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Family history of breast cancer in men with non-*BRCA* male breast cancer: implications for cancer risk counseling

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Abstract

Purpose: The role of genetic predisposition in male breast cancer (MBC) patients who test negative for a *BRCA* mutation is unclear. The aim of this study is to define the association between MBC and family history of breast cancer in patients without mutations in *BRCA1 or BRCA2*.

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AUTHOR CONTRIBUTIONS

Conception and design: Calip, Saam, Hoskins

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Collection and assembly of data: Kidd, Cox, Bernhisel, Saam

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Conflict of Interest: Mr. Kidd, Mr. Bernhisel, Dr. Cox, Mr. Evans, Dr. Saam and Dr. Lancaster received salary support and have ownership interest (stock options) in Myriad Genetics Laboratories, Inc. At the time of submission, Dr. Calip reports current employment with Flatiron Health, Inc., which is an independent subsidiary of the Roche group. Drs. Calip and Hoskins Dr. Hoskins report receiving research support from Pfizer, Inc. for work unrelated to this project. Dr. Rauscher declares he has no conflict of interest.

Ethical approval: The study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The University of Illinois at Chicago Institutional Review Board (IRB), Chicago, IL approved the study (IRB Protocol # 2015–1176). The need for informed consent was waived under the approval of the IRB due to the retrospective design.

Methods: We conducted an unmatched case-control study with men who received commercial testing for germline mutations in cancer susceptibility genes, including 3,647 MBC cases who tested negative for deleterious mutations in *BRCA1/BRCA2*, and 4,269 men with a personal history of colorectal cancer who tested negative for mutations in DNA mismatch repair genes to serve as controls. Associations between family history of breast cancer and MBC were estimated using unconditional multivariable logistic regression with adjustment for age, race/ethnicity and year of testing.

Results: Breast cancer in a first- or second-degree relative was associated with a four-fold increased odds of MBC (OR, 4.7; 95% CI, 4.1, 5.3). Associations with MBC were strongest for family history of breast cancer in 2 or more first-degree relatives (FDR) (OR, 7.8; 95% CI, 5.2, 11.6), for probands and FDR diagnosed at age <45 years (OR, 6.9; 95% CI, 3.9, 12.4), and for family history of MBC (OR, 17.9; 95% CI 7.6, 42.1). Findings were confirmed in a sensitivity analysis of MBC cases who tested negative on a 25-gene pan-cancer panel.

Conclusions: MBC patients without mutations in *BRCA1/2* have significantly higher odds of a family history of breast cancer, suggesting the existence of unidentified MBC susceptibility alleles.

Keywords

male breast cancer; genetics; BRCA1; BRCA2; family history

INTRODUCTION

Male breast cancer (MBC) accounts for nearly 1% of all breast cancer, with approximately 2,000 new cases diagnosed in the United States annually [1]. Epidemiologic studies identified a number of risk factors for the disease, including conditions that increase the estrogen/testosterone ratio (e.g., obesity, cryptorchidism, orchiectomy, and Klinefelter's syndrome), exposure to ionizing radiation, gynecomastia and a personal history of prostate cancer [2–4]. Family history of breast cancer in a first-degree relative (FDR) is also an important risk factor for MBC [5–7].

Overall, the presence of breast cancer in a female FDR is associated with a 2–3 fold increase in risk for MBC in population-based studies [7,6]. A substantially higher risk of MBC is reported for men with germline mutations in genes responsible for the Hereditary Breast and Ovarian Cancer syndrome (HBOC), especially those with mutations in *BRCA2* [8,9]. The *BRCA2* gene was isolated through positional cloning techniques in a series of families who tested negative for a *BRCA1* mutation, but appeared to be transmitting a highly penetrant breast cancer susceptibility allele that included MBC in the phenotype [10]. Subsequent studies indicated that the *BRCA2* gene is responsible for approximately 8% of all MBC [11,12]. Germline mutations in *BRCA2* confer a dramatically increased relative risk of breast cancer for male mutation carriers [13], resulting in a cumulative lifetime MBC risk of 7% [4,9]. The breast cancer risk to female relatives of MBC patients harboring a *BRCA2* mutations is also substantially increased. Female *BRCA2* carriers have at least a 50% risk of developing breast cancer by age 70 [14,15]. A number of studies have investigated the role that moderate penetrance genes predisposing to female breast cancer may play in the

etiology of MBC [16–26]. The combined frequency of pathogenic variants in moderate penetrance genes was approximately the same as for *BRCA2* in one study [26]. Still, up to 85% of MBC cases do not have a detectable germline pathogenic variant in any known breast cancer susceptibility genes [26] and the contribution of genetic factors in these cases is unknown. Detailed analysis of family cancer history in a large sample of MBC cases who received comprehensive molecular analysis for HBOC is needed to provide epidemiologic data to better define the role of additional MBC susceptibility alleles.

An important element of the clinical evaluation of individuals with MBC is accurate assessment of cancer risk for unaffected relatives. This is straightforward in families transmitting a *BRCA* mutation, given the ability to determine the genotype of at-risk family members and the extensive literature on cancer risks for *BRCA* mutation carriers [9,14,15,27,28]. However, we are unaware of any studies reporting a detailed analysis of family history of breast cancer in MBC cases who do not carry a *BRCA* mutation. Several authors reported that the breast cancer risk for women with a male relative with MBC is similar to the risk conferred by having a female relative with breast cancer [29,30], but these reports did not determine the *BRCA* mutation status of the MBC cases studied. As a result, it is possible that the risks reported were driven largely by the subgroup of families with a *BRCA* mutation, thereby inflating risk estimates for the *BRCA*-negative families. Since 90% of men with MBC test negative for a *BRCA* mutation [11,12,26, 31], the lack of reliable risk estimates specifically for relatives of men with non-*BRCA* MBC represents an important gap in our ability to provide accurate cancer risk counseling. The aim of this case-control study is to characterize the association of family history of breast cancer with a diagnosis of MBC in men who test negative for mutations in the *BRCA* genes. We hypothesize that *BRCA*-negative MBC is associated with a family history of breast cancer. The STROBE guidelines for reporting observational studies were followed in the design and reporting of this study [32].

METHODS

Patients and data collection

We identified case and control subjects for this study by querying a database containing clinical and demographic information, family cancer history and results of germline DNA testing of cancer susceptibility genes for all individuals undergoing testing at a commercial genetic testing laboratory in the United States between September 2006 and June 2012. Cases were selected from males with a personal history of breast cancer who had single-syndrome testing for HBOC with full-length sequencing analysis of *BRCA1/2* and tested *negative* for deleterious mutations. Unmatched controls were selected from a sample of males with a personal history of colorectal cancer who had single-syndrome DNA testing for the Lynch syndrome with full length sequencing and large rearrangement analysis of the mismatch repair (MMR) genes *MLH1, MSH2, MSH6, PMS2*, and *EPCAM* (large rearrangement analysis only) and tested *negative* for deleterious mutations in all genes tested. We chose this control group since the principles of case-control study design require that controls are selected from the same source as cases [33]. There is no known association between colon cancer and breast cancer in families not transmitting the Lynch syndrome,

therefore the prevalence of a family history of breast cancer among men with colon cancer who test negative for the Lynch syndrome should closely approximate the prevalence in the general population. We excluded from all analyses any potential case or control subjects who were diagnosed with their index cancer at ages <20 years (n=25), 80+ years (n=496), had unknown age (n=496), or had unknown race/ethnicity (n=2,121).

Because a small number of *BRCA*-negative MBC patients harbor deleterious mutations in moderate penetrance genes [26], we conducted a sensitivity analysis with a second set of MBC cases and male colon cancer controls who tested negative for deleterious mutations in all genes on a 25-gene, pan-cancer panel test that included the moderate penetrance breast cancer susceptibility genes associated with MBC [26]. The 25-gene panel included *BRCA1, BRCA2, APC, ATM, BARD1, BMPR1A*, *BRIP1*, *CDH1, CDK4*, *CDKN2A*, *CHEK2*, *EPCAM, MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *PTEN, RAD51C*, *RAD51D*, *SMAD4*, *STK11*, and *TP53*. Sequencing and large rearrangement analyses were performed for all genes on the panel (except *EPCAM*, which was tested by large rearrangement analysis only). All variants classified as “likely pathogenic” or “pathogenic” by the testing laboratory’s variant classification program [34] are coded as “deleterious mutations” for this analysis.

Information on personal cancer history, age at diagnosis, race/ethnicity, and family cancer history was obtained from a standard test request form submitted by the ordering healthcare provider at the time that DNA testing was ordered. Family history information provided was not confirmed by medical record review. For this study, a first-degree family history of breast cancer included any male or female first-degree relative with a diagnosis of breast cancer. A second-degree family history included a diagnosis of breast cancer in any female or male second-degree relative. Age at diagnosis was ascertained for family members with a history of breast cancer.

This study was approved by the institutional review board of the University of Illinois at Chicago. The data that support the findings of this study are available from Myriad Genetics Laboratories, Inc. but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Myriad Genetics Laboratories, Inc.

Statistical analysis

Odds ratios (OR) and corresponding 95% confidence intervals (CI) for associations of family history of breast cancer with odds of being a *BRCA* non-carrier MBC case were estimated from unconditional logistic regression models adjusting for age (continuous), year of testing (categorical), and reported racial/ethnic background (White, Black, Asian, Latino, Multi-ethnic, Other). We performed stratified analyses examining associations by both proband and affected FDR age at diagnosis (age <45 and 45+ years), relation of affected relative to proband, and gender of the affected relative. Sensitivity analyses were performed that (i) excluded patients who were carriers of a variant of uncertain significance (VUS); (ii) excluded patients with Ashkenazi ancestry; and (iii) included only cases and controls who tested negative for deleterious mutations in all genes on a 25-gene, pan-cancer panel test.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients

In all, 3,647 *BRCA*-negative MBC cases and 4,269 controls are included in the primary analyses. The sensitivity analysis of participants testing negative for all genes on a 25-gene pan-cancer panel included 568 MBC cases and 1,761 controls. Demographic and clinical characteristics among *BRCA*-negative MBC cases and controls included in the primary analysis are listed in Table 1. By unmatched design of the study, MBC cases and controls differed by age (median in years; *BRCA*-negative cases: 62, and controls: 46), ethnicity and Ashkenazi ancestry. Personal history of a non-breast or non-colon cancer was also less prevalent among *BRCA*-negative MBC cases compared to controls (11% vs. 24%), and DNA testing of MBC cases was less likely to reveal a VUS.

Associations between non-BRCA male breast cancer and a family history of breast cancer

Table 2 presents the association between family history of breast cancer and *BRCA*-negative MBC. Compared with men who reported no first- or second-degree relatives with breast cancer, those with a first- or second-degree family history of breast cancer had a more than four-fold greater odds of being a MBC case (OR, 4.7; 95% CI, 4.1, 5.3). Odds of being a MBC case were more than seven-fold higher (OR, 7.8; 95% CI, 5.2, 11.6) among men with two or more affected first-degree relatives. Associations were similar for men with only an affected second-degree relative and those with an affected FDR (OR, 5.5 and 4.3, respectively). Age at diagnosis of the proband had no impact on the overall strength of the association with an affected FDR (OR, 4.2 for both Proband < 45 and 45+ years). However, the association was stronger when both the proband and a FDR were diagnosed at age <45 (OR, 6.9; 95% CI, 3.9, 12.4).

Analyses of the relation between family history of breast cancer and MBC stratified by the gender of the affected relative are shown in Table 3. Compared to men reporting no affected first- or second-degree relative, there were greatly increased odds of being a MBC case among participants with a first- or second-degree male relative affected with breast cancer (OR, 17.9; 95% CI 7.6, 42.1) and among those with both male and female relatives affected (OR, 15.7; 95% CI, 4.4, 55.3). The ORs were not attenuated by having a second- vs. first-degree male relative affected.

Results from sensitivity analyses that excluded cases and controls with VUS or Ashkenazi ancestry were similar to our main approach with respect to the size of the effect estimates and their statistical significance (supplemental Tables s1 and s2). Notably, the sensitivity analysis involving MBC cases and controls who tested negative for deleterious mutations on a 25-gene pan-cancer panel confirmed the results of the primary analysis with similar direction of associations, although in some cases the size of the effect was attenuated (Table 4). The OR of being a MBC case for men with family history of any FDR with breast cancer was 1.4 (95% CI, 1.0, 1.9), and the OR was 2.6 (1.1, 5.7) for MBC cases diagnosed before

age 45. A similar pattern was seen in the sensitivity and primary analyses in terms of higher OR for MBC cases diagnosed at age <45 years when a FDR was diagnosed at age < 45, although the CI crossed equivalence in the sensitivity analysis due to the small number of cases and controls in this subgroup (OR 3.3; 95% CI, 0.6, 16.9). For men having family history of MBC, the OR for being a MBC case was 14.6 (95% CI, 2.7, 77.9), which was similar to the result for this subgroup in the main analysis (OR 17.9).

DISCUSSION

To our knowledge, this study of more than 4,000 MBC cases represents the largest study published to date investigating the association between MBC and family history of breast cancer with full length sequencing of the *BRCA* genes in all MBC cases. Previous studies that analyzed the association between MBC and family history of breast cancer either did not determine mutation status of study participants [29,30,35] or included a much smaller sample size and did not report associations specific to the *BRCA*-negative subgroup [11]. Anderson and Badzioch [29] compared the observed/expected ratio of breast cancer in family members of 88 cases of MBC from the MD Anderson Cancer Center. These authors found a two-fold increase in the observed number breast cancers in female relatives of MBC patients [29], consistent with our finding of an OR of 4.6 for the association between *BRCA*-negative MBC and any female relative with breast cancer. Bevier and colleagues [30] reported an analysis from the Swedish Family Cancer Registry which contains robust linkage of family members throughout the country and information on cancer diagnoses in linked individuals. The study included approximately 2 million women who were linked to their biologic parents and other relatives. The investigators demonstrated associations between MBC and family history of breast cancer similar to those reported here, with a relative risk (RR) of breast cancer of 2.48 and 1.73 for women with a brother or a father with MBC, respectively [30]. This is similar to our finding of an OR of 3.9 for the association between *BRCA*-negative MBC and 1 affected female FDR. We also found similar associations with MBC and multiple FDR with female breast cancer, with an OR of 7.5 reported here and a RR of 5.45 in the Swedish study. However, that study included only 66 cases of MBC, limiting their ability to perform stratified analyses due to wide confidence intervals. Similar associations with family history were reported in a study of MBC from the SEER registry, but the results of that study are confounded by the probable inclusion of *BRCA* mutation carriers in the study group since the study was undertaken prior to the identification of *BRCA2* [7]. Although the main findings of the studies cited above are similar to ours, they are all limited by the inability to account for the effect that *BRCA* mutation carriers had on the risk estimates generated, since the *BRCA* carrier status of the MBC cases was unknown.

A population-based study of 94 MBC cases from the United Kingdom (UK) [11] that included detailed family history information and *BRCA* mutation status for all study participants reported a RR of breast cancer in a female FDR of 2.4 for the entire study cohort, with 8% of the study cohort identified as *BRCA* mutation carriers. We report OR of 3.9 for the same family history combination in the *BRCA*-negative subgroup. Notably, that analysis was not stratified by mutation carrier status and did not provide risk estimates for the relatives of men testing negative for a *BRCA* mutation. To our knowledge, our study is

the first detailed analysis of the association between MBC and family history of breast cancer that provides data specific for *BRCA* non-carriers, and it includes the largest cohort of MBC cases with known mutation status published to date.

Our results provide strong evidence for genetic predisposition in non-*BRCA* male breast cancer. The associations we observed between family history of breast cancer and non-*BRCA* MBC are similar to the OR reported for the associations between various family history scenarios and *BRCA*-related female breast cancer in a case-control study [36]. Similarly, Pritzlaff and colleagues reported no significant difference in the prevalence of a family history of breast cancer between the 18% of MBC cases testing positive for a pathogenic variant on a multigene panel test compared to the MBC cases who tested negative. That study is consistent with our finding that MBC is strongly associated with a family history of breast cancer among individuals testing negative with a 25-gene panel test that includes the moderate penetrance genes associated with MBC [26]. The population-based study of MBC from the UK cited above [11] also supports the hypothesis that additional MBC risk alleles exist. Those investigators estimated that the *BRCA* genes accounted for only 15% of the excess familial breast cancer risk in female FDR of MBC cases. Taken together, the data support the hypothesis that unidentified risk alleles exist that confer risk for both male and female breast cancer.

Strengths and limitations

A major strength of this study is the large sample size of MBC cases that are confirmed to be non-carriers of a *BRCA* mutation, which permits detailed subgroup analyses of different family history patterns with robust statistical power. As noted above, this is the largest study of MBC cases with known *BRCA* carrier status reported to date. However, this study has several limitations. First, there were significant differences between the case and control groups in terms of age at diagnosis and personal history of other cancers. This is not surprising due to the unmatched study design. However, this study design provided greater statistical efficiency and allowed us to test the effect of these covariates, which would not have been possible if cases and controls were matched on those variables [37]. Importantly, an unmatched design does not increase bias in observational studies that adjust for relevant covariates [37]. Second, the study design relied on self-report of family history of breast cancer. There is evidence that women accurately report family history of breast cancer [38], but the accuracy among men is unknown and under-reporting among MBC cases is possible. This would have the effect of attenuating the association between MBC and family history of breast cancer. Though speculative, another possibility is that men with a personal history of colon cancer referred for MMR gene testing (the control group) under-reported their family history of breast cancer relative to MBC cases, which would inflate the association between *BRCA*-negative MBC and family history of breast cancer. However, 8.7% of the control group in this study reported a FDR with breast cancer, which is nearly identical to the 7.7% rate reported for the general population in the United States [39]. Therefore, reporting bias resulting from underreporting in the control group is unlikely to account for the associations observed.

The potential for selection bias must also be considered. It is doubtful that there was substantial enrichment for family history of breast cancer among MBC cases as the result of bias in referral for *BRCA* testing for several reasons. First, the most widely used set of oncology practice guidelines in the U.S. published by the National Comprehensive Cancer Network [40] began recommending *BRCA* testing for all men with MBC regardless of family history prior to the study period. As a result, it was standard practice in the U.S. to order *BRCA* testing for all MBC patients during the study period. Furthermore, 28% of our MBC cases reported a FDR with breast cancer, which is only modestly higher than the 20–25% rate of an affected FDR noted in several population-based studies of MBC [6,41,42].

The findings reported here may be useful to inform risk counseling by suggesting the general pattern and magnitude of breast cancer risk in families with *BRCA*-negative MBC. However, despite the fact that odds ratios approximate relative risks for rare diseases like MBC [43], odds ratios reported here should not be used in an effort to estimate cumulative lifetime risks for at-risk family members of MBC cases.

CONCLUSION

This study provides evidence for genetic susceptibility to breast cancer in families with MBC that are not transmitting deleterious mutations in the *BRCA* genes. Moderate penetrance genes predisposing to female breast cancer [16–26] may account for some of the effects seen in *BRCA*-negative MBC, but do not fully explain the association between family history of breast cancer and a diagnosis of MBC. Findings suggest the existence of unidentified risk alleles for MBC that also predispose to female breast cancer. The results can provide guidance for counseling family members of MBC patients who test negative for mutations in the *BRCA* genes. Further work is needed to confirm these findings, including studies designed to generate cumulative risk estimates for unaffected family members of men with breast cancer who do not carry a *BRCA* mutation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Descriptive characteristics of BRCA noncarrier male breast cancer cases and controls

	BRCA (−) male breast cancer cases (n=3647) No. (%)	Controls (n=4269) No. (%)	*P**
Age at index cancer diagnosis, years			
Median (interquartile range)	62 (53 – 69)	46 (40 – 53)	<0.001
20–29	26 (0.7)	180 (4.2)	<0.001
30–39	135 (3.7)	863 (20.2)	
40–49	491 (13.5)	1746 (40.9)	
50–59	931 (25.5)	829 (19.4)	
60–69	1230 (33.7)	438 (10.3)	
70–79	834 (22.9)	213 (5.0)	
Ethnicity			
White/European	2533 (69.5)	2848 (66.7)	<0.001
Black	286 (7.8)	255 (6.0)	
Asian	54 (1.5)	141 (3.3)	
Latino	131 (3.6)	288 (6.7)	
Native American	43 (1.2)	66 (1.5)	
Near/Middle Eastern	34 (0.9)	38 (0.9)	
Other	34 (0.9)	48 (1.1)	
Multi-ethnic	532 (14.6)	585 (13.7)	
Ashkenazi ancestry			
No	3336 (91.5)	4142 (97.0)	<0.001
Yes	311 (8.5)	127 (3.0)	
Year of testing			
2006	105 (2.9)	148 (3.5)	0.012
2007	433 (11.9)	427 (10.0)	
2008	468 (12.8)	588 (13.8)	
2009	517 (14.2)	686 (16.1)	
2010	670 (18.4)	799 (18.7)	
2011	701 (19.2)	791 (18.5)	
2012	753 (20.6)	830 (19.4)	
Any VUS			
No	3584 (98.3)	4005 (93.8)	<0.001
Yes	63 (1.7)	264 (6.2)	
Personal history of non-breast/colon cancer			
No	3240 (88.8)	3236 (75.8)	<0.001
Yes	407 (11.2)	1033 (24.2)	

*Wilcoxon rank-sum test for comparison of medians and χ^2 test for categorical variables

Table 2.

Family history of breast cancer among male breast cancer cases who are noncarriers of a BRCA mutation

	BRCA (−) male breast cancer cases (n=3647)	Controls (n=4269)	Adjusted OR[a]	(95% CI)
No affected first- or second-degree relative	2007 / 3647	3636 / 4269	1.0	Reference
Any affected first- or second-degree relative	1640	633	4.7	(4.1, 5.3)
Any affected first-degree relative	1037	374	4.3	(3.7, 5.0)
Any affected second-degree relative	889	319	6.3	(5.3, 7.4)
Only second-degree relative affected	603	259	5.5	(4.6, 6.7)
Number of affected first-degree relatives				
1 first-degree relative	833	339	3.9	(3.3, 4.6)
2+ first-degree relatives	204	35	7.8	(5.2, 11.6)
Age of affected first-degree relative				
Affected first-degree relative age <45 years[b]	199	78	4.8	(3.5, 6.5)
Affected first-degree relative age 45+ years[b]	837	283	4.2	(3.6, 5.0)
Proband age of diagnosis: <45 years				
No affected first- or second-degree relative	193 / 349	1558 / 1819	1.0	Reference
Any affected first-degree relative[b]	66	129	4.2	(3.0, 6.0)
Affected first-degree relative age <45 years[b]	26	32	6.9	(3.9, 12.4)
Affected first-degree relative age 45+ years[b]	40	92	3.7	(2.4, 5.6)
Proband age of diagnosis: 45+ years				
No affected first- or second-degree relative	1814 / 3298	2078 / 2450	1.0	Reference
Any affected first-degree relative[b]	971	245	4.2	(3.6, 5.0)
Affected first-degree relative age <45 years[b]	173	46	4.1	(2.8, 5.8)
Affected first-degree relative age 45+ years[b]	797	191	4.4	(3.6, 5.3)

[a] Multivariable unconditional logistic regression models adjusted for: age, year of testing, and ethnicity.

[b] Rows stratified by age may not add up to unstratified row due to missing data.

Table 3.

Family history of breast cancer among male breast cancer cases who are noncarriers of BRCA mutations, stratified by affected relatives' gender

	BRCA (−) male breast cancer cases (n=3647)	Controls (n=4269)	Adjusted OR[a]	(95% CI)
No affected first- or second-degree relative	2007 / 3647	3636 / 4269	1.0	Reference
Any affected first- or second-degree relative				
Male relative affected	66	7	17.9	(7.6, 42.1)
Female relative affected	1601	629	4.6	(4.0, 5.2)
Both male and female relatives affected	28	3	15.7	(4.4, 55.3)
Any affected first-degree relative				
Male relative affected	31	4	10.8	(3.4, 34.1)
Female relative affected	1017	371	4.2	(3.6, 4.9)
Both male and female relatives affected	12	1	15.1	(1.8, 126.1)
Any affected second-degree relative				
Male relative affected	36	3	27.6	(7.7, 98.3)
Female relative affected	862	317	6.1	(5.2, 7.2)
Both male and female relatives affected	9	1	25.7	(3.0, 220.0)
No first-degree affected relative, second-degree relative affected only				
Male relative affected	24	3	20.1	(5.3, 75.8)
Female relative affected	582	257	5.4	(4.5, 6.5)
Both male and female relatives affected	3	1	8.3	(0.8, 91.6)
Number of affected first-degree relatives				
1 affected male first-degree relative	29	4	9.2	(2.9, 29.4)
2+ affected male first-degree relatives	2	0	-	-
1 affected female first-degree relative	824	337	3.9	(3.3, 4.6)
2+ affected female first-degree relatives	193	34	7.5	(5.0, 11.4)
Both male and female first-degree relatives affected	12	1	15.1	(1.8, 126.1)

[a]Multivariable unconditional logistic regression models adjusted for: age, year of testing, and ethnicity.

Table 4.

Family history of breast cancer among male breast cancer cases who are noncarriers of deleterious mutations on a multigene panel test

	Multigene panel test (−) male breast cases (n=568)	Controls (n=1751)	Adjusted OR[a]	(95% CI)
No affected first- or second-degree relative	368 / 568	1254 / 1751	1.0	Reference
Any affected first- or second-degree relative	200	497	1.3	(1.0, 1.7)
Any affected first-degree relative	124	264	1.4	(1.0, 1.9)
Any affected second-degree relative	114	290	1.4	(1.0, 1.9)
Only second-degree relative affected	76	233	1.2	(0.8, 1.7)
Number of affected first-degree relatives				
1 first-degree relative	95	230	1.3	(1.0, 1.8)
2+ first-degree relatives	29	34	1.7	(0.9, 3.1)
Gender of affected first- or second-degree relatives				
Any male relative affected	9	4	14.6	(2.7, 77.9)
Any female relative affected	191	493	1.2	(1.0, 1.6)
Age of affected first-degree relative				
Affected first-degree relative age <45 years[b]	20	42	1.4	(0.8, 2.8)
Affected first-degree relative age 45+ years[b]	92	204	1.4	(1.0, 1.9)
Proband age of diagnosis: <45 years				
No affected first- or second-degree relative	36 / 57	482 / 645	1.0	Reference
Any affected first-degree relative[b]	10	64	2.6	(1.1, 5.7)
Affected first-degree relative age <45 years[b]	2	11	3.3	(0.6, 16.9)
Affected first-degree relative age 45+ years[b]	7	51	2.2	(0.9, 5.4)
Proband age of diagnosis: 45+ years				
No affected first- or second-degree relative	332 / 511	772 / 1106	1.0	Reference
Any affected first-degree relative[b]	114	200	1.3	(0.9, 1.8)
Affected first-degree relative age <45 years[b]	18	31	1.3	(0.7, 2.6)
Affected first-degree relative age 45+ years[b]	85	153	1.3	(0.9, 1.9)

[a]Multivariable unconditional logistic regression models adjusted for: age, year of testing, and ethnicity.

[b]Rows stratified by age may not add up to unstratified row due to missing data.