The Relationship between a Polymorphism in *CYP17* with Plasma Hormone Levels and Prostate Cancer[1]

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Abstract

The *A2* allele of the *CYP17* gene has been thought to be associated with increased functional activity of this steroidogenic enzyme. Consequently, the *A2* allele has been examined as a biomarker of individual susceptibility to hormone-related diseases among men and women. We prospectively assessed the association between the *A2* allele of *CYP17* and prostate cancer risk among 590 cases and 782 controls in a case-control study nested within the Physicians' Health Study cohort. We also evaluated associations between *CYP17* genotype and plasma steroid hormones among controls and the potential interaction between *CYP17* and *SRD5A2* V89L polymorphisms in relationship with prostate cancer risk and circulating steroid hormone levels. We observed a borderline significant association between the *A2* allele and prostate cancer risk (odds ratio, 1.23; 95% confidence interval, 0.99–1.54), however, we did not observe evidence of a gene-dosage effect (*versus A1/A1* genotype: *A1/A2* genotype; odds ratio, 1.26; 95% confidence interval, 0.99–1.59; *A2/A2* genotype: odds ratio, 1.17; 95% confidence interval, 0.85–1.61). The *A2* allele was not overrepresented among cases with advanced prostate cancer. Among controls, carriers of the *A2* allele had steroid hormone levels similar to noncarriers. We also found no evidence of a gene-gene interaction between *CYP17* and *SRD5A2* V89L polymorphisms on prostate cancer risk or endogenous steroid hormone levels. These results suggest that *CYP17* genotype may possibly confer a small increased susceptibility to prostate cancer but is not a strong predictor of endogenous steroid hormone levels in men.

Introduction

Evidence from studies in both animals and humans support a role for androgens in prostate carcinogenesis (1, 2). Variation in lifetime exposure to endogenous androgens may underlie interindividual differences in prostate cancer risk and racial/ethnic differences in prostate cancer incidence. Polymorphisms in genes involved in androgen biosynthesis, transport, and metabolism (*SRD5A2*[3] and *CYP17*) and the activation of androgen-responsive genes in prostate cells (*androgen receptor* and *amplified in breast-1*) are reasonable candidates to evaluate as surrogate markers of altered long-term androgen exposure and biomarkers of prostate cancer susceptibility (Refs. 3–7 and reviewed in 8).

CYP17 encodes a cytochrome P450 enzyme (P450c17α) that is involved in the biosynthesis of androgens. A single-bp change (T-C) in the 5′-transcribed but untranslated region of *CYP17* has been positively associated with familial polycystic ovarian syndrome and male pattern baldness (9), disorders associated with excess androgen production. This bp substitution in *CYP17* was originally hypothesized to create an additional binding site for the transcription factor Sp-1, that may lead to increased transcription of the enzyme and enhanced steroid hormone production. However, in an *in-vitro* assay, Kristensen *et al.* (10) did not observe Sp-1 binding at this polymorphic site or within the promoter sequence of *CYP17*; whether other regulatory factors differentially bind to this polymorphic motif remains unknown. The *A2* allele (C nucleotide) of *CYP17* has been studied extensively in relation to hormonal-related cancers among men and women (Refs. 5, 6, 11–13 and reviewed in 14). Among healthy pre- and postmenopausal women, the *A2/A2 CYP17* genotype has been associated with modestly higher levels of circulating estrogens (12, 15). In a large study among Caucasian men (n = 621; Ref. 16), *CYP17* genotype was not associated with circulating androgen levels, whereas results from case-control studies evaluating *CYP17* genotype and prostate cancer risk have been contradictory. In a study among Caucasians from the United States (n = 96 cases and n = 159 controls), Lunn *et al.* (5) observed the *A2* allele to be overrepresented among prostate cancer cases (*A1/A2* and *A2/A2* genotypes: OR, 1.7; 95% CI: 1.0–3.1). In a smaller study (n = 63 cases and n = 126 controls with benign prostatic hyperplasia), Gsur *et al.* (17) observed a positive association limited to men with the *A2/A2* genotype (*versus A1/A1* genotype: OR, 2.80; 95% CI: 1.02–7.76). In contrast, in a study

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[3] The abbreviations used are: *CYP17*, *cytochrome P450c17α gene*; OR, odds ratio; CI, confidence interval; SRD5A2; 5-α reductase type II; AAG, 3α-androstanediol glucuronide; WHR, waist-to-hip ratio; DHT, dihydrotestosterone; SHBG, sex hormone-binding globulin.

comprised of Swedish Caucasians ($n = 178$ cases and $n = 160$ controls), Wadelius *et al.* (6) reported an increased risk with the *A1/A1* genotype (*versus A1/A2* and *A2/A2* genotypes: OR, 1.61; 95% CI; 1.02–2.53). A more recent study among Japanese in Japan ($n = 252$ cases and $n = 131$ controls) also reported men with the *A1/A1* genotype to have increased risk of prostate cancer (*versus A2/A2* genotype: OR, 2.57; 95% CI; 1.39–4.78; Ref. 18).

In the prostate, conversion of testosterone to the more active androgen, DHT, is catalyzed by SRD5A2. The V89L polymorphism (leucine allele) of *SRD5A2* has been associated with lower circulating AAG levels, a surrogate marker of SRD5A2 activity, among Asian and Caucasian men (4, 16, 19). Racial/ethnic differences in V89L allele frequencies have also been hypothesized to explain a proportion of racial/ethnic variation in prostate cancer incidence (19). In a previous study within the Physician's Health Study (4), no significant association was observed between the V89L alleles and prostate cancer risk. An additional study among Caucasians also does not support an association between this genetic variant and prostate cancer risk (5).

To evaluate further whether *CYP17* genotype is associated with prostate cancer risk among Caucasian men, we investigated the relationship in a large nested case-control study within the Physicians' Health Study. We also examined the relationship between *CYP17* genotype and endogenous plasma steroid hormone levels to assess the biological relevance of this polymorphism among men. We also studied the potential interaction between *CYP17* and *SRD5A2* V89L polymorphisms in relationship with prostate cancer risk as well as the combined influence of these genetic variants on circulating androgen levels.

Materials and Methods

Study Population. The source population for this study was the Physicians' Health Study cohort, initiated in 1982 as a randomized, double-blinded, placebo-controlled trial of aspirin and β-carotene among 22,071 healthy and predominantly Caucasian (93%) United States male physicians, aged 40–84 years. Men were excluded at baseline if they had a history of myocardial infarction, stroke, or transient ischemic attack, unstable angina, cancer (except nonmelanoma skin cancer), current renal or liver disease, peptic ulcer, gout, contraindications to the use of aspirin, current use of aspirin or other platelet-active agents, or current use of vitamin A or β-carotene supplements.

Study participants completed two mailed questionnaires before randomization, and additional questionnaires at 6 and 12 months and annually thereafter. WHRs were calculated from torso and hip measurements reported on the 1989 questionnaire. Men reported their hair balding pattern at age 45 on the 1991 questionnaire; there were five choices ranging from full hair to almost no hair. A blood specimen was collected from two-thirds of the men ($n = 14{,}916$) before randomization. Prostate cancer cases and matched controls were drawn from among the participants who supplied blood specimens. For men reporting prostate cancer diagnosis on the follow-up questionnaire, medical records and pathology reports were obtained and reviewed by study physicians to confirm the diagnosis and to determine stage at diagnosis (modified Whitmore-Jewett classification scheme; Ref. 20), tumor grade, and Gleason score. If pathological staging was not available, the case was considered to be of indeterminate stage unless metastasis was clinically evident. We categorized cases as high stage/grade if diagnosed at stages C or D and/or had a Gleason score of ≥ 7 or poor histological differentiation.

For each case, one or two controls were randomly selected from among the men who returned a blood specimen and who had not been diagnosed with prostate cancer by the date of case diagnosis. Cases and controls were matched on age, within 1 year ($\pm$ 2 years for elderly cases) and smoking status (current, former, or never) at baseline. The nested case-control study consists of 600 incident prostate cancer cases and 804 controls; 590 cases and 782 controls were successfully genotyped for *CYP17*. The study sample for the genotype-steroid hormone analysis is composed of 377 controls that were included in a previous study investigating the relationship between sex steroid hormones levels and prostate cancer risk in the Physicians' Health Study (2). The protocol was approved by the Institutional Review Board at Brigham and Women's Hospital, Boston, MA.

Laboratory Assays. *CYP17* genotyping analysis was performed by the Taqman allelic discrimination method (21) using the ABI 7700 Sequence Detection System (Applied Biosystems, Foster City, CA). This assay measures fluorescent intensity released from allele-specific fluorogenic probes and allows for high-throughput genotyping without post-PCR processing. A 97-bp fragment that included the T-C polymorphism was amplified in a 96-plate format using the following primers: 5′-AGGCCTCCTTGTGCCCTAGA-3′ and 5′-GAGCCACGAGCTCCCACAT-3′. The fluorescently labeled, allele-specific probes were: FAM-CTTCTACTCCAC***T***GCTGTCTTGCCTG-TAMRA and VIC-CTTCTACTCCAC***C***GCTGTCTTGCCT-TAMRA. Primers and probes were designed using Primer Express software (Applied Biosystems). Genomic DNA was used (40 ng) per 25 μl reaction, with 900 nM of each primer, 100 nM of the FAM probe, 200 nM of the VIC probe, and 1× Taqman Universal PCR Master Mix (Applied Biosystems). Amplification conditions were 2 min at 50°C, 10 min at 95°C, and 40 cycles of 15 s at 95°C and 1 min at 63.5°C. The *Msp*AI restriction enzyme was used to identify homozygous (*CC* and *TT*) controls required for this genotyping assay. Sequence Detection System software (Applied Biosystems) was used to determine *CYP17* genotype, and all genotyping was performed by laboratory personnel unaware of case-control status. To assess genotyping reproducibility, a random 10% selection of the case-control sample was regenotyped; all genotypes matched initial designated genotypes. The genotyping methods for the V89L polymorphism of *SRD5A2* have been previously described (4).

Plasma steroid hormone fractions of estradiol, testosterone, SHBG, DHT, and AAG were measured as previously described (2). Intra-assay coefficients of variation for each hormone fraction were $< 9\%$.

Statistical Analysis. The χ^2 test was used to compare allele and genotype frequencies between cases and controls. ORs and 95% CIs were calculated using unconditional logistic regression controlling for the matching variables at baseline: age (5-year intervals) and smoking status (never, former, and current). Indicator variables for all three genotypes were created using the *A1/A1* genotype as the reference category in the multivariate models. Because a gene-dosage effect on prostate cancer risk was not apparent, genotype was also evaluated as a dichotomous variable with *A1/A2* and *A2/A2* subjects combined. We used linear regression to evaluate the potential relationships between the physiological conditions, male pattern baldness, and WHR, which have been associated with abnormal circulating androgen levels, by calculating age-adjusted least-

squared means for each genotype. We also performed case-only analyses to evaluate associations between *CYP17* genotype and stage/grade of prostate cancer among all cases and in strata of age (dichotomized at the median age at blood draw: ≤ 61 years and > 61 years). The combined effect of *CYP17* and *SRD5A2* V89L genotypes on prostate cancer risk was evaluated with the *CYP17, A1/A1,* and *SRD5A2, V/V* group serving as the reference category. The interaction between *CYP17* and *SRD5A2* genotypes was evaluated by including the gene-gene interaction term into the unconditional multivariate logistic regression models. The Wald test was used to assess the statistical significance of the interaction.

Linear regression models were used to evaluate associations between *CYP17* genotype and circulating steroid hormone levels among controls, controlling for the matching variables. Least-squared geometric mean hormone levels were estimated, and differences in hormone levels between genotypes were evaluated with the *A1/A1* group as the reference category. We adjusted for SHBG levels in analyses evaluating the association between *CYP17* genotype and testosterone levels, because we have previously observed that plasma testosterone adjusted for SHBG is a stronger predictor of prostate cancer risk than total testosterone levels (2). The natural logarithm of the plasma hormone values were used in the analysis to reduce the skewness of the regression residuals. Hormone values >3 interquartile ranges from the 75th percentile were treated as outliers and were excluded (estradiol, $n = 1$; testosterone, $n = 1$; DHT, $n = 2$; AAG, $n = 1$). We also evaluated associations between the combination of *CYP17* and *SRD5A2* V89L genotypes and plasma androgen levels with the *A1/A1, V/V* group as the reference category. The interaction between the *CYP17-SRD5A2* genotypes was assessed by including the gene-gene interaction term in the linear regression models. We used the SAS statistical package for all analyses (SAS Institute, Inc., Cary, NC).

Results

The distributions of *CYP17* genotypes were in accordance with Hardy-Weinberg equilibrium among both cases ($\chi^2 = 0.83$; *df*, 1; $P = 0.36$) and controls ($\chi^2 = 2.62$; *df*, 1; $P = 0.11$). Among controls, the frequency of the *A2* allele was similar to that reported among Caucasians (5, 6, 13). The *A2* allele was not significantly overrepresented among cases (cases, 41% *versus* controls, 39%; $P = 0.17$). There was also no significant difference in genotype frequencies between cases and controls ($\chi^2 = 3.49$; *df*, 2; $P = 0.18$). Compared with the *A1/A1* genotype, the adjusted ORs for *A1/A2* and *A2/A2* genotypes were 1.26 (95% CI, 0.99–1.59) and 1.17 (95% CI, 0.85–1.61), respectively (Table 1). The adjusted OR for men with at least one *A2* allele was 1.23 (95% CI, 0.99–1.54). Results did not change when excluding nonwhite racial/ethnic groups (~5% of cases and controls).

Compared with controls, the *A2* allele was not overrepresented among prostate cancer cases with high stage/grade disease (42% *versus* 39%; $P = 0.14$). In case-only analyses, the *A2* allele was not associated with stage/grade of disease (high stage/grade, 42% *versus* low stage/grade, 40%; $P = 0.43$). We also observed no material difference in genotype frequencies between high and low stage/grade disease ($\chi^2 = 1.69$; *df*, 2; $P = 0.43$). In case-only analyses, the frequency of the *A2* allele was similar among men with high and low stage/grade disease in both older (>61 years: 40% *versus* 40%; $P = 0.97$) and younger cases (≤ 61 years: 44% *versus* 40%; $P = 0.32$).

Table 1 *CYP17* Genotype and prostate cancer risk in the Physicians' Health Study

CYP17 genotype	Cases *n* (%)	Controls *n* (%)	OR (95% CI)[a]
A1/A1	202 (34)	305 (39)	1.00
A1/A2	290 (49)	350 (45)	1.26 (0.99–1.59)
A2/A2	98 (17)	127 (16)	1.17 (0.85–1.61)
A1/A2+A2/A2	388 (66)	477 (61)	1.23 (0.99–1.54)

[a] Unconditional logistic regression adjusted for age and smoking status. *A1/A1* is the reference genotype.

We also evaluated associations between *CYP17* genotype and phenotypes associated with an abnormal hormonal milieu. Among controls, WHRs were nonsignificantly elevated among men with the *A2/A2* genotype [*A1/A1* genotype (reference; $n = 269$), WHR (mean) = 0.94, *A1/A2* ($n = 319$), WHR = 0.94, $P = 0.94$; *A2/A2* ($n = 109$), WHR = 0.95, $P = 0.16$]. Similar associations were observed among cases and when cases and controls were analyzed together [cases and controls: *A1/A1* genotype (reference; $n = 447$), WHR = 0.94; *A1/A2* ($n = 563$), WHR = 0.95, $P = 0.64$; *A2/A2* ($n = 192$), WHR = 0.96, $P = 0.02$]. We also evaluated the association between *CYP17* genotype and hair balding patterns. No correlation was observed between the *A2* allele or *A2/A2* genotype and baldness pattern among young (≤ 61 years) or old men (>61; data not shown).

In *CYP17* genotype-plasma steroid hormone analyses, we calculated least-squared geometric mean hormone levels among controls for each genotype (Table 2). Compared with *A1* homozygotes, carriers of one or more *A2* alleles did not have significantly elevated levels of any hormone fraction.

We next examined the interaction between *CYP17* and *SRD5A2* V89L polymorphisms and prostate cancer risk. An earlier study within this cohort found no significant relationship between the SRD5A2 V89L polymorphism and prostate cancer risk (4). In the present study, compared with men homozygous at both loci (*A1/A1* and *V/V* genotypes), we did not observe consistent associations between carriers of additional hypothesized high- or low-risk *CYP17* or *SRD5A2* V89L alleles and risk of prostate cancer (Table 3). We did observe a borderline significant association among men with the *A1/A2* and *V/V* genotypes (OR, 1.68; 95% CI, 1.20–2.35) and a significant trend for the V89L genotype limited to men with the *A1/A2* genotype ($P = 0.04$); however, the overall test for interaction between these polymorphisms was not statistically significant ($P = 0.60$).

In analyses of the relationship between *CYP17* and *SRD5A2* genotypes and steroid hormone levels among controls, we calculated geometric mean plasma androgen levels for each genotype combination. Compared with men homozygous for both the *A1* and *V* alleles, men with other genotype combinations did not have significantly increased or decreased mean levels of testosterone or AAG (Table 4). We did observe nonsignificant trends for elevated testosterone levels across *SRD5A2* genotypes within strata of *CYP17* genotype, however, absolute levels did not depend on *CYP17* genotype. The overall test for this interaction was nonsignificant ($P = 0.46$). For AAG, a trend was observed for decreasing levels across *SRD5A2* genotypes among men with *A1/A1* and *A1/A2* genotypes; this test for interaction was also not significant ($P = 0.82$).

Discussion

In this prospective case-control study among Caucasian men, we observed a borderline significant association between car-

Table 2 Least-squared geometric mean hormone levels[a] among controls by *CYP17* genotype[b]

Hormone	*CYP17* genotype (*n*)			*P* trend
	A1/A1 (138)	*A1/A2* (175)	*A2/A2* (64)	
Estradiol (pg/ml), 95% CI	33.8	32.4 (30.7, 34.2)	33.7 (30.8, 36.8)	
P		0.30	0.94	0.72
Testosterone (ng/ml)[c], 95% CI	4.5	4.5 (4.2, 4.7)	4.8 (4.4, 5.2)	
P		0.83	0.24	0.35
AAG (ng/ml), 95% CI	6.3	6.2 (5.7, 6.6)	6.5 (5.8, 7.4)	
P		0.71	0.58	0.71
DHT (ng/ml), 95% CI	0.34	0.34 (0.31, 0.36)	0.35 (0.31, 0.40)	
P		0.72	0.82	0.93

[a] Adjusted for age and smoking status at baseline.
[b] *A1/A1* genotype is the reference for all comparisons.
[c] Also adjusted for SHBG.

Table 3 The combination of *CYP17* and *SRD5A2* V89L polymorphisms and prostate cancer risk

CYP17 genotype	*SRD5A2* V89L genotype			*P* trend
	V/V	*V/L*	*L/L*	
A1/A1				
OR[a]	1.00	1.33	0.90	0.57
95% CI	(Ref.)	(0.91–1.93)	(0.45–1.82)	
n[b]	94/160	93/119	14/26	
A1/A2				
OR	1.68	1.19	1.10	0.04
95% CI	(1.20–2.35)	(0.83–1.71)	(0.63–1.92)	
n	158/161	102/145	26/40	
A2/A2				
OR	1.27	1.28	1.91	0.61
95% CI	(0.81–2.00)	(0.79–2.06)	(0.71–5.12)	
n	47/63	41/55	9/8	
P trend	0.07	0.83	0.28	*P* interaction, 0.60

[a] Adjusted for age and smoking status.
[b] Number of cases/controls.

riage of the *CYP17 A2* allele and prostate cancer risk. However, we did not observe a gene-dosage effect; the borderline positive association was stronger in those heterozygous for the *A2* allele. We did not find the *A2* allele to be overrepresented among men with aggressive prostate cancer regardless of age at diagnosis. In addition, we did not detect mean steroid hormone levels to be significantly elevated among carriers of the *A2* allele or evidence of a gene-gene interaction between *CYP17* and *SRD5A2* V89L polymorphisms on prostate cancer risk or endogenous steroid hormone levels.

A positive association first reported by Carey *et al.* (9) between the *A2* allele of *CYP17* and hyperandrogenic diseases, polycystic ovarian syndrome, and male pattern baldness, led to the selection of *CYP17* as a candidate gene for study in relation to hormonal-related cancers. We and others have provided preliminary results to support the proposed hypothesis that this genetic variant may have a modest effect on estrogen biosynthesis among women (12, 15). However, data from multiple studies suggests that this polymorphism in *CYP17* does not independently predict increased risks of breast cancer or advanced breast cancer among Caucasian postmenopausal women (13, 14).

This *CYP17* polymorphism has also been evaluated among men as a marker of lifetime steroid hormone exposure and cancer risk. Among Caucasian men of Scottish ancestry, the *A2* allele was positively associated with increased risk of male breast cancer (*A2* allele: OR, 2.10; 95% CI, 1.04–4.27; Ref. 22). However, results have been inconsistent in the published studies that have examined the association between *CYP17* genotype and prostate cancer risk. In a North Carolinian Caucasian population, Lunn *et al.* (5) observed a borderline significant association between the *A1/A2* genotype and prostate cancer risk (*versus A1/A1*: *A1/A2*; OR, 1.7; 95% CI, 1.0–3.2; *A2/A2*; OR, 1.7; 95% CI, 0.7–4.2). In a smaller study, Gsur *et al.* (17) also reported increased risk for Caucasian men homozygous for the *A2* allele. In contrast, among Japanese men ($n = 252$ cases and $n = 131$ controls), Habuchi *et al.* (18) observed men with the *A1/A1* genotype to have increased risk of prostate cancer (*versus A2/A2* genotype: OR, 2.57; 95% CI, 1.39–4.78) and benign prostatic hyperplasia (OR, 2.44; 95% CI, 1.26–4.72). Similarly, in a Swedish study, (cases, $n = 178$; controls, $n = 160$), Wadelius *et al.* (6) also reported a significant elevation in risk for the *A1/A1* genotype (*versus A2* carriers: OR, 1.61; 95% CI, 1.02–2.53). Our findings among Caucasians in the United States are more similar to those of Lunn *et al.* (5), as we also observed a marginally significant relation between carrying the *A2* allele and prostate cancer risk, and a significant positive association for men with the *A1/A2* genotype. The opposing findings of the previous studies may be attributable to inaccurate genotype frequency estimates resulting from small sample sizes (all studies have less than ~250 cases and ~160 controls). Linkage disequilibrium between the *A1* and *A2* alleles of *CYP17* with different functionally relevant polymorphisms in specific ethnic groups may explain the contradictory findings observed in studies conducted in different white or nonwhite ethnic populations.

Table 4 Least-squared geometric mean hormone levels by *CYP17* and *SRD5A2* V89L genotypes among controls

Testosterone, pg/mL (95% CI)[a]				
CYP17 genotype	*SRD5A2* V89L genotype			*P* trend
	V/V	*V/L*	*L/L*	
A1/A1	4.3 (Ref.)	4.6 (4.1, 5.0)	5.4 (4.4, 6.6)	0.23
n,[b] *P*[c]	74	53, 0.46	11, 0.06	
A1/A2	4.3 (4.0, 4.7)	4.5 (4.1, 4.8)	4.8 (4.2, 5.5)	0.19
n, P	73, 0.91	77, 0.61	24, 0.24	
A2/A2	4.7 (4.2, 5.3)	4.8 (4.2, 5.5)	5.0 (3.4, 7.4)	0.67
n, P	32, 0.24	28, 0.18	3, 0.51	
P trend	0.32	0.64	0.07	*P* interaction, 0.46
AAG, pg/mL (95% CI)[d]				
CYP17 genotype	*SRD5A2* V89L genotype			*P* trend
	V/V	*V/L*	*L/L*	
A1/A1	6.6 (Ref.)	5.9 (5.2, 6.8)	6.1 (4.5, 8.1)	0.11
n,[b] *P*[c]	74	53, 0.23	11, 0.60	
A1/A2	6.4 (5.7, 7.1)	6.1 (5.4, 6.8)	5.7 (4.7, 6.9)	0.21
n, P	73, 0.70	77, 0.29	24, 0.19	
A2/A2	6.9 (5.8, 8.2)	6.0 (5.0, 7.2)	8.4 (4.8, 14.6)	0.38
n, P	32, 0.67	28, 0.41	3, 0.41	
P trend	0.85	0.77	0.93	*P* interaction, 0.82

[a] Adjusted for age, smoking and SHBG.
[b] Number of controls.
[c] *P* value.
[d] Adjusted for age and smoking.

In a large study of the relationship between *CYP17* genotype and circulating steroid hormone levels among men (n = 621), Allen *et al.* (16) did not observe an association between the *A2* allele and endogenous androgen levels. Our results support the previous observation that men with the *A2* allele do not have substantially higher circulating androgen levels. Furthermore, we also did not observe a combined influence of *CYP17* and *SRD5A2* V89L polymorphisms on AAG or testosterone levels or an interaction between these loci on prostate cancer risk.

The relatively low prevalence of the variant alleles (*A2* and *L*), and a moderate sample size limited our ability to thoroughly evaluate differences in mean hormone levels and relative risks for all *CYP17* and *SRD5A2* V89L genotype combinations. In the future, larger studies will be needed to examine gene-gene interactions and to detect a significant positive association with the *A2/A2* genotype, if a weak relation exists. In this relatively large, prospective case-control study among Caucasian men, we observed evidence suggesting a possible weak association between the *A2* allele of *CYP17* and prostate cancer risk. However, our data does not suggest a role for *CYP17* genotype as a modifier of androgen metabolism in men.

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