Accuracy and Outcomes of Screening Mammography in Women With a Personal History of Early-Stage Breast Cancer

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Context Women with a personal history of breast cancer (PHBC) are at risk of developing another breast cancer and are recommended for screening mammography. Few high-quality data exist on screening performance in PHBC women.

Objective To examine the accuracy and outcomes of mammography screening in PHBC women relative to screening of similar women without PHBC.

Design and Setting Cohort of PHBC women, mammogram matched to non-PHBC women, screened through facilities (1996-2007) affiliated with the Breast Cancer Surveillance Consortium.

Participants There were 58 870 screening mammograms in 19 078 women with a history of early-stage (in situ or stage I-II invasive) breast cancer and 58 870 matched (breast density, age group, mammography year, and registry) screening mammograms in 55 315 non-PHBC women.

Main Outcome Measures Mammography accuracy based on final assessment, cancer detection rate, interval cancer rate, and stage at diagnosis.

Results Within 1 year after screening, 655 cancers were observed in PHBC women (499 invasive, 156 in situ) and 342 cancers (285 invasive, 57 in situ) in non-PHBC women. Screening accuracy and outcomes in PHBC relative to non-PHBC women were cancer rates of 10.5 per 1000 screens (95% CI, 9.7-11.3) vs 5.8 per 1000 screens (95% CI, 5.2-6.4), cancer detection rate of 6.8 per 1000 screens (95% CI, 6.2-7.5) vs 4.4 per 1000 screens (95% CI, 3.9-5.0), interval cancer rate of 3.6 per 1000 screens (95% CI, 3.2-4.1) vs 1.4 per 1000 screens (95% CI, 1.1-1.7), sensitivity 65.4% (95% CI, 61.5%-69.0%) vs 76.5% (95% CI, 71.7%-80.7%), specificity 98.3% (95% CI, 98.2%-98.4%) vs 99.0% (95% CI, 98.9%-99.1%), abnormal mammogram results in 2.3% (95% CI, 2.2%-2.5%) vs 1.4% (95% CI, 1.3%-1.5%) (all comparisons $P < .001$). Screening sensitivity in PHBC women was higher for detection of in situ cancer (78.7%; 95% CI, 71.4%-84.5%) than invasive cancer (61.1%; 95% CI, 56.6%-65.4%), $P < .001$; lower in the initial 5 years (60.2%; 95% CI, 54.7%-65.5%) than after 5 years from first cancer (70.8%; 95% CI, 65.4%-75.6%), $P = .006$; and was similar for detection of ipsilateral cancer (66.3%; 95% CI, 60.3%-71.8%) and contralateral cancer (66.1%; 95% CI, 60.9%-70.9%), $P = .96$. Screen-detected and interval cancers in women with and without PHBC were predominantly early stage.

Conclusion Mammography screening in PHBC women detects early-stage second breast cancers but has lower sensitivity and higher interval cancer rate, despite more evaluation and higher underlying cancer rate, relative to that in non-PHBC women.

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THE HIGH PREVALENCE OF BREAST cancer survivors is due to general gains in life expectancy and to improved survival in women with a personal history of breast cancer (PHBC), attributable to improvements in local and systemic treatments and early detection. Women with PHBC are at risk of developing second breast cancers, which can be ipsilateral (in-breast recurrence or new ipsilateral cancer) or contralateral; risk of a second breast cancer was recently estimated at 5.4 to 6.6 per 1000 woman-years.[1] The consensus is that PHBC women may benefit from early detection of second breast cancers, although evidence of screening benefit in these women comes from nonrandomized studies[2-5] and extrapolation of benefit from randomized population mammography screening trials. Screening or surveillance mammography (referred to here as screening)[1,6] is usually recommended by guidelines and consensus recommendations for follow-up of PHBC women.[7-12]

Several reviews have concluded that little quality evidence is available on mammography screening accuracy in

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PHBC women[6,13,14]; most studies are based on selected series, are limited to women who had second breast cancers or further breast surgery,[3,6,15-18] or use methods that do not allow estimation of specificity.[6] Studies of screening in PHBC women predominantly report only the proportion of second cancers detected by mammography, in the range of 10% to 80%.[6,13,14] Standard measures of screening performance in PHBC women, such as cancer detection rates or interval cancer rates for ipsilateral and contralateral cancers, are not available from screening programs. Furthermore, interest exists in using adjunct imaging such as higher-cost magnetic resonance imaging to screen PHBC women[19,20] despite lack of reliable data on mammography screening in these women.

Valid estimates of the accuracy of screening mammography are therefore needed to guide clinical practice and policy in this setting and to inform clinicians and PHBC women of expected screening outcomes. This study examines the accuracy and outcomes of screening mammography and factors associated with screening outcomes in women with a PHBC who participated in mammography screening through facilities affiliated with the Breast Cancer Surveillance Consortium (BCSC). Context on screening mammography outcomes from the same practices in women of approximately population risk came from a comparison group with no reported breast cancer history and with a mammogram matched to PHBC women on breast density, age group, and mammography registry and year.

METHODS

Setting

Participants were women receiving mammograms at facilities in 5 of the 7 mammography registries of the National Cancer Institute–funded BCSC, which collects demographic and mammography information from women undergoing mammography at participating community-based facilities. Each registry links data on screened women to their state or the Surveillance, Epidemiology, and End Results cancer registries to ascertain breast cancer diagnoses. Five registries collect both cancer registry and pathology outcomes data for complete capture of second cancers and were sources for this study: Carolina Mammography Registry (North Carolina), Group Health Breast Cancer Screening Project (Washington State), New Hampshire Mammography Network, New Mexico Mammography Project, and Vermont Breast Cancer Surveillance System. Information about the BCSC is available at http://breastscreening.cancer.gov/.

Each registry and the BCSC Statistical Coordinating Center received institutional review board approval for either active or passive consenting processes or a consent waiver to enroll women, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant, and all registries and the Statistical Coordinating Center received a federal certificate of confidentiality and other protection for identities of women, physicians, and facilities in this research.

Screening Examinations

Screening mammograms from 1996 to 2007 in PHBC women were identified. Women (44 509) with an initial early-stage breast cancer,[1] including diagnoses of ductal carcinoma in situ or American Joint Committee on Cancer[21] stage I to II invasive carcinoma, were eligible for inclusion. Cancer registry and pathology databases were used to ascertain whether a woman had a breast cancer diagnosis, the diagnosis date, and cancer characteristics. Excluded were women with bilateral mastectomy for first cancer. A mammogram performed at least 6 months after first breast cancer diagnosis was defined as *screening* if it was indicated as a routine screen by the radiologist or technologist, not within 9 months of a previous breast imaging examination, not a unilateral mammogram in a woman with breast-conserving surgery, and not from a woman self-reporting a lump or nipple discharge. Screening mammograms with at least 1 year of follow-up for ascertaining second cancer diagnoses were included. Women meeting the inclusion criteria and receiving at least 1 screening mammogram with a final Breast Imaging Reporting and Data System (BI-RADS)[22] assessment of 0 to 5 were eligible (eFigure, available at http://www.jama.com).

Comparison Group

Screening examinations in non-PHBC women were matched 1:1 to screens of PHBC women, based on Breast Imaging Reporting and Data System[22] breast density, 10-year age group, and mammography registry and year. Screening mammograms were defined with BCSC definitions with criteria similar to those of PHBC women (bilateral mammogram indicated for screening in women with no reported symptoms, no mammogram in the previous 9 months, and at least 1 year of follow-up).[23]

Demographic Characteristics

Age group, self-reported race/ethnicity, family breast cancer history, menopausal status, time since last mammogram, and history of breast plastic surgery (implants, reduction, or reconstruction) were collected at the screening.

Cancer Characteristics and Follow-up

Time since first cancer was the difference between the screening mammogram date and the date of first breast cancer diagnosis. For first cancer, type (ductal carcinoma in situ, stage I or II invasive), radiation therapy, adjuvant systemic therapy, and surgery (breast-conserving surgery, mastectomy) were computed from all cancer registry records and pathology databases that were within 6 months of initial diagnosis. For missing surgery information, self-reported mastectomy and lumpectomy history (collected at a mammogram within 18 months after diagnosis and before a second cancer diagnosis) was used to impute primary surgery.

In all screening participants, mammograms were considered to be associated with an outcome of breast cancer if ductal carcinoma in situ or invasive carcinoma was observed within 1 year of the screen.

Statistical Analysis and Measures of Accuracy

Because some mammography facilities add spot-compression magnification views to routine screening views as a standard part of screening PHBC women, accuracy measures were based on the final assessment at the end of imaging evaluation, using the BI-RADS[22] scale. If the initial examination assessment was BI-RADS score 0 without biopsy recommendation or was 1, 2, or 3 with immediate follow-up recommendation, we looked for a final assessment in imaging examinations up to 90 days after screening and before breast biopsy. A positive final assessment result included BI-RADS assessments of 4 or 5, or 0 or 3 with recommendation for biopsy, fine-needle aspiration, or surgical consultation.[1,23,24] A negative final assessment result included BI-RADS assessments of 1 or 2; assessment of 3 without recommendation for biopsy, fine-needle aspiration, or surgical consultation; or assessment of 0 with normal or short-interval follow-up recommendation. Final assessment was considered missing if the last BI-RADS assessment was 0 with recommendation for additional imaging, unspecified evaluation, or missing recommendation (eFigure).

Accuracy measures were based on standard BCSC definitions.[23] A positive mammogram result associated with breast cancer diagnosis during follow-up (within 1 year of screen) was defined as a true positive (or false positive if not associated with cancer diagnosis). A negative mammogram result not associated with breast cancer during follow-up was a true negative (or false negative if associated with cancer during follow-up). Cancer rate (number of cancers observed during follow-up among 1000 screening mammograms), cancer detection rate (number of true-positive results among 1000 mammograms), interval cancer rate (number of false-negative results among 1000 mammograms), abnormal interpretation rate (proportion of mammograms found to be positive), and positive predictive value of biopsy recommendation (proportion of positive results associated with cancer diagnosis during follow-up)[25] were based on standard BCSC definitions.[23] Accuracy analyses excluded mastectomy-side recurrences (which would not have been examined with mammography) in PHBC women.

Frequency distributions of screens and cancer characteristics were computed separately for screening mammograms in women with and without PHBC and were compared with χ^2 tests. Accuracy and outcome measures and 95% confidence intervals (CIs) were computed within cohorts and compared with score statistics obtained from generalized estimating equation analyses. In PHBC screens, accuracy and cancer rates were examined by breast density, time since first cancer diagnosis, type of first breast cancer, screening interval, and treatment variables associated with first cancer. Post hoc logistic regression tested for differences in sensitivity by systemic therapy for first cancer (none, chemotherapy, endocrine therapy, or both), adjusting for exact age, breast density, stage and treatment of first cancer, and mammography registry. Generalized estimating equations were used to calculate all CIs and to fit regression models accounting for correlation in women with multiple screening mammograms. $P<.05$ (2-sided) was considered statistically significant. Analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

There were 58 870 screening mammograms in 19 078 women with PHBC and 58 870 matched screening examinations in 55 315 women without PHBC (TABLE 1). A higher proportion of screening mammograms from PHBC women relative to matched non-PHBC screens was associated with a family history of breast cancer (23.2% vs 17.6%), postmenopausal status (91.6% vs 87.5%), history of breast plastic surgery (6.9% vs 0.8%), and receipt of mammography between 9 and 14 months since the previous screen (82.7% vs 43.1%); all $P<.001$. Women with PHBC had 655 second cancers (499 invasive, 156 ductal carcinoma in situ) and women without PHBC had 342 cancers (285 invasive, 57 ductal carcinoma in situ) within 1 year of screening mammography. Ductal carcinoma in situ occurred in a higher proportion of second cancers in the PHBC than in the non-PHBC group (23.8% vs 16.7%; $P=.009$).

TABLE 2 reports accuracy measures and outcomes for all screening examinations. Cancer rates were 11.1 per 1000 screens in PHBC women, or 10.5 per 1000, excluding 40 mastectomy-side recurrences that would not have been examined with mammography, relative to 5.8 per 1000 screens in non-PHBC women. Cancer rates, cancer detection rate, and interval cancer rate were 1.3 to 2.6 times higher for PHBC screens compared with matched screens. PHBC screens were more frequently associated with additional imaging (additional mammography views or ultrasonography) than matched screens (18.1% vs 8.3%; $P<.001$), which was largely due to more same-day additional imaging in PHBC screens relative to matched screens (12.4% vs 1.3%; $P<.001$) rather than recall for additional imaging (7.1% vs 7.8%; $P<.001$). PHBC women were more likely to have a recommendation for fine-needle aspiration, biopsy, or surgical consultation after assessment (2.2% vs 1.4%; $P<.001$). Ultrasonography was performed as part of the evaluation (same day, before, or at final assessment) of positive screening mammogram results (1874 positive screen results) less frequently in PHBC-positive screens than in matched screens (32.3% vs 38.8%; $P=.004$).

Screening sensitivity in PHBC was lower (65.4%; 95% CI, 61.5%-69.0%) compared with that in non-PHBC

screens (76.5%; 95% CI, 71.7%-80.7%), $P<.001$. This relatively lower screening sensitivity was largely due to lower sensitivity for detection of invasive cancer in PHBC (61.1%; 95% CI, 56.6%-65.4%) relative to that in the matched group (75.7%; 95% CI, 70.4%-80.3%), $P<.001$. In PHBC screens, cancer detection rate was higher in women whose first cancer was ductal carcinoma in situ relative to invasive cancer (Table 2), and this was evident for detection of both ductal carcinoma in situ and invasive second cancers. Sensitivity was similar for detection of ipsilateral (66.3%; 95% CI, 60.3%-71.8%) and contralateral cancer (66.1%; 95% CI, 60.9%-70.9%), $P=.96$; and sensitivity was higher for detection of ductal carcinoma in situ (78.7%; 95% CI, 71.4%-84.5%) than for invasive cancer (61.1%; 95% CI, 56.6%-65.4%), $P<.001$.

Accuracy, cancer rates, cancer detection rate, and interval cancer rate in PHBC women are reported by age, breast density, screening interval, time since first cancer diagnosis, type of first cancer, treatment for first breast cancer, and breast plastic surgery history (TABLE 3) (data used in the calculations are shown in eTable 1). TABLE 4 shows screening sensitivity for these variables by second cancer laterality. Accuracy measures, cancer rates, and interval cancer rate were associated with age, although the lower sensitivity in women younger than 50 years was more evident for contralateral cancer detection. Sensitivity and specificity decreased and abnormal interpretation rate, cancer rates, cancer detection rate, and interval cancer rate increased with increasing BI-RADS[22] density categories. Sensitivity was 69.6% (95% CI, 63.3%-75.3%) in less dense breasts (BI-RADS category 1-2) and was higher than the sensitivity of 60.2% (95% CI, 54.0%-66.2%) in more dense breasts (BI-RADS category 3-4), $P=.03$.

Specificity and positive predictive value increased, sensitivity and cancer detection rate varied, and abnormal interpretation rate decreased with increasing time since first cancer diag-

Table 1. Characteristics of Screening Mammograms in Women With a Personal History of Breast Cancer (PHBC) and Matched Screening Mammograms in Women Without a PHBC

	No. (%)			
	Women (n = 19 078) With PHBC		Women (n = 55 315) Without PHBC	
	Screening Mammograms[a]	Second Breast Cancers Within 1 Year of Screening[b]	Screening Mammograms[a]	Breast Cancers Within 1 Year of Screening[b]
Screening examinations, total	58 870	655	58 870	342
Age at mammography, y				
<40	727 (1.2)	14 (1.9)	727 (1.2)	0
40-49	6104 (10.4)	98 (1.6)	6104 (10.4)	18 (0.3)
50-59	14 532 (24.7)	165 (1.1)	14 532 (24.7)	50 (0.3)
60-69	14 795 (25.1)	130 (0.9)	14 795 (25.1)	90 (0.6)
70-79	15 171 (25.8)	165 (1.1)	15 171 (25.8)	113 (0.7)
≥80	7541 (12.8)	83 (1.1)	7541 (12.8)	71 (0.9)
BI-RADS breast density				
1, Almost entirely fatty	3448 (7.5)	18 (0.5)	3448 (7.5)	9 (0.3)
2, Scattered fibroglandular tissue	22 155 (48.3)	224 (1.0)	22 155 (48.3)	117 (0.5)
3, Heterogeneously dense	17 885 (39.0)	219 (1.2)	17 885 (39.0)	116 (0.6)
4, Extremely dense	2418 (5.3)	39 (1.6)	2418 (5.3)	17 (0.7)
Missing data	12 964 (22.0)	155 (1.2)	12 964 (22.0)	83 (0.6)
Race/ethnicity				
White, non-Hispanic	47 489 (84.2)	531 (1.1)	47 119 (83.3)	285 (0.6)
Black, non-Hispanic	2018 (3.6)	21 (1.0)	2027 (3.6)	9 (0.4)
Hispanic	4707 (8.3)	45 (1.0)	4783 (8.5)	14 (0.3)
Asian/Pacific Islander	984 (1.7)	10 (1.0)	1115 (2.0)	12 (1.1)
Other	1234 (2.2)	13 (1.1)	1496 (2.6)	8 (0.5)
Missing data	2438 (4.1)	35 (1.4)	2330 (4.0)	14 (0.6)
Family history of breast cancer				
No	37 956 (76.8)	381 (1.0)	41 065 (82.4)	187 (0.5)
Yes	11 459 (23.2)	169 (1.5)	8744 (17.6)	81 (0.9)
Missing data	9455 (16.1)	105 (1.1)	9061 (15.4)	74 (0.8)
Menopausal status				
Pre	3580 (6.9)	74 (2.1)	5945 (11.2)	15 (0.3)
Peri	763 (1.5)	19 (2.5)	722 (1.4)	4 (0.6)
Post	47 187 (91.6)	483 (1.0)	46 600 (87.5)	313 (0.7)
Missing data	7340 (12.5)	79 (1.1)	5603 (9.5)	10 (0.2)
Time since last mammogram, mo				
No previous mammogram	106 (0.2)	4 (3.8)	1581 (2.9)	18 (1.1)
9-14	47 872 (82.7)	511 (1.1)	23 799 (43.1)	94 (0.4)
15-23	7358 (12.7)	84 (1.1)	14 743 (26.7)	95 (0.6)
≥24	2579 (4.5)	46 (1.8)	15 122 (27.4)	108 (0.7)
Missing data	955 (1.6)	10 (1.0)	3625 (6.2)	27 (0.7)
Time since first breast cancer diagnosis, y[c]				
<1	4416 (7.5)	61 (1.4)		
1-2	14 139 (24.0)	144 (1.0)		
3-4	14 085 (23.9)	139 (1.0)		
5-6	10 664 (18.1)	123 (1.2)		
7-9	9681 (16.4)	116 (1.2)		
≥10	5885 (10.0)	72 (1.2)		
Stage of initial breast cancer diagnosis[c]				
Ductal carcinoma in situ	12 140 (20.6)	197 (1.6)		
Invasive, stage I	29 558 (50.2)	281 (1.0)		
Invasive, stage II	17 172 (29.2)	177 (1.0)		

(continued)

Table 1. Characteristics of Screening Mammograms in Women With a Personal History of Breast Cancer (PHBC) and Matched Screening Mammograms in Women Without a PHBC (continued)

	No. (%)			
	Women (n = 19 078) With PHBC		Women (n = 55 315) Without PHBC	
	Screening Mammograms[a]	Second Breast Cancers Within 1 Year of Screening[b]	Screening Mammograms[a]	Breast Cancers Within 1 Year of Screening[b]
Primary surgery[c]				
Breast conserving without radiation	7503 (13.0)	132 (1.8)		
Breast conserving with radiation	29 986 (51.9)	335 (1.1)		
Mastectomy	20 232 (35.1)	157 (0.8)		
Missing data	1149 (2.0)	31 (2.7)		
Radiation therapy[c]				
None	20 872 (36.2)	246 (1.2)		
Any	36 862 (63.8)	380 (1.0)		
Missing data	1136 (1.9)	29 (2.6)		
Adjuvant systemic therapy[c]				
Neither	28 003 (50.6)	363 (1.3)		
Chemotherapy	7765 (14.0)	91 (1.2)		
Endocrine therapy	14 127 (25.5)	103 (0.7)		
Both	5472 (9.9)	47 (0.9)		
Missing data	3503 (6.0)	51 (1.5)		
Self-reported history of breast implant, reduction, or reconstruction[d]				
No	41385 (93.1)	445 (1.1)	48839 (99.2)	259 (0.5)
Yes	3088 (6.9)	25 (0.8)	380 (0.8)	1 (0.3)
Missing data	14397 (24.5)	185 (1.3)	9651 (16.4)	82 (0.8)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; PHBC, personal history of breast cancer.
[a] Percentages were computed after exclusion of missing values.
[b] Percentages calculated based on row denominator.
[c] Data on first breast cancer diagnosis for PHBC only.
[d] Distribution for each variable (by laterality) available from the authors.

nosis (Table 3). Sensitivity in the initial 5 years from first cancer (60.2%; 95% CI, 54.7%-65.5%) was lower than sensitivity after 5 years (70.8%; 95% CI, 65.4%-75.6%), $P = .006$. Cancer detection rate also differed between the initial 5 years (5.8/1000 screens; 95% CI, 5.0-6.7) and after the initial 5 years (8.1/1000 screens; 95% CI, 7.1-9.3) from first cancer diagnosis, $P < .001$, predominantly because of increased cancer detection rate for invasive cancer between the initial 5 years (3.7/1000 screens; 95% CI, 3.1-4.4) and after the initial 5 years (6.2/1000 screens; 95% CI, 5.3-7.2), $P < .001$.

Specificity and abnormal interpretation rate were associated with time since previous mammogram (Table 3); however, most PHBC screens occurred between 9 and 14 months after previous mammography. Sensitivity, abnormal interpretation rate, positive predictive value, cancer rates, and cancer detection rate were higher in women with previous ductal carcinoma in situ relative to those with previous invasive cancer (Table 3), although the sensitivity difference was more evident for detection of ipsilateral (second) cancers (Table 4).

Specificity was higher and abnormal interpretation rate lower in women who had received mastectomy relative to breast-conserving surgery for first cancer. Radiation therapy was associated with a very small but significant specificity reduction and abnormal interpretation rate increase. Cancer rates, cancer detection rate, and interval cancer rate varied between women who had breast-conserving surgery with or without radiation or mastectomy (Table 3): the highest cancer detection and interval cancer rates were observed in women treated with breast-conserving surgery without radiation for their first cancer. Sensitivity, abnormal interpretation rate, and positive predictive value were higher in women who had not received any systemic therapies, as were underlying cancer rates and cancer detection rate (Table 3). After adjusting for age, density, stage and treatment of first cancer, and mammography registry, women with chemotherapy were significantly less likely to have their cancer detected by mammography (odds ratio [OR] = 0.45; 95% CI, 0.22-0.94) than women without systemic therapy. Women with endocrine therapy alone (OR = 0.63; 95% CI, 0.35-1.15) or combined with chemotherapy (OR = 0.69; 95% CI, 0.29-1.67) also had lower sensitivity than women with no therapy, but this was nonsignificant.

Sensitivity and positive predictive value were lower in screens with self-reported breast plastic surgery history relative to no plastic surgery (lower sensitivity was more apparent when reduction was excluded), but overall this was not significant (Table 3). The lower sensitivity in screens with self-reported breast plastic surgery was evident mainly for contralateral cancer (Table 4); however, the number in this group was small.

Stage and node status for cancers occurring within 1 year of screening are in eTable 2, with generally similar stage distributions for interval cancers in both cohorts, although invasive interval cancers were more likely to be stage I than stage II in PHBC women compared with non-PHBC women. Screen-detected cancers had a favorable profile in PHBC women and matched screens, with the majority being early-stage cancers.

COMMENT

Breast cancer survivors represent an increasing group and are at risk of cancer in the conserved and contralateral breast. To our knowledge, we report the first comprehensive study of accuracy

measures of mammography screening in PHBC women that includes both ipsilateral and contralateral breast screening outcomes, providing evidence to inform practice and guide recommendations on mammography screening in PHBC women.[7,9,10] Key findings are that mammography screening in PHBC women detects cancers at an early stage but has lower accuracy than screening in women without PHBC, despite a higher rate of additional evaluation and higher underlying cancer rates in PHBC women. Our study also shows that screening mammography in PHBC women has a relatively high interval cancer rate, although most interval cancers in these women had favorable tumor stage profiles.

Because population mammography screening accuracy differs across screening programs and countries, a major strength of our study is integration of matched screens from women without PHBC, providing context on screening accuracy in mammography registries that contributed data to this study and allowing judgment about the generalizability of our findings. It also allows an understanding of mammography screening outcomes and how these differ in PHBC women relative to non-PHBC women, as highlighted in Table 2. Measures of screening accuracy should, however, be interpreted with awareness that these calculations were based on final assessment (at completion of imaging evaluation). Our design of matching screening mammograms for characteristics including breast density and age group allowed us to validly compare screening accuracy between the 2 groups. Although different numbers of women were required to achieve the necessary mammogram-level matching, our estimates for cancer rates, cancer detection rate, and interval cancer rate are reported per 1000 screening examinations, with follow-up set at 12 months for all screens, allowing unbiased comparison of these rates between the 2 groups. Furthermore, the majority of women in both groups reported having mammography before that included in our analysis (Table 1); hence, our estimates represent predominantly incident (repeated) screening outcomes and allow analytically for clustering in women with multiple screens.

In general, screening did not perform as well in PHBC women relative to that in women without PHBC: sensitivity and specificity were lower for PHBC women,

Table 2. Screening Mammography Accuracy and Outcomes in Women With a Personal History of Breast Cancer (PHBC) and Matched Screening Mammograms in non-PHBC Women

Measure of Accuracy or Outcome (Total Screens or Total Cancers, Both Groups)	Screens With PHBC (95% CI)[a]	Screens Without PHBC (95% CI)[b]	*P* Value
No. of screening mammograms (117 660 screens) [117 740 screens][c]	58 830 [58 870][c]	58 830 [58 870][c]	
No. of in situ or invasive breast cancers (956 cancers) [997 cancers][c]	615 [655][c]	341 [342][c]	
Cancer rate/1000 mammograms[d] (117 660 screens) [117 740 screens][c]	10.5 (9.7-11.3) [11.1 {10.3-12.0}][c]	5.8 (5.2-6.4) [5.8 {5.2-6.5}][c]	<.001 <.001
No. of cancers detected on screening mammography	402	261	
CDR/1000 mammograms (117 660 screens)	6.8 (6.2-7.5)	4.4 (3.9-5.0)	<.001
DCIS detection rate (117 660 screens)	2.0 (1.7-2.4)	0.8 (0.6-1.0)	<.001
Invasive cancer detection rate (117 660 screens)	4.8 (4.3-5.4)	3.7 (3.2-4.2)	.002
CDR/1000 mammograms in PHBC of DCIS (12 135 screens)[e]	11.5 (9.8-13.6)		
CDR/1000 mammograms in PHBC of invasive cancer (46 695 screens)[f]	5.6 (5.0-6.3)		
No. of interval cancers	213	80	
ICR/1000 mammograms (117 660 screens)	3.6 (3.2-4.1)	1.4 (1.1-1.7)	<.001
Interval cancers, % (956 cancers)	34.6 (31.0-38.5) [213/615]	23.5 (19.3-28.3) [80/341]	<.001
Mammograms with additional same-day imaging or recommendation, based on initial screening recommendation, % (117 422 screens)	18.1 (17.6-18.6) [10 612/58 696]	8.3 (8.1-8.5) [4862/58 726]	<.001
AIR, based on final assessment (117 660 screens)[g]	2.3 (2.2-2.5) [1377/58 830]	1.4 (1.3-1.5) [847/58 830]	<.001
Mammograms positive and recommended for fine-needle aspiration, biopsy, or surgical consultation, based on final recommendation, % (117 640 screens)	2.2 (2.1-2.3) [1280/58 815]	1.4 (1.3-1.5) [798/58 825]	<.001
Sensitivity, % (956 screens associated with cancer)[g]	65.4 (61.5-69.0) [402/615]	76.5 (71.7-80.7) [261/341]	<.001
Sensitivity for detection of invasive cancers, % (749 screens associated with invasive cancer)[g]	61.1 (56.6-65.4) [284/465]	75.7 (70.4-80.3) [215/284]	<.001
Sensitivity for detection of DCIS, % (207 screens associated with DCIS)[g]	78.7 (71.4-84.5) [118/150]	80.7 (68.4-89.0) [46/57]	.74
Specificity, % (116704 screens not associated with cancer)[g]	98.3 (98.2-98.4) [57 240/58 215]	99.0 (98.9-99.1) [57 903/58 489]	<.001
PPV, % (2224 positive screen results)[h]	29.2 (26.8-31.7) [402/1377]	30.8 (27.8-34.0) [261/847]	.42

Abbreviations: AIR, abnormal interpretation rate; CDR, cancer detection rate; CI, confidence interval; DCIS, ductal carcinoma in situ; ICR, interval cancer rate; PPV, positive predictive value.

[a] Forty PHBC screens from women with a history of mastectomy, associated with ipsilateral cancer recurrence during follow-up, were excluded from analysis of accuracy; all rates are per 1000 screens, and all percentages are shown with numerator and denominator.

[b] Forty screens without PHBC (matched screening examinations) were excluded from analysis of accuracy; all rates are per 1000 screens, and all percentages are shown with numerator and denominator.

[c] Numbers and rates in square brackets include 40 screens with ipsilateral cancer (recurrence on mastectomy side), or 40 matched screens in the cohort without PHBC.

[d] Cancer rate refers to all cancers identified in screening participants (screen-detected and interval cancers).

[e] CDR in women with PHBC of DCIS (12135 screens) included DCIS detection rate of 4.9 per 1000 mammograms (95% CI, 3.8-6.3) and invasive CDR of 6.7 per 1000 mammograms (95% CI, 5.4-8.3).

[f] CDR in women with PHBC of invasive cancer (46695 screens) included DCIS detection rate of 1.3 per 1000 mammograms (95% CI, 1.0-1.6) and invasive CDR of 4.3 per 1000 mammograms (95% CI, 3.8-5.0).

[g] Estimates based on positive mammogram results are defined as Breast Imaging Reporting and Data System (BI-RADS) assessments 4 or 5 or a BI-RADS assessment of 0 or 3 with a recommendation for biopsy, fine-needle aspiration, or surgical consultation. Negative mammogram results included BI-RADS assessments 1 or 2 or an assessment of 3 without recommendation for biopsy, fine-needle aspiration, or surgical consultation. Missing final result was BI-RADS assessment of 0 with recommendation for additional imaging or unspecified evaluation or missing recommendation. All remaining assessments of 0 were considered negative.

[h] Percentage of positive mammogram results on final imaging assessment associated with a cancer diagnosis.

Table 3. Screening Mammography Accuracy and Cancer Rates in Women With a Personal History of Breast Cancer (n = 58830 Screens)

	% (95% CI)				Rate (95% CI)		
	Sensitivity	Specificity	AIR[a]	PPV[b]	Cancer[c]	Cancer Detection[d]	Interval Cancer[e]
Age at mammography, y							
<50	51.0 (41.4-60.4)[f]	97.8 (97.4-98.1)[f]	2.9 (2.6-3.4)[f]	26.5 (20.9-33.0)[f]	15.2 (12.6-18.4)[f]	7.8 (5.9-10.2)	7.5 (5.7-9.8)[f]
50-59	64.0 (56.0-71.3)[f]	98.1 (97.9-98.4)[f]	2.5 (2.3-2.8)[f]	26.4 (22.2-31.2)[f]	10.3 (8.8-12.1)[f]	6.6 (5.4-8.1)	3.7 (2.9-4.9)[f]
60-69	71.8 (63.3-78.9)[f]	98.3 (98.1-98.5)[f]	2.3 (2.0-2.5)[f]	26.7 (22.2-31.8)[f]	8.4 (7.0-10.0)[f]	6.0 (4.9-7.4)	2.4 (1.7-3.3)[f]
≥70	69.2 (63.1-74.7)[f]	98.6 (98.4-98.7)[f]	2.1 (1.9-2.3)[f]	34.1 (29.9-38.5)[f]	10.4 (9.2-11.9)[f]	7.2 (6.2-8.4)	3.2 (2.6-4.0)[f]
BI-RADS breast density; excludes 12 956 screens missing data							
1, Almost entirely fatty	73.3 (46.7-89.6)	99.0 (98.6-99.3)[f]	1.3 (1.0-1.7)[f]	24.4 (14.1-39.0)	4.4 (2.6-7.2)[f]	3.2 (1.8-5.8)[f]	1.2 (0.4-3.1)[f]
2, Scattered fibroglandular tissue	69.4 (62.8-75.3)	98.4 (98.2-98.6)[f]	2.2 (2.0-2.4)[f]	29.6 (25.7-33.8)	9.4 (8.2-10.8)[f]	6.5 (5.6-7.7)[f]	2.9 (2.3-3.7)[f]
3, Heterogeneously dense	61.2 (54.4-67.5)	98.3 (98.1-98.5)[f]	2.4 (2.1-2.6)[f]	30.0 (25.8-34.5)	11.5 (10.0-13.2)[f]	7.1 (5.9-8.4)[f]	4.5 (3.6-5.6)[f]
4, Extremely dense	55.3 (39.5-70.1)	97.7 (97.0-98.3)[f]	3.1 (2.5-3.9)[f]	28.0 (19.0-39.2)	15.7 (11.4-21.6)[f]	8.7 (5.7-13.3)[f]	7.0 (4.4-11.3)[f]
Time since last mammogram; excludes 1061 screens missing data, mo							
9-14	63.8 (59.4-67.9)	98.5 (98.3-98.6)[f]	2.2 (2.0-2.3)[f]	29.7 (27.0-32.6)	10.1 (9.2-11.0)	6.4 (5.8-7.2)	3.7 (3.2-4.2)
15-23	70.5 (59.5-79.6)	98.0 (97.6-98.3)[f]	2.8 (2.4-3.2)[f]	27.0 (21.3-33.5)	10.6 (8.5-13.2)	7.5 (5.7-9.7)	3.1 (2.1-4.7)
≥24	67.5 (51.7-80.1)	97.7 (97.0-98.2)[f]	3.3 (2.7-4.1)[f]	31.4 (22.5-41.9)	15.5 (11.4-21.1)	10.5 (7.2-15.3)	5.1 (2.9-8.7)
Time since first breast cancer diagnosis, y							
<1	64.0 (49.9-76.0)[f]	97.0 (96.4-97.4)[f]	3.7 (3.2-4.3)[f]	19.5 (14.1-26.3)[f]	11.4 (8.6-14.9)	7.3 (5.1-10.3)[f]	4.1 (2.6-6.5)
1-2	59.7 (51.0-67.8)[f]	97.8 (97.6-98.1)[f]	2.7 (2.4-3.0)[f]	20.3 (16.5-24.6)[f]	9.1 (7.7-10.8)	5.5 (4.4-6.8)[f]	3.7 (2.8-4.8)
3-4	59.3 (50.8-67.2)[f]	98.4 (98.2-98.6)[f]	2.1 (1.9-2.4)[f]	26.8 (22.0-32.1)[f]	9.6 (8.1-11.4)	5.7 (4.6-7.1)[f]	3.9 (3.0-5.1)
5-6	75.4 (66.9-82.4)[f]	98.5 (98.3-98.8)[f]	2.3 (2.0-2.6)[f]	36.8 (31.0-43.0)[f]	11.1 (9.3-13.2)	8.3 (6.8-10.3)[f]	2.7 (1.9-3.9)
7-9	63.7 (54.6-71.9)[f]	98.8 (98.5-99.0)[f]	2.0 (1.7-2.3)[f]	37.7 (31.0-44.8)[f]	11.7 (9.7-14.1)	7.4 (5.9-9.4)[f]	4.2 (3.1-5.7)
≥10	74.3 (62.8-83.2)[f]	99.2 (98.9-99.4)[f]	1.7 (1.4-2.1)[f]	51.5 (41.7-61.2)[f]	11.9 (9.4-15.0)	8.8 (6.7-11.6)[f]	3.1 (1.9-4.8)
Type of first breast cancer							
DCIS	72.9 (66.2-78.7)[f]	98.0 (97.8-98.3)[f]	3.1 (2.8-3.4)[f]	37.4 (32.6-42.5)[f]	15.8 (13.7-18.2)[f]	11.5 (9.8-13.6)[f]	4.3 (3.3-5.6)
Invasive cancer	61.9 (57.2-66.4)[f]	98.4 (98.3-98.5)[f]	2.1 (2.0-2.3)[f]	26.1 (23.5-28.9)[f]	9.1 (8.2-10.0)[f]	5.6 (5.0-6.3)[f]	3.4 (3.0-4.0)
Primary surgery; excludes 1149 screens missing data							
Breast conserving without radiation	63.6 (55.1-71.4)	97.9 (97.6-98.2)[f]	3.1 (2.8-3.6)[f]	35.6 (29.7-41.9)[f]	17.6 (14.9-20.8)[f]	11.2 (9.1-13.8)[f]	6.4 (4.8-8.5)[f]
Breast conserving with radiation	64.8 (59.5-69.7)	98.0 (97.8-98.2)[f]	2.7 (2.5-2.9)[f]	26.9 (23.9-30.0)[f]	11.2 (10.0-12.4)[f]	7.2 (6.3-8.3)[f]	3.9 (3.3-4.7)[f]
Mastectomy	65.0 (56.1-72.9)	99.0 (98.9-99.1)[f]	1.4 (1.2-1.5)[f]	27.5 (22.6-33.1)[f]	5.8 (4.8-7.0)[f]	3.8 (3.0-4.7)[f]	2.0 (1.5-2.8)[f]
Radiation therapy; excludes 1136 screens missing data							
None	64.5 (58.0-70.6)	98.6 (98.5-98.8)[f]	2.0 (1.8-2.2)[f]	33.1 (28.8-37.7)[f]	10.4 (9.1-11.9)	6.7 (5.7-7.9)	3.7 (3.0-4.6)
Any	64.5 (59.5-69.2)	98.2 (98.0-98.3)[f]	2.5 (2.3-2.6)[f]	26.3 (23.5-29.3)[f]	10.0 (9.0-11.1)	6.5 (5.7-7.3)	3.6 (3.0-4.2)
Adjuvant systemic therapy; excludes 3501 screens missing data							
None	71.0 (66.0-75.5)[f]	98.3 (98.1-98.4)	2.6 (2.4-2.8)[f]	33.8 (30.4-37.4)[f]	12.4 (11.2-13.8)[f]	8.8 (7.8-10.0)[f]	3.6 (3.0-4.4)
Any, chemotherapy or endocrine	54.1 (47.5-60.6)[f]	98.4 (98.2-98.6)	2.0 (1.8-2.2)[f]	21.5 (18.2-25.1)[f]	8.0 (7.0-9.1)[f]	4.3 (3.6-5.2)[f]	3.7 (3.0-4.5)
Self-reported history of breast implant, reduction, or reconstruction; excludes 14 387 screens missing data							
No	66.0 (61.3-70.3)	98.5 (98.4-98.6)	2.2 (2.0-2.3)[f]	31.0 (28.1-34.2)	10.2 (9.2-11.2)[f]	6.7 (6.0-7.5)[f]	3.5 (2.9-4.1)
Yes	50.0 (29.4-70.6)	98.8 (98.3-99.1)	1.5 (1.1-2.0)[f]	21.3 (11.8-35.4)	6.5 (4.2-10.0)[f]	3.2 (1.7-6.0)[f]	3.2 (1.7-6.0)

Abbreviations: AIR, abnormal interpretation rate; BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; DCIS, ductal carcinoma in situ; PPV, positive predictive value.

[a] Percentage with positive mammogram results based on final imaging assessment.

[b] Percentage of positive mammogram results on final imaging assessment associated with a cancer diagnosis.

[c] Cancer rates per 1000 screening mammograms (all screen-detected and interval cancers identified).

[d] Cancer detection rates per 1000 screening mammograms (based on true-positive mammograms).

[e] Interval cancer rates per 1000 screening mammograms (based on false-negative mammograms).

[f] $P < .05$ based on score statistics obtained in generalized estimating equation analyses.

and screening examinations were approximately twice as likely to be recommended for additional imaging or biopsy. Screening positive predictive value was similar in both groups, in part because of the higher cancer incidence in PHBC women. Cancer rates, cancer detection rate, interval cancer rate, and the proportion of cancers that were interval cancers were significantly higher in PHBC women, highlighting their higher underlying risk of breast cancer, as well as their relatively lower screening sensitivity. Despite the lower sensitivity, the stage distribution of screen-detected cancers shows that mammography is effective in detecting early-stage second breast cancers in PHBC women because the majority were ductal carcinoma in situ or stage I cancers. Our findings support annual mammography screening recommendations in PHBC women[7,8,10] but also highlight issues needing further evaluation.

We report a relatively high interval cancer rate in PHBC women, even though the majority of screens were conducted between 9 and 14 months after the previous mammogram. We cannot compare our interval cancer rate to that of other studies because, to our knowledge, this is the first report of interval cancer rate for screening PHBC women that factors ascertainment of both ipsilateral and contralateral breast outcomes and a relative interval cancer rate for matched screens in women without PHBC. One other study of population-based screening of women with PHBC,[26] based on 114 women with contralateral cancer, reported sensitivities of 59.6% overall and 70.8% for the subgroup with annual mammography. Screening specificity was 98.3% and the proportion of contralateral breast cancers that were interval cancers was 34.2%[26] (similar to data in Table 2); however, interval cancer rate was not reported. Buist et al[1] recently reported that about one-third of second breast cancers in BCSC women were not screen detected. Comparison of our work with other studies of PHBC women is not appropriate because the latter generally reports the proportion of second cancers detected by mammography in selected series of PHBC women and does not provide valid data on all measures of screening accuracy.[6,13]

We used final assessment to calculate screening accuracy rather than initial interpretation based only on the screening mammogram because a substantial number of PHBC women had additional imaging on the same day as the screen. We were unable to distinguish the extent to which this represented evaluation of screen-detected abnormalities or additional imaging

Table 4. Detection of Ipsilateral and Contralateral Breast Cancers in Women With a Personal History of Breast Cancer

	Detection of Ipsilateral Cancers (n = 258)		Detection of Contralateral Cancers (n = 333)	
	No./Total[a]	Sensitivity (95% CI)	No./Total[a]	Sensitivity (95% CI)
Overall screening mammography sensitivity	171/258	66.3 (60.3-71.8)	220/333	66.1 (60.9-70.9)
Age at mammography, y				
<50	34/60	56.7 (44.0-68.5)	18/41	43.9 (29.7-59.2)[b]
50-59	47/76	61.8 (50.5-72.0)	43/66	65.2 (53.0-75.6)[b]
60-69	36/47	76.6 (62.5-86.5)	52/72	72.2 (61.0-81.2)[b]
≥70	54/75	72.0 (61.0-80.9)	107/154	69.5 (61.9-76.2)[b]
BI-RADS breast density				
1, Almost entirely fatty	4/5	80.0 (NC)[c]	7/9	77.8 (NC)[c]
2, Scattered fibroglandular tissue	66/93	71.0 (60.8-79.4)	75/108	69.4 (60.2-77.3)
3, Heterogeneously dense	51/86	59.3 (48.7-69.1)	69/109	63.3 (54.1-71.7)
4, Extremely dense	11/16	68.8 (43.3-86.4)	10/22	45.5 (26.5-65.9)
Time since last mammogram, mo				
9-14	124/197	62.9 (56.0-69.4)	178/269	66.2 (60.4-71.5)
15-23	27/37	73.0 (56.7-84.8)	26/38	68.4 (52.2-81.1)
≥24	10/13	76.9 (47.8-92.4)	14/23	60.9 (40.2-78.2)
Time since first breast cancer diagnosis, y				
<1	17/22	77.3 (55.6-90.2)	14/24	58.3 (38.3-75.9)[b]
1-2	34/57	59.6 (46.5-71.5)	39/66	59.1 (46.9-70.2)[b]
3-4	45/69	65.2 (53.3-75.5)	35/64	54.7 (42.6-66.2)[b]
5-6	33/43	76.7 (61.9-87.0)	53/70	75.7 (64.4-84.3)[b]
7-9	25/42	59.5 (44.6-72.8)	45/67	67.2 (55.3-77.2)[b]
≥10	17/25	68.0 (47.8-83.1)	34/42	81.0 (66.3-90.2)[b]
Type of first breast cancer				
Ductal carcinoma in situ	83/112	74.1 (65.2-81.4)[b]	52/72	72.2 (60.8-81.3)
Invasive cancer	88/146	60.3 (52.1-67.9)[b]	168/261	64.4 (58.4-69.9)
Primary surgery				
Breast conserving without radiation	55/83	66.3 (55.5-75.6)	29/48	60.4 (46.1-73.1)
Breast conserving with radiation	99/154	64.3 (56.4-71.5)	108/165	65.5 (57.9-72.3)
Mastectomy	NA	NA	75/110	68.2 (59.1-76.1)
Radiation therapy				
None	55/83	66.3 (55.5-75.6)	85/131	64.9 (56.4-72.5)
Any	99/154	64.3 (56.4-71.5)	128/194	66.0 (59.1-72.2)
Adjuvant systemic therapy				
None	110/153	71.9 (64.3-78.4)[b]	130/180	72.2 (65.3-78.2)[b]
Any, chemotherapy or endocrine	40/78	51.3 (40.2-62.3)[b]	74/131	56.5 (48.0-64.6)[b]
Self-reported history of breast implant, reduction, or reconstruction				
No	119/181	65.7 (58.5-72.3)	152/227	67.0 (60.6-72.7)
Yes	2/3	66.7 (NC)[c]	7/16	43.8 (22.5-67.6)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; NA, not applicable.
[a] Number of screen-detected cancers (ie, positive screen results associated with ipsilateral or contralateral cancer during follow-up) and total number of cancers observed at 12 mo (ie, number of screens associated with ipsilateral or contralateral cancer during follow-up). For each variable, total in columns may not equal the overall total because of missing data.
[b] $P < .05$, based on score statistics obtained in generalized estimating equation analyses.
[c] Not calculated (NC) if fewer than 10 events.

performed as standard of care for PHBC women at some facilities. An absolute estimate of screening "recall rate" that includes callback for additional imaging could therefore not be estimated. Our "abnormal" assessment measure was based on a recommendation for biopsy or surgical consultation, whereas studies of population breast screening accuracy often consider recommendations for additional imaging as a positive result. Thus, our abnormal interpretation rate, sensitivity, and specificity are not directly comparable to the recall rate, sensitivity, and specificity usually reported in population screening evaluations, and studies focusing on PHBC women have not reported screening recall rates.[6,13] Our study provides valid relative estimates of accuracy measures, including a significantly higher abnormal interpretation rate and lower sensitivity and specificity in PHBC women relative to non-PHBC women. We also found that additional imaging at initial screening was more than twice as frequent among PHBC women, although this was predominantly due to same-day additional imaging in PHBC women.

Screening examinations of PHBC women revealed an approximately 2-fold higher risk of breast cancer during follow-up relative to screens of women without PHBC, matched for age, breast density, mammography registry, and year. Underlying cancer rates were lower in PHBC women who had mastectomy rather than breast-conserving surgery for the first cancer and were similar to cancer rates in the matched non-PHBC cohort (Tables 2 and 3), which is consistent with recent risk models that estimated that lifetime risk of breast cancer in PHBC women is a function of the number of breasts at risk for developing another cancer.[20] This may also partly account for the higher specificity and lower cancer rates found in PHBC women with mastectomy in our data. Our study shows that PHBC women have heterogeneous risk for developing another breast cancer; thus, consideration of a more tailored screening approach might be warranted in some PHBC women, according to our estimates for underlying cancer rates and screening sensitivity. The highest observed cancer rates in our PHBC cohort (>12 cancers/1000 screens, or greater than twice the cancer rates in non-PHBC women) were in women younger than 50 years, women with extremely dense breasts, women with previous ductal carcinoma in situ, women who received breast-conserving surgery without radiation or did not receive any systemic therapy, and those with interscreening interval greater than 2 years.

We were surprised to find higher mammography sensitivity (evident for ipsilateral and contralateral cancer) in women who had not received systemic therapy, for whom underlying cancer rates were also higher compared with those who received chemotherapy or endocrine therapy. Examination of this association, after adjusting for relevant variables, showed significantly reduced sensitivity only in women who received chemotherapy. Because receipt of systemic therapy was based on cancer registry information, the data might have been incomplete. Further research examining whether this finding may be due to potential confounding by biological factors associated with first cancer treatment (for example, hormone receptor status) would be valuable. Similarly, some of our findings should be interpreted with consideration of possible confounding by factors associated with the first cancer and its treatment. For example, the higher cancer rates, cancer detection rate, and screening sensitivity in PHBC women whose first cancer was ductal carcinoma in situ may be reflecting the effect of use of systemic therapy (usually not used for ductal carcinoma in situ and frequently used for invasive cancer), which reduces the risk of another breast cancer, rather than a differential biological susceptibility in women with personal history of ductal carcinoma in situ relative to invasive cancer.

The interval cancer rate we report for PHBC women might raise concerns about whether the potential benefit of screening is fully realized in these women. Although there is interest in adjunct screening for PHBC women,[19,20,27] there is no evidence that this improves clinical end points and no consensus regarding which of these women (other than those with proven cancer gene mutations) should have adjunct imaging. Furthermore, despite a relatively high interval cancer rate in PHBC women, interval cancers were predominantly early stage, although the proportion of stage IIB and III cancers was slightly higher than that of non-PHBC interval cancers. Thus, although mammography screening is less sensitive in PHBC women, our study provides evidence that both screen-detected and interval cancers are, in general, equally early stage among PHBC women and those without PHBC. These data neither support nor negate a role for adjunct screening in PHBC women but suggest that adjunct screening should be studied in women younger than 50 years, women with denser breasts, or those who received chemotherapy for their first cancer because screening these women had the lowest sensitivity among PHBC women. The data also raise consideration of exploring alternate approaches, such as biomarkers, for future screening in PHBC women. Evaluation of adjunct (or alternate) screening might be considered in PHBC subgroups in whom unacceptably high interval cancer rates were found (for example, interval cancer rate ≥6 cancers/1000 screens), including women younger than 50 years, women with extremely dense breasts, and those who received breast conservation without radiotherapy for their first cancer.

Our findings on interval cancers in PHBC women raise several possibilities. First, PHBC women may have different host factors predisposing them not only to risk of a second breast cancer but also to breast cancers that are less likely to be detected with screening, possibly because of more rapid growth or other tumor biology characteristics. Second, they may partly re-

flect higher breast awareness by PHBC women, who might seek help promptly for breast symptoms. Third, assuming that many interval cancers in PHBC women are symptomatic diagnoses is reasonable, but some interval cancers may be due to adjunct screening (magnetic resonance imaging or ultrasonography) occurring in between mammography screenings. We did not have data to examine adjunct screening as a possible explanation for the early-stage interval cancers in PHBC women, but guidelines for magnetic resonance imaging screening in high-risk women were available at the end of our study.[19]

This study provides evidence that screening mammography detects early-stage breast cancers in PHBC women but has lower accuracy relative to screening women without PHBC. Despite a relatively high interval cancer rate, interval cancers in PHBC women had generally favorable stage distributions. Our work also shows that screening outcomes and breast cancer rates in PHBC women are associated with various factors, including the treatment received for the first cancer, so these women have heterogeneous underlying risks for a second breast cancer, and a more tailored screening strategy than currently recommended might be warranted.

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