Association of SULT1A1 Phenotype and Genotype with Prostate Cancer Risk in African-Americans and Caucasians

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Abstract

Exposure to heterocyclic amines may increase prostate cancer risk. Human sulfotransferase 1A1 (SULT1A1) is involved in the bioactivation of some dietary procarcinogens, including the *N*-hydroxy metabolite of the food-borne heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo(4,5-*b*) pyridine. This study compares a polymorphism in the *SULT1A1* gene, SULT1A1 enzyme activity, meat consumption, and the risk of prostate cancer in a population based case-control study. Prostate cancer patients ($n = 464$) and control individuals ($n = 459$), frequency matched on age and ethnicity, provided informed consent, answered a survey, and provided a blood sample. Platelets were isolated for phenotype analysis, and DNA was isolated from lymphocytes for genotype determination. Meat consumption was assessed using a dietary questionnaire. Caucasians homozygous for the *SULT1A1*1* high activity allele were at increased risk for prostate cancer [odds ratio (OR), 1.68; 95% confidence interval (CI), 1.05–2.68] compared with individuals homozygous for the low-activity allele. The association between *SULT1A1* genotype and prostate cancer risk in African-Americans did not reach significance (OR, 1.60; 95% CI, 0.46–5.62). When SULT1A1 activity was considered, there was a strong association between increased SULT1A1 activity and prostate cancer risk in Caucasians (OR, 3.04; 95% CI, 1.8–5.1 and OR, 4.96; 95% CI, 3.0–8.3, for the second and third tertiles of SULT1A1 activity, respectively) compared with individuals in the low enzyme activity tertile. A similar association was also found in African-American patients, with ORs of 6.7 and 9.6 for the second and third tertiles of SULT1A1 activity (95% CI, 2.1–21.3 and 2.9–31.3, respectively). When consumption of well-done meat was considered, there was increased risk of prostate cancer (OR, 1.42; 95% CI, 1.01–1.99 and OR, 1.68; 95% CI, 1.20–2.36 for the second and third tertiles, respectively). When SULT1A1 activity was stratified by tertiles of meat consumption, there was greater risk of prostate cancer in the highest tertile of meat consumption. These results indicate that variations in SULT1A1 activity contributes to prostate cancer risk and the magnitude of the association may differ by ethnicity and be modified by meat consumption.

Introduction

Prostate cancer is the second leading cause of cancer deaths among men. Incidence of prostate cancer and deaths from that disease are significantly higher in African-American men compared with Caucasians (1). Some epidemiological studies have indicated a positive association between meat consumption and prostate cancer risk, but this finding has not been consistent across studies (2). There are also indications that consumption of foods high in animal fat is associated with risk of more advanced disease, and this risk is greater in African-Americans than in Caucasians (3). The mechanistic basis of this association has not been well-defined, but it has been proposed that intake of animal products increases prostate cancer risk due to dietary fat contained in these products (2, 4–6). However, consumption of meat cooked at high temperatures also results in exposure to heterocyclic amines (HCAs), compounds that are mutagenic in the Ames assay (7) and are carcinogenic in animal models (8). Exposure of rats to 2-amino-1-methyl-6-phenylimidazo(4,5-*b*) pyridine (PhIP), the most mass-abundant HCA, results in the formation of prostate tumors (9). Furthermore, recent animal studies have shown organ differences in response to PhIP exposure, with the prostate only requiring short-term administration to produce tumors (10).

HCAs require metabolic activation to exert their mutagenic/carcinogenic effects. The first step involves hydroxylation catalyzed by cytochrome P4501A2 in human liver. Subsequent metabolism of the *N*- hydroxy HCA by *N*-acetyltransferases and sulfotransferases (SULTs) generate electrophiles capable of adducting to DNA and initiating carcinogenesis (11, 12). Of these two activating pathways, recent studies have suggested that in humans, sulfation catalyzed by SULT1A1 may be the more relevant pathway of PhIP activation (13).

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In humans, SULTs are expressed in a wide variety of tissues, including liver, lung, brain, skin, breast, kidney, gastrointestinal tissue, and platelets (14–18). To date, at least 10 human cytosolic SULT isoforms have been identified and assigned to two major subfamilies, the phenol SULT1 family and the hydroxysteroid SULT2 family (19). Of the phenol SULT1 subfamily, SULT1A1 is the most highly expressed isoform. It is found in most epithelial tissues and is the most abundant hepatic sulfotransferase, with levels in that tissue 10 times greater than all of the other isoforms (20, 21). SULT1A1 catalyzes the sulfation of a host of structurally diverse compounds, such as small phenols, steroids, iodothyronines, environmental estrogen-like compounds, and heterocyclic and aromatic amines (22, 33).

A common genetic polymorphism in exon 7 of the *SULT1A1* gene results in an amino acid change (Arg to His) at position 213 of the translated protein. This amino acid change generates a protein with decreased enzymatic activity (24) and decreases the efficiency of SULT1A1-catalyzed binding of *N*-OH-PhIP to DNA (25). This polymorphism in *SULT1A1* has been investigated in relation to several cancers, including prostate cancer. The variant *SULT1A1*2* allele was associated with increased risk of breast cancer in one study, but when consumption of well-done meat was included in the model, *SULT1A1*1* increased the risk of breast cancer (26). Another study found no association between *SULT1A1* genotype and risk of breast cancer, but did find that the *SULT1A1*1* allele was associated with age of onset of breast cancer and also with the incidence of tumors at sites other than breast in breast cancer patients (27). *SULT1A1*1* has been associated with reduced risk of colorectal cancer (28, 29) and with increased risk of lung cancer (30). Steiner *et al.* (31) reported a lack of association between *SULT1A1* genotype and risk of prostate cancer. Because studies in our laboratory have indicated that the *SULT1A1* genotype accounts for <30% of the phenotypic variation observed in SULT1A1 activity in platelets (25), we examined both *SULT1A1* genotype and SULT1A1 phenotype in a case-control study of prostate cancer risk. We also investigated the potential interaction among well-done meat, SULT1A1 phenotype and genotype, and risk of prostate cancer.

Materials and Methods

Study Population. Prostate cancer patients recruited to this case-control study were incident, histologically confirmed prostate cancer cases, diagnosed from 1996 through 2002. Prostate cancer cases were consented and recruited from the University of Arkansas for Medical Sciences University Hospital and the Central Arkansas Veterans Health Care System in Little Rock, and the Jefferson Regional Medical Center in Pine Bluff, Arkansas. Population-based control participants were frequency matched to cases on ethnicity, age (±5 years), and county of residence. Control participants were primarily identified from Arkansas State driver's license records and mass mailing databases. The appropriate Institutional Review Board approvals were obtained for the study protocol. Exclusion criteria for the case-control study included a history of cancer (other than nonmelanoma skin cancer), uncontrolled cardiovascular disease, hepatic dysfunction as determined by bilirubin >1.5 mg/dl, aspartate aminotransferase >40 units/liter, alkaline phosphatase >140 units/liter, and abnormal renal function as determined by blood urea nitrogen >20 mg/dl and serum creatinine >1.8 mg/dl. Each participant provided a blood sample from which lymphocytes and platelets were separated as described previously (32).

SULT1A1 Genotyping. DNA was extracted from lymphocytes of study participants using a commercial kit (Qiagen Inc., Valencia, CA). Genotyping for the *SULT1A1*1* common allele and the *SULT1A1*2* variant allele was performed as described previously (33). Briefly, gene-specific primers and PCR were used to amplify a 281-bp fragment of the *SULT1A1* gene containing the polymorphic base. Genotype was determined by exposing the PCR product to the endonuclease *Hae*II (New England Biolabs, Beverly, MA) and resolving the resulting fragments on a 3% Metaphor agarose gel (FMC BioProducts, Rockland, ME). The fragments were visualized by ethidium bromide staining and UV transillumination. The polymorphism consists of a G to A transition at nucleotide 638 in exon 7 (*SULT1A1*2*), which abolishes the recognition site for the endonuclease, preventing enzymatic digestion of the PCR product. Digestion of the PCR product homozygous for the *SULT1A1*1* common allele generates two fragments; heterozygotes exhibit all three of the bands. Genotyping for *SULT1A1*3* alleles (Met223Val) was performed by subjecting an aliquot of the PCR product to digestion with the endonuclease *Nla*III. Individuals homozygous for Met223 exhibit two bands on digestion and Met223Val heterozygotes show three bands, whereas Val223 homozygotes are unaffected by this restriction digest.

SULT1A1 Phenotyping. Platelet cytosol for the SULT1A1 phenotyping assay was prepared as described previously (25). Protein determinations were performed using the Bio-Rad Protein Assay kit (Bio-Rad, Hercules, CA) according to the Bradford method, using BSA as a standard. Platelet cytosols were assayed for SULT1A1 activity using a simple colorimetric procedure first described by Mulder *et al.* (34) and modified by Frame *et al.* (42) to fit a microtiter plate format. Platelet cytosols (~15 μg) from study participants were incubated at 37°C for 45 min in 50 mM potassium phosphate buffer (pH 6.5) containing 5 mM $MgCl_2$, 20 μM 3′-phosphoadenosine 5′-phosphosulfate, 5 mM *p*-nitrophenyl sulfate and 0.1 mM 2-naphthol (total volume 100 μl). The reaction was terminated by adding 100 μl of 0.25 M Tris-HCL (pH 8.7). SULT1A1-catalyzed liberation of *p*-nitrophenyl from *p*-nitrophenyl sulfate was measured by determining absorbance at 405 nm using a SpectraMax model 250 spectrophotometric plate reader (Molecular Devices) and quantified using the extinction coefficient (18,200 $cm^{-1}\ M^{-1}$), which directly correlates with the concentration of 2-naphthylsulfate formed (34). Assays were performed in triplicate along with controls that did not contain 2-naphthol. SULT1A1 activity is reported as nmol/min/mg.

Meat Consumption. Each study participant completed a dietary habits questionnaire, part of which was designed to assess meat consumption and cooking methods. Previous studies have suggested that measuring exposure to individual HCAs gave no significant advantage over assessing HCA exposure by measuring the sum of 5 meats (burgers, steaks, pork chops, bacon, and sausage) cooked well or very well done (35). Therefore, we summed burgers, steaks, pork chops, bacon, and sausage that were reported as cooked well done or very well done to estimate exposure to HCAs.

Statistical Analysis. The Wilcoxon rank sum test was used to test the hypothesis that the distribution of baseline characteristics was the same for cases and controls. The χ^2 test was used for categorical variables to test the hypothesis that the distribution was the same for cases and controls. Hardy-Weinberg equilibrium tests for *SULT1A1* genotype were performed on the control study participants. Unconditional logistic regression was used to calculate odds ratios (ORs; an estimate of relative

Table 1 Selected characteristics of prostate cancer cases and controls[a]

Characteristic	Cases (n = 464)	Controls (n = 459)	P^b
Age (yrs)	68	66	<0.001
Ethnicity			
Caucasian	353	358	
African-American	111	101	<0.6
Body mass index (Kg/m^2)	27	27	<0.5
Genotype			
*SULT1A1*2/*2*	51 (11.3%)	62 (15.4%)	
*SULT1A1*1/*2*	191 (42.5%)	186 (46.1%)	
*SULT1A1*1/*1*	208 (46.2%)	155 (38.5%)	<0.04
SULT1A1 activity[c]	1.49	1.09	<0.0001
Meat consumption (median)[d]	43.74	36.97	<0.025

[a] Continuous variables expressed as the median.
[b] *P*s as determined by Wilcoxon rank-sum tests and Fisher's exact test for categorical variables.
[c] Activity units are nmol/min/mg protein.
[d] Meat consumption consists of the sum of burgers, steak, pork chops, bacon, and sausage cooked well or very well done in units of grams per day.

risk) to evaluate the association among genotype, tertiles of SULT1A1 activity, and odds of prostate cancer. The primary covariates used in the analysis were: (*a*) age as a continuous variable; and (*b*) race as a dichotomous variable. Tertiles for SULT1A1 activity were created using the distribution of activity among the controls. Modification of the effect of genotype and SULT1A1 activity on the risk of prostate cancer by age and ethnicity (*P*s for interactions) was examined by statistical tests of the first order interaction term in the logistic regression models. Linear trend analyses for SULT1A1 activity were conducted by creating a variable using activity scores based on the median values of activity for the first, second, and third activity tertiles. Potential confounding of the association among genotype, phenotype, and cancer risk by other related risk factors was explored using Spearman rank correlation analysis and multivariate logistic regression models. If the potential confounder caused a significant change in the log likelihood estimate ($P < 0.05$) and a >20% change in the β-coefficient, it was kept in the model for additional multivariate analysis. Associations between genotype and phenotype were evaluated using ANOVA, with phenotype as the continuous variable. Differences in phenotype by race were evaluated using Student's *t* test of means. All of the *P*s reported are two-sided. All of the analyses were performed using the statistical software package STATA (STATA Corporation, College Station, TX).

Results

***SULT1A1* Genotype and Subject Characteristics.** Table 1 describes selected characteristics of the study population. The median age of the control subjects was 66 years compared with 68 years in the prostate cancer patients. Overall, control study subjects were younger than the individuals with prostate cancer ($P < 0.001$). There were no differences in the cases and controls when race or body mass index (BMI) was considered. For the SULT1A1 genotype, the Hardy-Weinberg equilibrium assumption was tested in the control individuals using a χ^2 test, and we found no deviation from equilibrium ($P = 0.37$). There was a significant difference ($P < 0.04$) in the distribution of *SULT1A1* genotype comparing prostate cancer cases with controls with the *SULT1A1*1* high-activity genotype being overrepresented in the cases compared with noncases (46.2% and 38.5%, respectively). When SULT1A1 enzymatic activity in platelets was examined, prostate cancer cases had significantly higher median activity than the controls (1.49 nmol/min/mg protein in cases compared with 1.09 nmol/min/mg protein for the controls; $P < 0.0001$). Correlation analyses revealed statistically significant correlations between SULT1A1 activity and SULT1A1 genotype, and ethnicity (with African-Americans having higher activity). Median consumption of five meats cooked well or very well done was significantly higher in prostate cancer cases compared with control individuals (43.74 grams/day compared with 36.97 grams/day, respectively; $P < 0.025$).

***SULT1A1* Genotype and Phenotype among Prostate Cancer Patients and Controls.** Table 2 shows the relationship between SULT1A1 genotype and phenotype in relation to prostate cancer risk. Genotype data were available for 450 prostate cancer patients and 403 control individuals. When all of the subjects are considered, there is an increased risk of prostate cancer for individuals possessing the *SULT1A1*1/*1* genotype [OR, 1.69; 95% confidence interval (CI), 1.10–2.61] after adjusting for age and race. BMI had no effect on genotype, phenotype, or prostate cancer risk. The direction of the ORs indicates elevated risk of prostate cancer with increasing numbers of *SULT1A1*1* alleles, with evidence for trend being statistically significant (test for trend, $P = 0.002$). When tests for interaction were performed, there was no evidence for interaction between *SULT1A1* genotype and age ($P = 0.49$), BMI (0.19), or meat consumption ($P = 0.29$). Additionally, no interaction between SULT1A1 activity and age, BMI, or meat consumption was evident. There was a significant difference ($P = 0.006$) in distribution of *SULT1A1* genotypes by race in the control population.

Table 2 also details SULT1A1 phenotype among prostate cancer patients and controls. Phenotype data were available for 377 prostate cancer patients and 227 control individuals. Tertiles of activity were derived from the distribution of SULT1A1 activity in the control population. The two higher SULT1A1 activity tertiles were associated with increased risk of prostate cancer (OR, 2.62; 95% CI, 1.64–4.19 and OR, 3.92; 95% CI, 2.45–6.43 for the second and third tertiles of activity, respectively) compared with the lowest activity tertile. When tertiles of meat consumption were considered, there was evidence for elevated risk of prostate cancer with increasing meat consumption (OR, 1.68; 95% CI, 1.2–2.36 for the highest tertile of meat consumption; Table 2).

Table 2 Association among SULT1A1 genotype, enzyme activity, and odds of prostate cancer[a]

	# cases/ # controls	Odds ratio (95% confidence interval)	P_{trend}
Genotype			
*SULT1A1*2/*2*	51/62	1.0 (Reference)	
*SULT1A1*1/*2*	191/186	1.25 (0.81–1.93)	
*SULT1A1*1/*1*	208/155	1.66 (1.07–2.56)	<0.01
SULT1A1 Activity[b]			
Tertile 1 (0.021–0.65)	50/76	1.0 (Reference)	
Tertile 2 (0.66–1.375)	142/75	3.23 (1.95–5.50)	
Tertile 3 (1.38–5.03)	185/76	5.47 (3.25–9.16)	<0.001
Meat consumption[c]			
Tertile 1 (0.198–22.87)	115/152	1.0 (Reference)	
Tertile 2 (22.9–55.78)	162/152	1.42 (1.01–1.99)	
Tertile 3 (56–474.7)	177/156	1.68 (1.20–2.36)	<0.003

[a] Unconditional logistic regression models adjusted for age, race, and meat consumption.
[b] Tertiles derived from distribution among controls with first tertile used as the reference group. Activity units are nmol/min/mg protein.
[c] Meat consumption the sum of five meats cooked well done in grams/day.

Table 3 SULT1A1 genotype, phenotype, and meat consumption, and odds of prostate cancer

	Consumption of meat cooked well done			P_{trend}
	Low OR[a] (95% CI)	Med OR (95% CI)	High OR (95% CI)	
Genotype				
*SULT1A1*2/*2*	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	
*SULT1A1*1/*2*	1.22 (0.79–1.89)	0.99 (0.46–2.12)	0.67 (0.25–1.78)	
*SULT1A1*1/*1*	1.65 (1.06–2.56)	1.88 (0.72–4.88)	1.11 (0.52–2.36)	0.74
SULT1A1 Activity				
Tertile 1 (0.021–0.65)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	
Tertile 2 (0.66–1.375)	3.29 (1.96–5.52)	3.63 (1.58–8.34)	3.91 (1.31–11.67)	
Tertile 3 (1.38–5.03)	5.45 (3.25–9.16)	4.89 (1.50–15.88)	8.27 (3.36–20.38)	0.02

[a] Odds ratio (OR) from conditional logistical regression, adjusted for age and race. *SULT1A1* genotype X meat consumption *P* interaction = 0.29. SULT1A1 phenotype X meat consumption *P* interaction = 0.64. CI, confidence interval.

***SULT1A1* Genotype, Phenotype, Meat Consumption, and Prostate Cancer Risk.** We then examined the potential association among SULT1A1 phenotype, genotype, and well-done meat in relation to risk of prostate cancer (Table 3). When *SULT1A1* genotype was stratified by categories of meat consumption, there was no association between increasing numbers of *SULT1A1*1* alleles and tertiles of meat consumption and prostate cancer risk (P_{trend} = 0.74). When the relationship between SULT1A1 activity and prostate cancer risk in the context of increasing consumption of well-done meat was examined, there was a significant trend of increased prostate cancer risk with higher categories of meat consumption (P = 0.02).

***SULT1A1* Genotype, Phenotype, and Prostate Cancer Risk Stratified by Ethnicity.** Because there was an association between *SULT1A1* genotype and ethnicity, we examined prostate cancer risk by genotype and phenotype stratified by ethnicity (Table 4). The *SULT1A1*1* allele was more prevalent in African-Americans compared with Caucasians (49.5% *versus* 35.2%, respectively). When ethnicity was considered, there was a statistically significant effect of the *SULT1A1*1/*1* genotype on prostate cancer risk in the Caucasian population (OR, 1.68; 95% CI, 1.05–2.68). Tests for trend of elevated prostate cancer risk with increasing numbers of *SULT1A1*1* alleles were statistically significant (P_{trend} = 0.02). In the African-American population, the association of *SULT1A1* genotype with prostate cancer risk did not achieve statistical significance. ORs for African-Americans homozygous for the high activity allele were 1.60 with 95% CI of 0.46–5.62. Tests for trend were also nonsignificant (P_{trend} = 0.36). An additional genetic polymorphism in SULT1A1 common in African-Americans, but rare in Caucasians, has been described (36). When this allele, designated *SULT1A1*3*, was examined in African-American study participants, there was no association with SULT1A1 phenotype (ANOVA P = 0.31). Additionally, this allele showed no association with risk of prostate cancer in the African-American study subjects (OR, 1.09; 95% CI, 0.56–2.13).

When SULT1A1 phenotype was examined, however, the OR for the highest tertile of activity in African-Americans was 9.6 (95% CI, 2.9–31.3), and this association was statistically significant ($P < 0.003$). There was also an association between SULT1A1 activity and prostate cancer risk in the Caucasians. The highest tertile of SULT1A1 activity was associated with an OR of 4.96 (95% CI, 3.0–8.3).

African-American prostate cancer cases also consumed significantly more meat than did Caucasian patients (50.9% *versus* 35.1% in the highest tertile of meat consumption; P = 0.001). When meat consumption and prostate cancer risk were considered by ethnicity, there was an association between increased meat consumption and elevated prostate cancer risk in both African-Americans and Caucasians (Table 4).

SULT1A1 Activity by Genotype and Case Status. We examined the distribution of SULT1A1 phenotype stratified by race and case status (Table 5). The mean SULT1A1 activity in the control population was significantly higher in African-Americans compared with Caucasians. When all of the controls are considered, there is a significant association between genotype and phenotype. When the controls are stratified by race, the association remained for the Caucasians but was not significant in the African-Americans. When cases are examined, again, SULT1A1 activity is higher in the African-American population. As with the controls, there was a significant asso-

Table 4 SULT1A1 genotype, enzyme activity, and odds of prostate cancer stratified by ethnicity[a]

	# cases/# controls	Odds ratio (95% confidence interval)	P_{trend}
African-Americans			
SULT1A1 genotype			
*SULT1A1*2/*2*	5/6	1.0 (Reference)	
*SULT1A1*1/*2*	42/41	1.27 (0.36–4.55)	
*SULT1A1*1/*1*	59/46	1.60 (0.46–5.62)	<0.36
SULT1A1 activity			
Tertile 1 (0.49–0.65)[b]	5/21	1.0 (Reference)	
Tertile 2 (0.67–1.375)	34/21	6.7 (2.1–21.3)	
Tertile 3 (1.41–4.36)	35/22	9.6 (2.9–31.3)	<0.003
Meat consumption			
Tertile 1 (2.1–22.6)[b]	15/26	1.0 (Reference)	
Tertile 2 (22.9–55.5)	40/35	1.95 (0.87–4.39)	
Tertile 3 (56.2–423.9)	57/51	2.23 (1.02–4.86)	<0.04
Caucasians			
SULT1A1 genotype			
*SULT1A1*2/*2*	46/56	1.0 (Reference)	
*SULT1A1*1/*2*	149/145	1.18 (0.75–1.88)	
*SULT1A1*1/*1*	149/109	1.68 (1.05–2.68)	<0.02
SULT1A1 activity			
Tertile 1 (0.021–0.65)[b]	30/54	1.0 (Reference)	
Tertile 2 (0.66–1.37)	125/55	3.04 (1.8–5.1)	
Tertile 3 (1.38–5.03)	148/55	4.96 (3.0–8.3)	<0.0001
Meat consumption			
Tertile 1 (0.20–22.9)[b]	100/126	1.0 (Reference)	
Tertile 2 (23.2–55.8)	122/117	1.34 (0.92–1.94)	
Tertile 3 (56.1–474.7)	120/105	1.59 (1.08–2.32)	<0.02

[a] Adjusted for age in unconditional logistic regression models.
[b] Tertiles derived from distribution among controls with first tertile used as the reference group.

Table 5 Distribution of mean sulfotransferase activity by genotype and case status

	Mean activity[a]	Activity stratified by genotype			P^b
		*SULT1A1*1/*1*	*SULT1A1*1/*2*	*SULT1A1*2/*2*	
All controls	1.29	1.60 ± 1.04 (n = 93)	1.24 ± 0.87 (n = 89)	0.80 ± 0.47 (n = 28)	<0.0001
Caucasians	1.17	1.52 ± 1.04 (n = 59)	1.12 ± 0.78 (n = 67)	0.77 ± 0.49 (n = 24)	<0.0009
African-Americans	1.62[c]	1.73 ± 1.04 (n = 34)	1.57 ± 1.06 (n = 22)	0.99 ± 0.31 (n = 4)	<0.38
All cases	1.75	2.10 ± 1.27 (n = 177)	1.57 ± 0.87 (n = 168)	1.09 ± 0.47 (n = 44)	<0.00001
Caucasians	1.62	1.96 ± 1.24 (n = 135)	1.46 ± 0.78 (n = 134)	1.06 ± 0.43 (n = 41)	<0.00001
African-Americans	2.24[c]	2.53 ± 1.30 (n = 42)	2.0 ± 1.10 (n = 34)	1.42 ± 0.97 (n = 3)	<0.085
All study participants	1.58	1.93 ± 1.22 (n = 270)	1.45 ± 0.88 (n = 257)	0.98 ± 0.49 (n = 72)	<0.00001
Caucasians	1.47	1.83 ± 1.20 (n = 194)	1.35 ± 0.79 (n = 201)	0.96 ± 0.47 (n = 65)	<0.00001
African-Americans	1.97[c]	2.18 ± 1.25 (n = 76)	1.83 ± 1.10 (n = 56)	1.18 ± 0.65 (n = 7)	<0.046

[a] Activity in units of nmol/min/mg protein.
[b] One way ANOVA.
[c] Mean activity significantly higher than Caucasian controls (Student's t test of means $P < 0.001$).

ciation between genotype and phenotype when all of the cases are considered. However, this association is not significant in the African-American population. When the analysis was performed for all of the study subjects, the association between genotype and phenotype is evident for both African-Americans and Caucasians, although it is not as statistically robust as with the Caucasian population.

Discussion

In this study, we determined both genotype and phenotype for SULT1A1, and evaluated their contribution to prostate cancer risk. We found a significant association between *SULT1A1* genotype and prostate cancer risk in Caucasians but not in African-Americans. However, when SULT1A1 activity was examined in relation to prostate cancer risk, there was a clear association between high SULT1A1 activity and prostate cancer risk, including among African-Americans. There was also evidence that increased meat consumption is associated with prostate cancer risk.

Prostate cancer is characterized by substantial variations in incidence by ethnicity and geographical location. Chinese men have the lowest rates of prostate cancer in the world, whereas African-American men have the highest (37–39). The fact that immigrants to Westernized countries from countries with low incidence of certain cancers reach the rates of the indigenous population within approximately three generations indicates an environmental component to risk of disease (40). Diet, particularly consumption of meat and dietary fat, has been positively associated with prostate cancer risk (2, 4–6). Whereas meat is a source of dietary fat, cooking meat at high temperatures also generates a class of food-borne mutagens, the HCAs. The most mass-abundant HCA is PhIP, a compound that has been demonstrated to produce prostate tumors in rodents (9). Recent studies by Sinha *et al.* (41) demonstrated an association between PhIP exposure and breast cancer risk. Using a HCA database, the authors were able to estimate exposure to specific HCAs from food-frequency questionnaires, and demonstrated that PhIP was more strongly associated with breast cancer than intake of red meat alone. It has been suggested that breast and prostate cancer have similar etiologies, with dietary factors playing a key role in both (42). One study from New Zealand, however, did not find a clear association between HCA intake and prostate cancer risk, but did find a possible association between well-done beefsteak and the HCA, 2-amino-1,6-dimethylfuro[3,2-e]imidazo[4,5-6]pyridine, and risk of prostate cancer (43).

By themselves, HCAs are poor mutagens and must be metabolically activated to produce mutagenic/carcinogenic effects. Biotransformation of the HCA by cytochrome P4501A2 in the liver produces an *N*-hydroxy metabolite that can undergo additional metabolism by *N*-acetyltransferases or SULTs to generate electrophiles capable of binding to cellular nucleophiles, including DNA (11, 12, 44, 45). Studies by Kaderlik *et al.* (46) suggests that *N*-hydroxy-PhIP produced in the liver is stable enough to be carried via the circulation to target tissues such as prostate, where subsequent metabolism can generate DNA-binding species. Human prostate tissue has been shown to metabolically activate *N*-hydroxy-PhIP to DNA-binding species (47), and transplantation of human prostate into athymic mice followed by exposure to PhIP resulted in PhIP-DNA adducts in ~95% of samples (48). Whereas these studies examined the *N*-acetyltransferase pathway of HCA activation, heterologous expression of human *N*-acetyltransferase and SULT enzymes in *Salmonella typhimurium* and mutagenicity testing of HCAs suggested that *N*-OH-PhIP was activated specifically by SULT1A1 (13). *SULT1A1* transcript has been detected in human prostate (49); therefore, a role for SULT1A1 in PhIP-induced prostate carcinogenesis is biologically plausible. In the current study, we observed a modest association between increased consumption of meats reported to be high in HCA content and prostate cancer risk. Additionally, there was a significant trend of increased risk of prostate cancer when SULT1A1 activity was considered in the context of increased meat consumption.

It is possible that substances in meat other than HCAs are responsible for the observed increase in prostate cancer risk associated with meat consumption. It is also possible that, given the broad substrate specificity of SULT1A1, exposures other than HCAs impact risk of prostate cancer in relation to SULT1A1 phenotype. For example, SULT1A1 can metabolize chemopreventive agents such as curcumin, a pigment derived from turmeric and (−)-epicatechin, a flavonoid found in tea (50, 51). Rapid elimination of these substances via sulfation could negate their beneficial effects, and thus, influence cancer risk. Alternatively, sulfation of some substrates, such as steroids and some isoflavones, can prolong the circulating half-life of the molecule. It is possible that sulfation could be potentiating an unidentified molecule, leading to increased prostate

cancer risk. Recent studies have also identified 2-methoxyestradiol, an antiangiogenic metabolite of estradiol, as an endogenous substrate for SULT1A1 (52). More rapid sulfation and elimination of this endogenous molecule could potentially contribute to cancer risk. Regardless of the exact mechanism, this study shows that high SULT1A1 activity is positively correlated with prostate cancer risk.

In contrast with the present study, a report by Steiner *et al.* (31) found no association of *SULT1A1* genotype with prostate cancer risk. This difference is likely due to the size of the respective study populations. The study population from the current study consisted of 403 prostate cancer patients and 450 control individuals, whereas that of Steiner consisted of 134 patients and 184 control individuals, all of Caucasian origin. Although their results did not achieve statistical significance, Steiner also reported a lower frequency of the *SULT1A1*2/*2* genotype in prostate cancer patients compared with control individuals, which is consistent with the current study.

We also examined the relationship between SULT1A1 phenotype and prostate cancer risk using platelets as a source of enzyme. Studies have demonstrated that SULT1A1 appears to be coordinately regulated across tissues, in that high activity in one tissue correlates with high activity in other tissues, including platelets (53–56). For this reason, platelets have been used in human studies as a surrogate for SULT1A1 activity in other tissues. Whereas the correlation between platelet activity and activity found in prostate tissue has not been specifically tested, it is likely that, as with all of the other tissues tested, this correlation would be observed. Previous studies from our laboratory demonstrated that the *SULT1A1*1/SULT1A1*2* polymorphism accounted for only approximately 20–30% of the observed variation in platelet phenotype (35). Therefore, we also examined SULT1A1 phenotype in platelets isolated from study participants using an assay that has been validated as specific for SULT1A1 activity when platelets are used as the enzyme source (32). When control subjects were examined, we found no effect of potential confounders such as age, smoking, and BMI on SULT1A1 activity. However, there was a significant difference in phenotype between African-American and Caucasians, with African-Americans having higher enzymatic activity. This is consistent with earlier studies by Anderson *et al.* (57), who found significantly higher basal platelet SULT1A1 activity in African-Americans compared with Caucasians. When genotype-dependent SULT1A1 phenotype was examined, there was a significant correlation between *SULT1A1* genotype and SULT1A1 phenotype. When the analysis was stratified by race, however, the association between *SULT1A1* genotype and phenotype in Caucasians remained, whereas there was no significant correlation between *SULT1A1* genotype and phenotype in African-Americans. These findings could be due to lower numbers of African-American participants in the study, but could also suggest the existence of other modulators of SULT1A1 phenotype that is present in African-Americans but not Caucasians. An additional genetic polymorphism in SULT1A1 common in African-Americans, but rare in Caucasians, has been described (36). When this allele, designated *SULT1A1*3*, was examined in this study, no association was found with risk of prostate cancer in the African-American study subjects. Therefore, genetic factors other than *SULT1A1*3* may modulate SULT1A1 activity in African-Americans.

When SULT1A1 activity was examined in relation to prostate cancer risk, there was a significant association between increasing SULT1A1 activity and prostate cancer risk. This association remained when subjects were stratified by race, and the effect of SULT1A1 phenotype on prostate cancer risk was more pronounced in the African-American study population than in the Caucasians. This disparity could be due to differences in numbers of participants between the two groups and should be examined in a larger population of African-Americans. Nevertheless, this finding is intriguing, given that African-Americans are reported to have higher basal SULT1A1 activity than Caucasians and also have higher incidence of prostate cancer.

The results of this study support a role for SULT1A1 in the etiology of prostate cancer. Increased risk conferred by the genotype examined was modest compared with the effect of SULT1A1 phenotype. This suggests that other factors contribute to the variation in SULT1A1 activity.

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Association of SULT1A1 Phenotype and Genotype with Prostate Cancer Risk in African-Americans and Caucasians

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