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Estrogen-related genes and their contribution to racial differences in breast cancer risk

Kerryn W. Reding,

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop M4-B874, Seattle, WA 98109-1024, USA

Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle, WA, USA

Chu Chen,

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop M4-B874, Seattle, WA 98109-1024, USA

Department of Epidemiology, University of Washington, Seattle, WA, USA

Kimberly Lowe,

Exponent, Seattle, WA, USA

David R. Doody,

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop M4-B874, Seattle, WA 98109-1024, USA

Christopher S. Carlson,

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop M4-B874, Seattle, WA 98109-1024, USA

Department of Epidemiology, University of Washington, Seattle, WA, USA

Christina T. Chen,

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop M4-B874, Seattle, WA 98109-1024, USA

John Houck,

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop M4-B874, Seattle, WA 98109-1024, USA

Linda K. Weiss,

Cancer Centers Program, National Cancer Institute, Rockville, MD, USA

Polly A. Marchbanks,

Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

Leslie Bernstein,

Beckman Research Institute, City of Hope, Duarte, CA, USA

Robert Spirtas,

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Correspondence to: Kerryn W. Reding, kreding@u.washington.edu.

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George Washington University School of Public Health and Health Services, Washington, DC, USA

Jill A. McDonald,

Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

Brian L. Strom,

Center for Clinical Epidemiology and Biostatistics and Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, USA

Ronald T. Burkman,

Department of Obstetrics and Gynecology, Baystate Health, Springfield, MA, USA

Michael S. Simon,

Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA

Jonathan M. Liff,

Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

Janet R. Daling, and

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop M4-B874, Seattle, WA 98109-1024, USA

Kathleen E. Malone

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop M4-B874, Seattle, WA 98109-1024, USA

Department of Epidemiology, University of Washington, Seattle, WA, USA

Kerryn W. Reding: kreding@u.washington.edu

Abstract

Racial differences in breast cancer risk, including the risks of hormone receptor subtypes of breast cancer, have been previously reported. We evaluated whether variation in genes related to estrogen metabolism (*COMT*, *CYP1A1*, *CYP1B1*, *CYP17A1*, *CYP19A1*, *ESR1*, *GSTM1*, *GSTP1*, *GSTT1*, *HSD17B1*, *SULT1A1*, and *UGT1A1*) contributes to breast cancer risk and/or racial differences in risk within the CARE study, a multi-centered, population-based case-control study of breast cancer. Genetic variation was assessed as single nucleotide polymorphisms (SNPs), haplotypes, and SNP-hormone therapy (HT) interactions within a subset of 1,644 cases and 1,451 controls, including 949 Black women (493 cases and 456 controls), sampled from the CARE study population. No appreciable associations with breast cancer risk were detected for single SNPs or haplotypes in women overall. We detected SNP-HT interactions in women overall within *CYP1B1* (rs1800440; $p_{\text{het}} = 0.003$) and within *CYP17A1* (rs743572; $p_{\text{het}} = 0.009$) in which never users of HT were at a decreased risk of breast cancer, while investigated among racial groups, we detected evidence of an SNP-HT interaction with *CYP1B1* in White women (p value = 0.02) and with *CYP17A1* in Black women (p value = 0.04). This analysis suggests that HT use may modify the effect of variation in estrogen-related genes on breast cancer risk, which may affect Black and White women to a different extent.

Keywords

Breast cancer; Genetic variation; Racial disparities; Gene-environment interactions; Hormone therapy

Introduction

The lifetime risk of breast cancer is lower in Black women than in White women. However, Black women often present with more aggressive disease, including a larger portion of estrogen receptor (ER)-negative and progesterone receptor (PR)-negative tumors, and have poorer outcomes [1–7]. Support for genetic contributions to these racial differences comes from studies observing that racial disparities persist after controlling for known risk factors, including access to health care, treatment, sociodemographic factors, and pathologic features, as well as studies demonstrating similarities in the pathology of breast cancer in indigenous African women and African American women [1, 8, 9]. These observations do not, however, negate the possibility that environmental or lifestyle factors may also partially explain the disparities in breast cancer between White and Black women.

Environmental factors could conceivably contribute to observed racial differences in incidence of breast cancer subtypes and the corresponding mortality differences. Prior studies have demonstrated that associations between breast cancer risk and hormone-related risk factors (e.g., hormone therapy (HT) use, breastfeeding, and parity) differ according to breast cancer subtypes [10–15]. In addition, the distribution of these risk factors differs across racial/ethnic groups (e.g., Black women are less likely than White women to be users of HT; ref: [16]). Furthermore, elevated concentrations of endogenous estrogen in Black women have been observed in some [17–19] but not all studies [20, 21]. However, any potential differences in endogenous hormone concentrations may be due to both genetic factors [22] and hormone-related environmental factors, such as body mass index (BMI) [23].

It is plausible that gene–environment interactions within hormonal pathways may contribute to the racial differences in breast cancer incidence and mortality, particularly given the observed variation by race in distributions of hormone receptor status, hormone-related risk factors, and genetic factors. Specifically, variation in genes that are involved in estrogen biosynthesis, metabolism, and response, such as *CYP17A1*, *CYP11B1*, and *ESR1*, may differentially influence breast cancer risk for women with different hormone receptor subtypes. Thus far, relatively few studies have investigated the role of genetic variation in estrogen pathways on the risk of breast cancer in Black versus White women [24–27], and most of these have included small samples of Black women [11, 13, 14]. In addition, because of the high levels of within-race genetic diversity that have been observed in African and African American populations [28–30], it may be important to account for the percent of African ancestry in Black women by use of ancestry informative markers (AIM) in studies examining differences between White and Black women. Furthermore, with most studies investigating breast cancer risk factors focused on White women, the etiology of breast cancer in Black women is relatively understudied [31]. Using a case–control study that oversampled Black women in order to optimize numbers for subsequent analyses, we examined whether single nucleotide polymorphisms (SNPs), haplotypes, or gene–environment interactions with HT use were associated with breast cancer overall and by ER/PR subtypes among Black women and White women.

Materials and methods

Study design and data collection

The Women's Contraceptive And Reproductive Experiences (CARE) study was a population-based case–control study of incident invasive breast cancer with a primary objective to investigate reproductive factors associated with breast cancer risk. The CARE study was conducted with five participating sites in Atlanta, Georgia; Detroit, Michigan; Los Angeles, California; Philadelphia, Pennsylvania; and Seattle, Washington. The methods

have been described previously [32] and thus are presented briefly here. Women aged 35–64 years who were diagnosed with invasive breast carcinoma between July 1, 1994, and April 30, 1998; resided in one of the five geographic areas; and had no previous history of in situ or invasive breast carcinoma were eligible as cases. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry was used to identify cases, with the exception of the Philadelphia site where case ascertainment was conducted by field center staff. At all sites, study staff reviewed pathology reports and/or tumor registry abstracts from hospitals, clinics, and pathology laboratories for each breast cancer patient. Younger women and Black women were oversampled to approximate a uniform distribution across strata. Sampling for cases and controls was density based [33]. Potential controls were identified from the same geographic region as cases using random digit dialing with unclustered, equal-probability sampling of phone numbers [34, 35]. Each study participant completed an in-person interview that collected information on reproductive history, including histories of use of oral contraceptives and menopausal hormone therapy, exercise, health, family histories, and demographics. Of the 5,982 eligible breast cancer cases identified and selected, 4,575 (76.5%) were interviewed. Of the 5,956 eligible women selected as controls, 4,682 (78.6%) were interviewed.

Blood samples were sought from all subjects with first-degree family history of breast cancer and from a random sample of those without such history. The random selection for blood draw used selection probabilities specific to study center, case–control status, race, age, and reference date. The targeted percentage of women providing blood draws was approximately 30% of study participants. In all, 995 White controls, 1,151 White cases, 456 Black controls, and 493 Black cases (totaling 3,095 women) provided blood samples available for use in this analysis (representing 80.2% of cases and 74.3% of controls approached). This study was approved by the Institutional Review Committees at the participating centers, and all women gave written informed consent prior to participation and blood draw.

Pathology

Information was collected on tumor characteristics, including estrogen and progesterone receptor status, histology, and stage. Pathology data were extracted from SEER files at four of the centers; in Philadelphia, data were obtained from review of pathology reports, medical records, and hospital registry abstracts.

Laboratory methods

DNA was extracted from buffy coats using the manual phenol–chloroform method. Genotyping was performed by Dr. Chu Chen's laboratory with SNP assays using 5'-nuclease (Taqman) technology. The methods for the following polymorphisms have been described previously: *COMT* Val158Met (rs4680; [36]), *CYP1A1* m1 (rs4646903; [37]), *CYP1A1* m2 (rs1048943; [38]), *CYP1A1* m3 (rs4986883; [39]), *CYP1A1* m4 (rs1799814; [38]), *CYP1B1* Arg48Gly (rs10012; [38]), *CYP1B1* Ala119Ser (rs1056827; [38]), *CYP1B1* Gly188Gly (rs9341247; [38]), *CYP1B1* Leu432Val (rs1056836; [38]), *CYP1B1* Asn453-Ser (rs1800440; [38]), *CYP17A1* 5'UTR T/C [40], *CYP19A1* TTTA microsatellite repeats [41], *ESR1* PvuII intronic SNP (rs2234693; [42]), *ESR1* XbaI intronic SNP (rs9340799; [42]), *ESR1* "TA" microsatellite repeat [43], *GSTP1* Ile105Val (rs1695; [44]), *GSTM1* null [44] and rs1065411 [45], *GSTT1* null [44], *SULT1A1* Arg213His (rs9282861; [38]), and *UGT1A1* "TA" microsatellite repeat [38]. For *HSD17B1* Ser312Gly (rs605059) SNP, we performed a PCR–RFLP assay; conditions available upon request from the author. For the 21 polymorphisms, the amount of missing genotype data ranged from 1.4% (for *ESR1* PvuII SNP, *CYP1B1* Arg48Gly, Gly188Gly, and Asn453Ser) to 2.9% (for *ESR1* "TA")

microsatellite repeat) of women with missing genotype data with a mean 1.8% ($n = 55$) of women missing genotype data per polymorphism.

We estimated the percent of African ancestry using 128 ancestry informative markers described by Kosoy et al. [46] in 856 women who self-identified as Black or African American in our study (863 of the 949 Black women had available blood samples for AIMs testing; of the 863, 7 were removed from analysis due to low AIMs values [ranging from 1.8 to 12.3% with a mean of 7.1% African ancestry], leaving 856 Black women in the analysis of AIMs data). Using the AIM genotypes, we estimated the population structure in the Black women with the Yoruban (YRI) and CEPH (Centre d'Etude du Polymorphisme Humain) from Utah (CEU) HapMap populations as anchors (STRUCTURE v2.3.1) [47, 48].

Statistical methods

Percentages presented in the tables were adjusted to account for the sampling weights within the study population. Pearson's chi-square test was used for tests of associations in bivariate analyses. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated for breast cancer risk using logistic regression. For analyses involving breast cancer ER/PR subtypes, polytomous logistic regression was used. Gene-environment interactions and tests of heterogeneity were conducted using Wald's test statistic. Adjustment for multiple comparisons in the analysis of genetic variation was done using the Benjamini Hochberg multiple comparisons method [49]. In the tables, we indicated which comparisons were statistically significant at the 0.05 level (unadjusted) and then also indicated (with symbol, ‡) which were significant after adjustment for multiple testing.

We investigated the presence of confounding factors in logistic regression models. Variables which altered the magnitude of a risk estimate by 10% and were not likely to be consequences of genotype were considered as potential confounding factors. We included age at diagnosis, study site, family history, and race in models because these factors were used in the selection of women to participate in the subset providing blood samples. In logistic regression models limited to Black women, we adjusted additionally for percent African ancestry. The logistic regression models took into account the sampling weights by using the svy command in Stata v.11.

HT use was categorized in several ways: (1) as ever/never use; (2) as recent use (never use, current use [within 6 months], >6 months to <5 years since last use, and ≥5 years since last use); and (3) as duration of use (never use, short-term use: <60 months of use, and long-term use: ≥60 months of use). The type of estrogen-progestin therapy (EPT) used was categorized as (1) ever/never use of sequential EPT (daily estrogen; 5–14 days of progestin) and (2) ever/never use of continuous EPT (daily estrogen; 25+ days of progestin). The estrogen-alone therapy (ET) variable was categorized as ever/never use.

Haplotype frequencies were estimated for genes with multiple SNPs genotyped in this project using two SNPs in each of the *CYP1A1*, *CYP1B1*, and *ESR1* genes. In selecting SNPs for haplotype analysis, we excluded synonymous SNPs and non-synonymous SNPs in which the amino acid substitution only minimally impacted protein structure (e.g., changing from one hydrophobic amino acid to another; Ref. [50]). Based on this, we excluded T5639C and T6235C in *CYP1A1*; and Gly188Gly and Val432Leu in *CYP1B1*; in addition, we excluded *CYP1B1* Arg48Gly due to it being in strong linkage disequilibrium (LD) with Ala119Ser (in both White and Black women). Haplotype estimation was performed using Phase v.2.1. We limited our statistical analysis to haplotypes for which there was ≥5% frequency overall. In our dataset, we combined the two haplotypes for an individual into a diplotype based on the most probable haplotypes estimated from the Phase software that uses an expectation-maximization (EM) algorithm [51]. Although we did not have

information on gametic phase, phase was ambiguous for only one diplotype in *CYP1B1* (TA/GG) and *ESR1* (CG/TA) due to individuals being heterozygous at both loci. ORs and 95% CIs were calculated for each combined haplotype (or diplotype) using the combined haplotype with the highest frequency as the referent category.

Hardy–Weinberg equilibrium

Testing for deviation from Hardy–Weinberg equilibrium (HWE) was performed within the controls stratified by race using a χ^2 goodness-of-fit test. We detected deviation from HWE arising from excessive homozygosity in Black women for *CYP1B1* Arg48Gly and Ala119Ser SNPs (p value = 0.0008 and 0.003, respectively). Because the frequency of genetic variants differs by race, and because there is considerable admixture in the Black population, it was not surprising to find SNPs with an excess of homozygotes in Black women. Excess homozygosity is consistent with population stratification, especially when allele frequencies differ widely between subpopulations, as did these two SNPs (54.2% T in Blacks and 22.6% T in Whites for Ala119Ser in *CYP1B1*; [52]). Because we did not detect deviation from HWE in White women, we feel comfortable in ruling out genotyping errors as the cause of excess homozygosity in Black women. We elected to keep those SNPs in our haplotype analysis and adjusted for population substructures using principal components derived from AIMs data in Black women. Even if adjustment using AIMS data is insufficient to remove all of the potential impact, we are reassured by the report by Wacholder et al. [53], estimating that the amount of bias arising from population stratification in a case–control study is minimal.

Results

Demographic and hormone-related characteristics of breast cancer cases and controls are presented overall and stratified by race in Table 1. Cases were significantly more likely than controls to have a first-degree family history of breast cancer ($p < 0.001$); this difference was observed separately in White ($p < 0.001$) and Black women ($p = 0.001$). Overall, cases had a lower BMI than controls ($p = 0.03$), and White cases were more likely to have a lower BMI than White controls ($p = 0.01$); this association was not observed in Black women. No other significant differences were detected by case–control status. However, significant differences were observed between White and Black cases, such that a greater percentage of White women had first-degree family history of breast cancer, were ever users of EPT or ET, had their first child at age 30 years or older, were menopausal at the time of study, were college graduates, and had a BMI less than 25.

A few single variants were nominally significantly associated with breast cancer risk in our analysis (Supplemental Table 1), though we observed no genotypes of single SNPs to be associated with breast cancer risk after adjustment for multiple testing. Although there were substantial differences by race in the distributions of genotypes for many of the SNPs examined, we did not detect statistical evidence of differences in breast cancer risk by race for any single genotype.

In the haplotype analyses, there was the suggestion of a difference in breast cancer risk by race in relation to the *CYP1A1* haplotype (Table 2). The greater percentage of White women in the analysis appear to be driving the overall 30% reduction in risk as our data do not show a similar reduction in risk shared by Black women. However, the test of heterogeneity was not statistically significant (0.07), and the ORs did not remain significant after adjustment for multiple testing.

We investigated the potential for SNP–HT interactions for each of the 21 SNPs among post-menopausal women of both racial groups combined. The risk of breast cancer varied

according to HT use for one SNP each in *CYP1B1* and *CYP17A1* (Table 3). For *CYP1B1* Asn453Ser (rs1800440), a decreased risk of breast cancer among carriers of the G allele was limited to never users of HT (OR = 0.4 [95% CI, 0.2–0.7] vs. OR = 1.2 [95% CI, 0.8–1.7] in ever users; $p_{\text{het}} = 0.003$). For the SNP (rs743572) at 5' UTR in *CYP17A1*, a decreased risk of breast cancer among carriers of the C allele was also limited to never users of HT (OR = 0.5 [95% CI, 0.3–0.9] vs. OR = 1.2 [95% CI, 0.8–1.6] in ever users; $p_{\text{het}} = 0.009$).

Between the two SNPs that indicated SNP–HT interactions in both racial groups combined, we evaluated the interactions further by race, as well as by HT regimen; however, this investigation was limited by small numbers. For *CYP1B1* Asn453Ser, the interaction with HT was apparent in White women ($p_{\text{het}} = 0.02$) but not in Black women ($p_{\text{het}} = 0.53$), although a difference would be difficult to detect in our dataset given the small number of Black women with the variant allele. For the *CYP17A1* 5' UTR SNP, we detected evidence of an interaction among Black women ($p_{\text{het}} = 0.04$) but not among White women ($p_{\text{het}} = 0.13$). Adding complexity to the SNP–HT interaction is that post-menopausal Black women were significantly less likely to be users of any HT (45.7%) than White women (55.3%; p value < 0.001).

In further analyses investigating recency and duration of HT use, there were statistically significant SNP–HT interactions by recency of HT use for the SNPs reported above for *CYP1B1* and *CYP17A1* ($p_{\text{het}} = 0.008$ and 0.003, respectively) but not for duration of HT use (data not shown). When investigated according to HT type, we did not detect evidence for interactions with ever use by type of regimen (estrogen-alone therapy, estrogen–progestin continuous therapy, or estrogen–progestin sequential therapy). After adjustment for multiple comparisons, only the SNP–HT interactions for ever use of HT in both racial groups combined remained statistically significant.

Because the proportion of hormone receptor subtypes differed between Black and White women in our dataset, we explored whether the risk of ER/PR subtypes varies in relation to haplotypes by racial groups (Supplemental Table 2). We observed that Black women were at a reduced risk of ER+/PR+ breast cancer in relation to two *CYP1A1* haplotypes (CA/CG: OR = 0.3 [95% CI, 0.1–0.8]; CA/AA: OR = 0.1 [95% CI, 0.0–0.4]). These risk estimates differed from the risk estimates observed in White women for the same haplotypes ($p_{\text{het}} = 0.01$). However, after controlling for the multiple tests of heterogeneity, no p values remained significant.

Given the differences in the mean age at diagnosis between these racial groups reported in the literature [2], we also explored whether there were racial differences in haplotype effects within age groups (Supplemental Table 3). We observed a difference by race in the risk of breast cancer associated with the *CYP1B1* haplotypes among women 35–44 years of age (p value = 0.01). However, this difference was no longer significant after adjustment for multiple tests.

Discussion

While the lifetime risk of breast cancer is lower in Black women than in White women, Black women have a higher breast cancer-related mortality than White women [1, 2, 8]. Given the racial differences that have been observed in breast cancer, including variation in age at diagnosis and proportion of breast cancer subtypes, it has been hypothesized that biological or genetic differences may play a role in breast cancer disparities. In addition, the distribution of hormone-related environmental factors, including age at first birth, BMI, breastfeeding history, parity, and HT use, differs by race [31, 54]. Furthermore, genetic and environmental differences by race may underlie the differences in circulating estrogen

concentrations between Black and White women [17–19]. As a result, it is plausible that gene–environment interactions in hormonal pathways may contribute to the racial differences observed in breast cancer.

Of the prior studies to report on genetic variation and breast cancer risk in Black women, SNPs in estrogen metabolism genes have been reported in several [24, 26, 27, 55] but not all studies [56–58] to be associated with breast cancer risk. However, none of the previous studies reported positive findings with the SNP in *CYP17A1*, nor the SNPs comprising the *CYP1B1* and *CYP1A1* haplotypes, although many of these studies were conducted in small samples of Black women [24, 26, 27, 56–58].

We observed no relationship between individual SNPs and breast cancer risk overall or by race. Despite this, we chose to investigate haplotypes as the unit of genetic variation because haplotype analyses integrate information from multiple SNPs [59, 60]. Individual non-synonymous SNPs can alter protein structure, and haplotypes of such SNPs can have unpredictable functional outcomes that an individual SNP analysis could not detect.

Our observation of a 30% reduction in breast cancer risk associated with the CA/CG haplotype in *CYP1A1* in women overall was largely attributable to the reduced risk in White women; however, after adjustment for multiple testing, this was no longer significant. The reduced risks of ER+/PR+ breast cancer associated with several haplotypes in *CYP1A1* in Black women are consistent with the reduction in risk of ER+/PR+ breast cancer observed in Black women reported in the literature. However, the findings of the haplotype analysis stratified by hormone receptor subtype need to be interpreted with caution because the data became sparse when several factors were investigated simultaneously.

Previous studies have investigated potential SNP–HT interactions in estrogen-related genes in populations of predominantly White women [55, 61–65]. Of those to include *CYP1B1* Asn453Ser, Rebbeck et al. [55] reported no SNP–HT interaction, while Diergaarde et al. [65] observed EPT interactions with multiple SNPs in *CYP1B1*. Specifically, Diergaarde et al. reported a reduction in breast cancer risk associated with carrying the G allele of *CYP1B1* Asn453Ser among never users (OR = 0.8 [95% CI, 0.5–1.1]) and an increased risk among ever users of EPT (for use <10 years: 2.0 [95% CI, 1.1–3.5]; for use ≥10 years: 2.2 [95% CI, 1.2–3.8]).

Estrogens are extensively metabolized by cytochrome P450 (CYP) enzymes, and CYP1B1 in particular is highly expressed in the female breast [66]. The CYP1A1 and CYP1B1 enzymes play a role in the conversion of estrogens into the 2- and 4-hydroxy estrogens, respectively [67, 68]. These hydroxy estrogens, also known as catechol estrogens, have been shown to exert genotoxic effects on cells through the formation of reactive oxygen species and DNA adducts [69]. The genotoxic capacity of the 4-hydroxy estrogen appears to surpass that of the 2-hydroxy estrogen [69, 70]. Several *CYP1B1* variants, including the 453Ser variants, are associated with higher hydroxylation activity [71]. Given the role of these enzymes in estrogen metabolism, it is conceivable that HT might modify the impact of these variant alleles. Our findings of an SNP–HT interaction with the *CYP1B1* 453 variant among White women are consistent with those from Diergaarde et al. In light of the null findings reported by Rebbeck et al. [55], however, further interpretation should await the results from pooled analyses.

Of the studies investigating SNP–HT interactions which included the *CYP17A1* 5′ UTR, one study observed no interaction [65], while three studies reported interactions in which there was an increased risk associated with the variant allele among HT users [61–63]. Specifically, the Marie-Genica Consortium reported an increased breast cancer risk of 1.13 (95% CI, 1.04–1.23) associated with the TC genotype for every 5 years of HT use [61].

Chen et al. [62] reported a 1.5-fold increased risk associated with the TC/CC genotypes (95% CI, 0.99–2.31) for long-term HT users compared to never and short-term users with TT genotype. Justenhoven et al. [63] reported a threefold increased risk associated with the CC genotype (95% CI, 1.39–7.25) among long-term HT users compared to never users. Our results are consistent with these prior reports observing increased cancer risk associated with TC/CC genotypes among ever users compared to decreased risks among non-users. We found no evidence that the risk among HT users differed by duration or type of HT use according to genotype. This is despite the fact that the primary analysis of HT use and breast cancer risk in this study population previously reported differing risks based on HT type and duration, indicating that our study's HT data were sufficiently detailed to examine whether SNP–HT interactions differed by type and duration [72].

CYP17A1 is involved in the estrogen biosynthesis with its conversion of pregnenolone and progesterone to androgen and estrogen, respectively [73]. While the *CYP17A1* 5' UTR variant is believed to increase promotor activity, studies examining its association with breast cancer risk have been weak [71]. It is plausible that a potential association with an overall risk of breast cancer is obscured by effect modification with HT use. Our data contribute to the mounting reports of interactions with HT use and provide data on an interaction within Black women.

The impact of an SNP–HT interaction could affect White and Black women differently due to the racial differences in the proportion of women who are users of HT. In this case, the reduced risk of breast cancer among never users of HT would be experienced by a greater proportion of Black than White women. Furthermore, it is plausible that the increased lifetime estrogen exposure among Black women may interact with genetic factors, but this is not easily studied because the lifetime exposure to estrogens is due to a multitude of factors (including a combination of BMI, high parity, earlier age at first birth, lack of breast-feeding history) and their collective effect on circulating estrogen concentrations.

Although our study contained one of the larger samples of Black women designed to investigate breast cancer risk associated with genetic variation, we were constrained in our ability to examine statistical differences in genetic associations between racial groups due to small numbers when stratified by race. Additional limitations included our reliance on registry-based sources of tumor information and the associated lack of centralized pathology review of the tumors; however, a recent analysis conducted using data from the Detroit and Los Angeles sites demonstrated substantial agreement between SEER registry and our study's pathology data, indicating a high reliability of SEER tumor data [74]. In addition, our observations of racial differences in the risk of ER/PR subtypes are in agreement with previous reports in the literature [1–6], indicating that misclassification of ER/PR status is likely not to be a major concern in this study.

In our study, we observed SNP–HT interactions in which reduced risks of breast cancer in relation to genetic variants in *CYP1B1* and *CYP17A1* were only present in never users of HT. We also observed the suggestion of racial differences in SNP–HT interactions within the estrogen metabolism pathway. Moreover, due to the differences in estrogen-related exposures between Black and White women, SNP–HT interactions involving estrogen-metabolizing genes may contribute to racial differences in breast cancer incidence. Our findings lend some support to the hypothesis that genetic factors related to the metabolism of estrogens may contribute to breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of breast cancer cases and controls

	Case ^a			Control ^a			p value difference by case status	p value difference by race (in cases)
	All women n (%)	Black women n (%)	White women n (%)	All women n (%)	Black women n (%)	White women n (%)		
Age group								
35-39	309 (15.1)	91 (13.8)	218 (15.8)	232 (14.2)	71 (13.0)	161 (14.9)	0.86	0.72
40-44	247 (16.5)	83 (17.8)	164 (15.8)	248 (17.8)	79 (18.4)	169 (17.4)		
45-49	263 (17.2)	83 (18.4)	180 (16.5)	239 (18.2)	74 (18.8)	165 (17.9)		
50-54	296 (18.4)	87 (18.7)	209 (18.3)	234 (17.6)	75 (18.3)	159 (17.3)		
55-59	271 (16.6)	90 (16.8)	181 (16.9)	269 (17.1)	84 (17.3)	185 (17.0)		
60-64	261 (16.0)	62 (14.5)	199 (16.8)	229 (15.0)	73 (14.3)	156 (15.4)		
Race								
White	1,151 (64.6)	-	-	995 (64.6)	-	-	0.97	-
Black	493 (35.4)	-	-	456 (35.4)	-	-		
Study center								
Atlanta	318 (19.3)	108 (19.8)	210 (18.9)	308 (19.1)	117 (20.7)	191 (18.3)	0.75	<0.001
Detroit	214 (14.8)	83 (17.1)	131 (13.6)	251 (16.6)	96 (20.1)	155 (14.8)		
Los Angeles	440 (27.2)	184 (35.2)	256 (22.7)	356 (26.8)	150 (32.6)	206 (23.7)		
Philadelphia	184 (15.4)	89 (24.0)	95 (10.8)	149 (15.6)	67 (22.3)	82 (11.4)		
Seattle	491 (23.3)	32 (3.8)	459 (34.0)	387 (21.8)	26 (3.3)	361 (31.9)		
First-degree relative with breast cancer								
Yes	616 (17.8)	147 (15.2)	469 (19.2)	344 (9.9)	88 (8.6)	256 (10.5)	<0.001	0.02
No	978 (82.2)	331 (84.8)	647 (80.8)	1,067 (90.1)	354 (91.4)	713 (89.5)		
Unknown	53	18	35	40	14	26		
EPT ^b								
Never	200 (37.0)	87 (59.4)	113 (24.6)	192 (34.2)	87 (51.3)	105 (24.6)	0.15	<0.001
Former	76 (14.8)	23 (11.2)	53 (11.9)	80 (17.5)	28 (17.2)	52 (13.8)		
Current	334 (48.2)	47 (29.4)	287 (63.5)	302 (48.2)	54 (31.5)	248 (61.6)		
Unknown	11		9	13	3	8		

	Case ^d			Control ^a			<i>p</i> value difference by case status	<i>p</i> value difference by race (in cases)
	All women <i>n</i> (%) <i>n</i> = 1,647	Black women <i>n</i> (%) <i>n</i> = 493	White women <i>n</i> (%) <i>n</i> = 1,151	All women <i>n</i> (%) <i>n</i> = 1,451	Black women <i>n</i> (%) <i>n</i> = 456	White women <i>n</i> (%) <i>n</i> = 995		
ET ^b								
Never	427 (64.0)	118 (76.6)	309 (67.8)	367 (58.8)	119 (73.0)	248 (62.3)	0.12	0.004
Former	76 (15.0)	21 (11.1)	55 (14.0)	78 (14.8)	21 (11.9)	57 (13.3)		
Current	107 (21.0)	18 (12.3)	89 (18.2)	129 (26.4)	29 (15.0)	100 (24.4)		
Unknown	11		9	13	3	8		
Age at first live birth								
<30	1,089 (67.5)	378 (75.4)	711 (63.2)	1,009 (71.9)	365 (81.7)	644 (66.5)	0.05	<0.001
30+	194 (11.5)	36 (7.7)	158 (13.6)	172 (10.4)	29 (5.5)	143 (13.2)		
No births/unknown	364 (21.0)	82 (16.9)	282 (23.2)	270 (17.7)	62 (12.5)	208 (20.3)		
Menopausal status								
Not menopausal	973 (58.7)	308 (60.8)	665 (57.6)	793 (55.9)	244 (56.0)	549 (55.9)	0.07	0.02
Known natural menopause	303 (19.2)	97 (21.3)	206 (18.1)	274 (19.1)	94 (20.5)	180 (18.3)		
Known induced menopause	118 (7.3)	36 (7.5)	82 (7.8)	154 (10.6)	54 (11.1)	100 (10.2)		
Known menopause, but type unclear	25 (1.5)	2 (0.5)	23 (2.0)	29 (1.7)	7 (1.3)	22 (2.0)		
Assumed natural menopause	225 (13.3)	50 (9.8)	175 (15.2)	201 (12.7)	57 (11.1)	149 (13.6)		
Education								
High school or less	588 (38.1)	234 (49.3)	354 (31.9)	540 (39.0)	211 (47.6)	329 (34.3)	0.81	<0.001
Some college	531 (32.3)	157 (29.8)	374 (33.6)	468 (31.1)	161 (34.0)	307 (29.5)		
College grad or greater	528 (29.7)	105 (20.9)	423 (34.5)	443 (29.9)	84 (18.5)	359 (36.2)		
BMI (kg/m ²)								
<25	937 (54.9)	179 (35.7)	758 (65.4)	776 (52.0)	168 (36.0)	608 (60.7)	0.03	<0.001
25–29	441 (27.8)	177 (35.3)	264 (23.7)	388 (26.5)	156 (31.8)	232 (23.5)		
30+	263 (17.3)	136 (29.1)	127 (10.8)	285 (21.6)	132 (32.2)	153 (15.8)		
Unknown	6	4	2	2	0	2		

EPT^aestrogen–progestin therapy, ET^aestrogen-alone therapy

^aPercentages are adjusted for sampling weights and may not sum to 1 due to rounding

^bAmong post-menopausal women

Table 2
Risk of breast cancer associated with haplotypes in women overall and stratified by race

Haplotype ^a	All women				White women				Black women			
	Case ^b n (%)	Control ^b n (%)	OR ^c	95% CI	Case n (%)	Control n (%)	OR ^c	95% CI	Case n (%)	Control n (%)	OR ^c	95% CI
CYP1A1												
CA/CA	1,452 (89.1)	1,274 (88.4)	1.0	(ref)	980 (86.5)	843 (85.2)	1.0	(ref)	472 (95.7)	431 (94.2)	1.0	(ref)
CA/CG	86 (4.9)	95 (6.5)	0.7	0.5–1.0 *	68 (5.9)	82 (8.6)	0.6	0.4–0.9	18 (3.1)	13 (2.7)	1.0	0.4–2.3
CA/AA	95 (5.3)	75 (5.0)	1.0	0.7–1.5	89 (7.6)	64 (6.1)	1.2	0.8–1.8	6 (1.1)	11 (3.1)	0.3	0.1–1.0
												$p_{het}^d = 0.07$
CYP1B1												
TA/GA	558 (37.4)	492 (36.1)	1.0	(ref)	334 (31.1)	319 (33.2)	1.0	(ref)	224 (49.3)	173 (41.6)	1.0	(ref)
TA/TA	183 (13.0)	189 (13.8)	0.9	0.7–1.2	91 (8.8)	87 (8.7)	1.0	0.7–1.5	92 (20.8)	102 (23.6)	0.7	0.5–1.1
TA/GG	136 (8.1)	114 (8.2)	1.0	0.7–1.4	117 (10.3)	105 (11.5)	1.0	0.7–1.4	19 (3.9)	9 (1.9)	1.7	0.6–4.6
GA/GA	435 (26.8)	397 (29.3)	0.9	0.7–1.1	336 (29.5)	280 (29.8)	1.1	0.8–1.4	99 (21.8)	117 (28.2)	0.7	0.5–1.0 *
GA/GG	240 (14.6)	185 (12.6)	1.2	0.9–1.6	221 (20.2)	164 (16.8)	1.4	1.0–1.8 *	19 (4.2)	21 (4.6)	0.8	0.4–1.9
												$p_{het}^d = 0.13$
ESR1												
CG/TA	578 (34.3)	521 (35.2)	1.0	(ref)	431 (37.2)	405 (39.8)	1.0	(ref)	147 (28.7)	116 (26.3)	1.0	(ref)
CG/CG	402 (25.0)	370 (26.9)	1.0	0.8–1.2	306 (27.4)	268 (28.4)	1.1	0.8–1.4	96 (20.2)	102 (24.1)	0.8	0.5–1.2
CG/TG	264 (17.2)	211 (15.7)	1.2	0.9–1.6	151 (13.3)	107 (11.3)	1.3	1.0–1.8	113 (24.7)	104 (24.1)	1.1	0.7–1.6
TG/TA	162 (10.5)	150 (11.1)	1.1	0.8–1.5	89 (7.4)	78 (7.8)	1.1	0.7–1.6	73 (16.5)	72 (17.5)	1.1	0.6–1.7
TA/TA	204 (13.0)	158 (11.1)	1.3	1.0–1.7	162 (14.6)	120 (12.7)	1.3	1.0–1.8	42 (9.9)	38 (8.0)	1.1	0.6–2.0
												$p_{het}^d = 0.80$

Bold indicates statistical significance at 0.05 level

OR odds ratio, CI confidence interval, p_{het} p value testing heterogeneity

* Due to rounding; $p < 0.05$

^a Haplotypes for CYP1A1 were composed of Thr461Asn and Ile462Val, respectively; for CYP1B1, were Ala119Ser and Asn453Ser, respectively; for ESR1, were PvuII and XbaI, respectively, shown here as the combination of haplotypes (or diplotype) estimated as the most likely for an individual

^b Percentages are adjusted for sampling weights; number of cases and controls in haplotype analysis does not sum to total because less frequent haplotypes (<1% in a cell) were removed from the analysis

^c Adjusted for age, geographic study site, first-degree family history of breast cancer, and race (AIMS markers in Black women)

^d Testing heterogeneity in risk associated with haplotypes between races

Table 3
The risk of breast cancer associated with selected SNPs among post-menopausal women, stratified by use of HT

SNP	All women				Never HT use				Ever HT use			
	Case ^a n (%)	Control ^a n (%)	OR ^b	95% CI	Case ^a n (%)	Control ^a n (%)	OR ^b	95% CI	Case ^a n (%)	Control ^a n (%)	OR ^b	95% CI
<i>CYP1B1</i>												
Asn453Ser (rs1800440)												
AA	487 (76.1)	486 (76.2)	1.0	(ref)	175 (86.9)	144 (79.4)	1.0	(ref)	297 (70.3)	322 (74.9)	1.0	(ref)
AG/GG	174 (23.9)	162 (23.8)	1.0	0.7–1.3	40 (13.1)	42 (20.6)	0.4	0.2–0.7	126 (29.7)	111 (25.2)	1.2	0.8–1.7
												$P_{\text{het}} = 0.003^{\ddagger}$
<i>Black women</i>												
AA	172 (95.9)	189 (91.2)	1.0	(ref)	92 (96.4)	86 (93.1)	1.0	(ref)	77 (95.1)	100 (89.4)	1.0	(ref)
AG/GG	9 (4.1)	19 (8.8)	0.3	0.1–1.0	4 (3.6)	8 (6.9)	0.4	0.1–3.4	5 (4.9)	10 (10.6)	0.5	0.1–1.9
												$P_{\text{het}} = 0.533$
<i>White women</i>												
AA	315 (66.2)	297 (68.0)	1.0	(ref)	83 (76.0)	58 (61.6)	1.0	(ref)	220 (63.2)	222 (69.4)	1.0	(ref)
AG/GG	165 (33.8)	143 (32.0)	1.1	0.8–1.5	36 (24.0)	34 (38.4)	0.5	0.2–1.0	121 (36.8)	101 (30.6)	1.3	0.9–2.0
												$P_{\text{het}} = 0.017$
<i>CYP17A1</i>												
5' UTR (rs743572)												
TT	241 (38.4)	234 (35.4)	1.0	(ref)	96 (48.7)	65 (33.0)	1.0	(ref)	137 (33.0)	158 (36.6)	1.0	(ref)
TC/CC	406 (61.6)	415 (64.6)	0.9	0.7–1.2	113 (51.3)	122 (67.0)	0.5	0.3–0.9	279 (67.0)	275 (63.4)	1.2	0.8–1.6
												$P_{\text{het}} = 0.009^{\ddagger}$
<i>Black women</i>												
TT	73 (45.5)	82 (39.0)	1.0	(ref)	49 (54.6)	37 (37.9)	1.0	(ref)	23 (33.5)	43 (39.8)	1.0	(ref)
TC/CC	103 (54.5)	126 (61.0)	0.8	0.5–1.3	45 (45.4)	57 (62.1)	0.5	0.2–1.1	56 (66.5)	67 (60.2)	1.7	0.7–3.7
												$P_{\text{het}} = 0.038$
<i>White women</i>												
TT	168 (34.9)	152 (33.4)	1.0	(ref)	47 (41.9)	28 (26.8)	1.0	(ref)	114 (32.9)	115 (35.4)	1.0	(ref)
TC/CC	303 (65.1)	289 (66.6)	1.0	0.7–1.3	68 (58.1)	65 (73.2)	0.6	0.3–1.2	223 (67.1)	208 (64.6)	1.1	0.7–1.6

Models are adjusted for age, geographic study site, first-degree family history of breast cancer, and AIMs markers (in Black women)