The UDP-Glucuronosyltransferase 2B17 Gene Deletion Polymorphism: Sex-Specific Association with Urinary 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol Glucuronidation Phenotype and Risk for Lung Cancer

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Abstract

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone is a potent and abundant procarcinogen found in tobacco smoke, and glucuronidation of its major metabolite, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), by UDP-glucuronosyltransferases (UGT) including UGT2B17 is an important mechanism for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone detoxification. Both copies of the *UGT2B17* gene are deleted in ~10% of Whites and the deletion is associated with a reduction in NNAL glucuronidation activity *in vitro*. In this study, we examined the effects of the *UGT2B17* deletion (0/0) on NNAL glucuronidation rates in a sample of 82 healthy cigarette smokers and further examined its effects on lung cancer risk in a separate case-control study. In the healthy smokers study, a lower urinary ratio of NNAL-glucuronide to NNAL was observed in women with the *UGT2B17* deletion (0/0) as compared with women with either the wild-type or heterozygous genotypes ($P = 0.058$). There were no significant differences in this ratio by genotype in men ($P = 0.597$). In the case-control study of 398 lung cancer patients and 697 community controls, the *UGT2B17* deletion (0/0) was associated with a significant increase in risk of lung cancer in women (odds ratio, 2.0; 95% confidence interval, 1.01-4.0). The risk for the subset of women with lung adenocarcinoma was 2.8 (95% confidence interval, 1.2-6.3). The deletion was not associated with other lung histologic types in women and was not associated with the risk for any lung histologic types in men. The association of the *UGT2B17* deletion with increased lung adenocarcinoma in women is consistent with its association with decreased NNAL glucuronidation rates in women and with studies showing that NNAL is a selective inducer of lung adenocarcinoma in experimental animals. (Cancer Epidemiol Biomarkers Prev 2007;16(4):823–8)

Introduction

Lung cancer is the leading cause of cancer mortality in the United States. Tobacco smoking causes ~80% of all lung cancers (1), but only ~15% of lifetime smokers develop this malignancy (2). Heritable traits in the population likely explain why some smokers develop lung cancer (3-6), and the identification of genetic variants that regulate the activation and detoxification of tobacco smoke carcinogens is necessary to identify high-risk smokers and develop targeted interventions.

The nicotine-derived, tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is one of the most potent and abundant carcinogens in tobacco and tobacco smoke (7, 8). The concentrations of NNK in mainstream tobacco smoke are 3 to 15 times higher than the concentrations of benzo(*a*)pyrene, another major tobacco smoke carcinogen (9). NNK induces predominantly lung adenocarcinomas in rodents independent of the route of administration (7). The experimental dose of NNK that induces lung adenocarcinoma in rodents (10) is similar to the estimated lifetime exposure (40 years) of a two-pack-per-day smoker on a per weight basis (7, 8). NNK is also thought to cause oral cavity and pancreatic cancers (7, 11). In most tissues, NNK is efficiently converted to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) by carbonyl reduction. Like NNK, NNAL induces lung adenocarcinoma in rodents (7, 11, 12).

Glucuronidation is the major detoxification pathway for NNAL (7, 13-17). Both the *O*- and *N*-glucuronide forms of glucuronidated NNAL (NNAL-Gluc) have been detected in urine samples obtained from active cigarette smokers (18-20), passively exposed individuals (21, 22), and tobacco chewers (19, 23). There is a high degree of variability in the urinary ratios of NNAL-Gluc/NNAL (18, 20) and NNAL-*O*-Gluc/NNAL-*N*-Gluc (19), suggesting that genetic variation in NNAL metabolism may affect individual capacity to detoxify NNK and form NNAL-glucuronides. Variability in the levels of NNAL-*O*-Gluc and NNAL-*N*-Gluc formation was observed in *in vitro* assays of human liver microsomal specimens (24-26). The UDP-glucuronosyltransferase (UGT) family of genes mediates glucuronidation activity, and we previously examined polymorphisms in UGTs that might account for the variability in NNAL glucuronidation. Polymorphisms in the *UGT2B7* and *UGT1A4* genes, which glucuronidate NNAL-*O*-Gluc and NNAL-*N*-Gluc, respectively (26), were associated with lowered rates of NNAL glucuronidation.

UGT2B17 is a family 2B UGT that glucuronidates xenobiotics, carcinogens, and C_{19} steroids (27, 28). UGT2B17 is expressed in liver and multiple extrahepatic tissues including the lung (27). Previous kinetic analysis indicated that a percentage of NNAL detoxification is mediated by UGT2B17, contributing to ~40%

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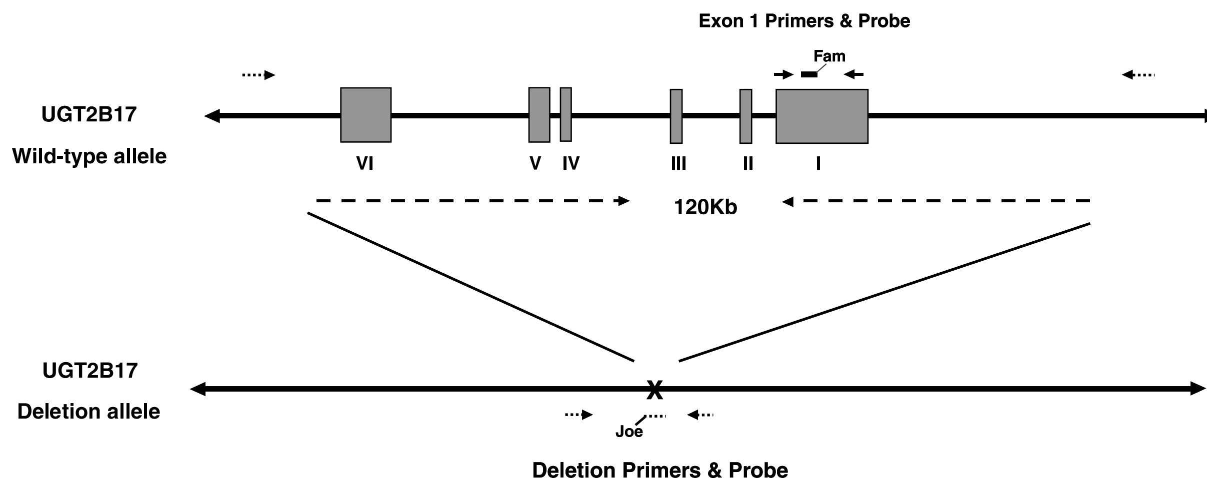

Figure 1. Gene structure and primer and probe locations for the UGT2B17 multiplex real-time PCR assay. *I* to *VI,* exons of the *UGT2B17* gene on the wild-type allele. The deletion allele is shown below the wild-type allele, indicating that the 120 kb are deleted including the entire *UGT2B17* gene. *Dashed arrows,* primers that will amplify the deletion allele; *dashed line* (*with fluorescent label Joe*), deletion probe. *Solid arrows,* primers that will amplify exon 1 of *UGT2B17* from the wild-type allele; *solid line* (*with fluorescent label Fam*), deletion probe.

of NNAL glucuronidation in human liver microsomes (24). The K_m values for NNAL are 5- to 15-fold higher for other hepatic NNAL-glucuronidating UGTs, including UGT1A4, 1A9, and 2B7, than for UGT2B17 (17, 24, 25).

Two studies identified a polymorphic deletion of the entire *UGT2B17* gene (29, 30). We observed that the deletion of the *UGT2B17* gene is significantly associated with a reduced rate of NNAL glucuronidation *in vitro* in human liver microsomes (24). The current study was conducted to determine, first, whether the *UGT2B17* gene deletion results in a functional change on the *in vivo* rates of NNAL glucuronidation and, second, whether it is associated with the risk of lung cancer.

Materials and Methods

Subjects. The studies of NNAL glucuronidation were conducted in a sample of current cigarette smokers who participated in a larger study of tobacco smoke biomarkers that has been previously described (31). Briefly, a community-based cross-sectional study of racial differences in cigarette smoke biomarkers was undertaken in 162 healthy subjects living in lower Westchester County (NY). Volunteers were recruited from the town of Mt. Vernon (NY) and surrounding areas with the assistance of community and civic leaders, word of mouth, and various forms of mass media. Written informed consent was obtained from all subjects using an approved consent form. Trained interviewers used a structured questionnaire that contained detailed items on demographics, smoking, and other lifestyle factors. We collected urine samples to measure a number of tobacco smoke metabolites, including NNAL and NNAL-Gluc, and whole blood (10 mL) for genomic DNA extraction. For the current study, these subjects were genotyped for the *UGT2B17* deletion polymorphism. The results are described for the 82 White subjects only because the case-control study was conducted in a nearly all-White population and because the prevalence of the *UGT2B17* deletion in Blacks is too low to provide meaningful data.

The case-control study was conducted at the H. Lee Moffitt Cancer Center (Tampa, FL) from 2000 to 2003. Cases (n = 398) were newly diagnosed subjects with histologically confirmed lung cancer and no past history of other tobacco-related cancers. Controls (n = 697) were selected from community residents attending the Lifetime Cancer Screening facility of the Moffitt Cancer Center. Control subjects were randomly selected from thousands of community residents who underwent prostate-specific antigen testing, skin examinations, endoscopy, or mammography. Spiral computed tomography for lung cancer was not done at the clinic. The Lifetime Cancer Screening facility conducts community outreach and education programs throughout the Tampa Bay area, including lecture series, screening events, health fairs, literacy programs, and community-based partnerships. A list of control IDs were matched against the hospital patient database to identify subjects, if any, who might have developed cancer. All control subjects with a new cancer diagnosis were excluded from this study. Ninety-nine percent of the hospital patients and ninety-seven percent of clinic patients who were asked to participate in the study consented. All study subjects signed a consent form approved by the institutional review board. A trained interviewer administered a structured questionnaire that obtained lifestyle and smoking history information including levels of education, occupation, year of smoking onset, current smoking status, number of cigarettes smoked per day, and years since quitting (for former smokers). The medical chart of the case subjects was reviewed to obtain diagnostic and pathology records.

***UGT2B17* Deletion Genotyping.** Blood or oral buccal mucosa cells were collected from each subject using collection methods previously described, and genomic DNA was purified using standard phenol/chlorophorm extraction procedures (32). Details describing the polymorphic deletion of the entire *UGT2B17* gene have been described elsewhere (29, 30). For large-scale sample screening, we developed a high-throughput assay using real-time PCR with allelic discrimination. Each reaction included two primers and one 6-FAM–labeled probe to amplify exon 1 of UGT2B17, and two primers and one JOE-NHS-ester–labeled probe (spanning the deletion cut site) that amplify only if the deletion is present (Fig. 1). Due to high sequence homology between *UGT2B17* and other *UGT* genes and pseudogenes, primers were designed using Blast 2.2.14,[3] maximizing for 3′ sequence mismatches with other homologous genes (Table 1), with primers obtained from Integrated DNA Technologies (Coralville, IA). Reactions (20 μL) were done in 384-well plates using the ABI 7900 HT Sequence Detection System, with incubations

[3] http://www.ncbi.nlm.nih.gov/BLAST/

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done at 50°C for 2 min; 95°C for 15 min; and 40 cycles of 94°C for 1 min, 60°C for 1 min 30 s. Reactions included QuantiTect Multiplex PCR Master Mix (1× final concentration; Qiagen, Valencia, CA), 0.4 μmol/L for each primer, 0.2 μmol/L for each probe, and 20 to 100 ng of DNA. Negative controls (no DNA template) were run on every plate and genotypes were assigned by the automatic calling feature of the allelic discrimination option in SDS 2.2.2 software (Applied Biosystems, Foster City, CA).

Although the use of a single primer set and two probes has become common practice for single-nucleotide polymorphism genotyping and has recently been used in an analysis of a small deletion polymorphism (33), the amplification of both the wild-type and deletion alleles using a single PCR primer set could not be done in the present study due to the large size (~120 kb) of the *UGT2B17* gene deletion. We piloted our new method using two PCR primer sets in combination with two probes in a blinded study of 63 normal liver genomic DNA samples previously characterized for *UGT2B17* deletion genotypes (24). We found 100% concordance when comparing this real-time method versus previously validated PCR-RFLP methods. In a second blinded quality-control study that included repeat analysis of 96 oral buccal cell genomic DNA samples from individual subjects, there was again 100% concordance for the *UGT2B17* genotype.

Statistical Methods. Subject characteristics were described by means, SDs, and percentages. Student's *t* test was calculated to determine differences in mean urinary glucuronidation ratios by genotype for women and men. The risk of lung cancer associated with the *UGT2B17* deletion (0/0) was modeled using unmatched logistic regression analyses, adjusting for known lung cancer risk factors including age, body mass index (BMI), education level, and pack-years of smoking. The reference group in the initial models was the UGT2B17 wild-type genotype (+/+). Lung cancer risk was estimated for the heterozygote genotype (+/0) and the homozygote deletion (0/0). The data were also modeled using the combined (+/+) and (+/0) groups as the reference. The data were stratified by sex, and sex-specific risks associated with the deletion genotype were calculated. Histologic-specific analyses were calculated for lung adenocarcinoma and all other types combined. Each group was compared with the entire series of controls, again stratified by sex. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using SPSS 13.0 (SPSS, Inc., Chicago, IL). The Hosmer and Lemeshow goodness-of-fit test was calculated to determine the relationship between observed and expected values.

Results

***In vivo* Studies of NNAL Glucuronidation in Smokers.** The mean urinary ratio of NNAL-Gluc to NNAL was 3.6 (Fig. 2). When stratifying by *UGT2B17* genotypes, the ratio was 3.7 in *UGT2B17* (+/+) subjects, 3.8 in *UGT2B17* (+/0) subjects, and 2.4 in subjects with both UGT2B17 alleles deleted (0/0).

Table 1. Primer and probe sequences for the *UGT2B17* genotype assay

Primer name	Primer composition (5′-3′)
Exon 1 (forward)	TGAAAATGTTCGATAGATGGACATATAGTA
Exon 1 (reverse)	GACATCAAATTTTGACTCTTGTAGTTTTC
Exon 1 (probe)	6-FAM-TACATTTTGGTCATATTTTTCACAAC TACAAGAATTGT-BHQ1
Deletion (forward)	TTTAATGTTTTCTGCCTTATGCCAC
Deletion (reverse)	AGCCTATGCAATTTTCATTCAACATAG
Deletion (probe)	JOE-ACTACACTGAGATTTACAAAAGAATTC TGTCAGGATATAG-BHQ1

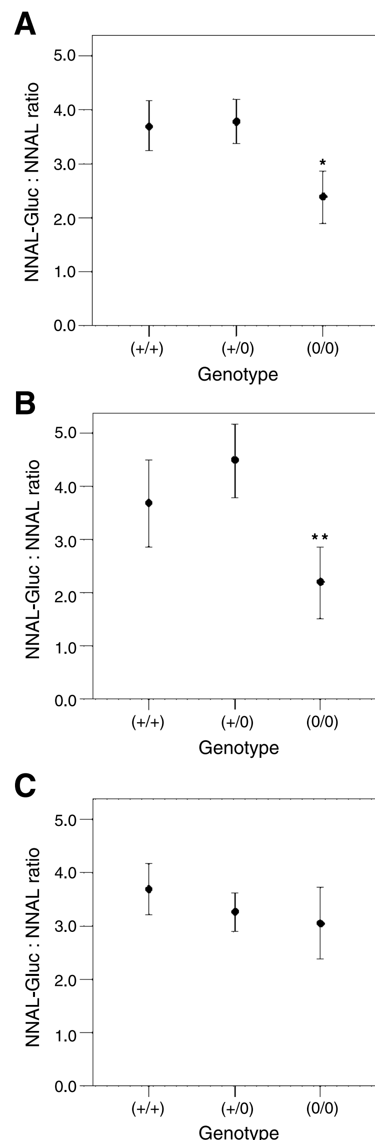

Figure 2. Urinary NNAL glucuronidation rates grouped by *UGT2B17* deletion genotype. Urinary NNAL glucuronidation rates are indicated by the ratio of NNAL-Gluc/NNAL for 82 non-Hispanic White smokers (**A**). Results stratified by sex are shown for 41 females (**B**) and 41 males (**C**). *Points,* mean; *bars,* SE. Significant (all subjects; *, P = 0.049) or near-significant (women only; **, P = 0.058) associations were observed comparing the NNAL-Gluc/NNAL ratios in subjects with the *UGT2B17* (0/0) genotype versus subjects with the *UGT2B17* (+/+) or (+/0) genotype as determined by Student's *t* test.

The difference in the mean ratio between the deletion genotype (0/0) and the other combined genotypes was statistically significant (P = 0.049). When stratifying by gender, there was a near-significant association between the *UGT2B17* deletion and urinary NNAL-Gluc/NNAL ratios in women (P = 0.058). The mean ratio of urinary NNAL-Gluc/NNAL in women was 3.8 overall, 3.7 in *UGT2B17* (+/+) subjects, 4.5 for *UGT2B17* (+/0) heterozygotes, and 2.1 for subjects with the *UGT2B17* (0/0) genotype. No association was observed between *UGT2B17* genotypes and urinary NNAL-Gluc/NNAL ratios in men (P = 0.597), in which the mean ratio was 3.4 overall and 3.6, 3.1, and 3.0 in males with the *UGT2B17* (+/+), (+/0), and (0/0) genotypes, respectively.

Case-Control Results. The basic demographic characteristics of the lung cancer case-control subjects are shown in

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Table 2. Age, sex, BMI, smoking status, education level, and case histology of 398 lung cancer cases and 697 controls

	Cases [*n* (%)]	Controls [*n* (%)]	*P*
Mean age*	64.1 ± 9.9	58.3 ± 10.3	<0.01
Women (%)	175 (44)	324 (46)	0.42
Mean BMI*	26.8 ± 5.0	27.3 ± 4.9	<0.01
Smoking status (%)			
Never smokers	35 (9)	268 (38)	<0.01
Former smokers	205 (52)	291 (42)	
Current smokers	108 (40)	138 (20)	
Pack-years*	56.0 ± 38.9	23.5 ± 30.7	<0.01
Years of education (%)			
<High school degree	63 (16)	30 (4)	<0.01
High school degree	246 (62)	392 (56)	
College degree	59 (15)	167 (24)	
Postgraduate degree	30 (8)	108 (15)	
Histology (%)			
Adenocarcinoma	151 (38)		
Squamous cell carcinoma	100 (27)		
Non–small-cell carcinoma	69 (17)		
Small-cell carcinoma	39 (10)		
Large-cell carcinoma	24 (6)		
Mixed histology/other	15 (4)		

*Mean ± SD.

Table 2. About 55% were men, and the mean age of cases and controls was 64 ± 9.9 versus 58 ± 10.3 years, respectively. A significantly ($P < 0.01$) higher percentage of cases than controls ever smoked cigarettes (91% versus 62%). The mean pack-years of smoking was 56 for cases and 24 for controls. Forty percent of controls and 23% of cases were college educated. The mean BMI of cases and controls was 26.8 ± 5.0 versus 27.3 ± 4.9, respectively. Among the case group, the most frequent histology was adenocarcinoma (38%), followed by squamous cell carcinoma (27%). There was no significant interaction between smoking and the *UGT2B17* gene deletion. Consequently, smoking was adjusted for as a covariate because it was a significant independent predictor of lung cancer risk.

The prevalence of the *UGT2B17* deletion polymorphism in the control population was consistent with that expected by Hardy-Weinberg equilibrium (P = 0.31). The polymorphic prevalence of the UGT2B17 homozygous deletion in our study controls was 10.5%, which is similar to that reported for other White subjects (29, 30, 34). There was no association between the *UGT2B17* (0/0) genotype and the overall risk of lung cancer by multivariate analysis when comparing homozygous-deleted subjects to subjects homozygous for the wild-type UGT2B17 allele (OR, 1.14; 95% CI, 0.71-1.82; data not shown) or to subjects with one or both copies of the *UGT2B17* gene [(+/+) or (+/0) subjects; OR, 1.29; 95% CI, 0.82-2.04; data not shown]. Similarly, a significant association was not observed when comparing subjects with the wild-type *UGT2B17* (+/+) genotype to subjects with one or two deletion alleles [(+/0) or (0/0) subjects; OR, 0.81; 95% CI, 0.61-1.08; data not shown].

Table 3 shows lung cancer association results stratified by sex. No association was observed between *UGT2B17* genotype and lung cancer risk in men. In women, a near-significant increased risk was observed for individuals with the *UGT2B17* (0/0) genotype (OR, 1.8; 95% CI, 0.9-3.7) versus the wild-type *UGT2B17* (+/+) group; the risk associated with the *UGT2B17* (+/0) genotype was 0.8 (95% CI, 0.5-1.3). We also combined subjects with the *UGT2B17* (+/+) and (+/0) genotypes to serve as the reference group in comparison with the *UGT2B17* deletion (0/0) genotype. Using this reference group, a significant risk associated with the *UGT2B17* deletion (0/0) was observed in women (OR, 2.0; 95% CI, 1.0-4); there was no association in men (OR, 0.9; 95% CI, 0.4-1.7).

In histology-specific analysis, the risk of lung adenocarcinoma associated with *UGT2B17* genotypes is shown in Table 4. Using the *UGT2B17* (+/+) and (+/0) genotypes as the reference group, there was a significant increased risk associated with the *UGT2B17* (0/0) deletion (OR, 2.8; 95% CI, 1.2-6.3) in women, but there was no increased risk for lung adenocarcinoma in men (OR, 1.0; 95% CI, 0.4-2.3). When using models adjusted for smoking-status (e.g., nonsmoker, former smoker, current smoker) instead of pack-years, the risk of adenocarcinoma in women was 2.9 (95% CI, 1.3-6.3). There was no significant association between *UGT2B17* genotypes and the risk of other lung cancer histologies in men or in women (data not shown). All of the *P* values from the Hosmer and Lemeshow goodness-of-fit test statistics indicated that the logistic regression models were acceptable.

Discussion

We previously observed that the deletion of the *UGT2B17* gene is significantly associated with a reduced rate of NNAL glucuronidation *in vitro* in human liver microsomes. In the present study, the *UGT2B17* deletion was associated with decreased levels of urinary NNAL glucuronidation and with increased risk of lung cancer in women. In particular, the *UGT2B17* deletion (0/0) genotype was specifically associated with an increased risk for lung adenocarcinoma in women and not with other histologic types of lung cancer. The finding of a significantly increased risk in only one subgroup of subjects should be interpreted carefully because of the small number of subjects with the homozygous deletion genotype. However, the possibility that the findings in this study are a false positive seems to be unlikely because the positive association with adenocarcinoma and the null association with squamous cell carcinoma are consistent with experimental studies that have shown that NNK and NNAL selectively induce lung adenocarcinomas in laboratory rodents independent of the route of administration (7, 11, 12). Further, the increases in cigarette NNK concentrations over the past several decades are correlated with the increases in lung adenocarcinoma rates relative to other histologic types of lung cancer (35). The likelihood that the increased risk for adenocarcinoma in this study is not an artifact is further supported by the fact that the association of *UGT2B17* (0/0) with lower urinary NNAL glucuronide levels was observed in a healthy population (from the New York City area) that was independent of the case-control study (subjects recruited from Florida).

It is uncertain why the association is specific to women. UGT2B17 expression is not altered by estrogens (36), although androgens down-regulate UGT2B17 transcription (37-39). The expression of the UGT2B17 protein may be higher in women

Table 3. Distribution of genotypes by sex and risk of lung cancer

UGT2B17 genotype	Cases (%)	Controls (%)	OR (95% CI)*
Men			
(+/+)	121 (54)	176 (47)	Reference
(+/0)	83 (37)	156 (42)	0.7 (0.4-1.1)
(0/0)	19 (9)	41 (11)	0.7 (0.4-1.5)
(+/+) + (+/0)	204 (91)	332 (89)	Reference
(0/0)	19 (9)	41 (11)	0.9 (0.4-1.7)
Women			
(+/+)	91 (52)	161 (50)	Reference
(+/0)	58 (33)	131 (40)	0.8 (0.5-1.3)
(0/0)	26 (15)	32 (10)	1.8 (0.9-3.7)
(+/+) + (+/0)	149 (85)	292 (90)	Reference
(0/0)	26 (15)	32 (10)	2.0 (1.01-4.0)

*OR and 95% CI adjusted for age, BMI, education level, and pack-years.

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Table 4. Distribution of *UGT2B17* genotypes by sex and risk of lung adenocarcinoma

UGT2B17 genotype	Cases (%)	Controls (%)	OR (95% CI)*
Men			
(+/+)	36 (52)	176 (47)	Reference
(+/0)	26 (37)	156 (42)	0.7 (0.4-1.3)
(0/0)	8 (11)	41 (11)	0.9 (0.4-2.3)
(+/+) + (+/0)	62 (89)	332 (89)	Reference
(0/0)	8 (11)	41 (11)	1.0 (0.4-2.3)
Women			
(+/+)	40 (49)	161 (50)	Reference
(+/0)	26 (32)	131 (40)	0.7 (0.4-1.4)
(0/0)	15 (19)	32 (10)	2.4 (1.01-5.7)
(+/+) + (+/0)	66 (81)	292 (90)	Reference
(0/0)	15 (19)	32 (10)	2.8 (1.2-6.3)

*OR and 95% CI adjusted for age, BMI, education level, and pack-years.

then in men, and the deletion of this gene would therefore be expected to cause a greater total reduction in UGT2B17 expression in women then in men. The hypothesis that women have higher expression of UGT2B17 is consistent with the higher urinary glucuronidation rates of women versus men observed in this study. Another possible explanation for this finding is that women may be more susceptible to tobacco carcinogens than men. Some data indicate that women have higher levels of polycyclic aromatic hydrocarbon–induced DNA damage caused by tobacco smoke than men (40, 41), although there are data on sex differences in NNAL-induced adducts. Other genetic polymorphisms have been found to have sex-specific effects for lung cancer, including male-specific associations with CYP1A1 (42) and female-specific associations with methylenetetrahydrofolate reductase (43).

The UGT2B17 polymorphism is an ~120-kb deletion of the entire *UGT2B17* gene, including all coding exons, introns, and much of the 5′ and 3′ flanking regions. Although *UGT2B17* is located in the *UGT2B* gene cluster, a genomic region of chromosome 4 that encompasses six other UGTs, this deletion site does not overlap with other genes in flanking regions. The observed association with lung cancer and the *UGT2B17* deletion in this study is likely a direct result of the lack of UGT2B17 protein in these individuals. However, other polymorphisms might be in linkage disequilibrium with the *UGT2B17* deletion. *UGT2B17*, the first gene in the *UGT2B* gene cluster, is located >390 kb upstream from *UGT2B15*. We determined linkage disequilibrium across this genomic region using the International HapMap Project genotypes (44). No substantial linkage disequilibrium was found between *UGT2B17* and other *UGT* gene loci. The HapMap project has not yet determined the genotypes of single-nucleotide polymorphisms in the *UGT2B15* gene; thus, linkage disequilibrium between *UGT2B17* and *UGT2B15* cannot be tested directly.

We previously showed that UGT2B17 has the highest activity for glucuronidation of NNAL (24) in the UGT superfamily. There are at least three other UGT isozymes that glucuronidate NNAL including 2B7, 1A4, and 1A9 (17, 25). Functional variants in one or more of these UGTs might also be associated with the risk for smoking-related cancers. Missense polymorphisms in both *UGT2B7* and *UGT1A4* are associated with altered rates of NNAL-*O*-Gluc and NNAL-*N*-Gluc formation, respectively (26). A small study found a 4-fold increase in lung cancer risk associated with the UGT1A7*3 variant (45). Although UGT1A7 does not glucuronidate NNAL (17), it mediates the detoxification of the tobacco smoke carcinogens benzo(*a*)pyrene and 2-hydroxyamino-1-methyl-6-phenylimidazo pyridine (46-48). Larger studies will be required to fully evaluate potentially combined high-risk UGT genotypes and lung cancer risk.

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