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JNCI J Natl Cancer Inst (2015) 107(7): djv109

doi:10.1093/jnci/djv109
First published online April 22, 2015
Article

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Five-Year Risk of Interval-Invasive Second Breast Cancer

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Abstract

Background: Earlier detection of second breast cancers after primary breast cancer (PBC) treatment improves survival, yet mammography is less accurate in women with prior breast cancer. The purpose of this study was to examine women presenting clinically with second breast cancers after negative surveillance mammography (interval cancers), and to estimate the five-year risk of interval-invasive second cancers for women with varying risk profiles.

Methods: We evaluated a prospective cohort of 15 114 women with 47 717 surveillance mammograms diagnosed with stage 0-II unilateral PBC from 1996 through 2008 at facilities in the Breast Cancer Surveillance Consortium. We used discrete time survival models to estimate the association between odds of an interval-invasive second breast cancer and candidate predictors, including demographic, PBC, and imaging characteristics. All statistical tests were two-sided.

Results: The cumulative incidence of second breast cancers after five years was 54.4 per 1000 women, with 325 surveillance-detected and 138 interval-invasive second breast cancers. The five-year risk of interval-invasive second cancer for women with referent category characteristics was 0.60%. For women with the most and least favorable profiles, the five-year risk ranged from 0.07% to 6.11%. Multivariable modeling identified grade II PBC (odds ratio [OR] = 1.95, 95% confidence interval [CI] = 1.15 to 3.31), treatment with lumpectomy without radiation (OR = 3.27, 95% CI = 1.91 to 5.62), interval PBC presentation (OR = 2.01, 95% CI 1.28 to 3.16), and heterogeneously dense breasts on mammography (OR = 1.54, 95% CI = 1.01 to 2.36) as independent predictors of interval-invasive second breast cancers.

Conclusions: PBC diagnosis and treatment characteristics contribute to variation in subsequent-interval second breast cancer risk. Consideration of these factors may be useful in developing tailored post-treatment imaging surveillance plans.

Advances in screening and treatment of primary breast cancer have improved survival for many women, and the number of breast cancer survivors will continue to increase (1–3). Women surviving their initial breast cancer diagnosis remain at risk of subsequent local/regional recurrence in the index breast or new primary cancers in the contralateral breast ("second breast cancers"), which are associated with increased rates of distant metastases and breast cancer mortality (4,5).

Post-treatment imaging surveillance is an essential element in survivorship care, as the earlier detection of second breast cancers permits interventions to improve survival and maintain quality of life (6,7). Surveillance mammography after breast cancer treatment is associated with decreased breast cancer mortality (8–11). Current surveillance recommendations are for physical examination and annual mammography (12–14), as studies to date have not identified other tests that improve patient outcomes (15–17).

Received: July 3, 2014; **Revised:** November 7, 2014; **Accepted:** March 23, 2015

Yet screening mammography has lower sensitivity in women with a personal history of breast cancer, particularly within the first five years of primary breast cancer (PBC) diagnosis (18), possibly because of patient, tumor, and treatment factors (19), or other as yet unidentified factors. Approximately 35% of second breast cancers present as interval cancers following a negative screening mammogram (10,18,20). Recent evidence also suggests that interval cancers presenting after negative mammographic screening may be more biologically aggressive (21).

Supplemental surveillance as an adjunct to mammography may lead to earlier detection and treatment of second cancers, if applied in appropriate groups of women. In this study, we estimated interval-invasive second breast cancer risk during the first five years of post-treatment surveillance. In addition, we sought to identify characteristics of women most likely to present with interval-invasive second breast cancers based on factors known at the time of PBC diagnosis and treatment—patient demographic, tumor, and imaging characteristics.

Methods

Study Setting and Data Sources

We included surveillance mammograms for women with prior breast cancer performed from 1996 through 2008 at facilities in five Breast Cancer Surveillance Consortium (BCSC) registries (22): Carolina Mammography Registry (North Carolina), Group Health Registry (Washington State), New Hampshire Mammography Network, New Mexico Mammography Project, and Vermont Breast Cancer Surveillance System. Registries collected data from community radiology facilities including patient characteristics and clinical information. Radiologists' assessments, recommendations, and mammographic breast density used the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) (23). Breast cancer diagnoses and tumor characteristics were obtained by linking BCSC data to pathology databases, regional Surveillance, Epidemiology, and End Results (SEER) programs, and state tumor registries. Data were pooled at a Statistical Coordinating Center (SCC). Registries and the SCC received institutional review board approval for data collection and analysis. All procedures were Health Insurance Portability and Accountability Act–compliant, and registries and the SCC received a Federal Certificate of Confidentiality for the identities of women, physicians, and facilities.

Participants

We included all women with incident ductal carcinoma in situ (DCIS) or stage I-II invasive carcinoma diagnoses, except those treated with bilateral mastectomy. We identified women who received mammography at BCSC facilities within two years before primary breast cancer diagnosis or one year afterward. We defined a surveillance mammogram as one indicated as a routine examination by the radiologist or technologist, excluding examinations within nine months of a prior mammogram or where the woman reported symptoms (18–20). For each woman we included all surveillance mammograms after PBC diagnosis until the first of diagnosis of second breast cancer, death, or disenrollment from the health care system (for women in the Group Health registry) and included no subsequent mammograms after the first of these events. Because some women may have received mammograms outside of the BCSC, women were also censored at the time of a discrepancy six months or more between observed and self-reported time of prior mammography in the BCSC database.

Measures and Definitions

Demographic characteristics, history of first-degree relatives with breast cancer, and menopausal status were obtained on a self-administered questionnaire (22) completed by women at each mammography visit. Breast density was categorized by radiologists using BI-RADS breast density categories (23): 1 = almost entirely fat, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, 4 = extremely dense.

PBCs were classified by stage, grade, hormone receptor status, receipt of adjuvant systemic therapy (chemotherapy or hormonal therapy), and primary surgery (breast conservation, mastectomy) based on records from cancer registry and pathology databases that included treatments received within six months of initial diagnosis. Stage was defined using the American Joint Committee on Cancer (AJCC) staging system, 6th edition (24). Time since PBC was the difference between PBC diagnosis date and surveillance mammogram date. For missing cancer registry surgery information, self-reported mastectomy and lumpectomy history (collected within 18 months after diagnosis and before second breast cancer diagnosis) was used.

PBC mode of detection was defined using previously established definitions (25): screen-detected (closest screening mammogram within two years prior to diagnosis is positive), interval cancer (closest screening mammogram prior to diagnosis is negative), clinical/diagnostic detection (only diagnostic mammograms prior to cancer diagnosis), or other (screening mammogram with missing results or with follow-up recommended but no subsequent mammogram). In classifying mode of detection, including mammograms up to two years before PBC diagnosis enabled accounting for women screened at either one- or two-year intervals. Women with no screening or diagnostic mammograms in two years before PBC diagnosis or 30 days afterward were considered to have missing mode of detection data. In sensitivity analyses, we redefined mode of detection using a one year look-back period (26).

Second breast cancer outcomes were defined as DCIS or invasive breast cancer in either the index or contralateral breast, identified within 12 months of a surveillance mammogram and prior to the next surveillance mammogram by either tumor registry or institutional pathology data. Second breast cancer outcomes were further defined as surveillance-detected if the initial surveillance mammogram was positive (radiologist's BI-RADS (23) assessment of 0, 4, 5, or 3 with recommendation for immediate evaluation). An interval-invasive second cancer was defined when an invasive second cancer was observed after an initial surveillance mammogram with negative results (radiologist's BI-RADS assessment of 1, 2, or 3 without recommendation for immediate follow-up).

Statistical Analysis

Treating the surveillance mammography examination as the unit of analysis, we evaluated the distribution of surveillance mammograms, second breast cancers, and interval-invasive second cancers by demographic, imaging and surveillance characteristics, and characteristics of the first cancer and its treatment. We summarized follow-up available for women with and without second cancer diagnoses using lasagna plots (27,28), allowing for longitudinal trend examination (29). We compared observed incidence rates across surveillance rounds using a chi-square test (two-sided). We estimated the overall incidence rate for second cancers and the incidence rate for

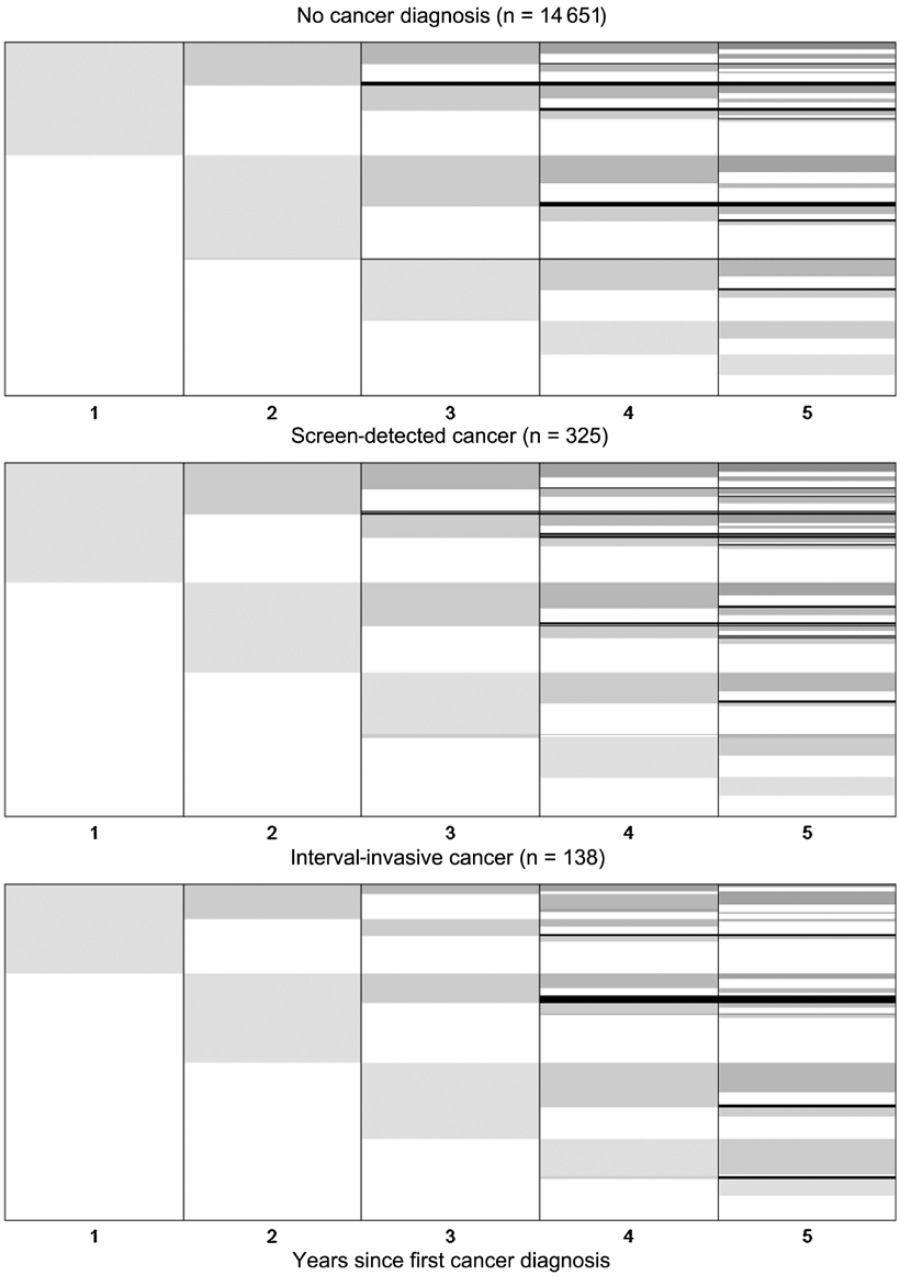

Figure 1. Number of mammograms available and length of follow-up stratified by outcome. Colors shading from **light gray** to **dark gray** indicate total number of screening mammograms at or prior to the current year. **White** indicates no mammography in that year. **Black** indicates censored from observation because of death, cancer diagnosis, disenrollment from Group Health, or discrepancy between self-report and database time since prior mammography.

surveillance-detected and interval-invasive second cancers using discrete-time survival models.

We also used discrete-time survival models to estimate the five-year cumulative probability of an interval-invasive cancer following PBC treatment (30,31). We parameterized our model by assuming a logistic relationship between the probability of an interval-invasive breast cancer at each surveillance mammography round and covariates of interest. We first fit a "minimally adjusted model" separately for each covariate of interest, adjusting for BCSC registry and surveillance round. We then fit a "fully adjusted" model that included all covariates simultaneously. Estimates of the probability of an interval-invasive second cancer at each screening round were aggregated across rounds to give a woman-level estimate of the five-year cumulative probability of an interval-invasive cancer.

To better understand the range of risk for an interval-invasive second breast cancer for women with varying combinations of risk factors, the fully adjusted model was also used to generate risk estimates for three profiles. The first "referent" profile used referent categories for all predictors. Women in this profile were non-Hispanic white, post-menopausal, age 60 to 69 years, with no family history of breast cancer, who were diagnosed with stage I, grade I, hormone receptor–positive first cancers, treated with mastectomy and who received no adjuvant therapy. The most favorable and least favorable risk profiles were created after the fully adjusted model was developed. The most favorable profile used referent categories for non-statistically

Table 1. Distribution of variables in women with a personal history of breast cancer who underwent surveillance mammography, 1996–2008*

Variable (proportion missing data for variable where applicable)	No. surveillance mammograms (%)	No. screen-detected second cancers (%)	No. invasive interval second cancers (%)
Total	47 717 (100)	325	138
Demographic characteristics			
Age at mammography, y			
<40	596 (1.2)	3 (0.9)	7 (5.1)
40–49	5283 (11.1)	42 (12.9)	25 (18.1)
50–59	12 621 (26.4)	84 (25.8)	41 (29.7)
60–69	12 120 (25.4)	83 (25.5)	19 (13.8)
70–79	11 564 (24.2)	75 (23.1)	36 (26.1)
80+	5533 (11.6)	38 (11.7)	10 (7.2)
Race/ethnicity (3.6%)			
White, non-Hispanic	39 423 (85.7)	277 (88.8)	110 (84.6)
Black, non-Hispanic	1582 (3.4)	8 (2.6)	4 (3.1)
Hispanic	3262 (7.1)	17 (5.4)	11 (8.5)
Asian, Pacific Islander	737 (1.6)	5 (1.6)	3 (2.3)
Other	1000 (2.2)	5 (1.6)	2 (1.5)
Menopausal status (13.2%)			
Post	37 614 (90.9)	248 (86.7)	93 (82.3)
Peri-	740 (1.8)	7 (2.4)	4 (3.5)
Pre-	3042 (7.3)	31 (10.8)	16 (14.2)
First-degree family history of breast cancer (15.4%)			
No	30 883 (76.5)	191 (69.2)	85 (71.4)
Yes	9507 (23.5)	85 (30.8)	34 (28.6)
First cancer diagnosis and treatment characteristics			
Age at first breast cancer, y (0%)			
<40	1579 (3.3)	12 (3.7)	15 (10.9)
40–49	9448 (19.8)	71 (21.8)	36 (26.1)
50–59	13 116 (27.5)	87 (26.8)	31 (22.5)
60–69	11 783 (24.7)	84 (25.8)	29 (21)
70–79	9274 (19.4)	58 (17.8)	20 (14.5)
80+	2517 (5.3)	13 (4)	7 (5.1)
Stage of first breast cancer (0%)			
0	9431 (19.8)	111 (34.2)	31 (22.5)
I	23 349 (48.9)	135 (41.5)	59 (42.8)
II-IIA	10 680 (22.4)	61 (18.8)	29 (21)
IIB	4257 (8.9)	18 (5.5)	19 (13.8)
Grade of first invasive cancer (14.6%)			
Grade I	8115 (24.8)	49 (28)	13 (13.8)
Grade II	14 128 (43.2)	66 (37.7)	40 (42.6)
Grade III	10 461 (32.0)	60 (34.3)	41 (43.6)
Hormone receptor status of invasive first cancer (14.3%)			
ER+ or PR+	27 907 (85.1)	146 (83)	67 (76.1)
ER- and PR-	4893 (14.9)	30 (17)	21 (23.9)
Primary surgery (3.2%)			
Mastectomy	15 964 (34.5)	57 (18.9)	32 (23.7)
Breast conserving with radiation	23 808 (51.5)	168 (55.6)	72 (53.3)
Breast conserving without radiation	6440 (13.9)	77 (25.5)	31 (23)
Adjuvant systemic therapy (6.3%)			
None	21 882 (48.9)	195 (66.3)	64 (49.2)
Endocrine therapy only	11 800 (26.4)	45 (15.3)	21 (16.2)
Chemotherapy only	6353 (14.2)	34 (11.6)	31 (23.8)
Chemotherapy and endocrine therapy	4738 (10.6)	20 (6.8)	14 (10.8)
Imaging and surveillance characteristics			
Mode of detection of first cancer (9.8%)			
Screen-detected	27 657 (64.3)	180 (64.3)	57 (45.2)
Interval cancer in screening	7046 (16.4)	53 (18.9)	32 (25.4)
Clinical/diagnostic detected	6443 (15.0)	33 (11.8)	34 (27)
Other	1880 (4.4)	14 (5)	3 (2.4)
BI-RADS breast density (24.1%)			
1 - Almost entirely fatty	2707 (7.5)	9 (3.7)	2 (1.9)
2 - Scattered fibroglandular tissue	17 013 (47.0)	109 (44.7)	38 (36.5)
3 - Heterogeneously dense	14 527 (40.1)	110 (45.1)	54 (51.9)
4 - Extremely dense	1971 (5.4)	16 (6.6)	10 (9.6)

Table 1. *Continued*

Variable (proportion missing data for variable where applicable)	No. surveillance mammograms (%)	No. screen-detected second cancers (%)	No. invasive interval second cancers (%)
Time since last mammogram (0.6%), mo			
9–14	40 361 (85.1)	255 (79.7)	117 (85.4)
15–23	5470 (11.5)	45 (14.1)	13 (9.5)
24+	1611 (3.4)	20 (6.2)	7 (5.1)
Time since first breast cancer diagnosis (0%), y			
<1	4775 (10.0)	35 (10.8)	14 (10.1)
1–2	13 293 (27.9)	73 (22.5)	43 (31.2)
3–4	12 600 (26.4)	71 (21.8)	35 (25.4)
5–6	8801 (18.4)	76 (23.4)	25 (18.1)
7–9	6467 (13.6)	53 (16.3)	14 (10.1)
≥10	1781 (3.7)	17 (5.2)	7 (5.1)

* n = 15 114 women. BI-RADS = American College of Radiology's Breast Imaging Reporting and Data System; ER = estrogen receptor; PR = progesterone receptor.

significant variables in the model and used the most favorable category for statistically significant predictors. The least favorable risk profile used referent categories for non-statistically significant predictors and the least favorable category for statistically significant predictors.

Missingness in individual covariates ranged from 0% to 24%. For the fully adjusted multivariable model, we used multiple imputation via chained equations to impute missing data (32,33). This method imputed each missing variable using a regression model conditional on all the other variables in the model; this was repeated for all variables with missing data. Five imputations were performed, and estimates were combined across imputations using standard methods for multiple imputation (34).

All analyses were performed using R 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided.

Results

The study population included 47 717 surveillance mammograms in 15 114 women with a personal history of breast cancer. Median age at diagnosis was 60 years (interquartile range [IQR] = 50–70 years). Most women were white, non-Hispanic (86%), postmenopausal (91%), and 24% reported a first degree relative with breast cancer. PBCs were predominantly hormone receptor–positive (85%). Most women received breast conservation and radiation therapy (52%) or mastectomy (35%), with a minority of women (14%) receiving breast conservation without radiation. Assessment of follow-up as measured by time from PBC diagnosis to last surveillance mammogram within the BCSC demonstrated a range of follow-up from less than one year to more than ten years, with median follow-up time between three and four years. Most women returned for multiple surveillance rounds, with a median of three mammograms/woman (IQR = 1–4), and 40 361 mammograms (85%) were obtained within nine to 14 months of a prior mammogram. Lasagna plots summarize the number of mammograms and length of follow-up stratified by outcome of interest (Figure 1). A minority of women had five mammograms within the five years of surveillance (contiguous gray shaded area from left to right). Others received less frequent surveillance, had moved out of BCSC catchment areas, or entered our cohort less than five years prior to the end of study follow-up. Additional demographic, primary cancer, treatment, and imaging characteristics of the study population are presented in Table 1. Cancer detection rates and interval-invasive cancer rates per 1000 exams stratified by patient and primary breast cancer characteristics are shown in Supplementary Table 1 (available online).

Second Breast Cancers

Of the 463 second breast cancers diagnosed during the five-year follow-up period, 325 (70%) were surveillance-detected and 138 (30%) were interval-invasive breast cancers. The cumulative incidence rate was 54.4 per 1000 women. There was no statistically significant difference in observed incidence rates by surveillance round ($P = .91$), which ranged from 9.2 to 10.7 per 1000 mammograms. The proportion of surveillance-detected and interval-invasive breast cancers also did not vary statistically significantly across surveillance rounds ($P = .84$).

Five-Year Risk of Interval-Invasive Second Breast Cancer

We estimated the five-year cumulative probability of an interval-invasive second breast cancer after PBC treatment, initially fitting separate models for each covariate of interest, adjusted for BCSC registry and surveillance round only. Estimates from these minimally adjusted models ranged from 0.4% for women with almost entirely fatty breast density to 4.5% for women younger than 40 years at PBC diagnosis (Table 2).

The fully adjusted multivariable model, which included all covariates of interest simultaneously, identified grade of first cancer ($P = .047$), primary surgical treatment of first cancer ($P < .001$), PBC mode of detection ($P = .004$), and breast density on surveillance mammography ($P = .024$) as independent predictors of interval-invasive second breast cancers (Table 3). Specifically, women with intermediate-grade, compared with low-grade, primary invasive cancers had an elevated risk of interval-invasive second breast cancer (OR = 1.95, 95% confidence interval (CI) = 1.15 to 3.31). Women treated with breast conservation and radiation therapy had an elevated risk compared with women who underwent mastectomy (OR = 2.13, 95% CI = 1.35 to 3.36), and women treated with breast conservation without radiation therapy had further increased risk (OR = 3.27, 95% CI = 1.91 to 5.62). Women whose PBCs presented as interval cancers after a negative screening mammogram (OR = 2.01, 1.28 to 3.16) or women whose PBCs were detected clinically or on diagnostic

Table 2. Cumulative probability of interval-invasive second breast cancer within five years of primary breast cancer diagnosis*

Characteristics	Cumulative 5-yr probability, % (95% CI)
Demographic characteristics	
Race/ethnicity	
White, non-Hispanic	1.4 (1.1 to 1.7)
Black, non-Hispanic	1.7 (0.3 to 4.0)
Hispanic	1.8 (0.8 to 3.4)
Asian, Pacific Islander	2.5 (0.0 to 5.8)
Other	1.0 (0.0 to 2.6)
Menopausal status	
Post	1.3 (1.0 to 1.6)
Pre-, Peri-	2.6 (1.5 to 3.8)
First-degree family history of breast cancer	
No	1.4 (1.1 to 1.8)
Yes	1.8 (1.2 to 2.5)
First cancer diagnosis and treatment characteristics	
Age at first breast cancer, y	
<40	4.5 (2.3 to 7.2)
40–49	1.8 (1.2 to 2.5)
50–59	1.2 (0.8 to 1.6)
60–69	1.3 (0.8 to 1.8)
70–79	1.1 (0.7 to 1.7)
80+	1.5 (0.5 to 2.7)
Stage of first breast cancer	
0	1.6 (1.1 to 2.3)
I	1.2 (0.9 to 1.6)
II-IIA	1.4 (0.9 to 1.9)
IIB	2.3 (1.3 to 3.4)
Grade of first invasive cancer	
Grade I	0.8 (0.3 to 1.3)
Grade II	1.4 (1.0 to 2.0)
Grade III	1.9 (1.3 to 2.5)
Hormone receptor status of invasive first cancer	
ER+ or PR+	1.2 (0.9 to 1.6)
ER- and PR-	2.2 (1.2 to 3.1)
Primary surgery	
Mastectomy	1.0 (0.6 to 1.3)
Breast conserving with radiation	1.5 (1.2 to 2.0)
Breast conserving without radiation	2.4 (1.6 to 3.2)
Adjuvant systemic therapy	
None	1.4 (1.0 to 1.8)
Endocrine therapy only	0.9 (0.6 to 1.4)
Chemotherapy only	2.3 (1.5 to 3.3)
Chemotherapy and endocrine therapy	1.6 (0.8 to 2.5)
Imaging and surveillance characteristics	
Mode of detection of first cancer	
Screen-detected	1.0 (0.7 to 1.3)
Interval cancer in screening	2.2 (1.4 to 3.0)
Clinical/diagnostic detected	2.7 (1.8 to 3.7)
Other	0.8 (0.0 to 1.9)
BI-RADS breast density	
1 - Almost entirely fatty	0.4 (0.0 to 0.9)
2 - Scattered fibroglandular tissue	1.1 (0.8 to 1.5)
3 - Heterogeneously dense	1.9 (1.3 to 2.5)
4 - Extremely dense	2.5 (1.1 to 4.3)
Time since first breast cancer diagnosis (0%), y	
<1	1.9 (1.2 to 2.9)
1–2	1.7 (0.7 to 3.1)
3–4	1.4 (0.9 to 2.0)
5–6	1.4 (0.8 to 2.0)
7–9	1.0 (0.4 to 1.9)
≥10	1.7 (0.4 to 4.6)

* Separate models were constructed for each covariate, adjusted only for Breast Cancer Surveillance Consortium registry and surveillance round. All statistical tests were two-sided. BI-RADS = American College of Radiology's Breast Imaging Reporting and Data System; CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor.

imaging were also more likely to have interval-invasive second breast cancers (OR = 2.12, 95% CI = 1.29 to 3.50) compared with women with screen-detected PBCs. While under surveillance, women with heterogeneously dense breasts on mammography, compared with scattered fibroglandular tissue, had higher odds ratios for interval-invasive second breast cancer (OR = 1.54, 1.01 to 2.36). Of note, in the fully adjusted multivariable model, age at diagnosis, hormone receptor status, and first-degree family history were not statistically significant predictors of subsequent interval–invasive breast cancer. In sensitivity analyses, regardless of whether a one-year or two-year look-back period was used to define mode of detection, women whose PBCs were detected clinically or on diagnostic imaging were more likely to have interval-invasive second cancers compared with women with screen-detected PBCs.

Range of Cumulative Probability Across Varying Risk Profiles

To better understand the range of risk for an interval-invasive second breast cancer for women with varying combinations of risk factors, the fully adjusted model was used to estimate the cumulative probability of this outcome (Figure 2). A woman with referent category characteristics for all predictors had a 0.60% probability of an interval-invasive second breast cancer after five rounds of annual surveillance mammography. To create the most favorable risk profile, we adjusted the base-case referent profile to reflect the most favorable categories of statistically significant predictors: screen-detected PBC, grade I, treated with mastectomy, and fatty breast tissue on surveillance mammography. A woman with this profile had a projected cumulative probability of an interval-invasive second breast cancer of 0.07%. To create the least favorable risk profile, we adjusted the base-case referent profile to include the following characteristics: clinically detected PBC, grade II, treated with lumpectomy without radiation therapy, and extremely dense breast tissue on mammography. For a woman with this risk profile, the five-year cumulative probability was 6.11%.

Discussion

We identified predictors of increased five-year risk of interval-invasive second breast cancer after PBC treatment. Our results indicate that factors known at the time of PBC diagnosis and treatment can predict subsequent second breast cancer outcomes, and that the cumulative probability of an interval-invasive second breast cancer during this period varies substantially for women with different combinations of these characteristics,

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Table 3. Fully adjusted multivariable model of interval-invasive second breast cancer within five years of primary breast cancer diagnosis*

Characteristics	Fully Adjusted OR (95% CI)	P†
Demographic characteristics		
Race/ethnicity	--	.807
White, non-Hispanic	Referent	--
Black, non-Hispanic	1.16 (0.39 to 3.45)	.792
Hispanic	1.26 (0.61 to 2.59)	.532
Asian, Pacific Islander	1.89 (0.53 to 6.72)	.325
Other	0.73 (0.18 to 2.99)	.663
Menopausal status	--	--
Post	Referent	--
Pre-, Peri-	1.05 (0.48, 2.31)	.909
First degree family history of breast cancer	--	--
No	Referent	--
Yes	1.42 (0.93 to 2.19)	.108
First cancer diagnosis and treatment characteristics		
Age at first breast cancer, y	--	.399
<40	1.94 (0.69 to 5.42)	.208
40–49	0.98 (0.47 to 2.02)	.953
50–59	0.80 (0.48 to 1.33)	.388
60–69	Referent	--
70–79	0.91 (0.51 to 1.62)	.745
80+	1.16 (0.50 to 2.70)	.736
Stage of first breast cancer	--	.336
0	1.22 (0.75 to 1.99)	.419
I	Referent	--
II-IIA	0.86 (0.52 to 1.40)	.533
IIB	1.41 (0.78 to 2.55)	.257
Grade of first invasive cancer	--	.047
Grade I	Referent	--
Grade II	1.95 (1.15 to 3.31)	.014
Grade III	1.87 (0.96 to 3.64)	.064
Hormone receptor status of invasive first cancer	--	--
ER+ or PR+	Referent	--
ER- and PR-	1.11 (0.68 to 1.81)	.679
Primary surgery	--	<.001
Mastectomy	--	--
Breast conserving with radiation	2.13 (1.35 to 3.36)	.001
Breast conserving without radiation	3.27 (1.91 to 5.62)	<.001
Adjuvant systemic therapy	--	.577
None	Referent	--
Endocrine therapy only*	0.71 (0.42 to 1.21)	.21
Chemotherapy only	1.10 (0.61 to 1.99)	.753
Chemotherapy and endocrine therapy	0.92 (0.47 to 1.78)	.799
Imaging and surveillance characteristics		
Mode of detection of first cancer	--	.004
Screen-detected	Referent	--
Interval cancer in screening	2.01 (1.28 to 3.16)	.002
Clinical/diagnostic detected	2.12 (1.29 to 3.50)	.003
Other	0.79 (0.25 to 2.52)	.688
BI-RADS breast density	--	.024
1 - Almost entirely fatty	0.25 (0.06 to 1.03)	.054
2 - Scattered fibroglandular tissue	Referent	--
3 - Heterogeneously dense	1.54 (1.01 to 2.36)	.045
4 - Extremely dense	1.65 (0.78 to 3.48)	.189
Time since last mammogram, mo	--	.256
9–14	Referent	--
15–23	0.73 (0.40 to 1.34)	.312
24+	1.62 (0.73 to 3.60)	.234
Time since first breast cancer diagnosis, y	--	.502
<1	Referent	--
1–2	0.92 (0.48 to 1.76)	.795
3–4	0.68 (0.40 to 1.14)	.143
5–6	0.61 (0.31 to 1.19)	.148
7–9	0.44 (0.18 to 1.11)	.081
≥10	0.75 (0.21 to 2.70)	.659

* Model is adjusted for all covariates included in table plus Breast Cancer Surveillance Consortium registry and number of prior surveillance mammograms. All statistical tests were two-sided. BI-RADS = American College of Radiology's Breast Imaging Reporting and Data System; CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor.
† For variables with more than two levels, P value in first row for that covariate is for omnibus Wald test of any difference across levels of the covariate.

from 0.07% in women with the most favorable risk profile to 6.11% in women with the least favorable profile.

Because approximately 70% of in-breast recurrences occur within five years of treatment (35–37), our study focused on this surveillance period. Our results extend previous BCSC reports identifying predictors of second breast cancer diagnosis (20) and interval second cancer presentation within one year of negative surveillance mammography (18,19). Houssami, et al. (19) identified age at PBC diagnosis younger than 40 years as the strongest predictor of an interval-invasive breast cancer, along with breast-conserving surgery without radiation, increased mammographic breast density, and first-degree family history of breast cancer. When considering a longer five-year surveillance horizon, multivariable modeling indicated that local treatment and breast density remained statistically significant predictors, but age at diagnosis and family history were not. PBC grade and mode of detection were additional independent predictors in this analysis.

The differences in statistically significant predictors between two studies from the same mammography registries and study period can be attributed to the more stringent inclusion criteria used in this study. To estimate the five-year cumulative probability of interval-invasive second breast cancers, we needed to capture data regarding mammography use around the time of a woman's PBC diagnosis and also to identify all post-treatment mammograms. This was not required in the prior study with a more limited one-year follow-up period after surveillance mammography (19). As a consequence, the overall sample size of women (15 114 vs 20 941) and surveillance mammograms (47 717 vs 67 819) is relatively smaller but allowed longer-term follow-up. The proportion of missing data for the predictors of interest was also smaller in this study, in particular, PBC mode of detection was not included in the model of one-year surveillance outcomes because of the proportion of missing data (19). In the current analysis, we were able to consider this predictor because greater than 90% of mode of detection data was captured. Another consequence of the smaller size of this current study is the inclusion of fewer women younger than 40 years of age at PBC diagnosis (1579 vs 2701) and fewer interval second breast cancers (15 vs 29) in these women, and fewer women

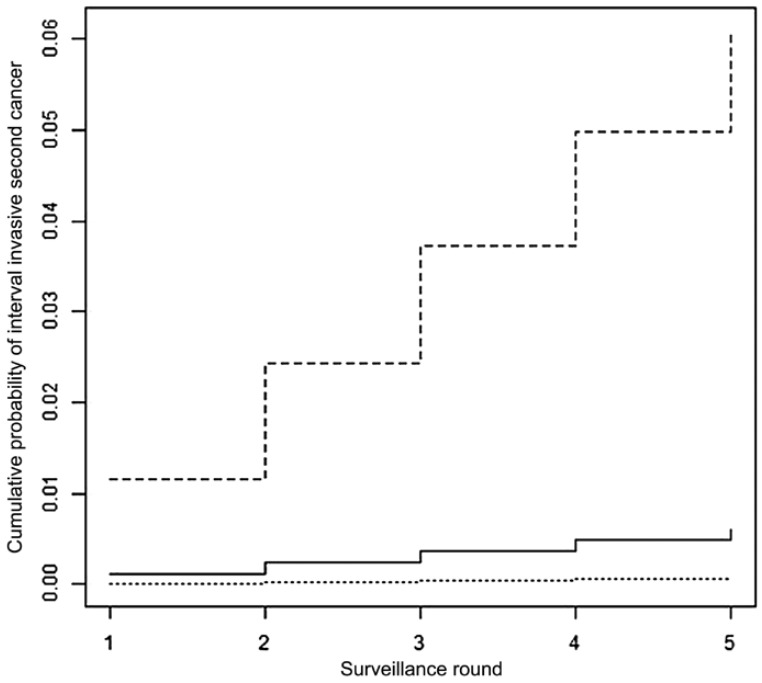

Figure 2. Cumulative probability of interval-invasive second breast cancer for women with varying risk profiles. All profiles are for women who are non-Hispanic white, postmenopausal, age 60–69 years, stage I first cancers, ER+ or PR+ first cancers, and received no adjuvant therapy (non-statistically significant referent categories for predictors). Additional characteristics predictive of interval cancer risk are varied across profiles. **Dotted line** (most favorable risk profile): grade I first cancer, mastectomy, American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) 1 breast density, screen-detected first cancer. **Solid line** (referent category for all characteristics): grade I first cancer, lumpectomy with radiation, BI-RADS 2 breast density, screen-detected first cancer. **Dashed line** (least favorable risk profile): grade II first cancer, lumpectomy without radiation, BI-RADS 4 breast density, clinically detected first cancer.

older than 80 years of age (2517 vs 3178), decreasing power to detect a statistically significant difference in interval-invasive cancer rates by age at diagnosis in the fully adjusted model.

Our results suggest that aggressive tumor biology in a woman's first breast cancer, which influences detection by screening mammography (21,38), may continue to mediate her subsequent surveillance outcomes. This is consistent with emerging evidence about the heterogeneity of breast cancer as a disease (39–41). Molecular profiling of breast cancers, which includes identifying genes associated with proliferation, is increasingly being used to guide treatment decisions (42–44). When molecular profiling is not performed it is possible to approximate breast cancer subtypes using information from immunohistochemical analysis (42) on the presence or absence of hormone receptors, human epidermal growth factor receptor (HER2), and histologic grade.

While PBC hormone receptor status, grade, size, nodal status, and stage were included as predictors in our analysis, evaluation of chemotherapy and endocrine therapy was limited. As this information is incompletely captured by the SEER registry (45), our findings that 85% of breast cancers were hormone receptor–positive and only 37% percent received endocrine therapy likely reflect both the limited ascertainment of treatment by the registry as well as potential underuse of appropriate therapy. We were also not able to evaluate HER2 or HER2-targeted therapy. This was an optional data element in BCSC tumor registries during our study period (46), and the relatively high proportion of missing values precluded use of HER2 in the predictive model. Additional studies are needed to evaluate the contribution of HER2 status and breast cancer subtype to mammographic surveillance outcomes.

Considerations for reducing the incidence of interval-invasive second breast cancer events include interventions to improve primary treatment for initial breast cancer, such as increasing use of radiation therapy in women choosing breast conserving therapy and appropriate endocrine treatment or increasing post-treatment adherence with current guideline recommendations for annual surveillance mammography. Our findings also raise the possibility that the selective application of adjunctive testing to supplement surveillance mammography, either with a more frequent surveillance interval (47) or with another modality such as breast MRI (48–51) or ultrasound (52), could reduce interval-invasive second breast cancers. However, population-based data on surveillance breast MRI or ultrasound is sparse, and evaluation of these modalities was not an aim for this analysis. Further studies are needed to examine the potential contribution of supplemental modalities or alternative regimens to improving surveillance outcomes.

In summary, our results suggest that factors related to PBC diagnosis and treatment—increased breast density, higher grade PBCs, interval PBC presentation, and breast conservation treatment without radiation therapy—contribute to variation in subsequent-interval second breast cancer risk. Consideration of these factors may help breast cancer survivors and their physicians develop post-treatment breast imaging plans that are tailored to patient-specific risks and preferences.

Funding

This work was supported by a National Cancer Institute–funded Program Project grant (P01CA154292) and the Breast Cancer Surveillance Consortium (HHSN261201100031C). Additional support was provided by National Institutes of Health grant K07CA128816 (to JML) and the National Breast Cancer Foundation (NBCF Australia to NH).

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Notes

We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study. A list of the Breast Cancer Surveillance Consortium (BCSC) investigators and procedures for requesting BCSC data for research purposes are provided at: http://breastscreening.cancer.gov/. The collection of cancer and vital status data used in this study was supported in part by several state public health departments and cancer registries throughout the United States. For a full description of these sources, please see: http://breastscreening.cancer.gov/work/acknowledgement.html.

References

1. Parry C, Kent EE, Mariotto AB, et al. Cancer survivors: a booming population. *Cancer Epidemiol Biomarkers Prev*. 2011;20(10):1996–2005.
2. American Cancer Society. *Breast Cancer Facts & Figures 2013–2014*. In. Atlanta: American Cancer Society, Inc.; 2013.
3. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin*. 2012;62(4):220–241.
4. Anderson SJ, Wapnir I, Dignam JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. *J Clin Oncol*. 2009;27(15):2466–2473.
5. Komoike Y, Akiyama F, Iino Y, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer. *Cancer*. 2006;106(1):35–41.
6. Houssami N, Ciatto S, Martinelli F, et al. Early detection of second breast cancers improves prognosis in breast cancer survivors. *Ann Oncol*. 2009;20(9):1505–1510.
7. Lu WL, Jansen L, Post WJ, et al. Impact on survival of early detection of isolated breast recurrences after primary treatment for breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2009;114(3):403–412.
8. Houssami N, Ciatto S. Mammographic surveillance in women with a personal history of breast cancer: How accurate? How effective? *Breast*. 2010;19(6):439–445.
9. Lash TL, Fox MP, Buist DSM, et al. Mammography surveillance and mortality in older breast cancer survivors. *J Clin Oncol*. 2007;25(21):3001–3006.
10. Lu W, Schaapveld M, Jansen L, et al. The value of surveillance mammography of the contralateral breast in patients with a history of breast cancer. *Eur J Cancer*. 2009;45(17):3000–3007.
11. Paszat L, Sutradhar R, Grunfeld E, et al. Outcomes of surveillance mammography after treatment of primary breast cancer: a population-based case series. *Breast Cancer Res Treat*. 2009;114(1):169–178.
12. Katcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology Clinical Practice Guideline update. *J Clin Oncol*. 2013;31(7):961–965.
13. National Comprehensive Cancer Network. *Breast Cancer, v.1.2012*. In. NCCN Clinical Practice Guidelines in Oncology; 2012.
14. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *J Clin Oncol*. 2012;30(14):1715–1724.
15. de Bock GH, Bonnema J, van Der Hage J, et al. Effectiveness of routine visits and routine tests in detecting isolated locoregaional recurrences after treatment for early-stage invasive breast cancer: a meta-analysis and systematic review. *J Clin Oncol*. 2004;22(19):4010–4018.
16. GIVIO Investigators. Impact of follow-up testing on survival and health-related qualtiy of life in breast cancer patients: a multicenter randomized controlled trial. *JAMA*. 1994;271(50):1587–1592.
17. Palli D, Russo A, Saieva C, et al. Intensive vs clinical follow-up after treatment of primary breast cancer: 10 year update of a randomized trial. *JAMA*. 1999;281(17):1586.
18. Houssami N, Abraham LA, Miglioretti DL, et al. Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. *JAMA*. 2011;305(8):790–799.
19. Houssami N, Abraham LA, Kerlikowske K, et al. Risk model for second screen-detected or interval breast cancers in women with a personal history of breast cancer participating in mammography screening. *Cancer Epidemiol Biomarkers Prev*. 2013;22(5):946–961.
20. Buist DSM, Abraham LA, Barlow WE, et al. Diagnosis of second breast cancer events after initial diagnosis of early stage breast cancer. *Breast Cancer Res Treat*. 2010;124(3):863–873.
21. Kirsch VA, Chiarelli AM, Edwards SA, et al. Tumor characteristics associated with mammographic detection of breast cancer in the Ontario breast screening program. *J Natl Cancer Inst*. 2011;103(12):1–9.
22. Breast Cancer Surveillance Consortium. Breast Cancer Surveillance Consortium, a research resource for evaluating breast cancer screening performance in the United States. http://breastscreening.cancer.gov.
23. American College of Radiology. *Breast Imaging Reporting and Data System Atlas*. In. Reston, VA: American College of Radiology.; 2003.
24. American Joint Commission on Cancer. *Manual for Staging of Cancer*. 6th ed. ed. Philadelphia; 2002.
25. Ballard-Barbash R, Taplin SH, Yankaskas BC, et al. Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. *AJR*. 1997;169(10):1001–1008.
26. Gierach GL, Ichikawa L, Kerlikowske K, et al. Relationship between mammographic density and breast cancer death in the Breast Cancer Surveillance Consortium. *J Natl Cancer Inst*. 2012;104(16):1218–1227.
27. Swihart BJ, Caffo B, James BD, et al. Lasagna plots: a saucy alternative to spaghetti plots. *Epidemiology*. 2010;21(5):621–625.
28. Gao H, Buist DSM, Lash TL, et al. Lasagne plots made in different (statistical) ovens. *Epidemiology*. 2012;23(6):934.
29. Cox DR. Regression models and life tables. *J Royal Stat Soc*. 1972;34:184–220.
30. Prentice RL, Gloeckler LA. Regression analysis of grouped survival data with application to breast cancer data. *Biometrics*. 1978;34(3):57–67.
31. Singer J, Willett JB. *Applied longitudinal data analysis: modeling change and event occurrence*. New York: Oxford University Press; 2003.
32. Raghunathan TW, Lepkowski JM, Van Hoewyk J, et al. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Survey Methodol*. 2001;27(1):85–95.
33. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16(3):219–242.
34. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. New York.: J. Wiley & Sons; 1987.
35. Early Breast Cancer Trialists' Cooperative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. *Lancet*. 2005;365(9472):1687–1717.
36. Early Breast Cancer Trialists' Cooperative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366(9503):2087–2106.
37. Early Breast Cancer Trialists' Cooperative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378(9793):771–784.
38. Buist DS, Porter PL, Lehman C, et al. Factors contributing to mammography failure in women aged 40–49 years. *J Natl Cancer Inst*. 2004;96(19):1432–1440.
39. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. *Nature*. 2012;490(7418):61–70.
40. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A*. 2001;98(19):10869–10874.
41. Wirapati P, Sotiriou C, Kunkel S, et al. Meta-analysis of gene expression profiles in breast cancer: toward a unified understanding of breast cancer subtyping and prognosis signatures. *Breast Cancer Res*. 2008;10(4):R65.
42. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes - dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. 2011;22(8):1736–1747.
43. Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: classification, prognostication, and prediction. *Lancet*. 2011;378(9805):1812–1823.
44. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. *New Engl J Med*. 2009;360(8):790–800.
45. Du XL, Key CR, Dickie L, et al. Information on chemotherapy and hormone therapy from tumor registry had moderate agreement with chart reviews. *J Clin Epidemiol*. 2006;59(1):53–60.
46. Reichman ME, Altekruse S, Li CI, et al. Feasibility study for collection of HER2 data by National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program central cancer registries. *Cancer Epidemiol Biomarkers Prev*. 2010;19(1):144–147.
47. Arasu VA, Joe BN, Lvoff NM, et al. Benefit of semiannual ipsilateral mammogrpahic surveillance following breast conservation therapy. *Radiology*. 2012;264(2):371–377.
48. Abramovici G, Mainiero MB. Screening breast MR imaging: Comparison of interpretation of baseline and annual follow-up studies. *Radiology*. 2011;259(1):85–91.
49. Arazi-Kleinman T, Skair-Levy M, Slonimsky E, et al. Is screening MRI indicated for women with a personal history of breast cancer? Analysis based on biopsy results. *AJR*. 2013;201(4):919–927.
50. Brennan S, Liberman L, Dershaw DD, et al. Breast MRI screening of women with a personal history of breast cancer. *AJR*. 2010;195(2):510–516.
51. Schacht DV, Yamaguchi K, Lai J, et al. Importance of a personal history of breast cancer as a risk factor for the development of subsequent breast cancer: results from screening breast MRI. *AJR*. 2014;202(2):289–292.
52. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA*. 2012;307(13):1394–1404.

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