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# The UGT2B17 gene deletion polymorphism and risk of prostate cancer. A case-control study in Caucasians

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## Abstract

**Condensed Abstact—**The functional polymorphic deletion of the androgen metabolizing UGT2B17 gene was examined for involvement in incident prostate cancer risk. In this study of 411 Caucasian cases and 397 Caucasian controls, the UGT2B17 deletion is not associated with prostate cancer risk.

**Background—**UDP-glucuronosyltransferase (UGT) 2B17 is a phase II metabolizing enzyme that mediates the glucuronidation of $C_{19}$ steroids. A deletion polymorphism in the *UGT2B17* gene is associated with a substantial reduction in glucuronidation activity *in vitro*.

**Methods—**We examined the association between the *UGT2B17* deletion polymorphism and the risk of incident prostate cancer in a population-based study from central Arkansas that included 411 Caucasian cases and 397 Caucasian controls. We developed a novel high-throughput procedure that uses real-time PCR and allelic discrimination for genotyping analysis.

**Results—**The prevalence of the *UGT2B17* deletion [(0/0)] was 12% in the controls, which was consistent with previous population estimates and with Hardy Weinberg equilibrium. There was no association between the *UGT2B17* deletion polymorphism and prostate cancer risk in unconditional logistic regression analysis. Compared to the wild type group (+/+), the adjusted odds ratio (OR) was 0.89 (95% CI = 0.55–1.45) for the homozygous deletion (0/0), and the OR was 0.99 (95% CI = 0.73–1.35) for the heterozygote group (+/0).

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**Conclusion—**These findings show that the UGT2B17 deletion polymorphism is not associated with prostate cancer risk in Caucasians.

### Keywords

prostate; cancer; UGT; deletion; polymorphism

## Introduction

UDP-glucuronosyltransferases (UGTs) are a superfamily of phase II detoxification enzymes that catalyze the glucuronidation of a variety of compounds including steroid hormones, bilirubin, pharmaceuticals, and carcinogens [1–3]. Several UGTs exhibit activity against $C_{19}$ steroids; of these *UGT2B15* and *UGT2B17* are the only isoforms that are expressed in human prostate [4]. Elevated serum androgen levels have been implicated as a risk factor for prostate cancer, but study results have not been consistent [5–9]. Polymorphic variants in androgen metabolizing enzymes may alter androgen levels and therefore affect risk for prostate cancer. Data from two recent studies indicate the presence of a prevalent polymorphic deletion of the entire *UGT2B17* gene [10,11]. This deletion polymorphism is associated with significantly reduced glucuronidation rates of several compounds [12]. In a recent study, Park et al [13] found that the homozygous *UGT2B17* gene deletion significantly increased the risk of prostate cancer in Caucasians. They observed no association in African-American subjects. In the current study, we examined the association of this deletion polymorphism with risk for prostate cancer in a large Arkansas-based Caucasian population using a novel real-time PCR approach that distinguishes between the 3 genotypes of the UGT2B17 deletion polymorphism.

## Materials and Methods

### Study Population

Subjects with incident prostate cancer, diagnosed from 1998–2003 in central Arkansas, were recruited into the study within six months of their diagnosis. The patients were recruited from the University of Arkansas for Medical Sciences, the University Hospital in Little Rock, the Central Arkansas Veteran's Health Care System in Little Rock, and the Jefferson Regional Medical Center in Pine Bluff, Arkansas. These institutions treat the vast majority of cancer patients in the Little Rock metropolitan area. The medical records were reviewed to obtain information on tumor pathology and post-diagnostic PSA testing results. All subjects had histologically-confirmed prostate cancer. Community controls were recruited primarily from a mass-mailing database that covers 80% of Arkansas residents. This database was supplemented by records from the Arkansas State Driver's License records. Elderly controls were also identified and recruited from the Centers for Medicare and Medicaid Services records. The controls were frequency matched to cases on age (± 5 years) and race.

Exclusion criteria for the case-control study included a history of cancer (except nonmelanoma skin cancer), uncontrolled cardiovascular disease, and hepatic dysfunction. All subjects were interviewed by a trained interviewer using a structured lifestyle questionnaire, and were asked to provide a blood sample for DNA analysis and prostate-specific antigen (PSA) measurements. PSA levels were collected for 99% of the cases and 52% of the controls.

The appropriate institutional review board approvals were obtained for the study protocol, and further details of the methods have been previously published [14]. The study population consists of 411 Caucasian cases and 397 Caucasian controls which provided >95% power to detect a statistically significant OR of 2.0 at an exposure rate of 10%, which has been observed for the *UGT2B17* homozygous deletion.

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### UGT2B17 deletion polymorphism genotyping methodology

Details describing the *UGT2B17* gene deletion polymorphism have been reported elsewhere [10,11]. For large sample screening, we developed a high-throughput genotyping assay using real-time PCR with allelic discrimination. Although the use of two primers and two probes has become common practice for SNP genotyping and has recently been used in an analysis of a small deletion polymorphism [15], the amplification of both the *UGT2B17* wild-type and deletion alleles could not be performed using the same set of PCR primers due to the large size (~120Kb) of the *UGT2B17* gene deletion polymorphism. 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 (that spans the deletion cut site) that amplify only if the deletion is present (Figure 1). Due to high sequence homology between *UGT2B17* other UGT genes and pseudogenes, primers were designed using Blast 2.2.14 (http://www.ncbi.nlm.nih.gov/BLAST/) maximizing for 3′ sequence mismatches with other homologous genes (Table 1), with primers obtained from Integrated DNA Technologies (Coralville, IA). Reactions (20 μl) were performed in 384-well plates using the ABI 7900 HT Sequence Detection System, with incubations performed 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 sec. Reactions included QuantiTect Multiplex PCR Master Mix (1x final concentration; Qiagen, Valencia, CA), 0.4 μM for each primer, 0.2 μM for each probe, and 20–100 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). Individuals homozygous for the wild-type allele (intact UGT2B17 gene) are represented as (+/+), heterozygous individuals are represented as (+/0), and individuals who were homozygous for the UGT2B17 gene deletion allele (UGT2B17 null) are represented as (0/0).

To validate the new genotyping methodology, we used 63 normal human liver genomic DNA specimens that has been previously described [16]. The methodology was also validated using 96 oral buccal cell genomic DNA samples from cancer-free community residents. Details of this study have also been reported previously [17]. DNA from both of these studies was extracted using a commercial kit (Qiagen Inc., Valencia, CA).

### Statistical Analysis

Deviation from Hardy-Weinberg equilibrium in the controls was tested using $?^2$ analysis. Unconditional logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (CI) associated with prostate cancer risk. Potential confounders were identified by Spearman rank correlation analyses and multivariate regression models, including stepwise regression models. Age (continuous), pack-years of smoking (continuous), and family history of prostate cancer (categorical) were found to be significant predictors of prostate cancer risk, and were entered into the final models. All statistical analyses were conducted using SPSS 15.0 statistical software (SPSS 15.0, SPSS Inc., Chicago IL).

## Results

The genotyping method was initially tested in a blinded study of 63 normal liver genomic DNA samples by comparing the findings from the real-time method to that using a previously-validated methodology [12]. This previous methodology differentiated between PCR amplifications of the two highly homologous genes *UGT2B15* and *UGT2B17* (95% homology in nucleotide sequence). Briefly, the previous method of genotyping included 3 PCR amplification reactions: exon 1 of *UGT2B17* or the highly-homologous *UGT2B15* was amplified using sense and antisense primers that contained 1 or 2 bp mismatches between *UGT2B15* or *UGT2B17* sequences. This was followed by gene-specific restriction fragment length polymorphism (RFLP) to confirm the presence of *UGT2B17* or *UGT2B15*. A third PCR

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reaction amplified the *UGT2B17* deletion allele with primers spanning the deletion cut-site, as previously described [11,12]. We found 100% concordance when comparing the high-throughput real-time method versus our previously validated RFLP methodology. In a second blinded quality-control study that included the 96 oral buccal cell genomic DNA samples, samples were genotyped in duplicate by real-time PCR, and again there was 100% concordance for the *UGT2B17* genotype.

The basic demographic characteristics of the cases and controls are shown in Table 2. The mean age of the cases was higher than the controls (66 vs. 62), and the cases had a higher mean amount of smoking pack-years than the controls (30 vs. 22). More cases than controls were ever smokers (72% vs. 59%) and heavy smokers (39% vs. 28%). In subset analysis by smoking level, subjects were classified into light and heavy smoking categories (stratified at the median for all smokers in the study population). More cases than controls (19% vs. 8%) had a family history of prostate cancer. The mean PSA level was 42 ng/ml in cases and 1.6 ng/ml in controls. There were no controls with PSA levels above 10 ng/ml. Among the 302 case subjects with a Gleason score, 59% had a score of 6 or less.

The *UGT2B17* genotype frequencies, OR, and 95% CI are shown in Table 3. The frequency of the UGT2B17 deletion (0/0) genotype in controls was 12%, which was similar to that observed in other Caucasian study populations [11–13,18]. The *UGT2B17* gene deletion polymorphism was determined to be consistent with Hardy-Weinberg equilibrium for the control population.

There was no significant difference in the prevalence of the *UGT2B17* deletion genotype between prostate cancer cases (10%) and controls (12%). The OR, adjusted for age, smoking, and family history of prostate cancer, was not significant when comparing deletion homozygote subjects (0/0) (OR=0.89, 95% CI 0.55–1.45) or heterozygote subjects (+/0) (OR=0.99, 95% CI 0.73–1.35) to wild type subjects (+/+) (Table 3). There was also no association with prostate cancer risk when collapsing genotype categories. The risk when comparing all other subjects to the wild-type group was 0.97 (95% CI 0.73–1.30). Alternatively, when comparing deletion homozygotes to the combined heterozygotes and wild-type group, the OR was 0.89 (95% CI 0.56–1.43).

When stratified by smoking level (non-smokers, light-smokers, and heavy-smokers), there was also no association between UGT2B17 genotype and prostate cancer risk. The adjusted OR was not elevated when comparing deletion homozygote subjects (0/0) or heterozygote subjects (+/0) to wild type subjects (+/+) in any of the three smoking categories (Table 4). There was also no association with prostate cancer risk in any of the three smoking categories when collapsing genotype categories.

Analysis was also conducted in the subset of individuals who have no family history of prostate cancer to avoid potential bias if other, more penetrant, genetic factors are involved in prostate cancer risk. This subset of individuals without family history of prostate cancer had a similar frequency of the UGT2B17 deletion (11% in the cases and 12% in the controls) as the overall population. In addition, logistic regression analysis indicated no association of the UGT2B17 genotype with prostate cancer in this subset of individuals. The OR, adjusted for age and smoking, was not significant when comparing deletion homozygote subjects (0/0) (OR=1.01, 95% CI 0.61–1.69), or heterozygote subjects (+/0) (OR=1.03, 95% CI 0.74–1.43), to wild type subjects (+/+) when individuals with a family history of prostate cancer were excluded (Supplementary Table 1).

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## Discussion

This study did not detect an association between the *UGT2B17* gene deletion polymorphism and risk for prostate cancer in Caucasians. It was previously reported that the *UGT2B17* deletion polymorphism was not associated with an increased risk of prostate cancer in African-Americans from Arkansas [13], but was associated with an increased risk (OR=1.9) in Caucasian subjects from Florida that included 293 cases and a similar number of controls [13]. One difference between our study and the previous finding is that the real-time PCR genotyping technique employed in the present study is a high-throughput method that facilitates genotyping for large sample sets with the automated assignment of genotypes, whereas the traditional PCR techniques used in the previous study require gel electrophoresis and the manual calling of genotypes [12,13]. The current method also distinguishes between heterozygous (+/0) and homozygous (+/+) *UGT2B17* genotypes, a distinction not performed in the previous study. However, the prevalence of the *UGT2B17* deletion (0/0) in the control groups of both studies was similar (11–12%), which is consistent with other reports in samples of healthy individuals [11,12,18]. It is possible that the lack of association in the current study is due in part to undetected prostate cancer in the controls. Approximately half of the control subjects were not screened for PSA; therefore some controls may have had latent prostatic adenocarcinoma. However, none of the controls that were screened for PSA had a value above 10 ng/ml, indicating that there was little or no misclassification of controls. The Gleason score distribution among cases in this study was very similar to that reported in a case series of 54,200 subjects [19], indicating that the case population was representative of the stage at which most prostate tumors are detected in the PSA screening era. Therefore the differences between these two studies might reflect chance, lack of control for unknown confounders, or some other factor that might mediate a potential affect of *UGT2B17* on prostate cancer risk.

The lack of association of the *UGT2B17* gene deletion polymorphism with prostate cancer may be due in part to the down-regulation of *UGT2B17* transcription by androgens in the prostate [20–22]. This may result in low expression of *UGT2B17* in the prostate compared to *UGT2B15* expression, which is not regulated by androgens [21,22]. A deletion in the *UGT2B17* gene would therefore not result in a dramatic difference in overall androgen glucuronidation rates within the prostate, which would consequently have little overall impact on the risk for prostate cancer. Another potential consideration in understanding the role of glucuronidation in prostate cancer is the presence of functional polymorphisms in *UGT2B15.* Some studies have examined the association between polymorphisms in *UGT2B15* and prostate cancer risk but the results have been conflicting [23–26]. Larger studies enabling us to examine functional polymorphisms in both genes and their interactions will be necessary to better evaluate the role of glucuronidating enzymes and risk for prostate cancer.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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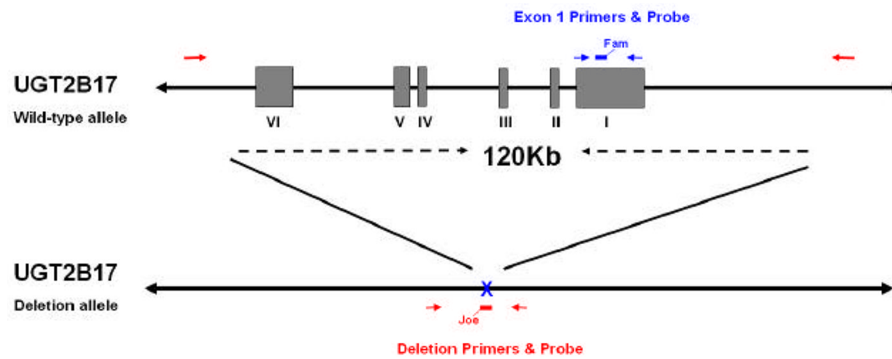


**Figure 1.**
Gene structure and primer and probe locations for the *UGT2B17* multiplex real-time PCR assay. The roman numerals I–VI indicate the exons of the *UGT2B17* gene on the wild-type allele. The deletion allele is shown below the wild-type allele indicating the 120 kb that are deleted, including the entire *UGT2B17* gene. Red arrows indicate the primers that will amplify the deletion allele and the red bar (with fluorescent label Joe) indicates the deletion probe. Blue arrows indicate the primers that will amplify exon 1 of *UGT2B17* from the wild-type allele and the blue bar (with fluorescent label Fam) indicates the deletion probe.

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**Table 1**

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

| primer name | primer composition (5′ to 3′) |
| --- | --- |
| Exon 1 – forward | TGAAAATGTTCGATAGATGGACATATAGTA |
| Exon 1 – reverse | GACATCAAATTTTGACTCTTGTAGTTTTC |
| Exon 1 – probe | 6-FAM-TACATTTTGGTCATATTTTTCACAACTACAAGAATTGT-BHQ1 |
| Deletion – forward | TTTAATGTTTTCTGCCTTATGCCAC |
| Deletion – reverse | AGCCTATGCAATTTTCATTCAACATAG |
| Deletion – probe | JOE-ACTACACTGAGATTTACAAAAGAATTCTGTCAGGATATAG-BHQ1 |

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**Table 2**

Demographics of the prostate cancer cases and controls.

| Demographic | Cases (n=411) | Controls (n=397) |
|---|---|---|
| Age (years)[a] | 66 ± 8 | 62 ± 11 |
| Smoking (pack-years)[a] | 30 ± 35 | 22 ± 32 |
| Non-smokers | 28% | 42% |
| Light-smokers | 33% | 31% |
| Heavy-smokers | 39% | 28% |
| Family history of prostate cancer | 19% | 8% |
| PSA level (ng/ml),[ab] | 42 ± 437 | 1.6 ± 1.7 |
| Gleason score = 6[c] | 59% | NA[d] |
| Gleason score > 6[c] | 41% | NA |

[a] Mean ± Standard Deviation shown for continuous variables.

[b] PSA levels are shown when available (405 cases and 205 controls).

[c] Gleason scores were available for 302 cases.

[d] NA, not applicable

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**Table 3**

Genotype frequencies and risk of prostate cancer.

| ***UGT2B17* genotype**[a] | **Cases (%)** | **Controls (%)** | **OR (95% CI)**[b] |
|---|---|---|---|
| (+/+) | 201 (49) | 190 (48) | 1.00 (Ref.) |
| (+/0) | 168 (41) | 159 (40) | 0.99 (0.73–1.35) |
| (0/0) | 42 (10) | 48 (12) | 0.89 (0.55–1.45) |
| (+/+) | 201 (49) | 190 (48) | 1.00 (Ref.) |
| (+/0) + (0/0) | 210 (51) | 207 (52) | 0.97 (0.73–1.30) |
| (+/+) + (+/0) | 369 (90) | 349 (88) | 1.00 (Ref.) |
| (0/0) | 42 (10) | 48 (12) | 0.89 (0.56–1.43) |

[a]The three genotypes of the UGT2B17 deletion polymorphism are shown as: (+/+), two alleles of the UGT2B17 gene; (+/0), one allele of the UGT2B17 gene and one gene deletion allele; (0/0), UGT2B17 null, two copies of the deletion allele.

[b]Adjusted for age, smoking pack-years, and family history of prostate cancer.

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## Table 4

Genotype frequencies and risk of prostate cancer in non-, light-, and heavy-smoking categories.

| ***UGT2B17* genotype**[a] | **Cases (%)** | **Controls (%)** | **OR (95% CI)**[b] |
|---|---|---|---|
| Non-smokers | | | |
| (+/+) | 61 (53) | 76 (48) | 1.00 (Ref.) |
| (+/0) | 44 (38) | 63 (39) | 0.84 (0.49–1.44) |
| (0/0) | 10 (9) | 21 (13) | 0.62 (0.26–1.49) |
| (+/+) | 61 (53) | 76 (48) | 1.00 (Ref.) |
| (+/0) + (0/0) | 54 (47) | 84 (52) | 0.79 (0.47–1.31) |
| (+/+) + (+/0) | 105 (91) | 139 (87) | 1.00 (Ref.) |
| (0/0) | 10 (9) | 21 (13) | 0.67 (0.29–1.56) |
| Light-smokers[c] | | | |
| (+/+) | 65 (49) | 61 (50) | 1.00 (Ref.) |
| (+/0) | 50 (37) | 42 (35) | 1.25 (0.70–2.21) |
| (0/0) | 19 (14) | 18 (15) | 1.10 (0.49–2.46) |
| (+/+) | 65 (49) | 61 (50) | 1.00 (Ref.) |
| (+/0) + (0/0) | 69 (51) | 60 (50) | 1.20 (0.71–2.04) |
| (+/+) + (+/0) | 115 (86) | 103 (85) | 1.00 (Ref.) |
| (0/0) | 19 (14) | 18 (15) | 1.00 (0.46–2.16) |
| Heavy-smokers[c] | | | |
| (+/+) | 75 (46) | 53 (46) | 1.00 (Ref.) |
| (+/0) | 74 (46) | 54 (46) | 0.94 (0.57–1.56) |
| (0/0) | 13 (8) | 9 (8) | 0.97 (0.38–2.47) |
| (+/+) | 75 (46) | 53 (46) | 1.00 (Ref.) |
| (+/0) + (0/0) | 87 (54) | 63 (54) | 0.95 (0.58–1.54) |
| (+/+) + (+/0) | 149 (92) | 107 (92) | 1.00 (Ref.) |
| (0/0) | 13 (8) | 9 (8) | 1.00 (0.40–2.45) |

[a]The three genotypes of the UGT2B17 deletion polymorphism are shown as: (+/+), two alleles of the UGT2B17 gene; (+/0), one allele of the UGT2B17 gene and one gene deletion allele; (0/0), UGT2B17 null, two copies of the deletion allele.

[b]Adjusted for age, smoking pack-years (except non-smokers), and family history of prostate cancer.

[c]Light- versus heavy-smoker categories, subjects stratified at the median for all smokers in the study population.