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ORIGINAL ARTICLE

Associations between Polymorphisms in Phase II Enzymes and Circulating Sex-Steroid Hormones in White Postmenopausal Women

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Objectives: The purpose of this cross-sectional study was to examine whether single nucleotide polymorphisms (SNPs) in enzymes that metabolize sex steroid hormones were associated with the blood levels of these hormones in postmenopausal women and if the use of menopausal hormone therapy (MHT) could modify this association.

Methods: Baseline data were collected from 932 postmenopausal women enrolled in the Minnesota Green Tea Trial. Participants filled out a questionnaire about their demographics, lifestyle factors, and medical and reproductive history. Free, bioavailable, and total serum levels of reproductive hormones were measured through liquid chromatography/tandem mass spectrometry. For genotyping of *UGT1A1* (rs10928303), *UGT1A4* (rs10929301, rs11673726), *UGT1A6* (rs1105879, rs2070959, rs6759892), *UGT1A8* (rs10167119), *UGT2B7* (rs7439366), and *SULT1A1* (rs9282861, rs1968752), mass spectrometry based on multiplex methods and TaqMan assays were performed. Adjusted linear models were fit to assess the associations between SNPs and blood hormones using age, body mass index (BMI), and MHT as covariates.

Results: The mean age was 59.8 years, and the mean BMI was 25.1 kg/m^2. Past or recent use of MHT was reported by 41.2% of the participants. SNPs in *SULT1A1* (rs1968752 and rs9282861) and *UGT1A4* (rs11673726) genes were significantly associated with estrone levels, whereas SNPs in *UGT1A6* (rs6759892) and *UGT1A8* (rs10167119) genes were significantly associated with bioavailable estradiol levels.

Conclusions: There was no evidence that MHT use modified the association between SNPs and sex-steroid hormone levels; however, further studies are needed to establish the potential clinical significance of *UGT1A4* (rs11673726), *UGT1A6* (rs6759892), and *UGT1A8* (rs10167119) SNPs and the modulation of hormone levels in postmenopausal women.

Key Words: Menopausal hormone therapy, Sulfotransferases, UDP-glucuronosyltransferases

INTRODUCTION

Phase II enzymes, such as Catechol-O-methyltransferase (COMT), UDP-glucuronosyltransferases (UGT) and sulfotransferases (SULT) are important for the metabolism of sex-steroid hormones [1,2]. These enzymes catalyze conjugation reactions, which lead to excretion of estrogen metabolites. Single nucleotide polymorphisms (SNPs) in genes encoding for these enzymes may influence their activity, which would also influence the hormonal environment in the breast tissue. It has been suggested that genetic polymorphisms that lead to decreased activity of these enzymes may increase the risk of breast cancer due to increased hormonal exposure [3]. In premenopausal women, it has been shown that variants in the genes *SUT1A1*, *UGT2B4*, *SULT1E1*,

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and *UGT1A1* were significantly associated with altered levels of estradiol and dehydroepiandrosterone [4]. In postmenopausal women diagnosed with breast cancer, genetic variations in *UGT1A1* and *UGT2B15* and *SULT1A1* were associated with differences in estradiol and testosterone levels [1]. While there seems to exist significant associations between certain polymorphisms in phase II enzymes and blood levels of sex-steroid hormones, there are several reported SNPs in phase II enzyme genes that remain unexplored, such as *UGT1A4* (rs11673726) and *UGT1A6* (rs6759892).

The purpose of this cross-sectional study was to examine whether polymorphisms in enzymes that metabolize sex-steroid hormones were associated with blood levels of these hormones in postmenopausal women and if menopausal hormone therapy (MHT) use was an important modifier of this association.

MATERIALS AND METHODS

Study population

Baseline data collected from postmenopausal women enrolled in the Minnesota Green Tea Trial (MGTT) were used for the current analysis. The MGTT was a randomized, double-blinded, placebo-controlled trial sought to determine the effects of consumption of green tea catechins for 12 months on biomarkers of breast cancer risk (clinical trial ID No. NCT00917735) [5]. In order to be eligible for the trial, subjects had to be generally healthy, postmenopausal, between the ages of 50 and 70 years, and they had to have been diagnosed with heterogeneously or extremely dense breasts according to the Breast Imaging Reporting and Data System (BI-RADS) criteria [6] on a recent screening mammogram. Women were not eligible to participate in the trial if they met one or more of the following criteria: regular green tea consumption (more than one cup/week), tested positive for hepatitis B or C, elevated liver enzymes, previous diagnosis of breast cancer, history of cancer in the past 5 years, presence of breast implants, current or recent (within 6 month) use of hormone modification therapy, currently taking methotrexate or etanercept, body mass index (BMI) lower than 18.5 kg/m^2 or greater than 40 kg/m^2, currently participating in a weight loss program, weight change of more than 10 lbs over the previous year, alcohol intake greater than 7 servings per week, and current smoker. Written consent was obtained from all subjects and the trial protocol was approved by the University of Minnesota, the University of Southern California, and the University of Pittsburgh Institutional Review Boards (IRB No. 0806M36121).

Reproductive history and hormones

A comprehensive health history questionnaire was administered to subjects to obtain information about demographics, lifestyle factors, medical history, and reproductive history. Estradiol (pg/mL), estrone (pg/mL), androstenedione (ng/mL), and testosterone (ng/mL) were measured in serum at the Quest Diagnostics Nichols Institute (San Capistrano, CA, USA) by liquid chromatography/tandem mass spectrometry (LC/MS/MS). The sensitivities of the assays were: 2 pg/mL for estradiol, 10 pg/mL for estrone, 5 ng/dL for androstenedione, and 1 ng/dL for testosterone. Half of the minimum detectable value was assigned to samples that were below the detection limit. The average intra-assay coefficients of variation (CVs) were 11% for estrone, 20.5% for estradiol, 11.6% for androstenedione, and 13.1% for testosterone. The average inter-assay CVs were 14.4%, 26.1%, 13.7%, and 15.9% for estrone, estradiol, androstenedione, and testosterone, respectively.

Genotyping of UGT and SULT polymorphisms

All genotyping assays were performed at the University of Minnesota Molecular Epidemiology and Biomarkers Research Laboratory. DNA was extracted from buffy coat samples using the Qiagen DNAeasy blood and tissue kit method (Qiagen, Gaithersburg, MD, USA). For genotyping of *UGT1A1* (rs10928303), *UGT1A4* (rs10929301, rs11673726), *UGT1A6* (rs1105879, rs2070959, rs6759892), *UGT1A8* (rs10167119), *UGT2B7* (rs7439366), and *SULT1A1* (rs9282861, rs1968752), a combination of mass spectrometry based on multiplex methods (Sequenom, San Diego, CA, USA) and TaqMan (Applied Biosystems, Foster City, CA, USA) assays were performed. SNPs not passing quality control in the multiplex methods were analyzed with the TaqMan assay. Call rates for individual polymorphisms were greater than 96%.

Statistical analyses

Mean, median, standard deviation and range were used to describe the distribution of continuous variables. Frequency distributions were used to describe categorical variables.

MHT use was classified into three categories: No use, recent use (women who were using MHT within the

Table 1. Selected characteristics of postmenopausal women with dense breasts who participated in the Minnesota Green Tea Trial

Variable	n	Value	Minimum	Maximum
Age (y)	932	59.8 ± 4.9	50	71
Body mass index (kg/m^2)	932	25.1 ± 3.7	18.2	43.7
Age at menopause (y)	891	49.1 ± 5.5	24.9	61.9
Estrone[a] (pg/mL)	932	24 (15)	5	1738
Estradiol[a] (pg/mL)	932	4 (7)	1	1290
Bioavailable estradiol[a] (pg/mL)	932	1.6 (3.3)	0.1	586.4
Androstenedione[a] (pg/mL)	932	510 (300)	25	2110
Testosterone[a] (pg/mL)	932	170 (120)	5	710
Bioavailable testosterone[a] (pg/mL)	932	42.7 (36.8)	0.8	262.1
Sex-hormone binding globulin[a] (nmol/L)	932	71 (46.3)	8.9	241
Past/recent use of menopausal hormone therapy	923			
Yes		380 (41.2)		
No		543 (58.8)		
Genotype				
SULT1A1 (rs1968752)	915			
CC		363 (39.7)		
AC		426 (46.6)		
AA		123 (13.4)		
SULT1A1 (rs9282861)	899			
GG		411 (45.7)		
AG		381 (42.4)		
AA		107 (11.9)		
UGT1A1 (rs10929303)	911			
CC		573 (62.9)		
CT		282 (31.0)		
TT		56 (6.1)		
UGT1A4 (rs10929301)	912			
CC		267 (29.3)		
CG		453 (49.7)		
GG		192 (21.1)		
UGT1A4 (rs11673726)	899			
GG		374 (41.6)		
GT		411 (45.7)		
TT		114 (12.7)		
UGT1A6 (rs1105879)	912			
GG		111 (12.2)		
GT		415 (45.5)		
TT		386 (42.3)		
UGT1A6 (rs2070959)	895			
AA		396 (44.2)		
AG		395 (44.1)		
GG		104 (11.6)		

Table 1. Continued

Variable	n	Value	Minimum	Maximum
UGT1A6 (rs6759892)	912			
GG		151 (16.6)		
GT		445 (48.8)		
TT		316 (34.6)		
UGT1A8 (rs10167119)	912			
CC		143 (15.7)		
CT		436 (47.8)		
TT		333 (36.5)		
UGT2B7 (rs7439366)	912			
CC		207 (22.7)		
CT		455 (49.9)		
TT		250 (27.4)		

Data are presented as mean ± standard deviation or frequency (%).
[a]Median and interquartile range are displayed.

past 5 years prior to enrolling in the study), and past use (women who had used MHT more than 5 years prior to enrolling in the study). Due to the skewness of the hormone levels, log-transformations were performed prior to data analyses. Adjusted general linear models were fit to assess the associations between reproductive hormones and use of MHT, adjusting for age and BMI. We also fit general linear models to look at the interaction between single nucleotide genotypes and MHT use on levels of blood hormone, adjusted for age and BMI. Mean estimates were backtransformed to obtain geometric mean values and 95% confidence intervals for blood hormone levels. Bonferroni correction was applied to multiple comparisons between genotypes.

Hardy–Weinberg equilibrium in allele distribution was tested for all genes using chi-square. All statistical analyses were carried out using IBM SPSS Statistics for Windows (ver. 25.0; IBM, Armonk, NY, USA), and a P value < 0.05 was considered statistically significant.

RESULTS

The great majority of the participants in this study were white (97%), followed by 1.1% Asians, 0.8% African Americans, 1% other or mixed races. Table 1 summarizes the subjects' characteristics. A total of 932 subjects were included in the analyses. The mean age of the subjects was 59.8 years and mean BMI was 25.1 kg/m^2. Recent or past use of MHT was reported by 41.2% of subjects.

Table 2 shows the geometric mean values of sex-steroid hormones by category of MHT use. While no significant associations between MHT use and levels of estrone, estradiol, and sex-hormone binding globulin (SHBG) were found, levels of androstenedione were lower for women who reported recent use of MHT, compared with women who reported never using MHT ($P = 0.004$). On the other hand, bioavailable testosterone levels were higher in recent users of MHT compared with past users ($P = 0.044$).

All gene polymorphisms were in Hardy–Weinberg equilibrium as evidenced by non-significant chi-square tests between expected and observed allele frequencies. Table 3 shows the associations between SNPs in genes involved in catabolism of sex-steroid hormones and blood levels of sex-steroid hormones. There were significant associations between estrone levels and *SULT1A1* (rs1968752 and rs9282861) and *UGT1A4* (rs11673726) genotypes. Women carrying the AA genotypes for both *SULT1A1* genes had higher estrone levels compared to AG for rs9282861 ($P = 0.013$) and compared to AC and CC for rs1968752 ($P = 0.008$). Higher estrone levels were found in those carrying the *UGT1A4* (rs11673726) TT genotype compared with the GG genotype ($P = 0.040$). The GG genotype of *UGT1A6* (rs6759892) was associated with higher bioavailable estradiol levels compared with the GT genotype ($P = 0.016$). Similarly, the CC genotype of *UGT1A8* (rs10167119) was associated with higher bioavailable

Table 2. Adjusted geometric means of reproductive hormones by menopausal hormone therapy use in postmenopausal women with dense breasts who participated in the Minnesota Green Tea Trial

Reproductive hormones	Menopausal hormone therapy			*P* value[b]
	No use	Past use	Recent use	
No. of participants	529	168	215	
Estrone[a] (pg/mL)	23.7 (22.5, 22.8)	23.0 (21.0, 25.1)	22.1 (20.5, 23.9)	0.351
Estradiol[a] (pg/mL)	3.60 (3.26, 3.97)	3.54 (2.97, 4.22)	3.40 (2.92, 3.97)	0.838
Bioavailable estradiol[a] (pg/mL)	1.62 (1.46, 1.80)	1.53 (1.27, 1.84)	1.57 (1.33, 1.85)	0.847
Androstenedione[a] (pg/mL)	516.4 (495.4, 538.3)	473.1 (439.5, 508.2)	456.0[c] (428.5, 486.4)	0.003
Testosterone[a] (pg/mL)	159.6 (151.4, 168.3)	144.5 (131.5, 158.8)	158.8 (146.2, 172.6)	0.176
Bioavailable testosterone[a] (pg/mL)	41.1 (38.7, 43.6)	32.5[d] (31.7, 39.2)	42.0 (38.3, 46.1)	0.025
SHBG[a] (nmol/L)	68.4 (65.5, 71.4)	71.8 (66.4, 77.4)	66.7 (62.2, 71.4)	0.365

MHT: menopausal hormone therapy, SHBG: sex-hormone binding globulin.
[a]Models were fit using the log base 10. Values represent geometric means that were back transformed. All models were adjusted for age and body mass index.
[b]*P* for univariate test.
[c]Significantly different than 'no use', $P = 0.004$.
[d]Significantly different than 'recent use', $P = 0.044$.

estradiol levels compared with the CT genotype. No other significant associations between hormone levels and genotypes were found.

We looked at whether MHT use modified the association between the SNPs analyzed and levels of sex-steroid hormones by including MHT use as an interaction term in the general linear models. The interaction between MHT use and SNPs was not significant, suggesting that MHT use did not modify the association between the SNPs presented in Table 3 and sex-steroid hormones.

DISCUSSION

The present cross-sectional analysis was conducted to examine the relationships between SNPs on genes involved in sex-steroid hormone catabolism and levels of sex-steroid hormones, as well as the role of MHT use as a potential modifier of these relationships.

MHT use was not associated with levels of estrogens, but we found that both androstenedione and bioavailable testosterone were significantly associated with MHT use.

The *SULT1A1* (rs9282861) SNP leads to a G to A transition and consequent substitution of Arginine (Arg) for Histidine (His) at codon 213. In a previous study, individuals who were homozygous for *His*/*His* (AA) were reported to have only about 10% of SULT1A1 enzyme activity compared to the *Arg*/*Arg* (GG) allele [7]. We found that women who were homozygous for the AA allele had higher levels of estrone compared with those carrying the AG allele. Given previous evidence that breast cancer risk increases in postmenopausal women with higher levels of estrone [8], our findings support the notion that *SULT1A1* (rs9282861) polymorphism may modify the risk of breast cancer in postmenopausal women. Indeed, a previous study found a significant association between the AA allele and increased risk for postmenopausal breast cancer and the association was stronger for women with a higher BMI [9]. We also looked at another SNP in the *SULT1A1* gene (rs1968752) and found that women carrying the AA genotype had higher levels of estrone compared with the AC and CC genotypes.

UGTs catalyze the transfer of glucuronic acid from UDP-glucuronic acid to several endogenous and exogenous substrates. These enzymes contribute to the maintenance of sex-steroid hormone levels in the body by catalyzing the transfer of glucuronic acid to these hormones, which stimulates their excretion. Eight polymorphisms in UGT genes were investigated in the present study and three of them were significantly associated with sex-steroid hormones. Similar to the findings for *SULT1A1* polymorphisms, women with the TT genotype for *UGT1A4* (rs11673726) had increased levels of estrone compared with the GG genotype. The GG genotype of *UGT1A6* (rs6759892) and the CC genotype of *UGT1A8* (rs10167119) were associated with

Table 3. Associations between SNPs in genes involved in catabolism of sex-steroid hormones and blood levels of sex-steroid hormones and mammographic density in postmenopausal women who participated in the Minnesota Green Tea Trial

Genotype	SNP	n	Geometric means[a] (95% CI)			
			Bioestradiol (pg/mL)	Estrone (pg/mL)	Biotestosterone (pg/mL)	Androstenedione (pg/mL)
SULT1A1	1968752	912				
CC		363	1.53 (1.5, 1.7)	22.6 (21.3, 24.0)	39.3 (36.6, 42.2)	484.2 (461.3, 509.3)
AC		426	1.56 (1.4, 1.7)	22.6 (21.4, 23.9)	40.5 (37.8, 43.2)	492.0 (469.9, 515,2)
AA		123	1.92 (1.5, 2.4)	26.8 (24.3, 29.7)[b]	41.8 (36.9, 47.3)	527.2 (484.2, 574.1)
P trend			0.185	0.008*	0.664	0.238
SULT1A1	9282861	899				
GG		411	1.55 (1.4, 1.7)	23.2 (22.0, 24.5)	42.1 (36.8, 48.0)	517.6 (472.1, 567.5)
AG		381	1.56 (1.4, 1.8)	22.1 (20.9, 23.4)	40.4 (37.7, 43.3)	489.8 (466.7, 514.0)
AA		107	1.91 (1.5, 1.7)	26.6 (23.9, 29.6)[c]	39.3 (36.8, 42.2)	490.9 (468.8, 514.0)
P trend			0.258	0.013*	0.670	0.549
UGT1A1	10929303	911				
CC		573	1.56 (1.4, 1.7)	23.1 (22.0, 24.2)	40.5 (38.3, 42.9)	490.9 (472.1, 510.5)
CT		282	1.70 (1.5, 2.0)	23.5 (22.0, 25.1)	39.5 (36.4, 42.8)	496.6 (468.8, 524.8)
TT		56	1.37 (1.0, 1.9)	22.0 (18.9, 25.5)	38.9 (32.3, 46.8)	511.7 (450.8, 580.8)
P trend			0.397	0.713	0.827	0.808
UGT1A4	10929301	912				
CC		267	1.61 (1.4, 1.9)	23.0 (21.5, 24.7)	39.7 (36.5, 43.1)	502.3 (474.2, 532.1)
CG		453	1.49 (1.3, 1.7)	22.5 (21.4, 23.8)	39.2 (36.8, 41.8)	480.8 (460.3, 503.5)
GG		192	1.83 (1.5, 2.2)	24.9 (23.0, 27.0)	43.1 (39.1, 47.5)	511.7 (477.5, 547.0)
P trend			0.153	0.115	0.278	0.267
UGT1A4	11673726	899				
GG		374	1.58 (1.4, 1.8)	22.4 (21.2, 23.8)	39.8 (37.1, 42.8)	500.0 (475.3, 524.8)
GT		411	1.51 (1.3, 1.7)	23.2 (21.9, 24.5)	39.1 (36.6, 41.8)	480.8 (459.2, 504.7)
TT		114	2.06 (1.6, 2.6)	26.2 (23.6, 29.2)[d]	45.7 (40.2, 52.0)	514.0 (469.9, 561.0)
P trend			0.059	0.040*	0.100	0.343
UGT1A6	1105879	912				
GG		111	1.97 (1.6, 2.5)	24.4 (21.9, 27.2)	40.5 (35.5, 46.1)	504.7 (461.3, 552.1)
GT		415	1.52 (1.3, 1.7)	23.4 (22.1, 24.7)	40.3 (37.7, 43.0)	488.6 (466.7, 512.9)
TT		386	1.58 (1.4, 1.8)	22.6 (21.3, 23.9)	39.9 (37.2, 42.8)	495.4 (472.1, 520.0)
P trend			0.138	0.399	0.977	0.820
UGT1A6	2070959	895				
AA		396	1.59 (1.4, 1.8)	22.4 (21.2, 23.8)	39.4 (36.8, 42.3)	495.4 (472.1, 518.8)
AG		395	1.53 (1.3, 1.7)	23.5 (22.2, 24.9)	40.7 (38.0, 43.6)	489.8 (466.7, 514.0)
GG		104	2.01 (1.6, 2.5)	24.9 (22.3, 27.7)	41.0 (35.8, 46.9)	509.3 (464.5, 558.5)
P trend			0.120	0.213	0.763	0.764
UGT1A6	6759892	912				
GG		151	2.00 (1.6, 2.4)	25.3 (23.1, 27.7)	42.6 (38.1, 47.6)	500.0 (462.4, 539.5)
GT		445	1.44 (1.3, 1.6)[e]	22.6 (21.4, 23.8)	38.6 (36.2, 41.2)	483.1 (461.3, 504.7)
TT		316	1.64 (1.4, 1.9)	23.0 (21.6, 24.5)	41.2 (38.1, 44.5)	505.8 (479.7, 533.3)
P trend			0.016*	0.109	0.242	0.398

Table 3. Continued

Genotype	SNP	n	Geometric meansa (95% CI)			
			Bioestradiol (pg/mL)	Estrone (pg/mL)	Biotestosterone (pg/mL)	Androstenedione (pg/mL)
UGT1A8	10167119	912				
CC		143	1.99 (1.6, 2.4)	25.6 (23.3, 28.1)	43.0 (38.4, 48.2)	503.5 (464.5, 544.5)
CT		436	1.47 (1.3, 1.6)[f]	22.6 (21.4, 23.9)	39.2 (36.6, 41.9)	484.2 (462.4, 507.0)
TT		333	1.61 (1.4, 1.8)	22.9 (21.5, 24.3)	40.3 (37.3, 43.4)	502.3 (476.4, 528.4)
P trend			0.033*	0.072	0.380	0.508
UGT2B7	7439366	912				
CC		207	1.61 (1.4, 1.9)	22.9 (21.1, 24.7)	39.2 (35.6, 43.0)	478.6 (448.7, 511.7)
CT		455	1.57 (1.4, 1.8)	23.4 (22.2, 24.7)	41.4 (38.8, 44.2)	503.5 (481.9, 526.0)
TT		250	1.61 (1.4, 1.9)	22.9 (21.3, 24.6)	38.7 (35.6, 42.3)	487.5 (459.2, 517.6)
P trend			0.959	0.813	0.406	0.412

SNP: single nucleotide polymorphism, SULT: sulfotransferase, UGT: UDP-glucuronosyltransferases, CI: confidence interval.
*$P < 0.05$.
[a]Adjusted for age, body mass index, and menopausal hormone therapy use.
[b]Significantly different from AC and CC genotypes, $P < 0.02$.
[c]Significantly different from AG, $P = 0.01$.
[d]Significantly different from GG, $P = 0.034$.
[e]Significantly different from GG, $P = 0.014$.
[f]Significantly different from CC, $P = 0.028$.

higher levels of bioavailable estradiol compared with the GT and TT genotypes, respectively. These findings suggest that polymorphisms in *UGT1A4* (rs11673726), *UGT1A6* (rs6759892) and *UGT1A8* (rs10167119) may be of clinical significance, as they may play a role in the levels of bioavailable estradiol and estrone in postmenopausal women. Although previous studies have reported increased risk of breast cancer in those carrying the GG genotype of *UGT1A6* (rs6759892) [10,11], future studies are needed to confirm the clinical significance of these findings and whether or not genetic polymorphisms in *UGT1A4* (rs11673726) and *UGT1A8* (rs10167119) are also associated with increased risk of breast cancer in postmenopausal women.

One limitation of this study is that the findings cannot be generalized to premenopausal women or postmenopausal women who are not white, as the great majority of the participants (97%) were postmenopausal white women. Furthermore, the clinical significance of some of the SNPs assessed such as *UGT1A4* (rs11673726) and *UGT1A6* (rs6759892) and *UGT1A8* (rs10167119) is unknown, although this study suggests that these polymorphisms are associated with levels of estrone and bioavailable estradiol. To our knowledge, this is the first study that looked at these two polymorphisms in relation to sex-steroid hormones in postmenopausal women. In addition, previous studies have not differentiated between bioavailable and free levels of circulating hormones.

In conclusion, polymorphisms in *SULT1A1* (rs9282861, rs1968752), and *UGT1A4* (rs11673726) genes were associated with estrone levels, whereas *UGT1A6* (rs6759892) and *UGT1A8* (rs10167119) variants were associated with bioavailable estradiol levels in postmenopausal women. However, there was no evidence that use of MHT modified the association between these hormones and the polymorphisms studied. Findings from this cross-sectional study suggest a potential clinical significance of *UGT1A* and *SULT1A* enzymes in modulating estrone and bioavailable estradiol levels in white postmenopausal women with dense breasts.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sparks R, Ulrich CM, Bigler J, Tworoger SS, Yasui Y, Rajan KB, et al. UDP-glucuronosyltransferase and sulfotransferase polymorphisms, sex hormone concentrations, and tumor receptor status in breast cancer patients. Breast Cancer Res 2004; 6: R488-98.
2. Sak K. The Val158Met polymorphism in COMT gene and cancer risk: role of endogenous and exogenous catechols. Drug Metab Rev 2017; 49: 56-83.
3. Dumas I, Diorio C. Polymorphisms in genes involved in the estrogen pathway and mammographic density. BMC Cancer 2010; 10: 636.
4. Yong M, Schwartz SM, Atkinson C, Makar KW, Thomas SS, Newton KM, et al. Associations between polymorphisms in glucuronidation and sulfation enzymes and mammographic breast density in premenopausal women in the United States. Cancer Epidemiol Biomarkers Prev 2010; 19: 537-46.
5. Samavat H, Dostal AM, Wang R, Bedell S, Emory TH, Ursin G, et al. The Minnesota Green Tea Trial (MGTT), a randomized controlled trial of the efficacy of green tea extract on biomarkers of breast cancer risk: study rationale, design, methods, and participant characteristics. Cancer Causes Control 2015; 26: 1405-19.
6. American College of Radiology; BI-RADS Committee. ACR BI-RADS breast imaging and reporting data system: breast imaging atlas. 4th ed. Reston: American College of Radiology; 2003.
7. Raftogianis RB, Wood TC, Weinshilboum RM. Human phenol sulfotransferases SULT1A2 and SULT1A1: genetic polymorphisms, allozyme properties, and human liver genotype-phenotype correlations. Biochem Pharmacol 1999; 58: 605-16.
8. Yang G, Gao YT, Cai QY, Shu XO, Cheng JR, Zheng W. Modifying effects of sulfotransferase 1A1 gene polymorphism on the association of breast cancer risk with body mass index or endogenous steroid hormones. Breast Cancer Res Treat 2005; 94: 63-70.
9. Xiao J, Zheng Y, Zhou Y, Zhang P, Wang J, Shen F, et al. Sulfotransferase SULT1A1 Arg213His polymorphism with cancer risk: a meta-analysis of 53 case-control studies. PLoS One 2014; 9: e106774.
10. Hu DG, Mackenzie PI, McKinnon RA, Meech R. Genetic polymorphisms of human UDP-glucuronosyltransferase (UGT) genes and cancer risk. Drug Metab Rev 2016; 48: 47-69.
11. Justenhoven C, Obazee O, Winter S, Rabstein S, Lotz A, Harth V, et al. The UGT1A6_19_GG genotype is a breast cancer risk factor. Front Genet 2013; 4: 104.