VOLUME 36 · NUMBER 20 · JULY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cumulative Risk Distribution for Interval Invasive Second Breast Cancers After Negative Surveillance Mammography

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Published at jco.org on May 2, 2018.

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0732-183X/18/3620w-2070w/$20.00

ABSTRACT

Purpose
The aim of the current study was to characterize the risk of interval invasive second breast cancers within 5 years of primary breast cancer treatment.

Methods
We examined 65,084 surveillance mammograms from 18,366 women with a primary breast cancer diagnosis of unilateral ductal carcinoma in situ or stage I to III invasive breast carcinoma performed from 1996 to 2012 in the Breast Cancer Surveillance Consortium. Interval invasive breast cancer was defined as ipsilateral or contralateral cancer diagnosed within 1 year after a negative surveillance mammogram. Discrete-time survival models—adjusted for all covariates—were used to estimate the probability of interval invasive cancer, given the risk factors for each surveillance round, and aggregated across rounds to estimate the 5-year cumulative probability of interval invasive cancer.

Results
We observed 474 surveillance-detected cancers—334 invasive and 140 ductal carcinoma in situ—and 186 interval invasive cancers which yielded a cancer detection rate of 7.3 per 1,000 examinations (95% CI, 6.6 to 8.0) and an interval invasive cancer rate of 2.9 per 1,000 examinations (95% CI, 2.5 to 3.3). Median cumulative 5-year interval cancer risk was 1.4% (interquartile range, 0.8% to 2.3%; 10th to 90th percentile range, 0.5% to 3.7%), and 15% of women had ≥ 3% 5-year interval invasive cancer risk. Cumulative 5-year interval cancer risk was highest for women with estrogen receptor– and progesterone receptor–negative primary breast cancer (2.6%; 95% CI, 1.7% to 3.5%), interval cancer presentation at primary diagnosis (2.2%; 95% CI, 1.5% to 2.9%), and breast conservation without radiation (1.8%; 95% CI, 1.1% to 2.4%).

Conclusion
Risk of interval invasive second breast cancer varies across women and is influenced by characteristics that can be measured at initial diagnosis, treatment, and imaging. Risk prediction models that evaluate the risk of cancers not detected by surveillance mammography should be developed to inform discussions of tailored surveillance.

J Clin Oncol 36:2070-2077. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Breast cancer screening and treatment are increasingly tailored to women's risks, but imaging surveillance after primary breast cancer (PBC) treatment remains a one-size-fits-all approach. Current clinical guidelines[1-4] are consistent in recommending annual mammography for all women, except those who were treated with bilateral mastectomy, based on reports of absolute mortality reduction of 17% to 28% for second breast cancers identified by early detection.[5]

Risk-based surveillance offers the potential to further tailor the use of imaging and improve outcomes for women with a personal history of breast cancer by focusing supplemental imaging on women who are at increased risk of an adverse surveillance outcome with mammography alone—an interval invasive second breast cancer diagnosed within 1 year of a negative mammogram. These interval cancers have been reported to represent approximately 35% of invasive second breast cancers in either the index or contralateral breast.[6,7] Considerations for reducing the incidence of interval invasive second breast cancer events that have been considered include interventions to improve the primary treatment of initial breast cancer and more intensive surveillance imaging regimens. Use of mammography at

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.76.8267

DOI: https://doi.org/10.1200/JCO.2017.76.8267

semiannual intervals[8] or selective supplemental surveillance imaging, with magnetic resonance imaging (MRI)[9-11] or breast ultrasound,[11-13] may increase early detection of second breast cancers.[11,14,15]

Moving toward acceptance and implementation of a risk-based surveillance paradigm is complex and multifaceted. Initial steps toward this goal include understanding the predictors of interval second cancer risk over time. In a cohort of 15,114 women with a personal history of breast cancer, significant predictors of interval invasive second breast cancers included tumor, treatment, and imaging-related factors.[16] In an important next step, the underlying population level risk distribution of interval invasive second breast cancers in women with prior breast cancer must also be characterized. This critical information is needed to inform the process of designing and evaluating potential interventions for reducing adverse surveillance outcomes.

In this study, we have extended the multivariable model that was previously used to identify predictors of interval invasive second breast cancer,[16] expanding the study population to include more than 3,000 additional women and more than 17,000 additional surveillance mammograms. We have also added potential predictors to the multivariable model. The purpose of our study was to characterize the underlying population distribution of the risk of adverse surveillance outcomes in a cohort of women receiving surveillance mammography after PBC treatment.

METHODS

We included surveillance mammograms that were performed from 1996 to 2012 at facilities in five Breast Cancer Surveillance Consortium (BCSC) registries: Carolina Mammography Registry (North Carolina), Kaiser Permanente Washington Registry, New Hampshire Mammography Network, San Francisco Mammography Registry, and Vermont Breast Cancer Surveillance System.[17] Data collected by these registries were linked to breast cancer and tumor characteristics in pathology databases, regional SEER programs, and state tumor registries. Pooled data were analyzed at a central statistical coordinating center. Each registry and the statistical coordinating center received institutional review board approval for data collection and analysis and have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities who are participants in this research. All procedures were Health Insurance Portability and Accountability Act compliant.

Participants

Eligible women had a history of unilateral PBC diagnosed from 1996 to 2012—either ductal carcinoma in situ (DCIS) or American Joint Commission on Cancer 7th edition[18] stage I to III invasive carcinoma—and received mammography at BCSC facilities. To include women who were receiving mammography around the time of the PBC diagnosis, we searched the BCSC database for women with a mammogram within 2 years before or 1 year after PBC diagnosis. We excluded women who had unknown PBC laterality or stage, bilateral synchronous breast cancers at diagnosis, metachronous breast cancer diagnosis in either breast within 6 months of PBC diagnosis, or who were treated with bilateral mastectomy. Surveillance mammograms were defined as mammograms that were obtained at least 6 months after PBC diagnosis without self-reported symptoms, or imaging in the prior 9 months, and indicated as routine examinations by the radiologist or technologist.[6,7,16,19] Surveillance mammograms that were not followed by 1 year of complete cancer capture were excluded. For each woman, all surveillance mammograms after PBC were included until the first occurrence of one of the following: diagnosis of second breast cancer, disenrollment, death, or the difference between a woman's self-reported time since the last mammogram and the observed time was greater than 6 months—indicating the possibility of mammograms missing in our database. Cancer recurrence ipsilateral to the side of mastectomy was excluded. Exclusions and censoring mechanisms were the same as those previously described.[16]

Outcomes

Primary outcome was interval invasive second cancer, which was defined as an invasive second breast cancer observed within 1 year after a surveillance mammogram with a negative final result. Surveillance-detected cancers were defined as DCIS or invasive second breast cancers observed within 1 year after a positive surveillance mammogram. The surveillance mammography cancer detection rate was calculated as the number of surveillance-detected cancers per 1,000 examinations. The interval invasive cancer rate was defined as invasive cancer in the ipsilateral or contralateral breast that was diagnosed within 1 year after a surveillance mammogram with negative results, per 1,000 examinations. Additional measures and definitions are in listed the Appendix (online only).

Statistical Analysis

We used discrete-time survival models to estimate the 5-year cumulative probability of an interval invasive cancer following PBC.[20-23] The model was based on a logistic relationship between the probability of an interval invasive breast cancer and the covariates of interest. According to a previously developed approach,[22] separate logistic regression models were fit to estimate the relationship between the probability of an interval invasive breast cancer and each covariate of interest. In addition to adjusting for the covariate of interest, each model also adjusted for mammography round, time since last mammogram, and BCSC registry. On the basis of this model, the predicted probability of an interval invasive cancer at each surveillance round was generated for each covariate category and adjusted for the proportion of women who were not censored by the competing events of screen-detected cancer or death.[22] Finally, adjusted probabilities were aggregated across surveillance rounds to obtain 5-year cumulative risks of interval invasive cancer for each covariate category.

A fully adjusted model that included all covariates simultaneously was fit to obtain adjusted odds ratios and confidence intervals. Cumulative probabilities, adjusted for competing risks, were computed for each woman on the basis of this model.

We used multiple imputation via chained equations to impute missing data.[24,25] This method imputes missing values for each variable using a regression model conditional on all the other variables in the model and was repeated for each covariate that was missing data. The fully adjusted model and histogram were based on the results obtained after using standard methods to combine estimates from five imputations.[26] All analyses were performed using R 3.2.3 (https://www.r-project.org/), and all statistical tests were two sided.

RESULTS

Study Population

After applying exclusion criteria and censoring, the final data set included 65,084 surveillance mammograms in 18,366 women with a personal history of unilateral PBC (Table 1). At the examination level, median age was 64 years (interquartile range [IQR], 56 to 74 years). Most surveillance mammograms were performed in white (83%), postmenopausal (90%) women, and 24% of examinations were performed in women with a first-degree family history of breast cancer. Most mammograms (85%) occurred within 9 to 14 months of a prior mammogram.

Table 1. Characteristics of 65,084 Surveillance Mammograms in 18,366 Women With a Personal History of Breast Cancer

Variable (percent missing)	Surveillance Mammogram	Surveillance-Detected Second Cancer*	Interval-Detected Invasive Cancer
Total	65,084 (100)	474	186
Demographic characteristics			
Age at mammography, years (0%)			
< 40	720 (1.1)	8 (1.7)	7 (3.8)
40-49	6,124 (9.4)	43 (9.1)	24 (12.9)
50-59	16,488 (25.3)	113 (23.8)	67 (36.0)
60-69	18,570 (28.5)	135 (28.5)	43 (23.1)
70-79	15,010 (23.1)	113 (23.8)	31 (16.7)
≥ 80	8,172 (12.6)	62 (13.1)	14 (7.5)
Race/ethnicity (4.3%)			
White, non-Hispanic	51,907 (83.3)	373 (82.7)	136 (77.7)
Black, non-Hispanic	4,122 (6.6)	30 (6.7)	20 (11.4)
Hispanic	1,420 (2.3)	7 (1.6)	5 (2.9)
Asian, Pacific Islander	3,701 (5.9)	32 (7.1)	10 (5.7)
Other	1,157 (1.9)	9 (2.0)	4 (2.3)
Menopausal status (9.4%)			
Post-	53,247 (90.3)	382 (87.8)	132 (81.0)
Peri-	1,470 (2.5)	15 (3.4)	6 (3.7)
Pre-	4,230 (7.2)	38 (8.7)	25 (15.3)
First-degree family history of breast cancer (2.2%)			
No	48,502 (76.2)	330 (71.3)	134 (74.4)
Yes	15,125 (23.8)	133 (28.7)	46 (25.6)
BMI group (kg/m^2) (36.8%)			
Underweight (< 18.5)	745 (1.8)	4 (1.3)	2 (1.6)
Normal (18.5-24.9)	17,224 (41.9)	117 (39.1)	56 (45.5)
Overweight (25.0-29.9)	12,872 (31.3)	99 (33.1)	35 (28.5)
Obese I (30.0-34.9)	6,326 (15.4)	55 (18.4)	17 (13.8)
Obese II or greater (≥ 35)	3,967 (9.6)	24 (8.0)	13 (10.6)
Primary breast cancer diagnosis and treatment characteristics			
Age at PBC, years (0%)			
< 40	2,202 (3.4)	19 (4.0)	17 (9.1)
40-49	12,932 (19.9)	103 (21.7)	49 (26.3)
50-59	19,045 (29.3)	134 (28.3)	61 (32.8)
60-69	16,595 (25.5)	123 (25.9)	35 (18.8)
70-79	11,231 (17.3)	73 (15.4)	15 (8.1)
≥ 80	3,079 (4.7)	22 (4.6)	9 (4.8)
Histology of PBC (0.8%)			
Ductal	55,303 (85.6)	410 (86.9)	152 (81.7)
Lobular	4,171 (6.5)	23 (4.9)	13 (7.0)
Mixed	5,105 (7.9)	39 (8.3)	21 (11.3)
Stage of PBC (0%)			
DCIS	13,587 (20.9)	149 (31.4)	36 (19.4)
I	28,447 (43.7)	202 (42.6)	84 (45.2)
IIA	12,134 (18.6)	70 (14.8)	28 (15.1)
IIB-IIIC	10,916 (16.8)	53 (11.2)	38 (20.4)
Grade of primary invasive cancer (10.1%)			
1	10,804 (23.3)	79 (28.5)	17 (12.8)
2	20,603 (44.5)	122 (44.0)	65 (48.9)
3	14,873 (32.1)	76 (27.4)	51 (38.3)
Hormone receptor status of primary invasive cancer (10.0%)			
ER or PR positive	38,928 (84.0)	246 (83.4)	97 (71.9)
ER and PR negative	7,401 (16.0)	49 (16.6)	38 (28.1)
Primary surgery (2.3%)			
Mastectomy	23,216 (36.5)	101 (21.9)	44 (24.4)
Breast conserving with radiation	30,753 (48.4)	245 (53.0)	99 (55.0)
Breast conserving without radiation	9,625 (15.1)	116 (25.1)	37 (20.6)
Adjuvant systemic therapy (6.4%)			
None	25,964 (42.6)	262 (59.5)	69 (39.4)
Endocrine therapy only	16,953 (27.8)	88 (20.0)	36 (20.6)
Chemotherapy only	10,584 (17.4)	53 (12.0)	48 (27.4)
Chemotherapy and endocrine therapy	7,439 (12.2)	37 (8.4)	22 (12.6)
Imaging characteristics			
Mammogram type (1.1%)			
Film	30,298 (47.0)	230 (49.0)	91 (49.2)
Digital†	34,098 (53.0)	239 (51.0)	94 (50.8)

(continued on following page)

Table 1. Characteristics of 65,084 Surveillance Mammograms in 18,366 Women With a Personal History of Breast Cancer (continued)

Variable (percent missing)	Surveillance Mammogram	Surveillance-Detected Second Cancer*	Interval-Detected Invasive Cancer
BI-RADS breast density (14.5%)			
a-Almost entirely fatty	5,642 (10.1)	32 (8.4)	9 (5.8)
b-Scattered fibroglandular tissue	26,395 (47.5)	174 (45.8)	61 (39.6)
c-Heterogeneously dense	20,961 (37.7)	159 (41.8)	73 (47.4)
d-Extremely dense	2,619 (4.7)	15 (3.9)	11 (7.1)
Mode of PBC detection (10.1%)			
Screen detected	36,953 (63.2)	286 (67.1)	79 (47.6)
Interval cancer in screening	9,007 (15.4)	61 (14.3)	40 (24.1)
Clinical/diagnostic detected	9,565 (16.3)	62 (14.6)	36 (21.7)
Other	2,984 (5.1)	17 (4.0)	11 (6.6)
Time since last mammogram, months (0.6%)			
9-14	55,192 (85.3)	367 (77.9)	152 (83.1)
15-23	7,339 (11.3)	64 (13.6)	23 (12.6)
≥ 24	2,181 (3.4)	40 (8.5)	8 (4.4)
Time since PBC diagnosis, years (0%)			
< 1	5,343 (8.2)	35 (7.4)	22 (11.8)
1-2	14,754 (22.7)	94 (19.8)	49 (26.3)
3-4	14,138 (21.7)	87 (18.4)	31 (16.7)
5-6	11,198 (17.2)	85 (17.9)	24 (12.9)
7-9	11,310 (17.4)	84 (17.7)	35 (18.8)
> 10	8,341 (12.8)	89 (18.8)	25 (13.4)

NOTE. Data are presented as No. (%), unless noted otherwise.
Abbreviations: BI-RADS, American College of Radiology Breast Imaging Reporting and Data System; BMI, body mass index; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PBC, primary breast cancer; PR, progesterone receptor.
*Surveillance-detected cancers include invasive and noninvasive second breast cancers.
†Includes 154 exams in which tomosynthesis was performed (one with surveillance-detected cancer that was diagnosed during follow-up).

At the individual level, most women returned for multiple surveillance rounds, with a median of three mammograms per woman (IQR, one to five mammograms). Median follow-up from the date of diagnosis to the most recent surveillance mammogram was 5 years (IQR, 2 to 8 years). Median age at PBC diagnosis was 59 years (IQR, 50 to 68 years). The majority of PBCs were DCIS or stage I ductal carcinomas (65%). Among patients with invasive PBCs, 45% had intermediate grade and 84% were estrogen receptor– and progesterone receptor (ER/PR) –positive. Most PBCs were screen detected (63%), whereas 32% presented either as interval breast cancers after a negative screening mammogram or with clinical symptoms without a screening mammogram in the preceding 2 years. Primary surgery included mastectomy (37%) and lumpectomy with (48%) or without (15%) radiation therapy.

During the surveillance period, 474 surveillance-detected second breast cancers—334 invasive and 140 DCIS—and 186 interval invasive cancers were diagnosed (Table 1). Cancer detection rate was 7.3 per 1,000 examinations (95% CI, 6.6 to 8.0). Interval invasive cancer detection rate was 2.9 per 1,000 exams (95% CI, 2.5 to 3.3).

Characteristics of 186 interval invasive breast cancers are listed in Table 2. Among cancers for which data was available, 55% of interval cancers were American Joint Commission on Cancer stage I, 23% were late stage (IIB or greater), 25% were large (> 2 cm), 45% were high grade, and 27% were node positive. In addition, 34% had ER-/PR-negative receptor status.

Five-Year Risk of Interval Invasive Second Breast Cancer

Depending on specific individual characteristics of the woman, tumor, or imaging examination, the 5-year cumulative risk of interval invasive second breast cancer from the minimally adjusted model varied from 0.6% to 3.6%, (Table 3). Risk was highest for women younger than 40 years old at PBC diagnosis (3.6%; 95% CI, 2.0% to 5.4%), pre- or perimenopausal during surveillance (2.6%; 95% CI, 1.7% to 3.7%), had ER-/PR-negative PBC (2.6%; 95% CI, 1.7% to 3.5%), had interval presentation of

Table 2. Characteristics of 186 Interval-Detected Invasive Breast Cancers

Variable (percent missing)	No. (%)
Total	186 (100.0)
AJCC stage (21.5%)	
I	80 (54.8)
IIA	33 (22.6)
IIB-IV	33 (22.6)
Tumor size (mm) (18.8%)	
0-10	53 (35.1)
11-15	36 (23.8)
16-20	25 (16.6)
> 20	37 (24.5)
Grade (30.7%)	
1	17 (13.2)
2	54 (41.9)
3	58 (45.0)
Hormone receptor status (25.3%)	
ER or PR positive	92 (66.2)
ER and PR negative	47 (33.8)
Nodal status (14.5%)	
Negative	116 (73.0)
Positive	43 (27.0)

Abbreviations: AJCC, American Joint Commission on Cancer; ER, estrogen receptor; PR, progesterone receptor.

Table 3. Cumulative Probability of Interval Invasive Second Breast Cancer Within 5 Years of PBC Diagnosis

Characteristic	Cumulative 5-Year Probability, % (95% CI)*
Demographic characteristics	
Race/ethnicity	
White, non-Hispanic	1.2 (0.9 to 1.5)
Black, non-Hispanic	3.2 (1.8 to 5.2)
Hispanic	1.6 (0.4 to 3.2)
Asian, Pacific Islander	1.3 (0.5 to 2.4)
Other	1.6 (0.4 to 3.3)
Menopausal status	
Post-	1.1 (0.9 to 1.4)
Pre- and peri-	2.6 (1.7 to 3.7)
First-degree family history of breast cancer	
No	1.3 (1.1 to 1.6)
Yes	1.4 (1.0 to 2.0)
BMI group (kg/m^2)	
Underweight (< 18.5)	1.4 (0.0 to 3.9)
Normal (18.5-24.9)	1.7 (1.1 to 2.4)
Overweight (25.0-29.9)	1.5 (0.9 to 2.2)
Obese I (30.0-34.9)	1.4 (0.7 to 2.3)
Obese II or greater (≥ 35)	1.8 (0.8 to 2.9)
Primary breast cancer diagnosis and treatment characteristics	
Age at PBC, years	
< 40	3.6 (2.0 to 5.4)
40-49	1.8 (1.3 to 2.4)
50-59	1.5 (1.1 to 2.0)
60-69	0.9 (0.6 to 1.3)
70-79	0.6 (0.3 to 1.0)
≥ 80	1.4 (0.6 to 2.2)
Histology of PBC	
Ductal	1.3 (1.0 to 1.5)
Lobular	1.4 (0.7 to 2.3)
Mixed	1.8 (1.1 to 2.8)
Stage of PBC	
DCIS	1.2 (0.8 to 1.7)
I	1.4 (1.1 to 1.7)
IIA	1.1 (0.7 to 1.6)
IIB-IIIC	1.6 (1.1 to 2.2)
Grade of primary invasive cancer	
1	0.8 (0.4 to 1.2)
2	1.5 (1.1 to 2.0)
3	1.6 (1.1 to 2.2)
Hormone receptor status of primary invasive cancer	
ER or PR positive	1.3 (0.9 to 1.6)
ER and PR negative	2.6 (1.7 to 3.5)
Primary surgery	
Mastectomy	0.9 (0.6 to 1.2)
Breast conserving with radiation	1.5 (1.2 to 1.9)
Breast conserving without radiation	1.8 (1.1 to 2.4)
Adjuvant systemic therapy	
None	1.2 (0.9 to 1.6)
Endocrine therapy only	1.0 (0.7 to 1.4)
Chemotherapy only	2.2 (1.6 to 2.8)
Chemotherapy and endocrine therapy	1.4 (0.8 to 2.0)
Imaging characteristics	
Mammogram type	
Film	1.4 (1.0 to 1.7)
Digital†	1.3 (1.0 to 1.6)
BI-RADS breast density	
a-Almost entirely fatty	0.7 (0.2 to 1.1)
b-Scattered fibroglandular tissue	1.0 (0.7 to 1.4)
c-Heterogeneously dense	1.6 (1.2 to 2.0)
d-Extremely dense	1.9 (0.9 to 3.3)
Mode of PBC detection	
Screen detected	1.0 (0.8 to 1.3)
Interval cancer in screening	2.2 (1.5 to 2.9)
Clinical/diagnostic detected	1.8 (1.2 to 2.5)
Other	1.9 (0.8 to 3.0)
Time since PBC diagnosis, years	
< 1	1.7 (0.9 to 2.9)
1-2	1.6 (1.1 to 2.4)
3-4	1.2 (0.8 to 1.6)
5-6	1.0 (0.6 to 1.5)
7-9	1.5 (0.9 to 2.3)
> 10	1.4 (0.7 to 2.2)

(continued in next column)

Table 3. Cumulative Probability of Interval Invasive Second Breast Cancer Within 5 Years of PBC Diagnosis (continued)

Abbreviations: BI-RADS, American College of Radiology Breast Imaging Reporting and Data System; BMI, body mass index; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PBC, primary breast cancer; PR, progesterone receptor.

*Separate models were constructed for each covariate, adjusted only for Breast Cancer Surveillance Consortium registry, surveillance round, and time since last mammogram.

†Includes 154 exams in which tomosynthesis was performed (one with screen-detected cancer that was diagnosed during follow-up).

PBC (2.2%; 95% CI, 1.5% to 2.9%), and were treated with breast conservation without radiation (1.8%; 95% CI, 1.1% to 2.4%). Cumulative 5-year risk was lowest for women who were age 70 to 79 years at diagnosis (0.6%; 95% CI, 0.3% to 1.0%), had grade 1 PBC (0.8%; 95% CI, 0.4% to 1.2%), or who underwent mastectomy for primary surgery (0.9%; 95% CI, 0.6% to 1.2%). In the fully adjusted multivariable model, significant predictors of interval invasive second breast cancer included the following PBC characteristics: earlier stage, higher invasive cancer grade, nonductal histology, hormone receptor–negative status, interval-detected PBC, and breast conservation without radiation (Appendix Table A1, online only). Whereas black race as a specific characteristic was associated with a 3.2% 5-year risk, race and ethnicity, overall, was not a significant predictor in the fully adjusted model. Increasing breast density also seemed to be associated with increasing risk, but was not significant in the fully adjusted model ($P = .07$).

Frequency Distribution of Interval Invasive Second Breast Cancer Risk

In the study cohort of 18,366 women, the frequency distribution of estimated cumulative 5-year risk of interval invasive second breast cancer for each woman in the cohort ranged from 0.1% to 29.2% (Fig 1). Median risk of an interval cancer was 1.4% (IQR, 0.8% to 2.3%). Thirty-five percent of women had a 5-year risk of ≤ 1%, and 15% of women had ≥ 3% 5-year interval invasive cancer risk.

Among 2,359 women with invasive PBC and a 5-year risk of interval invasive second cancer of ≥ 3%, 80% were younger than 60 years old, 97% had intermediate-grade or high-grade tumors, and 75% had primary cancers that were non–screen detected. Of 1,190 women with dense breasts upon first surveillance mammogram and whose PBCs presented as interval cancers, 39% (n = 464) had a projected 5-year risk of interval invasive second cancer of ≥ 3%. Among women with invasive PBC and the lowest decile of risk (n = 1,637), all women were age ≥ 40 years at diagnosis, 52% had low-grade tumors, and 82% had screen-detected breast cancers.

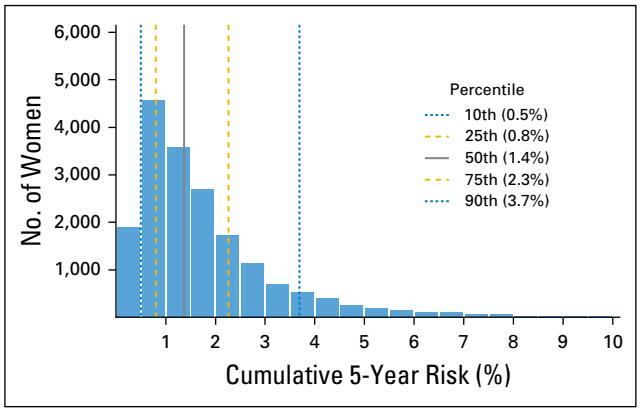

Fig 1. Frequency distribution of cumulative 5-year risk of interval invasive breast cancer on the basis of 18,366 women.

DISCUSSION

We determined the population distribution of the 5-year cumulative risk of interval invasive second breast cancers in women receiving surveillance mammography. Whereas the full range of adverse surveillance outcome risk varied widely across women, from 0.1% to 29.2%, most women had relatively low risk, with 35% of women having a 5-year risk of $< 1\%$, and 50% of women having risk of $\leq 1.4\%$. Conversely, our multivariable model also indicated that some women were at substantially higher risk, with 15% of women having a 5-year risk of $\geq 3\%$.

The cumulative multivariable model in this study extended a previous model[16] with additional sample size and potential predictors of risk, including body mass index (BMI), breast cancer histology (ductal, lobular, or mixed), and mammography type (film *v* digital). Although studies have demonstrated an association between increasing BMI and primary postmenopausal breast cancer,[27,28] breast cancer recurrence, and mortality,[29-31] BMI was not significantly associated with interval invasive second cancer risk in this analysis. Risk of interval invasive cancer after negative mammography did not vary significantly between film or digital mammography, which supports the combined analysis of both types of surveillance imaging.

Our results suggest that aggressive biology in a woman's first breast cancer, which influences detection by screening mammography,[32-35] likely continues to mediate subsequent surveillance outcomes. Of the interval cancers in this study, 23% were late stage (IIB or higher), with 34% of cancers having ER-/PR-negative status, and 45% having high grade. Twenty-seven percent were node-positive tumors despite receipt of surveillance mammography within the prior year, which suggests an adverse biologic profile. This is additionally supported by the strong concordance of tumor characteristics—ER/PR, grade, and histology—observed between first and second breast cancers.[36,37] Breast cancer histology of either lobular or mixed lobular and ductal was significantly associated with an increased risk of interval invasive second breast cancer compared with ductal histology, and is consistent with reports that lobular breast cancers may be more difficult to detect mammographically.[38-44] As PBCs that initially presented as interval cancers were also associated with interval invasive second breast cancers, our study results suggest that the mode of detection of PBCs should be considered when making surveillance imaging plans.

Strengths of this study include the large, diverse sample of breast imaging facilities in the BCSC, which serve a geographically and racially representative sample of the US population, and are likely to reflect clinical radiology practice. To determine surveillance outcomes, mammography data were linked to local pathology databases as well as to state and tumor registries, to provide comprehensive capture of cancer outcomes. Whereas contralateral breast cancers are captured by cancer registries as new primary cancers, in-breast recurrences are variably captured; thus, information from BCSC pathology registries provides important supplemental information on these second breast cancers that is not available in many other data sets. Our current analyses extend the work to predict the risk of screening mammography outcomes[45] into the surveillance setting as an initial step toward developing risk-based surveillance strategies for women after breast cancer treatment.

Limitations of this analysis include an inability to consider human epidermal growth factor receptor 2 (HER2) as a predictor variable, which was an optional data element in SEER tumor registries before 2009.[46] The relatively high proportion of missing values precluded its use in the predictive model, and also precluded additional classification of primary breast cancers into subtypes on the basis of ER/PR, HER2 receptor status, and grade. BCSC registries also do not report information on the carriage of genetic mutations, such as BRCA1 or BRCA2; however, in our analysis, women with a positive family history of breast cancer, which would include most women with genetic mutations, were not at significantly increased risk for interval invasive second breast cancers.

Additional work is needed to develop a risk model for surveillance mammography outcomes. Determination of model calibration and discrimination is also needed to assess the ability to predict risk at the population and individual levels. In addition, digital breast tomosynthesis (DBT) is rapidly diffusing into clinical practice as the front-line examination for breast cancer screening and surveillance. Whereas results indicate that DBT screening is associated with reduced recall rates and increased cancer detection,[47-50] evidence on performance and outcomes for surveillance is more sparse. To date, a single study of DBT for surveillance has been published,[51] which reported reduced recall rates, suggesting that the improved performance observed in general screening may be extended to the surveillance setting. As DBT use increases, updating risk models for surveillance mammography to include cancer detection with tomosynthesis will be important.

Supplemental surveillance with MRI or ultrasound has been suggested as one of several potential approaches for reducing the incidence of interval invasive second breast cancer events. Although supplemental imaging detects additional cancers beyond those found on mammography, it is unclear whether supplemental imaging is effective in reducing interval cancer rates or breast cancer mortality in this population of women.[15] To date, the evidence, although promising, is limited by sample size. In the largest published study of MRI surveillance, Lehman et al[10] evaluated 915 women with a personal history of breast cancer. MRI sensitivity for detecting second breast cancer was 80% (16 of

20). In a prospective multisite study of ultrasound screening in which 53% of women had a personal history of breast cancer, adding ultrasound to mammography increased sensitivity from 56% (33 of 59) to 85% (50 of 59) in these women.[14] An MRI substudy that added MRI to mammography in 275 women with prior breast cancer increased sensitivity from 50% (two of four) to 100% (four of four).[14] A more recent prospective multisite study in women with a personal history of breast cancer[11] demonstrated that the sensitivity of mammography and ultrasound (82% [14 of 17]) was not statistically different from that of mammography alone (53% [nine of 17]); however, adding MRI to mammography increased sensitivity from 53% (nine of 17) to 100% (17 of 17).[11] No studies to date have reported mortality reductions with supplemental surveillance imaging.

Additional evidence is also needed to determine and reach consensus on what level of interval breast cancer risk warrants supplemental surveillance imaging to optimize long-term outcomes for women with treated breast cancer. When considering the use of medications for breast cancer risk reduction, the US Preventive Services Task Force recommends shared decision making about chemoprevention when 5-year risk exceeds $\geq$ 3%.[52] Because supplemental surveillance imaging beyond mammography is likely to have both potential benefits and harms, this 3% risk over a 5-year timeframe may serve as a starting point for studying interventions to decrease the risk of interval invasive second breast cancers. If applied to the cohort in the current analysis, 15% of women with a $\geq$ 3% 5-year risk of interval invasive cancer risk would be eligible to study the impact of supplemental surveillance imaging on second breast cancer detection.

In conclusion, among women with treated breast cancer, the risk of adverse surveillance mammography outcome varied widely. Whereas one half of women had a 5-year risk of interval invasive second cancer of $\leq$ 1.4%, 15% of women had a 5-year risk that was twice as high at $\geq$ 3%. Risk prediction models should be developed that evaluate the risk of cancers that are not detected by surveillance mammography to identify women who might benefit most from supplemental surveillance imaging.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Funded by the Breast Cancer Surveillance Consortium Program Project (Grant No. P01-CA154292). Data collection for this work was additionally supported, in part, by the National Cancer Institute (Grant No. U54-CA163303). N.H. received research support through a National Breast Cancer Foundation Australia Breast Cancer Research Leadership Fellowship.

Prior Presentation

Presented at the 2017 Society of Breast Imaging Annual Meeting, Los Angeles, CA, April 6-9, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cumulative Risk Distribution for Interval Invasive Second Breast Cancers After Negative Surveillance Mammography

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Consulting or Advisory Role: GE Healthcare
Research Funding: GE Healthcare

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No relationship to disclose

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Consulting or Advisory Role: GE Healthcare
Research Funding: GE Healthcare
Travel, Accommodations, Expenses: GE Healthcare

Louise M. Henderson
No relationship to disclose

Rebecca A. Hubbard
No relationship to disclose

Acknowledgment

We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study. The collection of cancer and vital status data used in this study was also 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://www.bcsc-research.org/work/acknowledgement.html.

Appendix

Methods: Measures and Definitions

Demographic information, including race and ethnicity, menopausal status, first-degree family history of breast cancer, and height and weight for body mass index calculation was obtained through a self-administered questionnaire at each mammography visit. For each woman in the cohort, primary breast cancer (PBC) characteristics (age at diagnosis, mode of detection, histology, stage,18 grade, hormone receptor status), surgical treatment, and adjuvant systemic therapy were recorded. The mode of detection of PBC[16] was defined as screen detected if the closest screening mammogram within 2 years before diagnosis was positive, interval detected if the closest screening mammogram before diagnosis was negative, clinical/diagnostic detected if there were only diagnostic mammograms performed for symptomatic evaluation before cancer diagnosis, or other if there was a screening mammogram with missing results or no subsequent mammogram after follow-up was recommended. In classifying the mode of detection, including screening mammograms up to 2 years before PBC diagnosis enabled us to account for women who were screened at either annual or biennial intervals.

Mammography examination level characteristics (age at mammogram, mammogram type [film or digital, which included both digital mammography and digital breast tomosynthesis], time since last mammogram, time since PBC diagnosis, and American College of Radiology Breast Imaging Reporting and Data System [BI-RADS] breast density [D'Orsi CJ, et al: American College of Radiology, 2003; D'Orsi CJ, et al: American College of Radiology, 2013]) were also obtained. Time since PBC diagnosis was defined as the interval between the date of PBC diagnosis and the date of surveillance mammogram.

The primary outcome of interest was interval invasive second cancer, which was defined as an invasive second breast cancer observed within 1 year after a surveillance mammogram with a negative final result. A final BI-RADS assessment (D'Orsi CJ, et al: American College of Radiology, 2013) was based on the original assessment made at the time of the surveillance mammogram. If the original assessment was BI-RADS assessment 0 (needs additional imaging evaluation) or if the assessment was missing, then additional imaging—up to 90 days after the original exam—was used to obtain a final assessment. All other examinations had final assessments that were equal to their original assessments. A final result was considered negative if the mammogram was assigned a final BI-RADS assessment category of 1 (negative), 2 (benign), or 3 (probably benign finding). Final results were considered positive if the mammograms were assigned a final BI-RADS assessment category of 4 (suspicious abnormality) or 5 (highly suggestive of malignancy).

Table A1. Fully Adjusted Multivariable Model of Interval Invasive Second Breast Cancer Risk

Characteristic	Fully Adjusted OR (95% CI)	*P**
Demographic characteristics		
Race/ethnicity	—	.243
White, non-Hispanic	Referent	
Black, non-Hispanic	2.01 (1.12 to 3.61)	
Hispanic	1.19 (0.48 to 2.95)	
Asian, Pacific Islander	1.04 (0.52 to 2.08)	
Other	1.11 (0.41 to 3.04)	
Menopausal status	—	.869
Post-	Referent	
Pre- and peri-	1.05 (0.59 to 1.85)	
First-degree family history of breast cancer	—	.400
No	Referent	
Yes	1.16 (0.82 to 1.62)	
BMI group (kg/m^2)	—	.705
Underweight (< 18.5)	1.04 (0.32 to 3.34)	
Normal (18.5-24.9)	Referent	
Overweight (25.0-29.9)	1.09 (0.74 to 1.60)	
Obese I (30.0-34.9)	1.11 (0.67 to 1.84)	
Obese II or greater (≥ 35)	1.49 (0.87 to 2.55)	
PBC diagnosis and treatment characteristics		
Age at PBC, years	—	.056
< 40	2.54 (1.10 to 5.83)	
40-49	1.42 (0.82 to 2.47)	
50-59	1.34 (0.88 to 2.05)	
60-69	Referent	
70-79	0.65 (0.35 to 1.20)	
≥ 80	1.44 (0.68 to 3.06)	
Histology of PBC	—	.037
Ductal	Referent	
Lobular	1.42 (0.78 to 2.57)	
Mixed	1.81 (1.12 to 2.91)	
Stage of PBC	—	.047
DCIS	1.68 (0.91 to 3.11)†	
I	Referent	
IIA	0.63 (0.40 to 1.00)	
IIB-IIIC	1.01 (0.64 to 1.60)	
Grade of primary invasive cancer	—	.016
1	Referent	
2	2.05 (1.18 to 3.57)	
3	1.36 (0.73 to 2.53)	
Hormone receptor status of primary invasive cancer	—	.011
ER or PR positive	Referent	
ER and PR negative	1.85 (1.15 to 2.98)	
Primary surgery	—	< .001
Mastectomy	Referent	
Breast conserving with radiation	2.32 (1.56 to 3.43)	
Breast conserving without radiation	2.53 (1.58 to 4.05)	
Adjuvant systemic therapy	—	.739
None	Referent	
Endocrine therapy only	0.86 (0.56 to 1.32)	
Chemotherapy only	1.18 (0.72 to 1.93)	
Chemotherapy and endocrine therapy	1.01 (0.57 to 1.81)	
Imaging characteristics		
Mammogram type	—	.541
Film	Referent	
Digital‡	0.90 (0.64 to 1.26)	
BI-RADS breast density	—	.070
a-Almost entirely fatty	0.65 (0.34 to 1.26)	
b-Scattered fibroglandular tissue	Referent	
c-Heterogeneously dense	1.42 (1.00 to 2.03)	
d-Extremely dense	1.62 (0.84 to 3.11)	
Mode of PBC detection	—	.010
Screen detected	Referent	
Interval cancer in screening	1.87 (1.27 to 2.75)	
Clinical/diagnostic detected	1.37 (0.89 to 2.11)	
Other	1.70 (0.91 to 3.18)	
Time since last mammogram, months	—	.603
9-14	Referent	
15-23	1.11 (0.70 to 1.74)	
≥ 24	1.44 (0.68 to 3.02)	
Time since PBC diagnosis, years	—	.180
< 1	1.25 (0.73 to 2.16)	
1-2	Referent	
3-4	0.64 (0.39 to 1.05)	
5-6	0.53 (0.29 to 0.96)	
7-9	0.76 (0.41 to 1.42)	
> 10	0.62 (0.27 to 1.39)	

Abbreviations: BI-RADS, American College of Radiology Breast Imaging Reporting and Data System; BMI, body mass index; DCIS, ductal carcinoma in situ; ER, estrogen receptor; OR, odds ratio; PBC, primary breast cancer; PR, progesterone receptor.

*Also adjusts for Breast Cancer Surveillance Consortium registry and surveillance round. *P* value is for omnibus Wald test of any difference across levels of the covariate.

†OR compares surveillance mammograms after a diagnosis of DCIS with those after a diagnosis of stage I, grade 1, or ER/PR positive.

‡Includes 154 exams in which tomosynthesis was performed (one with screen-detected cancer that was diagnosed during follow-up).