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Genetic variants in microRNAs and breast cancer risk in African American and European American women

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Abstract

MicroRNAs (miRNAs) are an integral part of the post-transcriptional machinery of gene expression and have been implicated in the carcinogenic cascade. Single nucleotide polymorphisms (SNPs) in miRNAs and risk of breast cancer have been evaluated in populations of European or Asian ancestry, but not among women of African ancestry. Here we examined 145 SNPs in 6 miRNA processing genes and in 78 miRNAs which target genes known to be important in breast cancer among 906 African American (AA) and 653 European American (EA) cases and controls enrolled in the Women's Circle of Health Study (WCHS). Allele frequencies of most SNPs (87%) differed significantly by race. We found a number of SNPs in miRNAs and processing genes in association with breast cancer overall or stratified by estrogen receptor (ER) status. Several associations were significantly different by race, with none of the associations being significant in both races. Using a polygenic risk score to combine the effects of multiple SNPs, we found significant associations with the score in each subgroup analysis. For ER-positive

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cancer, each unit increment of the risk score was associated with a 51% increased risk in AAs (OR=1.51, 95% CI=1.30–1.74, $p=3.3*10^{-8}$) and a 73% increased risk in EAs (OR=1.73, 95% CI=1.45–2.06, $p=1.4*10^{-9}$). These data show, for the first time, that miRNA-related genetic variations may underlie the etiology of breast cancer in both populations of African and European ancestries. Future studies are needed to validate our findings and to explore the underlying mechanisms.

Keywords

microRNA; SNP; breast cancer; epidemiology; estrogen receptor; polygenic risk score

Introduction

In women, breast cancer is the most common non-skin cancer diagnosed in the United States. In 2011, an estimated 230,480 new cases of breast cancer were diagnosed in women, and an estimated 39,520 women died from the disease [1]. The incidence rates of breast cancer were higher in European American (EA) women while the death rates were higher in African American (AA) women [2]. Studies have also shown that AA women tend to develop estrogen receptor (ER) negative tumors at an earlier age, and EA women are more likely to develop ER positive tumors at later ages [3–8]. The disparities in breast cancer incidence and survival between AA and EA populations have been attributed to several factors, including disease management, access to proper care, and biological influences. A recent study of the disparity in breast cancer mortality between AA and EA women concluded that differences in mortality are driven by higher hazard rates of breast cancer death in AA women, irrespective of ER expression [9]. In that work, the authors suggest that other biological factors may play a role in breast cancer disparities [9].

MicroRNAs (miRNAs) are small, noncoding RNAs that bind to the 3’ UTR of target mRNAs, and silence gene expression by inducing degradation of target mRNAs or inhibition of protein translation [10]. Because miRNAs may regulate approximately 60% of human genes [11], the relationship between miRNAs and human diseases has been extensively explored in the last decade. Many studies have demonstrated differential gene expression of miRNAs between normal and diseased tissue in cancer, and specific miRNAs have been linked to carcinogenic properties, including resistance to apoptosis, unchecked proliferation, angiogenesis, limited growth inhibition, and the propensity to invade and metastasize (reviewed in [12]). Aberrant miRNA expression patterns have been identified in breast cancer [13–15]. Of note, racial differences in miRNA expression have been observed in several studies. Son et al found that miRNA expression profiles in non-small cell lung cancer were different between Korean and Western populations [16]. In another study, a number of miRNAs were significantly differentially expressed in uterine leiomyoma between AA and EA women [17]. However, whether miRNA expression profiles are different in breast cancer tissues between AA and EA women is still unknown.

Functional genetic variations can affect gene expression or activity and thereby modify cancer risk. This might be particularly important for genetic variations in miRNA genes,

considering the fact that at least 60% of human protein-encoding genes are regulated by miRNAs. miRNAs can serve as either tumor suppressor genes or oncogenes. Genetic variations in miRNA genes can affect the levels of mature miRNAs, and consequently alter the mRNA expression levels of the target genes. Furthermore, SNPs in miRNA processing genes likely alter the production of miRNAs and SNPs in miRNA binding sites in target genes may change the interaction between miRNAs and target genes and subsequently their expression. SNPs in miRNA genes, miRNA processing genes, and binding sites in target genes have been tested in relation to the risk of several types of cancer, including breast cancer [18–21]. However, to the best of our knowledge, no previous studies have examined these relationships in women of African ancestry.

In this study, we employed a candidate gene approach for identifying SNPs in miRNA processing genes and in miRNA precursors (pre-miRNAs) that target genes known to play a role in breast cancer. We analyzed a total of 145 SNPs that present in 78 pre-miRNAs and 6 miRNA processing genes for associations with breast cancer risk in a large case-control study of AA and EA women.

Study Population and Methods

Study population

The Women's Circle of Health Study (WCHS) was designed specifically to study the role of genetic and non-genetic factors in relation to aggressive breast cancer risk in AA and EA women. Study design, enrollment, and collection of data and biospecimens have been described in detail previously [22]. Briefly, women diagnosed with incident breast cancer were identified through both hospital-based case ascertainment in targeted hospitals that had large referral patterns of AAs in four boroughs of the metropolitan New York City area, and using population-based case ascertainment in seven counties in New Jersey (NJ) through the NJ State Cancer Registry. The eligibility criteria for cases were: self-identified AA and EA women, 20–75 years of age at diagnosis, no previous history of cancer other than non-melanoma skin cancer, recently diagnosed with primary, histologically confirmed breast cancer, and English speaking. Controls without a history of any cancer diagnosis other than non-melanoma skin cancer living in the same area as cases were identified through random digit dialing and were matched to cases by self-reported race and 5-year age categories. To increase enrollment of AA women, particularly those with lower socioeconomic status, cases and controls were also invited to participate through community recruitment efforts as described in details previously [23]. Following agreement to participate, in-person interviews were conducted to complete informed consent and to query participants on a number of potential risk factors, including medical history, family history of cancer, diet, physical activity, and other lifestyle factors. Anthropometric measures were taken, and biospecimens were collected. Blood and/or saliva samples were collected for later extraction of DNA. Permission to obtain pathology data, including ER status, as well as tumor tissue blocks was included in the informed consent form. This study was approved by the Institutional Review Boards at Roswell Park Cancer Institute (RPCI), the Cancer Institute of New Jersey (CINJ) – Robert Wood Johnson Medical School (RWJMS), Mount Sinai School of Medicine (MSSM), and the participating hospitals in NYC. At the time of genotyping

(April 2010), DNA and data were available from 491 AA cases and 415 AA controls. We selected 336 EA cases and 317 EA controls from the WCHS by frequency matching them to AA cases and controls by 5-year age group.

Identification of SNPs

For this study, we focused on miRNA genes that are predicted to regulate key breast cancer genes (*BRCA1/2*, *p53*, *PTEN*, *CHEK2*, *ATM*, *NBS1*, *RAD50*, *BRIP1*, *PALB2*, *ER*, *PR* and *ERBB2*). A total of 146 miRNAs fit the criteria. We searched Entrez SNP (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=snp) for SNPs in premiRNA regions of these selected miRNAs and in binding sites of target genes and identified 99 SNPs with minor allele frequencies (MAFs) greater than 0.05 in either EAs or AAs. For miRNA processing genes, including *AGO1*, *AGO4*, *DGCR8*, *XPO5*, *PACT*, and *TARBP2*, we searched an extended genomic region 15kb from both 3' and 5' ends of each gene. Genotype data were downloaded from HapMap (23) and other resequencing projects through the Genome Variation Service at Seattle SNP (http://gvs.gs.washington.edu/GVS/), and multi-population tagSNPs to capture variations in both populations of European and African ancestry were selected using the TAGster program [24]. In total, 154 SNPs were selected for genotyping.

SNP genotyping

Genomic DNA extracted from blood or saliva samples was evaluated and quantified by Nanodrop UV-spectrometer (Thermo Fisher Scientific Inc., Wilmington, DE) and PicoGreen-based fluorometric assay (Molecular Probes, Invitrogen Inc., Carslbad, CA), and stored at −80°C until analysis. To control for potential bias due to population admixture, a panel of 108 ancestry informative markers (AIMs) that have been shown to be effective in correcting this bias in case-control studies were chosen [25]. Selected SNPs and AIMs were genotyped by Illumina GoldenGate genotyping assay (Illumina Inc., San Diego, CA) at the Genomics Facility at RPCI. Five percent duplicates and two sets of in-house trio samples were included for genotyping quality control purposes. No SNP violated Mendelian heritability. Six SNPs failed genotyping due to poor clustering or abnormal heterozygosity and were excluded. The average successful genotyping rate for each sample and each SNP was ≥99%. Three additional SNPs failed Hardy-Weinberg equilibrium and were excluded. As a result, a total of 145 SNPs were analyzed (Supplementary Table S1).

Statistical analysis

STRUCTURE program was used to estimate the proportion of European ancestry for each woman based on the genotype data of AIMs. Descriptive characteristics were analyzed by student t-test or chi-square test using SAS 9.3 (SAS Institute, Cary, NC). All genotype analyses were performed for AA and EA populations separately, using PLINK program if not otherwise specified. Genotypic (co-dominant) models were assumed for SNP effects. When genotype frequency of the rare homozygote was ≤5% in both populations, it was collapsed with the heterozygote (dominant model) for power considerations. In addition, recessive models were also explored. To test if there was a linear dose-effect of the variant alleles, SNPs were coded as 0, 1 and 2 according to the copy number of the variant allele

and tested using log-additive genetic models. A best model was selected for each SNP by considering both sample size and direction of associations across genotypes. Univariate single SNP analysis was first performed. Covariates, including age, body mass index (BMI), proportion of European ancestry, family history of breast cancer, and education, were then adjusted in multivariate logistic regression models to derive odds ratios (ORs) and 95% confidence intervals (CIs). Multiple comparison error was controlled by 10,000 permutations for SNP analyses. To test whether the associations of SNPs with breast cancer differed between AA and EA women, modification effect by race was examined by including an interactive term between race and each SNP in the model based on all women and tested using likelihood ratio tests. In addition to overall breast cancer risk, the analyses were also stratified by ER status within each race following the same analytical approaches.

Polygenic risk score

In addition to single SNP analysis, we also performed multi-marker analyses by using a modified method of the weighted polygenic risk score as described previously [26]. In brief, this multi-marker risk score was calculated as a sum of the number of risk genotypes (dominant and recessive models) and risk alleles (additive model), depending on the final model chosen for each SNP, weighted by the regression coefficients from logistic regression. For SNPs associated with a decreased risk, the reference and comparison groups were flipped so that the genotypes or alleles counted were associated with an increased risk. For a pair of SNPs located within 500kb on the same chromosome and in high linkage disequilibrium ($r^2 \geq 0.8$), only one SNP with stronger association from the pair was selected to be included in the polygenic score. For easier interpretation, the final score was standardized by dividing the sum of regression coefficients and then multiplying the expected maximum of number of risk genotypes and alleles, therefore, each unit of the polygenic score equals to one risk genotype or allele. The score was analyzed as a continuous variable in the logistic regression model with adjustment for the same set of covariates as described above.

Results

Description of study population

Table 1 outlines the characteristics of the study population. AA women tended to have a higher BMI than EA women (31.4 vs 27.3 kg/m^2), were less likely to use HRT (86% non-users in AAs vs. 75% non-users in EAs), and tended to have lower frequencies of family history of breast cancer (13.4% vs 21.0%), when compared to EA cases. The majority of women had college and graduate school education, but rates of women who pursued higher education were lower in AAs (57.6%) vs. EAs (82.2%). As expected, family history of breast cancer was higher in the cases than controls for both AAs and EAs, and controls were more highly educated. Among EAs, HRT use was slightly higher among cases, although the association was not statistically significant.

Differences in allele frequencies of SNPs between AA and EA women

Chromosomal location and minor allele frequency (MAF) of the 145 SNPs included in the final analysis are shown in Supplementary Table S1. MAFs of 126 of the 145 SNPs (87%)

in the controls were significantly different between AA and EA women ($p \leq 0.05$), 31 of which have the minor allele flipped between AAs and EAs.

Associations of SNPs in miRNA genes and processing genes with breast cancer risk

Top-ranked significant associations between SNPs in miRNA genes and overall breast cancer risk are shown in Table 2 for AAs and EAs separately. Among AA women, three SNPs, including rs7354931 in *AGO4*, rs12586258 in *hsa-miR-758*, and rs2018562 in *hsa-miR-513a-2* were associated with risk of breast cancer. The most significant SNP rs12586258 was associated with an almost 40% decreased risk in a dominant genetic model (OR=0.61, 95% CI=0.42–0.89, p=0.01). Among EA women, we identified seven SNPs, including rs2059691 in *PACT*, rs1527423 in *hsa-miR-106b*, rs1834306 in *hsa-miR-100*, rs11107973 in *hsa-miR-331*, rs10144193 in *hsa-miR-544*, rs1951032 in *hsa-miR-487*, rs5750504 in *hsa-miR-659*, that were significantly associated with breast cancer risk (Table 2). The most significant SNP rs1951032 was associated with an 81% increased risk in a dominant genetic model (OR=1.81, 95% CI=1.26–2.61, p=0.001). However, none of the above associations remained significant after correction for multiple comparisons. Interestingly, none of the SNPs showed a significant association with breast cancer in both AA and EA populations. In fact, five out of the above eight SNPs showed differential associations between AA and EA populations with a p for interaction by race <0.05 (Table 2).

Stratified analysis by ER status

When stratified by ER status, eight SNPs were associated with ER-positive cancer risk in AAs, with only one SNP, rs2018562 in *hsa-miR-513a-2*, being previously associated with overall breast cancer risk in AAs (OR=1.51, 95% CI=1.03–2.22, p=0.04) (Table 3). This same SNP was also associated with ER-negative cancer risk in AAs (OR=1.74, 95% CI=1.06–2.86, p=0.03), indicating that the association was not restricted to either subtype by ER status. Among EAs, nine SNPs were associated with ER-positive cancer risk (Table 3). These include the five SNPs previously associated with overall cancer risk in EAs (rs1834306 in *hsa-miR-100*, rs11107973 in *hsa-miR-331*, rs10144193 in *hsa-miR-544*, rs1951032 in *hsa-miR-487*, and rs5750504 in *hsa-miR-659*). The risk allele of the most significant SNP, rs5750504 in *hsa-miR-659*, was associated with an increased risk (per copy of the A allele: OR=1.45, 95% CI=1.12–1.87, p=0.005 in an additive genetic model). When tested for interaction by race, 3 of the 17 SNPs associated with ER-positive cancer risk in either AAs or EAs showed differential associations by race (p for interaction by race <0.05; Table 3).

For ER-negative cancer, four SNPs, which were not found in association with overall cancer risk, were associated specifically with ER-negative cancer risk in AAs, including the most significant SNP rs107822 in *hsa-miR-219* (OR=1.99, 95% CI=1.24–3.19, p=0.004) (Table 4).Three other SNPs were found in significant association with ER-negative breast cancer in EAs, including the most significant SNP rs2281611 in *hsa-miR-495* (OR=2.29, 95% CI=1.19–4.39, p=0.01) (Table 4). Only 1 of the 7 SNPs, rs2281611 in *hsa-miR-495I*, associated with ER-negative cancer risk in either AAs or EAs showed differential associations by race (p for interaction by race <0.05; Table 4).

Associations with polygenic risk score

A polygenic risk score was derived to examine the combined effects of significant single SNPs in relation to overall breast cancer risk in AA and in EA women, and stratified by ER status within each race category. The SNPs, designated risk allele or genotype, expected range of the polygenic score, mean and standard deviation of the score in cases and controls, and risk estimates per unit of the score are shown in Table 5. In each subgroup, breast cancer patients had higher polygenic risk score than controls, and per unit increment of the score was associated with significantly increased risk. The most significant results were found for ER+ cancer risk. Among AAs, per unit of the polygenic score was associated with a more than 50% increased risk of ER+ cancer risk (OR=1.51, 95% CI=1.30–1.74, $p=3.3*10^{-8}$). Among EAs, per unit of the polygenic score was associated with a more than 70% increased risk of ER+ cancer risk (OR=1.73, 95% CI=1.45–2.06, $p=1.4*10^{-9}$).

Discussion

In this study, we aimed to examine potential relationships between miRNA genetic variants in AA and EA women in relation to breast cancer risk. To achieve this goal, we analyzed 145 SNPs in miRNAs and miRNA processing genes associated with breast cancer from 906 AA women and 653 EA women enrolled in the WCHS study. There were marked differences in allele frequencies of SNPs in miRNAs examined in this study between populations of African and European ancestry. We found a number of SNPs in miRNAs and processing genes in association with overall breast cancer risk and stratified by ER status in either EA or AA women. Given the sample size, none of the associations remained significant after controlling for multiple comparisons. Nevertheless, using a polygenic risk score to combine the number of risk alleles or genotypes weighted by their effect sizes, we found highly significant associations between the risk score and breast cancer overall and by ER status. To our knowledge, this is the first study of its kind to investigate miRNA gene variants in breast cancer in both AA and EA women.

The associations between SNPs in miRNA genes and breast cancer risk have been previously studied, with rs11614913 in *hsa-miR-196a2* and rs2910164 in *hsa-miR-146a* found to be significant [27,28,18,19,29], although the associations are not consistent across the studies [30–32]. We included both of these SNPS in our study but, unfortunately, rs2910164 in *hsa-miR-146a* was dropped out due to low genotyping quality. For rs11614913 in *hsa-miR-196a2*, no association was observed in either the EA or AA population or by ER status. Our results are consistent with the report from Catucci *et al*. In their analysis of 1,894 German and Italian breast cancer patients and 2,760 healthy women, they failed to observe a significant association between rs11614913 in *hsa-miR-196a2* and breast cancer [32]. Lack of association was also observed in a recent study in an EA case-control study in Australia [30].

Overall, we observed 10 SNPs that were significantly associated with breast cancer in either EA or AA women. None of these SNPs have been previously investigated in relation to breast cancer. Interestingly, three of these significant SNPs, rs12586258 in *hsa-miR-758*, rs10144193 in *hsa-miR-544* and rs1951032 in *hsa-miR-487*, are located in a shared miRNA cluster on chromosome 14, which may potentially be the largest tumor suppressor miRNA

cluster. In addition, a fourth SNP in the chromosome 14 miRNA cluster, rs2281611 in *hsa-miR-495*, was associated with ER negative breast cancer in EA women in our study. This cluster has been shown to be down-regulated through epigenetic alteration in ovarian tumors, hepatocellular carcinomas, and gliomas [33–36]. Further studies should be conducted to identify the potential role of this miRNA cluster in breast cancer etiology. Although all three SNPs are located in the primary miRNA regions, not the precursor or mature miRNA regions, studies have shown that genetic variations in primary miRNA regions might affect the secondary structures of the primary transcripts of miRNAs and thereby alter the production of mature miRNAs. More interestingly, the effect of these three SNPs might not be limited to the miRNAs which they are close to. Since miRNAs tend to be transcribed together (e.g. miRNAs in the chromosome 14 cluster) and then spliced into individual miRNAs, genetic variations in primary miRNA regions have the potential to modify the expression of multiple mature miRNAs originating from the same primary transcripts.

The biogenesis of miRNAs is a complex process involving multiple proteins and RNAs (10). The major players include DROSHA, DGCR8, RAN, XPO5, DICER, and AGO family members. In this study, we evaluated tagSNPs in *AGO1*, *AGO4*, *DGCR8*, *XPO5*, *PACT*, and *TARBP2* genes. We found that *AGO4* gene variants were consistently associated with breast cancer among AA women (overall and ER positive), which have not been previously reported. The main function of the AGO protein family is to act cooperatively to silence both perfectly and partially complementary target RNAs bearing multiple small RNA-binding sites. Because of the potential overlap in function among the family members (e.g. AGO1, AGO3 and AGO4), the exact role of AGO4 in miRNA function is still unclear. Notably, *AGO4* was found to be overexpressed in colon cancers with distant metastases [37]. This finding may provide some insight into the aggressive behavior of breast tumors in AA women.

There were significant interactions between SNPs and race on breast cancer risk in our analyses. It is notable that no associations were observed in both AA and EA populations. Although the significant racial difference could be due to chance because of our moderate sample size, the findings may reflect the fact that the genomic structures are quite different between EAs and AAs. In fact, 126 of 145 genotyped SNPs showed significant MAF differences between EA and AA women in the control group. These differences in associations by race are also commonly reported in the literature. For example, among 11 EA GWAS SNPs, Zheng et al found that only two SNPs (2q35 and FGFR2 loci) were associated with breast cancer in AA women [38]. Thus, our results provide an impetus to pursue more genetic susceptibility studies in the AA populations.

One limitation of our study is the lack of a validation population. Our sample size became relatively limited after stratification by race and ER status, and none of the associations remained significant after correcting for multiple comparisons. Although the associations of the polygenic risk score and breast cancer risk were highly significant in our analyses, the SNPs chosen to be included in the scores have not been validated in an independent population, which may include false positive SNPs, and the effect sizes of the SNPs may have been inflated given our sample size. Therefore, we cannot exclude the possibility of

false positive findings in our study. However, the highly significant associations with the polygenic risk scores may provide support to our hypothesis of a role of miRNA genetic variations in breast cancer etiology. AA women are more likely to be diagnosed at a younger age than EAs. We enrolled all eligible AA women, but randomly frequency matched eligible EAs by 5 year age categories. We also initially limited eligibility to women 65 years or younger because of low participation of older women without breast cancer to case-control studies. Thus, the overall study population is relatively younger than many other studies. The high proportion of premenopausal women in this study needs to be considered in relation to generalizability of our findings to populations of older age.

To the best of our knowledge, this is the first study to investigate the role of SNPs in miRNA genes and miRNA processing genes in the etiology of breast cancer in a large population with both AA and EA women. We found prevalent differences in allele frequencies in SNPs in miRNAs, and significant associations between risk of breast cancer risk and a number of SNPs in miRNA genes and in miRNA processing genes, as well as a polygenic risk score, in either AA or EA women. Some of the SNPs showed significant interactions with ancestry. Additional studies are needed to confirm the associations and explore the genetic basis and underlying molecular mechanisms of the associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive characteristics of African American and European American breast cancer cases and controls

Characteristics	African American			European American		
	Case (n=491)	Control (n=415)	P	Case (n=336)	Control (n=317)	P
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age	50.8 (10.0)	50.2 (8.9)	0.40	50.5 (8.4)	50.4 (8.3)	0.93
Body mass index	31.2 (6.8)	31.6 (7.7)	0.47	26.9 (6.0)	27.7 (7.4)	0.15
% European ancestry	0.09 (0.15)	0.10 (0.16)	0.13	0.98 (0.07)	0.99 (0.03)	0.09
	Count (%)	Count (%)		Count (%)	Count (%)	
Menopausal status			0.07			0.44
Premenopausal	300 (61.1)	229 (55.2)		203 (60.6)	182 (57.6)	
Postmenopausal	191 (38.9)	186 (44.8)		132 (39.4)	134 (42.4)	
Family history			0.29			0.003
Yes	71 (14.5)	50 (12.0)		86 (25.6)	51 (16.1)	
No	420 (85.5)	365 (88.0)		250 (74.4)	266 (83.9)	
Education			0.07			0.002
Less than high school	71 (14.5)	49 (11.8)		7 (2.1)	4 (1.3)	
High school	154 (31.4)	110 (26.5)		73 (21.7)	32 (10.1)	
College and graduate school	266 (54.2)	256 (61.7)			256 (76.2)	281 (88.6)
Hormone replacement therapy			0.94			0.35
Yes	66 (13.6)	57 (13.7)		88 (26.2)	73 (23.0)	
No	421 (86.4)	358 (86.3)		248 (73.8)	244 (77.0)	

Footnote:

* P derived from student t-test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

Abbreviation: SD: standard deviation.

Table 2

Top ranked SNPs associated with breast cancer risk in African American and European American women

Gene/miRNA	SNP	Genotype	AA			EA			P for interaction with race
			# Case/Control	OR (95% CI)	P	# Case/Control	OR (95% CI)	P	
AGO4	rs7354931	CC	429/356	1.00	0.03	326/306	1.00	0.99	0.47
		CA/AA	42/55	0.63 (0.41–0.96)					
PACT	rs2059691	GG/GA	445/389	1.00	0.92	283/283	1.00	0.04	0.22
		AA	24/21	1.03 (0.56–1.89)		46/27	1.72 (1.03–2.87)		
hsa-miR-106b	rs1527423	AA	37/37	1.00	0.64	90/110	1.00	0.02	0.37
		AG/GG	436/375	1.12 (0.69–1.82)		238/200	1.50 (1.07–2.11)		
hsa-miR-100	rs1834306	GG/GA	248/221	1.00	0.77	267/230	1.00	0.03	0.05
		AA	225/191	1.04 (0.8–1.36)		62/79	0.64 (0.44–0.95)		
hsa-miR-331	rs11107973	AA/AG	305/285	1.00	0.18	256/267	1.00	0.02	0.18
		GG	169/127	1.22 (0.92–1.62)		72/42	1.65 (1.08–2.52)		
hsa-miR-758	rs12586258	GG	417/336	1.00	0.01	169/170	1.00	0.33	0.01
		GA/AA	56/76	0.61 (0.42–0.89)		159/140	1.17 (0.85–1.6)		
hsa-miR-544	rs10144193	AA	187/167	1.00	0.81	198/219	1.00	0.004	0.03
		AT/TT	287/244	1.03 (0.79–1.36)		130/91	1.65 (1.18–2.31)		
has-mir-487	rs1951032	GG	430/364	1.00	0.23	176/198	1.00	0.001	0.005
		GA/AA	38/44	0.75 (0.47–1.19)		110/73	1.81 (1.26–2.61)		
hsa-miR-659	rs5750504	TT	145/110	1.00	0.19	98/118	1.00	0.03	0.01
		TA/AA	328/302	0.82 (0.61–1.10)		231/192	1.45 (1.04–2.03)		
hsa-miR-513a-2	rs2018562	AA	133/143	1.00	0.04	190/178	1.00	0.97	0.36
		AG	225/193	1.25 (0.92–1.70)		117/113	0.97 (0.70–1.36)		
		GG	115/75	1.64 (1.13–2.39)		22/19	1.04 (0.54–2.01)		
		Per copy G allele		1.28 (1.06–1.54)	0.01		1.00 (0.77–1.29)	0.98	0.12

Footnote: Odds ratios and p-values adjusted for age, body mass index (BMI), proportion of European ancestry, family history of breast cancer, and education.

Abbreviations: OR: odds ratio; CI: confidence interval.

Table 3

Top ranked SNPs associated with estrogen receptor (ER) positive breast cancer risk in African American and European American women

Gene/miRNA	SNP	Genotype	AA			EA			P for interaction with race
			# Case/Control	OR (95% CI)	P	# Case/Control	OR (95% CI)	P	
AGO4	rs16822342	AA	155/229	1.00	0.04	180/277	1.00	0.84	0.42
		AG/GG	87/183	0.71 (0.51–0.99)		20/33	0.94 (0.52–1.69)		
AGO4	rs3820276	GG	111/232	1.00	0.01	188/287	1.00	0.52	0.11
		GC/CC	131/179	1.51 (1.1–2.08)		12/23	0.79 (0.38–1.63)		
XPO5	rs11077	AA	39/45	1.00	0.05	76/127	1.00	0.68	0.06
		AC/CC	203/366	0.63 (0.4–1)		124/183	1.08 (0.75–1.56)		
hsa-miR-548a-2	rs878175	AA	59/110	1.00	0.58	154/210	1.00	0.02	0.04
		AG/GG	183/302	1.11 (0.77–1.61)		46/100	0.6 (0.4–0.91)		
hsa-miR-106b	rs1527423	AA	23/37	1.00	0.88	55/110	1.00	0.05	0.19
		AG/GG	219/375	0.96 (0.55–1.66)		144/200	1.49 (1.01–2.21)		
hsa-miR-455	rs2060133	CC	49/65	1.00	0.12	149/209	1.00	0.04	0.9
		CG/GG	193/345	0.72 (0.47–1.09)		50/101	0.66 (0.44–0.99)		
hsa-miR-606	rs12266981	GG	186/344	1.00	0.02	199/309	1.00	0.99	0.98
		GA/AA	55/66	1.6 (1.07–2.4)		1/0			
hsa-miR-100	rs1834306	GG/GA	125/221	1.00	0.67	167/230	1.00	0.01	0.02
		AA	116/191	1.07 (0.78–1.49)		33/79	0.56 (0.35–0.88)		
hsa-miR-331	rs11107973	AA/AG	161/285	1.00	0.58	155/267	1.00	0.03	0.13
		GG	81/127	1.1 (0.78–1.55)		44/42	1.7 (1.06–2.73)		
hsa-miR-544	rs10144193	AA	86/167	1.00	0.23	125/219	1.00	0.04	0.44
		AT/TT	156/244	1.22 (0.88–1.7)		74/91	1.49 (1.01–2.19)		
has-mir-487	rs1951032	GG	216/364	1.00	0.88	118/198	1.00	0.05	0.2
		GA/AA	24/44	0.96 (0.56–1.64)		62/73	1.53 (1.01–2.31)		
hsa-miR-628	rs8041885	AA	92/124	1.00	0.03	160/245	1.00	0.75	0.29
		AG/GG	150/288	0.69 (0.49–0.97)		39/64	0.93 (0.59–1.46)		
hsa-miR-628	rs8041044	CC	95/123	1.00	0.01	161/245	1.00	0.66	0.23
		CA/AA	147/288	0.65 (0.46–0.91)		39/65	0.9 (0.58–1.42)		

Gene/miRNA	SNP	Genotype	AA			EA			P for interaction with race
			# Case/Control	OR (95% CI)	P	# Case/Control	OR (95% CI)	P	
hsa-miR-122a	rs17669	AA/AG	212/338	1.00	0.05	188/291	1.00	0.90	0.24
		GG	29/73	0.63 (0.39–1)		12/18	1.05 (0.49–2.28)		
DGCR8	rs9606241	AA/AG	228/382	1.00	0.62	94/159	1.00	0.03	0.26
		GG	14/28	0.85 (0.43–1.64)		26/22	1.99 (1.09–3.64)		
hsa-miR-659	rs5750504	TT	76/110	1.00	0.08	57/118	1.00	0.02	0.05
		TA	104/215	0.71 (0.49–1.04)		94/144	1.33 (0.88–2.02)		
		AA	62/87	1.06 (0.68–1.65)		49/48	2.13 (1.27–3.56)		
		Per copy A allele		1.01 (0.81–1.26)	0.93		1.45 (1.12–1.87)	0.005	0.04
hsa-miR-513a-2	rs2018562	AA/AG	180/336	1.00	0.04	188/291	1.00	0.93	0.28
		GG	61/75	1.51 (1.03–2.22)		12/19	0.97 (0.45–2.06)		

Footnote: Odds ratios and p-values *a*djusted for age, body mass index (BMI), proportion of European ancestry, family history of breast cancer, and education.

Abbreviations: OR: odds ratio; CI: confidence interval; ER: estrogen receptor

Table 4

Top ranked SNPs associated with estrogen receptor (ER) negative breast cancer risk in African American and European American women

Gene	SNP	Genotype	AA			EA			P for interaction with race
			# Case/Control	OR (95% CI)	P	# Case/Control	OR (95% CI)	P	
hsa-miR-219	rs107822	GG	29/174	1.00	0.004	24/180	1.00	0.17	0.5
		GA/AA	78/235	1.99 (1.24–3.19)		27/130	1.52 (0.84–2.77)		
hsa-mir-595	rs4909238	AA/AG	77/338	1.00	0.03	37/248	1.00	0.16	0.81
		GG	27/70	1.76 (1.05–2.95)		14/61	1.64 (0.82–3.26)		
hsa-miR-204	rs7861254	GG	37/106	1.00	0.04	28/166	1.00	0.77	0.3
		vs. GG	70/306	0.62 (0.39–0.99)		23/144	0.91 (0.5–1.67)		
hsa-miR-608	rs4919510	CC	43/153	1.00	0.42	41/204	1.00	0.03	0.18
		CG/GG	64/259	0.83 (0.54–1.29)		10/106	0.45 (0.21–0.94)		
hsa-miR-758	rs7141987	AA	2/19	1.00	0.36	8/94	1.00	0.03	0.83
		AG/GG	104/392	2.01 (0.45–8.93)		43/210	2.41 (1.08–5.37)		
hsa-miR-495	rs2281611	CC	62/233	1.00	0.92	15/151	1.00	0.01	0.03
		CA/AA	45/179	0.98 (0.63–1.51)		36/159	2.29 (1.19–4.39)		
hsa-miR-513a-2	rs2018562	AA	25/143	1.00	0.03	26/178	1.00	0.33	0.46
		AG/GG	82/268	1.74 (1.06–2.86)		25/132	1.35 (0.74–2.47)		

[*] *Footnote:* Odds ratios and p-values*a*djusted for age, body mass index (BMI), proportion of European ancestry, family history of breast cancer, and education.

Abbreviations: OR: odds ratio; CI: confidence interval; ER: estrogen receptor

Table 5

Polygenic risk score and breast cancer risk in African American and European American women

Subgroup	SNPs (risk genotype or allele)	Expected range of polygenic risk score	Mean (SD) of polygenic score in cases	Mean (SD) of polygenic score in controls	OR (95% CI) per unit of composite genetic score	P
Overall risk in AAs	rs7354931(CC), rs12586258(GG), rs2018562(G allele)	0–4.0	3.0 (0.8)	2.8 (0.8)	1.44 (1.21–1.71)	$3.3*10^{-5}$
Overall risk in EAs	rs2059691(AA), rs1527423(AG/GG), rs1834306(GG/GA), rs11107973(GG), rs1951032(GA/AA), rs5750504(TA/AA)	0–6.0	3.7 (1.2)	3.3 (1.2)	1.37 (1.18–1.59)	$3.2*10^{-5}$
ER+ in AAs	rs16822342(AA), rs3820276(GC/CC), rs11077(AA), rs12266981(GA/AA), rs8041044(CC), rs17669(AA/AG), rs2018562(GG)	0–7.0	3.0 (1.2)	2.5 (1.1)	1.51 (1.30–1.74)	$3.3*10^{-8}$
ER+ in EAs	rs878175(AA), rs1527423(AG/GG), rs2060133(CC), rs1834306(GG/GA), rs11107973(GG), rs1951032(GA/AA), rs9606241(GG), rs5750504(A allele)	0–9.0	4.6 (1.3)	3.9 (1.2)	1.73 (1.45–2.06)	$1.4*10^{-9}$
ER− in AAs	rs107822(GA/AA), rs4909238(GG), rs7861254(GG), rs2018562(AG/GG)	0–4.0	2.1 (0.8)	1.7 (0.9)	1.73 (1.35–2.22)	$1.4*10^{-5}$
ER− in EAs	rs4919510(CC), rs7141987(AG/GG), rs2281611(CA/AA)	0–3.0	2.4 (0.9)	1.9 (1.0)	1.73 (1.22–2.45)	$2.0*10^{-3}$
Triple negative in AAs	rs107822 (GA/AA), rs4909238(GG), rs7861254(GG), rs2185743(AA), 3008372(GA/AA), rs543412(GG), rs2217653(AG/GG)	0–7.0	3.5 (1.3)	2.7 (1.4)	1.49 (1.21–1.83)	$2.0*10^{-4}$
Triple negative in EAs	rs11100610(AA), rs5905010(GC/CC)	0–2.0	1.1 (0.6)	0.6 (0.7)	2.86 (1.47–5.55)	$2.0*10^{-3}$

Footnote: Odds ratios and p-values *a*djusted for age, body mass index (BMI), proportion of European ancestry, family history of breast cancer, and education. Weighted composite genetic score is calculated as the sum of the number of risk allele or genotype weighted by their effect sizes of top ranked SNPs in each subgroup, which is then standardized to make 1 unit of the score equal to 1 risk allele or genotype, depending on the genetic model used for each SNP.

Abbreviations: SD: standard deviation; OR: odds ratio; CI: confidence interval