Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2011 September ; 20(9): 1937–1943. doi: 10.1158/1055-9965.EPI-11-0419.

Functional polymorphisms in UDP-glucuronosyltransferases and recurrence in tamoxifen-treated breast cancer survivors

Thomas P. Ahern[1,2], **Mariann Christensen**[3], **Deirdre P. Cronin-Fenton**[4], **Kathryn L. Lunetta**[5], **Håvard Søiland**[6], **Jennifer Gjerde**[7], **Jens Peter Garne**[8,9], **Carol L. Rosenberg**[10], **Rebecca A. Silliman**[2,10], **Henrik Toft Sørensen**[4,9], **Timothy L. Lash**[2,4,10], and **Stephen Hamilton-Dutoit**[3]

[1]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[2]Department of Epidemiology, Boston University School of Public Health, Boston, MA

[3]Institute of Pathology, Aarhus University Hospital, Aarhus, Denmark

[4]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

[5]Department of Biostatistics, Boston University School of Public Health, Boston, MA

[6]Department of Surgery, Stavanger University Hospital, Stavanger, Norway

[7]Hormone Laboratory, Haukeland University Hospital, Bergen, Norway

[8]Department of Surgery, Aalborg Hospital, Aarhus University Hospital, Aarhus, Denmark

[9]On behalf of the Danish Breast Cancer Cooperative Group

[10]Department of Medicine, Boston University School of Medicine, Boston, MA

Abstract

Background—Tamoxifen is oxidized by cytochrome-P450 enzymes (e.g., CYP2D6) to two active metabolites, which are eliminated via glucuronidation by UDP-glucuronosyltransferases (UGTs). 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 one 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 1 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 odds ratio for the UGT polymorphisms 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 for UGT2B7*2 variant alleles = 0.91 (95% CI: 0.65, 1.3); adjusted OR for 1 or 2 UGT1A8*3 variant alleles = 0.75 (0.41, 1.4)]. 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.

Keywords

Epidemiology; breast neoplasms; UDP-glucuronosyltransferases; tamoxifen

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) (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-glucuronosyltransferases (UGTs) (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 two-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 two- and five-fold lower glucuronidation activity toward 4HT and endoxifen, respectively (9, 10). *UGT1A8* harbors two variant alleles; one (*2/rs1042597) 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 *et al* and Wegman *et al* 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 using a population-based case-control design; the methods have been detailed elsewhere (11).

Briefly, the source population consisted of women aged 35 to 69 years, residing on Denmark's Jutland Peninsula, who were diagnosed with 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: (1) women whose primary tumors expressed ER and who were treated with tamoxifen for at least one year (ER+/TAM+), and (2) women whose primary tumors did not express ER, who were not treated with tamoxifen, and who survived for at least one year after diagnosis (ER−/TAM−). We included the ER−/TAM− 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 one year of tamoxifen treatment (if in the ER+/TAM+ group) or after surviving at least one year beyond diagnosis (if in the ER−/TAM− 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 (+/- 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 1 September 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, Foster City, California, USA) were used to genotype the *UGT2B15**2 and *UGT1A8**3 alleles, as detailed in Table 1. Genotyping of *CYP2D6**4 also was performed with a commercially available TaqMan kit (kit# C-27102431-D0) (11). A high proportion of the nucleotides flanking the *UGT2B7**2 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 kilobase 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]). Based on 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 one 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 χ^2 test statistics.

We used logistic regression models to estimate the odds ratio (approximating the rate ratio because of the control sampling strategy) associating UGT polymorphisms with breast cancer recurrence among women taking tamoxifen (ER+/TAM+). The analyses were repeated in the group of women who did not take tamoxifen (ER−/TAM−) to evaluate non-tamoxifen mediated associations between UGT genotypes and breast cancer recurrence. Logistic regression models were specified two ways for each of the UGTs: (1) conditioned on the matching factors, and (2) 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 two-sided (alpha=0.05). Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Characteristics of cases and controls

In the ER+/TAM+ group, we identified 541 breast cancer recurrence cases, to whom we matched 541 breast cancer controls. In the ER−/TAM− 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 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+/TAM+ group were postmenopausal and diagnosed with stage II or III tumors, which is expected based on the DBCG criteria used to assign women to tamoxifen treatment during the 1985-2001 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 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% of all cases and controls. Among controls in the ER+/TAM+ and ER−/TAM− 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+/TAM+ and ER−/TAM− groups, none of the UGT SNPs was associated with breast cancer recurrence in either conditional or adjusted models [in the ER +/TAM+ group, for *UGT2B15**2: adjusted OR for two variant alleles compared with 2 normal alleles = 1.0 (95% CI: 0.70, 1.5); for *UGT2B7**2: adjusted OR for two variant alleles

compared with 2 normal alleles = 0.91 (95% CI: 0.65, 1.3); for *UGT1A8**3: adjusted OR for 1 or 2 variant alleles compared with 2 normal alleles = 0.75 (0.41, 1.4)]. 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 UDP-glucuronosyl transferase 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. Re-absorption 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+ 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 linkage disequilibrium with the target SNP [R^2=1; D'=1 (95% CI: 0.95, 1)]. Since 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, but also because adjustment for known recurrence risk factors did little to change the estimated odds ratios.

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.

Acknowledgments

Grant Support: US National Cancer Institute at the National Institutes of Health (R01 CA118708 [TLL] and T32 CA09001-35 [TPA]); Danish Cancer Society (DP06117 [SHD]); Karen Elise Jensen Foundation [HTS]; Congressionally Directed Medical Research Programs (BC073012 [TPA]).

References

1. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 365:1687–717. [PubMed: 15894097]
2. Borges S, Desta Z, Li L, Skaar TC, Ward BA, Nguyen A, et al. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther. 2006; 80:61–74. [PubMed: 16815318]
3. Lim YC, Desta Z, Flockhart DA, Skaar TC. Endoxifen (4-hydroxy-N-desmethyl-tamoxifen) has anti-estrogenic effects in breast cancer cells with potency similar to 4-hydroxy-tamoxifen. Cancer Chemother Pharmacol. 2005; 55:471–8. [PubMed: 15685451]
4. Lazarus P, Blevins-Primeau AS, Zheng Y, Sun D. Potential role of UGT pharmacogenetics in cancer treatment and prevention: focus on tamoxifen. Ann N Y Acad Sci. 2009; 1155:99–111. [PubMed: 19250197]
5. Nishiyama T, Ogura K, Nakano H, Ohnuma T, Kaku T, Hiratsuka A, et al. Reverse geometrical selectivity in glucuronidation and sulfation of cis- and trans-4-hydroxytamoxifens by human liver UDP-glucuronosyltransferases and sulfotransferases. Biochemical pharmacology. 2002; 63:1817–30. [PubMed: 12034366]
6. Zheng Y, Sun D, Sharma AK, Chen G, Amin S, Lazarus P. Elimination of antiestrogenic effects of active tamoxifen metabolites by glucuronidation. Drug Metab Dispos. 2007; 35:1942–8. [PubMed: 17620345]
7. Sun D, Sharma AK, Dellinger RW, Blevins-Primeau AS, Balliet RM, Chen G, et al. Glucuronidation of active tamoxifen metabolites by the human UDP glucuronosyltransferases. Drug Metab Dispos. 2007; 35:2006–14. [PubMed: 17664247]
8. Levesque E, Beaulieu M, Green MD, Tephly TR, Belanger A, Hum DW. Isolation and characterization of UGT2B15(Y85): a UDP-glucuronosyltransferase encoded by a polymorphic gene. Pharmacogenetics. 1997; 7:317–25. [PubMed: 9295060]
9. Levesque E, Delage R, Benoit-Biancamano MO, Caron P, Bernard O, Couture F, et al. The impact of UGT1A8, UGT1A9, and UGT2B7 genetic polymorphisms on the pharmacokinetic profile of mycophenolic acid after a single oral dose in healthy volunteers. Clin Pharmacol Ther. 2007; 81:392–400. [PubMed: 17339869]
10. Blevins-Primeau AS, Sun D, Chen G, Sharma AK, Gallagher CJ, Amin S, et al. Functional significance of UDP-glucuronosyltransferase variants in the metabolism of active tamoxifen metabolites. Cancer Res. 2009; 69:1892–900. [PubMed: 19244109]
11. Lash TL, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, et al. CYP2D6 Inhibition and Breast Cancer Recurrence in a Population-Based Study in Denmark. Journal of the National Cancer Institute. 2011; 103:489–500. [PubMed: 21325141]
12. Cronin-Fenton D, Lash TL. Clinical epidemiology and pharmacology of CYP2D6 inhibition related to breast cancer outcomes. Expert Reviews in Clinical Pharmacology. 2011 In press.
13. Nowell SA, Ahn J, Rae JM, Scheys JO, Trovato A, Sweeney C, et al. Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. Breast Cancer Res Treat. 2005; 91:249–58. [PubMed: 15952058]
14. Wegman P, Elingarami S, Carstensen J, Stal O, Nordenskjold B, Wingren S. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res. 2007; 9:R7. [PubMed: 17244352]
15. Blichert-Toft M, Christiansen P, Mouridsen HT. Danish Breast Cancer Cooperative Group--DBCG: History, organization, and status of scientific achievements at 30-year anniversary. Acta Oncol. 2008; 47:497–505. [PubMed: 18465316]

16. Moller S, Jensen MB, Ejlertsen B, Bjerre KD, Larsen M, Hansen HB, et al. The clinical database and the treatment guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience and future promise. Acta Oncol. 2008; 47:506–24. [PubMed: 18465317]

17. Albert C, Vallee M, Beaudry G, Belanger A, Hum DW. The monkey and human uridine diphosphate-glucuronosyltransferase UGT1A9, expressed in steroid target tissues, are estrogen-conjugating enzymes. Endocrinology. 1999; 140:3292–302. [PubMed: 10385426]

18. Yong M, Schwartz SM, Atkinson C, Makar KW, Thomas SS, Stanczyk FZ, et al. Associations between polymorphisms in glucuronidation and sulfation enzymes and sex steroid concentrations in premenopausal women in the United States. J Steroid Biochem Mol Biol. 2011; 124:10–8. [PubMed: 21193038]

19. Lash TL, Lien EA, Sorensen HT, Hamilton-Dutoit S. Genotype-guided tamoxifen therapy; time to pause for reflection? Lancet Oncology. 2009; 10:825–33. [PubMed: 19647203]

Table 1

Characteristics of the UDP-glucuronosyltransferase 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

Table 2

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

	ER+/TAM+, n (%)		ER−/TAM− Group, n (%)	
	Cases	**Controls**	**Cases**	**Controls**
*UGT2B15*2* 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
*UGT2B7**2 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
*UGT1A8**3 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
CYP2D6 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*				
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)

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2012 September 1.

	ER+/TAM+, n (%)		ER−/TAM− Group, n (%)	
	Cases	**Controls**	**Cases**	**Controls**
Menopausal status at diagnosis*				
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*				
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

*Variable used to match control subjects to recurrence cases using risk-set sampling.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2012 September 1.

Table 3

Associations between polymorphisms in UDP-glucuronosyl transferase enzymes and breast cancer recurrence

	ER+/TAM+			ER−/TAM−		
	Cases/controls	**Conditional OR[a] (95% CI)**	**Adjusted OR[b] (95% CI)**	**Cases/controls**	**Conditional OR[a] (95% CI)**	**Adjusted OR[b] (95% CI)**
*UGT2B15**2						
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)
*UGT2B7**2						
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)
*UGT1A8**3						
2 normal alleles	502/494	1. reference	1. reference	284/283	1. reference	1. reference
≥1 variant allele[c]	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)

	Concordant ER+/TAM+ (94% of original ER+/TAM+ cases and controls)		Concordant ER−/TAM− (74% of original ER−/TAM− cases and controls)	
	Cases/controls	**Adjusted OR[b] (95% CI)**	**Cases/controls**	**Adjusted OR[b] (95% CI)**
CYP2D6*4, no variant alleles				
*UGT2B15*2*				
2 normal alleles	81/75	1. ref	36/28	1. ref
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)
*UGT2B7*2*				
2 normal alleles	71/61	1. ref	31/34	1. ref
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)
*UGT1A8*3*				
2 normal alleles	249/269	1. ref	117/116	1. ref
≥ 1 variant allele[c]	11/11	1.1 (0.42, 2.6)	2/3	0.62 (0.08, 4.7)

	Concordant ER+/TAM+ (94% of original ER+/TAM+ cases and controls)		Concordant ER−/TAM− (74% of original ER−/TAM− cases and controls)	
	Cases/controls	Adjusted OR[b] (95% CI)	Cases/controls	Adjusted OR[b] (95% CI)
CYP2D6*4, 1 or 2 variant alleles				
*UGT2B15*2*				
2 normal alleles	54/45	1. ref	22/22	1. ref
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)
*UGT2B7*2*				
2 normal alleles	42/40	1. ref	14/15	1. ref
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)
*UGT1A8*3*				
2 normal alleles	164/156	1. ref	71/72	1. ref
≥ 1 variant allele[c]	7/10	0.94 (0.29, 3.1)	3/4	1.1 (0.19, 6.0)

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

[b] 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).

[c] There were no *UGT1A8*3* homozygous variant cases or controls in the ER−/TAM− stratum, so analyses were carried out with heterozygotes combined with variant homozygotes.