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Family History and Risk of Second Primary Breast Cancer after *In Situ* Breast Carcinoma

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Abstract

Background—Incidence rates of *in situ* breast carcinomas have increased due to widespread adoption of mammography. Very little is known about why some women with *in situ* breast cancer later develop second primary breast cancers.

Methods—In this population-based nested case-control study among in situ breast cancer survivors, including 539 cases with a second primary breast cancer and 994 matched controls, we evaluated the association between first degree family history of breast cancer and risk of developing a second primary breast cancer.

Results—First degree family history of breast cancer was associated with an increased risk of developing a second primary breast cancer among women with a previous *in situ* breast cancer (odds ratio (OR)=1.33, 95% confidence interval (CI):1.05, 1.69) and those with two or more affected first degree relatives had an even higher risk (OR=1.94, 95% CI:1.15, 3.28). Those whose relative was diagnosed at less than 50 years old were more likely to develop a second primary breast cancer (OR=1.78, 95% CI:1.24, 2.57). No difference in risks associated with number or age of affected relatives were observed by menopausal status.

Conclusions—Results from this study suggest that first degree family history of breast cancer may be an important risk factor for development of a second primary breast cancer among women with a previous *in situ* breast cancer.

Impact—Given the growing population of *in situ* breast cancer survivors, a better understanding of risk factors associated with development of a second primary breast cancer is needed to further understand risk.

Introduction

Incidence rates of *in situ* breast carcinomas have increased dramatically since the widespread adoption of mammography for breast cancer (1-4). More than 63,000 women are diagnosed with *in situ* breast cancer every year in the United States, which accounts for approximately 20% of all incident breast cancer diagnoses (4). Compared to the risk women in the general population have of developing a first primary breast cancer, women with a

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history of *in situ* breast cancer are at a substantially higher risk of developing a second primary breast cancer. The risk of a second primary *in situ* tumor is 4.2 to 7.2-fold higher and the risk of a second primary invasive breast cancer is 3.4 to 8.6-fold higher in *in situ* breast cancer survivors compared with women in the general population (5-7). Risk of a second primary breast cancer among *in situ* breast cancer survivors varies with patient and clinical characteristics, although current epidemiological evidence is limited.

Family history of breast cancer has previously been shown to be associated with risk of *in situ* and invasive breast cancer (8-10). Compared to women without a family history of breast cancer, women with one first degree affected relative have almost twice the risk of developing breast cancer and women with more than one first degree affected relative have 3-4 times higher risk (8, 10, 11). Younger age at diagnosis of the first degree relative has also been shown to be associated with higher risk of breast cancer (11). Little is known about the relationship between family history of breast cancer and risk of second primary breast cancer among *in situ* breast cancer survivors. One previous study found that, among women with a history of *in situ* breast carcinoma, those with a family history of breast cancer were at a 50% increased risk of developing a second contralateral breast cancer (12). A previous study among women with invasive breast cancer found a non-significant increased risk of second invasive contralateral breast cancer among women with a strong family history; a significant association was observed among women with an estrogen receptor (ER)-negative second tumor (13). More studies are needed to further understand the role of family history on risk of developing a second primary breast cancer among women with *in situ* breast cancer.

Given the growing numbers of newly diagnosed *in situ* breast cancer, research aimed at identifying factors associated with second breast cancer events is needed in order to develop and/or improve risk prediction and preventive strategies. Using data from a nested case-control study of women with *in situ* breast cancer, we evaluated the association between first degree family history of breast cancer and risk of developing a second *in situ* or invasive breast cancer.

Materials and Methods

We conducted a population-based nested case-control study designed to evaluate factors associated with risk of second primary breast cancer among women with a previously diagnosed *in situ* breast carcinoma. The underlying cohort consisted of women identified through the Cancer Surveillance System (CSS), the SEER population-based registry which serves western Washington State, who were diagnosed with *in situ* breast carcinoma between January 1, 1995 and June 30, 2013 between the ages of 30 and 79 residing in the 13-county area covered by the CSS. Women from the cohort of *in situ* breast carcinoma patients were classified as cases if they developed an ipsilateral or contralateral second primary breast cancer, either invasive or *in situ*, at least 6 months following an initial diagnosis. Patients who underwent bilateral mastectomy for their initial *in situ* breast carcinoma were excluded. Those who did not have a second breast cancer event during the study period were eligible as controls and were individually matched 2:1 to cases on 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 carcinoma lesion. The case group consisted of 573 incident cases of second primary breast cancer and the control group consisted of 1,096 women with a history of *in situ* breast carcinoma who did not develop a second primary breast cancer. Among 826 identified eligible cases, 573 (69.4%) were enrolled. Among 1,951 eligible controls, 1,096 (56.2%) were enrolled. Reasons for non-participation included women who were unable to communicate, not interested, could not be located (particularly for those diagnosed in earlier years of the study), or did not consider themselves to be diagnosed with breast cancer since they had an in situ tumor. Both ipsilateral and contralateral second breast cancers were included in this study. All contralateral second breast cancers were considered second primary breast cancers. For ipsilateral cases, medical records based on evidence of the classification by the patients' physician were used to determine whether the 2nd tumor was a recurrence or second primary breast cancer event. Written, informed consent was obtained from study participants and the study was approved by the Institutional Review Board (IRB) at the Fred Hutchinson Cancer Research Center.

Data Collection

Data on demographic, epidemiologic, and clinical factors were collected by trained interviewers via telephone and/or medical record abstraction. Information on epidemiologic risk factors, tumor characteristics, and treatment history was abstracted from medical records. Medical records were sought from all treating physicians and facilities in order to obtain complete medical information. Data was collected across multiple time points including date of first *in situ* diagnosis and reference date, which was the date of second primary breast cancer diagnosis for cases and assigned reference date for controls. The reference date for controls was based on the interval between the first *in situ* tumor and the second primary breast cancer event of the matched case. Information on family history of breast cancer was obtained through interview and medical records. Informed consent was required from all participants. After completing the study interview, women were asked to provide consent for medical record access. For deceased enrolled participants, consent was waived for medical record abstraction only. Of participants enrolled in the study, 69% had both interview and medical record data available, while 12% had only interview data and 19% had only medical record available.

Statistical Analysis

Using conditional logistic regression, odds ratios (ORs) and their associated 95% confidence intervals (CIs) were calculated to evaluate the associations between first degree family history of breast cancer and risk of second primary breast cancer. Models were implicitly adjusted for matching factors. Other potential confounders listed in Table 1 were considered, but inclusion of these variables did not alter the observed risk estimates by at least 10% and therefore were not included in the final models presented. Potential effect modification by menopausal status, *in situ* breast carcinoma grade, *in situ* breast carcinoma treatment, *in situ* breast carcinoma histology/presence of comedo necrosis, and ER status and laterality of second breast cancer were considered and likelihood ratio tests were used to test these interactions. Continuous variables were used to calculate p-values for trend tests.

For analysis, variables were created using interview data as the primary source and medical review data as supplemental when interview data was missing. After combining both sources, 83 were missing data for family history of breast cancer and were excluded from all analyses. This left 43 controls with no matched case and 10 cases with no matched controls who were subsequently dropped from analyses. This resulted in 539 cases and 994 controls available for analysis. Analyses were conducted using SAS v9.3 (SAS Institute, Cary, NC).

Results

Cases and controls were similar with respect to age and year of first breast cancer diagnosis, grade and treatment of first breast cancer, menopausal status at 1st diagnosis and reference date, and smoking status (Table 1). Cases were more likely to be overweight or obese at the first breast cancer diagnosis and reference date compared to controls. Of the 539 cases, 68% (n=368) were invasive second primary breast cancers while the remaining cases were *in situ* tumors. More than half of the cases were diagnosed with contralateral breast cancer (n=296), 239 were diagnosed with ipsilateral breast cancer, and 4 cases were diagnosed with bilateral breast cancer.

In situ breast cancer survivors with a first degree family history of breast cancer were more likely to develop a second primary breast cancer (OR=1.33, 95% CI: 1.05, 1.69) (Table 2). Survivors with two or more affected first degree family members had a greater increased risk (OR=1.94, 95% CI: 1.15, 3.28). Further, *in situ* survivors whose affected relative was less than 50 years old were more likely to develop a second primary breast cancer (OR=1.78, 95% CI: 1.24, 2.57). Estimates were similar among all cases and among invasive cases only. The observed results were attenuated somewhat when analyses were limited to those women whose first *in situ* cancer diagnosis was DCIS. DCIS survivors with a first degree family history of breast cancer were more likely to develop a second primary breast cancer, although it did not reach statistical significance (OR=1.26, 95% CI: 0.97, 1.63). DCIS survivors with two or more affected first degree family members had a greater increased risk (OR=1.78, 95% CI: 1.02, 3.10) and those with affected relative was less than 50 years old were more likely to develop a second primary breast cancer (OR=1.56, 95% CI: 1.05, 2.33).

When stratified by menopausal status, an increased risk of developing a second primary breast cancer was observed among postmenopausal women (OR=1.56, 95% CI: 1.13, 2.16) but not pre-/peri-menopausal women (OR=1.15, 95% CI: 0.77, 1.71); however, the interaction was not significant (all cases P=0.31) (Table 3). An increased risk of developing a second primary breast cancer was observed for survivors with two or more affected relatives among both pre-/peri-menopausal (OR=2.30, 95% CI: 0.97, 5.48) and postmenopausal women (OR=1.75 (0.88, 3.49), though neither reached statistical significance. A significant increased risk of second primary breast cancer was observed for survivors with an affected relative aged less than 50 at diagnosis among both pre-/peri-menopausal women (OR=2.02, 95% CI: 1.14, 3.59) and postmenopausal women (OR=1.80, 95% CI: 1.03, 3.13).

When stratified by ER status of the second primary breast cancer, associations between first degree family history of breast cancer and risk of developing a second primary breast cancer

were only observed among those cases with ER+ tumors (Table 4). A first degree family history of breast cancer was associated with an increased risk of an ER+ second primary breast cancer (OR=1.49, 95% CI: 1.07, 2.07), whereas no association was observed for ER- second primaries (OR=1.00, 95% CI: 0.49, 2.03). Having 2 or more affected first degree relatives was associated with a two-fold increased risk of ER+ invasive second primary breast cancer (OR=2.04, 95% CI: 1.03, 4.04) but not with ER- invasive breast cancer (OR=0.79, 95% CI: 0.07, 8.97). Similarly, a stronger association among those with an affected first degree relative diagnosed before age 50 was observed among ER+ invasive cases (OR=2.03, 95% CI: 1.24, 3.31) but not ER- invasive cases (OR=0.67, 95% CI: 0.24, 1.86). However, a test of heterogeneity was not significant ($P_{heterogeneity}$=0.16). Stratification by grade of the first *in situ* tumor showed a stronger association between first degree family history of breast cancer and risk of second primary breast cancer with higher grade tumors than lower grade tumors (Grade 1/2 (well differentiated/moderately differentiated): OR=0.82, 0.43, 1.55; Grade 3/4 (poorly differentiated/no differentiation): OR=1.40, 95% CI: 0.95, 2.06), though neither reached statistical significance. No differences in risk were observed when the results were stratified by treatment for *in situ* breast cancer, laterality of the second breast cancer or *in situ* breast carcinoma histology/presence of comedo necrosis.

Discussion

In this population-based case-control study among *in situ* breast cancer survivors, our results suggest that a first degree family history of breast cancer was associated with an increased risk of developing a second primary breast cancer. Further, those with two or more affected first degree relatives and those with relatives diagnosed with breast cancer before age 50 were at an even greater risk of developing a second primary breast cancer.

Previous meta-analyses have shown that family history of breast cancer is associated with a 2-fold increased relative risk of developing an initial breast cancer (8, 10). Only one previous study was identified which assessed the association between family history of breast cancer and risk of developing a second primary breast cancer after *in situ* breast carcinoma (12). Similar to our study, this study found an increased risk of second primary breast among *in situ* breast cancer survivors with a family history of breast cancer. However, this increased risk was limited to contralateral breast cancer and no association was observed among women with subsequent ipsilateral breast cancer. In our study, we found no difference in the observed association by laterality of the second breast cancer. Our results also showed that risk of developing a second breast cancer after an *in situ* tumor increased with the number of affected relatives and with the presence of relatives affected at a younger age (<50). These factors may give additional information in determining risk for *in situ* breast cancer survivors.

The association between family history of breast cancer and risk of developing a second primary breast cancer among *in situ* breast cancer survivors was stronger among postmenopausal women than pre-/peri-menopausal women. However, further analysis showed that an increased risk was observed among all women with two or more affected relatives or an affected relative aged less than 50 years at diagnosis, regardless of menopausal status. These findings suggest that a simple assessment of the presence or

absence of any first-degree family history of breast cancer (yes/no) may be insufficient for assessing family history-based risk of a second breast cancer among pre-/peri-menopausal women. More studies are needed to support this finding.

The observed increased risk of breast cancer with positive family history was observed among women whose second primary breast cancer was ER+ but not among those with an ER- second primary breast cancer. Family history of breast cancer has been shown to be associated with both ER+ and ER- first primary breast cancers (14). A previous study of breast cancer survivors showed that those with a family history of breast cancer had a higher risk of developing a second ER- breast cancer and the association was stronger among those whose first primary breast cancer was also ER-, whereas this association was not observed among those with ER+ tumors (13). The authors suggested that use of anti-estrogen therapies among ER+ women may explain their findings. Our study primarily included cases with ER+ second breast cancers and we may have had limited power to detect an association among those with ER- second breast cancers. We also only observed an increased risk of second breast cancers among women whose first *in situ* tumor was of higher grade (3 or 4) and not among those with lower grade first *in situ* tumors (grade 1 or 2). Tumor grade has been shown to be associated with genetic predisposition to developing both *in situ* and invasive breast cancer (15). Women with a family history of breast cancer may be more likely to develop higher grade tumors than those without a positive family history and therefore may be more likely to develop a second breast cancer.

Current treatment for *in situ* breast carcinoma typically consists of lumpectomy and radiation therapy or mastectomy. Survival rates for *in situ* breast carcinoma are extremely high, with one study estimating that 96-98% of *in situ* breast carcinoma patients are alive 10 years after diagnosis (16). It has been suggested that some *in situ* breast carcinoma patients may be unlikely to have their carcinoma progress to invasive cancer or have a recurrence and that these women may be over-treated by current standard care (17). Currently there is no way to distinguish among *in situ* breast carcinoma patients with respect to future breast cancer diagnoses. More studies are needed to identify risk factors for second breast cancers among *in situ* breast carcinoma patients in order to better inform clinical decision making and surveillance.

Our study is the largest comprehensive, population-based study of *in situ* breast carcinoma survivors designed to examine risk factors for development of second breast cancers. Major strengths of our study were the large number of second primary breast cancers in our population, the comprehensive collection of data on epidemiological and clinical factors, and centralized histopathological reviews. Patient recall of information related to the first breast cancer diagnosis is a limitation, particularly among older women or women whose first diagnosis was longer ago. Modest response rates may have introduced selection bias into our study and influenced our findings. By including women who were alive as well as deceased, we achieved greater generalizability of our study. Another limitation of our study is that some women may have been unable to report whether their family members had in situ or invasive breast cancer. Future studies which are able to differentiate between family history of in situ or invasive breast cancer are needed to further explore these relationships.

In summary, our results suggest that first degree family history of breast cancer may be an important risk factor for development of a second primary breast cancer among *in situ* breast cancer survivors. Further research is needed to confirm these associations and increase our understanding of the role of family history and risk of second primary breast cancer. Given the growing population of *in situ* breast cancer survivors, a better understanding of risk factors associated with development of a second primary breast cancer is needed to further understand risk for this group of women.

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Abbreviations

OR	odds ratio
CI	confidence interval
ER	estrogen receptor
DCIS	ductal carcinoma in situ

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Table 1

Demographic and Clinical Factors by Case-Control Status Among Women with Carcinoma In Situ of the Breast

	Study Participants (N(%))	
	First Degree Family History of Breast Cancer	
Characteristics	**No (n=1094)**	**Yes (n=439)**
Age at 1st breast cancer diagnosis		
<50	367 (33.6)	164 (37.4)
50–59	386 (35.3)	144 (32.8)
60–69	225 (20.6)	92 (21.0)
70–79	116 (10.6)	39 (8.9)
Year of 1st breast cancer diagnosis		
1995–1997	231 (21.1)	103 (23.5)
1998–2000	247 (22.6)	112 (25.5)
2001–2004	311 (28.4)	105 (23.9)
2005–2013	305 (27.9)	119 (27.1)
Race/Ethnicity		
Non-Hispanic white	976 (89.2)	403 (91.8)
Hispanic white	22 (2.0)	10 (2.3)
Black	22 (2.0)	5 (1.1)
Asian/Pacific Islander	57 (5.2)	16 (3.6)
Native American	16 (1.5)	5 (1.1)
Unknown	1	0
Body mass index at 1st breast cancer diagnosis		
<25	499 (47.3)	197 (46.9)
25-<30	309 (29.3)	128 (30.5)
≥30	247 (23.4)	95 (22.6)
Unknown	39	19
Body mass index at reference		
<25	445 (43.8)	174 (42.2)
25-<30	308 (30.3)	144 (35.0)
≥30	263 (25.9)	94 (22.8)
Unknown	78	27
Smoking status at 1st breast cancer diagnosis		
Never smoker	594 (56.0)	243 (57.2)
Former smoker	355 (33.5)	137 (32.2)
Current smoker	111 (10.5)	45 (10.6)
Unknown	34	14
Grade of 1st tumor		
1 – well differentiated	30 (3.8)	10 (3.3)
2 – moderately differentiated	227 (28.6)	92 (30.0)
3 – poorly differentiated	252 (31.7)	88 (28.7)

	Study Participants (N(%))	
	First Degree Family History of Breast Cancer	
Characteristics	**No (n=1094)**	**Yes (n=439)**
4 – undifferentiated	285 (35.9)	117 (38.1)
Unknown	300	132
Radiation treatment for 1st breast cancer		
Yes	529 (48.4)	192 (43.7)
No	565 (51.7)	247 (56.3)
Surgery for 1st breast cancer		
Biopsy only	36 (3.3)	20 (4.6)
Lumpectomy without nodal dissection	751 (68.7)	303 (69.0)
Lumpectomy with sentinal node biopsy	55 (5.0)	20 (4.6)
Lumpectomy with nodal dissection	45 (4.1)	9 (2.1)
Mastectomy	207 (18.9)	87 (19.8)
Laterality of 2nd breast cancer		
Ipsilateral	154 (42.2)	85 (48.9)
Contralateral	210 (57.5)	86 (49.4)
Bilateral	1 (0.3)	3 (1.7)
Menopausal status at 1st breast cancer diagnosis		
Pre/Peri-menopausal	417 (39.2)	183 (43.5)
Postmenopausal	646 (60.8)	238 (56.5)
Unknown	31	18
Menopausal status at reference		
Pre/Peri-menopausal	191 (18.2)	91 (21.9)
Postmenopausal	856 (81.8)	324 (78.1)
Unknown	47	24

Table 2

Relationship between Family History of Breast Cancer and Risk of Second Breast Cancer Among Women with Carcinoma In Situ of the Breast

	Controls	All Cases		Invasive Cases	
	n(%)	n(%)	OR (95% CI)[1]	n(%)	OR (95% CI)[1]
DCIS and LCIS (n=1,533)					
1st Degree Family History of Breast Cancer					
No	729 (73.3)	365 (67.7)	1 [Ref]	247 (67.1)	1 [Ref]
Yes	265 (26.7)	174 (32.3)	1.33 (1.05, 1.69)	121 (32.9)	1.37 (1.02, 1.84)
# of First Degree Relatives with Breast Cancer					
0	729 (73.6)	365 (67.8)	1 [Ref]	247 (67.1)	1 [Ref]
1	224 (22.6)	141 (26.2)	1.25 (0.96, 1.62)	100 (27.2)	1.33 (0.97, 1.82)
2+	37 (3.7)	32 (6.0)	1.94 (1.15, 3.28)	21 (5.7)	1.87 (0.97, 3.60)
Age at Diagnosis of 1st Degree Family Member					
No history	729 (74.5)	365 (69.0)	1 [Ref]	247 (68.4)	1 [Ref]
≥50	176 (18.0)	98 (18.5)	1.11 (0.83, 1.49)	66 (18.3)	1.20 (0.84, 1.73)
<50	73 (7.5)	66 (12.5)	1.78 (1.24, 2.57)	48 (13.3)	1.68 (1.09, 2.58)
DCIS Only (n=1,333)					
1st Degree Family History of Breast Cancer					
No	638 (73.3)	318 (68.8)	1 [Ref]	213 (68.1)	1 [Ref]
Yes	233 (26.8)	144 (31.2)	1.26 (0.97, 1.63)	100 (32.0)	1.30 (0.94, 1.79)
# of First Degree Relatives with Breast Cancer					
0	638 (73.5)	318 (69.0)	1 [Ref]	213 (68.1)	1 [Ref]
1	195 (22.5)	115 (25.0)	1.18 (0.89, 1.56)	81 (25.9)	1.25 (0.88, 1.77)
2+	35 (4.0)	28 (6.1)	1.78 (1.02, 3.10)	19 (6.1)	1.73 (0.87, 3.43)
Age at Diagnosis of 1st Degree Family Member					
No history	638 (74.5)	318 (70.2)	1 [Ref]	213 (69.4)	1 [Ref]
≥50	152 (17.7)	82 (18.1)	1.10 (0.80, 1.50)	56 (18.2)	1.23 (0.83, 1.81)
<50	67 (7.8)	53 (11.7)	1.56 (1.05, 2.33)	38 (12.4)	1.42 (0.89, 2.28)

Notes: 5 participants missing information on # of first degree relatives and 26 missing information on age of family member

[1] Models were implicitly adjusted for matching factors, no further adjustment

Table 3

Relationship between Family History and Risk of Second Breast Cancer Stratified by Menopausal Status Among Women with Carcinoma In Situ of the Breast

	Pre-/Peri-menopausal			Postmenopausal		
	Controls	All Cases		Controls	All Cases	
	n(%)	n(%)	OR (95% CI)[a]	n(%)	n(%)	OR (95% CI)[a]
First Degree Family History of Breast Cancer						
No	270 (70.5)	147 (67.7)	1 [Ref]	438 (75.8)	208 (68.0)	1 [Ref]
Yes	113 (29.5)	70 (32.3)	1.15 (0.77, 1.71)	140 (24.2)	98 (32.0)	1.56 (1.13, 2.16)
# of First Degree Relatives with Breast Cancer						
0	270 (70.9)	147 (67.7)	1 [Ref]	438 (76.0)	208 (68.2)	1 [Ref]
1	99 (26.0)	57 (26.3)	1.02 (0.66, 1.60)	115 (20.0)	80 (26.2)	1.52 (1.07, 2.17)
2+	12 (3.2)	13 (6.0)	2.30 (0.97, 5.48)	23 (4.0)	17 (5.6)	1.75 (0.88, 3.49)
Age at Diagnosis of First Degree Family Member						
No history	270 (71.2)	147 (67.7)	1 [Ref]	438 (77.3)	208 (70.3)	1 [Ref]
≥50	76 (20.1)	37 (17.1)	0.82 (0.49, 1.39)	91 (16.1)	57 (19.3)	1.39 (0.93, 2.06)
<50	33 (8.7)	33 (15.2)	2.02 (1.14, 3.59)	38 (6.7)	31 (10.5)	1.80 (1.03, 3.13)

[a]Models were implicitly adjusted for matching factors, no further adjustment

Table 4

Relationship between Family History and Risk of Second Breast Cancer Stratified by Estrogen Receptor Status of the Second Breast Cancer Among Women with Carcinoma In Situ of the Breast

	ER+		ER-	
	Invasive Cases		Invasive Cases	
	n(%)	OR (95% CI)[a]	n(%)	OR (95% CI)[a]
First Degree Family History of Breast Cancer				
No	192 (66.0)	1 [Ref]	46 (73.0)	1 [Ref]
Yes	99 (34.0)	1.49 (1.07, 2.07)	17 (27.0)	1.00 (0.49, 2.03)
# of First Degree Relatives with Breast Cancer				
0	192 (66.0)	1 [Ref]	46 (73.0)	1 [Ref]
1	79 (27.2)	1.42 (0.99, 2.04)	16 (25.4)	1.04 (0.51, 2.16)
2+	20 (6.9)	2.04 (1.03, 4.04)	1 (1.6)	0.79 (0.07, 8.97)
Age at Diagnosis of First Degree Relative				
No history	192 (67.4)	1 [Ref]	46 (74.2)	1 [Ref]
≥50	54 (19.0)	1.22 (0.82, 1.83)	10 (16.1)	1.45 (0.59, 3.54)
<50	39 (13.7)	2.03 (1.24, 3.31)	6 (9.7)	0.67 (0.24, 1.86)

Abbreviations: estrogen receptor, ER

Note: 14 cases with second primary invasive breast cancer missing ER status for second tumor

[a]Models were implicitly adjusted for matching factors, no further adjustment