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Family history and age at onset of breast cancer in Hispanic and non-Hispanic white women

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Abstract

Objectives—To evaluate the association between family history of breast cancer and breast cancer risk among Hispanic and non-Hispanic white (NHW) women.

Methods—Logistic regression models were used to compute unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using data collected from the 4-Corners Breast Cancer Study, a population-based case–control study of breast cancer conducted in the Southwest United States (3,074 NHW and 1,647 Hispanic women).

Results—The association between family history of breast cancer and early-onset breast cancer risk differs among NHW and Hispanic women. Among women<50 years old, having a family history of breast cancer was associated with a greater increase in risk among NHWs, with an OR of 2.34 (95% CI: 1.64–3.35) when compared to an OR of 1.32 (95% CI: 0.82–2.19) for Hispanics. This difference in risk was not observed among women 50 years and older, with an OR of 1.69 (95% CI: 1.34–2.13) for NHW and 1.47 (95% CI: 1.03–2.10) for Hispanics.

Conclusions—Family history of breast cancer poses a greater risk for early-onset breast cancers among NHW when compared to Hispanic women and may reflect ethnic differences in certain predisposing genetic factors that promote breast cancer development.

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Keywords

Breast neoplasms; Hispanic Americans; Genetic predisposition to disease

Introduction

Breast cancer is the leading cause of incident cancer and the second leading cause of cancer deaths among women in the United States [1]. However, incidence and mortality rates differ substantially by racial/ethnic group [2–5]. For example, the incidence rate in non-Hispanic Whites (NHW) is highest at 132.5/100,000 women in comparison to African Americans (118.0/100,000) and Hispanics (89.3/100,000) [5]. The reasons for the observed disparities are not completely understood.

One plausible explanation for ethnic disparities in breast cancer rates could be the differences in the prevalence of known breast cancer risk factors, such as age at menarche and menopause, parity, age at first birth, and obesity (in postmenopausal women). A recent study by Chlebowski et al. [6] demonstrated that adjustment for these established risk factors accounted for much of the variation observed in breast cancer incidence rates between racial/ethnic groups. However, even after adjustment for potential confounders, rates of breast cancer statistically differed across the groups.

Family history of breast cancer, a likely surrogate for genetic predisposition as well as shared environment, represents one of the strongest risk factors for breast cancer. Family history accounts for an estimated 5.5% excess lifetime risk for women with one affected first-degree relative and 13.3% for women with two or more first-degree relatives with breast cancer [7]. There is a genetic variation across ethnic populations, and these genetic differences may contribute to ethnic disparities in breast cancer incidence and survival. If there are ethnic-specific genetic factors that play a role in breast cancer predisposition, then family history of breast cancer may pose a different risk among different ethnic populations.

There is a paucity of studies evaluating the relationship between family history and breast cancer risk among Hispanic women. Overall, these studies suggest that family history does increase risk for breast cancer among Hispanic women; however, there are very few studies that specifically address whether family history poses a different risk when compared to NHW women. One of the earlier studies to evaluate this found lower familial aggregation of breast cancer among Hispanics when compared to NHW and African-Americans [8]. In the most recent and largest study, Li et al. [9] studied 712 women from the New Mexico Women's Health Study and concluded that Hispanic women appeared to have a slightly higher risk estimate associated with a positive family history, with an odds ratio (OR) of 1.7 [95% confidence intervals (CI): 1.1–2.5] when compared to an OR of 1.4 (95% CI: 1.0–2.0) for NHW women. In both ethnic groups, a higher risk was observed in premenopausal when compared with postmenopausal women, and among women diagnosed before age 50 when compared with women diagnosed at a later age. This difference by menopausal status and age was more pronounced among NHW women than Hispanic, suggesting that there may be differing patterns of risk associated with family history of breast cancer in the two ethnic groups. However, this study was unable to take into account the important factors such as family size and age of onset for family members.

To better characterize the ethnic-specific differences in breast cancer rates, we evaluated the association between family history and breast cancer risk among Hispanic and NHW women in the 4-Corners Breast Cancer Study. Among the few studies that have evaluated the relationship between family history of breast cancer and breast cancer risk among Hispanic

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women, this study represents the largest comparative study to assess the relationship among Hispanic and NHW women. This analysis will account for factors not considered in previous reports, such as the influence of both family size and age at onset of family members.

Materials and methods

Study population

Women aged 25–79 at diagnosis of breast cancer, or date of selection for controls, were recruited for a population-based case–control study of breast cancer conducted collaboratively in the 4-Corners region of the Southwest United States (Arizona, Colorado, New Mexico, and Utah) between 2000 and 2005. Cases were diagnosed between 1999 and 2002. Control subjects were selected at random from computerized drivers' license lists in New Mexico and Utah or from commercially available lists in Arizona and Colorado for ages up to 64 years; subjects aged 65 and older were selected from Center for Medicare Studies lists. Nearly one-third of the cohort is Hispanic by self-report. Complete selection and recruitment procedures for this study have been described in detail elsewhere [10]. Of all selected subjects, we were able to contact 75% of Hispanic cases, 66% of Hispanic controls, 85% of NHW cases, and 75% of NHW controls. Cooperation rates were 55% for Hispanic and 64% for NHW cases, and 35% for Hispanic and 47% in NHW controls. Participants and non-participants were similar with respect to characteristics influencing participation [11]. Each site received human subjects' research approval to recruit subjects and obtained written informed consent from each participant.

Data collection

A questionnaire was administered by a trained interviewer using computer-assisted personal interview software (see complete questionnaire at http://zorro.hrc.utah.edu/breast.html). Interviews were audio recorded for quality assurance. Information was obtained about diet, medical history, physical activity, menstrual history and use of hormones, pregnancy history, family history of cancer, and tobacco and alcohol exposures. Information was collected for the year prior to diagnosis for the cases and one year before the date of selection for controls.

Women were asked about first-degree family history of cancer during the 3-h, laptop administered in-home interview. They reported the current vital status and the age of the relative at cancer diagnosis. A first-degree relative is defined as a mother, father, sister, brother, son, or daughter (blood relation). Information about other potentially confounding variables in our analyses was collected during this same interview using methods described previously [10]. All data were collected retrospectively using the year prior to diagnosis as the referent year for cases, and the year prior to selection for controls. We excluded all secondary cases of primary breast cancer (n = 98 NHW and 48 Hispanic), women who did not know their family history (n = 51 NHW and 37 Hispanic), and women who did not self-report as being primarily of NHW or Hispanic ethnicity (n = 36). A total of nine women reported a family history among a male relative, and these women were included in the analysis. In total, the sample size for this analysis was 3074 NHW women (1,503 cases and 1,571 controls) and 1,647 Hispanic women (766 cases and 881 controls).

Statistical analyses

All statistical analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, NC). Chi-square tests and t-tests were initially utilized to compare characteristics between cases and controls among Hispanic and NHW 4-Corners participants. Univariate and multivariable logistic regression models were used to compute the ethnic-specific unadjusted and adjusted

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ORs and 95% CIs. The following potentially confounding variables were adjusted for in the multivariable models: parity (0, 1–2, 3–4, 5 or more children), age of first birth (<20, 20–24, 25–29, 30 years or more), body mass index at the date of diagnosis or referent year (<25, 25–29.9, 30 kg/m^2 or more), menopausal status at the date of diagnosis or referent year (pre, peri, postmenopausal), age (years, continuous), age of menarche (<12, 12, 13,>14 years old), center (AZ, CO, NM, UT), education (did not graduate from high school, high school graduate or equivalent, some college, bachelors degree, or higher) and number of first-degree female relatives (≤1, 2, 3, ≥4). Given that there were minimal missing data, values for individuals with missing data on these covariate variables were imputed based on group mean values and included in the analyses.

To take into account family size, the number of first-degree family members was determined by calculating the total number of female first-degree relatives who had lived to the age of 50 years old at the time of diagnosis or selection. Positive family history was defined as any first-degree relative who was diagnosed with breast cancer, which was acquired by self-report from participants. For all subgroup analyses (i.e., age, menopausal status, and family history), subgroups were determined according to participant characteristics at the time of diagnosis or selection. For all analyses stratified by menopausal status, premenopausal and perimenopausal women were combined into one group. We evaluated interactions with ethnicity by creating cross-product variables in ethnic-combined regression models. Univariate and multivariable logistic regression models were also used to evaluate the relationship between ethnicity and family history among cases and controls separately.

Results

The distributions of the study participants in this population-based case–control study with respect to study site, age, menopausal status, family history of breast cancer, and family size are listed in Table 1. Overall, the number of first-degree family members with breast cancer was higher in cases when compared to controls for both NHWs and Hispanics (Table 1). However, NHW cases were more likely to have at least one or more family members with breast cancer when compared to Hispanic cases (23.2 vs. 16.6%, respectively). NHW cases had a significantly smaller family size (number of first-degree female relatives) when compared to NHW controls, but no significant difference was observed for Hispanic women. When comparing the number of sisters or female relatives over the age of 50 among cases and controls, no significant difference was observed for either NHW or Hispanic women. Among both cases and controls, Hispanic women had a larger family size, higher number of first-degree female relatives over age 50 years, and higher number of sisters when compared to NHW women.

Individuals who did not know their family history were excluded from this analysis; however, there was no significant difference between cases and controls with respect to whether they knew about their family history among NHWs (1.4 vs. 1.8%, respectively, p = 0.41) or Hispanics (1.8 vs. 2.5%, respectively, p = 0.30). In addition, there were no significant differences in knowledge of family history when comparing breast cancer cases (p = 0.52) and controls (p = 0.22) by ethnic group.

We initially examined the relationship between having a family history of breast cancer among a first-degree family member and breast cancer risk among NHWs and Hispanics according to age and menopausal status at the time of case diagnosis (or control selection). Among women <50 years old, family history was associated with a significant increase in risk among NHW women only, with an OR of 2.34 (95% CI: 1.64–3.35) when compared to an OR of 1.32 (95% CI: 0.82–2.19) in Hispanics (Table 2). A comparable increase in risk was observed among women 50 years and older, with an OR of 1.69 (95% CI: 1.34–2.13)

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for NHW and 1.47 (95% CI: 1.03–2.10) for Hispanics. Similar results were observed when stratifying by menopausal status (pre versus post), where we observe a larger increase in risk for NHW women when compared to Hispanic women among premenopausal women only (data not shown). The difference in ORs between Hispanics and NHWs approached significance among premenopausal women ($p = 0.10$) when stratified based on menopausal status, and among women <50 years of age ($p = 0.08$) when stratified based on age.

Ethnic-specific risk estimates according to the age of the case as well as their diagnosed breast cancer relatives are also presented in Table 2. Among NHW women who were under the age of 50 years, the observed risk for breast cancer was higher for women with a family member who was diagnosed before the age of 50 years, with an OR of 3.02 (95% CI: 1.77–5.16) when compared to an OR of 1.96 (95% CI: 1.29–3.05) for those with a relative diagnosed at 50 years or older. However, the difference in risk estimates when comparing those with a relative who was diagnosed before 50 vs. after 50 years of age did not reach statistical significance ($p = 0.20$). Among younger Hispanic women, age of family member at breast cancer diagnosis was not associated with breast cancer risk, with an OR of 1.35 (95% CI: 0.72–2.52) for women with a family member who was diagnosed before the age of 50 years when compared to an OR of 1.49 (95% CI: 0.63–3.53) for those with a relative diagnosed at 50 years or older.

Among older NHW women (50 years or older), risk estimates did not differ based on the age of diagnosis for the relative, with an OR of 1.64 (95% CI: 1.09–2.47) for women with a family member who was diagnosed before the age of 50 years when compared to an OR of 1.72 (95% CI: 1.32–2.25) for those with a relative diagnosed at 50 years or older (Table 2). Among older Hispanic women, there was a modest difference based on the age of diagnosis for the relative, with an OR of 1.21 (95% CI: 0.70–2.08) for women with a family member who was diagnosed before the age of 50 years when compared to an OR of 1.74 (95% CI: 1.11–2.72) for those with a relative diagnosed at 50 years or older. However, this observed difference in risk based on age of relative diagnosis was not significant ($p = 0.28$).

Among both NHW and Hispanic women, there was no evidence of a difference in risk based on the number of first-degree relatives with breast cancer; however, the sample sizes were small for women with more than one affected first-degree relative (Table 3). Among NHW women, the ORs were 1.87 (95% CI: 1.53–2.28) for one affected first-degree relative and 1.71 (95% CI: 1.03–2.84) for two affected first-degree relatives when compared to no affected first-degree relatives. Among Hispanic women, the ORs were 1.34 (95% CI: 0.99–1.82) and 1.60 (95% CI: 0.77–3.33), respectively.

Discussion

Similar to other studies, our results suggest that family history of breast cancer is a risk factor for breast cancer among Hispanic women. However, these data also suggest that family history presents a different risk pattern among Hispanic when compared to NHW women. Specifically, among women who were <50 year old, having a family history of breast cancer was associated with a greater increase in risk among NHWs when compared to Hispanics. This difference in risk was not observed among women aged 50 years and older.

These findings suggest that family history, a well-recognized risk factor for breast cancer, may be a contributing factor to the relatively higher rates observed among NHW women. In the United States, the incidence rate of breast cancer among Hispanic women is approximately one-third less than that of NHW women. The population prevalence of known risk factors as a possible explanatory factor for racial and ethnic differences in breast cancer rates has been previously explored, along with differences in screening (prevalence

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and frequency) and treatment (quality and patterns of care) [3,6,12]. However, differences in rates remain even after considering these factors, which provide additional evidence of ethnic differences in the relationship between breast cancer risk factors and breast cancer risk [6,13].

The few comparative studies that have previously addressed whether family history poses a different magnitude of risk when compared to NHW women also suggest differing patterns of risk among ethnic groups. Bondy et al. [8] found lower familial aggregation of breast cancer among Hispanics when compared to NHW and African-Americans. In another population-based case–control study, Li et al. [9] also observed ethnic-differences in risk; however, their findings were not consistent with our findings. Overall, they found that Hispanic women appeared to have a slightly higher risk estimate associated with a positive family history when compared to NHW women. The conflicting results observed between our study and their study could be due to various factors. Our study had some advantages, such as a sample size that was over twice as large and the ability to account for other important factors such as family size and age of relative at diagnosis.

Overall, these results suggest that family history plays a larger role in the development of early-onset breast cancers among NHW women when compared with Hispanic women. The relationship between family history of breast cancer and breast cancer risk may be attributed to certain inherited genetic factors, shared environmental, and lifestyle factors, or a combination of both. Family history and early age at onset together are typically considered hallmarks of genetic risk. The ethnic differences we observed in family history risk estimates were observed among women with an age at onset under 50 years. This could suggest that the observed ethnic differences are more likely to be due to genetic differences in breast cancer risk.

It is unknown as to which genetic factors contribute to this difference by ethnicity. With respect to known hereditary breast cancer genes, the population prevalence of mutations in BRCA1 and BRCA2 has not been well documented among Hispanics. A recent study estimated the prevalence of BRCA1 mutations to be 3.5% (95% CI: 2.1–5.8%) in Hispanics, which was the higher than other ethnic minority populations [14]. Genetic testing in a group of high-risk Hispanic families at the City of Hope Medical Center in California found that 31% (34/110) had BRCA1/2 mutations [15]. In contrast, McKean-Cowdin et al. [16] concluded that mutations in genes other than BRCA contribute to risk of cancer in Hispanic families since many who had a family history did not have evidence of mutation. These inconsistent findings, along with our results, further support the notion that predictive models of genetic risk based on family history need to be validated in ethnic-specific cohorts.

There are several strengths to this study, such as our ability to account for a number of important factors (i.e., family size, age of onset for relatives, knowledge of family history, and other potential confounders), a large sample size and a considerable representation of Hispanic women. Our study also has limitations, such as the inability to consider second-degree family relatives. However, second-degree family history has recently been suggested as unnecessary in assessing breast cancer risk [17]. In addition, family history was collected by self-report, which could possibly introduce inaccuracies and a potential reporting bias by ethnicity. However, Ziogas and Anton-Culver [18] compared validity of reporting family history in population-based registries of breast, ovarian, and colorectal cancer probands and found a high reliability of reporting which did not vary by race or ethnicity. Similarly, there was no significant difference between cases and controls in this study with respect to whether they knew about their family history of breast cancer within each ethnic group, as well as when comparing cases and controls by ethnicity.

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Another limitation is the inherent possibility of participation bias in a case–control study design. A collaborative reanalysis of 52 epidemiological studies of primarily NHW women indicated that 12% of women with breast cancer had one affected relative and 1% had two or more [7]. In our study, 23.2% of NHW cases reported a family history of breast cancer, which could be higher because family history may have been more influential on participation due to the retrospective study design. Furthermore, we had limited power to evaluate certain subgroup interactions. Thus, further studies are warranted to confirm our findings.

In summary, our findings indicate that family history poses a greater risk for early-onset breast cancers among NHW when compared to Hispanic women. These results suggest that some of the predisposing genetic factors that contribute to the development of breast cancer may differ across ethnic populations.

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Table 1

Demographic characteristics of the 4-Corner's study population according to ethnicity and case–control status[a]

Characteristic	NHW			Hispanic		
	Cases (*n* = 1,503)	Controls (*n* = 1,571)	*p*[b]	Cases (*n* = 766)	Controls (*n* = 881)	*p*[b]
Center—*n* (%)						
Arizona	228 (15.2)	300 (19.1)	< .01	163 (21.3)	199 (22.6)	< .01
Colorado	314 (20.9)	292 (18.6)		161 (21.0)	192 (21.8)	
New Mexico	633 (42.1)	608 (38.7)		346 (45.2)	313 (35.5)	
Utah	328 (21.8)	371 (23.6)		96 (12.5)	177 (20.1)	
Age at diagnosis or selection—*n* (%)			< .01			< .01
< 50 years	523 (34.8)	525 (33.4)		344 (44.9)	333 (37.8)	
50–69 years	794 (52.8)	768 (48.9)		360 (47.0)	437 (49.6)	
70+ years	186 (12.4)	278 (17.7)		62 (8.1)	111 (12.6)	
Menopausal status—*n* (%)			.02			.02
Premenopausal	338 (22.5)	333 (21.2)		225 (29.4)	208 (23.6)	
Perimenopausal	188 (12.5)	153 (9.7)		94 (12.3)	108 (12.3)	
Postmenopausal	977 (65.0)	1085 (69.1)		447 (58.4)	565 (64.1)	
Number of first degree relatives with breast cancer—*n* (%)			< .01			.15
0	1,154 (76.8)	1,341 (85.4)		639 (83.4)	765 (86.8)	
1	311 (20.7)	201 (12.8)		110 (14.4)	101 (11.5)	
2 or more	38 (2.5)	29 (1.9)		17 (2.2)	15 (1.7)	
Average no. of first-degree female relatives—mean (SD)	3.6 (1.9)	3.7 (1.9)	< .01	5.1 (2.4)	5.3 (2.5)	.15
Average number of first-degree female relatives ≥50 years—mean (SD)	2.0 (1.3)	2.0 (1.4)	.69	2.4 (1.8)	2.5 (2.0)	.23
Average number of sisters—mean (SD)	0.9 (1.2)	1.0 (1.2)	.30	1.5 (1.63)	1.6 (1.8)	.13

[a] Women were excluded if they were secondary cases of primary breast cancer (*n* = 98 NHW and 48 Hispanic), or did not know their family history (*n* = 51 NHW and 37 Hispanic) or did not self-report as being primarily of NHW or Hispanic ethnicity (*n* = 36)

[b] *p* is based on the comparison between cases and controls among Hispanics or NHWs using a two-sided Chi-square test or *t*-test

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Table 2

Age-specific ORs for breast cancer among Hispanic and NHW women with at least one-first-degree relative with a history of breast cancer and according to relative's age at diagnosis of breast cancer[a]

Family history of breast cancer	Age at diagnosis < 50 years				Age at diagnosis ≥50 years			
	Case *n* (%)	Control *n* (%)	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Case *n* (%)	Control *n* (%)	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]
NHW								
No	401 (77)	463 (88)	1.00 (reference)	1.00 (reference)	753 (77)	878 (84)	1.00 (reference)	1.00 (reference)
Yes	122 (23)	62 (12)	2.27 (1.63–3.17)	2.34 (1.64–3.35)	227 (23)	168 (16)	1.58 (1.26–1.97)	1.69 (1.34–2.13)
Relative diagnosed < 50 years	56 (11)	23 (4)	2.81 (1.70–4.65)	3.02 (1.77–5.16)	60 (6)	47 (5)	1.49 (1.00–2.21)	1.64 (1.09–2.47)
Relative diagnosed > 50 years	66 (13)	39 (7)	1.95 (1.29–2.97)	1.96 (1.29–3.05)	163 (17)	116 (11)	1.64 (1.27–2.12)	1.72 (1.32–2.25)
Hispanic								
No	299 (87)	299 (90)	1.00 (reference)	1.00 (reference)	340 (81)	466 (85)	1.00 (reference)	1.00 (reference)
Yes	45 (13)	34 (10)	1.32 (0.82–2.13)	1.32 (0.82–2.19)	82 (19)	82 (15)	1.37 (0.98–1.92)	1.47 (1.03–2.10)
Relative diagnosed < 50 years	30 (9)	22 (7)	1.36 (0.77–2.42)	1.35 (0.72–2.52)	29 (7)	34 (6)	1.17 (0.70–1.96)	1.21 (0.70–2.08)
Relative diagnosed > 50 years	15 (4)	10 (3)	1.50 (0.66–3.39)	1.49 (0.63–3.53)	52 (12)	46 (8)	1.55 (1.02–2.36)	1.74 (1.11–2.72)

[a] Women were excluded if they were secondary cases of primary breast cancer (*n* = 98 NHW and 48 Hispanic), or did not know their family history (*n* = 51 NHW and 37 Hispanic) or did not self-report as being primarily of NHW or Hispanic ethnicity (*n* = 36)

[b] OR and 95% CI from an unadjusted, unconditional logistic regression model

[c] OR and 95% CI from an unconditional logistic regression model adjusted for center (Arizona, Colorado, New Mexico, Utah), age (years, continuous), menopausal status at date of diagnosis or referent year (pre, peri, postmenopausal), parity (0, 1–2, 3–4, 5 or more children), age of first birth (<20, 20–24, 25–29, 30 years or more), body mass index at date of diagnosis or referent year (<25, 25–29.9, 30 kg/m^2 or more), age of menarche (<12, 12, 13, ≥14 years old), education (did not graduate from high school, high school graduate or equivalent, some college, bachelors degree or higher), and number of first-degree female relatives 50 years of age or older (≤1, 2, 3, ≥4)

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Table 3

Ethnic-specific ORs for breast cancer based on number of first degree relatives with a history of breast cancer[a]

Number of first-degree relatives with breast cancer	NHW				Hispanic			
	Case *n* (%)	Control *n* (%)	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]	Case *n* (%)	Control *n* (%)	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]
None	1154 (77)	1341 (85)	1.0 (reference)	1.0 (reference)	639 (84)	765 (87)	1.0 (reference)	1.0 (reference)
One	311 (20)	201 (13)	1.80 (1.48–2.18)	1.87 (1.53–2.28)	110 (14)	101 (11)	1.30 (0.98–1.74)	1.34 (0.99–1.82)
Two or more	38 (3)	29 (2)	1.52 (0.93–2.49)	1.71 (1.03–2.84)	17 (2)	15 (2)	1.36 (0.67–2.74)	1.60 (0.77–3.33)

[a] Women were excluded if they were secondary cases of primary breast cancer (n = 98 NHW and 48 Hispanic), or did not know their family history (n = 51 NHW and 37 Hispanic), or did not self-report as being primarily of NHW or Hispanic ethnicity (n = 36)

[b] OR and 95% CI from an unadjusted, unconditional logistic regression model

[c] OR and 95% CI from an unconditional logistic regression model adjusted for center (Arizona, Colorado, New Mexico, Utah), age (years, continuous), menopausal status at date of diagnosis or referent year (pre, peri, postmenopausal), parity (0, 1–2, 3–4, 5 or more children), age of first birth (<20, 20–24, 25–29, 30 years or more), body mass index at date of diagnosis or referent year (<25, 25–29.9, 30 kg/m^2 or more), age of menarche (<12, 12, 13, ≥14 years old), education (did not graduate from high school, high school graduate or equivalent, some college, bachelors degree or higher) and number of first-degree female relatives 50 years of age or older (≤1, 2, 3, ≥4)

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