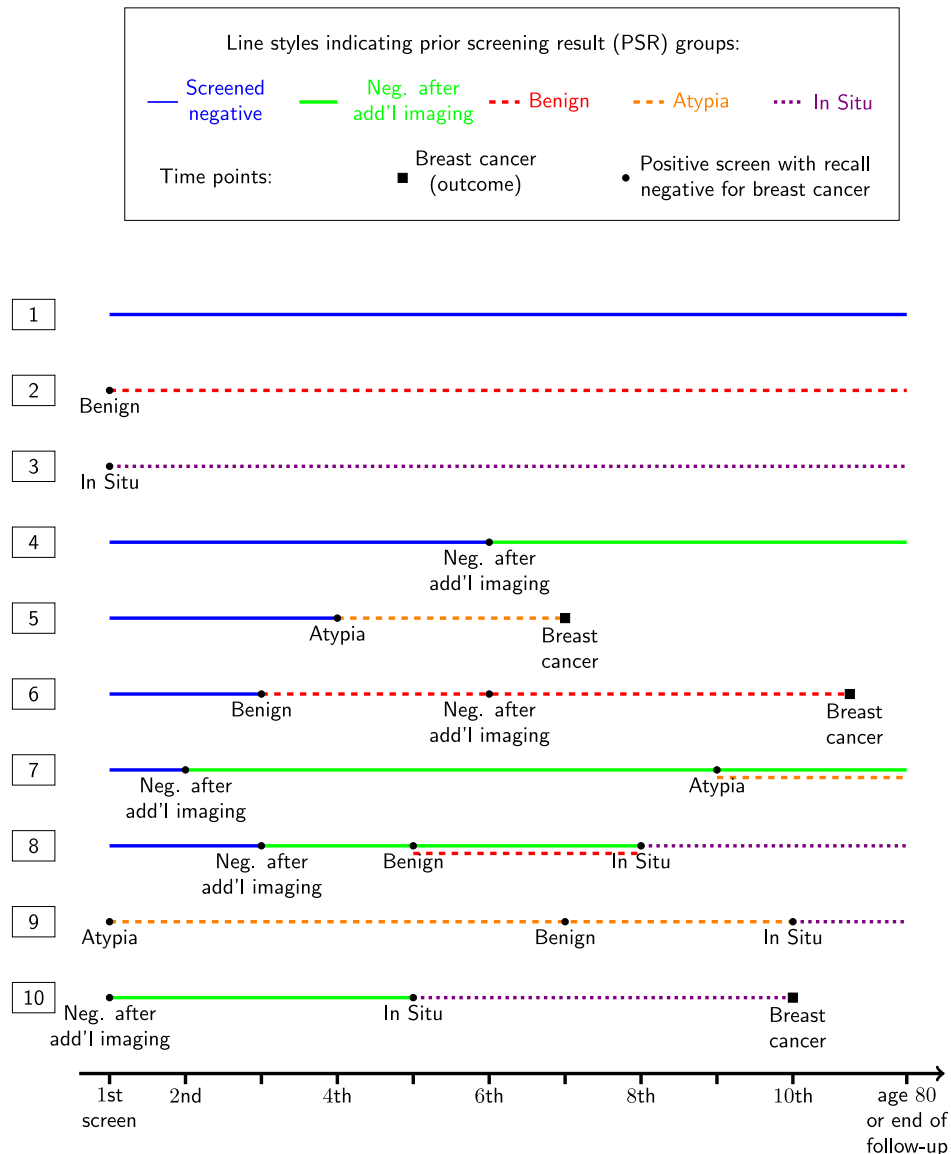
contributed follow-up time to the negative-after-additional-imaging PSR group from her second screen until the end of follow-up and, in addition, to the atypia PSR group (a higher level) from the ninth screen until the end of follow-up. Because of a likely change in risk associated with the treatment of the subsequent in situ lesion, woman 9 in Figure 1 contributed follow-up time to the atypia PSR group from the 1st screen until the in situ diagnosis at the 10th screen and to the in situ PSR group from the 10th screen until the end of follow-up. The same principle applies to woman 8 and woman 10 at the in situ diagnosis. As for our data, only 0.1% of the women contributed overlapping follow-up time to more than 1 PSR group (Supporting Table 2 and Fig. 1 [women 7 and 8]).

Note that the contribution of follow-up time to PSR groups corresponds simply to risks calculated in coherent, independent analyses of each positive-screen PSR group. For a woman with a PSR group move, censoring her contribution of follow-up to her first group at the group move would mean censoring at an event correlated with the outcome. Therefore, we have not censored a woman's contribution of follow-up to PSR groups 2 and 3 at subsequent group moves except for moves to PSR group 5 due to treatment of the in situ lesion. Because statistical comparisons of women who screened negative with each of the other PSR groups required independent follow-up contributions to the groups compared, a woman contributed follow-up time to the group that screened negative only while she had no history of positive screening results. This made the group an identical reference group for each of the other PSR groups. Furthermore, this censoring for a minor proportion of women who screened negative did not affect the estimated risk of breast cancer for the group.

Descriptive statistics are presented as frequencies and proportions and as means and standard deviations.

The absolute risks of breast cancer were presented as incidence rates (IRs) per 1000 woman-years with 95% confidence intervals (CIs) stratified by PSR groups. The age-standardized IR was calculated according to the age distribution of women who screened negative in 5-year intervals. The relative risk of breast cancer was presented as the incidence rate ratio (IRR) by PSR groups and was estimated with Poisson regressions, with women who screened negative used as the reference for each group. The IRRs were adjusted for age as a categorical variable of 5-year intervals.

We used a nonparametric test for trend across ordered groups (an extension of the Wilcoxon rank-sum test) to test for trends in histopathological tumor characteristics of the subsequent breast cancers by PSR group.



**Figure 1.** Inclusion in prior screening result groups is shown for 10 examples of screened women. Neg. after add'l imaging indicates negative after additional imaging.

Among the women with subsequent breast cancer, the same nonparametric test for trend was applied to the detection mode of the subsequent breast cancer (screen-detected vs not screen-detected), the age at diagnosis of a prior premalignant lesion or first positive screen, the age at diagnosis of subsequent breast cancer, and the follow-up time within the PSR group before the detection of the subsequent breast cancer by PSR group.

Several sensitivity analyses were performed. Analyses of absolute and relative risks as well as the comparison of histopathological characteristics of subsequent breast cancer were repeated in a setting where women

contributed follow-up time only to the current PSR group (ie, censoring of the contribution of follow-up time to the prior PSR group at the PSR group change). Now, each outcome was associated with a unique PSR group; however, this introduced censoring at an event correlated with an increased risk of the outcome.

We repeated analyses of absolute and relative risks with a diagnosis period of 1 year (increased from 6 months) to explore the sensitivity to tumors potentially missed at screening.

To explore the sensitivity of the regression method, the relative risk of breast cancer for each PSR group was

re-estimated via Cox regression with hazard ratios adjusted for age as a continuous variable (with the linearity assumption verified). To evaluate the possibility of bias due to heterogeneity in the reference group with respect to the age at first screening, we repeatedly applied Cox regression to compare women entering each positive-screen PSR group and in each age interval (50-54, 55-59, 60-64, or 65-69 years) with all women who screened negative up to and including the same age interval (regardless of the age at first screening).

We considered a 2-sided *P* value less than .05 to be statistically significant. Data preparations and analyses were performed with Stata (version 15; StataCorp, College Station, Texas).

## RESULTS

We followed 762,643 women who underwent 3,170,081 screening examinations from 1995 through 2016; 3,084,910 (97%) were negative, and 85,171 (3%) were positive and included a recall. In total, 19,837 benign cases, 1568 atypia cases, and 3659 in situ lesions were diagnosed, and 21,015 women were diagnosed with breast cancer independently of the detection mode (Table 2 and Supporting Table 3).

A total of 17,816 women were diagnosed with breast cancer among 724,547 women with only negative prior screens (IR, 2.4/1000 woman-years; 95% CI, 2.4-2.5/1000 woman-years; Table 3). The absolute risk of breast cancer increased by PSR group: the age-standardized IR was 4.4/1000 woman-years (95% CI, 4.3-4.5/1000 woman-years) after a prior screening examination that was concluded to be negative after additional imaging, 4.7/1000 woman-years (95% CI, 4.5-5.0/1000 woman-years) after a recall with benign biopsy, 6.9/1000 woman-years (95% CI, 5.9-7.9/1000 woman-years) after atypia, and 9.5/1000 woman-years (95% CI, 8.7-10.4/1000 woman-years) after in situ. In comparison with women who screened negative the relative risks of breast cancer (estimated as age-adjusted IRRs) were 1.8 (95% CI, 1.8-1.9) after negative additional imaging, 2.0 (95% CI, 1.9-2.1) after benign biopsy, 2.9 (95% CI, 2.5-3.3) after atypia, and 3.8 (95% CI, 3.5-4.2) after in situ.

We next examined characteristics of subsequent breast cancers by PSR group (Table 4). Although tumors were remarkably similar in diameter and histological grade across PSR groups, we noted a trend in the lymph node status. Breast cancers in negatively screened women were more likely to be lymph node-positive, and there

**TABLE 2.** Age at First Screening and Number of Screening Examinations per Woman Within the Study Population

	Women	
	No.	%
Age at first screening per woman		
<55 y	488,457	64.0
55-59 y	118,997	15.6
60-64 y	84,513	11.1
>64 y	70,676	9.3
No. of screening examinations per woman		
1	131,063	17.2
2	116,430	15.2
3	98,321	12.9
4	90,854	11.9
5	86,144	11.3
6	84,711	11.1
7	76,163	10.0
8	45,623	6.0
9	22,740	3.0
≥10	10,594	1.4
Contribution of follow-up time for each prior screening result group <sup>a</sup>		
Screened negative	724,547	94.9
Negative after additional imaging	55,621	7.3
Benign	19,837	2.6
Atypia	1568	0.2
In situ	3659	0.5
Outcome		
Subsequent breast cancer	21,015	2.8

There were 762,643 women and 3,107,081 screening examinations in BreastScreen Norway in 1995-2016 (for more details, see Supporting Table 3). The contribution of follow-up time to the prior screening result groups is summarized by the number of women followed within each group.

<sup>a</sup>Some women may have been included in several groups.

was a trend of the proportion of lymph node-positive cancers decreasing as the presumed malignancy potential of the prior PSR group increased. The distributions of the estrogen and progesterone receptor status did not differ statistically across PSR groups.

The detection mode of subsequent breast cancers showed an association with PSR groups. A decreasing proportion of screen-detected breast cancers was observed with an increasing presumed malignancy potential of PSRs (Table 5). Among women with subsequent breast cancer, the age at the detection of a prior premalignant lesion or the first positive screen (the start of follow-up in the PSR group among women with outcomes) and the age at the detection of subsequent breast cancer were positively associated with the presumed malignancy potential of the PSR group. The time from the detection of a premalignant lesion or the first negative screen (the start of follow-up) to breast cancer was inversely associated with the presumed malignancy potential of the PSR group. However, because a woman could move only to a higher level PSR group,

**TABLE 3.** Crude and Age-Standardized IRs and IRRs of Breast Cancer With 95% CIs According to Prior Screening Result Groups Among Participants in BreastScreen Norway, 1995-2016

	Women, No.	Woman-Years	Follow-Up Time, Median (IQR), y	Breast Cancer, No.	IR per 1000 Woman-Years (95% CI)	Age-Standardized IR per 1000 Woman-Years (95% CI) <sup>a</sup>	IRR (95% CI) <sup>b</sup>
Screened negative	724,547	7,378,483	11.2 (5.6-14.2)	17,816	2.4 (2.4-2.5)	2.4 (2.4-2.5)	Reference
Negative after additional imaging	55,621	462,390	8.2 (4.2-12.1)	2071	4.5 (4.3-4.7)	4.4 (4.3-4.5)	1.8 (1.8-1.9)
Benign	19,837	173,891	8.7 (4.2-12.7)	834	4.8 (4.5-5.1)	4.7 (4.5-5.0)	2.0 (1.9-2.1)
Atypia	1568	12,722	7.7 (4.2-11.8)	89	7.0 (5.7-8.6)	6.9 (5.9-7.9)	2.9 (2.5-3.3)
In situ	3659	26,811	6.7 (3.2-10.8)	253	9.4 (8.3-10.7)	9.5 (8.7-10.4)	3.8 (3.5-4.2)

Abbreviations: CI, confidence interval; IQR, interquartile range (25th-75th percentile range); IR, incidence rate; IRR, incidence rate ratio.

<sup>a</sup>The IRs were age-standardized to the age distribution of the women screening negative in 5-year intervals.

<sup>b</sup>The age-adjusted IRRs were calculated by Poisson regression with age as a categorical variable in 5-year intervals with respect to the prior screening result group that screened negative.

**TABLE 4.** Histopathological Tumor Characteristics of Subsequent Breast Cancers by Prior Screening Result Groups

		Screened Negative		Negative After Additional Imaging		Benign		Atypia		In Situ		<i>P</i> <sup>a</sup>
		No.	%	No.	%	No.	%	No.	%	No.	%	
Tumor diameter	Mean (SD), mm	15,443	17.4 (11.8)	1860	17.6 (12.1)	729	17.6 (12.0)	86	17.1 (12.9)	164	15.9 (12.1)	.16
	≤20 mm	11,490	70.1	1322	69.0	531	70.6	61	70.9	148	74.0	.56
	>20 mm	4912	29.9	594	31.0	221	29.4	25	29.1	52	26.0	
	Unknown	1414		155		82		3		53		
Histological grade	1	4247	25.0	515	25.9	203	25.3	23	26.7	52	24.3	.29
	2	8265	48.6	952	47.9	387	48.3	48	55.8	110	51.4	
	3	4500	26.5	519	26.1	211	26.3	15	17.4	52	24.3	
	Unknown	804		85		33		3		39		
Lymph node status	Positive	4943	29.1	546	27.5	204	25.8	24	28.6	47	20.9	.001
	Negative	12,054	70.9	1438	72.5	588	74.2	60	71.4	178	79.1	
	Unknown	819		87		42		5		28		
Progesterone receptor status	Positive	10,585	66.8	1308	68.4	523	69.5	57	68.7	116	64.1	.24
	Negative	5272	33.2	604	31.6	229	30.5	26	31.3	65	35.9	
	Unknown	1959		159		82		6		72		
Estrogen receptor status	Positive	13,675	85.5	1680	87.3	656	86.2	70	84.3	157	86.3	.22
	Negative	2313	14.5	244	12.7	105	13.8	13	15.7	25	13.7	
	Unknown	1828		147		73		6		71		

The results are presented as frequencies and proportions if not otherwise specified.

<sup>a</sup>A nonparametric test for trend across ordered groups (an extension of the Wilcoxon rank-sum test) was used. For each *P* value calculation, observations with unknown values were excluded.

each woman with a group move would by definition participate at an older age in the higher level group in comparison with the lower level group (and at the same age with subsequent breast cancer in both groups). That is, she would, by design, contribute to a trend of increasing age at inclusion in a PSR group.

Several sensitivity analyses supported our main results. The results showed no sensitivity to the possible heterogeneity in the reference group with respect to the age at first screening (Supporting Table 4) or a longer diagnosis period to exclude potential tumors missed at screening (Supporting Table 5).

## DISCUSSION

We observed an increased long-term risk of breast cancer among women with a prior recall interpreted as negative and among women recalled and diagnosed with a pre-malignant lesion in comparison with those who screened negative. The risk was 2-fold after negative additional imaging or a benign biopsy, 3-fold after the detection of atypia, and 4-fold after the detection of in situ in comparison with after a negative screening result.

Breast cancer is a complex disease, and its prognosis is determined by several predictors (eg, histopathological tumor characteristics).<sup>16</sup> It could potentially be overly simplistic to focus on the risk of breast cancer by PSR

**TABLE 5.** Age, Detection Mode, and Time to Breast Cancer Among Women With Subsequent Breast Cancer by Prior Screening Result Groups

	Screened Negative	Negative After Additional Imaging	Benign	Atypia	In Situ	<i>P</i> <sup>a</sup>
Age at prior premalignant lesion or first negative screen, mean (SD), y	55.9 (5.4)	57.6 (5.5)	57.3 (5.4)	58.2 (5.3)	58.9 (5.9)	<.001
Age at subsequent breast cancer, mean (SD), y	63.4 (7.0)	63.7 (6.2)	63.8 (6.2)	64.0 (6.5)	64.3 (6.6)	<.001
Detection mode of breast cancer, No. (%)						
Screen-detected	9543 (53.6)	1109 (53.5)	425 (51.0)	39 (43.8)	27 (10.7)	<.001
Not screen-detected	8273 (46.4)	962 (46.5)	409 (49.0)	50 (56.2)	226 (89.3)	
Time to breast cancer, mean (SD), y <sup>b</sup>	7.0 (4.4)	5.7 (4.1)	6.1 (4.3)	5.4 (3.8)	5.1 (3.5)	<.001

<sup>a</sup>A nonparametric test for trend across ordered groups (an extension of the Wilcoxon rank-sum test) was used. For each *P* value calculation, observations with unknown values were excluded.

<sup>b</sup>Number of years from the detection of the premalignant lesion or the first negative screen until the diagnosis of breast cancer.

group without consideration of prognostic and predictive tumor characteristics of the subsequent breast cancers by prior PSR groups.

A lower proportion of breast cancers after in situ were lymph node–positive in comparison with breast cancers after the other PSR groups. This might be related not only to the treatment received for the in situ lesion but also to the close follow-up of these women after treatment and thus the increased possibilities of early detection of cancer. Except for the lymph node status, the characteristics of the subsequent breast cancers did not differ statistically significant by prior PSR group. We identified a higher proportion of subsequent breast cancers detected outside the program among women with in situ in comparison with the other PSR groups. This was possibly due to the women's older age at inclusion and the control regimen for those diagnosed with DCIS. We observed a statistically significant increase by PSR group both in the age at diagnosis of the prior premalignant lesion and in the age at diagnosis of the subsequent breast cancer. However, the mean age at the subsequent breast cancer was practically 64 years for all PSR groups, whereas the mean age at the diagnosis of prior premalignant lesions ranged from approximately 57 years for the negative-after-additional-imaging and benign-biopsy groups to approximately 59 years for the in situ group. This might be related to the design of the study, where a woman could move from a lower level PSR group to a higher level PSR one and contribute follow-up time to more than 1 group.

An increased risk of breast cancer for women with a prior premalignant lesion could indicate a biological predisposition for being more likely to develop the disease. An increased risk of developing breast cancer could be due to the progression of a premalignant lesion into a malignant lesion or to an overall increased biological susceptibility for developing a malignant breast lesion, regardless of the location in the breast or breasts.<sup>11</sup> However, there might

also be missed cases both radiologically<sup>12,17</sup> and histopathologically.<sup>18</sup> Positioning issues and mammographic density could introduce masking effects. Furthermore, if the mammograms show a suspicious lesion actually containing malignant histology, the diagnostic biopsy (sample) might be free from malignant cells while the histology of the sample confirms the mammographic finding.

As part of the follow-up procedure after an in situ diagnosis, Norwegian women undergo mammography annually and see their surgeon 1, 2, 5, and 10 years after treatment of the disease is finished.<sup>19</sup> This ensures the detection of a relapse or new breast cancer at an early stage. It has been suggested that women with a history of benign biopsies and also women recalled without a biopsy could benefit from more frequent mammography or more intensive screening.<sup>11,20</sup> Identification of a suspicious premalignant lesion allows monitoring to look for changes indicating active progression. However, intensified screening could introduce negative consequences to the women as well as financial costs for the health care system. Although some women with a prior diagnosis of a premalignant lesion could experience short-term or lasting stress related to intensified screening, other women could experience greater confidence and reassurance, especially with comprehensive education about the purpose of heightened surveillance. Our data indicated an increased risk of developing breast cancer for women with a prior premalignant lesion, whereas our results do not indicate a particularly higher risk for worse tumor characteristics at the time of diagnosis for these women. A proposal for stratified screening frequency should be evaluated in analyses including other perspectives to address the balance between benefits and harms of more frequent screening and the use of other modalities for these women. The future success of stratified screening depends on, among other things, cost-effectiveness, perceptions of policy changes, implications for attendance, available resources, and implementation.<sup>21,22</sup>

In this study, we did not consider in which breast or in which quadrant of the breast the lesions were detected because the aim of our study was to estimate the risk of a woman experiencing a subsequent diagnosis of breast cancer according to her previous screening results, regardless of location. For a woman attending breast cancer screening, both breasts are examined at each screening. Thus, the optimal screening regimen depends on each woman's overall risk of breast cancer. A previous study has suggested an increased risk of breast cancer indicated by prior benign breast disease in other locations of the same breast and in the other breast.<sup>23</sup>

The strengths of this study included the long follow-up within the cohort (1995-2016) and a large sample size (21,015 breast cancers were diagnosed within the follow-up of 762,643 women). Furthermore, all cancer cases are reported by law to the Cancer Registry of Norway,<sup>14</sup> and this ensures a complete capture of cancer cases. Several sensitivity analyses supported our main results and demonstrated the consistency of the results across models.

In conclusion, we observed an increased long-term risk of breast cancer among women with a prior pre-malignant lesion diagnosed as a result of their participation in BreastScreen Norway. The observed risk increased with the presumed malignancy potential of the lesion or lesions. Further knowledge about this risk and the benefits and harms related to stratified screening is needed.

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## CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

## AUTHOR CONTRIBUTIONS

**Marie Lilleborge:** Conceptualization, data curation, formal analysis, visualization, writing—original draft, and writing—review and editing. **Ragnhild S. Falk:** Conceptualization and writing—review and editing. **Hege Russnes:** Conceptualization and writing—review and editing. **Torill Sauer:** Conceptualization and writing—review and editing. **Giske Ursin:** Conceptualization and writing—review and editing. **Solveig Hofvind:** Conceptualization and writing—review and editing.

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