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Association of Progesterone Receptor Gene (*PGR*) variants and breast cancer risk in African American Women

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Abstract

Background—Prolonged exposure to combined hormone replacement therapy (estrogen plus progestin) increases a woman's risk of breast cancer whereas estrogen-only hormone replacement therapy does not. This suggests that progesterone may play a role in breast carcinogenesis. Association studies have reported inconsistent relationships between progesterone receptor gene variants and breast cancer.

Methods—A population- based case-control study in three counties of the Philadelphia Metropolitan area was undertaken. We evaluated eight *PGR* candidate SNPs and eighteen *PGR* tagging SNPs in 487 breast cancer cases and 843 controls using multivariable logistic regression with adjustment for combined hormone replacement therapy use. Separate analyses were conducted for European Americans (EA: 399 cases, 490 controls) and African Americans (AA: 88 cases, 353 controls).

Results—In EAs, no significant associations were observed with the investigated *PGR* variants. In AAs, two tagging SNPs (*rs590688* and *rs10895054*) were statistically significantly associated with breast cancer. For *rs590688*, each addition of the C allele was protective compared to the G allele (OR=0.56, 95% CI: 0.39–0.82, p-value 0.003, corrected p-value 0.03). For *rs10895054*, each addition of the T allele increased the risk of breast cancer compared to the A allele nearly three-fold (OR=2.9, 95% CI: 1.47–6.02, p value 0.002, corrected p value 0.04). Three haplotype blocks, all containing *rs590688*, were found to be significantly associated with breast cancer risk. Environmental exposures, namely parity and obesity modified the effect of both SNPs on breast cancer risk in EA.

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The authors declare that they have no conflicts of interest.

Conclusion—This is the first study to find an association between two *PGR* variants and breast cancer in AA women. These results suggest that studies of *PGR* variants in other non-White populations may reveal additional cancer associations of interest.

Keywords

Progesterone receptor; Breast Cancer; genotype; hormone replacement therapy; risk

Introduction

Prolonged exposure to estrogen is clearly implicated in the development of breast cancer. Early menarche, late menopause, reduced parity, later maternal age of first live birth, and obesity are all associated with prolonged estrogen exposure and increased breast cancer risk [1]. The role of progesterone and progesterone receptors in the development of malignancy is not as clear. Interestingly, the Women's Health Initiative demonstrated that prolonged exposure to combined hormone replacement therapy including estrogen plus progestin increases a post-menopausal woman's risk of breast cancer, whereas estrogen-only hormone replacement therapy does not [2,3]. This finding has been reported in several other studies [4–9]. This suggests that progestins (a synthetic form of progesterone) may play a role in breast carcinogenesis. Interestingly, physiologic exposure to progesterone does not appear to increase and may actually reduce breast cancer risk [10,11]. The role of progesterone in breast tissue is not well defined, although it appears that the hormone may stimulate progesterone receptor mediated transcription of genes that both stimulate and inhibit breast tissue differentiation [12]. Because the progesterone receptor is crucial to the function of progesterone and progestins, it has been hypothesized that a progesterone receptor variant could alter the effect of progesterone on breast cells and thus, influence breast cancer risk.

The progesterone receptor is coded by *PGR* located on chromosome 11q22.1. *PGR* encodes two progesterone receptor isoforms with different promoters and different translational start sites. This results in two gene products: PRA is 94KDa and acts as a transcriptional repressor; PRB is 114 Kda and acts as a transcriptional activator [12]. *PGR* is polymorphic with greater than 800 described SNPs [13].

Candidate gene association studies have reported associations between *PGR* variants and various hormonally related diseases such as endometrial and ovarian cancer [14–19], endometriosis [20], impaired implantation after in vitro fertilization [21], and recurrent miscarriages [22,23]. Some studies have found an association with *PGR* variants and breast cancer, but the results have not been consistent [24–26,14,27–31,16]. To further explore the role of *PGR* in steroid hormone-related disease, we conducted a case control study to examine whether variability in *PGR* is related to breast cancer risk, whether this relationship varies by race and whether environmental factors related to hormone exposure modify the effect of *PGR* on breast cancer risk.

Materials and Methods

Study Design and Data Collection

The Women's Insights and Shared Experiences (WISE) study is a population based case-control study of postmenopausal women conducted in a 3-county area of metropolitan Philadelphia in which incident breast and endometrial cancer cases were identified through hospitals and validated using the Pennsylvania State Cancer Registry. Frequency-matched controls were identified from the community using random digit dialing. Additional details of the WISE study design can be found in studies by Bunin et al. [32] and Strom et al. [33]. The source population for this study was Philadelphia County (PA), Delaware County (PA),

and Camden County (NJ). Potentially eligible cases were women residing in these counties at the time of diagnosis who were ages 50 to 79 years old and were newly diagnosed with breast cancer between July 1, 1999 and June 30, 2002. Genomic DNA was obtained from buccal swabs as previously described. Additional details of our study design, which included ascertainment of both breast and endometrial cancer cases and matched controls, have been previously reported [28].

Laboratory Methods

Buccal swabs were obtained by mail from each participant. Extraction of genomic DNA was done using QIAamp 96 DNA Buccal Swab Biorobot kit and done on a 9604 Biorobot (Qiagen, Inc., Valencia, CA). No whole genome amplification was done before genotype analysis. We identified 8 candidate single nucleotide polymorphisms (SNPs) in the *PGR* gene with a minor allele frequency (MAF) greater than or equal to 5% which were reported in the literature to have some clinical relevance using NCBI Entrez Gene SNP Geneview. The variants selected were *rs1042838*, *rs1042839*, *rs11571171*, *rs3740753*, *rs500760*, *rs566351*, *rs660149*, and *rs7116336*.

In addition to identifying candidate SNPs, we also selected nineteen haplotype tagging SNPs (htSNPs) using SNPbrowser 4.0. htSNPs are representative SNPs in regions of high linkage disequilibrium. The identification and genotyping of a set of tag SNPs allows for the identification of genetic variation within a chromosomal region without genotyping every SNP in that region [34]. In this study, htSNPs were considered if they had a haplotype $R^2 > 95\%$ and a MAF greater than or equal to 5%. The tag SNPs selected were as follows: *rs11224561*, *rs10895054*, *rs11224580*, *rs471767*, *rs492457*, *rs506487*, *rs518382*, *rs538915*, *rs553272*, *rs635984*, *rs11224580*, *rs1379131*, *rs1824126*, *rs495997*, *rs507141*, *rs537681*, *rs590688*, *rs601040*, and *rs653752*.

Genotyping was performed via Taqman Open Array Platform. A total of 1,364 subjects underwent genotyping. Adequate genotype data could not be obtained from thirty-four (34) participants. Four SNPs (*rs11571171*, *rs566351*, *rs11224561*, and *rs1824126*) were excluded from the analysis because of high failure rates ($>10\%$). Two additional SNPs (*rs495997* and *rs3740753*) were excluded from the analysis due to significant deviations from Hardy-Weinberg Equilibrium ($p < 10^{-5}$) in the control population. To assess the impact of SNP genotypes on breast cancer risk, we used the homozygous wild type genotype (wt/wt) based on the common allele as the referent category and assessed the relative risk associated with heterozygous and homozygous variant carriers (var/*).

Statistical Methods

We conducted separate analyses for EA and AA women to avoid the potential for confounding based on race (population stratification bias). A study participant's race was determined by self report. Differences in baseline characteristics between cases and controls were assessed using chi-squared tests for categorical variables and t-tests for continuous variables.

In order to assess the association of genetic variants with breast cancer risk, we estimated odds ratios, their corresponding 95% confidence intervals, and associated p-values using logistic regression. We assessed potential confounding due to endogenous or exogenous hormone exposures such as combined hormone replacement use, parity, age at first live birth, age of menopause/menarche, and BMI by including them in the multivariable logistic regression model. We adjusted for multiple comparisons using the false discovery rate method described by Benjamini and Hochberg [35]. We also explored the possibility of

interaction between all genotypes and these hormone exposures. All analyses were performed using STATA (version 11.0, STATA Corporation, College Station, TX

We used Haploview to generate haplotype blocks and visualize linkage disequilibrium from our genotype dataset. To investigate haplotype associations, we first used the EM algorithm to estimate haplotype frequencies and then used a generalized linear models framework to obtain haplotype odds ratios using the R programs Haplo.em and Haplo.stats (R version 2.8.0) [36].

Results

Baseline characteristics of cases and controls are presented in Table 1. In both the EA and AA cohorts, the only characteristic that differed significantly between cases and controls was parity, with cases having a much higher proportion of nulliparous women.

Measures of environmental hormonal exposure, including parity, age at first term pregnancy, age at menarche, age at menopause, and BMI) were all considered as potential confounders. None of these variables were associated with any of our exposures (PGR variants) or our outcome (breast cancer), and thus, by definition, were not confounders. Because there is ample data demonstrating that combined estrogen/progesterone-containing hormone replacement therapy (chrt) increases risk of breast cancer (compared to estrogen-only hormone replacement therapy), we decided *a priori* to adjust for CHRT in our models. CHRT use was defined as use of combined estrogen and progesterone hormone replacement therapy for greater than 3 years.

Tables 2a and 2b show the associations between each PGR variant and risk of breast cancer in the study population. In EAs, no significant main effects were observed in any of the *PGR* variants studied. In AAs, two SNPs (*rs590688* and *rs10895054*) were found to be statistically significantly associated with breast cancer. For *rs590688*, each addition of the variant (C allele) was found to be protective compared to the wild type allele (G allele) (OR 0.56 (95% CI: 0.39–0.82), p value 0.003, corrected p value 0.03). For *rs10895054*, each addition of the variant (T allele) increased the risk of breast cancer compared to the wild type allele (A) (OR 2.9 (95% CI: 1.47–6.02), p value 0.002, corrected p value 0.04).

To explore further why these two variants (*rs590688* and *rs10895054*) were found to be significantly associated with breast cancer in the AA population but not in the EA population, we investigated whether environmental exposures modified the effect of the gene variant on breast cancer risk. Because the number of homozygous variants was small, we combined heterozygotes and variant homozygotes into the logistic regression analysis and used wildtype homozygotes as the reference category. Of note, we did not correct for multiple testing for this portion of the analysis. In EAs, the presence of the *rs590688* variant (C allele) decreases breast cancer risk (see Table 3), however this finding is not significant. However, the variant is associated with increased breast cancer risk in the presence of nulliparity (OR 3.07 (95% CI: 1.25–7.57, p value 0.014) or a BMI ≥ 30.0 (OR 5.7 (95% CI: 1.3–24, p value 0.018). In EAs with the *rs590688* variant, CHRT use and menarche ≥ 14 years were associated with a decreased risk of breast cancer (OR 0.33 (95% CI: 0.14–0.755, p value 0.003) and OR 0.297 (95% CI: 0.11–0.799, p value 0.009) respectively). In AAs with the *rs590688* variant, menarche ≥ 14 years was also associated with a decreased risk of breast cancer (OR 0.177 (95% CI: 0.37–0.857, p value 0.031)) (See Table 4). No other statistically significant interactions were observed in AAs with the *rs590688* variant, possibly due to insufficient power in this subgroup. In EAs, the presence of the *rs10895054* variant increases breast cancer risk, albeit not significantly so. However, for EAs with the *rs10895054* variant, nulliparity and a BMI of ≥ 30.0 was associated with a decreased risk of

developing breast cancer (OR 0.29 (95% CI: 0.125–0.67, p value 0.004) and OR 0.17 (95% CI: 0.05–0.67, p value 0.01) respectively) (See Table 4). There were no statistically significant interactions seen in the AA subgroup, again, possibly due to limited power in this subgroup. Because both the EA and AA subgroups have relatively small sample sizes, these results should be interpreted with caution. For EAs with either variant (*rs590688* or *rs10895054*), the presence of nulliparity alters the association with breast cancer, so that it is in the opposite direction of the variant's main effect. One could conclude that the main effect of the variant is 'diluted' in EAs by the increased proportion of nulliparous women in that subgroup (see Table 1). However, the presence of a BMI ≥ 30.0 , also alters both variant's association with breast cancer so that it is in the opposite direction of the main effect, and BMI ≥ 30.0 is more common in AAs (see Table 1). Thus, the discrepancy in the variants effect in the EA population and AA population is currently unexplained by interactions with environmental factors that were measured in this study.

In AA, three haplotype blocks (all containing *rs590688*) were found to be significantly associated with breast cancer risk (see Table 4). However, it appears that the effect of each of these haplotypes on our outcome is being driven by the main effect of the individual SNP, *rs590688* that happens to be in strong linkage disequilibrium with *rs601040* and *rs537681* (See Figure 1). The variant, *rs10895054*, was not found to be in strong linkage disequilibrium with any other SNP's investigated in this study. Again, we did not correct for multiple testing in this portion of the analysis.

Discussion

We report that two PGR tagging SNPs (*rs590688* and *rs10895054*) are significantly associated with breast cancer in our AA cohort. Why this association was found in AAs, but not EAs is unclear. Confounding by ethnicity (population stratification bias) refers to false-positive associations found in racially heterogeneous populations where both the disease and allele frequency vary by race. To avoid the potential for confounding by ethnicity, we stratified our analysis based on race. However, AAs are a highly admixed population, composed of both African and EA ancestry. Breast Cancer incidence varies by race, with breast cancer being less common in AA women, then in women of European descent [37]. The control allele frequencies of *rs590688* (EAs: C 0.5054, G 0.4946; AAs C 0.5209, G 0.4791) and *rs10895054* (EAs: A 0.8337, T 0.1663; AAs: A 0.9725, T 0.0275) were similar in AAs and EAs. Because a requirement for population stratification is that differences in allele frequencies exist across populations [38], confounding by ethnicity is unlikely to explain the different results obtained in each race.

Another possible explanation for the discrepancy in results is due to gene-environment interactions. In this study, we examined environmental factors related to hormone exposure. We do report a few gene-environment interactions (see Table 4), however these results should be interpreted with caution due to our small sample size. Regardless, even if these interactions are real, they do not explain the discrepancy in findings between AAs and EAs. It is possible that the discrepancy in our results may be due the interaction between *rs590688* and *rs10895054* and environmental or genetic factors that we did not measure in our study.

To minimize false-positive associations, we adjusted our p values in our main analysis for multiple comparisons using the Benjamini and Hochberg method [35]. Despite this correction, we still cannot rule out the possibility that our findings are due to chance alone, and thus need to be confirmed in larger epidemiologic studies.

One candidate SNP, *rs1042838*, was associated with breast cancer in prior studies [26,27,24], but was not found to be significantly associated with breast cancer in our study.

In these prior studies, the magnitude of the effect was small ($OR < 1.5$); our study is only powered to detect odds ratios greater than 1.9. Thus, there may be a real association between *rs1042838* and breast cancer, but our study was under powered to detect it in either subgroup. Likewise, there may be associations between other SNPs that we studied and breast cancer, however, if the magnitude of the association was small ($OR < 1.9$), we were not powered to detect this.

Our study is a candidate gene association study, and thus has many of the limitations associated with these studies. Breast cancer is a complex disease and is likely the result of interplay between many genes and the environment, limiting our power to find an association between just one gene and this outcome. In addition, breast cancer is a heterogeneous disease composed of many biological subtypes that behave differently and respond differently to therapy. Different biologic subtypes may have different genetic origins. We limited our study population to women who were 50 to 79 years old, capturing mainly postmenopausal women. Breast cancer in pre-menopausal women is more likely to be hormone receptor negative, behave more aggressively, and is associated with a poorer prognosis when compared to post-menopausal breast cancer. In addition, a recent study looking at gene expression profiling in breast cancers, identified over-expression of 367 gene sets that could differentiate tumors from pre-menopausal and post-menopausal women, indicating that breast cancer in pre-menopausal women may be a distinct entity [39]. Thus, by limiting our study to post-menopausal, we eliminate some disease heterogeneity, but certainly not all.

In conclusion, we report that two SNPs in PGR (*rs590688* and *rs10895054*) are significantly associated with breast cancer in our AA cohort. This is the first study that reports this association. These findings need to be confirmed in larger epidemiologic studies.

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Figure 1.
Linkage disequilibrium (D') and haplotype blocks in *PGR* gene in African Americans

Table 1aBaseline Characteristics of European American Cases and Controls^a

Characteristic	Cases (n=399)	Controls (n=490)	p value
Age at reference date, years			
50–54	85 (21.3%)	96 (19.6%)	0.125
55–59	78 (19.5%)	115 (23.5%)	
60–64	64 (16%)	83 (16.9%)	
65–69	54 (13.5%)	82 (16.7%)	
70–74	59 (14.8%)	67 (13.7%)	
75–80	59 (14.8%)	47 (9.6%)	
chrt use	107 (26.8%)	144 (29.4%)	0.411
nulliparity	81 (20%)	56 (11%)	<0.0001
Mean maternal age of first live birth (SD)	24.1 (4.7)	24.3 (4.7)	0.58
Maternal age of first live birth 30 years	44 (11%)	68 (14%)	0.2
Mean number of live pregnancies (SD)	3.6 (1.9)	3.6 (1.9)	0.93
Mean age of menarche (SD)	12.6 (1.5)	12.7 (1.8)	0.3
Mean age of menopause (SD)	47.8 (5.9)	47.9 (6.2)	0.8
BMI			
<18.5	19 (3%)	35 (4%)	0.678
18.5–24	463 (69%)	609 (67%)	
25.0–29	143 (21%)	189 (21%)	
30.0+	50 (7%)	72 (8%)	

Table 1b

Baseline Characteristics of African American Cases and Controls

Characteristic	Cases (n=88)	Controls (n=353)	p value
Age at reference date, years			
50–54	15 (17.1%)	95 (26.9%)	0.095
55–59	20 (22.7%)	91 (25.8%)	
60–64	15 (17.1%)	55 (15.6%)	
65–69	22 (25%)	55 (15.6%)	
70–74	7 (7.9%)	37 (10.5%)	
75–80	9 (10.2%)	20 (5.7%)	
chrt use	4 (4.5%)	40 (11%)	0.06
nulliparity	15 (17%)	26 (7%)	0.005
Mean maternal age of first live birth (SD)	21 (5.2)	21 (4.7)	0.8
Maternal age of first live birth 30 years	5 (6%)	20 (6%)	0.995
Mean number of live pregnancies (SD)	4.1 (2.5)	4.1 (2.4)	0.95
Mean age of menarche (SD)	12.9 (3.4)	12.7 (1.9)	0.5
Mean age of menopause (SD)	46 (8.0)	45.6 (7.9)	
BMI			
<18.5	8 (3%)	11 (1.8%)	0.286
18.5–24	130 (48.7%)	305 (49.3%)	
25.0–29	87 (32.6%)	180 (29%)	
30.0+	42 (19%)	123 (20%)	

Abbreviations: SD, standard deviation; BMI, body mass index

^aData is composed of both numbers and percentages and means and standard deviations

Table 2aOdds Ratios for twenty *PGR* variants in European American Women

PGR SNP	Genotype	Cases	Controls	Per allele OR (95% CI)*	p value	corrected p value**
<i>RS1042839</i>	GG	251 (64%)	340 (71%)	1.41 (1.06–1.88)	0.017	0.34
	GA	143 (36%)	137 (29%)			
	AA	0 (0%)	0 (0%)			
<i>RS10895054</i>	AA	250 (65%)	318 (71%)	1.19 (0.93–1.52)	0.17	0.47
	AT	118 (31%)	111 (25%)			
	TT	15 (4%)	19 (4%)			
<i>RS11224580</i>	CC	324 (84%)	343 (78%)	0.697 (0.50–0.97)	0.035	0.35
	CT	61 (16%)	93 (21%)			
	TT	2 (1%)	4 (1%)			
<i>RS11571271</i>	GG	358 (98%)	369 (95%)	0.49 (0.22–1.10)	0.085	0.43
	GT	9 (2%)	19 (5%)			
	TT	0 (0%)	0 (0%)			
<i>RS1379131</i>	AA	275 (71%)	303 (68%)	0.85 (0.65–1.12)	0.26	0.65
	AG	107 (28%)	132 (30%)			
	GG	5 (1%)	10 (2%)			
<i>RS471767</i>	AA	206 (54%)	220 (51%)	0.94 (0.77–1.15)	0.58	0.96
	AG	133 (35%)	161 (37%)			
	GG	44 (11%)	50 (11%)			
<i>RS492457</i>	AA	230 (60%)	262 (57%)	0.99 (0.80–1.22)	0.91	0.96
	AG	124 (32%)	163 (36%)			
	GG	32 (8%)	31 (9%)			
<i>RS506487</i>	CC	183 (48%)	211 (47%)	0.96 (0.78–1.18)	0.68	0.91
	CT	159 (41%)	190 (42%)			
	TT	39 (10%)	49 (11%)			

PGR SNP	Genotype	Cases	Controls	Per allele OR (95% CI)*	p value	corrected p value**
<i>RS507141</i>	GG	256 (67%)	302 (71%)	1.16 (0.89–1.50)	0.27	0.61
	GA	116 (30%)	112 (26%)			
	AA	11 (3%)	12 (3%)			
<i>RS518382</i>	CC	201 (52%)	249 (56%)	1.18 (0.96–1.45)	0.13	0.42
	CT	143 (37%)	163 (37%)			
	TT	41 (11%)	33 (7%)			
<i>RS537681</i>	TT	256 (67%)	300 (65%)	0.94 (0.73–1.22)	0.65	0.92
	TC	119 (31%)	151 (33%)			
	CC	9 (2%)	11 (2%)			
<i>RS538915</i>	GG	290 (77%)	367 (77%)	1.01 (0.74–1.4)	0.93	0.93
	GA	86 (23%)	107 (23%)			
	AA	0 (0%)	0 (0%)			
<i>RS553272</i>	TT	319 (84%)	341 (81%)	0.86 (0.62–1.20)	0.38	0.69
	TC	58 (15%)	76 (18%)			
	CC	5 (1%)	5 (1%)			
<i>RS590688</i>	GG	104 (27%)	110 (24%)	0.91 (0.75–1.10)	0.31	0.62
	GC	197 (50%)	234 (51%)			
	CC	89 (23%)	115 (25%)			
<i>RS601040</i>	GG	314 (86%)	340 (86%)	1.03 (0.71–1.53)	0.85	0.94
	GA	48 (13%)	53 (13%)			
	AA	3 (1%)	2 (1%)			
<i>RS635984</i>	GG	80 (21%)	106 (23%)	1.16 (0.96–1.4)	0.11	0.45
	GC	182 (47%)	221 (49%)			
	CC	126 (32%)	125 (28%)			
<i>RS653752</i>	GG	163 (42%)	185 (40%)	0.95 (0.78–1.15)	0.58	0.89
	GC	168 (43%)	200 (44%)			
	CC	57 (15%)	73 (16%)			

PGR SNP	Genotype	Cases	Controls	Per allele OR (95% CI)*	p value	corrected p value**
<i>RS660149</i>	CC	218 (56%)	254 (56%)	1.03 (0.84–1.28)	0.74	0.92
	CG	140 (36%)	164 (36%)			
	GG	32 (8%)	33 (7%)			
<i>RS7116336</i>	TT	314 (85%)	322 (80%)	0.69 (0.48–1.00)	0.053	0.35
	TA	56 (15%)	83 (20%)			
	AA	0 (0%)	0 (0%)			
<i>RS1042838</i>	CC	236 (68%)	255 (71%)	1.12 (0.84–1.48)	0.77	0.91
	CA	101 (29%)	92 (26%)			
	AA	9 (3%)	10 (3%)			

Table 2b

Odds Ratios for twenty PGR variants in African American women

PGR SNP	Genotype	Cases	Controls	Per allele OR (95% CI)	p value	corrected p value
<i>RS1042839</i>	GG	75 (87%)	327 (94%)	2.4 (1.1–5.2)	0.028	0.14
	GA	11 (13%)	20 (6%)			
	AA	0 (0%)	0 (0%)			
<i>RS10895054</i>	AA	70 (84%)	327 (95%)	2.9 (1.47–6.02)	0.002	0.04
	AT	12 (14%)	17 (5%)			
	TT	1 (1%)	1 (0.3%)			
<i>RS11224580</i>	CC	72 (82%)	266 (77%)	0.73 (0.43–1.23)	0.238	0.3
	CT	15 (17%)	69 (20%)			
	TT	1 (1%)	11 (3%)			
<i>RS11571271</i>	GG	84 (99%)	326 (99%)	1.28 (0.13–12.5)	0.828	0.83
	GT	1 (1%)	3 (1%)			
	TT	0 (0%)	0 (0%)			
<i>RS1379131</i>	AA	67 (76%)	251 (75%)	0.9 (0.57–1.44)	0.681	0.72
	AG	19 (22%)	70 (21%)			
	GG	2 (2%)	13 (4%)			
<i>RS471767</i>	AA	55 (65%)	181 (55%)	0.75 (0.50–1.13)	0.163	0.23
	AG	25 (29%)	126 (38%)			
	GG	5 (6%)	22 (7%)			
<i>RS492457</i>	AA	40 (46%)	142 (42%)	0.76 (0.54–1.07)	0.12	0.22
	AG	39 (45%)	143 (42%)			
	GG	7 (8%)	56 (16%)			
<i>RS506487</i>	CC	69 (80%)	271 (80%)	1.02 (0.61–1.7)	0.09	0.18
	CT	15 (17%)	61 (18%)			
	TT	8 (2%)	6 (2%)			

PGR SNP	Genotype	Cases	Controls	Per allele OR (95% CI)	p value	corrected p value
<i>RS507141</i>	GG	77 (88%)	321 (95%)	2.25 (1.06–4.8)	0.036	0.12
	GA	11 (12%)	17 (5%)			
	AA	0 (0%)	1 (0.3%)			
<i>RS518382</i>	CC	24 (31%)	153 (45%)	1.48 (1.05–2.08)	0.024	0.16
	CT	37 (48%)	135 (40%)			
	TT	16 (21%)	49 (15%)			
<i>RS537681</i>	TT	36 (42%)	104 (31%)	0.70 (0.49–0.99)	0.041	0.11
	TC	37 (44%)	163 (49%)			
	CC	12 (14%)	68 (20%)			
<i>RS538915</i>	GG	58 (67%)	251 (75%)	1.49 (0.90–2.5)	0.125	0.21
	GA	29 (33%)	84 (25%)			
	AA	0 (0%)	0 (0%)			
<i>RS553272</i>	TT	42 (49%)	200 (61%)	1.29 (0.90–1.8)	0.173	0.23
	TC	37 (44%)	103 (31%)			
	CC	6 (7%)	26 (8%)			
<i>RS590688</i>	GG	30 (35%)	63 (19%)	0.56 (0.39–0.82)	0.003	0.03
	GC	43 (50%)	195 (58%)			
	CC	13 (15%)	77 (23%)			
<i>RS601040</i>	GG	55 (70%)	190 (60%)	0.62 (0.4–0.96)	0.032	0.13
	GA	21 (27%)	94 (30%)			
	AA	2 (3%)	31 (10%)			
<i>RS635984</i>	GG	5 (6%)	26 (8%)	1.17 (0.80–1.7)	0.424	0.49
	GC	29 (33%)	123 (36%)			
	CC	53 (61%)	195 (57%)			
<i>RS653752</i>	GG	27 (32%)	85 (25%)	0.78 (0.56–1.1)	0.137	0.21
	GC	38 (45%)	160 (46%)			
	CC	20 (24%)	102 (24%)			

PGR SNP	Genotype	Cases	Controls	Per allele OR (95% CI)	p value	corrected p value
<i>RS660149</i>	CC	54 (63%)	180 (53%)	0.65 (0.43–0.98)	0.041	0.11
	CG	30 (35%)	128 (38%)			
	GG	2 (2%)	29 (8%)			
<i>RS7116356</i>	TT	64 (80%)	247 (76%)	0.8 (0.44–1.5)	0.48	0.53
	TA	16 (20%)	77 (24%)			
	AA	0 (0%)	0 (0%)			
<i>RS1042838</i>	CC	75 (87%)	309 (95%)	2.0 (0.98–4.19)	0.057	0.13
	CA	11 (13%)	16 (5%)			
	AA	0 (0%)	2 (1%)			

* Estimated from logistic regression matched on age, adjusted for combined hormone replacement use

** p values were corrected for multiple testing using the Benjamini-Hochberg method

Table 3a

RS10895054 and Breast Cancer Risk in European Americans

Variant OR	Effect Modifier	OR	95% CI	P value
1.30 (95% CI: .97–1.7)	Nulliparous	.29	0.13–0.67	0.004
	BMI >30.0	0.17	0.05–0.67	0.010

Table 3b

RS590688 and Breast Cancer Risk in European Americans

Variant OR	Effect Modifier	OR	95% CI	P value
0.87 (95% CI: 0.64–1.18)	Nulliparous	3.07	1.25–7.56	0.014
	BMI 30.0	5.7	1.3–24	0.018
	Menarche age 14	0.30	0.135–0.67	0.003
	CHRT	0.33	0.14–0.76	0.009

* Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; CHRT, combined hormone replacement therapy

Table 4

Haplotype analysis in African Americans

Block	SNP			Frequency	Haplotype	OR	P value
A	<i>rs601040</i>	<i>rs590688</i>	<i>rs537681</i>				0.043
	A	C	C	0.213	1	0.56 (0–1.12)	0.05
	G	C	C	0.17	5	0.53 (–0.14–1.2)	0.07
	G	C	T	0.102	6	0.42 (–0.41–1.25)	0.04
	G	G	C	0.03	7	1.94 (0.84–3.04)	0.2
B	G	G	T	0.474	base		
							0.0092
	A	C		0.21	1	0.59(0.05–1.13)	0.06
	G	C		0.28	3	0.42(–0.17–1.0)	0.004
	A	G		0.013	2	*	
C	G	G		0.5	base		
							0.0196
		C	C	0.39	1	0.56 (0.09–1.03)	0.02
		C	T	0.1	2	0.49 (–0.3–1.28)	0.08
		G	C	0.03	3	1.85 (.81–2.89)	0.25
		C	T	0.48	base		

* Block A: *rs601040*, *rs590688*, *rs537681*, Block B: *rs601040*, *rs590688*, Block C: *rs590688*, *rs537681*