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BRIEF REPORT

Diagnosis of second breast cancer events after initial diagnosis of early stage breast cancer

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Abstract To examine whether there are any characteristics of women or their initial tumors that might be useful for tailoring surveillance recommendations to optimize outcomes. We followed 17,286 women for up to 5 years after an initial diagnosis of ductal carcinoma in situ (DCIS) or early stage (I/II) invasive breast cancer diagnosed between 1996 and 2006. We calculated rates per 1,000 women years of recurrences and second breast primaries relative to demographics, risk factors, and characteristics of initial diagnosis: stage, treatment, mode of initial diagnosis. Nearly 4% had a second breast cancer event (314 recurrences and 344 second breast primaries). Women who used adjuvant hormonal therapy or were ≥80 years had the lowest rates of second events. Factors associated with higher recurrence and second primary rates included: initial DCIS or stage IIB, estrogen/progesterone receptor-negative, younger women (<50 years). Women with a family history or greater breast density had higher second primary rates, and women who received breast conserving surgery without radiation had higher recurrence rates. Roughly one-third of recurrences (37.6%) and second primaries (36.3%) were not screen-detected. Initial mode of diagnosis was a predictor of second events after adjusting for age, stage, primary treatment, and breast density. A recent negative mammogram should not falsely reassure physicians or women with new breast symptoms or changes because one-third of second cancers were interval cancers. This study does not provide any evidence in support of changing surveillance intervals for different subgroups.

Keywords Carcinoma · Ductal · Breast · Recurrence · Neoplasm recurrence · Local · Neoplasms · Second primary · Ultrasonography · Mammary · Diagnostic imaging · Breast neoplasms · Mammography

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Background

Breast cancer survivors remain at high risk of a second breast cancer for many years after initial diagnosis [1, 2]. Surveillance mammography aims to detect second breast cancers at earlier stages to decrease morbidity and ultimately improve survival [3]. Annual surveillance mammograms and clinical breast examination are recommended for women starting 1 year after initial diagnosis and no earlier than 6-months after radiation therapy is completed [4].

There are demonstrated benefits of surveillance mammography on reducing breast cancer mortality [5–7]. In a recent study, surveillance mammography reduced breast cancer mortality only for women with local recurrences and did not affect regional or distant recurrences; this provides compelling evidence that early detection of local recurrences drives mortality benefits [6].

We examined factors associated with surveillance mammography among survivors of early stage breast cancer in the Breast Cancer Surveillance Consortium (BCSC). We describe time to recurrence and second primary breast cancers by initial tumor characteristics, risk factors (including breast density), and mode of initial and subsequent detection.

Methods

This cohort study used pooled BCSC data from four registries: Group Health, Vermont Breast Cancer Surveillance System, New Hampshire Mammography Network, and New Mexico Mammography Project [8, 9]. Participating registries collect information on mammograms in their defined catchment areas and link women to pathology and state tumor registries or regional SEER programs to obtain population-based cancer data. These registries collect demographic and breast cancer risk factor data from a self-reported questionnaire completed at each mammogram.

The central statistical coordinating center (SCC) analyzed the data. Each registry and the SCC have received Institutional Review Board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant and all registries and the SCC have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities that are subjects of this research [10].

We included women who had a mammogram and were diagnosed with in situ or early stage (I/II) [11] breast cancer between 1996 and 2006 ($N = 25{,}640$). Starting from the initial breast cancer diagnosis, we determined whether any further breast cancer diagnoses occurred within the next 6-months. If so, we used the most invasive diagnosis in that period. We collected stage (0/I/IIA/IIB) [11], nodal status, estrogen (ER) and progesterone receptor (PR) status, and primary treatment from tumor registries.

We excluded women with evidence of prior breast cancer ($n = 2108$), unknown laterality or bilateral first cancer ($n = 769$), second breast cancer diagnoses $\leq$6 months ($n = 55$), missing stage or stage $\geq$III ($n = 3436$) or no definitive surgery ($n = 1298$), missing second cancer laterality ($n = 25$), and <6 months of follow-up after initial diagnosis ($n = 663$). This left a final sample of 17,286.

All women were followed for 5 years from initial diagnosis until the first of the following: second breast cancer, death, or the last day of available information from the cancer registry. We identified 658 second DCIS and invasive breast cancers. Laterality and histology (ductal, lobular or mixed, not otherwise specified or other) of the first and second invasive cancers were compared to distinguish between recurrences and new primaries. *Recurrences* were unilateral diagnoses in the ipsilateral breast and had to share the same histology as the primary tumor ($n = 314$). We defined 344 second events as *second primaries*, including 15 bilateral second events, 290 contralateral events, and 39 ipsilateral events whose histology differed from that of the initial tumor.

Self-administered questionnaires were used to collect race/ethnicity, self-reported lump before mammogram, menopausal status (last reported $\leq$6 months before first and second diagnosis), and first-degree breast cancer family history reported before initial diagnosis. Breast density was recorded by the interpreting radiologist using the Breast Imaging Reporting and Data Systems [12] four density categories and was included only if recorded less than or equal to 2 years before the mammogram used for initial detection mode.

We used established methods combining mammogram indication and results to classify detection mode at each diagnosis [13–15]. Mammograms were classified as screening (routine screening without evidence of a self-reported lump $\leq$30 days before the mammogram leading to the 1st diagnosis and with a radiologists' indication for exam noted as screening) [13] or diagnostic (additional evaluation of a recent mammogram, short-interval follow-up, evaluation of a breast problem including self-reported presence of a breast lump by patient or provider $\leq$30 days before diagnosis) [16]. We used the earliest screening exam $\leq$365 days before diagnosis to define detection mode. If the registry had no screening mammograms, we used the earliest diagnostic mammogram $\leq$365 days before the diagnosis (Fig. 1) [17]. If no mammogram was found $\leq$365 days before diagnosis, we used the first diagnostic mammogram $\leq$30 days after diagnosis, because diagnosis dates in tumor registries often represent the first evidence of cancer.

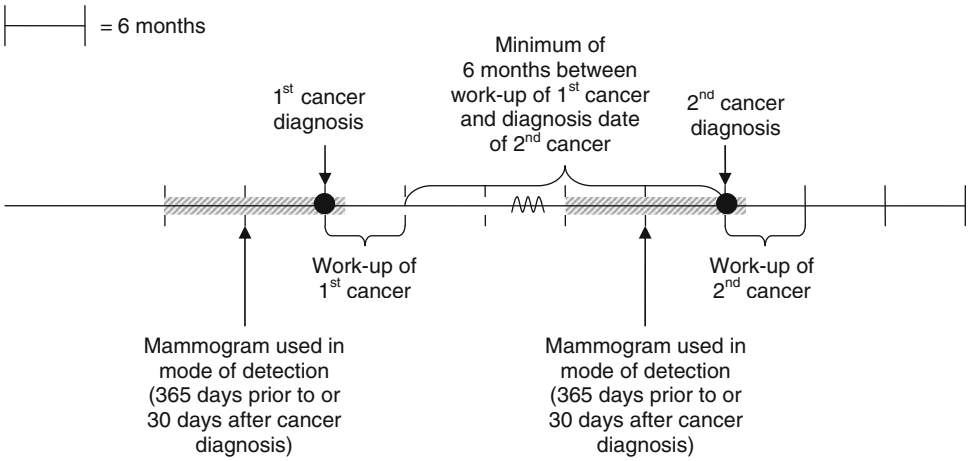

Fig. 1 Mammograms used to define detection mode for first and second cancer events. Most patient risk factors were based on responses to questionnaires completed within 6 months of the mammogram used for initial mode of detection. Breast density was recorded by the interpreting radiologist and was only included in the analysis if it was recorded within ≤2 years of the mammogram used for initial mode of detection. *Example* Assume a woman has her first breast cancer diagnosed on 1 January 2007. To determine the mode of detection we search for a mammogram from 1 January 2006–1 January 2007. If none is found then we also look ahead until 1 February 2007. Assume work-up of her first cancer finishes on 15 February 2007. We then begin looking for a second breast cancer diagnosis 6 months later (after 16 August 2007)

Detection mode was defined as: screen-positive, screen-negative (interval cancer following a negative screening exam), diagnostic-positive, or diagnostic-negative, using standard definitions [13–15, 18]. Mammograms with final BI-RADS® assessments of 4 or 5 were considered "positive," as were BI-RADS® assessments of 3 or 0 with a biopsy recommendation, surgical consult or fine needle aspiration. All others were considered "negative." The same strategy was used for the second diagnosis, with the added restriction that the mammogram had to follow the first cancer workup.

Analysis

Frequency distributions were computed for characteristics of women and first cancers. These were examined separately for three groups, those without a second cancer, those with a recurrence, and those with a second primary cancer. Cross-tabulations of initial detection mode and self-reported lump by detection mode of the second cancer were done separately by second breast event.

A *surveillance mammogram* was defined as any mammogram ≥6 months after the work-up of the first cancer and before the second cancer. Kaplan–Meier curves were used to summarize the relations between first cancer characteristics and surveillance mammography receipt.

We computed recurrence and new primary rates/1,000 woman years with 95% confidence intervals (CI) calculated on the Poisson distribution. We plotted the Nelson–Aalen estimate of the cumulative hazard function separately for each second events for certain characteristics. We also plotted an estimate of the hazard function for second events to detect any incidence peak.

We fit multivariable models using Cox regression to examine factors associated with second events; different models were created for each risk factor (breast density, initial detection mode, family history) and then one with all risk factors included. All models adjusted for stage, adjuvant therapy, age at diagnosis, and registry. We used SAS 9.0 for most analyses and generated hazard plots and multivariable models in Stata v.9.0.

Results

Stage I included 48.2% of the cohort, followed by stage II (33.1%), and DCIS (18.8%) (Table 1). Nearly 4% of the 17,286 women were diagnosed with a recurrence ($N = 314$) or second primary ($N = 344$). Among second cancers, 4% were stage III/IV, 21% were stage II, 33% were stage I, 22% were DCIS, and staging was unavailable for 19%.

At initial diagnosis, 35.8% of women were screen-detected, 15.6% screen interval-detected, 19.6% diagnostic detected, and 5.5% diagnostic interval-detected; 23.5% had an unknown initial diagnosis mode.

Time to first surveillance mammogram was rapid in the year following initial diagnosis; however, uptake did not markedly increase in the 18-months following diagnosis (Fig. 2a–c). Women diagnosed with stage IIB cancer had a lower and slower uptake (Fig. 2a). Women who were initially screen-detected were more likely to undergo surveillance than non screen-detected (67% by 6-months and

Table 1 Characteristics of women with early stage breast cancer (0, I, II) and their outcomes

	Total (17,286)		Women with no second breast cancer ($N = 16,628$)		Breast cancer recurrence[a] total ($N = 314$)		Second primary breast cancer total ($N = 344$)	
			N	Row %	*N*	Row %	*N*	Row %
Characteristics of 1st cancer diagnosis								
Stage at 1st diagnosis								
0	3,243	18.8	3,071	94.7	92	2.8	80	2.5
I	8,327	48.2	8,050	96.7	110	1.3	167	2.0
IIA	3,797	22.0	3,680	96.9	68	1.8	49	1.3
IIB	1,919	11.1	1,827	95.2	44	2.3	48	2.5
Nodal status								
No invasion	10,565	61.1	10,215	96.7	157	1.5	193	1.8
Invasion	3,476	20.1	3,340	96.1	65	1.9	71	2.0
Unknown	3,245	18.8	3,073	94.7	92	2.8	80	2.5
Hormone receptor								
ER−/PR−	2,097	12.1	1,994	95.1	60	2.9	43	2.1
ER−/PR+	215	1.2	205	95.3	8	3.7	2	0.9
ER+/PR−	1,310	7.6	1,270	96.9	24	1.8	16	1.2
ER+/PR+	9,131	52.8	8,861	97.0	109	1.2	161	1.8
Unknown	4,533	26.2	4,298	94.8	113	2.5	122	2.7
Primary surgery								
BCS without radiation therapy	3,150	18.2	2,971	94.3	120	3.8	59	1.9
BCS with radiation therapy	7,962	46.1	7,689	96.6	118	1.5	155	1.9
Mastectomy	6,174	35.7	5,968	96.7	76	1.2	130	2.1
Radiation therapy								
None	8,128	47.0	7,790	95.8	185	2.3	153	1.9
Any	8,944	51.7	8,637	96.6	128	1.4	179	2.0
Unknown	214	1.2	201	93.9	1	0.5	12	5.6
Adjuvant therapy								
Neither	8,388	48.5	8,038	95.8	170	2.0	180	2.1
Chemotherapy	2,496	14.4	2,380	95.4	61	2.4	55	2.2
Hormonal	3,744	21.7	3,636	97.1	47	1.3	61	1.6
Both	1,649	9.5	1,592	96.5	27	1.6	30	1.8
Unknown	1,009	5.8	982	97.3	9	0.9	18	1.8
Mode of detection of 1st cancer diagnosis								
Screen-detected (screen and positive)	6,183	35.8	5,984	96.8	87	1.4	112	1.8
Screen interval-detected (screen and negative)	2,702	15.6	2,597	96.1	44	1.6	61	2.3
Diagnostic detected (diagnostic and positive)	3,389	19.6	3,242	95.7	77	2.3	70	2.1
Diagnostic interval-detected (diagnostic and negative)	953	5.5	912	95.7	19	2.0	22	2.3
Unknown	4,059	23.5	3,893	95.9	87	2.1	79	1.9
Characteristics of women at 1st cancer diagnosis								
Age at 1st diagnosis								
18–39	710	4.1	668	94.1	25	3.5	17	2.4
40–49	3,411	19.7	3,253	95.4	87	2.6	71	2.1
50–59	4,616	26.7	4,452	96.4	78	1.7	86	1.9
60–69	3,864	22.4	3,732	96.6	57	1.5	75	1.9
70–79	3,291	19.0	3,164	96.1	50	1.5	77	2.3
≥80	1,394	8.1	1,359	97.5	17	1.2	18	1.3
Year of 1st diagnosis								
1996–1997	3,322	19.2	3,165	95.3	73	2.2	84	2.5

Table 1 continued

	Total (17,286)		Women with no second breast cancer ($N = 16,628$)		Breast cancer recurrence[a] total ($N = 314$)		Second primary breast cancer total ($N = 344$)	
			N	Row %	*N*	Row %	*N*	Row %
1998–1999	3,789	21.9	3,598	95.0	88	2.3	103	2.7
2000–2001	3,784	21.9	3,607	95.3	83	2.2	94	2.5
2002–2003	3,458	20.0	3,364	97.3	46	1.3	48	1.4
2004–2006	2,933	17.0	2,894	98.7	24	0.8	15	0.5
Race/ethnicity								
White	13,178	76.2	12,686	96.3	227	1.7	265	2.0
Black	132	0.8	124	93.9	5	3.8	3	2.3
Hispanic	1,884	10.9	1,823	96.8	39	2.1	22	1.2
Asian/Pacific Islander	242	1.4	233	96.3	2	0.8	7	2.9
Native American	303	1.8	293	96.7	8	2.6	2	0.7
Other	195	1.1	184	94.4	7	3.6	4	2.1
Unknown	1,352	7.8	1,285	95.0	26	1.9	41	3.0
Menopausal status (≤6 months of diagnosis)								
Pre-menopausal	2,485	14.4	2,377	95.7	57	2.3	51	2.1
Post-menopausal	9,757	56.4	9,435	96.7	142	1.5	180	1.8
Unknown	5,044	29.2	4,816	95.5	115	2.3	113	2.2
1st degree family history of breast cancer (before 1st diagnosis)								
No	11,247	65.1	10,855	96.5	195	1.7	197	1.8
Yes	2,881	16.7	2,764	95.9	46	1.6	71	2.5
Unknown	3,158	18.3	3,009	95.3	73	2.3	76	2.4
Breast density (before 1st diagnosis and within 2 years of mammogram used for mode of detection)								
Almost entirely fatty	493	2.9	480	97.4	11	2.2	2	0.4
Scattered fibroglandular	3,900	22.6	3,771	96.7	65	1.7	64	1.6
Heterogeneously dense	4,275	24.7	4,109	96.1	58	1.4	108	2.5
Extremely dense	930	5.4	885	95.2	21	2.3	24	2.6
Unknown	7,688	44.5	7,383	96.0	159	2.1	146	1.9

BCS breast conserving surgery, *ER* estrogen receptor, *PR* progesterone receptor

[a] Recurrent cancer includes a 2nd cancer in the same breast and with the same histology as the initial cancer

83% by 12-months vs. 54–58% by 6-months and 71–76% by 12-months, respectively). Women with unknown detection mode had the slowest uptake (32% by 6-months, 46% by 12-months) (Fig. 2b). Women receiving breast conserving surgery (BCS) with radiation had the most rapid and greatest uptake (64% by 6-months, 78% by 12-months) (Fig. 2c).

Overall second events rates/1,000 woman years were 5.37 for recurrence and 5.88 for second primaries. Among women without a second event, 53% were followed for 5 years (mean = 47 months). As a sensitivity analysis, we included women from the initial cohort with missing stage or surgery, multiple diagnoses in the initial 6-month period, bilateral cancer and missing laterality of the second event and observed slightly higher recurrence rates (6.56/1,000 woman years), but not of second primaries (6.03/1,000 woman years) (data not shown).

Initial stage was associated with recurrence and second primaries with the highest rates in women with DCIS (8.5 and 7.4, respectively) and stage IIB (7.1 and 7.8) vs. stages I (3.9 and 5.9) and IIA (5.3 and 3.8). Recurrence rates were higher for women with ER-negative tumors than those with ER+ tumors; however, second primary rates were higher only for women with ER−/PR− tumors. Second primary rates did not differ by primary therapy; however, recurrence rates were higher in women with BCS without radiation (Table 2). Recurrence rates decreased with increasing age at diagnosis, but rates of second primaries did not vary systematically except among women aged ≥80 years, whose rates were markedly lower. Higher breast density was associated with higher second primary rates (1.3 almost entirely fatty; 5.0 scattered fibroglandular; 7.7 heterogeneously and extremely dense), but there was no trend in recurrence rates.

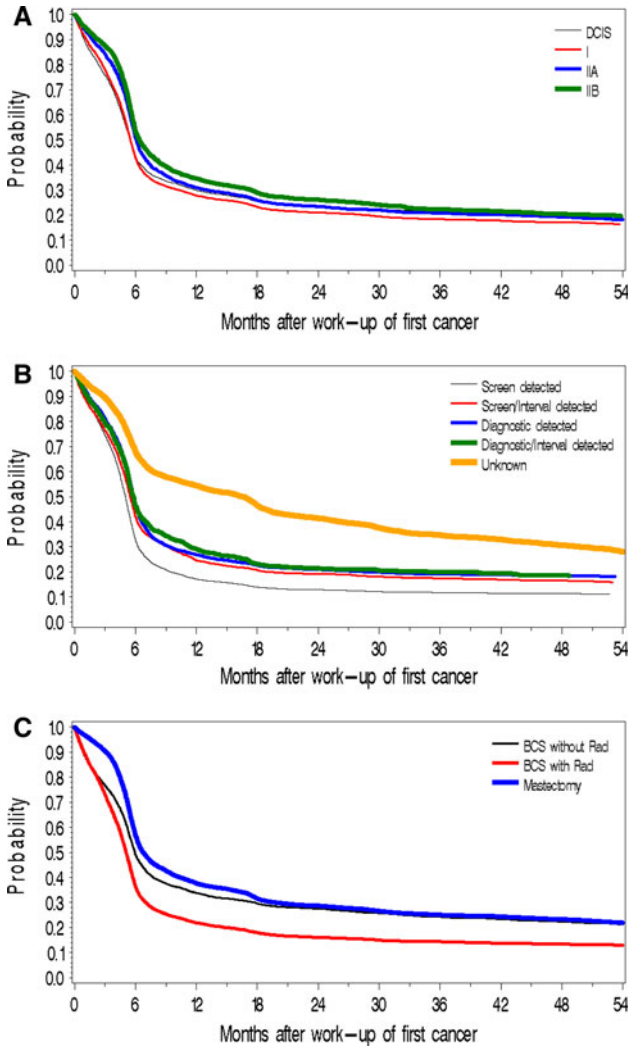

Fig. 2 Time to first surveillance mammogram by characteristics of initial cancer. **a** By stage at first diagnosis. **b** By mode of detection for initial diagnosis. **c** By treatment for initial diagnosis

Interval cancers accounted for 37.6% of recurrences and 36.3% of second primaries (data not shown). We could not define diagnosis mode for 28.1% (32.2% for recurrences and 24.4% for second primaries). Just over one-third of second events were diagnosed following a screening (19.7% recurrence, 24.7% second primaries) or diagnostic mammogram (10.5, 14.5%, respectively), and the rest were interval-detected following a screening (21.0, 21.2%) or a diagnostic exam (16.6, 15.1%). Few women reported a lump before the mammogram leading to their second cancer diagnosis: 8.0% of recurrences and 4.9% second primaries.

Some subgroups experienced higher recurrence rates, with no difference in second primaries, including premenopausal women, node positive women, women who were initially detected following a diagnostic mammogram, and women who initially had a self-reported lump. Women with a family history had higher rates of second primaries but not of recurrence. Notably, lower rates of second events were observed in women aged ≥80 years and adjuvant hormonal therapy users.

Mode of initial diagnosis was the only variable that was significantly associated with risk of a second cancer diagnosis after adjustment for other prognostic factors; women whose first cancer was diagnostic detected had significantly higher risk of a second cancer compared to women whose 1st cancer was screen-detected (Table 3). We conducted sensitivity analyses that included all prognostic factors and varied the combination of risk factors; hazard estimates did not vary in direction or significance in these sensitivity analyses and detection mode was the only significant risk factor (data not shown).

Discussion

This study provides important information on timing and detection of second breast cancer events after an initial diagnosis of early breast cancer. We identified certain subgroups with higher second breast cancer event rates. Surveillance may be particularly important for women <50 years or with initial DCIS, stage IIB, or ER− cancers as these subgroups had the highest 5-year cumulative hazards of recurrence and second primaries. Women with a family history of breast cancer had higher rates of second primaries but not recurrences. The only subgroups with a distinctly lower risk for either second event were women aged ≥80 years and those who received adjuvant hormonal therapy.

Randomized trials [19–22] provide critical information on prognostic factors. However, initial detection mode and breast density are less well understood as risk factors for second breast events. It is important to understand whether detection mode and characteristics of patients and tumors can be used to tailor surveillance recommendations to improve long-term outcomes, particularly if women could benefit from more or less surveillance during certain times following initial diagnosis. Our study was not designed to address the evidence gaps around recommendations on when to stop surveillance mammography since we followed women for only 5 years after initial diagnosis. It was designed to examine whether any characteristics of women or their initial tumors might be useful to guide recommendations around initial 5-year surveillance after early stage breast cancer diagnosis.

Several studies and expert reviews have demonstrated surveillance mammography is effective for improving long-term outcomes (e.g., breast cancer mortality) for women with early stage breast cancer [3–5], including at least one study demonstrating decreased breast cancer

Table 2 Rates (per 1,000 woman years) of breast cancer recurrences and second primaries by characteristics at initial diagnosis

	Breast cancer recurrences[a]			Second breast primaries		
	N	Rates	95% CI	*N*	Rates	95% CI
Characteristics of 1st cancer diagnosis and treatment						
Stage at 1st diagnosis						
0	92	8.5	(6.8, 10.4)	80	7.4	(5.8, 9.2)
I	110	3.9	(3.2, 4.7)	167	5.9	(5.0, 6.8)
IIA	68	5.3	(4.1, 6.7)	49	3.8	(2.8, 5.0)
IIB	44	7.1	(5.2, 9.5)	48	7.8	(5.7, 10.3)
Nodal status						
No invasion	157	4.4	(3.7, 5.1)	193	5.3	(4.6, 6.2)
Invasion	65	5.7	(4.4, 7.2)	71	6.2	(4.8, 7.8)
Hormone receptor						
ER−/PR−	60	9.0	(6.9, 11.6)	43	6.4	(4.7, 8.7)
ER−/PR+	8	10.8	(4.7, 21.3)	2	2.7	(0.3, 9.8)
ER+/PR−	24	5.5	(3.5, 8.2)	16	3.7	(2.1, 6.0)
ER+/PR+	109	3.6	(2.9, 4.3)	161	5.3	(4.5, 6.2)
Treatment						
BCS without radiation therapy	120	12.7	(10.6, 15.2)	59	6.3	(4.8, 8.1)
BCS with radiation therapy	118	4.2	(3.5, 5.1)	155	5.5	(4.7, 6.5)
BCS with and without radiation therapy	238	6.4	(5.6, 7.2)	214	5.7	(5.0, 6.5)
Mastectomy	76	3.6	(2.8, 4.5)	130	6.2	(5.2, 7.3)
Adjuvant therapy						
Neither	170	6.1	(5.3, 7.1)	180	6.5	(5.6, 7.5)
Chemotherapy	61	7.2	(5.5, 9.3)	55	6.5	(4.9, 8.5)
Hormonal	47	3.5	(2.5, 4.6)	61	4.5	(3.4, 5.8)
Both	27	4.4	(2.9, 6.4)	30	4.9	(3.3, 6.9)
Mode of 1st cancer diagnosis						
Screen-detected	87	4.1	(3.3, 5.1)	112	5.3	(4.4, 6.4)
Screen interval	44	4.8	(3.5, 6.4)	61	6.6	(5.1, 8.5)
Diagnostic detected	77	6.8	(5.4, 8.6)	70	6.2	(4.8, 7.9)
Diagnostic interval	19	5.9	(3.6, 9.2)	22	6.8	(4.3, 10.3)
Unknown	87	6.3	(5.1, 7.8)	79	5.8	(4.6, 7.2)
Characteristics of women at 1st cancer diagnosis						
Age at 1st diagnosis						
18–39	25	9.7	(6.3, 14.4)	17	6.6	(3.9, 10.6)
40–49	87	7.4	(5.9, 9.1)	71	6.0	(4.7, 7.6)
50–59	78	5.0	(3.9, 6.2)	86	5.5	(4.4, 6.8)
60–69	57	4.3	(3.3, 5.6)	75	5.7	(4.5, 7.1)
70–79	50	4.6	(3.4, 6.0)	77	7.0	(5.5, 8.8)
≥80	17	4.0	(2.3, 6.4)	18	4.2	(2.5, 6.7)
Race/ethnicity						
White	227	5.1	(4.5, 5.8)	265	5.9	(5.3, 6.7)
Black	5	11.2	(3.6, 26.1)	3	6.7	(1.4, 19.6)
Hispanic	39	6.3	(4.5, 8.6)	22	3.6	(2.2, 5.4)
Asian/Pacific Islander	2	2.5	(0.3, 9.1)	7	8.8	(3.5, 18.1)
Native American	8	7.9	(3.4, 15.6)	2	2.0	(0.2, 7.1)
Other	7	10.9	(4.4, 22.5)	4	6.3	(1.7, 16)
Menopausal status (≤6 months of diagnosis)						
Pre-menopausal	57	6.8	(5.2, 8.9)	51	6.1	(4.6, 8.0)
Post-menopausal	142	4.3	(3.7, 5.1)	180	5.5	(4.7, 6.4)
1st degree family history of breast cancer (before 1st diagnosis)						
No	195	5.2	(4.5, 6.0)	197	5.3	(4.6, 6.1)
Yes	46	4.9	(3.6, 6.5)	71	7.6	(5.9, 9.5)

Table 2 continued

	Breast cancer recurrences[a]			Second breast primaries		
	N	Rates	95% CI	*N*	Rates	95% CI
Breast density (before 1st diagnosis and within 2 years of mammogram used for mode of detection)						
Almost entirely fatty	11	7.0	(3.5, 12.6)	2	1.3	(0.2, 4.6)
Scattered fibroglandular	65	5.0	(3.9, 6.4)	64	5.0	(3.8, 6.3)
Heterogeneously dense	58	4.1	(3.1, 5.4)	108	7.7	(6.3, 9.3)
Extremely dense	21	6.8	(4.2, 10.4)	24	7.7	(5.0, 11.5)
Self-reported lump before mammogram used for mode of detection						
No	165	4.5	(3.8, 5.2)	218	5.9	(5.2, 6.8)
Yes	66	7.1	(5.5, 9.0)	52	5.6	(4.2, 7.3)

BCS breast conserving surgery, *ER* estrogen receptor, *PR* progesterone receptor, *CI* confidence interval

[a] Recurrent cancer includes a 2nd cancer in the same breast as the 1st cancer with the same histology for the 2nd breast cancer

mortality [6]. Scrutiny of over-diagnosis from screening mammography has increased [23]. The concern is that mammography identifies breast lesions with limited potential for malignancy and will trigger workup and treatment that may have no long-term impact on mortality [23]. Inappropriate screening harms women and healthcare systems by increasing anxiety and adding to unnecessary healthcare expenditures [24]. We know of no research that has attempted to quantify over-diagnosis from surveillance mammograms. This is important for breast cancer survivors, who may undergo additional treatment for a second cancer that may not influence long-term outcomes.

We hypothesized that the mode of initial detection might affect second event rates and when and how often women receive surveillance mammography. Women who were initially screen-detected were more likely than others to return for their first surveillance mammogram [4]. Some mammography facilities routinely perform diagnostic examinations for anyone—even asymptomatic patients—with a personal history of breast cancer, so it may be most appropriate to compare detection mode of second events by combining screen- and diagnostic-detected vs. interval-detected cancers. There are evidence gaps around how second breast cancer events are detected. A systematic review [7] found extensive variation across 10 studies ($N = 102$–7,000 patients) that reported on detection mode for recurrent breast cancers. In three studies, 73–88% of recurrences were detected from physical exam; this ranged from 12 to 54% in the remaining seven studies [7]. The range was also large for the proportion of recurrences detected by mammography (8–50%) [7]. Not surprisingly, Grunfeld's review [7] found that recurrent cancers detected by mammography were smaller and less invasive than were those detected through physical exam. Isolating the effect of surveillance mammography on long-term outcomes—such as mortality—remains challenging because of lead and length biases that impact the timing of when second events are detected. However, recent studies have attempted to isolate the influence of these biases, and findings keep suggesting that detection mode remains an independent prognostic factor [25–27]. Consistent with recent literature [25–27], women who were initially diagnosed following a diagnostic mammogram had significantly higher risks of second events even after adjusting for prognostic factors; this further suggests that mode of initial detection is an important prognostic factor for second cancer events.

Our finding that approximately 37% of second cancers were interval cancers serves as an important reminder—women, radiologists, oncologists, and primary care providers need to continue to be aware of newly arising symptoms and breast changes in both breasts (and chest wall) even after a recent negative screening or diagnostic mammogram. Houssami et al. [27] reported that 14% of second cancers were found by clinical breast exam alone. The absence of a breast lump at presentation should not reassure clinicians since lumps were present in only 8% of recurrences and 5% of second primaries at the mammogram leading to the second diagnosis; approximately 5% of women with no history of breast cancer report a breast lump at the time of a screening mammogram [9].

The 5-year relative survival rates for DCIS have remained unchanged at around 100% [28]. Many studies examining surveillance mammography have not included women with DCIS [6, 26, 29], who comprise ~20% of all breast cancer cases [30]. Importantly, in this study, women with initial DCIS have substantially higher second cancer rates regardless of initial treatment. This could reflect residual breast disease from initial diagnosis [31]. Clinically, this identifies an important sub-group of women who may benefit from increased surveillance mammography since second breast cancer event rates in this population mirrored women with stage IIB tumors.

Although our findings confirmed that the vast majority of women receive a first surveillance mammogram within 1-year of initial diagnosis, there are still opportunities to

Table 3 Multivariable global hazard of having a second breast cancer event diagnosed adjusted for all variables in the table

	Model 4[a] ($N = 8,662$)		
	HR	95% CI	P value
Breast density (before 1st diagnosis and within 2 years of mammogram used for mode of detection)			
Almost entirely fatty	Ref		0.6859
Scattered fibroglandular	1.07	(0.60, 1.90)	
Heterogeneously dense	1.20	(0.67, 2.13)	
Extremely dense	1.30	(0.68, 2.48)	
Mode of 1st cancer diagnosis			
Screen-detected	Ref		0.0008
Screen interval-detected	**1.38**	**(1.02, 1.86)**	
Diagnostic detected	**1.78**	**(1.35, 2.35)**	
Diagnostic interval-detected	1.32	(0.86, 2.04)	
1st degree family history of breast cancer (before 1st diagnosis)			
No	Ref		0.9442
Yes	1.01	(0.77, 1.32)	
Age at 1st diagnosis			
18–39	1.06	(0.61–1.83)	0.6809
40–49	0.99	(0.72–1.35)	
50–59	Ref		
60–69	1.08	(0.79–1.49)	
70–79	1.17	(0.84–1.65)	
80+	0.76	(0.44–1.30)	
Stage at 1st diagnosis			
0	**1.66**	**(1.25–2.21)**	0.003
I	Ref		
IIA	0.91	(0.66–1.26)	
IIB	1.12	(0.75–1.66)	
Adjuvant therapy			
Neither	Ref		0.0067
Chemotherapy	1.22	(0.86–1.75)	
Hormonal	**0.68**	**(0.51–0.93)**	
Both	0.75	(0.47–1.18)	

P values are based on likelihood ratio tests and are also adjusted for mammography registry

[a] $P \leq 0.05$

increase outreach to populations who do not return for a mammogram within 18-months of initial diagnosis. Examining surveillance mammography receipt is important for understanding timing and detection mode of second breast events. In this study, we could not determine what type of provider recommended surveillance or how women were reminded to receive mammography, both of which affect uptake and adherence [32, 33]. Continuity and coordination across health care providers may help ensure high adherence to mammography surveillance [3, 33, 34].

Identifying and correctly distinguishing between recurrences and second primaries is challenging and can be influenced by physician judgment, pathologists and available data from initial diagnosis. Our definition of recurrence was stricter than others [35–38] because we required the same laterality and histology. Previous studies have reported recurrence rates of 3%/year after DCIS, which is substantially higher than the 1%/year we observed. However, our observed second primary rates (0.6%/year invasive and 0.8%/year DCIS) are consistent with other cohorts [39, 40]. Using pathology databases to identify second events has additional limitations since some regional and distant recurrences may not have pathologic confirmation, which leads to under-ascertainment of distant recurrences. This should not affect our second breast cancer rates because they were ascertained through cancer registries. Distinguishing between recurrences and second primaries may be less critical when considering surveillance recommendations.

We limited our follow-up to 5 years because BCSC is not a closed cohort. We could not examine second events by comorbidities. Also, even with our large sample, we lacked enough numbers of women with stage IIIA ($N = 581$; 19 went on to have a recurrence (89% of these

having a regional recurrence) and 10 a second primary), so they were excluded. These women had a significantly shorter time to second breast cancer, and most of them received chemotherapy.

Strengths of our study include: studying outcomes from community-based mammography facilities in geographically diverse populations; including younger and older women; and including second events that did not rely exclusively on tumor registries. We know of only one other study that has included initial DCIS cases [27] and none that has included DCIS as a second event. Approximately 20% of diagnoses of incident breast cancer are DCIS, so DCIS is important for understanding the risk of second events.

Evidence to aid initial treatment decisions by using molecular markers will likely continue to improve breast cancer outcomes [21, 22]. However, we should not lose sight of our need to continue to consider tailored surveillance recommendations. This study does not provide evidence to support changing surveillance intervals for different subgroups. However, it does suggest that certain subgroups may benefit from increased surveillance: women who are young or have ER-negative tumors or DCIS or stage IIB disease. Surveillance may be less important for older women ($\geq$80 years) and for women using adjuvant hormonal therapy since rates of second cancers were low in these women. These data can also be used to help counsel women on detection mode for second cancers to seek care diligently for any symptoms that arise following a negative mammogram.

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