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Adiponectin pathway polymorphisms and risk of breast cancer in African Americans and Hispanics in the Women's Health Initiative

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Abstract

Background—Adiponectin, a protein secreted by the adipose tissue, is an endogenous insulin sensitizer with circulating levels that are decreased in obese and diabetic subjects. Recently, circulating levels of adiponectin have been correlated with breast cancer risk. Our previous work showed that polymorphisms of the adiponectin pathway are associated with breast cancer risk.

Methods—We conducted the first study of adiponectin pathways in African Americans and Hispanics in the Women's Health Initiative (WHI) SNP Health Association Resource (SHARe) cohort of 3,642 self-identified Hispanic women and 8,515 self-identified African American women who provided consent for DNA analysis. Single nucleotide polymorphisms (SNPs) from three genes were included in this analysis: *ADIPOQ, ADIPOR1* and *ADIPOR2*. The Genome-wide Human SNP Array 6.0 (909,622 SNPs) (www.affymetrix.com) was used.

Results—We found that rs1501299, a functional SNP of *ADIPOQ* that we previously reported was associated with breast cancer risk in a mostly Caucasian population, was also significantly associated with breast cancer incidence (HR for the GG/TG genotype: 1.23; 95% CI: 1.059–1.43) in African American women. We did not find any other SNPs in these genes to be associated with breast cancer incidence.

Conclusions—This is the first study assessing the role of adiponectin pathway SNPs in breast cancer risk in African Americans and Hispanics. RS1501299 is significantly associated with breast cancer risk in African American women. Impact: As the rates of obesity and diabetes increase in African Americans and Hispanics, adiponectin and its functional SNPs may aid in breast cancer risk assessment.

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Conflict of Interest: None

Keywords

adiponectin; polymorphisms; breast cancer; African Americans; Hispanics

Introduction

Breast cancer is the most common malignancy in women in developed countries. In 2013, it is estimated that 234,580 new cases of breast cancer will be diagnosed in the US[1]. Several studies have demonstrated an association between obesity, weight gain and breast cancer risk[2,3]. Furthermore, there is evidence that weight loss, and possibly a decrease in fat consumption, may lead to a decreased risk for breast cancer[4,5]. There has also been extensive research on the association of diabetes mellitus (DM) and the metabolic syndrome and breast cancer[6],[7]. In a meta-analysis of 20 case-control studies we reported a 20% increased risk for breast cancer in women with DM[8]. In the four cohort studies included in the same meta-analysis, breast cancer risk increased by 24% in patients with DM. The proposed mechanism underlying the increased risk of breast cancer in obese and/or diabetic subjects includes changes in levels of estrogens[9,10], insulin resistance, insulin-like growth factors (IGF) as well as IGF binding proteins[11,12].

The incidence of obesity in African Americans and Hispanics is higher than it is in Caucasians. Nearly 40% of African American women are obese, followed by Hispanics (29%), and Caucasians (22%)[13]. Thus, as obesity rates among Hispanics and African Americans continue to rise, there is an urgent need to identify the role that both obesity and adult weight gain play in the development of breast cancer in these minorities. Studies have been inconsistent in their results as to the relationship between obesity and breast cancer in Hispanics and African Americans compared with Caucasians[14]. This inconsistency has been attributed to differences in socioeconomic factors, access to care, and genetic factors[15]. Although there is very little data in Hispanics, there is a positive association between DM and breast cancer in African American women[16].

Several proteins produced by adipose tissue have been studied in relation to breast cancer risk. There is strong evidence that one of these adipokines, adiponectin, is inversely associated with breast cancer risk [17],[18]. Adiponectin, a protein secreted by the adipose tissue has been found to be an endogenous insulin sensitizer, the circulating levels of which are decreased in obese and diabetic subjects. Moreover, adiponectin has the potential of regulating the secretion of estrogens, TNF-α[19,20] and IGF[21].

Recently, circulating levels of adiponectin have been found to correlate with breast cancer risk [22,23,24]. More specifically, it has been shown that, after adjustment for body mass index (BMI), women with higher adiponectin levels had a 65% reduced risk for breast cancer[25,22,23]. Furthermore, the breast cancer cell lines MCF-7, MDB-MB-231 and T47D were found to express both adiponectin receptors ADIPOR1/R2[26,22] and exposure of T47D cells to adiponectin, significantly inhibiting their proliferation[22].

Several adiponectin polymorphisms have been shown to affect adiponectin levels and polymorphisms of both the ligand and its type 1 receptor (*ADIPOR1*), and have been associated with risk for insulin resistance, cardiovascular disease and DM[27,28,29,30,31,32,33]. We have shown that polymorphisms of *ADIPOQ* and *ADIPOR1* are associated with risk for breast, colon and prostate cancer in a mostly Caucasian population[34,35,36]. However, to date, the association of these polymorphisms with breast cancer risk in Hispanics and African Americans has not been addressed.

Materials and Methods

Study population

The Women's Health Initiative (WHI) is a long-term national health study that focuses on strategies for preventing common diseases such as heart disease, cancer and fracture in postmenopausal women. A total of 161,838 women aged 50–79 years old were recruited from 40 clinical centers in the USA between 1993 and 1998. WHI consists of an observational study, two clinical trials of postmenopausal hormone therapy (estrogen alone or estrogen plus progestin), a Calcium and Vitamin D Supplement Trial and a Dietary Modification Trial [37]. Study recruitment and exclusion criteria have been described previously [38]. Study protocols and consent forms were approved by the institutional review boards at all participating institutions. Medical history was updated annually (for women in the observational study) or semiannually (for women in the clinical trials) by mail and/or telephone questionnaires.

The WHI SNP Health Association Resource (SHARe) minority cohort includes 8,133 self-identified African American women and 3,422 self-identified Hispanic women from WHI who provided written informed consent for study participation and DNA analysis. Anthropometric characteristics as well as clinical variables were obtained during the study period. Anthropometric characteristics included BMI and waist-hip ratio. Clinical variables included age, family history of breast cancer, alcohol consumption, age at menarche, age at first birth, history of breastfeeding and age at menopause. Research was approved by the Northwestern University Institutional Review Board.

Genes

Single nucleotide polymorphisms (SNPs) from three genes were included in this analysis: *ADIPOQ, ADIPOR1* and *ADIPOR2*. Genotyped and imputed SNPs were included if they were between 20KB upstream and 10KB downstream of each gene. A total of 110 SNPs in African Americans and 102 in Hispanics from *ADIPOR1*, 130 in African Americans and 102 in Hispanics from *ADIPOQ* and 354 in African Americans and 289 in Hispanics from *ADIPOR2* were included in the analysis. SNPs were included if they had a minor allele frequency (MAF) more than 0.05.

Genotyping

DNA was extracted using specimens collected at time of enrollment. All samples, plus 2% blinded duplicates, were genotyped at Affymetrix Inc. (www.affymetrix.com) on the Genome-wide Human SNP Array 6.0 (909,622 SNPs). SNPs that were located on the Y chromosome or were Affymetrix quality control probes (not intended for analysis) were excluded ($n = 3280$). We also excluded SNPs that had call rates below 95% and concordance rates below 98%, leaving us 871,309 SNPs available for use in this study. The average concordance for blinded duplicate samples was 99.8%, and the average sample call rate after SNP exclusions was 99.8%.

Statistical Analysis

Imputation—Genotype imputation for African American and Hispanic women was carried out using a cosmopolitan reference panel[39] of all 1,000 Genomes Aug 2012 interim release individuals (http://www.1000genomes.org) by pre-phasing the data with SHAPE-IT v1.ESHG [40], and then imputing with IMPUTE2 v2.2.2 [41]. SNPs with an estimated r2>0.3 and MAF>0.05 were used for analysis.

Single SNP analysis—A cox proportional hazards regression model was fit for time-to-onset of breast cancer, separately for African American women, and for Hispanic women. To identify potential clinical covariates that might affect the incidence of breast cancer, we first conducted a stepwise regression model on the clinical covariates, and then included covariates found in either race/ethnicity, so that they could be meta-analyzed later. In the stepwise regression, we forced in covariates to adjust for genetic ancestry. To account for genetic ancestry differences among sample individuals, we calculated principal components (PCs) from the genome-wide SNP data on the subjects [42], separately for the two race/ethnicities, and used the first four PCs as covariates in the analysis. Then a regression model with a dominant genetic effect was considered for the three candidate SNPs for replication (as in Kaklamani et al[35]), and a model with an additive genetic effect was considered for the analysis of all of the SNPs in the three genes. The model was adjusted for the clinical covariates found previously. Finally, we ran a meta-analysis to combine the analysis of African Americans and Hispanics.

Gene-based analysis—For each of the three genes (*ADIPOQ*, *ADIPOR1*, *ADIPOR2*), we additionally tested all SNPs simultaneously through a kernel machine Cox regression model[43], similar to the single SNP analysis. This model gives an overall effect of an entire gene, and is more powered when there are multiple weaker signals that we were not powered well enough to detect by the single SNP analysis.

Results

Patient population

Table 1 summarizes the clinical variables included in this analysis. As shown 8,133 African American women and 3,422 Hispanic women were included in the analysis. Of these individuals 704 African American and 212 Hispanic women were found to have breast cancer. Mean body mass index (BMI) was 31.2 (6.3) for the African Americans and 29.1 (5.5) for Hispanics. Information on breast cancer risk factors, such as age at menarche and number of alcoholic beverages consumed per week, was available and is presented here for each ethnic group. Since the number of individuals who had information on whether their female relative had breast cancer was so small, we did not consider adjusting for it in our final model. Stepwise regression in African American women resulted in adding the covariate for age at menarche (p=0.000138) in our model. Age at menarche was also added in the stepwise regression in Hispanic women (p=0.0328).

Single SNP analysis

Table 2a shows the p-values for the three SNPs found previously to be associated with breast cancer risk[35] for each SNP genotype, and Table 2b shows each SNP genotype under a dominant model (as in Kaklamani et al[35]). P-values reported in the tables are not corrected for multiple comparisons; for replication significance using a Bonferonni correction, a p-value < 0.05/3=0.017 is required. Under a dominant model, the SNP rs1501299 replicates in African Americans (p=0.0067), but not in Hispanics (p=0.32, though the effect size in the Hispanics is in the same direction), and is in the same direction as found in our previous publication[35], with the G allele being deleterious. Rs1501299 has also been shown to correlate with adiponectin levels with the TT genotype having increased levels of adiponectin compared with GG[31].

We then considered all SNPs in *ADIPOQ*, *ADIPOR1* and *ADIPOR2* (Table 2c), and found that there are no additional significant associations identified after a Bonferroni correction (a Bonferroni correction for all the SNPs in African Americans would yield an alpha level of 0.05/594=0.000084, and in Hispanics 0.05/493=0.00010).

Analyses were also performed in subtypes of invasive and in situ cancers without conferring any significant results. Finally we performed logistic regressions of the ER, PR, and HER2 subtypes. Results did not reach statistical significance but the sample sizes were extremely small, making it difficult to reach any conclusions.

Gene-based analysis

P-values are reported without multiple comparison adjustment (Table 3). As shown none of the genes are found to have a significant association with breast cancer after correcting for multiple comparisons (a Bonferroni correction for the three genes and 3 phenotypes in the African Americans would be 0.05/9=0.006).

Discussion

In this investigation we found that rs1501299, a functional adiponectin SNP, is significantly associated with breast cancer risk in African Americans. After performing several analyses for all SNPs in *ADIPOQ*, *ADIPOR1* and *ADIPOR2* and correcting for multiple comparisons, we did not find any other SNP to be associated with breast cancer risk in this patient population. The rs1501299 SNP is in *ADIPOQ,* and has been shown to be significantly associated with serum adiponectin levels [35]. In our current data, under a dominant model, the GG genotype has a hazards ratio of 1.23 with a p-value of 0.0067 (Table 2b).

Previous studies have looked at the association between adiponectin pathway SNPs and breast cancer risk. Our own study suggested that three functional SNPs, two in *ADIPOQ* (rs2241766 and rs1501299) and one in *ADIPOR1* (rs7539542), were significantly associated with breast cancer[35]. This study included mostly Caucasians. Al Khaldi et al[44] also found that rs1501299 was associated with breast cancer in a population from Kuwait. However, another study did not find an association between adiponectin SNP and breast cancer risk[45]. This study is the first one to look at an African American and Hispanic population and is to date the largest conducted study.

Age-adjusted incidence of breast cancer is highest among Caucasian women followed by African American and Hispanic women[46,47]. However, the incidence of obesity is significantly higher in African Americans and Hispanics than Caucasians[13]. Studies on the role of obesity in Caucasians have established that obesity increases the risk for postmenopausal breast cancer. In African Americans limited data suggest a similar association, whereas in Hispanics data suggest that obesity may be protective in the development of breast cancer[14]. There seems to be a positive association between DM and breast cancer regardless of ethnic group [48] but there is no data on the role of adiponectin in breast cancer in African Americans and Hispanics.

The present study is limited by the relatively small number of breast cancer cases (704 for African Americans and 212 for Hispanics), especially when correcting for multiple comparisons. Our study was underpowered to look at subtypes of breast cancers, such as ER, PR and HER2. This is important to assess in future studies given the prevalence of triple negative breast cancer in African Americans[49]. However, to our knowledge, this is the largest study to date evaluating the role of adiponectin pathway SNPs in breast cancer risk and is the first to do so in an African American and Hispanic population.

Several studies have shown a correlation between serum adiponectin levels and breast cancer risk[18,17]. This effect is independent of BMI[23]. We first showed that adiponectin pathway SNPs are associated with breast, colon and prostate cancer risk[34,35,36].

Rs1501299 was found to be significantly associated with breast and prostate cancer risk in our studies.

In summary this study confirms the importance of rs1501299 in predicting breast cancer risk not only in Caucasian but also in African Americans. Future studies need to be powered to look at different breast cancer subgroups as well as all ethnic groups.

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Table 1

Demographics of population.

Covariate	African American Mean (SD)	Hispanic Mean (SD)
Total sample size	8133	3422
Female relative had breast cancer		
Yes	1216	405
No	1862	891
Missing	5055	2126
BMI	31.2 (6.3)	29.1 (5.5)
Waist-hip ratio	0.83 (0.068)	0.82 (0.065)
Age at menarche		
7–11	2013	889
12–13	4056	1672
≥14	2022	854
Missing	42	7
Age at last period	46.4 (7.4)	47.8 (6.3)
Alcohol servings per week	1.1 (4.3)	1.28 (3.8)
Age at first birth		
None	495	92
<20	2109	568
20–29	3182	1554
≥30	468	234
Missing	1879	974
Breastfeed at least one month		
No	4140	1451
Yes	3858	1940
Missing	135	31
Breast cancer incidence	704	212
Invasive breast cancer	354	116
In situ breast cancer	90	23
ER (Invasive/in situ only)		
No	108	21
Yes	229	83
Missing	107	35
PR (Invasive/in situ only)		

Covariate	African American Mean (SD)	Hispanic Mean (SD)
No	137	28
Yes	191	68
Missing	116	43
HER2 (Invasive)		
No	207	55
Yes	43	12
Missing	104	49

BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor; HER2: Human Epidermal Growth Factor Receptor 2

Breast Cancer Res Treat. Author manuscript; available in PMC 2013 December 01.

Table 2a

Prior known associations with breast cancer.

	rs #		AA Counts Case/Control	AA HR (CI)	AA P	AA r^2	Hisp Counts Case/Control	Hisp HR (CI)	Hisp P	Hisp r^2	Meta HR	Meta P
adipor1	rs7539542	GG	128/126	1	---	0.88	63/61	1	---	0.89	1	---
		GC	170/172	0.96 (0.80, 1.15)	0.66		154/164	0.84 (0.55, 1.28)	0.41		0.94 (0.79, 1.11)	0.47
		CC	63/63	0.97 (0.77, 1.24)	0.83		144/137	0.94 (0.62, 1.42)	0.75		0.97 (0.79, 1.19)	0.74
adipoq	rs2241766	TT	330/330	1	---	0.97	259/252	1	---	0.99	1	---
		TG	34/35	0.98 (0.75, 1.27)	0.87		98/104	0.91 (0.66, 1.24)	0.53		0.95 (0.78, 1.16)	0.61
		GG	2/1	2.58 (0.81, 8.25)	0.10		9/10	0.83 (0.34, 2.04)	0.69		1.27 (0.63, 1.6)	0.51
adipoq	rs1501299	TT	37/46	1	---	0.99	24/28	1	---	1	1	---
		TG	157/168	1.18 (0.91, 1.54)	0.60		143/153	1.012 (0.57, 1.79)	0.97		1.15 (0.91, 1.46)	0.25
		GG	172/152	1.41 (1.084, 1.83)	0.010		199/185	1.16 (0.66, 2.02)	0.21		1.36 (1.073, 1.72)	0.011

AA: African American women; Hisp: Hispanic women; Allele: Allele 1/Allele 2; AF Allele frequency of Allele 1; HR: Hazards ratio; CI: confidence interval; Meta: Meta-analysis; r^2: Estimated imputation r^2.

Table 2b

Prior known associations with breast cancer under a dominant model.

	rs #		AA Counts Case/Control	AA HR (CI)	AA P	AA r^2	Hisp Counts Case/Control	Hisp HR (CI)	Hisp P	Hisp r^2	Meta HR	Meta P
adipor1	rs7539542	GG	128/126	1	---	0.88	63/61	1	---	0.89	1	---
		GC/CC	233/235	1.00 (0.81, 1.25)	0.96		298/301	0.95 (0.70, 1.28)	0.72		0.98 (0.83, 1.17)	0.86
adipoq	rs2241766	TT	330/330	1	---	0.97	259/252	1	---	0.99	1	---
		TG/GG	36/36	0.39 (0.12, 1.23)	0.10		107/114	1.17 (0.48, 2.85)	0.73		0.77 (0.38, 1.57)	0.48
adipoq	rs1501299	TT	37/46	1	---	0.99	24/28	1	---	1	1	---
		TG/GG	329/320	1.23 (1.059, 1.43)	0.0067		342/338	1.14 (0.87, 1.51)	0.32		1.21 (1.062, 1.38)	0.0044

Breast Cancer Res Treat. Author manuscript; available in PMC 2013 December 01.

Table 2c

Univariate analysis of SNPs in relation to breast cancer time-to-onset, not adjusted for multiple comparisons. We show the most significant five SNPs for African American, Hispanics, and for the meta-analysis of both, respectively, in the three sections of the chart.

Gene	rs #	Allele	AA AF (case/control)	AA HR (CI)	AA P	AA r^2	Hisp AF (case/control)	Hisp HR (CI)	Hisp P	Hisp r^2	Meta HR	Meta P
adipoq	rs1501299	T/G	0.31/0.36	0.84 (0.75,0.94)	0.0031	0.99	0.26/0.29	0.9 (0.72,1.12)	0.36	1	0.85 (0.77,0.95)	0.0023
adipor2	chr12:1863750:D	G/GA	0.056/0.042	1.36 (1.07,1.72)	0.012	0.96	0.0074/0.0034			0.85	NA	
adipoq	rs6773957	G/A	0.48/0.45	1.14 (1.029,1.27)	0.013	1	0.57/0.53	1.15 (0.94,1.4)	0.17	1	1.15 (1.043,1.26)	0.0044
adipoq	rs1063538	C/T	0.48/0.45	1.14 (1.028,1.27)	0.013	1	0.57/0.53	1.15 (0.94,1.4)	0.16	1	1.14 (1.043,1.26)	0.0046
adipoq	chr3:186572864:I	CA/C	0.48/0.45	1.14 (1.028,1.27)	0.014	0.99	0.56/0.53	1.13 (0.93,1.38)	0.22	0.98	1.14 (1.039,1.25)	0.0059
adipor2	rs73041886	C/T	0.037/0.029	---	---	0.9	0.12/0.08	1.54 (1.13,1.1)	0.0059	0.91	---	---
adipor2	rs73041888	T/C	0.037/0.029	---	---	0.9	0.12/0.08	1.54 (1.13,1.1)	0.0059	0.91	---	---
adipoq	rs1648707	A/C	0.48/0.46	1.035 (0.92,1.16)	0.55	0.89	0.51/0.55	0.78 (0.64,0.95)	0.015	0.95	0.97 (0.88,1.066)	0.49
adipoq	rs6444174	C/T	0.15/0.15	1.016 (0.88,1.18)	0.84	1	0.05/0.03	1.73 (1.11,1.7)	0.015	1	1.07 (0.93,1.23)	0.34
adipoq	rs4632532	T/C	0.48/0.46	1.034 (0.92,1.16)	0.56	0.89	0.51/0.55	0.78 (0.64,0.96)	0.016	0.95	0.97 (0.88,1.067)	0.5
adipoq	rs3774261	G/A	0.47/0.44	1.14 (1.025,1.27)	0.015	1	0.57/0.53	1.15 (0.95,1.4)	0.16	1	1.14 (1.041,1.25)	0.0051
adipor2	rs7137757	C/T	0.18/0.16	1.15 (0.99,1.34)	0.064	0.86	0.12/0.089	1.43 (1.037,1.98)	0.029	0.81	1.2 (1.046,1.37)	0.0093
adipoq	rs3821799	C/T	0.46/0.43	1.12 (1.0052,1.24)	0.04	1	0.54/0.51	1.16 (0.95,1.41)	0.14	1	1.13 (1.027,1.24)	0.012
adipoq	rs6414520	G/A	0.34/0.37	0.88 (0.78,0.98)	0.022	0.99	0.28/0.31	0.89 (0.72,1.11)	0.31	0.99	0.88 (0.8,0.97)	0.013
adipoq	rs4686804	A/G	0.46/0.43	1.11 (1.0021,1.24)	0.046	0.99	0.54/0.51	1.16 (0.95,1.41)	0.14	0.99	1.12 (1.024,1.24)	0.014

AA: African American women; Hisp: Hispanic women; Allele: allele 1/allele 2; AF: allele frequency of allele 1; HR: Hazards ratio; CI: Confidence interval; Meta: Meta-analysis; r^2: Estimated imputation r^2.

Breast Cancer Res Treat. Author manuscript; available in PMC 2013 December 01.

Table 3

Gene-based analysis of all SNPs and variables.

Gene	BRCA AA P	BRCA Hisp P	Invasive AA P	Invasive Hisp P	In-situ AA P	In-situ Hisp P
adipor2	0.15	0.31	0.04	0.97	0.51	0.13
adipor1	0.16	0.81	0.8	0.63	0.26	0.3
adipoq	0.03	0.16	0.1	0.26	0.55	0.19

BRCA: total breast cancer incidence; Hisp: Hispanics; AA: African Americans; p: p-value.