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ORIGINAL PAPER

Reproductive and menopausal factors and risk of second primary breast cancer after in situ breast carcinoma

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Abstract

Purpose In situ breast cancer patients have a higher risk of developing a second primary breast cancer than women in the general population have of developing breast cancer. We have limited understanding of why some women with a previous in situ breast cancer develop second primary breast cancers while others do not.

Methods In this population-based nested case–control study, we evaluated the association between reproductive and menopausal factors and risk of developing a second primary breast cancer among women with a previous in situ breast cancer. Using conditional logistic regression, these associations were evaluated in 552 cases and 1032 individually matched controls.

Results Older age at menarche was associated with risk of second primary breast cancer among women with a previous in situ breast cancer (compared to age < 12, age 13: OR 0.60 (0.42, 0.85); age ≥ 14: OR 0.69 (0.47, 1.00); $P_{trend} = 0.07$). Breastfeeding for > 12 months was associated with a decreased risk of developing a second primary breast cancer (OR 0.62 (0.39, 0.98)). No associations were observed for other reproductive or menopausal factors evaluated.

Conclusions Results from this study suggest that reproductive factors may play a role in development of a second primary breast cancer after diagnosis of in situ breast carcinoma.

Keywords Breast cancer · Reproductive · In situ breast cancer · Menopausal hormone therapy

Introduction

Approximately 20% of all incident breast cancers in the United States are in situ tumors; rates of in situ breast cancer have risen substantially with increased rates of mammography [1, 2]. Women with a previous in situ breast tumor are at an increased risk of developing a second in situ breast tumor or a second primary invasive breast cancer compared to women in the general population without a personal history of breast cancer [3–5]. Several reproductive and menopausal factors have been shown to be associated with risk of in situ breast carcinoma and/or invasive breast cancer, including age at menarche [6, 7], age at menopause [6, 8], parity [7, 9–11], age at first full-term pregnancy [7, 9–12], duration of breastfeeding [10, 13], and use of exogenous hormones [7, 8, 14–19]. Few studies have assessed the relationships between these factors and risk of second primary breast cancer among women with a previous in situ breast cancer and those that have have found inconsistent results. In a study of 709 women with a previous ductal carcinoma in situ (DCIS), risk of second breast cancer was not significantly associated with age at menarche, nulliparity, age at first birth, or use of menopausal hormone therapy (mHT) [20]. A more recent cohort study similarly found no association between mHT and risk of second breast cancer among 1,036 women with a previous DCIS [21]. However, these studies had relatively few second breast cancers in their populations (103 and 209, respectively).

We hypothesized that the associations between breast cancer risk factors and second primary breast cancer would be similar in direction to the association observed with first primary breast cancer. We evaluated the association between reproductive and menopausal factors and risk of developing a second in situ or invasive breast cancer using data from a nested case–control study of women with a previous in situ breast cancer.

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Materials and methods

Using data from a previously described population-based nested case–control study among women with a previously diagnosed in situ breast carcinoma (either ductal or lobular carcinoma in situ) [22], we evaluated reproductive and menopausal factors associated with risk of second primary breast cancer. Briefly, women aged 30–79 diagnosed between January 1, 1995 and June 30, 2013 with in situ breast carcinoma in western Washington State were eligible for the study. Cases ($n = 573$) were women who developed a second primary breast cancer more than 6 months following their first in situ breast cancer diagnosis. Controls ($n = 1096$) were women who did not develop a second primary breast cancer during the study and were matched individually 2:1 to cases. The response rates for cases and controls were 69.5% and 56.2%, respectively. Matching factors were age, year of initial in situ breast carcinoma diagnosis, county of residence at diagnosis, surgical and radiation treatment, histology and grade of initial in situ breast tumor. The study was approved by the Institutional Review Board (IRB) at the Fred Hutchinson Cancer Research Center.

Data collection

Information on demographic, epidemiologic, and clinical factors was collected via a telephone questionnaire administered by trained interviewers and additional data on tumor characteristics, treatment, and breast cancer risk factors were collected through medical record review. Data were collected for the period prior to the first diagnosis up through the reference date, which, for cases, was the date of second primary breast cancer and, for controls, an assigned reference date. Data on reproductive and menopausal factors were obtained from both interview and medical records. Specifically, women were asked about their reproductive history, including pregnancy and breastfeeding history and timing of menarche and menopause, and history of use of oral contraceptives. Data on parity and age at first pregnancy were also abstracted from medical records. For patients who were deceased at the time of this study, data were collected from medical records. Questionnaires served as the primary source of data and were supplemented with data from medical records when questionnaire data were missing. Our study focused on the status of reproductive and menopausal factors at the time of the first diagnosis as many of the factors occurred prior to the first diagnosis. Participants were excluded from analysis if they were missing data on all reproductive and menopausal variables of interest (21 case–control pairs ($n = 21$ cases and 37 controls) and 27 additional controls (where the case had other control(s) with data available)). Our final sample included 552 cases and 1,032 controls available for analysis.

Statistical analysis

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the associations between reproductive and menopausal factors and risk of second primary breast cancer, overall and among invasive cases only, using conditional logistic regression. Matching factors were implicitly adjusted for in the analyses. Breastfeeding duration analyses were adjusted for number of full-term pregnancies. Other variables, including known breast cancer risk factors [race/ethnicity, family history of breast cancer, and body mass index (BMI)], were evaluated as potential confounders but inclusion of these factors did not materially change our estimates. Effect modification by menopausal status, ER status, and other tumor characteristics was evaluated. Where applicable, p values for trend tests were calculated using continuous variables. For analyses on menopausal hormone therapy use, only women who were postmenopausal at first diagnosis were included. Analyses were conducted using SAS v9.3 (SAS Institute, Cary, NC).

Results

Cases were more likely to have a family history of breast cancer and to be overweight or obese at the first in situ breast cancer diagnosis and reference compared to controls (Table 1). Cases were similar to controls on menopausal status, in situ tumor grade, and in situ treatments. The majority of cases developed a second breast cancer that was invasive (68%, $n = 378$). With respect to laterality, 55% of the second breast cancers among cases were contralateral, ($n = 304$), 44% were ipsilateral ($n = 244$), and 1% were bilateral ($n = 4$).

Older age at menarche was associated with a reduced risk of second primary breast cancer among women with in situ breast cancer and a moderate trend was observed (compared to those < 12, age 12: OR 0.79, 95% CI 0.55, 1.14; age 13: OR 0.60, 95% CI 0.42, 0.85; age ≥ 14: OR 0.69, 95% CI 0.47, 1.00; $P_{trend} = 0.07$) (Table 2). After adjustment for number of full-term pregnancies, breastfeeding for more than 12 months was associated with a decreased risk of developing a second primary breast cancer (OR 0.62, 95% CI 0.39, 0.98). This association was stronger among cases who developed a second invasive cancer (OR 0.52, 95% CI 0.30, 0.90). However, a trend was not observed among all cases or invasive cases and breastfeeding (yes/no) was not associated with second primary breast cancer. Menopausal hormone therapy use at 1st diagnosis was significantly

Table 1 Demographic and clinical factors by case–control status

Characteristics	Study participants [*N* (%)]	
	Controls ($n=1032$)	Cases ($n=552$)
Age at 1st breast cancer diagnosis		
< 50	355 (34.4)	194 (35.1)
50–59	361 (35.0)	187 (33.9)
60–69	218 (21.1)	113 (20.5)
70–79	98 (9.5)	58 (10.5)
Year of 1st breast cancer diagnosis		
1995–1997	226 (21.9)	116 (21.0)
1998–2000	225 (21.8)	144 (26.1)
2001–2004	292 (28.3)	142 (25.7)
2005–2013	289 (28.0)	150 (27.2)
Race/ethnicity		
Non-Hispanic white	935 (90.6)	489 (88.6)
Hispanic white	19 (1.8)	12 (2.2)
Black	17 (1.7)	13 (2.4)
Asian/Pacific Islander	47 (4.6)	29 (5.3)
Native American	14 (1.4)	8 (1.5)
Unknown	0	1
Family history of breast cancer		
Yes	265 (26.4)	173 (32.3)
No	740 (73.6)	362 (67.7)
Missing	27	17
BMI at 1st breast cancer diagnosis		
< 25	500 (50.0)	223 (42.2)
25–< 30	290 (29.0)	161 (30.4)
≥ 30	210 (21.0)	145 (27.4)
Unknown	32	23
Grade of 1st tumor		
1—Well differentiated	21 (2.8)	18 (4.6)
2—Moderately differentiated	232 (30.9)	103 (26.5)
3—Poorly differentiated	231 (30.7)	116 (29.9)
4—Undifferentiated	268 (35.6)	151 (38.9)
Unknown	280	164
Radiation treatment for 1st breast cancer		
Yes	495 (48.0)	255 (46.2)
No	537 (52.0)	297 (53.8)
Surgery for 1st breast cancer		
Biopsy only	32 (3.1)	24 (4.4)
Lumpectomy without nodal dissection	722 (70.0)	382 (69.2)
Lumpectomy with sentinal node biopsy	50 (4.8)	26 (4.7)
Lumpectomy with nodal dissection	36 (3.5)	19 (3.4)
Mastectomy	192 (18.6)	101 (18.3)
Laterality of 2nd breast cancer		
Ipsilateral	n/a	244 (44.2)
Contralateral	n/a	304 (55.1)
Bilateral	n/a	4 (0.7)
Menopausal status at 1st breast cancer diagnosis		
Pre/peri-menopausal	402 (40.2)	223 (41.5)
Postmenopausal	598 (59.8)	314 (58.5)
Unknown	32	15

Table 1 (continued)

Characteristics	Study participants [*N* (%)]	
	Controls ($n=1032$)	Cases ($n=552$)
Menopausal status at reference		
Pre/peri-menopausal	184 (18.6)	111 (21.1)
Postmenopausal	805 (81.4)	415 (78.9)
Unknown	43	26

inversely associated with risk of second primary breast cancer, particularly among invasive cases (OR 0.66, 95% CI 0.46, 0.95). This inverse association was stronger among those taking combination estrogen and progestin (OR 0.58, 95% CI 0.37, 0.92) than among those taking unopposed estrogen (OR 0.73, 95% CI 0.48, 1.11). No associations between age at first full-term pregnancy, number of full-term pregnancies, use of hormonal birth control in two years prior to first breast cancer diagnosis, or age at menopause and risk of second primary breast cancer among women with a previous in situ breast cancer were observed.

When stratified by ER status of the second breast cancer (Table 3), the association with breastfeeding (ever/never) was observed among women whose second breast cancer was ER− (OR 0.35, 95% CI 0.14, 0.87) but not ER+ (OR 0.89, 95% CI 0.58, 1.35), although a test of heterogeneity by ER status was not statistically significant (ER- compared to ER+: OR 0.56, 95% CI 0.29, 1.09, $p=0.09$). Age at menopause was moderately inversely associated with risk of second primary breast cancer among women whose second tumor was ER+ (OR 0.97, 95% CI 0.94, 1.00). Current mHT use at 1st diagnosis was inversely associated with risk of second primary breast cancer among women whose second tumor was ER+ (OR 0.68, 95% CI 0.47, 0.99), particularly among those who took combination estrogen and progestin (OR 0.63, 95% CI 0.40, 1.00). A statistically significant association was not observed among women whose second tumor was ER-. No other significant associations were observed by ER status.

When stratified by menopausal status, older age at first full-term pregnancy was associated with a moderate increase in risk of second primary invasive breast cancer among premenopausal women (per year: OR 1.05, 95% CI 0.99, 1.11) and a moderate decrease in risk among postmenopausal women (per year: OR 0.97, 95% CI 0.92, 1.01), which was suggestive of an interaction ($P_{\text{interaction}}=0.06$). No other differences by menopausal status were observed. We also considered these associations according to features of the initial in situ tumor. When stratified by in situ breast carcinoma grade, women with a grade 4 (undifferentiated) in situ breast carcinoma who were aged 30 or older at first full-term pregnancy were more likely to develop a second breast cancer (OR 3.41, 95% CI 1.15, 10.15); no association between age at first full-term pregnancy and risk of developing a second breast cancer was observed among women with in situ breast tumors grade 1/2 or grade 3. Differences in risk were not observed when the results were stratified by laterality of the second breast cancer or in situ breast carcinoma histology/presence of comedo necrosis (data not shown).

Discussion

Our results suggest that older age at menarche and breastfeeding duration may be associated with reduced risks of developing a second primary breast cancer among women with a previous in situ breast cancer diagnosis, but that other reproductive factors are not. Current menopausal hormone therapy at 1st diagnosis was inversely associated with risk of second primary breast cancer, particularly among those whose second primary breast cancer was ER+ and invasive.

Previous studies have shown that later age at menarche is associated with a decreased risk of primary breast cancer [6, 7]. Similarly, our results showed that later age at menarche was associated with a decreased risk of second primary breast cancer among women with a previous in situ breast cancer. Breastfeeding duration was associated with a decreased risk of second primary breast cancer among women with a previous in situ breast cancer, even after adjustment for number of full-term births, though a trend was not observed. Previous studies have shown that breastfeeding lowers the risk of first primary breast cancer which is consistent with the findings of our study [13]. Previous studies have also suggested that breastfeeding may particularly reduce the risk of triple-negative breast cancer [23–25]. Similarly, we found that the reduced risk of second primary breast cancer was stronger among those whose second breast cancer was ER-. It is likely that the same hormonal mechanisms involved in development of a first primary breast cancer are potentially relevant for development of a second primary breast cancer. However, we did not see an association between risk of second primary breast cancer among women with a previous in situ breast cancer and other established reproductive risk factors for breast cancer including age at first full-term pregnancy, parity, and age at menopause. This suggests that some risk factors for first and second primary breast cancer development may differ.

Table 2 Relationship between reproductive and menopausal factors and risk of second breast cancer

	Controls	All cases		Invasive cases	
	n (%)	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]
Age at menarche					
< 12	142 (16.2)	101 (22.6)	1 [Ref]	70 (23.4)	1 [Ref]
12	232 (26.4)	116 (26.0)	0.79 (0.55, 1.14)	73 (24.4)	0.77 (0.49, 1.21)
13	290 (33.0)	122 (27.3)	0.60 (0.42, 0.85)	91 (30.4)	0.66 (0.43, 1.01)
≥ 14	214 (24.4)	108 (24.2)	0.69 (0.47, 1.00)	65 (21.7)	0.63 (0.39, 1.01)
Continuous (1 year)			0.93 (0.85, 1.01)		0.93 (0.83, 1.03)
P_{trend}			0.07		0.14
Age at 1st full-term pregnancy[b]					
< 20	105 (13.8)	60 (14.8)	1.27 (0.81, 1.99)	43 (15.4)	1.21 (0.70, 2.10)
20–24	292 (38.4)	157 (38.7)	1 [Ref]	109 (38.9)	1 [Ref]
25–29	207 (27.2)	100 (24.6)	0.99 (0.69, 1.41)	68 (24.3)	1.07 (0.69, 1.65)
30+	156 (20.5)	89 (21.9)	1.12 (0.76, 1.66)	60 (21.4)	1.23 (0.76, 1.98)
Continuous (1 year)			1.00 (0.97, 1.03)		1.01 (0.97, 1.04)
P_{trend}			0.99		0.76
Number of full-term pregnancies					
Nulliparous	218 (21.3)	118 (21.4)	1 [Ref]	79 (21.2)	1 [Ref]
Parous	807 (78.7)	433 (78.6)	0.99 (0.76, 1.29)	298 (79.1)	1.00 (0.73, 1.38)
1	155 (15.2)	91 (16.7)	1.16 (0.81, 1.66)	54 (14.5)	1.06 (0.68, 1.66)
2	359 (35.2)	171 (31.4)	0.85 (0.63, 1.15)	124 (33.2)	0.94 (0.65, 1.36)
≥ 3	289 (28.3)	165 (30.3)	1.04 (0.75, 1.43)	116 (31.1)	1.02 (0.69, 1.49)
Ever breastfed[b]					
No	161 (23.4)	84 (24.4)	1 [Ref]	58 (25.2)	1 [Ref]
Yes	526 (76.6)	260 (75.6)	0.74 (0.51, 1.05)	172 (74.8)	0.68 (0.44, 1.04)
Breast feeding duration (in months)[b,c]					
Never	161 (23.5)	84 (24.6)	1 [Ref]	58 (25.2)	1 [Ref]
< 6	197 (28.8)	92 (26.9)	0.72 (0.48, 1.07)	61 (26.5)	0.69 (0.42, 1.13)
6–12	115 (16.8)	66 (19.3)	0.82 (0.50, 1.34)	44 (19.1)	0.88 (0.49, 1.59)
> 12	211 (30.9)	100 (29.2)	0.62 (0.39, 0.98)	67 (29.1)	0.52 (0.30, 0.90)
Every 6 months			0.99 (0.93, 1.06)		0.98 (0.90, 1.06)
P_{trend}			0.79		0.60
Use of hormonal birth control in 2 years prior to 1st breast cancer diagnosis					
No	935 (92.0)	495 (92.2)	1 [Ref]	342 (93.2)	1 [Ref]
Yes	81 (8.0)	42 (7.8)	0.94 (0.62, 1.42)	25 (6.8)	0.96 (0.56, 1.66)
Age at menopause[d]					
< 45	72 (12.1)	56 (16.1)	1 [Ref]	39 (16.3)	1 [Ref]
45–49	164 (27.7)	85 (24.5)	0.67 (0.41, 1.09)	57 (23.9)	0.71 (0.39, 1.26)
50–54	284 (47.9)	168 (48.4)	0.82 (0.53, 1.27)	117 (49.0)	0.86 (0.52, 1.45)
≥ 55	73 (12.3)	38 (11.0)	0.74 (0.43, 1.29)	26 (10.9)	0.77 (0.39, 1.54)
Continuous (1-year)			0.98 (0.96, 1.01)		0.99 (0.96, 1.02)
P_{trend}			0.23		0.53
Current HRT use at 1st diagnosis[e]					
No	318 (49.1)	213 (57.0)	1 [Ref]	152 (58.9)	1 [Ref]
Yes	330 (50.9)	161 (43.1)	0.75 (0.55, 1.02)	106 (41.1)	0.66 (0.46, 0.95)
Estrogen only	168 (25.9)	90 (24.1)	0.81 (0.57, 1.15)	60 (23.3)	0.73 (0.48, 1.11)
Estrogen + progestin	162 (25.0)	71 (19.0)	0.69 (0.48, 1.00)	46 (17.8)	0.58 (0.37, 0.92)

[a]Using conditional logistic regression, models were implicitly adjusted for the following matching factors: age, year of initial in situ breast carcinoma diagnosis, county of residence at diagnosis, surgical and radiation treatment, histology and grade of initial in situ breast tumor

[b]Among parous women

[c]Adjusted for number of full-term pregnancies

[d]Among postmenopausal women

[e]Among women who were postmenopausal prior to 1st diagnosis

Table 3 Relationship between reproductive and menopausal factors and risk of second breast cancer by ER status of second breast cancer

	ER+ cases		ER− cases	
	n (%)	OR (95% CI)[a]	*n* (cases)	OR (95% CI)[a]
Age at menarche				
< 12	72 (23.2)	1 [Ref]	13 (21.0)	1 [Ref]
12–13	160 (51.6)	0.66 (0.45, 0.97)	38 (61.3)	0.82 (0.34, 1.99)
≥ 14	78 (25.2)	0.74 (0.47, 1.16)	11 (17.7)	0.52 (0.18, 1.52)
Continuous (1 year)		0.96 (0.88, 1.06)		0.87 (0.70, 1.10)
P_{trend}		0.46		0.24
Age at 1st full-term pregnancy[b]				
< 20	47 (16.9)	1.67 (0.97, 2.87)	7 (11.7)	0.54 (0.17, 1.72)
20–24	104 (37.4)	1 [Ref]	25 (41.7)	1 [Ref]
25–29	71 (25.5)	1.17 (0.76, 1.79)	14 (23.3)	0.78 (0.32, 1.88)
30+	56 (20.1)	0.96 (0.59, 1.57)	14 (23.3)	0.96 (0.38, 2.45)
Continuous (1-year)		1.00 (0.96, 1.03)		0.99 (0.93, 1.06)
P_{trend}		0.79		0.81
Number of full-term pregnancies				
Nulliparous	82 (21.9)	1 [Ref]	14 (17.7)	1 [Ref]
Parous	292 (78.1)	0.98 (0.72, 1.34)	65 (82.3)	1.09 (0.54, 2.19)
1	56 (15.1)	1.08 (0.70, 1.66)	14 (17.7)	1.29 (0.51, 3.25)
2	112 (30.3)	0.84 (0.59, 1.20)	27 (34.2)	0.93 (0.42, 2.05)
≥ 3	120 (32.4)	1.09 (0.75, 1.58)	24 (30.4)	1.18 (0.52, 2.71)
Ever breast fed[b]				
No	54 (23.0)	1 [Ref]	18 (35.3)	1 [Ref]
Yes	181 (77.0)	0.89 (0.58, 1.35)	33 (64.7)	0.35 (0.14, 0.87)
Never	54 (23.2)	1 [Ref]	18 (35.3)	1 [Ref]
Breast feeding duration (in months)[b,c]				
< 6	63 (27.0)	0.86 (0.53, 1.40)	11 (21.6)	0.28 (0.09, 0.92)
6–12	50 (21.5)	1.24 (0.67, 2.28)	6 (11.8)	0.28 (0.07, 1.08)
>12	66 (28.3)	0.63 (0.36, 1.09)	16 (31.4)	0.54 (0.16, 1.79)
Continuous (per 6 months)		0.97 (0.89, 1.06)		0.99 (0.87, 1.14)
P_{trend}		0.47		0.92
Use of hormonal birth control in 2 years prior to 1st breast cancer diagnosis				
No	339 (92.4)	1 [Ref]	72 (93.5)	1 [Ref]
Yes	28 (7.6)	1.00 (0.59, 1.67)	5 (6.5)	1.06 (0.34, 3.31)
Age at menopause[d]				
< 45	48 (19.2)	1 [Ref]	6 (10.3)	1 [Ref]
45–49	62 (24.8)	0.55 (0.31, 0.99)	12 (20.7)	0.87 (0.21, 3.56)
50–54	104 (41.6)	0.58 (0.35, 0.98)	29 (50.0)	2.19 (0.61, 7.90)
≥ 55	36 (14.4)	0.61 (0.31, 1.18)	11 (19.0)	1.69 (0.37, 7.80)
Continuous (1-year)		0.97 (0.94, 1.00)		1.04 (0.96, 1.13)
P_{trend}		0.06		0.36
Current HRT use at 1st diagnosis[e]				
No	142 (55.7)	1 [Ref]	35 (60.3)	1 [Ref]
Yes	113 (44.3)	0.68 (0.47, 0.99)	23 (39.7)	0.75 (0.37, 1.55)
Current estrogen	65 (25.5)	0.72 (0.47, 1.11)	14 (24.1)	1.02 (0.45, 2.30)
Estrogen + progestin	48 (18.8)	0.63 (0.40, 1.00)	9 (15.6)	0.47 (0.17, 1.25)

[a]Using conditional logistic regression, models were implicitly adjusted for the following matching factors: age, year of initial in situ breast carcinoma diagnosis, county of residence at diagnosis, surgical and radiation treatment, histology and grade of initial in situ breast tumor

[b]Among parous women

[c]Adjusted for number of full-term pregnancies

Table 3 (continued)

[d]Among postmenopausal women

[e]Among women who were postmenopausal prior to 1st diagnosis

Our results showed that women who were currently taking menopausal hormone therapy at their 1st in situ breast cancer diagnosis were less likely to develop second breast cancers. Previous studies have shown menopausal hormone therapy use, particularly combination estrogen and progestin therapy, increases the risk of breast cancer [8]. Our finding is likely due to hormone therapy being a key driver of the risk of the first in situ cancer, but with stoppage of use after this diagnosis resulting in a lower risk of a second cancer due to removal of the main etiologic driver. However, due to the small number of women in our study who used menopausal hormone therapy after their first diagnosis, we were unable to stratify our results to determine whether the observed association was present in both groups.

Strengths of our study include its population-based study design, comprehensive data collection, and number of second primary breast cancers in our study. To our knowledge, this is the largest study designed to evaluate risk factors for second breast cancer events among women with a personal history of in situ breast carcinoma. Potential recall bias is a limitation of the case–control study design used for this study, which may have been greater for women with first diagnoses earlier in the study period. Additionally, selection bias may have been introduced into our study through modest response rates. We did not collect data on screening frequency of participants in our study following their first diagnosis and are unable to determine whether screening rates were different among cases and controls.

Our results suggest that some reproductive factors, age at menarche and breastfeeding, may be risk factors for second primary breast cancer after diagnosis of in situ breast carcinoma. Further studies are needed to elucidate the association between traditional risk factors for primary breast cancer and risk of second primary breast cancer among women with a previous in situ breast cancer. These results are important for this growing population.

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