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Family history of cancer in relation to breast cancer subtypes in African American women

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Abstract

Background—Evidence on the relation of family history of cancers other than breast cancer to breast cancer risk is conflicting and most studies have not assessed specific breast cancer subtypes.

Methods—We assessed the relation of first degree family history of breast, prostate, lung, colorectal, ovarian, cervical cancer, and lymphoma or leukemia, to risk of estrogen receptor positive (ER+), ER–, and triple negative breast cancer in data from the African American Breast Cancer Epidemiology and Risk Consortium. Multivariable logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results—There were 3,023 ER+ and 1,497 ER– breast cancer cases (including 696 triple negative cases) and 17,420 controls. First degree family history of breast cancer was associated with increased risk of each subtype: OR=1.76 (95% CI 1.57–1.97) for ER+, 1.67 (1.42–1.95) for ER–, and 1.72 (1.38–2.13) for triple negative breast cancer. Family history of cervical cancer was associated with increased risk of ER– (OR=2.39, 95% CI 1.36–4.20), but not ER+ cancer. Family history of both breast and prostate cancer was associated with increased risk of ER+ (3.40, 2.42–4.79) and ER– (2.09, 1.21–3.63) cancer, but family history of both breast and lung cancer was associated only with ER– cancer (2.11, 1.29–3.46).

Conclusions—A family history of cancers other than breast may influence risk of breast cancer and associations may differ by subtype.

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Impact—Greater surveillance and counseling for additional screening may be warranted for women with a family history of cancer.

Keywords

breast cancer; family history; African American women; estrogen receptor

Introduction

Having a mother, sister, or daughter with a breast cancer diagnosis is a well-known risk factor for breast cancer.(1) Among African American women, estimates of the relative risk for first degree family history of breast cancer range from 1.65 to 1.78,(2, 3) similar to findings from studies of European American and Asian women.(1, 4, 5) Among studies that reported results separately for estrogen receptor (ER) positive and ER– breast cancer, most reported similar associations by subtype,(3, 6–11) while one reported a stronger association with ER+ cancer(12) and two reported a stronger relation for ER– breast cancer.(13, 14) Only the Black Women’s Health Study reported on family history separately for ER+ and ER– breast cancer in African American women, with similar increases by subtype, but findings were based on small numbers.(3)

A first degree family history of cancers other than breast cancer may also increase breast cancer risk. Family history of prostate,(15, 16) lung,(17) ovarian,(18) and colon or colorectal cancer(3, 16) have been associated with greater risk of breast cancer in some, but not all studies that examined specific other cancers. In studies that examined combinations of cancers, risk of breast cancer was elevated for family history of breast and prostate cancers,(15) breast and ovarian cancers,(19, 20) and breast and colorectal cancers.(16, 21, 22) Among African American women, family histories of lung cancer,(23) colon cancer,(3) or both breast and prostate cancer(16) were associated with increased risk of breast cancer.

The objective of the present study was to investigate the relation of first degree family history of breast and other cancers to risk of ER+, ER–, and triple negative breast cancer in African American women.

Materials and methods

The African American Breast Cancer Epidemiology and Risk (AMBER) Consortium has been described in detail elsewhere.(24) The AMBER Consortium pools data on African American women from two cohort studies, the Black Women’s Health Study and the Multiethnic Cohort Study, and two case-control studies, the Carolina Breast Cancer Study and the Women’s Circle of Health Study. Informed consent was provided to each study by its participants. Each study and the consortium were approved by the relevant Institutional Review Boards.

The Black Women’s Health Study (BWHS) is a prospective cohort study that enrolled 59,000 African American women across the United States in 1995.(25) Participants were 21–69 years old at baseline when they completed an extensive health questionnaire and are followed with biennial questionnaires for data on incident diagnoses and other factors.

Incident breast cancers are identified through self-report on questionnaires or through linkage to state cancer registries. For the AMBER Consortium, a nested case-control study was created; cohort participants without breast cancer were frequency-matched to cases based on age (5-year categories), geographic region, and most recent completed questionnaire.

The Multiethnic Cohort Study (MEC) is a prospective cohort study that enrolled men and women in Los Angeles county and Hawaii from 1993 through 1996.(26) Participants were 45–75 years at baseline when they completed an extensive questionnaire and have been followed with questionnaires in 1999, 2003, and 2010 to update information. Breast cancer diagnoses are identified through linkage with the Los Angeles County Cancer Surveillance Program and the California Cancer Registry. A nested case-control study of African American women was created to pool MEC data with the AMBER Consortium. Controls, selected from women who had not developed breast cancer, were frequency-matched to cases on age (5-year categories) and most recent completed questionnaire,

The Carolina Breast Cancer Study (CBCS) is a case-control study that enrolled women in North Carolina from 1993 through 2001.(27) Participants were 20–74 years old and were interviewed in-person. Cases were identified through the North Carolina Central Cancer Registry, while controls were identified through Division of Motor Vehicle lists or Health Care Financing Administration lists. Controls were frequency-matched to cases based on age (5-year categories).

The Women's Circle of Health Study is a case-control study that enrolled women in New York from 2003 through 2008 and in New Jersey beginning in 2006.(28) Recruitment in New Jersey is ongoing. Participants were 20–75 years old and were interviewed in-person for data collection. Cases were identified through New York City hospitals and the New Jersey State Cancer Registry, while controls were identified through random digit dialing and community-based recruitment.(29) Controls were frequency-matched to cases based on age (5-year categories).

Each study confirmed incident breast cancer cases with data on ER, progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2) obtained from medical records and/or state cancer registries.(24) Cases were classified as ER+, ER–, and triple negative (TN; ER–/PR–/HER2–). Of the 5,736 potential cases, ER status was available for 4,520 cases (79%) at the time of this analysis. PR status was available for 4,301 cases (75%); HER2 status was available for fewer cases (2,927, 51%), due to more recent inclusion of HER2 in routine testing. There were no statistically significant differences between women with and without known receptor status by age or family history of breast cancer. In total, there were 3,023 ER+ cases, 1,497 ER– cases (including 696 triple negative cases), and 17,420 controls.

Participants were asked whether any parent, sibling, or child (first degree relative) had been diagnosed with breast cancer and whether the relative was diagnosed before age 50. Participants were also asked about first degree family history of ovarian, colorectal, prostate, lung, and cervical cancer, and lymphoma or leukemia.

Each study obtained detailed data on most known and suspected risk factors for breast cancer. Variables were centrally harmonized and evaluated as risk factors for breast cancer overall and for ER+, ER–, and TN breast cancer.(24, 30–33)

Statistical analysis

Multinomial logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the relation of family history of cancer to risk of ER+, ER–, and TN breast cancer. Multivariable models adjusted for the design variables – age (5-year categories), study (BWHS, CBCS, MEC, WCHS), geographic region (Northeast excluding New Jersey, New Jersey, South, Midwest, West), and questionnaire time period (1993–1998, 1999–2005, 2006–2014) – and recency of mammogram (never had a mammogram, mammogram within past 2 years, last mammogram more than 2 years ago). Additional variables were also assessed as potential covariates, but were not associated with family history of cancer and did not appreciably change the effect estimates: years of education (<12, 12, 13–15, 16, >16 years), menopausal status and age at menopause (premenopausal, <45, 45–49, 50–54, 55 years), years of use of postmenopausal estrogen together with progesterone (never used, <5, 5 years), age at menarche (<11, 11–12, 13–14, 15–16, 17 years), body mass index (<18.5, 18.5–24.9, 25–29.9, 30–34.9, 35–39.9, 40 kg/m²), years of oral contraceptive use (never used/<1, 1–9, 10 years), parity (nulliparous, 1, 2, 3, 4 births), age at first birth (<25, 25 years), lactation (parous and never breastfed, parous and ever breastfed), pack-years of cigarette smoking (never smoked, <20, 20 pack-years), and alcohol consumption (never drinker, former drinker, current drinker of <7 drinks/week, current drinker of 7 drinks/week). The missing indicator method was used to handle missing values for covariates. To test for interaction between family history of cancer at different cancer sites, interactions were examined by introducing cross-product terms into the models.(34) Analyses were conducted using SAS 9.3 statistical package (SAS Institute Inc., Cary, NC). Random effects meta-analyses of study-specific results were conducted using Stata/SE 11.2 statistical software (StataCorp LP, College Station, TX), with results tested for heterogeneity by the Cochran's Q statistic.(35)

Results

The prevalences of first degree family history of breast cancer and of cancers other than breast cancer were largely similar across studies (Table 1); the differences were statistically significant due to the large sample size. Among controls, 9.3% had a first degree relative with breast cancer and 22.7% had a first degree relative with a cancer other than breast cancer. Few controls had first-degree family history of both breast cancer and another cancer site (2.9%). Lung cancer was the most common other cancer among first degree relatives (7.7%), followed by prostate (7.6%) and colorectal cancer (6.2%).

The ORs for a first degree family history of breast cancer were similar by subtype: ER+ cancer (1.76, 95% CI 1.57–1.97), ER– cancer (1.67, 95% CI 1.42–1.95), and TN cancer (1.72, 95% CI 1.38–2.13) (Table 2). For each subtype, the ORs were higher if the relative was diagnosed before age 50. For example, for ER– cancer, the OR was 1.96 (95% 1.56–2.46) for having a relative diagnosed with breast cancer before age 50 and 1.46 (95% 1.15–

1.86) for a relative diagnosed at 50 or older. The ORs were also somewhat higher if the participant herself was diagnosed with breast cancer before age 45: the ORs for the association of having a first degree relative diagnosed with breast cancer before age 50 with risk of breast cancer before age 45 were all greater than 3.00 for ER+, ER- and TN breast cancer.

In assessing the relation of family history of other cancers to breast cancer risk, we looked first at risk of overall breast cancer. A first degree family history of breast cancer alone (with no other cancers among first degree relatives) was associated with a 1.58-fold risk (95% CI 1.38–1.82) (Table 3). The ORs for family history of each of the other cancers alone were close to 1.0, with the exception of cervical cancer, for which the OR for the association with overall breast cancer risk was 1.53 (0.94–2.47). Risk of breast cancer was tripled in women who had a family history of both breast and prostate cancer (OR=3.02, 95% CI 2.19–4.16, p -interaction<0.01). The OR for a family history of both breast and cervical cancer was 3.56 (95% CI 0.99–12.85), but this estimate was based on only 7 exposed breast cancer cases. Risk of breast cancer was significantly increased for women with a family history of three or more cancer sites, but only when breast cancer was one of the sites.

Next, we considered family history of a cancer diagnosis in relation to risk of specific breast cancer subtypes. The ORs for first degree family history of breast cancer alone were similar for ER+, ER-, and TN breast cancer (Table 4). A family history of cervical cancer was associated with ER- (OR=2.56, 95% CI 1.44–4.53) and TN (OR=3.04, 95% CI 1.57–5.87) breast cancer, but not with ER+ cancer. A family history of lung cancer was associated with a 20% increase in risk of ER+ cancer (95% CI 1.04–1.48), while a family history of prostate cancer was associated with a 24% increase in risk of ER+ cancer (95% CI 1.00–1.44). There were no significant associations with family history of any of the other sites, although the OR for the association of family history of ovarian cancer with risk of TN breast cancer was elevated (OR=1.53, 95% CI 0.89–2.65). The OR for a family history of both breast and prostate cancer was 3.40 (95% CI 2.42–4.79) for ER+ cancer, as compared with 1.62 for breast alone (p -interaction=0.02), and was 2.09 (95% CI 1.21–3.63) for ER- cancer, as compared with 1.50 for breast alone (p -interaction=0.11); for TN breast cancer, the corresponding OR was 1.60, as compared with 1.54 for breast alone (p -interaction=0.62). The ORs for breast and lung and for breast and colorectal cancer were also higher, although not significantly higher, than for breast cancer alone for some subtypes. Having a family history of breast cancer and two or more other cancer sites was associated with increased risk of each subtype, with the ORs ranging from 2.42 for ER+ to 2.78 for ER- cancer.

Results were similar across the four studies. For example, the ORs for first-degree family history of breast cancer in relation to breast cancer risk were 1.74 (95% CI 1.51–2.02) in BWHS, 1.59 (95% CI 1.19–2.14) in CBCS, 1.88 (95% CI 1.50–2.35) in MEC, and 1.55 (95% CI 1.22–1.97) in WCHS (p -heterogeneity=0.65). To assess the possibility of recall bias, we examined the associations separately in the case-control and cohort studies. The ORs for first-degree family history of breast cancer in relation to risk of breast cancer were 1.57 (95% CI 1.31–1.90) in the case-control studies and 1.80 (95% CI 1.60–2.03) in the cohort studies (p -heterogeneity=0.23).

Discussion

This large study provides convincing evidence that first degree family history of breast cancer is associated with ER+, ER-, and TN breast cancer in African American women and that having a relative diagnosed with breast cancer at a young age is a strong predictor of risk. Having a history of breast cancer together with prostate cancer was associated with a further increase in risk of each subtype. Family history of ovarian cancer was not associated with increased risk of ER+ or ER- cancer, but there was some evidence of a positive association with TN breast cancer. In addition, we observed an unexpected association of family history of cervical cancer with increased risk of ER- breast cancer.

Previous studies with data on African American women have also shown family history of breast cancer to be a strong risk factor for breast cancer.(2, 3, 16, 36–39) Only the BWHS and the Women’s CARE study also considered the relative’s age at diagnosis, and both observed a greater risk of breast cancer when the relative was diagnosed at a younger age.(2, 3) In the only study to present data in African American women by subtype, the BWHS, a similar increase was observed across subtypes.(3)

Findings according to subtype from other populations have been mixed. The association with family history of breast cancer has been similar across breast cancer subtypes,(3, 6–11, 40) stronger for ER+ breast cancer,(12, 41) and stronger for ER- or TN breast cancer.(13, 14, 42) The strongest evidence comes from a pooled analysis of 12 studies in the Breast Cancer Association Consortium, where an association with family history of breast cancer was present across subtypes, but with a stronger association for basal-like breast cancer.(40)

Only a few studies of African Americans have examined the relation of family history of cancers other than breast cancer to risk of breast cancer.(3, 16) In the BWHS, a family history of colon cancer was associated with increased risk of breast cancer, with a relative risk estimate of 1.35, but the study did not consider whether participants also had a family history of breast cancer.(3) In the Women’s Health Initiative, having a family history of both breast and prostate cancers was associated with a 2.34-fold increase in risk of breast cancer.(16) Neither of these studies presented data by breast cancer subtype. Limited data by subtype are available from other populations. In a predominantly European American population from the Iowa Women’s Health Study, a family history of prostate cancer was associated with increased risk of both ER+/PR+ and ER-/PR- breast cancer.(43) A family history of lung cancer was associated with increased risk of hormone receptor positive breast cancer in a case-control study in China.(44) No previous study has reported an association of family history of cervical cancer with increased risk of breast cancer.

Associations with family history of cancer could be explained in part by environmental or genetic factors shared within families. A family may have similar reproductive habits,(45–47) dietary patterns,(48) physical activity,(49, 50) or body size,(51, 52) each of which influences risk of various cancers.(53) Although knowledge of a family history of cancer influences cancer screening, individuals with a family history of cancer do not differ in lifestyle from individuals without knowledge of a family history.(54–56) Genetics play a role in breast cancer etiology.(57, 58) Heritable mutations in *BRCA1* or *BRCA2* genes are

associated with increased risk of both breast cancer and ovarian cancer.(59, 60) Germline mutations in the *BRCA1* and *BRCA2* genes have also been associated with increased risk of prostate and colorectal cancers,(59–61) while germline mutations in the *CHEK2* gene increase risk of breast, prostate, and colon cancers.(62)

Our observation of a strong increase in risk among participants with a family history of both breast and prostate cancer may relate to recent genetic findings. A family history of prostate cancer has been associated with mutation in the *RNASEL* gene in African Americans.(63) Mutations in this gene have also been associated with risk of breast and cervical cancers.(64) A potential mechanism linking the *RNASEL* gene and ER– breast cancer is inflammation. Inflammatory markers have been elevated in studies of hormone negative cancers.(65–67) *RNASEL* variants have been associated with elevated inflammatory biomarkers(68) and the enzyme encoded by the *RNASEL* gene has proinflammatory functions.(69)

Analyses of data from The Cancer Genome Atlas and other genomic data suggest that there are etiologic links between ovarian cancer and basal-like breast cancer,(70–73) which is primarily comprised of TN tumors. Consistent with those data, we observed a non-significant 53% increase in risk of TN breast cancer associated with a first degree family history of ovarian cancer. Genomic analyses also suggest that there are biologic similarities between basal-like breast cancer and lung cancer.(72, 73) In our data, the risk of TN breast cancer was significantly increased for a first degree family history of lung cancer only in the presence of a first degree family history of breast cancer.

African American women experience a higher prevalence of early onset breast cancer and of ER– breast cancer compared to European American women.(74–76) Because of the large sample size, we were able to informatively assess breast cancer risk by age and for breast cancer subtypes. We were also able to assess family history of cancers other than breast cancer. We controlled for multiple potential confounding factors. Participants' self-report of family history may have been incomplete and could have been subject to recall bias in the case-control studies. However, previous validation studies have shown that self-reported family cancer histories for first degree relatives are accurate for breast cancer(77) and results were similar across our studies, which included cohort studies in which family history data were provided before the participant was diagnosed with breast cancer. Additionally, the prevalence of family history of breast cancer among controls in the AMBER Consortium (9.3%) was similar to the prevalence in other studies.(78, 79) We did not have data on all cancer sites that may be of interest, such as the endometrium and pancreas.

In summary, the present findings suggest that family history of cancers other than breast cancer may indicate a higher inherited genetic susceptibility to breast cancer. Women who had both breast and prostate cancer-affected family members had a particularly high risk of both ER+ and ER– breast cancer. Greater surveillance and counseling for additional screening may be warranted.

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Table 1

Characteristics of cases and controls in the AMBER Consortium, by study.

Characteristics	BWHS		CBCS		MEC		WCHS		Total	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Age, years ^{a,b}										
<45	327 (19)	2,549 (24)	236 (29)	216 (27)	0 (0)	0 (0)	267 (25)	307 (25)	830 (18)	3,072 (18)
45–55	572 (33)	3,521 (33)	247 (31)	275 (35)	59 (6)	341 (7)	334 (31)	439 (36)	1,212 (26)	4,576 (26)
55–64	529 (30)	3,005 (28)	175 (22)	159 (20)	222 (23)	1,131 (24)	335 (31)	375 (31)	1,261 (28)	4,670 (27)
65	312 (18)	1,710 (16)	148 (18)	138 (18)	674 (71)	3,188 (68)	149 (14)	100 (8)	1,283 (28)	5,136 (29)
First degree family history of breast cancer ^b	270 (15)	1,008 (9)	132 (16)	88 (11)	140 (15)	385 (8)	184 (17)	141 (12)	726 (16)	1,622 (9)
First degree family history of cancers other than breast cancer										
Prostate cancer ^{a,b}	180 (10)	799 (7)	45 (6)	59 (8)	93 (10)	365 (8)	143 (13)	107 (9)	461 (10)	1,330 (8)
Lung cancer ^b	154 (9)	857 (8)	66 (8)	59 (8)	90 (9)	340 (7)	109 (10)	93 (8)	419 (9)	1,349 (8)
Colorectal cancer ^{a,b}	119 (7)	608 (6)	48 (6)	45 (6)	76 (8)	363 (8)	71 (7)	69 (6)	314 (7)	1,085 (6)
Ovarian cancer ^{a,b}	62 (4)	331 (3)	18 (2)	16 (2)	26 (3)	182 (4)	22 (2)	31 (3)	128 (3)	559 (3)
Lymphoma or leukemia ^{a,b}	22 (1)	88 (1)	32 (4)	17 (2)	22 (2)	87 (2)	28 (3)	33 (3)	103 (2)	224 (1)
Cervical cancer ^{a,b}	6 (0)	25 (0)	20 (3)	18 (2)	10 (1)	28 (1)	19 (2)	19 (2)	55 (1)	90 (1)

^a Chi-square test for difference between studies among cases, p<0.05

^b Chi-square test for difference between studies among controls, p<0.05

Table 2

Family history of breast cancer in relation to risk of breast cancer, overall and by subtype.

	Breast Cancer				ER+				ER-				Triple negative			
	Controls N	Cases N	OR ^a	(95% CI)	Cases N	OR ^a	(95% CI)	Cases N	OR ^a	(95% CI)	Cases N	OR ^a	(95% CI)	Cases N	OR ^a	(95% CI)
First degree family history of breast cancer																
No	15,798	3,794	1.00	Reference	2,525	1.00	Reference	1,269	1.00	Reference	584	1.00	Reference			
Yes	1,622	726	1.73	(1.56–1.92)	498	1.76	(1.57–1.97)	228	1.67	(1.42–1.95)	112	1.72	(1.38–2.13)			
Number of first degree relatives																
1	1,547	690	1.73	(1.56–1.92)	473	1.76	(1.56–1.97)	217	1.66	(1.41–1.95)	106	1.70	(1.36–2.13)			
2	75	36	1.85	(1.21–2.84)	25	1.86	(1.15–3.01)	11	1.81	(0.93–3.51)	6	2.02	(0.84–4.89)			
Relative's age at diagnosis																
<50 years	618	304	2.00	(1.74–2.30)	200	1.95	(1.64–2.33)	104	1.96	(1.56–2.46)	46	1.83	(1.32–2.54)			
50 years	625	297	1.56	(1.35–1.80)	207	1.64	(1.38–1.95)	90	1.46	(1.15–1.86)	44	1.40	(1.01–1.96)			
Unknown age	379	125	1.60	(1.31–1.95)	91	1.66	(1.31–2.11)	34	1.54	(1.07–2.21)	22	2.41	(1.54–3.78)			
Among participants age <45 years																
No	2,861	714	1.00	Reference	406	1.00	Reference	308	1.00	Reference	147	1.00	Reference			
Yes	211	116	2.02	(1.54–2.65)	67	2.05	(1.49–2.83)	49	1.97	(1.36–2.83)	22	1.75	(1.05–2.93)			
Relative's age at diagnosis																
<50 years	95	80	3.09	(2.23–4.27)	43	3.45	(2.29–5.21)	37	3.79	(2.43–5.91)	16	3.48	(1.86–6.49)			
50 years	76	31	1.31	(0.87–1.98)	22	1.32	(0.78–2.25)	9	0.68	(0.32–1.43)	4	0.53	(0.18–1.52)			
Unknown age	40	5	0.81	(0.36–1.81)	2			3			2					
Among participants age 45 years																
No	12,937	3,080	1.00	Reference	2,119	1.00	Reference	961	1.00	Reference	437	1.00	Reference			
Yes	1,411	610	1.69	(1.52–1.86)	431	1.71	(1.52–1.94)	179	1.60	(1.35–1.91)	90	1.72	(1.35–2.18)			
Relative's age at diagnosis																
<50 years	523	224	1.80	(1.53–2.10)	157	1.73	(1.42–2.10)	67	1.59	(1.21–2.09)	30	1.53	(1.03–2.26)			
50 years	549	266	1.59	(1.37–1.86)	185	1.68	(1.39–2.02)	81	1.63	(1.26–2.10)	40	1.62	(1.14–2.31)			
Unknown age	339	120	1.68	(1.37–2.06)	89	1.76	(1.38–2.25)	31	1.57	(1.07–2.30)	20	2.38	(1.48–3.81)			

^aMultivariable models adjust for age, study, geographic region, questionnaire time period, and recency of mammogram

Table 3

Family history of breast cancer and cancer at six other sites in relation to risk of breast cancer.

First degree family history of	Controls	Cases	OR ^a	(95% CI)
No cancer	9,735	2,374	1.00	Reference
One cancer site				
Breast cancer	914	393	1.58	(1.38–1.82)
Lung cancer	869	250	1.19	(1.01–1.39)
Prostate cancer	863	244	1.16	(0.99–1.36)
Colorectal cancer	624	171	1.17	(0.97–1.41)
Ovarian cancer	323	61	0.90	(0.68–1.21)
Lymphoma or leukemia	137	52	1.25	(0.88–1.78)
Cervical cancer	52	34	1.53	(0.94–2.47)
Two cancer sites				
Breast/Prostate	105	76	3.02	(2.19–4.16)
Breast/Lung	126	52	1.60	(1.13–2.27)
Breast/Colorectal	83	32	1.40	(0.89–2.22)
Breast/Ovarian	51	11	1.21	(0.62–2.37)
Breast/Lymphoma or leukemia	16	10	1.42	(0.60–3.33)
Breast/Cervical	5	7	3.56	(0.99–12.85)
Prostate/Colorectal	119	37	1.52	(1.03–2.24)
Prostate/Lung	73	25	1.54	(0.95–2.50)
Prostate/Ovarian	28	12	1.95	(0.94–4.02)
Prostate/Lymphoma or leukemia	17	9	2.39	(1.02–5.60)
Lung/Colorectal	91	17	0.91	(0.53–1.55)
Colorectal/Ovarian	27	10	1.73	(0.81–3.70)
2 sites other than breast	88	24	0.94	(0.58–1.54)
Three or more cancer sites				
Breast/Prostate/Lung	17	11	3.05	(1.35–6.89)
Breast/Lung/Colorectal	17	9	2.60	(1.12–6.03)
Breast and 2 other sites ^b	74	38	2.39	(1.57–3.64)
3 sites other than breast	47	15	1.37	(0.74–2.54)

^aMultivariable model adjusts for age, study, geographic region, questionnaire time period, and recency of mammogram^bOther than the listed combinations of cancer sites

Table 4
Family history of breast cancer and six other sites in relation to risk of breast cancer subtypes.

First degree family history of	ER+			ER-			Triple negative		
	Controls N	Cases N	OR ^a (95% CI)	Cases N	OR ^a (95% CI)	Reference	Cases N	OR ^a (95% CI)	Reference
No cancer	9,735	1,579	1.00	795	1.00	Reference	393	1.00	Reference
One cancer site									
Breast cancer	914	270	1.62 (1.39–1.89)	123	1.50 (1.21–1.86)		65	1.55 (1.17–2.06)	
Lung cancer	869	173	1.20 (1.00–1.44)	77	1.14 (0.89–1.48)		40	1.20 (0.85–1.69)	
Prostate cancer	863	179	1.24 (1.04–1.48)	65	0.98 (0.75–1.28)		30	0.92 (0.62–1.35)	
Colorectal cancer	624	119	1.19 (0.96–1.47)	52	1.12 (0.83–1.52)		21	0.92 (0.58–1.46)	
Ovarian cancer	323	37	0.79 (0.56–1.13)	24	1.15 (0.74–1.78)		15	1.53 (0.89–2.65)	
Lymphoma or leukemia	137	34	1.23 (0.83–1.84)	18	1.29 (0.77–2.19)		10	1.37 (0.70–2.70)	
Cervical cancer	52	13	0.95 (0.50–1.80)	21	2.56 (1.44–4.53)		14	3.04 (1.57–5.87)	
Two cancer sites									
Breast/Prostate	105	60	3.40 (2.42–4.79)	16	2.09 (1.21–3.63)		6	1.60 (0.69–3.74)	
Breast/Lung	126	31	1.37 (0.91–2.08)	21	2.11 (1.29–3.46)		16	3.32 (1.89–5.84)	
Breast/Colorectal	83	26	1.67 (1.03–2.71)	6	0.80 (0.33–1.92)		3	0.74 (0.22–2.45)	
Breast/Ovarian	51	9	1.43 (0.69–2.96)	2	0.70 (0.17–2.93)		1	0.79 (0.11–5.82)	
Prostate/Colorectal	119	29	1.64 (1.07–2.51)	8	1.19 (0.57–2.46)		5	1.70 (0.68–4.26)	
Prostate/Lung	73	19	1.61 (0.95–2.74)	6	1.34 (0.57–3.15)		4	1.89 (0.67–5.30)	
Lung/Colorectal	91	11	0.80 (0.42–1.52)	6	1.20 (0.52–2.80)		2	0.85 (0.21–3.53)	
2 other sites ^b	181	47	1.41 (1.00–1.98)	25	1.55 (0.99–2.43)		10	1.19 (0.61–2.33)	
Three or more cancer sites									
Breast/ 2 sites other than breast	108	40	2.42 (1.65–3.56)	18	2.78 (1.65–4.68)		8	2.65 (1.26–5.60)	
3 sites other than breast	47	8	1.04 (0.48–2.26)	7	2.23 (0.97–5.12)		2	1.39 (0.33–5.92)	

^aMultivariable models adjust for age, study, geographic region, questionnaire time period, and recency of mammogram

^bOther than the listed combinations of cancer sites