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ORIGINAL PAPER

ADRB2 G–G haplotype associated with breast cancer risk among Hispanic and non-Hispanic white women: interaction with type 2 diabetes and obesity

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Abstract
Introduction Polymorphisms in the beta-2-adrenergic receptor (*ADRB2*) gene have been studied in relation to risk of type 2 diabetes and obesity, risk factors that have received increased attention in relation to breast cancer. We evaluated the hypothesis that *ADRB2* variants (rs1042713, rs1042714) are associated with breast cancer risk in non-Hispanic white (NHW) and Hispanic (H) women using data from a population-based case–control study conducted in the southwestern United States.
Methods Data on lifestyle and medical history, and blood samples, were collected during in-person interviews for incident primary breast cancer cases (1,244 NHW, 606 H) and controls (1,330 NHW, 728 H). *ADRB2* genotypes for rs1042713(G/A) and rs1042714(G/C) were determined using TaqMan assays. The associations of each variant and corresponding haplotypes with breast cancer were estimated using multivariable logistic regression.
Results Two copies compared to one or zero copies of the *ADRB2 G–G* haplotype were associated with increased breast cancer risk for NHW women [odds ratio (OR), 1.95; 95 % confidence interval (95 % CI), 1.26–3.01], but with reduced risk for H women [OR, 0.74; 95 % CI, 0.50–1.09]. Effect estimates were strengthened for women with a body mass index (BMI) $\geq$25 kg/m^2 [H: OR, 0.50; 95 % CI, 0.31–0.82; NHW: OR, 3.85; 95 % CI, 1.88–7.88] and for H women with a history of diabetes [H: OR, 0.32; 95 % CI, 0.12–0.89].
Conclusions These data suggest that ethnicity modifies the association between the *ADRB2 G–G* haplotype and breast cancer risk, and being overweight or obese enhances the divergence of risk between H and NHW women.

Keywords Breast cancer · Hispanic · Beta-2-adrenergic receptor · Haplotypes · Obesity · Diabetes

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Introduction

Obesity has been reported to be positively associated with risk for breast cancer in postmenopausal women [1–4]. The association in premenopausal women is less certain, although some studies report an inverse association [1, 5]. Type 2 diabetes is an obesity-related disease that may be associated with 10–20 % excess risk of breast cancer [6]. Given these associations, it is plausible to suspect that genetic factors related to obesity and type 2 diabetes may influence breast cancer risk. Hispanics in the southwestern United States are reported to have an increased prevalence of type 2 diabetes and obesity [7–9], but paradoxically are

at lower risk for breast cancer than non-Hispanic white women [10]. A different distribution of genetic factors associated with diabetes and obesity may influence this ethnic disparity in breast cancer risk.

The '4-Corners Breast Cancer Study' (4-CBCS) is a population-based case–control study of breast cancer in Hispanic and non-Hispanic white (NHW) women between the ages of 25 and 79 living in Arizona, Colorado, New Mexico, and Utah. The study was designed to investigate the differences between Hispanic/American Indian and NHW women for breast cancer risk factors, including genetic variants hypothesized to influence energy balance and obesity through estrogen and insulin-related pathways [11]. The present analysis evaluated the associations of the beta-2-adrenergic receptor (*ADRB2*) SNPs rs1042713 and rs1042714 with risk of breast cancer. We also sought to determine any statistical interactions between these SNPs and their haplotypes with ethnicity, diabetes, and obesity.

ADRB2, located on chromosome 5q31-q32, consists of a single exon of 2,015 nucleotides, encoding a 413 amino acid protein for the beta-2-adrenergic receptor. The beta-2-adrenergic receptor is a member of the G-protein-coupled adrenergic receptor family and functions in adipose tissue by stimulating lipolysis, which affects lipid mobilization within human fat cells and the regulation of energy expenditure [12]. The two most common polymorphisms found within *ADRB2* code for amino acid changes at positions 16 [arginine to glycine-Arg16Gly (rs1042713)] and 27 [glutamic acid to glutamine-Glu27Gln (rs1042714)] [13]. These polymorphisms are reported to be associated with the risk of diabetes [14, 15] and may play a role in obesity risk [16–20]. However, recent literature has documented mixed findings for obesity [19, 21, 22], and *ADRB2* polymorphisms are thought to influence risk of diabetes independent of obesity [14].

To date, only two epidemiologic studies have examined the association of genetic variation in *ADRB2* with breast cancer risk among postmenopausal breast cancer [23, 24] and neither included Hispanic women. Huang et al. reported a non-statistically significant inverse association (OR 0.67, 95 % CI 0.38–1.18) between rs1042714 Glu vs. Gln/Gln in a case–control study of Japanese women [23]. A report from the American Cancer Society Cancer Prevention Study II Nutrition Cohort did not detect any statistically significant associations for four *ADRB2* tag SNPs among postmenopausal women [24].

Methods

The data for this study are drawn from the 4-CBCS: study methods have been previously described [25–28]. Cases were ascertained through the statewide surveillance epidemiology and end results (SEER) tumor registries in Utah and New Mexico and the Center for Disease Control and Prevention National Program of Cancer Registries in Colorado and Arizona. All primary incident cases diagnosed with in situ or invasive breast cancer (ICDO sites C50.0-C50.6 and C50.8-C50.9) between October 1999 and May 2004 and with histological confirmation were eligible. Registries provided information on clinical characteristics, including estrogen and progesterone receptor tumor status. The Generally Useful Ethnic Search System (GUESS) program was utilized to initially identify eligible Hispanic women by surname [29].

Controls under the age of 65 years were randomly selected from commercial mailing lists in Arizona and Colorado and from driver's license lists in New Mexico and Utah. Controls 65 years of age and older were randomly selected from the Center for Medicare Services (CMS) lists in all four states. Controls were frequency-matched to cases on ethnicity and 5-year age groups.

All participants signed informed written consent prior to participation. Human Subjects Institutional Review Boards approved the study at each institution. Sixty-eight percent of the eligible women contacted completed the study protocol, for a total of 2,325 cases (798 H; 1,527 NHW) and 2,616 controls (945 H; 1,671 NHW) [26]. Data for diet and lifestyle risk factors were collected by trained and certified interviewers using computerized questionnaires as previously reported [26]. The 'referent period' was the year prior to date of diagnosis for cases and date of selection for controls. Information was collected for medical history and medication use, reproductive history, family history, diet, physical activity, use of tobacco and alcohol, height, weight history, and other lifestyle factors.

Body mass index (BMI) was calculated as weight in kilograms/height in m^2 and categorized according to WHO criteria (<25 as normal; 25–29.9 as overweight; 30+ as obese). An extensive diet history questionnaire was used that included foods from the southwestern area of the United States [26]. A modified version of the Cross Cultural Activity Participation Survey (CAPS) [30] was used to collect data for physical activity at home, work, and during leisure, by intensity and frequency, during referent year and at ages 15, 30, and 50. Total MET minutes of activity were calculated and reported as MET values [26, 31].

Menopausal status on the referent date was coded based on an algorithm previously described [26]. 'Recent hormone exposure' was defined as HRT use or pre- or perimenopausal status during the 2 years prior to the referent date. Diabetes history was categorized by the following self-reported responses—'Yes,' 'borderline,' or 'No'—based upon the question 'Ever told before *referent date* that you had diabetes or high blood sugar?' [26].

Blood samples were collected and DNA extracted for approximately 75 % of participants, except for those in Utah (94 %). Fifteen markers were used to characterize genetic admixture based on a two-population model that included European and Native ancestry using the program STRUCTURE 2.0 [11, 32, 33], as previously reported [11]. *ADRB2* SNPs were assayed using TaqMan assays (Applied Biosystems, Foster City, CA, USA). Each 5-μl reaction contained 20 ng of genomic DNA, primers, probes, and TaqMan Universal PCR Master Mix (containing AmpErase UNG, AmpliTaq Gold enzyme, dNTPs, and reaction buffer). PCR was carried out under the following conditions: 50 °C for 2 min to activate UNG, 95 °C for 10 min, followed by 40 cycles of 92 °C for 15 s, and 60 °C for 1 min using 384-well duel-block ABI 9700 PCR machines. Fluorescent endpoints of the TaqMan reactions were measured using an ABI 7900HT sequence detection instrument. For quality control measures, a portion of the sample was analyzed in duplicate with the study samples that did not yield quality readings. Overall, rs1042713 and rs1042714 had high genotyping success rates among the eligible sample population (97.8 and 98.3 %, respectively), and the proportion missing for rs1042713 and rs1042714 was 0.022 and 0.017, respectively.

ADRB2 rs1042713 genotypes were defined as *GG*, *GA*, and *AA*, and rs1042714 as *CC*, *CG*, and *GG*. The homozygous wild types were used as the referent categories. Dominant and recessive model associations were evaluated as well as haplotypes between the SNPs. Genotype distributions were evaluated for agreement with Hardy–Weinberg equilibrium (HWE) by the Pearson χ^2 test among controls. Descriptive statistics were calculated for all covariates, and p values for t tests and χ^2 tests were reported. Genotype distributions were calculated by case versus control status and stratified by ethnicity; p values were calculated by the Mantel–Haenszel χ^2 test for significant differences between groups. Haplotype analysis was conducted, and probability scores for haplotype combinations were included in the regression models. Haplotype probabilities were categorized into probability-weighted dosage variables for each subject [34, 35].

Genotype and haplotype associations were estimated as crude odds ratios (ORs) with 95 % confidence intervals (CIs) by unconditional logistic regression. Significant associations, using a threshold for statistical significance of a p value <0.05, were then adjusted for potential confounders using multivariable logistic regression models [36]. Covariates were considered potential confounders if their univariate p values for association with breast cancer were ≤ 0.20, and their inclusion produced a change in the point estimate for the main effects of the *ADRB2* genotypes/haplotypes of ≥ 10 % [37]. Covariates considered included center, BMI, menopausal status, diabetes history, percentage of genetic admixture, height, parity, aspirin use, family history, age at menarche, recent hormone therapy use, physical activity, calories consumed per day, and smoking status.

Modification of the genotype/haplotype effects by ethnicity, BMI, and diabetes was modeled as multiplicative interactions in the multivariable logistic regression analyses [38]. The statistical significance of the interactions was evaluated using the difference in maximum likelihood estimates, which has a χ^2 distribution with two degrees of freedom. All statistically significant p values were adjusted for multiple comparisons using the Bonferroni-adjusted p value method [39]. We considered adjusted p values of 0.15 or less as potentially important for interaction tests. All data analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

A total of 2,574 NHW (1,244 cases, 1,330 controls) and 1,334 Hispanic women (606 cases, 728 controls) were included in the analyses. Hispanic women were significantly different from NHW for all variables, with the exception of recent estrogen use. The majority of women were older than 50 years at the time of diagnosis. Hispanic cases were slightly, but significantly ($p = 0.03$), younger (52.6 years) than their controls (54.0 years; Table 1). Average BMI was higher in Hispanics than NHW. Hispanic cases were slightly less overweight than their controls ($p = 0.01$). There was a total of 404 (H: 200; NHW: 204) women with diabetes and 70 women with borderline disease (H: 33; NHW 37). A larger proportion of Hispanics were diabetic or borderline diabetic than NHW women.

Both *ADRB2* polymorphisms were in HWE in each ethnic group (rs1042713 H: p value $= 0.96$, NHW: p value $= 0.41$ and rs1042714 H: p value $= 0.92$, NHW: p value $= 0.39$). Three haplotypes were identified with frequencies estimated as follows: *A–G* (0.392); *G–C* (0.362); *G–G* (0.246). Although ethnic groups differed significantly in the frequency of both *ADRB2* polymorphisms, genotype proportions did not differ by case–control status within ethnic groups (Table 2). Hispanics had a slightly higher proportion of the rs1042713 *AA* genotype compared to NHW, while NHW women had a higher proportion of the rs1042714 *CC* genotype. About 65 % of NHW women had 0 copies of the *G–G* haplotype compared to 45 % of Hispanics, and about 60 % of Hispanics had 0 copies of the *G–C* haplotype compared to 35 % of NHW.

Table 3 reports results for the crude associations of *ADRB2* polymorphisms and haplotypes with breast cancer risk by ethnicity. The *ADRB2* polymorphisms were not associated with breast cancer risk. While none of the three

Table 1 Characteristics of study population, stratified by ethnicity and case–control status, 4-CBCS, 1999–2004 ($n = 3{,}908$)

	Non-Hispanic white ($n = 2{,}574$)					Hispanic ($n = 1{,}334$)					p value[b]
	Case		Control		p value[a]	Case		Control		p value[a]	
	No.	Percentage	No.	Percentage		No.	Percentage	No.	Percentage		
Total subjects	1,244		1,330			606		728			
Center					0.08					0.33	<0.001
Arizona	171	13.6	263	19.8		123	20.3	164	22.5		
Colorado	257	20.7	218	16.4		120	19.8	132	18.1		
New Mexico	494	39.7	496	37.3		263	43.4	251	34.5		
Utah	322	25.9	353	26.5		100	16.5	181	24.9		
Education level					0.21					0.05	<0.001
High school or less	310	24.9	353	26.5		348	57.4	390	53.6		
Some college	459	36.9	499	37.5		172	28.4	203	27.9		
Bachelor degree/higher	475	38.2	478	35.9		86	14.2	135	18.5		
Parity					<0.001					0.07	<0.001
Nulliparous	210	16.9	188	14.1		57	9.4	70	9.6		
1–2	543	43.7	541	40.7		247	40.8	251	34.5		
3–4	400	32.2	458	34.4		217	35.8	285	39.2		
5+	91	7.3	143	10.8		85	14.0	122	16.8		
Menopausal status					0.07					0.20	<0.001
Pre-/peri-menopausal	430	34.6	415	31.2		243	40.1	267	36.7		
Post-menopausal	814	65.4	915	68.8		363	59.9	461	63.3		
Recent estrogen use[c]					0.04					0.23	0.1043
Yes	992	79.7	1,016	76.4		468	77.2	542	74.5		
No	252	20.2	314	23.6		138	22.8	186	25.6		
Family history, 1st degree					<0.001					0.01	0.0045
Yes	277	22.5	201	15.4		107	18.0	90	12.7		
No	952	77.5	1,106	84.6		486	82.0	617	87.3		
Diabetes history					0.42					0.71	<0.001
Yes	91	7.3	113	8.5		90	14.9	110	15.1		
Borderline	22	1.8	15	1.1		12	2.0	21	2.9		
No	1,130	91.0	1,200	90.4		504	83.2	596	82.0		
Body mass index (kg/m^2)[d]					0.30					0.06	<0.001
<25	578	46.5	601	45.4		198	32.7	204	28.1		
25–29.9	370	29.7	379	28.6		212	35.0	259	35.7		
30+	296	23.8	345	26.0		196	32.3	263	36.2		

Table 1 continued

	Non-Hispanic white (n = 2,574)					Hispanic (n = 1,334)					p value[f]
	Case		Control		p value[e]	Case		Control		p value[e]	
	Mean	(sd)	Mean	(sd)		Mean	(sd)	Mean	(sd)		
Age (years)	55.4	11.0	56.2	12.2	0.09	52.6	11.1	54.0	12.0	0.03	<0.001
Body mass index (kg/m^2)[c]	26.8	6.0	27.0	6.2	0.62	28.1	6.0	29.0	6.2	0.01	<0.001
Total METs (minutes/week)	1,430	1,738	1,486	1,816	0.43	1,312	1,940	1,233	1,754	0.44	0.002
Calories (kilocalories)	2,180	1,032	2,101	984	0.05	2,737	1,414	2,684	1,439	0.50	<0.001

Percentages may not add up to 100 due to rounding

METs metabolic equivalent for task

[a] Case–control comparison within ethnicity. Mantel–Haenszel χ^2 p values from χ^2 tests

[b] Ethnic group comparison, regardless of case–control status. Mantel–Haenszel χ^2 p values from χ^2 tests

[c] Recent hormone exposure, within 2 years of referent year (1 year prior to date of diagnosis for cases and 1 year prior to date of selection for controls)

[d] Body mass index (BMI) calculated as kilograms (kg)/meters (m)^2

[e] Case–control comparison within ethnic group. p values from t tests

[f] Ethnic group comparison, regardless of case–control status. p values from t tests

ADRB2 haplotypes were associated with breast cancer risk for the total sample, having two copies of the *G–G* haplotype compared to zero copies had a statistically significant positive association in NHW women (OR 1.84, 95 % CI 1.18–2.84; Table 3). In contrast, there was a non-significant inverse association in Hispanic women (OR 0.85, 95 % CI 0.58–1.24). The dominant model was not significantly associated with breast cancer for the total sample or by ethnic group. However, the recessive model of '0 + 1 vs. 2' had a stronger crude association with breast cancer risk among NHW women (OR 1.92, 95 % CI 1.25–2.97; Table 3). The magnitude of the associations did not change meaningfully in the Hispanics.

Neither of the *ADRB2* polymorphisms were associated with the hypothesized interaction effects with ethnicity, diabetes, and BMI; however, the interaction between ethnicity and the *G–G* haplotype was statistically significant (p value = 0.004). An ethnic by haplotype variable was constructed to further examine the joint association between ethnicity and the *G–G* haplotype in the recessive model, adjusting for potential confounders including center, BMI at referent year, menopausal status, history of diabetes, and genetic admixture. There was a positive association between the *G–G* haplotype in the recessive model and breast cancer risk among NHW (OR 1.95, 95 % CI 1.26–3.01; Table 4). Although the inverse association observed for Hispanics was not statistically significant (OR 0.74, 95 % CI 0.50–1.09), the heterogeneity test for difference between ethnic groups was significant (p = 0.004; p adj = 0.012) (Table 4). A significant inverse association was observed for Hispanics with two copies of the *G–G* haplotype (OR 0.32, 95 % CI 0.12–0.89) compared to NHW (OR 4.71, 95 % CI 0.50–44.56) among women with a history of diabetes or borderline disease (Table 5). In contrast, the respective odds ratios in women without diabetes or borderline disease were 0.90 (95 % CI 0.59–1.39) for Hispanics and 1.86 (95 % CI 1.19–2.92) for NHW. The multiplicative two-way interaction with history of diabetes was also significant when modeled as an interaction with the *G–G* haplotype (p = 0.025; p adj = 0.075). The three-way multiplicative interaction between the ethnic-specific haplotype and diabetes, however, was not statistically significant (p for interaction = 0.137), likely due to the small cell sizes. Results were comparable with the exclusion of subjects with borderline disease from the stratified analyses. Overweight and obese NHW women (BMI ≥25 kg/m^2) with two copies of the *G–G* haplotype had an increased risk of breast cancer (OR 3.85, 95 % CI 1.88–7.88) while Hispanics had a reduced risk (OR 0.50, 95 % CI 0.31–0.82; Table 5). The respective odds ratios in normal-weight women were 1.12 (95 % CI 0.62–2.01) in NHW and 1.73 (95 % CI 0.86–3.52) in Hispanics. The two-way multiplicative interaction effect between obesity and the *G–G* haplotype was not statistically

Table 2 Genotype characteristics of study population, stratified by ethnicity and case–control status, 4-CBCS, 1999–2004 ($n = 3{,}908$)

	Non-Hispanic white ($n = 2{,}574$)					Hispanic ($n = 1{,}334$)					p value[b]
	Case		Control		p value[a]	Case		Control		p value[a]	
	No.	Percentage	No.	Percentage		No.	Percentage	No.	Percentage		
Total subjects	1,244		1,330			606		728			
ADRB2 (rs1042713) genotype											
G/G, homozygous wild type	499	41.3	520	39.8	0.90	180	30.5	236	33.0	0.41	<0.001
G/A, heterozygous	535	44.3	613	46.9		296	50.1	346	48.3		
A/A, homozygous variant	174	14.4	173	13.3		115	19.5	134	18.7		
ADRB2 (rs1042714) genotype											
G/G, homozygous wild type	403	33.0	427	32.6	0.62	359	60.4	415	58.0	0.50	<0.001
G/C, heterozygous	591	48.4	629	48.0		202	34.0	263	36.7		
C/C, homozygous variant	226	18.5	255	19.5		33	5.6	38	5.3		
Haplotype *A–G*, copy number											
0	539	43.3	548	41.2	0.67	197	32.5	250	34.3	0.54	<0.001
1	531	42.7	609	45.8		294	48.5	344	47.3		
2	174	14.0	173	13.0		115	19.0	134	18.4		
Haplotype *G–G*, copy number											
0	815	65.5	851	64.0	0.77	275	45.4	330	45.3	0.65	<0.001
1	371	29.8	446	33.5		275	45.4	319	43.8		
2	58	4.7	33	2.5		56	9.2	79	10.9		
Haplotype *G–C*, copy number											
0	440	35.4	452	34.0	0.40	374	61.7	429	58.9	0.43	<0.001
1	578	46.5	623	46.8		199	32.8	261	35.9		
2	226	18.2	255	19.2		33	5.5	38	5.2		

Percentages may not add up to 100 due to rounding

ADRB2 adrenergic beta-2 receptor polymorphism

[a] Case–control comparison within ethnic group. *Mantel–Haenszel* χ^2 p values from χ^2 tests

[b] Ethnic group comparison, regardless of case–control status. *Mantel–Haenszel* χ^2 p values from χ^2 tests

significant ($p = 0.248$); however, the three-way interaction with the ethnic-specific haplotype and obesity was statistically significant ($p = 0.035$; p adj $= 0.105$).

Discussion

The aim of this analysis was to determine the associations of genetic variation in *ADRB2* (SNPs rs1042713, rs1042714) with breast cancer risk and to test for the presence of effect modification by ethnicity, diabetes, and BMI status. We did not find evidence for a direct association of these SNPs with breast cancer risk, but detected a significant recessive association for the *G–G* haplotype among NHW women. Further analysis revealed a statistically significant interaction between ethnicity and two copies of the *G–G* haplotype with increased risk in NHW and decreased risk in Hispanic women. This interaction was further enhanced in women that were overweight/obesity.

Cagliani et al. [40] concluded that the structure of the *ADRB2* haplotypes warranted the need for association studies and that these studies would benefit from identification of an ethnic-specific haplotype. This recommendation was based on evidence for ethnic-specific differences among five human populations from the National Institute of Environmental Health Sciences (NIEHS) SNPs Program [40]. Subsequently, we constructed haplotypes and tested associations and modifications of breast cancer risk and found ethnic differences. The complexity of the *ADRB2*-inferred haplotypes could be attributed to either the gene having been subjected to balancing selection or having undergone a selective sweep [40].

Variation within the promoter region of the *ADRB2* polymorphisms has been identified in a previous report [40]. For Europeans, all chromosomes carrying the Arg16 ('A' allele for rs1042713) and Gln27 ('C' allele for rs1042714) alleles display the same promoter structure; but in all other populations, the coding variants for haplotypes are split into two groups and have different alleles in their

Table 3 Univariable odds ratios (OR) and 95 % confidence intervals (CI) for *ADRB2* polymorphisms, 4-CBCS, 1999–2004 ($n = 3{,}908$)

Polymorphisms/haplotypes	Total ($n = 3{,}908$)			Non-Hispanic white ($n = 2{,}574$)		Hispanic ($n = 1{,}334$)	
	OR	95 % CI	*p* value	OR	95 % CI	OR	95 % CI
ADRB2 (rs1042713)							
GG	1.00	–		1.00	–	1.00	–
GA	0.97	0.84–1.11	0.38	0.91	0.77–1.08	1.12	0.88–1.44
AA	1.05	0.87–1.27	0.47	1.05	0.82–1.34	1.13	0.82–1.54
ADRB2 (rs1042713)							
GG	1.00	–		1.00	–	1.00	–
GA or *AA*	0.99	0.86–1.12	0.82	0.94	0.80–1.10	1.12	0.89–1.42
ADRB2 (rs1042714)							
GG	1.00	–		1.00	–	1.00	–
GC	0.98	0.86–1.13	0.93	1.00	0.83–1.19	0.89	0.70–1.12
CC	0.98	0.81–1.19	0.87	0.94	0.75–1.18	1.00	0.62–1.63
ADRB2 (rs1042714)							
GG	1.00	–		1.00	–	1.00	–
GC or *CC*	0.98	0.83–1.12	0.77	0.98	0.83–1.16	0.90	0.72–1.13
Haplotype *A–G*, copy number							
0	1.00	–		1.00	–	1.00	–
1	0.94	0.81–1.08	0.28	0.89	0.75–1.05	1.08	0.85–1.38
2	1.02	0.85–1.23	0.56	1.02	0.80–1.30	1.09	0.80–1.49
Continuous *A–G*	0.99	0.91–1.09	0.89	0.98	0.87–1.09	1.05	0.90–1.22
Haplotype *G–C*, copy number							
0	1.00	–		1.00	–	1.00	–
1	0.95	0.83–1.09	0.69	0.95	0.80–1.13	0.88	0.69–1.10
2	0.96	0.79–1.16	0.83	0.91	0.73–1.14	1.00	0.61–1.62
Continuous *G–C*	0.97	0.89–1.06	0.52	0.95	0.86–1.06	0.93	0.78–1.12
Haplotype *G–G*, copy number							
0	1.00	–		1.00	–	1.00	–
1	0.92	0.80–1.05	0.12	0.87	0.73–1.03	1.03	0.82–1.30
2	1.10	0.84–1.45	0.30	1.84	1.18–2.84	0.85	0.58–1.24
Continuous *G–G*	0.98	0.88–1.09	0.67	1.02	0.89–1.17	0.96	0.82–1.13
G–G, dominant model, copy number							
0	1.00	–		1.00	–	1.00	–
1 + 2	0.94	0.83–1.07	0.33	0.94	0.80–1.10	1.00	0.80–1.24
G–G, recessive model, copy number							
0 + 1	1.00	–		1.00	–	1.00	–
2	1.14	0.87–1.49	0.34	1.92	1.25–2.97	0.84	0.58–1.20

promoter regions, suggesting different transcriptional activity [40]. This difference in transcriptional activity could influence the ethnic differences observed for the association of the *G–G* haplotype with breast cancer in the present study; a possible explanation of these observations could be attributed to an unmeasured non-European allele of Native American ancestry in the promoter region of *ADRB2*.

The ethnic differences observed in the present results echo those from previous publications for genetic-association studies with breast cancer risk from the 4-CBCS [27, 28, 41]. Slattery et al. [28] examined the relationship between *IGF1*, *IRS-1*, *IRS-2*, and *IGFBP3* and breast cancer risk and found an increased risk of breast cancer among post-menopausal Hispanic women not recently exposed to hormones with the R allele of the G972R *IRS1* polymorphism; however, this effect was not found for NHW women. Conversely, post-menopausal NHW women not recently exposed to hormones showed an increased risk of breast cancer with the *IGF-1* 19 CA polymorphism, while there was no association among

Table 4 Interaction between ethnicity and *ADRB2 G–G* haplotype (model 0 + 1 vs. 2), 4-CBCS, 1999–2004 ($n = 3{,}908$)

ADRB2 G–G haplotype copy number	Non-Hispanic white ($n = 2{,}574$) OR (95 % CI)	Hispanic ($n = 1{,}334$) OR (95 % CI)	$p^{a}_{heterogeneity}$	p^{b}_{adj}
0 or 1	Referent	0.87 (0.71–1.08)	0.004	0.012
2	1.95 (1.26–3.01)	0.74 (0.50–1.09)		

Odds ratios (OR) and 95 % confidence intervals (CI) adjusted for center, BMI at referent yr., menopausal status, history of diabetes, and genetic admixture

[a] *P* value for heterogeneity test difference between NHW and Hispanic women

[b] Bonferroni-adjusted *p* value

Table 5 Enhancement of interaction between *ADRB2 G–G* haplotype (model 0 + 1 vs. 2) and ethnicity by history of diabetes and BMI status, 4-CBCS, 1999–2004 ($n = 3{,}908$)

ADRB2 G–G haplotype copy number	Non-Hispanic white ($n = 2{,}574$)		Hispanic ($n = 1{,}334$)		$p_{interaction}$	p^{d}_{adj}
	OR	95 % CI	OR	95 % CI		
Diabetes, yes[a]						
0 or 1	1.00	–	0.88	0.47–1.62	0.025[b]	0.075
2	4.71	0.50–44.56	0.32	0.12–0.89	0.137[c]	
Diabetes, no						
0 or 1	1.00	–	0.87	0.70–1.08		
2	1.86	1.19–2.92	0.90	0.59–1.39		
Overweight or obese (BMI $\geq$25 kg/m^2)						
0 or 1	1.00	–	0.87	0.66–1.14	0.248[b]	
2	3.85	1.88–7.88	0.50	0.31–0.82	0.035[c]	0.105
Normal weight (BMI <25 kg/m^2)						
0 or 1	1.00	–	0.89	0.64–1.23		
2	1.12	0.62–2.01	1.73	0.86–3.52		

Odds ratios (OR) and 95 % confidence intervals (CI) adjusted for center, menopausal status, genetic admixture, and either BMI at referent year or history of diabetes, depending on model

[a] History of diabetes includes borderline disease for test of effect modification

[b] *p* value for multiplicative two-way interaction between diabetes or obesity status with the *G–G* haplotype

[c] *p* value for multiplicative three-way interaction between diabetes or obesity status with the ethnic-specific haplotype

[d] Bonferroni-adjusted *p* value

Hispanics [28]. Our findings further support the hypothesis that variation in genes-regulating energy balance and susceptibility to obesity leads to ethnic differences in breast cancer risk. Nonetheless, the underlying mechanism for ethnic differences between Hispanic and NHW women for breast cancer remains to be established. As previously hypothesized, there is the possibility of unmeasured genetic variants in or near these genes, such as *ADRB2*, that could directly affect metabolism. Lai et al. [42] have suggested that a variety of other factors may operate, including differences in exposure to environmental mutagens or endogenous factors, or in host reactions to breast cancer carcinogens or unidentified oncogenes and/or tumor suppressor genes.

Although both *ADRB2* genotypes and haplotypes were assessed in an effort to identify additional genetic risk factors in the etiology of breast cancer, knowledge is limited as to the functionality of the *ADRB2* gene and its haplotypes and how they relate to the biological mechanisms associated with breast cancer. Biological studies in breast cancer cell lines have indicated a carcinogenic role for the beta-2-adrenergic receptors through the over-expression of the arachidonic acid-metabolizing enzymes cyclooxygenase-2 and lypoxygenases [43]. Arachidonic acid (AA) metabolism can produce mutagens that damage DNA and cause mutations. It has also been found that modulation of pathways for the AA-metabolizing enzymes cyclooxygenase-2 and lypoxygenases can result in suppression of tumor growth [44]. Biological evidence of this carcinogenic mechanism has been found for adenocarcinomas of the lungs, pancreas, and colon, all of which have demonstrated over-expression of the arachidonic-metabolizing enzymes, presumably under beta-adrenergic control [43, 45]. Plummer et al. [45] hypothesized that the beta-adrenergic regulation of the AA-mediated signaling occurs in breast

adenocarcinomas by way of G-protein-coupled inwardly rectifying potassium channels (GIRKI). The expression of mRNA encoded with GIRKI has been found in roughly 40 % of primary human breast cancer tissue samples. Vandewalle et al. [46] previously confirmed that the beta-adrenergic compounds stimulated cAMP production in breast cancer cells. The production of cAMP has been implicated with tumor growth mechanisms and in lactose production. There is also speculation that specific beta-adrenergic receptors coupled with G-protein could play a role with circulating catecholamines that could function in the growth and differentiation of the mammary glands [47]. The pathophysiological significance of the beta-adrenergic receptors remains uncertain, and more biological research is needed to explain their role in the development of breast cancer.

There are several strengths to this study. This study utilized population-based cases and controls to investigate the association between the two most common *ADRB2* polymorphisms and their haplotypes and breast cancer risk. Two previous studies have examined the association between *ADRB2* and breast cancer [23, 24]; however, neither one included both of the common *ADRB2* variants nor performed haplotype analyses. Additionally, this is the first study to report a significant positive association between an *ADRB2* haplotype and breast cancer risk among NHW women from a multi-centered study in the United States.

The depth of the available covariates also allowed for testing of effect modification and for adjustment of common confounders, although numbers were limited for testing effect modification by history of diabetes. The case–control study design is susceptible to common limitations, such as recall and selection bias. History of diabetes was based on self-report and not medical record review. Misclassification is possible when testing the interaction effects of diabetes with the *ADRB2* haplotype; however, a recent meta-analysis investigating the association between diabetes and breast cancer risk did not find differences in risk estimates for studies that measured diabetes based on self-report compared to those that used clinical information [48].

Although a false-positive result may occur in a genetic-association study due to low statistical power [49, 50], this study is unique as its sample size is substantial, allowing for sufficient power when testing for ethnic differences in breast cancer risk factors. Replication of this study among similar populations with ample sample size is important to assess the validity of our findings. There is also the possibility for genotyping error, which can introduce bias and result in false-positive findings [51]. In an effort to prevent such bias, dropouts were re-analyzed, and all genotypes were scored by two individuals with any discrepancies being scored by a third reader. Moreover, the genotypes were found to be in HWE.

Although the response rate for Hispanic women was low, previous analysis showed that while age appeared to be an important factor affecting participation, other relevant factors, including income, education, and urban/rural residence, did not significantly affect participation for either Hispanic cases or controls [52]. Additionally, the rates of the participation among those who agreed to provide blood specimens were similar for Hispanic and NHW women, and only 5 % fewer cases (76.6 %) provided a specimen compared to controls (82.4 %) [26].

Our results suggest that ethnicity modifies the association between the *ADRB2 G–G* haplotype and breast cancer risk and that elevated BMI enhances the divergence of risk between Hispanic and NHW women. Future research is needed to clarify these ethnic differences in the association between *ADRB2* haplotypes and breast cancer risk, especially when considering the modifying factors identified within our study. Obesity and diabetes are critical public health problems, and further exploration into their interaction effects with *ADRB2* haplotypes and breast cancer risk could account for underlying biological disparities in breast cancer incidence among different ethnic and racial populations.

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Conflict of interest The authors declare that they have no conflict of interest.

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