

## Research Article

## Functional Polymorphisms in UDP-Glucuronosyl Transferases and Recurrence in Tamoxifen-Treated Breast Cancer Survivors

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## Abstract

**Background:** Tamoxifen is oxidized by cytochrome-P450 enzymes (e.g., *CYP2D6*) to two active metabolites, which are eliminated via glucuronidation by UDP-glucuronosyl transferases (*UGT*). We measured the association between functional polymorphisms in key *UGTs* (*UGT2B15\*2*, *UGT2B7\*2*, and *UGT1A8\*3*) and the recurrence rate among breast cancer survivors.

**Methods:** We used the Danish Breast Cancer Cooperative Group registry to identify 541 cases of recurrent breast cancer among women with estrogen receptor-positive tumors treated with tamoxifen for at least 1 year ( $ER^+/TAM^+$ ), and 300 cases of recurrent breast cancer among women with estrogen receptor-negative tumors who were not treated with tamoxifen ( $ER^-/TAM^-$ ). We matched one control to each case on ER status, menopausal status, stage, calendar period, and county. *UGT* polymorphisms were genotyped from archived primary tumors. We estimated the recurrence OR for the *UGT* polymorphisms by using logistic regression models, with and without stratification on *CYP2D6\*4* genotype.

**Results:** No *UGT* polymorphism was associated with breast cancer recurrence in either the  $ER^+/TAM^+$  or  $ER^-/TAM^-$  groups [in the  $ER^+/TAM^+$  group, compared with two normal alleles: adjusted OR for two *UGT2B15\*2* variant alleles = 1.0 (95% CI, 0.70–1.5); adjusted OR for two *UGT2B7\*2* variant alleles = 0.96 (95% CI, 0.65–1.4); adjusted OR for one or two *UGT1A8\*3* variant alleles = 0.95 (0.49–1.9)]. Associations were similar within strata of *CYP2D6\*4* genotype.

**Conclusions:** Functional polymorphisms in key tamoxifen-metabolizing enzymes were not associated with breast cancer recurrence risk.

**Impact:** Our results do not support the genotyping of key metabolic enzyme polymorphisms to predict response to tamoxifen therapy. *Cancer Epidemiol Biomarkers Prev*; 20(9); 1937–43. ©2011 AACR.

## Introduction

Tamoxifen is a selective estrogen receptor (ER) modulator that binds the ER and inhibits breast cancer growth (1). Members of the cytochrome P450 enzyme

family (e.g., *CYP2D6*) catalyze phase I metabolism of tamoxifen to its most active metabolites, 4-hydroxy-tamoxifen (4HT) and 4-hydroxy-N-desmethyl tamoxifen (endoxifen; ref. 2). These metabolites bind the ER with approximately 100-fold higher affinity than tamoxifen itself and are ostensibly responsible for tamoxifen's protection against breast cancer recurrence (3). Most tamoxifen phase II reactions are catalyzed by UDP-glucuronosyl transferases (*UGT*; refs. 4, 5). *UGTs* catalyze the addition of glucuronide moieties to 4HT and endoxifen, which negates their anti-estrogenic properties (6) and promotes their excretion (7). Three *UGTs* are encoded by polymorphic genes. *UGT2B15* has a variant allele (\*2/rs1902023) that confers an approximately 2-fold increased rate of catalysis on the translated enzyme, compared with wild type (8). *UGT2B7* has a variant allele (\*2/rs7439366) that encodes an enzyme with approximately 2- and 5-fold lower glucuronidation activity toward 4HT and endoxifen, respectively (9, 10). *UGT1A8* harbors 2 variant alleles: one (\*2/rs1042597)

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doi: 10.1158/1055-9965.EPI-11-0419

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**Table 1.** Characteristics of the UGT SNPs

Gene	Variant/reference SNP	Location	Amino acid change	Expected change in function	Applied Biosystems kit number
UGT2B15	*2/rs1902023	4q13	85 D>Y	Increased	C-27028164-10
UGT2B7	*2/rs7439366	4q13	268 H>Y	Reduced	Custom TaqMan kit developed for proxy SNP rs7434332
UGT1A8	*3/rs17863762	2q37	277 C>Y	Eliminated	C-34418788-20

produces an enzyme with catalytic activity similar to the wild type, and the other (\*3/rs17863762) eradicates glucuronidation activity completely (10). Therefore, the *UGT2B15*\*2, *UGT2B7*\*2, and *UGT1A8*\*3 polymorphisms (Table 1) have the potential to alter substantially the elimination rates of 4HT and endoxifen, either prolonging or decreasing their circulating half-lives, and potentially modifying tamoxifen effectiveness.

A number of studies have measured the association between functional polymorphisms in genes encoding tamoxifen phase I enzymes (e.g., *CYP2D6*) and breast cancer recurrence in tamoxifen-treated women, including a recent study from our group (11). The sum of the evidence from these studies points to a null association (12).

Two earlier studies measured the association between the *UGT2B15*\*2 polymorphism and recurrence among tamoxifen-treated breast cancer patients (13, 14). Nowell and colleagues (13) and Wegman and colleagues (14) both observed a higher recurrence rate among carriers of the \*2 variant. However, neither association was measured precisely enough to provide clear evidence refuting a null relationship.

The objective of this study was to measure with high precision the associations between functional polymorphisms in *UGT2B15*, *UGT2B7*, and *UGT1A8* and breast cancer recurrence, while accounting for phase I metabolic status.

## Materials and Methods

This study was approved by the Regional Committee on Biomedical Research Ethics of Aarhus County, Denmark, and by the Boston University Medical Campus Institutional Review Board.

### Study population and data collection

We studied the association between *UGT* polymorphisms and breast cancer recurrence by using a population-based case-control design; the methods have been detailed elsewhere (11). Briefly, the source population consisted of women ages 35 to 69 years, residing on Denmark's Jutland Peninsula, who were diagnosed with Unio Internationale Contra Cancrum (UICC) stage I, II, or III primary breast cancer between 1985 and 2001 and who were reported to the Danish Breast Cancer Cooperative Group (DBCG) registry (15). Two groups were formed

from this study population: (a) women whose primary tumors expressed ER and who were treated with tamoxifen for at least 1 year (ER<sup>+</sup>/TAM<sup>+</sup>), and (b) women whose primary tumors did not express ER, who were not treated with tamoxifen, and who survived for at least 1 year after diagnosis (ER<sup>-</sup>/TAM<sup>-</sup>). We included the ER<sup>-</sup>/TAM<sup>-</sup> group to estimate the direct effect, if any, of the *UGT* variants on breast cancer recurrence risk. Cases were women who experienced a recurrence after at least 1 year of tamoxifen treatment (if in the ER<sup>+</sup>/TAM<sup>+</sup> group) or after surviving at least 1 year beyond diagnosis (if in the ER<sup>-</sup>/TAM<sup>-</sup> group). Eligible controls were women who were not diagnosed with a recurrence after the same amount of follow-up time as each matched case.

Cases of breast cancer recurrence were identified from the DBCG registry. Risk sets were specified for each case, matched on ER/TAM group membership, menopausal status at diagnosis, date of breast cancer surgery ( $\pm 12$  months), county of residence, and UICC tumor stage. One control was sampled at random and without replacement from the risk set of each case. Follow-up ended with the first of diagnosis of recurrent breast cancer, death from any cause, emigration from Denmark, or September 1, 2006.

### Tissue processing, DNA extraction, amplification, and genotyping

Procurement procedures for archived primary tumors, DNA extraction and amplification methods, and details about central confirmation of ER expression are described elsewhere (11). Commercially available TaqMan kits (Applied Biosystems) were used to genotype the *UGT2B15*\*2 and *UGT1A8*\*3 alleles, as detailed in Table 1. Genotyping of *CYP2D6*\*4 also was done with a commercially available TaqMan kit (kit C-27102431-D0; ref. 11). A high proportion of the nucleotides flanking the *UGT2B7*\*2 single-nucleotide polymorphism (SNP) are guanine or cytosine residues, which precludes development of an oligonucleotide probe for this locus. Using HaploView software (Broad Institute, Cambridge, Massachusetts), we downloaded public data from the International HapMap Project (version 2, release 22), and searched the 5 kb region flanking the target SNP (rs7439366) for candidate proxy SNPs with high estimated linkage disequilibrium (LD) parameters. We identified SNP rs7434332, estimated to be in perfect LD with *UGT2B7*\*2 [ $R^2 = 1$ ;  $D' = 1$  (95% CI, 0.95–1)]. On the basis

of these LD parameters, detecting a variant allele for the proxy SNP is essentially equivalent to detecting the *UGT2B7\*2* allele. A custom TaqMan kit for this proxy SNP was developed through contract with Applied Biosystems, Inc.

### Definitions of analytic variables

Genotypes were classified as 2 normal (wild-type) alleles, 1 variant allele, or 2 variant alleles by the auto-call feature of the analytic software (MXPro QPCR version 4.1; Stratagene). Because the *UGT1A8\*3* variant is rare, we additionally classified *UGT1A8* genotype as either 2 normal alleles or at least 1 variant allele. Impaired *CYP2D6* function was defined as presence of 1 or 2 copies of the \*4 variant allele (rs3892097). Normal *CYP2D6* function was defined as presence of 2 normal alleles.

Recurrence was classified according to DBCG convention as any type of breast cancer or metastasis diagnosed after the initial course of therapy. In addition to the matching factors, covariates included age at diagnosis (continuous), histologic grade (low, medium, or high), type of breast cancer surgery (mastectomy or breast conserving), and receipt of adjuvant systemic chemotherapy or radiotherapy.

### Statistical analysis

Within ER/TAM groups we tabulated the frequency and proportion of cases and controls according to *UGT* genotypes and tumor, treatment, and demographic characteristics. We tested whether genotype frequencies among controls were consistent with those predicted under Hardy-Weinberg equilibrium by calculating  $\chi^2$  test statistics.

We used logistic regression models to estimate the OR (approximating the rate ratio because of the control sampling strategy) associating *UGT* polymorphisms with breast cancer recurrence among women taking tamoxifen (ER<sup>+</sup>/TAM<sup>+</sup>). The analyses were repeated in the group of women who did not take tamoxifen (ER<sup>-</sup>/TAM<sup>-</sup>) to evaluate non-tamoxifen-mediated associations between *UGT* genotypes and breast cancer recurrence. Logistic regression models were specified 2 ways for each of the *UGTs*: (a) conditioned on the matching factors and (b) adjusting for tumor stage, menopausal status, receipt of adjuvant systemic chemotherapy, receipt of adjuvant radiotherapy, type of surgery, time to recurrence, and histologic grade. Conditional and adjusted models were also specified, in which all *UGT* variants were included as independent variables. We also applied these models to the subset of cases and controls whose ER expression was concordant in their original and repeated assays, within strata of genetically normal and impaired *CYP2D6* function.

All statistical tests were 2-sided ( $\alpha = 0.05$ ). Analyses were conducted by SAS version 9.2 (SAS Institute).

## Results

### Characteristics of cases and controls

In the ER<sup>+</sup>/TAM<sup>+</sup> group, we identified 541 breast cancer recurrence cases, to whom we matched 541 breast cancer controls. In the ER<sup>-</sup>/TAM<sup>-</sup> group, we enrolled 300 breast cancer recurrence cases, to whom we matched 300 breast cancer controls. Table 2 shows the distribution of the cases and controls according

**Table 2.** Characteristics of breast cancer recurrence cases and matched breast cancer controls according to tumor and treatment variables and *UGT* genotypes

	ER <sup>+</sup> /TAM <sup>+</sup> , n (%)		ER <sup>-</sup> /TAM <sup>-</sup> Group, n (%)	
	Cases	Controls	Cases	Controls
<i>UGT2B15*2</i> genotype				
2 normal alleles	151 (29)	140 (27)	85 (29)	87 (30)
1 variant allele	237 (45)	238 (46)	133 (46)	130 (45)
2 variant alleles	133 (26)	139 (27)	71 (25)	69 (24)
(Missing)	20	24	11	14
<i>UGT2B7*2</i> genotype				
2 normal alleles	127 (25)	113 (22)	53 (19)	63 (22)
1 variant allele	224 (44)	232 (46)	142 (50)	142 (50)
2 variant alleles	163 (32)	162 (32)	87 (31)	77 (27)
(Missing)	27	34	18	18
<i>UGT1A8*3</i> genotype				
2 normal alleles	502 (96)	494 (95)	284 (97)	283 (97)
1 variant allele	19 (3.6)	23 (4.4)	8 (2.7)	9 (3.1)
2 variant alleles	1 (0.2)	1 (0.2)	0 (0)	0 (0)
(Missing)	19	23	8	8

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Table 2. Characteristics of breast cancer recurrence cases and matched breast cancer controls according to tumor and treatment variables and UGT genotypes (Cont'd)

	ER <sup>+</sup> /TAM <sup>+</sup> , n (%)		ER <sup>-</sup> /TAM <sup>-</sup> Group, n (%)	
	Cases	Controls	Cases	Controls
<i>CYP2D6</i> phenotype				
Normal function (2 normal alleles)	299 (61)	308 (62)	167 (60)	173 (62)
Reduced function (1 or 2 variant alleles)	195 (39)	189 (38)	110 (40)	107 (38)
Diagnosis year <sup>a</sup>				
1985–1993	235 (43)	234 (43)	107 (36)	100 (33)
1994–1996	113 (21)	112 (21)	81 (27)	83 (28)
1997–2001	193 (36)	195 (36)	112 (37)	117 (39)
Age at diagnosis, y				
35–44	16 (3.0)	13 (2.4)	68 (23)	58 (19)
45–54	116 (21)	111 (21)	120 (40)	113 (38)
55–64	286 (53)	281 (52)	82 (27)	86 (29)
65–69	123 (23)	136 (25)	30 (10)	43 (14)
Menopausal status at diagnosis <sup>a</sup>				
Premenopausal	34 (6.3)	34 (6.3)	121 (40)	121 (40)
Postmenopausal	507 (94)	507 (94)	179 (60)	179 (60)
UICC tumor stage at diagnosis <sup>a</sup>				
I	9 (1.7)	9 (1.7)	25 (8.3)	25 (8.3)
II	250 (46)	250 (46)	153 (51)	153 (51)
III	282 (52)	282 (52)	122 (41)	122 (41)
Histologic grade				
I	108 (25)	144 (35)	27 (11)	23 (10)
II	234 (54)	215 (52)	125 (49)	98 (43)
III	92 (21)	57 (14)	103 (40)	106 (47)
(Missing)	107	125	45	73
Type of surgery				
Mastectomy	483 (89)	470 (87)	252 (84)	244 (81)
Breast-conserving	58 (11)	71 (13)	47 (16)	56 (19)
(Missing)	0	0	1	0
Radiation therapy				
Yes	183 (34)	191 (35)	128 (44)	123 (47)
No	358 (66)	350 (65)	166 (56)	137 (53)
(Missing)	0	0	6	40
Adjuvant systemic chemotherapy				
Yes	70 (13)	65 (12)	248 (83)	188 (63)
No	471 (87)	476 (88)	52 (17)	112 (37)
ER expression at centralized re-assay				
Positive	451 (92)	474 (96)	72 (26)	70 (25)
Negative	37 (7.6)	19 (3.9)	204 (74)	205 (75)
Not available	53	48	24	25

<sup>a</sup>Variable used to match control subjects to recurrence cases by using risk-set sampling.

to *UGT* genotypes, *CYP2D6* genotype, and key tumor treatment and demographic characteristics. Compared with controls, women with a recurrence had tumors of higher histologic grade, but were otherwise similar. A large proportion of cases and controls in the ER<sup>+</sup>/TAM<sup>+</sup> group were postmenopausal and diagnosed with stage II or III tumors, which is expected

on the basis of the DBCG criteria used to assign women to tamoxifen treatment during the 1985 to 2001 period (16). Subjects were initially assigned to 1, 2, or 5 years of tamoxifen treatment, based on clinical protocols at the time of diagnosis. Medical record review for a subset of cases and controls found that many women initially assigned to shorter tamoxifen protocols actually

**Table 3.** Associations between polymorphisms in UGT enzymes and breast cancer recurrence

	ER <sup>+</sup> /TAM <sup>+</sup>			ER <sup>-</sup> /TAM <sup>-</sup>		
	Cases/controls	Conditional OR <sup>a</sup> (95% CI)	Adjusted OR <sup>b</sup> (95% CI)	Cases/controls	Conditional OR <sup>a</sup> (95% CI)	Adjusted OR <sup>b</sup> (95% CI)
<b>UGT2B15*2</b>						
2 normal alleles	151/140	1 (reference)	1 (reference)	85/87	1 (reference)	1 (reference)
1 variant allele	237/238	0.91 (0.68–1.2)	1.0 (0.73–1.4)	133/130	1.1 (0.74–1.6)	0.96 (0.60–1.5)
2 variant alleles	133/139	0.83 (0.60–1.2)	1.0 (0.70–1.5)	71/69	1.1 (0.68–1.7)	0.87 (0.50–1.5)
<b>UGT2B7*2</b>						
2 normal alleles	127/113	1 (reference)	1 (reference)	53/63	1 (reference)	1 (reference)
1 variant allele	224/232	0.88 (0.65–1.2)	0.84 (0.58–1.2)	142/142	1.3 (0.82–2.0)	0.97 (0.57–1.7)
2 variant alleles	163/162	0.91 (0.65–1.3)	0.96 (0.65–1.4)	87/77	1.4 (0.85–2.2)	1.0 (0.57–1.8)
<b>UGT1A8*3</b>						
2 normal alleles	502/494	1 (reference)	1 (reference)	284/283	1 (reference)	1 (reference)
>1 variant allele <sup>c</sup>	20/24	0.75 (0.41–1.4)	0.95 (0.49–1.9)	8/9	0.89 (0.34–2.3)	0.95 (0.31–2.9)
		<b>Concordant ER<sup>+</sup>/TAM<sup>+</sup> (94% of original ER<sup>+</sup>/TAM<sup>+</sup> cases and controls)</b>			<b>Concordant ER<sup>-</sup>/TAM<sup>-</sup> (74% of original ER<sup>-</sup>/TAM<sup>-</sup> cases and controls)</b>	
<b>CYP2D6*4, no variant alleles</b>						
<b>UGT2B15*2</b>						
2 normal alleles	81/75	1 (reference)		36/28	1 (reference)	
1 variant allele	121/135	1.0 (0.63–1.7)		57/55	0.97 (0.45–2.1)	
2 variant alleles	61/74	1.0 (0.59–1.8)		27/35	0.50 (0.21–1.2)	
<b>UGT2B7*2</b>						
2 normal alleles	71/61	1 (reference)		31/34	1 (reference)	
1 variant allele	125/137	0.83 (0.51–1.4)		54/52	1.1 (0.50–2.3)	
2 variant alleles	64/81	0.81 (0.46–1.4)		32/32	0.84 (0.38–1.9)	
<b>UGT1A8*3</b>						
2 normal alleles	249/269	1 (reference)		117/116	1 (reference)	
≥1 variant allele <sup>c</sup>	11/11	1.1 (0.42–2.6)		2/3	0.62 (0.08–4.7)	
<b>CYP2D6*4, 1 or 2 variant alleles</b>						
<b>UGT2B15*2</b>						
2 normal alleles	54/45	1 (reference)		22/22	1 (reference)	
1 variant allele	86/84	0.93 (0.52–1.7)		35/43	0.72 (0.28–1.9)	
2 variant alleles	29/36	0.72 (0.34–1.5)		17/10	1.2 (0.34–3.9)	

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Table 3. Associations between polymorphisms in UGT enzymes and breast cancer recurrence (Cont'd)

	ER <sup>+</sup> /TAM <sup>+</sup>		ER <sup>-</sup> /TAM <sup>-</sup>	
	Cases/controls	Conditional OR <sup>a</sup> (95% CI)	Cases/controls	Adjusted OR <sup>b</sup> (95% CI)
<i>UGT2B7*2</i>				
2 normal alleles	42/40	1 (reference)	14/15	1. (reference)
1 variant allele	72/73	0.85 (0.44–1.6)	33/40	0.91 (0.30–2.8)
2 variant alleles	53/51	0.99 (0.49–2.0)	24/17	1.5 (0.41–5.1)
<i>UGT1A8*3</i>				
2 normal alleles	164/156	1 (reference)	71/72	1 (reference)
>1 variant allele <sup>c</sup>	7/10	0.94 (0.29–3.1)	3/4	1.1 (0.19–6.0)

<sup>a</sup>Estimated with logistic regression models conditioned on matching variables (time to recurrence, county of residence, menopausal status at diagnosis, and tumor stage).

<sup>b</sup>Estimated with logistic regression models adjusted for tumor stage (categorical, design variables), menopausal status at diagnosis (pre or post), receipt of adjuvant systemic chemotherapy (dichotomous), receipt of adjuvant radiotherapy (dichotomous), type of surgery (mastectomy or breast-conserving), time to recurrence (for risk-set sampling of controls, continuous), and histologic grade (categorical, design variables).

<sup>c</sup>There were no *UGT1A8\*3* homozygous variant cases or controls in the ER<sup>-</sup>/TAM<sup>-</sup> stratum, so analyses were carried out with heterozygotes combined with variant homozygotes.

received longer courses as the recommended duration increased to 5 years (11).

### UDP-glucuronosyl transferase polymorphisms and breast cancer recurrence

Genotypes of *UGT2B15\*2*, *UGT2B7\*2*, and *UGT1A8\*3* were successfully assayed for 94% or more of all cases and controls. Among controls in the ER<sup>+</sup>/TAM<sup>+</sup> and ER<sup>-</sup>/TAM<sup>-</sup> groups, observed genotype frequencies were consistent with those expected under Hardy–Weinberg equilibrium, and observed minor allele frequencies were similar to benchmark values reported in Caucasian samples (data not shown).

Table 3 summarizes the associations between the variant *UGTs* and breast cancer recurrence. In both the ER<sup>+</sup>/TAM<sup>+</sup> and ER<sup>-</sup>/TAM<sup>-</sup> groups, none of the *UGT* SNPs was associated with breast cancer recurrence in either conditional or adjusted models [in the ER<sup>+</sup>/TAM<sup>+</sup> group, for *UGT2B15\*2*: adjusted OR for 2 variant alleles compared with 2 normal alleles = 1.0 (95% CI, 0.70–1.5); for *UGT2B7\*2*: adjusted OR for 2 variant alleles compared with 2 normal alleles = 0.96 (95% CI, 0.65–1.4); for *UGT1A8\*3*: adjusted OR for 1 or 2 variant alleles compared with 2 normal alleles = 0.95 (0.49–1.9)]. These estimates did not differ substantially when we included all *UGT* SNPs in the same conditional or adjusted logistic regression models (data not shown), nor when we repeated analyses within strata of *CYP2D6\*4* genotype and included only women with concordant ER expression between diagnosis and re-assay (Table 3).

### Discussion

We observed no association between genetically modified *UGT* activity and the rate of breast cancer recurrence in a large population-based case–control study of tamoxifen-treated and untreated breast cancer patients. There are several plausible explanations for our null findings.

First, it is possible that glucuronide moieties are cleaved by enteric bacterial glucuronidase activity during enterohepatic circulation of the 4HT and endoxifen glucuronides. Reabsorption of restored active metabolites may negate any fluctuation in their plasma concentrations attributable to genetic variation in the *UGTs*.

Second, any effect of the *UGT* variants on excretion of active tamoxifen metabolites may be counteracted by simultaneous effects on estrogen metabolism. Sex steroids, including estradiol, are also deactivated and eliminated via glucuronidation (17, 18). The *UGT2B15\*2* polymorphism, for example, would be expected to speed clearance of 4HT, endoxifen, and estradiol simultaneously. So it may be that a harmful impact of lower tamoxifen metabolite concentrations is averted by a corresponding reduction in estradiol levels, at least in this population of predominantly postmenopausal ER<sup>+</sup> women.

Another possibility is that tamoxifen and its metabolites circulate in such vast molar excess to ER binding

sites on residual breast cancer cells that modest changes in their concentrations due to metabolic enzyme variants do not prevent their saturation of estradiol binding sites and inhibition of tumor growth (19).

To detect the *UGT2B7\*2* variant allele, we used a proxy SNP estimated to be in perfect LD with the target SNP [ $R^2 = 1$ ;  $D' = 1$  (95% CI, 0.95–1)]. Because these LD parameters were estimated with uncertainty in an independent sample of Caucasians, *UGT2B7\*2* genotype may have been misclassified in our study population. However, given the high and precise LD estimate, it is unlikely that the error is sufficient to have masked a truly non-null association.

Residual confounding is an unlikely source of bias in our measurements, primarily because no factor affecting recurrence is expected to be causally related to genotype, and also because adjustment for known recurrence risk factors did little to change the estimated ORs.

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In summary, we observed no association between functional polymorphisms in key *UGT* enzymes involved in phase II metabolism of tamoxifen, whether or not we took *CYP2D6\*4* genotype into account. These results do not support the notion that these biomarkers of metabolic enzyme activity can be used to improve the prediction of clinical response to adjuvant tamoxifen therapy.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Grant Support

This study was supported by U.S. National Cancer Institute at the NIH [R01 CA118708 (T.L. Lash) and T32 CA09001-35 (T.P. Ahern)]; Danish Cancer Society [DP06117 (S. Hamilton-Dutoit)]; Karen Elise Jensen Foundation (H.T. Sorensen); Congressionally Directed Medical Research Programs [BC073012 (T.P. Ahern)].

Received May 5, 2011; revised July 5, 2011; accepted July 8, 2011; published OnlineFirst July 12, 2011.

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*Cancer Epidemiol Biomarkers Prev* 2011;20:1937-1943. Published OnlineFirst July 12, 2011.

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