Radiology

Interval Breast Cancer Rates and Histopathologic Tumor Characteristics after False-Positive Findings at Mammography in a Population-based Screening Program[1]

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Purpose: To compare rates and tumor characteristics of interval breast cancers (IBCs) detected after a negative versus false-positive screening among women participating in the Norwegian Breast Cancer Screening Program.

Materials and Methods: The Cancer Registry Regulation approved this retrospective study. Information about 423 445 women aged 49–71 years who underwent 789 481 full-field digital mammographic screening examinations during 2004–2012 was extracted from the Cancer Registry of Norway. Rates and odds ratios of IBC among women with a negative (the reference group) versus a false-positive screening were estimated by using logistic regression models adjusted for age at diagnosis and county of residence.

Results: A total of 1302 IBCs were diagnosed after 789 481 screening examinations, of which 7.0% (91 of 1302) were detected among women with a false-positive screening as the most recent breast imaging examination before detection. By using negative screening as the reference, adjusted odds ratios of IBCs were 3.3 (95% confidence interval [CI]: 2.6, 4.2) and 2.8 (95% CI: 1.8, 4.4) for women with a false-positive screening without and with needle biopsy, respectively. Women with a previous negative screening had a significantly lower proportion of tumors that were 10 mm or less (14.3% [150 of 1049] vs 50.0% [seven of 14], respectively; $P < .01$) and grade I tumors (13.2% [147 of 1114] vs 42.9% [six of 14]; $P < .01$), but a higher proportion of cases with lymph nodes positive for cancer (40.9% [442 of 1080] vs 13.3% [two of 15], respectively; $P = .03$) compared with women with a previous false-positive screening with benign biopsy. A retrospective review of the screening mammographic examinations identified 42.9% (39 of 91) of the false-positive cases to be the same lesion as the IBC.

Conclusion: By using a negative screening as the reference, a false-positive screening examination increased the risk of an IBC threefold. The tumor characteristics of IBC after a negative screening were less favorable compared with those detected after a previous false-positive screening.

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Interval breast cancers (IBCs) are considered a shortcoming in mammographic screening because of unfavorable tumor characteristics compared with screening-detected cancers (1–6). IBCs, thus, represent a challenge since they both decrease the sensitivity of screening programs and contribute substantially to breast cancer mortality in the screened population. Moreover, 3%–35% of interval cancer cases may actually represent findings that were detectable but overlooked at the time of screening, further decreasing women's trust in mammography screening (7–9).

The IBC rate varies substantially between countries and population-based screening programs (9–13). Törnberg et al (13) compared the rates in six European countries with organized, population-based mammographic screening programs and found rates of IBC that ranged from 8.4 to 21.3 per 10 000 screenings. Differences in completion of cancer reporting were suggested as the main reason for the observed variation; different definitions, identification methods, and quantification methods were suggested as additional possible reasons for variable IBC rates (12–14).

In Europe, IBC is usually defined as a primary breast cancer diagnosed in women who had a screening negative for cancer (a negative screening) or negative work-up after abnormal screening, either before the next invitation to screening, or within a time period equal to the screening interval (15). In the United States, an IBC is defined as a breast cancer detected between screening mammographic examinations, with a usual screening interval of 1 year (16,17). Despite different definitions and screening intervals, to our knowledge no studies showed substantial differences in tumor characteristics such as histopathologic type, tumor size, grade, and lymph node involvement for IBCs diagnosed in Europe versus in the United States (12,14,18).

The rate of missed breast cancer in screening is reported to be 20%–30% of both screening-detected cancer and IBC after an informed review of the screening and diagnostic mammographic examinations and all available histopathologic analyses (7–9). Recent studies (19–23) showed an increased risk of subsequent screening-detected breast cancer after a previous false-positive screening. An increased risk of IBC might also be expected after a false-positive screening versus a negative screening. However, few studies have reported data on IBC after a false-positive screening examination, and their subsequent tumor characteristics (22–24). By expecting the same pattern for IBC as for screen-detected cancers, a shorter screening interval may result in detecting cancers at an earlier stage and potentially improve patient outcomes.

In the Norwegian Breast Cancer Screening Program, IBC rates have varied between 16 and 19 per 10 000 screenings after full-field digital mammography was implemented (11). About 70% of IBCs are diagnosed in the 2nd year of the screening interval. Our objective for this study was to compare estimated IBC rates by different definitions and to describe histopathologic characteristics of breast tumors detected in the interval after a previous negative versus a previous false-positive screening in our population-based screening program. We hypothesize that the rate of IBC is lower and the tumor characteristics are favorable when detected after a previous negative versus a false-positive screening.

Advances in Knowledge

- Twenty-four percent (1302 of 5425) of the breast cancers detected in women in a population-based screening program were interval breast cancers (IBCs).
- More than two-thirds of IBCs were diagnosed during the 2nd year of the screening interval at biennial screening.
- By using negative screening as the reference, adjusted odds ratios of IBC were 3.3 (95% confidence interval [CI]: 2.6, 4.2) and 2.8 (95% CI: 1.8, 4.4) for women with a false-positive screening without and with needle biopsy, respectively.
- The proportion of ductal carcinoma in situ was higher (17.6% [16 of 91] vs 5.0% [61 of 1211], respectively), whereas the proportion of invasive ductal carcinoma was lower (60.4% [55 of 91] vs 80.0% [969 of 1211], respectively) for IBCs diagnosed after a false-positive screening versus after a negative screening ($P < .001$ for both).

Implications for Patient Care

- The higher IBC rate after a false-positive screening suggests that women with a false-positive screening may benefit from being offered another mammographic examination within 1 year rather than the usual biennial screening.
- The vast majority of IBCs appeared after a negative screening, and only 7.0% (91 of 1302) appeared after a false-positive screening.
- On the basis of a retrospective review of 91 IBCs initially deemed to be false-positive findings, 42.9% (39 IBCs) were considered to represent the same lesion originally called back from screening.

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Abbreviations:
CI = confidence interval
IBC = interval breast cancer

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Conflicts of interest are listed at the end of this article.

Materials and Methods

This retrospective study was performed on the basis of data from the Norwegian Breast Cancer Screening Program. The program is administered by the Cancer Registry of Norway. The Cancer Registry Regulation gave approval with waiver of informed consent to perform surveillance, quality assurance, and studies on the basis of data collected as a part of invitation to and participation in the program (25).

Study Population and Data Source

The Norwegian Breast Cancer Screening Program is an organized population-based screening program that started as a pilot in four counties in 1996 and expanded nationwide, covering all 19 counties by 2005. The program serves approximately 600 000 women who are personally invited with a stated time and place for biennial mammographic screening. The program targets women born in birth cohorts corresponding to ages 50–69 years. However, the 2-year screening interval results in a real age range between 49 and 71 years at invitation. The participation rate was 75%. Additional details about the program have been described elsewhere (11).

Our study included information about 423 445 women who were screened with full-field digital mammography during calendar years 2004–2012. During this study period, 789 481 screening mammographic examinations (average, 1.9 for each woman) were performed, of which 15.9% (125 453 of 789 481) were prevalent and 84.1% (664 028 of 789 481) were subsequent screening examinations. The study population and cancer cases partly overlap with those used in some other studies from the program (26).

All data used in this study were extracted from databases at the Cancer Registry of Norway, which included information about the procedures related to the screening and all breast cancer cases diagnosed in the country. By law, cancer cases are reported to the Cancer Registry of Norway, with more than 99% of breast cancer data captured (27). We excluded data from one county because of use of digital mammography in a random sample of women between the years 2000 and 2005 and the use of digital breast tomosynthesis in a study setting in 2011 and 2012 (28).

Definition of Measures

The screening program performs independent double reading, which means that all screening mammographic examinations are read by two radiologists and given a score from 1 to 5 by each radiologist. A score of 1 indicates mammographic examinations negative for abnormality; 2, probably benign; 3, intermediate suspicion of malignancy; 4, probably malignant; and 5, a high suspicion of malignancy. If both radiologists give a score of 1, the screening examination is considered negative for malignacy. If one or both radiologists give a score of 2 or higher, a consensus or arbitration (consensus) meeting is used to determine whether to call the woman back for further assessment (recall) or not. About 7% of the examinations are discussed at consensus, whereas 3%–4% of the cases are recalled for further assessment, which includes additional diagnostic mammography and potentially ultrasonography, magnetic resonance imaging (additional imaging), and/or needle biopsy (29). Needle biopsy is performed in about 40% of the recalled women, whereas approximately 50% of the women who undergo biopsy are diagnosed with breast cancer (ductal carcinoma in situ or invasive breast cancer).

A true-negative screening was defined as a negative screening and no IBC diagnosed within the actual screening round. A true-positive screening was defined as a screening resulting in a recall for further assessment because of abnormal findings that led to a histologically proven breast cancer within a fixed period (6 months) after screening. A false-positive screening was defined as a screening leading to a recall for further assessment because of abnormal findings, but the assessment, with or without a needle biopsy, turned out to be negative for cancer within a fixed period (6 months). A false-negative screening or an IBC was defined as breast cancer diagnosed after a negative screening or after false-positive screening, either before the next screening (2 years) or within 2 years after the final screening among women who reach the upper age limit (30). This definition is in accordance with European guidelines (15). However, what constitute an IBC becomes subjective for cases diagnosed after a short interval follow-up ordered against current recommendations. To ensure appropriate comparison of IBC rates on the basis of objective information, we provided so-called technical definitions on the basis of date of screening, the result of the screening and further assessment, and date of diagnosis of the IBC. The three options for a more objective definition of IBC are as follows: *(a)* breast cancer diagnosed after a negative screening or more than 3 months after a false-positive screening and within 2 years after screening; *(b)* breast cancer diagnosed after a negative screening or more than 6 months after a false-positive screening and within 2 years after screening; and *(c)* breast cancer diagnosed after a negative screening or more than 12 months after a false-positive screening and within 2 years after screening. Numbers and rates for the different definitions are shown in Table 1. We used definition *b* for all further analyses in the article.

Some women in Norway might undergo mammography at a private clinic by choice in between the routine screenings obtained as a part of the organized program. However, information about the reason for undergoing additional mammography at private clinics is not available. Some of these women may undergo screening mammography at the private clinic, but their breast cancer is considered IBC according to the definitions previously described. Nevertheless, the completeness of breast cancer in the databases of the Cancer Registry of Norway (27) ensures a complete and valid rate of breast cancer. The unique personal identification number provided to all inhabitants in Norway at birth or when acquiring citizenship in combination with the completeness of cancer reporting make it

Table 1

Rates of Screening-detected Breast Cancers and IBCs

Parameter	Screening-detected Breast Cancer		IBC		No. of IBC/No. of IBC + No. of Screening-detected Breast Cancers (%)
	No. of Cancers	Rate per 10 000 Screenings	No. of Cancers	Rate per 10 000 Screenings	
Definition *a*	4031	51.1 (49.5, 52.6)	1394	17.7 (16.8, 18.7)	25.7 (24.5, 26.9)
Definition *b*	4123	52.2 (50.6, 53.8)	1302	16.6 (15.7, 17.5)	24.0 (22.9, 25.1)
Definition *c*	4155	52.6 (51.0, 54.2)	1270	16.2 (15.3, 17.1)	23.4 (22.3, 24.5)
Definition *d*	4134	52.4 (50.8, 54.0)	1291	16.4 (15.5, 17.3)	23.8 (22.7, 24.9)

Note.—Data in parentheses are 95% CIs. Results are for 789 481 full-field digital mammographic screening examinations performed in 423 445 women in the Norwegian breast cancer screening program, 2004–2012.

possible to identify all breast cancers among women screened.

The women receive an invitation with stated time and place for examination biennially. It means that the scheduled screening interval is aimed to be 2 years (365.3 × 2 = 730.6 days) between the last planned or performed screening examination and a new appointment. However, some women postpone their appointment and appear later, whereas others miss one or two screening rounds. Further, use of mobile units in rural areas urges us to do some modifications of the interval because the bus is in some areas only for a limited time. For this study population, the average and median time between scheduled appointments, as administered by the Cancer Registry, were 735 and 728 days, respectively (range, 180–2834 days). The average and median time between two screening examinations were 747 and 730 days, respectively, including regular and irregular participation patterns (range, 212–3106 days). The average and median time from screening examination to diagnosis of IBC were, respectively, 461 and 484 days (range, 17–731 days) for those screened negative, and 435 and 448 days (range, 185–723 days) for false-positive findings.

We followed women with IBC for 2 years after each screening, and the follow-up period ended December 31, 2014. We included the first diagnosed ductal carcinoma in situ or IBC in the analyses. If bilateral breast cancer was diagnosed, we chose the most malignant tumor based on morphologic subtype, followed by tumor size, grade, and lymph node involvement. Women exited the study population after a diagnosis of breast cancer.

To classify whether the IBC detected after a false-positive screening was the same lesion that caused further assessment, local radiologists at the 16 breast centers were asked to perform a retrospective review of previous screening and diagnostic mammographic examinations. On the basis of the findings, the IBC were classified as the same lesion as the one that caused further assessment, a lesion other than the one that caused further assessment, or classification not possible because previous mammographic examinations were not available for review.

Statistical Analysis

Cancer detection rate was provided as the proportion of breast cancer (ductal carcinoma in situ, invasive, and total) detected among all screened women. The rate of IBC was estimated according to the different definitions described above. We stratified results by time (in months) from screening to diagnosis of IBC.

We estimated rates and odds ratios for IBC by outcome of the screening before the IBC was discovered. We used negative screening as the reference and stratified false-positive findings into those who did and did not undergo needle biopsy. Women who underwent needle biopsy were further stratified into a previous false-positive biopsy of the ipsilateral or contralateral breast. Ipsilateral and contralateral IBC refer to presence in the same or opposite breast as the reason for the recall or biopsy, respectively. The most comprehensive screening result was chosen for each examination on the basis of the following hierarchy: false-positive findings after a needle biopsy, followed by false-positive findings after additional imaging only, and then a negative screening. Women with IBC after a false-positive findings at mammography with biopsy in both breasts were considered ipsilateral and contralateral. We used a generalized estimating equation with robust standard errors to fit a negative binomial regression model for estimating breast cancer rates and the 95% confidence interval (CI). In this study, tumor characteristics included histologic type, tumor size, grade, lymph node involvement, and hormonal receptor status.

We used generalized estimating equations with robust standard errors to account for within-woman correlation when estimating the odds ratio of IBC by adjusting for age, year of screening, and county of residence. We estimated the odds ratio with and without considering the laterality of the false-positive finding and eventual IBC. *P* values were calculated by the test of proportions for categorical variables and the *t* test for the continuous variables. Sensitivity analyses that used various methods, including the generalized estimating equation approach, for all definitions of IBC were performed (Appendix E1 [online]). *P* values less than .05 indicated statistical significance. All data analyses were conducted by using Stata (version 14; Stata Corporation, College Station, Tex).

Results

By using definition *b* as a base-case analysis (breast cancer diagnosed after a negative screening mammographic examination or >6 months after a false-positive screening and within 2 years), 4123 screening-detected cancers (801 ductal carcinoma in situ and 3322 invasive breast cancer) and 1302 (70 ductal

Table 2

IBCs and Ipsilateral and Contralateral IBC in the Norwegian Breast Cancer Screening Program by Previous Screening Outcome

Parameter	No. of Breast Cancers	No. of Screenings	Rate of IBC per 10 000 Screenings	Unadjusted OR	Adjusted OR*
All IBCs	1302	785 358	16.6 (15.7, 17.5)	…	…
After negative screening	1211	766 830	15.8 (14.9, 16.7)	Reference	Reference
After a false-positive screening	91	18 528	49.1 (40.0, 60.3)	…	…
After false-positive screening without needle biopsy	71	13 865	51.2 (40.6, 64.6)	3.3 (2.6, 4.1)	3.3 (2.6, 4.2)
False-positive without needle biopsy		…		…	…
Different lesion than the IBC	23	…	16.6 (11.0, 25.0)	…	…
Same lesion as the IBC	27	…	19.5 (13.4, 28.4)	…	…
Unknown, missing information	21	…	15.2 (9.9, 23.2)	…	…
After false-positive screening with needle biopsy	20	4663	42.9 (27.7, 66.4)	2.7 (1.8, 4.2)	2.8 (1.8, 4.4)
With biopsy in ipsilateral breast	17	…	36.5 (22.7, 58.6)	…	…
Different lesion than the IBC	2	…	4.3 (1.1, 17.1)	…	…
Same lesion as the IBC	12	…	25.7 (14.6, 45.3)	…	…
Unknown, missing information	3	…	6.4 (2.1, 19.9)	…	…
With biopsy in contralateral breast	3	…	6.4 (2.1, 19.9)	…	…

Note.—Data in parentheses are 95% CIs. OR = odds ratio.

* Adjusted for age and year at screening and county of residence; numbers above represent rates under biennial screening (2-year screening interval).

carcinoma in situ and 1232 invasive) IBCs were identified in our study sample (Table 1). The rate of screening-detected cancer was 52.2 (95% CI: 50.6, 53.8) per 10000 screenings and the rate of IBC was 16.6 (95% CI: 15.7, 17.5) per 10000 screeningss (Table 1). IBC represented 24.0% (95% CI: 22.9%, 25.1%) of all breast cancer cases diagnosed in the entire population-based screening program during the study period. The additional cases included as IBC in definition *a* versus *d* (1394 − 1291 = 103) were mainly women who underwent a biopsy as a part of their follow-up assessment and had their final diagnosis 3–6 months after screening.

Among the 1302 women with IBC, 93.0% (1211 of 1302) were diagnosed after a negative screening and 7.0% (91 of 1302) were diagnosed after a false-positive screening (71 women underwent further assessment with additional imaging and 20 women underwent further assessment with additional imaging and a benign needle biopsy) (Table 2). Age did not differ between women diagnosed after a negative versus a false-positive screening (median age, 59.8 years vs 60.5 years, respectively; P = .336), whereas time since previous screening did differ (median, 448 days vs 484 days, respectively; P = .007). The rate of IBC among women with a negative screening was 15.8 (95% CI: 14.9, 16.7) compared with 51.2 (95% CI: 41.8, 63.0) per 10000 screenings for women with a previous false-positive screening without biopsy, and 42.9 (95% CI: 27.7, 66.5) per 10000 screenings for those with a previous false-positive screening with biopsy. By using negative screening as the reference, adjusted odds ratios of IBC were 3.3 (95% CI: 2.6, 4.2) and 2.8 (95% CI: 1.8, 4.4) for women with a false-positive finding without and with biopsy, respectively. Analyses, by using alternative definitions of IBC described in Table 1, did not show statistical significant different odds ratios, except for definition *a* (Appendix E1 [online]).

In the retrospective review of the mammographic examinations of women with a false-positive screening before IBC, the radiologists determined that 42.8% (39 of 91) of the cases corresponded with the original abnormal finding resulting in recall for further assessment, whereas 30.8% (28 of 91) did not. For 26.4% (24 of 91), screening and/or diagnostic mammographic examinations were not available for review (Table 2). We found smaller tumor size (mean size, 14.9 mm vs 17.0 mm, respectively; P = .365) and less lymph node involvement (7.1% vs 27.3%, respectively; P = .035) among the 39 women, which corresponded to the IBCs initially identified but let go after diagnostic evaluation, versus the 42 women who were not identified at previous evaluations or for whom the mammographic examinations were not available for the retrospective review.

The proportion of ductal carcinoma in situ was 5.0% (61 of 1211) for IBC after a negative screening, 15.5% (11 of 71) for IBC diagnosed after a false-positive screening without biopsy (P < .001), and 25.0% (five of 20) for IBC after a false-positive screening with biopsy (P < .001) (Table 3). The proportion of invasive ductal cancers was higher for IBC found after a negative screening (80.0% [969 of 1211]) versus after a false-positive screening without biopsy (60.6% [43 of 71]; P < .01) and after a false-positive screening with biopsy (60.0% [12 of 20]; P = .03].

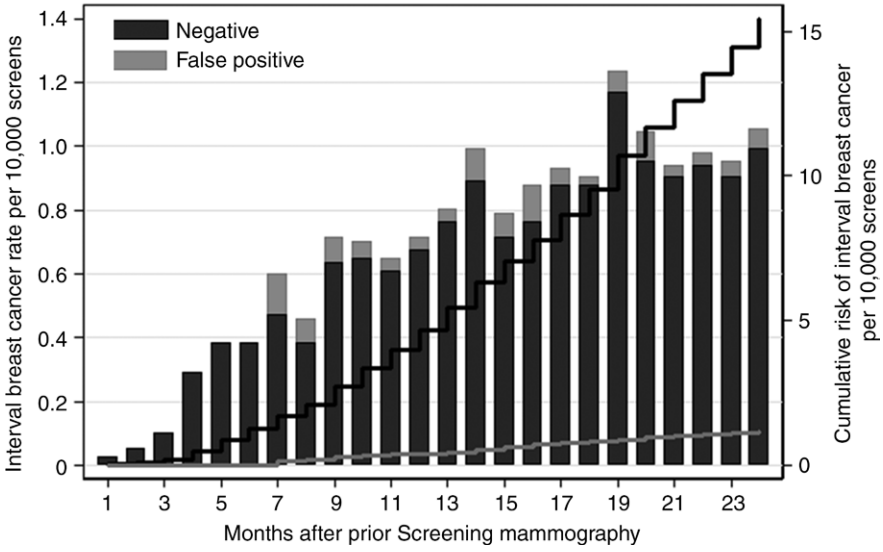
Mean and median tumor size was 22.9 mm and 20.0 mm, respectively, for invasive IBC diagnosed after a negative screening, compared with 17.5 mm and 15.5 mm, respectively, for those

Table 3

Histopathologic Tumor Characteristics of Screening-detected Cancer and IBC Diagnosed among Women Screened in the Norwegian Breast Cancer Screening Program

			IBC Previous Screening Outcome					IBC		
Parameter	All SDC	All IBC	Negative	All FP Findings	FP Findings without Biopsy	FP Findings with Biopsy	*P* Value, All SDC vs All FP Findings	*P* Value, FP Findings vs Negative Findings	*P* Value, FP Findings without Biopsy vs Negative Findings	*P* Value, FP with biopsy vs negative
Histopathologic type										
No. of cancers	4123	1302	1211	91	71	20				
Ductal carcinoma in situ (%)	19.4 (801)	5.4 (70)	4.5 (54)	17.6 (16)	15.5 (11)	25.0 (5)	.66	<.001	<.01	<.001
Invasive ductal carcinoma (%)	70.1 (2890)	78.3 (1019)	79.6 (984)	60.4 (55)	60.6 (43)	60.0 (12)	.05	<.001	<.01	.03
Invasive lobular carcinoma (%)	7.0 (288)	11.8 (153)	11.6 (141)	13.2 (12)	15.5 (11)	5.0 (1)	.02	.66	.33	.36
Other invasive (%)	305 (144)	4.6 (60)	4.3 (52)	8.8 (8)	8.5 (6)	10.0 (2)	<.01	.05	.10	.22
Invasive tumors										
No. of invasive tumors	3322	1232	1157	75	60	15				
Tumor size										
Mean (mm)	15.0	22.5	22.9	16.6	17.5	13.0	.19	<.001	<.01	.01
Median (mm)	13.0	20.0	20.0	14.0	15.5	10.5				
≤10 mm (%)	35.9 (1166/3248)	15.1 (169/1117)	14.3(150/1049)	27.9 (19/68)	22.2 (12/54)	50.0 (7/14)	.18	<.01	.11	<.01
10.1–20 mm (%)	44.2 (1435/3248)	38.8 (433/1117)	38.3 (402/1049)	45.6 (31/68)	50.0 (27/54)	28.6 (4/14)	.82	.23	.09	.46
>20 mm (%)	20 (646/3248)	46.1 (515/1117)	47.4 (497/1049)	26.5 (18/68)	27.8 (15/54)	21.4 (3/14)	.18	<.001	.01	.05
No. of tumors with information not available	74	115	108	7	6	1				
Grade										
I (%)	31.1 (1017/3274)	13.9 (165/1187)	13.2 (147/1114)	27.4 (18/73)	20.3 (12/59)	42.9 (6/14)	.24	<.01	.12	<.01
II (%)	48.4 (1586/3274)	47.0 (558/1187)	47.2 (526/1114)	43.8 (32/73)	40.7 (24/59)	57.1 (8/14)	.44	.57	.33	.46
III (%)	20.5 (671/3274)	39.1 (464/1187)	39.6 (441/1114)	31.5 (23/73)	39.0 (23/59)	0	.02	.17	.93	<.01
No. of tumors with information not available	48	45	43	2	1	1				
Lymph node involvement										
Positive (%)	24 (777/3252)	40 (456/1150)	41 (442/1080)	20 (14/70)	22 (12/55)	13 (2/15)	.45	<.001	.01	.03
No. of tumors with information not available	70	82	77	5	5	0				
Hormonal receptor status										
ER positive (%)	89 (2875/3222)	78 (942/1201)	78 (883/1132)	86 (55/69)	82 (45/55)	100 (14/14)	.33	.14	.50	.05
No. of tumors with information not available	100	31	25	6	5	1				
PR positive (%)	72 (2292/3196)	60 (710/1182)	60 (663/1113)	68 (47/69)	62 (34/55)	93 (13/14)	.51	.16	.74	.01
No. of tumors with information not available	126	50	44	6	5	1				

Note.—Data in parentheses are raw data. ER = estrogen receptor, FP = false-positive, PR = progesterone receptor, SDC = screening-detected cancer.



Distribution of IBCs by time since the previous screening mammographic examination among women screened in the Norwegian Breast Cancer Screening Program (2004–2012).

diagnosed after a false-positive screening without biopsy ($P < .01$) (Table 3). The proportions of grade I tumors after negative and false-positive screening without biopsy were 13.2% (147 of 1114) and 20.3% (12 of 59), respectively ($P = .12$). Overall, 40.9% (442 of 1080) of the IBC diagnosed after a negative screening were lymph node positive compared with 21.8% (12 of 55) after false-positive screening mammographic examination without biopsy ($P < .01$).The distribution of estrogen and progesterone receptor status did not significantly differ, except for negative screening versus false-positive screening with biopsy ($P = .05$ for estrogen receptor status and $P = .01$ for progesterone receptor status).

Less than a third of the women with IBC were diagnosed during the 1st year after screening, whereas more than two-thirds of women were diagnosed during the 2nd year between screening mammographic examinations, with peaks at 7, 14, 19, and 24 months after screening (Figure). This distribution by time did not differ significantly between IBC detected after a negative versus false-positive screening.

The distribution of histopathologic types (ductal carcinoma in situ, invasive ductal, invasive lobular, and other invasive cancers), grade, lymph node involvement, and hormonal receptor status did not significantly differ between women diagnosed during the 1st versus 2nd year of the screening interval (Table 4).

Discussion

We identified a threefold higher rate of IBC among women with a previous false-positive screening compared with those with a previous negative screening in their last biennial screening round. Nearly two-thirds of IBCs were diagnosed during the 2nd year between biennial screenings. IBC diagnosed after a previous false-positive screening contributed to 7.0% (91 of 1302) of the cases, and 42.9% (39 of 91) of these corresponded with the abnormality that originally triggered further assessment.

In terms of tumor characteristics of the IBC, less favorable distribution was observed among women with a negative versus false-positive screening, with or without biopsy. Age did not differ for the two groups, whereas time since previous screening until diagnosis of breast cancer was 36 days less for those screened negative versus for those who had a false-positive screening. The finding is consistent with the finding of more rapid-growing tumors among those detected after a negative versus a false-positive screening examination. However, the time difference is assumingly not of substantial influence for tumor progression. Histopathologic characteristics of the IBC detected after a false-positive screening were comparable with the screening-detected cancers.

Although we initially hypothesized that women with IBC after false-positive screening would have less favorable characteristics than those after negative screening, we did not find this to be the case. Almost half (39 of 91) of the abnormalities leading to recall for further assessment but deemed negative at diagnostic evaluation corresponded to the IBC found on the retrospective review of screening and diagnostic imaging. These tumors that were initially correctly identified as suspicious for cancer were assumed to be let go because of equivocal diagnostic imaging evaluation and/or insufficient sampling.

The smaller tumor size and less lymph node involvement among the cases initial identified but let go after diagnostic evaluation compared with those not identified as the same lesions that later appeared as an IBC make intuitive sense in retrospect: true IBCs (those identified after negative screening, and not identified in the retrospective review) would have less favorable prognostic characteristics because these are more likely to represent fast-growing tumors.

The rate of IBC after a false-positive screening including a needle biopsy was statistically higher for definition *a* compared with the other definitions. The additional cases are related to accepted time between screening and diagnosis for the different definitions, 6 months versus 3 months, respectively. The diagnostic delay experienced by these women could be because of women postponing further assessment or other delays related to scheduling of diagnostic services.

A woman's risk of an IBC during her lifetime is low and the risk of an

Table 4

Histopathologic Tumor Characteristics of IBC by Time after Screening Examination among Women Screened in the Norwegian Breast Cancer Screening Program

Parameter	All (*n* = 1302)	1–12 mo after Screening (*n* = 398)	13–24 mo after Screening (*n* = 904)	*P* Value
Histopathologic characteristics				
Ductal carcinoma in situ (%)	5 (70)	6 (23)	5 (47)	.67
Invasive ductal carcinoma (%)	78 (1019)	78 (311)	78 (708)	.94
Invasive lobular carcinoma (%)	12 (153)	11 (44)	12 (109)	.61
Other invasive (%)	5 (60)	5 (20)	4 (40)	.63
Invasive tumors				
No. of invasive tumors	1232	375	857	
Tumor size				
Mean (mm)	22.5	22.2	22.6	.62
Median (mm)	20.0	20.0	20.0	
≤10 mm (%)	15 (169/1117)	19 (61/330)	14 (108/787)	.04
10.1–20 mm (%)	39 (433/1117)	37 (121/330)	40 (312/787)	.35
>20 mm (%)	46 (515/1117)	45 (148/330)	47 (367/787)	.59
No. of tumors with information not available	115	45	70	
Grade				
I (%)	14 (165/1187)	16 (57/354)	13 (108/833)	.15
II (%)	47 (558/1187)	49 (174/354)	46 (384/833)	.34
III (%)	39 (464/1187)	35 (123/354)	41 (341/833)	.05
No. of tumors with information not available	45	21	24	
Lymph node involvement				
Positive (%)	40 (456/1150)	40 (137/344)	40 (319/806)	.94
No. with information not available	82	31	51	
Hormonal receptor status				
ER positive (%)	78 (942/1201)	79 (288/363)	78 (654/838)	.62
No. of tumors with information not available	31	12	19	
PR positive (%)	60 (710/1182)	59 (208/352)	61 (502/830)	.66
No. of tumors with information not available	50	23	27	

Note.—Data in parentheses are raw data. ER = estrogen receptor, PR = progesterone receptor.

IBC following a false-positive screening is even lower. However, our findings may suggest that women with a false-positive screening be offered another mammographic examination within 6 months or a year, rather than 2 years, to detect the cancer at an earlier stage. Implementation of more frequent screening would likely decrease the IBC rate, and potentially detect the cancers at an earlier stage, further improving the women's outcomes. In addition, such a screening policy would likely increase the overall trust in the screening program by personalizing the screening regimen on the basis of the increased risk for interval cancers after false-positive screening. However, the overall benefits and harms of earlier follow-up for women with a false-positive screening, including consideration of women's preferences, should be investigated before new policies are considered.

Most of the IBCs in our study were detected in the 2nd year of the screening interval, further suggesting that a shorter screening interval may be beneficial to decrease the rate of IBC, both for those with a negative and a previous false-positive screening. Documentation of IBC detected in the 2nd year of the biennial interval is further complicated by the fact that a false-positive screening might increase breast awareness and encourage women to seek a private clinic for mammography in the year between two screening mammographic examinations in the national program (31). If cancer is detected at private clinics in between two screening sessions, these cases are defined as IBC in the Norwegian screening program. Furthermore, by assuming all IBCs detected during the 2nd year of the interval to be detectable at screening after 1 year ($1302 \times 0.70 = 911$), the proportion of IBCs would decrease from about 24% [(1302/(4123 + 1302)] to less than 10% [(1302 − 911)/(1302 − 911) + (4123 + 911)] per 10 000 screenings. Only 30% of the IBCs were diagnosed during the 1st year of the screening interval. Tumor characteristics did not differ substantially between those detected in the 1st and 2nd year of the interval. Nevertheless, the relative benefits and harms of 1-year versus 2-year screening intervals remain heavily debated.

We explored different definitions of IBC in our analysis and chose the base-case definition (definition *b*) to be breast cancers diagnosed within 2 years after a negative screening or more than 6 months after a false-positive screening. The total number of women diagnosed with breast cancers do not differ between definitions, but the distribution of screening-detected versus IBC did differ between definitions. Rates of IBC were previously presented according to definition *d* (breast cancer diagnosed after a negative or false-positive screening, either before the next biennial screening or within 2 years among women who had reached the upper age limit for screening). We considered definition *b* to be the most objective because it allowed women a large amount of time—up to 6 months—to obtain diagnostic evaluation after abnormal screening.

There were several limitations to our study. Unfortunately, we were not able to adjust for mammographic

density or other known risk factors for breast cancer. Further, there was incomplete capture of some tumor characteristics, such as human epidermal growth factor receptor type 2 and Ki-67 protein. Despite the relatively high number of women with IBC in the study population, there were a fairly small number of cases diagnosed after a previous false-positive screening. Ideally, the mammographic examinations from all the IBCs should be reviewed to determine the false-negative rate because some of our IBCs were likely missed. The guidelines for the screening program in Norway recommends that radiologists review previous imaging for IBC. This is usually performed at each of the 16 breast centers without any common system of data collection. A nationwide informed review of IBC and screening-detected breast cancer is now underway in the country. Another limitation of our study relates to the generalizability to other populations. For example, in the United State, yearly screening is advocated by some groups, even though most guidelines recommend biennial screening. The Norwegian Breast Cancer Screening Program aims to invite the women to participate in 2-year screening intervals (730 days). However, the actual interval between two screening examinations average more than 730 days. Some women attend only after a reminder, whereas other women may drop a screening examination or two, which is why the average and median interval between two screening examinations exceed 2 years, which is substantially longer than the screening interval in the United States. Further, our program makes use of two radiologists who independently interpret each screening examination. This is not the normal practice in the United States.

Most of the women diagnosed with IBC do not gain substantially from participation in routine screening programs (3,32). IBC is thus a major issue in the weighting of the harms versus benefits of routine screening. Our findings indicate that the outcome of previous screening should be taken into consideration in risk prediction models to better stratify women into risk categories. Our results can thus help move population-based screening to a more risk-based approach that can emphasize minimizing the rate of IBC.

Risk-stratified screening on the basis of individual woman–level factors is expected to create more efficient screening both for women attending screening and for administrators by tailoring the use of different screening intervals and different imaging modalities. Recent studies (33) have shown that use of digital breast tomosynthesis can increase the rate of screening-detected breast cancer, whereas a lower rate of IBC is expected under tomosynthesis screening, and initial reports (34) suggest no significant decrease in IBC after implementation of tomosynthesis screening. Future research efforts regarding IBC rates on the basis of the outcome of previous screening examinations should include screening with tomosynthesis.

In summary, about one in four breast cancers detected among women who participated in the Norwegian Breast Cancer Screening Program were IBC. A previous recall for further assessment with a negative diagnostic outcome conferred a threefold higher risk of IBC compared with a negative screening. The consequences of short-term follow-up for this small subset of women with higher risk of IBC need further investigation to ensure that benefits outweigh the harms in a population-based screening setting.

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References

1. Vitak B, Olsen KE, Månson JC, Arnesson LG, Stål O. Tumour characteristics and survival in patients with invasive interval breast cancer classified according to mammographic findings at the latest screening: a comparison of true interval and missed interval cancers. Eur Radiol 1999;9(3):460–469.
2. Bordás P, Jonsson H, Nyström L, Lenner P. Survival from invasive breast cancer among interval cases in the mammography screening programmes of northern Sweden. Breast 2007;16(1):47–54.
3. Hofvind S, Holen Å, Román M, Sebuødegård S, Puig-Vives M, Akslen L. Mode of detection: an independent prognostic factor for women with breast cancer. J Med Screen 2016;23(2):89–97.
4. O'Brien KM, Dwane F, Kelleher T, Sharp L, Comber H. Interval cancer rates in the Irish national breast screening programme. J Med Screen 2015;22(3):136–143.
5. Fracheboud J, de Koning HJ, Beemsterboer PM, et al. Interval cancers in the Dutch breast cancer screening programme. Br J Cancer 1999;81(5):912–917.
6. Zackrisson S, Janzon L, Manjer J, Andersson I. Improved survival rate for women with interval breast cancer - results from the breast cancer screening programme in Malmö, Sweden 1976-1999. J Med Screen 2007;14(3):138–143.
7. Hofvind S, Skaane P, Vitak B, et al. Influence of review design on percentages of missed interval breast cancers: retrospective study of interval cancers in a population-based screening program. Radiology 2005;237(2):437–443.
8. Hoff SR, Abrahamsen AL, Samset JH, Vigeland E, Klepp O, Hofvind S. Breast cancer: missed interval and screening-detected cancer at full-field digital mammography and screen-film mammography-- results from a retrospective review. Radiology 2012;264(2):378–386.
9. Carbonaro LA, Azzarone A, Paskeh BB, et al. Interval breast cancers: absolute and proportional incidence and blinded review in a community mammographic screening program. Eur J Radiol 2014;83(2):e84–e91.
10. Bennett RL, Sellars SJ, Moss SM. Interval cancers in the NHS breast cancer screening programme in England, Wales and Northern Ireland. Br J Cancer 2011;104(4):571–577.
11. Hofvind S, Skaane P, Elmore JG, Sebuødegård S, Hoff SR, Lee CI. Mammographic performance in a population-based screening program: before, during, and after the transition from screen-film to full-field digital mammography. Radiology 2014;272(1):52–62.
12. Hofvind S, Yankaskas BC, Bulliard JL, Klabunde CN, Fracheboud J. Comparing interval breast cancer rates in Norway and North Carolina: results and challenges. J Med Screen 2009;16(3):131–139.
13. Törnberg S, Kemetli L, Ascunce N, et al. A pooled analysis of interval cancer rates in

six European countries. Eur J Cancer Prev 2010;19(2):87–93.

14. Bulliard JL, Sasieni P, Klabunde C, De Landtsheer JP, Yankaskas BC, Fracheboud J. Methodological issues in international comparison of interval breast cancers. Int J Cancer 2006;119(5):1158–1163.
15. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L. European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. Official publication of the European Communities. 4th ed. Luxembourg: European Communities, 2006.
16. Rosenberg RD, Yankaskas BC, Hunt WC, et al. Effect of variations in operational definitions on performance estimates for screening mammography. Acad Radiol 2000;7(12):1058–1068.
17. Sickles EA, D'Orsi CJ, Bassett LW, et al. ACR BI-RADS Mammography. In: ACR BI-RADS Atlas, Breast Imaging Reporting and Data System. Reston, Va: American College of Radiology, 2013.
18. Smith-Bindman R, Ballard-Barbash R, Miglioretti DL, Patnick J, Kerlikowske K. Comparing the performance of mammography screening in the USA and the UK. J Med Screen 2005;12(1):50–54.
19. von Euler-Chelpin M, Risør LM, Thorsted BL, Vejborg I. Risk of breast cancer after false-positive test results in screening mammography. J Natl Cancer Inst 2012;104(9):682–689.
20. Román M, Castells X, Hofvind S, von Euler-Chelpin M. Risk of breast cancer after false-positive results in mammographic screening. Cancer Med 2016;5(6):1298–1306.
21. Henderson LM, Hubbard RA, Sprague BL, Zhu W, Kerlikowske K. Increased Risk of Developing Breast Cancer after a False-Positive Screening Mammogram. Cancer Epidemiol Biomarkers Prev 2015;24(12):1882–1889.
22. McCann J, Stockton D, Godward S. Impact of false-positive mammography on subsequent screening attendance and risk of cancer. Breast Cancer Res 2002;4(5):R11.
23. Castells X, Torá-Rocamora I, Posso M, et al. Risk of Breast Cancer in Women with False-Positive Results according to Mammographic Features. Radiology 2016;280(2):379–386.
24. Román M, Quintana MJ, Ferrer J, Sala M, Castells X. Cumulative risk of breast cancer screening outcomes according to the presence of previous benign breast disease and family history of breast cancer: supporting personalised screening. Br J Cancer 2017;116(11):1480–1485.
25. Forskrift om innsamling og behandling av helseopplysninger i Kreftregisteret (Kreftregisterforskriften), Oslo, Helse- og omsorgsdepartementet, [Regulation on the collection and processing of data about health in the Cancer Registry of Norway (The Cancer Registry Regulation). Oslo, Norwegian Ministry of Health and Care Services]. https://lovdata.no/dokument/SF/forskrift/2001-12-21-1477. Published 2001. Accessed May 1, 2017.
26. Kreftregisteret.no. https://www.kreftregisteret.no/globalassets/mammografiprogrammet/dokumenter/papers-related-to-the-nbcsp_per_dec-1st-2016.pdf. Accessed July 1, 2017.
27. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 2009;45(7):1218–1231.
28. Skaane P, Bandos AI, Gullien R, et al. Prospective trial comparing full-field digital mammography (FFDM) versus combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration. Eur Radiol 2013;23(8):2061–2071.
29. Hofvind S, Geller BM, Rosenberg RD, Skaane P. Screening-detected breast cancers: discordant independent double reading in a population-based screening program. Radiology 2009;253(3):652–660.
30. Kreftregisteret, Kvalitetssikring i Mammografiprogrammet. Oslo: Kreftregisteret; 2004 [Cancer Registry of Norway. Quality Assurance in the Norwegian Breast Cancer Screening Program. Oslo, Cancer Registry of Norway, 2004]. http://www.kreftregisteret.no/Global/Kvalitetsmanualer/kvalitetsmanual mammografiprogrammet.pdf. Published 2004. Accessed May 1, 2017.
31. Hoff SR, Klepp O, Hofvind S. Asymptomatic breast cancer in non-participants of the national screening programme in Norway: a confounding factor in evaluation? J Med Screen 2012;19(4):177–183.
32. Eriksson L, Czene K, Rosenberg LU, Törnberg S, Humphreys K, Hall P. Mammographic density and survival in interval breast cancers. Breast Cancer Res 2013;15(3):R48.
33. Gilbert FJ, Tucker L, Young KC. Digital breast tomosynthesis (DBT): a review of the evidence for use as a screening tool. Clin Radiol 2016;71(2):141–150.
34. McDonald ES, Oustimov A, Weinstein SP, Synnestvedt MB, Schnall M, Conant EF. Effectiveness of Digital Breast Tomosynthesis Compared With Digital Mammography: Outcomes Analysis From 3 Years of Breast Cancer Screening. JAMA Oncol 2016;2(6):737–743.