

**Short Communication****Association of Genetic Polymorphisms in UGT1A1 with Breast Cancer and Plasma Hormone Levels<sup>1</sup>**

Chantal Guillemette,<sup>2</sup> Immaculata De Vivo, Susan E. Hankinson, Christopher A. Haiman, Donna Spiegelman, David E. Housman, and David J. Hunter

Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), Faculty of Pharmacy, Laval University, Quebec G1V 4G2, Canada [C. G.]; Department of Biology and Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139 [C. G., D. E. H.]; Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115 [I. D. V., S. E. H., D. J. H.]; Departments of Epidemiology [I. D. V., S. E. H., C. A. H., D. S., D. J. H.] and Nutrition [D. J. H.], Harvard School of Public Health, Boston, Massachusetts 02115; and Harvard Center for Cancer Prevention, Boston, Massachusetts 02115 [C. A. H., D. J. H.]

**Abstract**

**UDP-glucuronosyltransferases (UGTs) catalyze the detoxification and the elimination of a large number of endogenous and exogenous compounds in the liver and extrahepatic tissues. One of the UGT1A family members, UGT1A1, is involved in estradiol metabolism and, therefore, represents a candidate gene in breast carcinogenesis. A common insertion/deletion polymorphism in the TATA-box of the promoter region of UGT1A1 results in decreased initiation of transcription. In a previous study, we found a positive association between the UGT1A1 low-transcriptional alleles and premenopausal breast cancer risk in an African-American population. In the present study, we sought to determine whether the low-transcription UGT1A1 promoter allele, UGT1A1\*28 [A(TA)<sub>7</sub>TAA], was associated with increased breast cancer risk among primarily Caucasian women in a nested case-control study within the Nurses' Health Study cohort. No significant association between the UGT1A1\*28 [A(TA)<sub>7</sub>TAA] allele and breast cancer was observed. Compared with women homozygous for the UGT1A1\*1 [A(TA)<sub>6</sub>TAA] allele, the relative risk was 0.80 (confidence interval, 0.49–1.29) for women homozygous for the UGT1A1\*28 allele. The effect of the UGT1A1 genotype on plasma hormone levels in postmenopausal women not using hormone replacement was also evaluated, and overall, no significant differences in hormone levels by**

**genotypes were observed. When restricted to women who had at least one UGT1A1\*28 allele and a body mass index at blood draw of >27 kg/m<sup>2</sup>, particularly in combination with the cytochrome p450c17α genotype, estrone and estradiol levels tended to vary by UGT1A1 genotypes. The results presented do not support a strong association between the UGT1A1 promoter polymorphism and the risk of breast cancer.**

**Introduction**

UGT<sup>3</sup> represents one of the most important classes of phase II detoxification enzymes that catalyze the transfer of glucuronic acid to a large number of substrates in the liver and extrahepatic tissues (1). Compounds inactivated by glucuronic acid conjugation include steroid hormones, such as estrogens and catechol estrogens (2–5). Thus UGT enzymes may assist in the maintenance of steady-state levels of steroids in target tissues (6, 7). Moreover, there is evidence that one of the UGT1A family members, UGT1A1, is involved in E<sub>2</sub> inactivation (8, 9) and expressed in the mammary gland (8), and, therefore, represents a good candidate gene in breast carcinogenesis.

Interindividual variation in UGT1A1 expression is explained by a polymorphic alteration in the atypical TATA-box region of the UGT1A1 gene (10–12). This polymorphic site is characterized by a variation in the number of TA repeats in the A(TA)<sub>n</sub>TAA sequence of the promoter. The most common allele (UGT1A1\*1) contains six TA repeats, whereas the principal variant allele (UGT1A1\*28) contains seven TA repeats. Two other UGT1A1 alleles, the UGT1A1\*33 [A(TA)<sub>5</sub>TAA] allele and the UGT1A1\*34 [A(TA)<sub>8</sub>TAA] allele, have been found almost exclusively in the African-American population (13, 14). In a previous study, we investigated the association between breast cancer and A(TA)<sub>7</sub>TAA and A(TA)<sub>8</sub>TAA UGT1A1 alleles, which have been shown to have lower transcriptional activity *in vitro* (8). In the CBCS study, the alleles A(TA)<sub>7</sub>TAA and A(TA)<sub>8</sub>TAA were associated with a 2-fold increase in the risk of developing breast cancer in premenopausal African-American women.

In the present study, we evaluated, among primarily Caucasian women, the relationship between UGT1A1 alleles and breast cancer risk in a nested case-control study within the NHS cohort. Because decreased transcription of the UGT1A1 gene has been found to be associated with increased plasma levels of substrates of the UGT1A1 protein, *e.g.*, bilirubin, we also evaluated the relationship between the UGT1A1\*28 allele and circulating estrogen levels and the interaction between UGT1A1 and CYP17 polymorphisms.

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<sup>2</sup> To whom requests for reprints should be addressed, at Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), Faculty of Pharmacy, Laval University, Quebec G1V 4G2, Canada. E-mail: chantal.guillemette@crchul.ulaval.ca.

<sup>3</sup> The abbreviations used are: UGT, UDP-glucuronosyltransferase enzyme; NHS1, Nurses' Health Study 1; OR, odds ratio; CI, confidence interval; CYP17, cytochrome p450c17α; CBCS, North Carolina Breast Cancer Study; E<sub>2</sub>, estradiol; E<sub>1</sub>, estrone; BMI, body mass index; RR, relative risk.

## Materials and Methods

**Study Population.** The NHS was initiated in 1976, when 121,700 United States registered nurses between the ages of 30 and 55 returned an initial questionnaire reporting medical histories and baseline health-related exposures. Between 1989 and 1990, blood samples were collected from 32,826 women. Incident breast cancers are identified by self-report and confirmed by medical record review. Eligible cases in this study consisted of women from the subcohort with pathologically confirmed incident breast cancer who gave a blood specimen. Controls were matched to cases on the basis of year of birth, menopausal status, and postmenopausal hormone use, as well as time of day, month, and fasting status at blood draw. Menopause was defined as described previously (5). The nested case-control study consists of 461 incident breast cancer cases and 615 matched controls. The study sample for the plasma hormone analysis was restricted to postmenopausal controls not using hormone replacement therapy within 3 months of blood draw. The protocol was approved by the Committee on Human Subjects, Brigham and Women's Hospital, Boston, MA. Detailed information on exposure data and hormone assay have been described previously (15).

**Molecular Analysis.** All analyses were conducted with laboratory personnel blinded to case status. DNA was extracted from buffy coat fractions using the QIAGEN QIAamp Blood Kit (QIAGEN, Inc., Chatsworth, CA). DNA samples from cases and controls were genotyped for the dinucleotide insertion/deletion present in the promoter region of the *UGT1A1* gene using previously described methods (8).

**Statistical Methods.** ORs and 95% CIs were calculated using conditional and unconditional logistic regression. In addition to the matching variables, we adjusted for the following breast cancer risk factors: (a) BMI ( $\text{kg}/\text{m}^2$ ) at age 18 (continuous); (b) weight gain since age 18 ( $<5$ ,  $5$ – $19.9$ , and  $\geq 20$  kg); (c) age of menarche ( $<12$ ,  $12$ ,  $13$ , and  $\geq 13$  years); (d) parity/age at first birth (nulliparous; one to two children/age at first birth  $\leq 24$  years; one to two children/age at first birth  $\geq 24$  years; three children/age at first birth  $\leq 24$  years; and three or more children/age at first birth  $\geq 24$  years); (e) first-degree family history of breast cancer (yes/no); (f) history of benign breast disease (yes/no); and (g) duration of postmenopausal hormone use (never; past,  $<5$  and  $\geq 5$  years; current,  $<5$  and  $\geq 5$  years). We also adjusted for age at menopause (continuous in years) in analyses limited to postmenopausal women. Indicator variables for all three genotypes were created using the *UGT1A1*\*1/*UGT1A1*\*1 hypothesized low-risk genotypes as the reference category in the multivariable models. Genotype was also evaluated using a dichotomous variable with the *UGT1A1*\*1/*UGT1A1*\*28 and *UGT1A1*\*28/*UGT1A1*\*28 subjects combined, because a gene dosage effect on breast cancer risk was not apparent. Unconditional multivariable models controlling for the matching factors enabled all controls to be included in analyses, limiting the cases to specified histopathological characteristics. Interactions between genotypes and breast cancer risk factors were evaluated by including interaction terms in multivariate logistic regression models. The likelihood ratio test was used to assess the statistical significance of these interactions.

Mixed regression models were used to evaluate the association between genotype and circulating hormone levels among controls, controlling for BMI at blood draw and the matching variables (16). Hormone fractions were measured in two to three different batches; the laboratory batch was treated as a random variable in all hormone analyses except for dehydroepiandrosterone sulfate among never-users of hormone replacement, where a batch effect was not observed. We calculated least-square mean

plasma steroid hormone levels to evaluate the differences in hormone levels between the genotypes; this was limited to postmenopausal women. The *UGT1A1*\*1/*UGT1A1*\*1 group was used as the reference category. To examine the interactive effect of the *UGT1A1* gene and the *CYP17* gene on hormone levels, we used the SAS Proc Mixed procedure. The natural logarithm of the plasma hormone values was used in the analyses to reduce the skewness of the regression residuals. We used the SAS statistical package for all analyses (SAS Institute, Inc.).

## Results

Five controls and two cases could not be genotyped for *UGT1A1* promoter polymorphisms. In addition, because of their very low prevalence, women who had at least one *UGT1A1*\*33 allele [ $A(\text{TA})_5\text{TAA}$ ;  $n = 2$ ; one case and one control] and one *UGT1A1*\*34 allele [ $A(\text{TA})_8\text{TAA}$ ;  $n = 3$ ; two cases and one control] were not included in the analysis. Thus our study included 455 breast cancer cases and 609 controls. A total of 352 cases and 498 controls were postmenopausal, and 63 cases and 68 controls were premenopausal (Table 1); menopausal status was uncertain for 40 cases and 43 controls.

The prevalence of the homozygous *UGT1A1*\*28 genotype in the present population was very close to that observed in a population of healthy Europeans [9% in NHS cases and 10% in NHS controls compared with 11.3% in Beutler *et al.* (13)]. The calculated frequencies for the *UGT1A1*\*1 and *UGT1A1*\*28 alleles were 0.68 and 0.32, respectively, in the controls and 0.69 and 0.31, respectively, in the cases. Genotype frequencies were in Hardy-Weinberg equilibrium for cases ( $\chi^2 = 1.49$ ; degrees of freedom (*df*), 1;  $P = 0.22$ ) and controls ( $\chi^2 = 0.80$ ; *df*, 1;  $P = 0.37$ ). The prevalence of the *UGT1A1*\*33 and *UGT1A1*\*34 alleles was extremely low in the NHS, which was consistent with the fact that most women self-reported their ethnicity as Caucasian, with very few Asians (0.3%), Hispanics (0.1%), and African Americans (0.3%). The prevalence of the lower-transcriptional activity alleles was slightly higher in the African-American population (0.40 in the CBCS control group; Ref. 8) compared with the Caucasian population (0.32 for the NHS control group).

There was no significant association between the low-activity allele, *UGT1A1*\*28 [ $A(\text{TA})_7\text{TAA}$ ], and breast cancer (Table 1). Compared with women homozygous for the *UGT1A1*\*1 allele, the estimated RR for the *UGT1A1*\*28/\*28 genotype was 0.80 (CI, 0.49–1.29). A slightly but nonsignificantly higher RR was observed among premenopausal homozygotes (*UGT1A1*\*28/\*28 versus \*1/\*1; RR = 1.28; CI, 0.38–4.64) compared with postmenopausal women (RR = 0.80; CI, 0.47–1.36). No association was revealed in subgroups defined by age at menarche, menopausal status, and clinical and pathological characteristics. We observed that having both polymorphisms in *UGT1A1* (*UGT1A1*\*28) and *CYP17* (A2 polymorphism) did not affect the risk of developing breast cancer.

In the analysis of the relationship of genotype with plasma steroid hormone levels, we calculated least-square geometric mean levels for each *UGT1A1* genotype among postmenopausal women not currently using postmenopausal hormones (Table 2). Compared with women with the *UGT1A1*\*1/*UGT1A1*\*1 genotype, women with the *UGT1A1*\*1/*UGT1A1*\*28 and *UGT1A1*\*28/*UGT1A1*\*28 genotypes had nonsignificant elevated levels of  $E_1$ : 4.4% ( $P = 0.38$ ) and 8.0% ( $P = 0.15$ ), respectively. Because the synthesis of estrogens occurs principally in the adipose tissue in postmenopausal women, stratification was done according to BMI at blood draw (BMIs  $\leq 23$   $\text{kg}/\text{m}^2$ ,  $>23$   $\text{kg}/\text{m}^2$  and  $\leq 27$   $\text{kg}/\text{m}^2$ , and  $>27$

Table 1 Association between *UGT1A1* genotype and breast cancer risk. RRs and 95% CI for breast cancer risk by *UGT1A1* genotype and menopausal status

<i>UGT1A1</i> genotype	Cases	Controls	RR	Adjusted RR
All women	<i>n</i> = 455 (%)	<i>n</i> = 609 (%)		
*1/*1	218 (48)	276 (45)	1.0 <sup>a</sup>	1.0 <sup>b</sup>
*1/*28	196 (43)	272 (45)	0.93 (0.71–1.21) <sup>a</sup>	0.92 (0.69–1.22) <sup>b</sup>
*28/*28	41 (9)	60 (10)	0.85 (0.54–1.33) <sup>a</sup>	0.80 (0.49–1.29) <sup>b</sup>
*1/*28 + *28/*28	237 (52)	332 (55)	0.91 (0.71–1.18) <sup>a</sup>	0.90 (0.68–1.19) <sup>b</sup>
Premenopausal women	<i>n</i> = 63 (%)	<i>n</i> = 68 (%)		
*1/*1	29 (46)	30 (44)	1.0 <sup>c</sup>	1.0 <sup>d</sup>
*1/*28	26 (41)	30 (44)	0.91 (0.43–1.94) <sup>c</sup>	0.74 (0.30–1.79) <sup>d</sup>
*28/*28	8 (13)	8 (12)	1.03 (0.34–3.17) <sup>c</sup>	1.28 (0.35–4.64) <sup>d</sup>
*1/*28 + *28/*28	34 (54)	38 (56)	0.94 (0.46–1.90) <sup>c</sup>	0.85 (0.38–1.91) <sup>d</sup>
Postmenopausal women	<i>n</i> = 352 (%)	<i>n</i> = 498 (%)		
*1/*1	172 (49)	222 (45)	1.0 <sup>e</sup>	1.0 <sup>f</sup>
*1/*28	150 (43)	229 (46)	0.86 (0.64–1.15) <sup>e</sup>	0.82 (0.60–1.12) <sup>f</sup>
*28/*28	30 (9)	47 (9)	0.79 (0.47–1.32) <sup>e</sup>	0.80 (0.47–1.36) <sup>f</sup>
*1/*28 + *28/*28	180 (51)	276 (55)	0.84 (0.64–1.12) <sup>e</sup>	0.82 (0.61–1.10) <sup>f</sup>

<sup>a</sup> Conditional logistic regression adjusted for the matching variables: age, menopausal status, postmenopausal hormone use, date at blood draw, time at blood draw, and fasting status.

<sup>b</sup> Conditional logistic regression adjusted for the matching variables and age at menarche, parity, age at first birth, BMI at age 18, weight gain since age 18, benign breast disease, first-degree family history of breast cancer, and duration of postmenopausal hormone use.

<sup>c</sup> Unconditional logistic regression adjusted for the matching variables: age, date at blood draw, time at blood draw, and fasting status.

<sup>d</sup> Unconditional logistic regression adjusted for the matching variables, and age at menarche, parity, age at first birth, BMI at age 18, weight gain since age 18, benign breast disease, and first-degree family history of breast cancer.

<sup>e</sup> Unconditional logistic regression adjusted for the matching variables: age, postmenopausal hormone use, date at blood draw, time at blood draw, and fasting status.

<sup>f</sup> Unconditional logistic regression adjusted for the matching variables, and age at menarche, parity, age at first birth, BMI at age 18, weight gain since age 18, age at menopause, benign breast disease, first-degree family history of breast cancer, and duration of postmenopausal hormone use.

Table 2 Least-square geometric mean hormone levels among postmenopausal women not currently using postmenopausal hormones by *UGT1A1* and *CYP17* genotypes

Hormones	Genotypes <sup>a</sup>	Overall <sup>b</sup> ( <i>n</i> )	BMI ≤23 <sup>c</sup> ( <i>n</i> )	BMI >23 ≤27 <sup>c</sup> ( <i>n</i> )	BMI >27 <sup>c</sup> ( <i>n</i> )
<i>UGT1A1</i>					
E <sub>1</sub> -sulfate (pg/ml)	*1/*1	196.1 (111)	169.1 (35)	166.9 (34)	262.4 (42)
	*1/*28 or *28/*28	187.7 (146)	142.6 (38)	176.9 (57)	234.6 (51)
E <sub>1</sub> (pg/ml)	*1/*1	29.3 (121)	26.0 (36)	27.3 (38)	34.1 (47)
	*1/*28 or *28/*28	30.6 (153)	24.6 (38)	28.0 (60)	37.2 (55)
E <sub>2</sub> (pg/ml)	*1/*1	7.3 (120)	6.1 (35)	6.3 (38)	9.3 (47)
	*1/*28 or *28/*28	7.9 (153)	5.8 (38)	6.6 (60)	10.9 (55)
					<i>P</i> = 0.09
<i>UGT1A1</i> and <i>CYP17</i>					
E <sub>1</sub> -sulfate (pg/ml)	*1/*1 and A1/A1	196.7 (42)	191.3 (9)	189.3 (16)	230.6 (17)
	*1/*28 or *28/*28 and A1/A2 or A2/A2	172.7 (96)	121.5 (22)	178.2 (48)	206.4 (26)
E <sub>1</sub> (pg/ml)	*1/*1 and A1/A1	28.5 (46)	25.8 (9)	29.6 (17)	29.5 (20)
	*1/*28 or *28/*28 and A1/A2 or A2/A2	30.2 (101)	23.3 (22)	27.8 (49)	39.3 (30)
					<i>P</i> = 0.07
E <sub>2</sub> (pg/ml)	*1/*1 and A1/A1	6.9 (45)	5.4 (8)	6.7 (17)	8.6 (20)
	*1/*28 or *28/*28 and A1/A2 or A2/A2	7.5 (101)	5.6 (22)	6.4 (49)	11.0 (30)

<sup>a</sup> Participants with missing hormone levels removed from analysis.

<sup>b</sup> Controlling for age, date of blood draw, time of blood draw, fasting status, BMI, and laboratory batch.

<sup>c</sup> Controlling for age, date of blood draw, time of blood draw, fasting status, and laboratory batch. Only *P*s <0.10 are indicated. Genotypes were compared to *UGT1A1*\*1 homozygous women.

kg/m<sup>2</sup>). Comparing women with low (BMI ≤23 kg/m<sup>2</sup>) versus high (BMI >27 kg/m<sup>2</sup>) estrogen production, the elevation of circulating E<sub>2</sub> levels was greater in women who had at least one *UGT1A1*\*28 allele (87.9%) compared with *UGT1A1*\*1 homozygous women (52.4%). Within BMI subgroups, women who had at least one *UGT1A1*\*28 allele in the highest stratum of BMI (>27 kg/m<sup>2</sup>) had a nonsignificant increase in the level of E<sub>2</sub> (17.5%; *P* = 0.09) compared with *UGT1A1*\*1 homozygous women (Table 2). Furthermore, we evaluated the combination of *UGT1A1* and *CYP17* genotypes on hormone levels. In analyses limited to women with a BMI >27 kg/m<sup>2</sup> who had at

least one *UGT1A1*\*28 and one *CYP17*A2 allele (*n* = 30), there was a marginally significant increase in the levels of E<sub>1</sub> (33.2%; *P* = 0.07) and a nonsignificant elevation in E<sub>2</sub> (27.9%; *P* = 0.18) compared with *UGT1A1*\*1 and *CYP17* A1 homozygous carriers (*n* = 20).

## Discussion

An important role for the UGT enzymes is to maintain intracellular steady-state levels of steroids, including estrogens, in target tissues (6, 7). Accordingly, high levels of estrogen-



glucuronides have been observed in breast cyst fluid, suggesting their formation within the mammary gland (17, 18). We hypothesized that alteration in the glucuronidation pathway, which directly inactivates estrogens and catechol metabolites at their site of action (2–5), may potentially modify estrogen concentration and consequently estrogen-related cancer risk. Functional analyses of the transcriptional promoter activity demonstrated that allele *UGT1A1*\*28 has a 30% decrease in transcription and that the *UGT1A1*\*34 allele has a 50% decreased transcription, whereas the allele *UGT1A1*\*33 has a 20% increased transcription compared with the *UGT1A1*\*1 wild-type allele (8). Additional studies based on phenotypic measurements revealed that those who were carriers of at least one *UGT1A1*\*28 allele had much lower glucuronidation rates compared with homozygous *UGT1A1*\*1 (19, 20). On the basis of these functional studies (8, 13), women who had at least one low-transcriptional allele *UGT1A1*\*28 [A(TA)<sub>7</sub>TAA] were compared with women who had high-activity alleles *UGT1A1*\*1 [A(TA)<sub>6</sub>TAA]. The present study extends previous work among African-American women (200 cases and 200 controls) in the CBCS. In the CBCS study, the low-activity *UGT1A1* alleles were positively associated with invasive breast cancer among premenopausal women (OR, 1.8; 95% CI, 1.0–3.1; *P* = 0.06; Ref. 8), particularly among women with estrogen receptor-negative breast cancer (OR, 2.1; 95% CI, 1.0–4.2; *P* = 0.04) compared with estrogen receptor-positive breast cancer (OR, 1.3; 95% CI, 0.6–3.0; *P* = 0.5). In contrast, in the present NHS, a larger population-based prospective study, no influence of the *UGT1A1* polymorphism was observed on the susceptibility to breast cancer. Furthermore, we found no interaction between the *UGT1A1*\*28 and the *CYP17 A2* allele in relation to breast cancer risk.

In the analysis of hormone levels and UGT genotype among postmenopausal women not taking hormone replacement therapy, we observed a moderate increase in the levels of E<sub>1</sub> and E<sub>2</sub> associated with the *UGT1A1*\*28 allele alone and in combination with *CYP17 A2* polymorphism only in overweight women (BMI >27 kg/m<sup>2</sup>). However, this modest elevation in the plasma levels of estrogenic hormones in postmenopausal women may be insufficient for us to detect an altered risk of breast cancer. It is also well known that different UGT enzymes possess overlapping substrate specificity, including reactivity for estrogenic hormones (5). In the case of E<sub>2</sub> glucuronidation, although *UGT1A1* is the major UGT reported to date to actively conjugate E<sub>2</sub> (8, 9), other existing or not yet isolated UGTs may have a higher specificity and/or efficacy toward this steroid molecule (2, 21). In that case, a partial deficiency in *UGT1A1*, such as the one studied here, would have a limited impact on E<sub>2</sub> metabolism and, consequently, on breast cancer risk. The modest additional elevation of E<sub>2</sub> among the heaviest women who are carriers of at least one *UGT1A1*\*28 allele is suggestive of a possible contribution of the glucuronidation pathway, and especially of *UGT1A1*, in the maintenance of hormone homeostasis in situations where estrogens are present at higher concentrations.

Our results suggest that the decrease in transcription of the *UGT1A1* gene caused by the TA polymorphism is not sufficient to alter breast cancer risk in Caucasian women.

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