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Replication of five GWAS-identified loci and breast cancer risk among Hispanic and non-Hispanic white women living in the Southwestern United States

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Abstract

Genome-wide association studies (GWAS) have identified several loci as being associated with breast cancer in mostly European populations. We focus on *TNRC9* rs3803662, *FGFR2* rs1219648 and rs2981582, *MAP3K1* rs889312, and 2q35 rs13387042, to replicate in the 4-Corner's Breast Cancer Study of Hispanic ($N = 565$ cases and 714 controls) and non-Hispanic white (NHW) women ($N = 1177$ cases and 1330 controls). We evaluate associations by ethnicity, menopausal status, and tumor ER/PR status after adjusting for genetic admixture. *TNRC9* AA genotype was associated with significant increased risk among NHW women (OR 1.54, 95% CI 1.14, 2.08; P trend 0.003). Both polymorphisms of *FGFR2* were associated with statistically significant increased risk for NHW and Hispanic women; *MAP3K1* was not associated with risk among either ethnic group. The polymorphism on 2q35 was associated with a statistically significant increased risk among Hispanic women (OR 1.53, 95% CI 1.08, 2.15 for the AA genotype; P trend = 0.004). Associations were significantly different among pre/peri-menopausal women for *TNRC9* (P heterogeneity 0.008) and for 2q35 (P heterogeneity 0.08) for NHW and Hispanic women. Both *FGFR2* polymorphisms reduced risk of ER-/PR- tumors in the presence of the minor allele among NHW women. Among Hispanic women, polymorphisms of the *FGFR2* gene were associated with almost a twofold increase risk of an ER+/PR+ tumor, while non-significantly inversely associated with ER-/PR- tumors. Our data replicated some of the previously reported GWAS findings. Differences in associations were detected for NHW and Hispanic women by menopausal status and by ER/PR status of tumors.

Keywords

Breast cancer; Hispanic; *TNRC9*; *MAP3K1*; *FGFR2*; 2q35

Introduction

Genome-wide association studies (GWAS) of breast cancer have primarily focused on women of European ancestry [1–3]. These studies have identified new loci for replication and further evaluation. Replication studies in African American populations have had mixed success in confirming associations [4]. Among women of Asian ancestry approximately half of loci identified in women of European ancestry could be replicated [5]. Lack of replication of some loci could stem from differences in populations studied that varied by menopausal status, family history status, ethnicity, and other unique population characteristics. Confirmatory findings have been shown for a polymorphism in the fibroblast growth factor receptor 2 (*FGFR2*) gene, rs1219648 and in 2q35 rs13387042 in African American women [6]. This *FGFR2* polymorphism was originally reported by Hunter [2] while the 2q35 polymorphism was reported by Stacey et al. [7]. Two polymorphisms in the *FGFR2* gene, rs1219648 and rs2420946, were originally identified by Hunter among post-menopausal breast cancer cases [2]. A GWAS conducted by Easton and colleagues also identified a significant association with an *FGFR2* with breast cancer using marker rs2981582 [1]. The finding reported by Hunter was confirmed in three of the four populations assessed. In 2007, Easton also reported on a polymorphism in *MAP3K1*, rs889312, which has been confirmed in other populations and has been identified as involved in a potential key pathway for breast cancer [1, 3]. *TNRC9*, also known as Tox3, was originally identified as important by Easton and the rs3803662 polymorphism has recently been confirmed from deep sequencing studies as a key *TNRC9* SNP associated with breast cancer [8].

In this paper, given the confirmatory results from several studies in multiple populations, we focus on five polymorphisms, *TNRC9* rs3803662, *FGFR2* rs1219648 and rs2981582, *MAP3K1* rs889312, and 2q35 rs13387042, to replicate in a breast cancer case–control study among women living in the Southwestern United States. Replication of these findings from GWAS in Hispanic women has not been published. We use data collected from the 4-Corner's Breast Cancer Study conducted in Arizona, Colorado, New Mexico, and Utah to evaluate these associations. We consider differences in association that may stem from population characteristics including having a family history of breast cancer, menopausal status, and ER/PR status of tumors. We adjust for genetic admixture among Hispanic women.

Methods

Study participants were women living in Cochise, Coconino, Maricopa, Pima, Pinal, Santa Cruz, and Yuma Counties in Arizona, or the states of Colorado, New Mexico, or Utah at the time of diagnosis or selection [9]. Study hypotheses focused specifically on breast cancer in Hispanic women, therefore, sampling was stratified on ethnicity to select these women in larger proportion than their representation in the population. All Hispanic women between the ages of 25 and 79 who were diagnosed with breast cancer during the study period were eligible for the study. An age-matched sample of non-Hispanic white (NHW) women were randomly selected on a 1 to 1 ratio to the distribution of Hispanic cases in Arizona and Colorado; at a 4 to 1 ratio to the distribution of Hispanic cases in Utah; all Hispanic and non-Hispanic cases age 50 and under in New Mexico; and a 1 to 1 ratio for women over 50 in New Mexico. The GUESS program (Generally Useful Ethnic Search System) was used to

identify women who were Hispanic [10]. A detailed description of study methods and response rates has been published and are briefly described below [9].

Cases were histologically confirmed as having in situ or invasive breast cancer (ICDO sites C50.0–C50.6 and C50.8–C50.9) diagnosed between October 1999 and May 2004. State tumor registries were used to initially identify and confirm case eligibility. They also provided study data for ER and PR status of tumors. Of cases identified, 68% of women contacted participated. Of the cases participating, 565 Hispanic and 1177 non-Hispanic white cases had DNA available for analyses.

Controls were selected from the target populations to match ethnicity and 5-year age distribution of cases. In Arizona and Colorado, participants under 65 were randomly selected from a commercial mailing list; in New Mexico and Utah, controls under 65 years were randomly selected from drivers' license lists. In all states, women 65 years and older were randomly selected from Center for Medicare Services lists. Of controls identified 714 Hispanic and 1330 non-Hispanic white controls had DNA available for analyses.

All women identified were screened for eligibility prior to study enrollment. As part of the screening, women were asked to self-identify their race and ethnicity. Women initially identified as being Hispanic by the GUESS program who subsequently self-reported not being Hispanic/AI were ineligible for the study. All participants signed informed written consent prior to participation; the study was approved by the Institutional Review Board for Human Subjects at each institution. Respondents were given the option of having the interview administered in either English or Spanish. At the time of interview, respondents were again asked to self-identify their ethnicity and race as part of the study questionnaire. If a respondent described herself as belonging to more than one race or ethnic group, all were recorded. The questionnaire included information family history of first-degree relatives with breast cancer. As part of the interview, women were asked to "best describe your menstrual status on (referent date)" by selecting response from a card; this information was used to define individual menopausal status.

Genotyping

Genomic DNAs were isolated from blood from all study subjects. TaqMan assays for *TNRC9* rs3803662, *FGFR2* rs1219648 and rs2981582, *MAP3K1* rs889312, and 2q35 rs13387042 were purchased from Applied Biosystems (Foster City, CA) and run according to the manufacturer. Briefly, each 5 µl TaqMan reaction contained 20 ng of genomic DNA, primers, probes, and TaqMan Universal Master Mix (containing AmpErase UNG, AmpliTaq Gold polymerase, dNTPs, and reaction buffer). TaqMan reactions were carried out with the following procedure: 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 in an ABI 9700 PCR machine with 384 well format. Fluorescent endpoints of the TaqMan reactions were measured using an ABI 7900HT sequence detection instrument. All markers were in Hardy Weinberg equilibrium for both ethnic groups.

Statistical methods

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). The five loci were identified from GWAS studies. They were tested for Hardy–Weinberg equilibrium (HWE) within controls by ethnicity, and both R-square and D prime were calculated for the two loci in *FGFR2* within controls by ethnicity using the EM algorithm to estimate haplotype frequencies. A chi-square test was used to compare the minor allele frequencies between ethnicities within controls. Multiple logistic regression models were used to assess breast cancer risk associated with the five loci, and analyses were stratified by ethnicity and

adjusted for age at diagnosis/selection, study center and genetic admixture among Hispanic women. Methods for calculating genetic admixture have been described and were based on a two population model that included European and Native ancestry using the program Structure [11]. *P* values of linear dose response genotype effect were calculated by comparing the difference in the maximum likelihood estimates for a logistic regression model with and without the genotype of interest as ordinal using a chi-square test with one degree of freedom. Heterogeneity *P* values for differences in association between NHW and Hispanic women were determined by comparing the difference in maximum likelihood estimates for a logistic regression model with and without an interaction term between race and the genotype of interest using a chi-square test with one degree of freedom. We presented findings stratified by pre/peri-menopausal women as determined from data reported on the study questionnaire. We present findings stratified by ER and PR status of tumors for NHW and Hispanic women separately. No differences in association were detected by family history of breast cancer in first-degree relatives therefore those data are not presented.

Results

Study population characteristics are shown in Table 1. Most study participants were between 40 and 59 years of age and were post-menopausal. A family history of breast cancer in first-degree relatives was reported by 15.8% of NHW controls and 13.6% of Hispanic controls. Hispanic cases had more ER negative tumors than NHW women, although PR tumor status did not differ by ethnicity. The minor allele frequency (MAF) for the *TNRC9* and *MAP3K1* variants was significantly greater among Hispanic women, while the minor allele of the polymorphism at 2q35 was more common among NHW women.

No significant ethnic differences in associations were detected between NHW and Hispanic women for any of the five SNPs assessed, although magnitude of the association varied for NHW and Hispanic women (Table 2). *TNRC9* rs3803662 AA genotype was associated with increased risk among NHW women (OR 1.54, 95% CI 1.14, 2.08; *P* trend 0.003) but not among Hispanic women (OR 1.05, 95% CI 0.75, 1.46; *P* trend 0.82). Both polymorphisms of *FGFR2* were associated with statistically significant increased risk for both NHW and Hispanic women, while *MAP3K1* was not associated with risk among either ethnic group. The polymorphism on 2q35 (rs13387042) was associated with a statistically significant increased risk only among Hispanic women (OR 1.53, 95% CI 1.08, 2.15 for the AA genotype; *P* trend = 0.004).

No meaningful differences were detected for breast cancer risk between NHW and Hispanic women who were post-menopausal (Table 3). However, associations were significantly different among pre/peri-menopausal women for *TNRC9* rs3803662 (*P* heterogeneity 0.008) and of borderline significant difference for 2q35 rs13387042 (*P* heterogeneity 0.08) for NHW and Hispanic women. The AA genotype of *TNRC9* was associated with over a twofold increased risk of breast cancer among pre/peri-menopausal NHW women (OR 2.18, 95% CI 1.28, 3.73; *P* linear trend 0.0003) and was not associated with risk among Hispanic women (OR 0.86, 95% CI 0.51, 1.44; *P* linear trend 0.67). On the other hand the AA genotype of 2q35 rs13387042 significantly increased risk among Hispanic women (OR 1.94, 95% CI 1.12, 3.36; *P* linear trend 0.01) but was not associated with breast cancer among NHW pre/peri-menopausal women (OR 1.02, 95% CI 0.70, 1.50; *P* linear trend 0.88).

Associations by ER/PR tumor status (Table 4) revealed few findings. Among NHW women only 2q35 rs13387042 appeared to be uniquely associated with ER+/PR+ tumors. Both *FGFR2* polymorphisms reduced risk of ER–PR– tumors in the presence of the minor allele among NHW women. Among Hispanic women, both polymorphisms of the *FGFR2* gene

were associated with almost a twofold increase risk of an ER+/PR+ tumor in a dose-response manner, while non-significantly inversely associated with ER-/PR- tumors.

Discussion

Our replication of five SNPs identified from multiple GWAS of breast cancer in Hispanic and NHW women living in the Southwestern United States, showed that three SNPs replicated in Hispanic women, *FGFR2* rs1219648 and rs2981582 and the SNP located on 2q35 (rs13387042). Three SNPs also replicated among NHW women, *TNRC9* rs3803662 and both SNPs on *FGFR2*. While associations did not differ by family history, they appear to be slightly stronger for pre/peri-menopausal women. Of interest is the association between both *FGFR2* polymorphisms and ER/PR tumor status, in that among NHW women the minor allele is associated with reduced risk of ER-/PR- tumors. Among Hispanic women, there is a dose response increase in risk of an ER+/PR+ tumor associated with the minor allele of the *FGFR2* polymorphisms.

The two polymorphisms in *FGFR2* are in high LD with an r^2 of 0.93 for NHW and 0.88 for Hispanic women. Thus it is not surprising that findings for the two polymorphisms are similar. These associations for these SNPs were first reported by Easton and Hunter [1, 2] have since been replicated in several populations including studies of African Americans [12]. Hunter's report of a pooled estimate of a 20% increased risk with the heterozygote and 64% increased risk for homozygote variant among post-menopausal women is higher than we report here, although a similar trend in risk is observed. Easton reported findings similar to those by Hunter. Our risk estimates for post-menopausal Hispanic women are more similar to those reported by Hunter and Easton than are our findings for NHW women. *FGFR2* is a tumor suppressor gene that is often over-expressed in breast tumors [13]. It has been hypothesized that *FGFR2* is involved in signal transduction and transformation of mammary epithelial cell lines.

The findings for *TNRC9*, *MAP3K1*, and 2q35 have been replicated in some, but not other studies. *TNRC9* rs3803662 is near the 5' end of *TNRC9*, whose protein expression is implicated in breast cancer metastasis to bone [7]. The association with *TNRC9* rs3803662 was not confirmed in two studies of African American women [6, 12] although it has been shown to have strong signals in other studies, including studies involving deep sequencing of the gene [3, 8]. Neither *MAP3K1* rs889312 nor rs13387042 on 2q35 have been confirmed in studies of African American women [6, 12], however, another polymorphism of *MAP3K1*, rs16886165, has been reported in a multi-stage breast cancer GWAS study [3].

Several studies have examined these loci with breast cancer clinical features, including ER/PR status of tumors. A study by García-Closas and Chanock [14] did not observe any associations between these loci and ER- tumors. The increased risk was restricted to ER+ tumors and was seen for all five SNPs. Nordgard and colleagues observed *TNRC9* was up-regulated in luminal A, luminal B, and ErbB2+ tumors and down-regulated in basal-like subtype [15]. Our data suggest that *FGFR2* may influence ER/PR status of tumors, decreasing the likelihood of ER- tumors among NHW women while increasing the likelihood of ER/PR+ tumors among Hispanic women. Evaluation of molecular subtypes of breast cancer with GWAS data has been cited as an important component to identification of susceptibility loci [16].

Conclusions

Our results support the hypothesis that genetic factors differ by race and ethnicity as they relate to breast cancer. The importance of examining ethnicity/race associations as a

component of validating and replicating associations is critical to understand the complexity of disease associations among genetically admixed populations. Because of these differences, it also is important to examine GWAS in Hispanic admixed populations to identify polymorphisms that may be uniquely associated with these populations and could account for biological disparities in breast cancer incidence.

Abbreviations

NHW	Non-Hispanic white
OR	Odds ratios
CI	Confidence intervals
ER	Estrogen receptor
PR	Progesterone receptor
GWAS	Genome-wide association study
MAP	Mitogen-activated protein
FGFR	Fibroblast growth factor receptor
TRNC9	Trinucleotide repeat-containing 9
GUESS	Generally useful ethnic search system
AI	American Indian
SNP	Single nucleotide polymorphism
HWE	Hardy–Weinberg Equilibrium
MAF	Minor allele frequency

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References

1. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struwing JP, Morrison J, Field H, Luben R, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature*. 2007; 447(7148):1087–1093. [PubMed: 17529967]
2. Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, Wacholder S, Wang Z, Welch R, Hutchinson A, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet*. 2007; 39(7):870–874. [PubMed: 17529973]
3. Thomas G, Jacobs KB, Kraft P, Yeager M, Wacholder S, Cox DG, Hankinson SE, Hutchinson A, Wang Z, Yu K, et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). *Nat Genet*. 2009; 41(5):579–584. [PubMed: 19330030]

4. Ruiz-Narvaez EA, Rosenberg L, Cozier YC, Cupples LA, Adams-Campbell LL, Palmer JR. Polymorphisms in the TOX3/LOC643714 locus and risk of breast cancer in African-American women. *Cancer Epidemiol Biomarkers Prev.* 2010; 19(5):1320–1327. [PubMed: 20406955]
5. Long J, Shu XO, Cai Q, Gao YT, Zheng Y, Li G, Li C, Gu K, Wen W, Xiang YB, et al. Evaluation of breast cancer susceptibility loci in Chinese women. *Cancer Epidemiol Biomarkers Prev.* 2010; 19(9):2357–2365. [PubMed: 20699374]
6. Zheng W, Cai Q, Signorello LB, Long J, Hargreaves MK, Deming SL, Li G, Li C, Cui Y, Blot WJ. Evaluation of 11 breast cancer susceptibility loci in African-American women. *Cancer Epidemiol Biomarkers Prev.* 2009; 18(10):2761–2764. [PubMed: 19789366]
7. Stacey SN, Manolescu A, Sulem P, Rafnar T, Gudmundsson J, Gudjonsson SA, Masson G, Jakobsdottir M, Thorlacius S, Helgason A, et al. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet.* 2007; 39(7):865–869. [PubMed: 17529974]
8. Udler MS, Ahmed S, Healey CS, Meyer K, Struewing J, Maranian M, Kwon EM, Zhang J, Tyrer J, Karlins E, et al. Fine scale mapping of the breast cancer 16q12 locus. *Hum Mol Genet.* 2010; 19(12):2507–2515. [PubMed: 20332101]
9. Slattery ML, Sweeney C, Edwards S, Herrick J, Baumgartner K, Wolff R, Murtaugh M, Baumgartner R, Giuliano A, Byers T. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. *Breast Cancer Res Treat.* 2007; 102(1):85–101. [PubMed: 17080310]
10. Howard CA, Samet JM, Buechley RW, Schrag SD, Key CR. Survey research in New Mexico Hispanics: some methodological issues. *Am J Epidemiol.* 1983; 117(1):27–34. [PubMed: 6823950]
11. Sweeney C, Wolff RK, Byers T, Baumgartner KB, Giuliano AR, Herrick JS, Murtaugh MA, Samowitz WS, Slattery ML. Genetic admixture among Hispanics and candidate gene polymorphisms: potential for confounding in a breast cancer study? *Cancer Epidemiol Biomarkers Prev.* 2007; 16(1):142–150. [PubMed: 17220343]
12. Barnholtz-Sloan JS, Shetty PB, Guan X, Nyante SJ, Luo J, Brennan DJ, Millikan RC. FGFR2 and other loci identified in genome-wide association studies are associated with breast cancer in African-American and younger women. *Carcinogenesis.* 2010; 31(8):1417–1423. [PubMed: 20554749]
13. Grose R, Dickson C. Fibroblast growth factor signaling in tumorigenesis. *Cytokine Growth Factor Rev.* 2005; 16(2):179–186. [PubMed: 15863033]
14. Garcia-Closas M, Hall P, Nevanlinna H, Pooley K, Morrison J, Richesson DA, Bojesen SE, Nordestgaard BG, Axelsson CK, Arias JI, et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. *PLoS Genet.* 2008; 4(4):e1000054. [PubMed: 18437204]
15. Nordgard SH, Johansen FE, Alnaes GI, Naume B, Borresen-Dale AL, Kristensen VN. Genes harbouring susceptibility SNPs are differentially expressed in the breast cancer subtypes. *Breast Cancer Res.* 2007; 9(6):113. [PubMed: 18036273]
16. Kristensen VN, Borresen-Dale AL. SNPs associated with molecular subtypes of breast cancer: on the usefulness of stratified Genome-wide Association Studies (GWAS) in the identification of novel susceptibility loci. *Mol Oncol.* 2008; 2(1):12–15. [PubMed: 19383324]

Table 1

Description of study population of women living in the Southwestern United States

	White, non-Hispanic				Hispanic				χ^2 P value ^a
	Cases		Controls		Cases		Controls		
	N	%	N	%	N	%	N	%	
Age									
25–39	74	6.3	101	7.6	58	10.3	82	11.5	
40–49	348	29.6	347	26.1	193	34.2	198	27.7	
50–59	333	28.3	351	26.4	162	28.7	194	27.1	
60–69	283	24.1	300	22.6	106	18.8	163	22.8	
70–79	137	11.7	230	17.3	46	8.1	79	11.0	
Center									
AZ	165	14.0	263	19.8	116	20.5	161	22.5	
CO	237	20.2	218	16.4	108	19.1	132	18.4	
NM	464	39.5	495	37.2	248	43.9	245	34.2	
UT	309	26.3	353	26.6	93	16.5	178	24.9	
Menopause status									
Pre/Peri	414	35.3	413	31.1	230	40.9	260	36.4	
Post	758	64.7	915	68.9	333	59.1	454	63.6	
Family history of breast cancer									
No	879	77.0	1068	84.2	429	81.3	568	86.5	0.05
Yes	263	23.0	201	15.8	99	18.8	89	13.5	
Estrogen receptor (ER) status									0.03
Positive	632	80.3			279	74.8			
Negative	155	19.7			94	25.2			
Progesterone receptor (PR) status									0.62
Positive	518	69.1			242	67.6			
Negative	232	30.9			116	32.4			
ER/PR status									0.04
ER+/PR+	506	67.6			228	64.0			
ER+/PR–	90	12.0			35	9.8			

	White, non-Hispanic				Hispanic				χ^2 P value ^a
	Cases		Controls		Cases		Controls		
	N	%	N	%	N	%	N	%	
ER-PR+	11	1.5			13	3.7			
ER-PR-	141	18.9			80	22.5			
TNRC9 (rs3803662 G>A) ^b	1173	30	1328	27	564	40	714	39	<0.001
FGFR2 (rs1219648 A>G) ^b	1172	43	1328	40	565	47	714	41	0.56
FGFR2 (rs2981582 G>A) ^b	1172	42	1326	40	562	46	714	41	0.31
MAP3K1 (rs889312 A>C) ^b	1171	29	1327	29	564	44	714	41	<0.001
2q35 (rs13387042 G>A) ^{b,c}	1169	54	1328	52	564	41	713	36	<0.001

^aChi-square test of across race/ethnicity differences; within controls only for genotypes

^bMinor allele frequency

^cMinor allele assigned for NHW based on minor allele (A) for Hispanic

Table 2
Associations between GWAS-identified SNPs and breast cancer in NHW and Hispanic women living in the Southwestern US

	White, non-Hispanic			Hispanic			<i>P</i> heterogeneity ^b
	Controls	Cases		Controls	Cases		
	<i>n</i>	<i>n</i>	OR (95% CI)	<i>n</i>	<i>n</i>	OR ^a (95% CI)	
<i>TNRC9</i> (rs3803662)							0.11
GG	708	569	1.00	270	209	1.00	
GA	530	495	1.17 (0.99, 1.38)	332	260	1.00 (0.78, 1.28)	
AA	90	109	1.54 (1.14, 2.08)	112	95	1.05 (0.75, 1.46)	
<i>P</i> trend			0.003			0.82	
<i>FGFR2</i> (rs1219648)							
AA	474	380	1.00	253	150	1.00	
AG	645	582	1.12 (0.94, 1.33)	337	297	1.44 (1.12, 1.87)	
GG	209	210	1.26 (1.00, 1.59)	124	118	1.53 (1.10, 2.12)	
<i>P</i> trend			0.05			0.005	0.50
<i>FGFR2</i> (rs2981582)							
GG	487	384	1.00	254	151	1.00	
GA	642	581	1.14 (0.96, 1.36)	339	303	1.48 (1.14, 1.91)	
AA	197	207	1.33 (1.05, 1.68)	121	108	1.44 (1.03, 2.00)	
<i>P</i> trend			0.02			0.01	0.33
<i>MAP3K1</i> (rs889312)							
AA	673	587	1.00	249	181	1.00	
AC	528	481	1.05 (0.89, 1.24)	342	273	1.13 (0.87, 1.45)	
CC	126	103	0.93 (0.70, 1.24)	123	110	1.19 (0.86, 1.66)	
<i>P</i> trend			0.98			0.25	
<i>2q35</i> (rs13387042)							0.10
GG	302	257	1.00	299	191	1.00	
GA	659	562	1.00 (0.82, 1.22)	315	278	1.39 (1.09, 1.78)	
AA	367	350	1.11 (0.89, 1.39)	99	95	1.53 (1.08, 2.15)	
<i>P</i> trend			0.32			0.004	

^aOdds ratios adjusted for age and center and genetic admixture among Hispanic women

b P value for heterogeneity test difference between NHW and Hispanic women

Table 3

Associations between GWAS-identified loci and breast cancer among pre/peri and post-menopausal women living in the Southwestern US

White, non-Hispanic				Hispanics				<i>P</i> heterogeneity ^b	
Controls		Cases		Controls		Cases			
<i>n</i>		<i>n</i>	OR (95% CI)	<i>n</i>		<i>n</i>	OR ^a (95% CI)		
<i>Pre/peri-menopausal</i>									
<i>TNRC9</i> (rs3803662)									
GG	236	188	1.00			96	85	1.00	0.008
GA	151	182	1.51	(1.13, 2.02)			114	105	1.06 (0.71, 1.59)
AA	25	43	2.18	(1.28, 3.73)			50	40	0.86 (0.51, 1.44)
<i>P</i> trend			0.0003						0.67
<i>FGFR2</i> (rs1219648)									
AA	146	128	1.00			96	62	1.00	0.56
AG	204	219	1.21	(0.89, 1.64)			117	123	1.70 (1.12, 2.58)
GG	62	67	1.23	(0.81, 1.88)			47	45	1.42 (0.84, 2.40)
<i>P</i> trend			0.25						0.10
<i>FGFR2</i> (rs2981582)									
GG	151	130	1.00			93	60	1.00	0.76
GA	203	217	1.24	(0.91, 1.68)			118	124	1.72 (1.13, 2.62)
AA	58	66	1.32	(0.86, 2.03)			48	45	1.39 (0.82, 2.35)
<i>P</i> trend			0.14						0.12
<i>MAP3K1</i> (rs889312)									
AA	198	199	1.00			80	71	1.00	0.71
AC	163	174	1.06	(0.79, 1.42)			131	116	1.08 (0.72, 1.64)
CC	51	40	0.81	(0.51, 1.28)			48	43	1.00 (0.59, 1.71)
<i>P</i> trend			0.62						0.93
<i>2q35</i> (rs13387042)									
GG	93	91	1.00			113	80	1.00	0.08
GA	195	190	0.96	(0.67, 1.37)			114	107	1.36 (0.91, 2.03)
AA	124	131	1.02	(0.70, 1.50)			33	43	1.94 (1.12, 3.36)
<i>P</i> trend			0.88						0.01

	White, non-Hispanic				Hispanics				<i>P</i> heterogeneity ^b
	Controls		Cases		Controls		Cases		
	<i>n</i>	<i>n</i>	OR	(95% CI)	<i>n</i>	<i>n</i>	OR ^a	(95% CI)	
<i>Post-menopausal</i>									
<i>TNRC9 (rs3803662)</i>									
GG	472	379	1.00		173	123	1.00		0.89
GA	378	312	1.04	(0.85, 1.28)	217	154	0.98	(0.72, 1.34)	
AA	65	66	1.29	(0.89, 1.87)	62	55	1.19	(0.77, 1.85)	
<i>P</i> trend			0.25				0.54		
<i>FGFR2 (rs1219648)</i>									
AA	327	251	1.00		157	88	1.00		0.34
AG	441	361	1.07	(0.86, 1.33)	219	172	1.32	(0.95, 1.84)	
GG	147	143	1.29	(0.97, 1.72)	76	73	1.60	(1.05, 2.43)	
<i>P</i> trend			0.09				0.02		
<i>FGFR2 (rs2981582)</i>									
GG	335	253	1.00		161	91	1.00		0.60
GA	439	362	1.10	(0.88, 1.36)	220	177	1.35	(0.97, 1.88)	
AA	139	141	1.35	(1.01, 1.80)	72	63	1.46	(0.95, 2.25)	
<i>P</i> trend			0.05				0.06		
<i>MAP3K1 (rs889312)</i>									
AA	475	386	1.00		169	110	1.00		0.29
AC	365	307	1.04	(0.84, 1.27)	211	156	1.15	(0.83, 1.58)	
CC	74	62	1.02	(0.71, 1.47)	73	66	1.36	(0.89, 2.07)	
<i>P</i> trend			0.78				0.15		
<i>2q35 (rs13387042)</i>									
GG	209	165	1.00		184	109	1.00		0.40
GA	463	370	1.00	(0.78, 1.28)	201	171	1.44	(1.05, 1.98)	
AA	243	219	1.14	(0.86, 1.49)	66	52	1.32	(0.85, 2.05)	
<i>P</i> trend			0.34				0.08		

^a Odds ratios (OR) adjusted for age and center and genetic admixture among Hispanic women

^b *P* value for heterogeneity test difference between NHW and Hispanic women

Table 4

Associations between GWAS loci and ER/PR status among breast cancer cases living in the Southwestern US

	Controls		ER+/PR+ cases			ER+/PR- cases			ER-/PR-b cases				
	n	n	OR ^a	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)
White, non-Hispanic													
TNRC9 (rs3803662)													
GG	708	245	1.00		41	1.00		69	1.00				
GA	530	209	1.13	(0.91, 1.41)	42	1.33	(0.85, 2.09)	58	1.15	(0.79, 1.66)			
AA	90	48	1.58	(1.08, 2.31)	8	1.56	(0.71, 3.46)	14	1.71	(0.92, 3.18)			
P trend			0.03			0.14			0.12				
FGFR2 (rs1219648)													
AA	474	169	1.00		27	1.00		63	1.00				
AG	645	249	1.08	(0.86, 1.35)	49	1.35	(0.83, 2.19)	57	0.67	(0.46, 0.98)			
GG	209	84	1.14	(0.83, 1.55)	14	1.20	(0.61, 2.34)	20	0.74	(0.43, 1.26)			
AG/GG	854	333	1.09	(0.88, 1.36)	63	1.29	(0.81, 2.06)	77	0.69	(0.48, 0.98)			
P trend			0.39			0.43			0.10				
FGFR2 (rs2981582)													
GG	487	174	1.00		26	1.00		64	1.00				
GA	642	251	1.09	(0.87, 1.37)	49	1.45	(0.89, 2.37)	56	0.67	(0.46, 0.97)			
AA	197	78	1.10	(0.81, 1.51)	15	1.46	(0.75, 2.82)	19	0.75	(0.44, 1.29)			
GA/AA	839	329	1.10	(0.88, 1.36)	64	1.43	(0.89, 2.29)	75	0.69	(0.48, 0.98)			
P trend			0.46			0.17			0.10				
MAP3K1 (rs889312)													
AA	673	259	1.00		49	1.00		70	1.00				
AC	528	208	1.03	(0.83, 1.28)	31	0.80	(0.50, 1.28)	60	1.10	(0.76, 1.58)			
CC	126	34	0.70	(0.47, 1.05)	11	1.19	(0.60, 2.35)	9	0.65	(0.32, 1.34)			
P trend			0.29			0.91			0.58				
2q35 (rs13387042)													
GG	302	98	1.00		25	1.00		34	1.00				
GA	659	244	1.15	(0.87, 1.51)	43	0.77	(0.46, 1.29)	68	0.90	(0.58, 1.40)			
AA	367	159	1.34	(1.00, 1.80)	22	0.73	(0.40, 1.32)	37	0.91	(0.55, 1.48)			

Controls		ER+/PR+ cases			ER+/PR- cases			ER-/PR- ^b cases		
	<i>n</i>	<i>n</i>	OR ^a	(95% CI)	<i>n</i>	OR	(95% CI)	<i>n</i>	OR	(95% CI)
<i>P</i> trend			0.05			0.30			0.70	
<i>Hispanic</i>										
<i>TNRC9</i> (rs3803662)										
GG	270	82	1.00		10	1.00		35	1.00	
GA	332	105	1.02	(0.73, 1.43)	17	1.40	(0.62, 3.14)	36	0.83	(0.50, 1.36)
AA	112	40	1.10	(0.71, 1.72)	8	2.21	(0.83, 5.85)	9	0.54	(0.25, 1.17)
<i>P</i> trend			0.69			0.12			0.12	
<i>FGFR2</i> (rs1219648)										
AA	253	53	1.00		10	1.00		30	1.00	
AG	337	122	1.69	(1.18, 2.43)	20	1.51	(0.67, 3.24)	38	0.90	(0.54, 1.50)
GG	124	53	1.95	(1.26, 3.03)	5	0.97	(0.33, 3.05)	12	0.76	(0.37, 1.55)
	461	175	1.76	(1.25, 2.49)	25	1.36	(0.63, 2.89)	50	0.86	(0.53, 1.40)
<i>P</i> trend			0.002			0.83			0.45	
<i>FGFR2</i> (rs2981582)										
GG	254	55	1.00		10	1.00		29	1.00	
GA	339	118	1.58	(1.10, 2.27)	20	1.47	(0.67, 3.24)	40	0.99	(0.60, 1.66)
AA	121	54	1.97	(1.27, 3.05)	5	1.00	(0.33, 3.05)	11	0.73	(0.35, 1.52)
	460	172	1.69	(1.20, 2.38)	25	1.35	(0.63, 2.89)	51	0.92	(0.57, 1.51)
<i>P</i> trend			0.002			0.79			0.47	
<i>MAP3K1</i> (rs889312)										
AA	249	74	1.00		13	1.00		23	1.00	
AC	342	113	1.12	(0.80, 1.57)	14	0.85	(0.39, 1.85)	45	1.41	(0.83, 2.41)
CC	123	40	1.04	(0.67, 1.63)	8	1.27	(0.50, 3.19)	12	0.93	(0.45, 1.96)
<i>P</i> trend			0.75			0.73			0.87	
<i>2q35</i> (rs13387042)										
GG	299	69	1.00		11	1.00		25	1.00	
GA	315	120	1.71	(1.21, 2.40)	19	1.53	(0.71, 3.32)	41	1.57	(0.92, 2.66)
AA	99	38	1.75	(1.10, 2.79)	5	1.53	(0.51, 4.57)	14	1.60	(0.79, 3.25)
<i>P</i> trend			0.004			0.32			0.12	

^a Odds ratios adjusted for age and center and genetic admixture among Hispanic women

^b ER- /PR+ cases were too few to analyze