A Polymorphism in the *CYP17* Gene and Risk of Prostate Cancer[1]

Janet L. Stanford,[2] Elizabeth A. Noonan, Lori Iwasaki, Suzanne Kolb, Robert B. Chadwick, Ziding Feng, and Elaine A. Ostrander

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle 98109 [J. L. S., E. A. N., L. I., S. K., Z. F.]; Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle 98195 [J. L. S.]; Thetagen Division, New Chemical Entities, Inc., Bothell 98011 [R. B. C.]; and Divisions of Clinical Research and Human Biology, Fred Hutchinson Cancer Research Center, Seattle 98109 [E. A. O.] Washington

Abstract

Steroid hormones are important in the etiology and progression of prostate cancer, and expression of genes involved in hormone production may alter susceptibility. One such gene is *CYP17*, which encodes the cytochrome P450c17*a* enzyme responsible for the biosynthesis of testosterone. A T to C transition (A2 allele) in the 5′ promoter region of the gene is hypothesized to increase the rate of gene transcription, increase androgen production, and thereby increase risk of prostate cancer. To test this hypothesis, germ-line DNA samples from a large population-based study of incident prostate cancer cases ($n = 590$) and controls ($n = 538$) of similar age without the disease were genotyped.

The frequency of the A2 allele was similar in cases and controls. Compared with men with the A1/A1 genotype, the adjusted odds ratio was 0.81 for the A1/A2 and 0.87 for the A2/A2 genotype. Risk estimates did not vary substantially by age or race. However, stratification by family history of prostate cancer revealed that among white men with an affected first-degree relative, homozygotes for the A2 allele had a significant elevation in risk (odds ratio = 19.2; 95% confidence interval, 2.2–157.4) compared with men who were homozygous for the A1 allele (interaction $P = 0.0005$). These results suggest that the *CYP17* A2/A2 genotype predicts susceptibility to prostate cancer in white men with a family history of the disease. It is also possible that *CYP17* interacts with other genes that influence risk of familial prostate cancer.

Introduction

Prostate cancer is the most frequently diagnosed cancer among American men, with 1 in 6 (16%) men expected to incur a clinical diagnosis of the disease during their lifetime (1). Despite the morbidity and mortality associated with this cancer, the underlying genetic and environmental factors responsible for the development and progression of prostate cancer are unclear.

Steroid hormones are suspected to play a role in the growth of prostate cancer, and expression of genes regulating hormone levels may thereby affect disease risk. One such gene is *CYP17*, which encodes the cytochrome P450c17*a* enzyme that is involved in key steps of androgen production. The *CYP17* gene is located on chromosome 10q24.3 (2), and some individuals have a T to C substitution in the 5′ promoter region (3). The less common A2 allele creates an additional Sp1-type (CCACC box) promoter site (3) that is hypothesized to increase transcription of the gene (4, 5) and, thus, lead to higher androgen levels.

Several studies have examined the potential role of sequence variation in the *CYP17* gene in relation to prostate cancer incidence, but results have not been consistent. Two studies reported elevated risk estimates (ORs[3], 1.6 and 2.6) for prostate cancer associated with the A1/A1 genotype among men in Sweden (6) and Japan (7). However, other investigators found increased risk estimates of borderline statistical significance ranging from 1.7 to 2.8 associated with the A2/A2 genotype among United States (8), Austrian (9), and Japanese men (10). The largest study reported to date, which was based on data from the United States Physicians' Health Study cohort, found no association with the A2/A2 genotype (11). These discrepant results may reflect the limited sample size included in some studies or the use of selected hospital-based (7, 10) or urology clinic-based (8, 9) subjects; several studies used men with benign prostatic hyperplasia as a comparison group (8–10). Furthermore, the allele frequencies among control groups differed across studies. For example, the two studies from Japan reported that 28% (7) and 14.5% (10) of controls were homozygous for the A2 allele.

Given the importance of *CYP17* in androgen production and the conflicting epidemiological data on the *CYP17* polymorphism as a risk factor for prostate cancer, we completed a population-based study of the association between the *CYP17* genotype and prostate cancer risk.

Materials and Methods

Study Population. Subjects from King County, Washington were participants in a population-based case-control study of risk factors for prostate cancer in middle-aged men described previously (12). Briefly, white and black prostate cancer cases aged 40–64 years who were diagnosed with histologically confirmed prostate cancer during 1993–1996 were identified through the Seattle-Puget Sound Surveillance, Epidemiology, and End Results cancer registry. All of the men <60 years of

Received 7/20/01; revised 11/28/01; accepted 1/3/02.
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[1] Supported by NIH Grants RO1 CA82664 (to J. L. S.) and RO1 CA56678 (to J. L. S.).
[2] To whom requests for reprints should be addressed, at Division of Public Health Sciences Fred Hutchinson Cancer Research Center 1100 Fairview Avenue, North, MW-814 Seattle, WA 98109-1024. Phone: (206) 667-2715; Fax: (206) 667-2717; E-mail: jstanfor@fhcrc.org.

[3] The abbreviations used are: OR, odds ratio; BMI, body mass index; CI, confidence interval; DRE, digital rectal exam; PSA, prostate-specific antigen.

age and a 75% random sample of men ages 60–64 were invited to participate. Of the 753 patients interviewed for the study, 590 (78%) provided a blood sample yielding sufficient DNA for genotyping. Population controls of similar age (frequency matched on 5-year age group) were ascertained from King County through random digit telephone dialing (13). A total of 703 men without a history of prostate cancer were interviewed, and a blood sample for genotyping was available from 538 (77%). There were no differences between interviewed and genotyped in regard to age, race, family history of prostate cancer, indices of body size, income, education in cases or controls, or clinical characteristics of the cases.

Risk factor information was collected via in-person interviews and included medical history, prostate cancer screening history, family cancer history, lifestyle factors (smoking, alcohol use, and dietary intake), indices of body size (height, weight, and BMI), and demographic factors. After the interview, subjects were asked to provide a blood sample, which was drawn into liquid EDTA tubes and processed within 4–6 h. Aliquots of buffy coat were stored at −70°C. All of the forms and procedures were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Genotyping. Genomic DNA was purified from peripheral WBCs using a standard proteinase K digestion followed by phenol-chloroform extraction (14). DNA aliquot batches containing samples from both cases and controls were delivered to the laboratory for genotyping. Laboratory personnel were blinded as to the case-control status of samples.

The polymorphic site in the *CYP17* gene was amplified by using the following primer sequences: *CYP17* forward primer 5′-GGCCTCCTTGTGCCCTAGAGT-3′; *CYP17* reverse primer 5′-CCACGAGCTCCCACATGGT-3′; *CYP17* wild-type TaqMan probe VIC-CTACTCCACTGCTGTCTATCTTGCCTGCC-6-carboxytetramethylrhodamine; and *CYP17* mutant TaqMan probe 6FAM-CTACTCCACCGCTGTCTATCTTGCCTGC-6-carboxytetramethylrhodamine. The PCR reaction contained: 12.5 μl of 2 × Universal Master Mix, 900 nM of each PCR primer, 100 nM of wild-type TaqMan probe, 100 nM of mutant TaqMan probe, and 40 ng of genomic DNA. Temperature cycling was at 50°C for 2 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15 s then 66°C for 1 min.

The data were collected and automatically analyzed with the ABI Prism 7700 Sequence Detection System version 1.6.5. The genotyping reactions discriminated four groups of data points, which were classified into three genotypes and negative controls. TaqMan genotyping calls were confirmed by sequencing several samples of each allele. Quality control also involved genotyping 40 paired samples as blind duplicates, which were distributed across all of the genotyping batches. There was 100% agreement of *CYP17* genotype in the blind duplicate samples. Genotyping was performed by New Chemical Entities, Inc. (Bothell, WA), a research and genetic services company.

Statistical Methods. Unconditional logistic regression was used to compute ORs and 95% CIs for the risk of prostate cancer associated with *CYP17* genotype (15). Polychotomous logistic regression (16) was used to evaluate the association between clinical variables (stage of prostate cancer at diagnosis and tumor grade) and *CYP17* genotype. The statistical significance of possible gene-environment interaction was evaluated on a multiplicative scale by adding an interaction term to the model containing the main effect variables.

Established and suspected prostate cancer risk factors were examined for potential confounding effects on the *CYP17*-prostate cancer association, including age at reference date (age at diagnosis in cases, similar assigned age in controls), race, family history of prostate cancer in first-degree relatives, marital status, income, education, smoking history, alcohol consumption, history of benign prostatic hyperplasia, screening for prostate cancer (DRE or PSA blood test), dietary intake (total vegetables, cruciferous vegetables, total fat, and percentage of calories from fat, adjusted for total calories), recent physical activity (frequency per week of vigorous physical activity lasting at least 20 min in the year before reference date), and body size (height, weight, and BMI). These variables were added one at a time to a model containing *CYP17* genotype and age to assess confounding. Final models are adjusted for age (continuous), race (in models including both whites and blacks), and first-degree family history of prostate cancer.

Results

Characteristics of cases and controls, and associated risk estimates were examined to identify factors that might confound the *CYP17*-prostate cancer association (Table 1). Elevated ORs for prostate cancer were observed in African Americans (OR, 1.85), men with a first-degree family history of prostate cancer (OR, 1.94), men with a history of BPH diagnosed within 2 years of reference date (OR, 2.14), and men who reported screening for prostate cancer with PSA and DRE a year or more before reference date (OR, 3.12).

The genotype distribution of *CYP17* was examined in cases and controls (Table 2), and was found to be in Hardy-Weinberg equilibrium. The *CYP17* polymorphism was not associated with risk for prostate cancer overall, or specifically among white or black men (Table 2). Given the small number of African Americans and the racial differences in *CYP17* allele frequencies and risk of prostate cancer, subsequent analyses were limited to white cases and controls. Analyses of genotype by race (interaction $P = 0.56$) or by age (interaction $P = 0.84$) revealed no significant evidence that risk of prostate cancer associated with genotype varied according to these factors (data not shown). Furthermore, among prostate cancer cases, the genotype was not associated with mean age at diagnosis.

Several associations between *CYP17* genotype and risk for prostate cancer among whites were observed in defined subgroups (Table 3). Evidence of significant interaction was observed between genotype and family history of prostate cancer ($P = 0.0005$) and genotype and BMI ($P = 0.048$). Men with a first-degree relative with prostate cancer who were homozygous for the A2 allele (21 cases, 1 control) had a significantly increased risk for prostate cancer (OR, 19.2; 95% CI, 2.23–157.4) compared with men without a family history who were homozygous for the A1 allele. Among men in the highest category of BMI (≥ 30), the A2/A2 genotype was associated with a modest elevation in risk (OR, 3.54; 95% CI, 0.99–12.6) relative to the A1/A1 genotype. Clinical features of prostate cancer (stage of disease, tumor grade, and combined stage and grade indicator of tumor aggressiveness) were not associated with *CYP17* genotype. For example, compared with men homozygous for the A1 allele, the OR for A2/A2 homozygotes with less aggressive disease (localized stage and Gleason score 2–7) was 0.77 (95% CI, 0.5–1.2) and for aggressive disease (regional or distant stage or Gleason score 8–10) was 1.09 (95% CI, 0.7–1.8).

Discussion

Several previous case-control studies have examined the relationship between polymorphism in the *CYP17* promoter region

Table 1 Selected characteristics of study subjects and ORs and 95% CIs for prostate cancer

Characteristic	No. cases (%) (n = 590)	No. controls (%) (n = 538)	OR[a] (95% CI)
Age, years			
40–49	38 (6.4)	48 (8.9)	
50–54	123 (20.8)	106 (19.7)	
55–59	198 (33.6)	199 (37.0)	
60–64	231 (39.2)	185 (34.4)	
Race			
Caucasian	560 (94.9)	523 (97.2)	1.00
African-American	30 (5.1)	15 (2.8)	1.85 (0.98–3.48)
Education			
High school or less	117 (19.8)	101 (18.8)	1.00
Some college	166 (28.1)	148 (27.5)	0.99 (0.70–1.41)
BA/BS degree	160 (27.1)	152 (28.3)	0.93 (0.66–1.32)
Graduate school	147 (24.9)	137 (25.5)	0.94 (0.66–1.34)
First-degree family history of prostate cancer			
No	480 (81.4)	481 (89.4)	1.00
Yes	110 (18.6)	57 (10.6)	1.94 (1.37–2.74)
BMI			
18–23	147 (24.9)	113 (21.0)	1.00
24–26	225 (38.1)	194 (36.1)	0.89 (0.65–1.21)
27–29	125 (21.2)	140 (26.0)	0.68 (0.48–0.96)
≥30	93 (15.8)	91 (16.9)	0.79 (0.54–1.15)
Physical activity, times per week			
None	104 (17.6)	77 (14.3)	1.00
≤1	135 (22.9)	154 (28.6)	0.67 (0.46–0.97)
2–3	198 (33.6)	180 (33.5)	0.84 (0.59–1.20)
≥4	153 (25.9)	127 (23.6)	0.90 (0.61–1.31)
History of BPH[b]			
No	393 (66.6)	442 (82.2)	1.00
Yes, ≤2 years ago	70 (11.9)	26 (4.8)	2.14 (1.30–3.51)
Yes, 3–4 years ago	63 (10.7)	33 (6.1)	1.34 (0.83–2.18)
Yes, ≥5 years ago	64 (10.9)	37 (6.9)	1.22 (0.77–1.95)
Smoking habits			
Never	214 (36.3)	205 (38.1)	1.00
Former	275 (46.6)	249 (46.3)	1.04 (0.80–1.34)
Current	101 (17.1)	84 (15.6)	1.16 (0.82–1.64)
Number of alcohol drinks per week[c]			
Nondrinker	52 (8.8)	60 (11.2)	1.00
≤3	132 (22.4)	118 (21.9)	1.32 (0.84–2.06)
4–13	252 (42.7)	235 (43.7)	1.28 (0.84–1.93)
≥14	154 (26.1)	125 (23.2)	1.45 (0.94–2.26)
Prostate cancer screening history[d]			
Never	23 (3.9)	32 (5.9)	1.00
DRE only	138 (23.4)	317 (58.9)	0.60 (0.34–1.07)
PSA and DRE	429 (72.7)	189 (35.1)	3.12 (1.76–5.54)

[a] Adjusted for age.
[b] Benign prostatic hyperplasia diagnosed at specified time periods before reference date, adjusted for age and frequency of serum PSA blood test within the 5-year period before reference date.
[c] Lifetime alcohol intake from age 15 to reference date.
[d] Digital rectal exam or serum PSA test 1 or more years before reference date.

Table 2 Adjusted ORs and 95% CIs for prostate cancer by *CYP17* genotype stratified by race

Genotype	No. cases (%)	No. controls (%)	OR (95% CI)
All subjects			
A1/A1	238 (40.3)	194 (36.1)	1.00[a]
A1/A2	266 (45.1)	263 (48.9)	0.81 (0.63–1.05)
A2/A2	86 (14.6)	81 (15.1)	0.87 (0.61–1.26)
Caucasians			
A1/A1	228 (40.7)	188 (35.9)	1.00[b]
A1/A2	248 (44.3)	256 (48.9)	0.80 (0.61–1.04)
A2/A2	84 (15.0)	79 (15.1)	0.88 (0.61–1.27)
African-Americans			
A1/A1	10 (33.3)	6 (40.0)	1.00[b]
A1/A2	18 (60.0)	7 (46.7)	1.41 (0.35–5.68)
A2/A2	2 (6.7)	2 (13.3)	0.63 (0.06–6.56)

[a] Adjusted for age, race, and first-degree family history of prostate cancer.
[b] Adjusted for age and first-degree family history of prostate cancer.

and prostate cancer risk. Four investigations found borderline significant increases in the relative risk of prostate cancer associated with the hypothesized high-risk A2 allele (A1/A2 or A2/A2 genotype; Refs. 8–11), although two studies observed elevated risk estimates in men with the A1/A1 genotype (6, 7). We found no overall association between *CYP17* genotype and prostate cancer, but stratified analyses revealed several subgroups in which men with the A2/A2 genotype experienced a higher risk. Aside from age, earlier studies did not consider other hormonally related risk factors that may modify the *CYP17* polymorphism-prostate cancer association.

In a Swedish study (6) of hospital-based prostate cancer patients and population controls, men with the *CYP17* A1/A1 genotype had an elevation in prostate cancer risk (OR, 1.6; 95% CI, 1.0–2.5). A second hospital-based study conducted in Japan also found that A1/A1 homozygous men had a risk of 2.6 (95% CI, 1.4–4.8) relative to those with the A2/A2 genotype (7). These authors suggested that carriers of the A1 allele had an increased risk of prostate cancer (6, 7) and referenced an earlier small study demonstrating that men with the A1/A1 genotype had higher circulating levels of androstanediol glucuronide, a byproduct of androgen metabolism (17).

However, contradictory findings have been reported from other investigations. Lunn *et al.* (8), in a urology clinic-based case-control study of predominantly white men, found that carriers of the A2 allele (A1/A2 or A2/A2 genotype) had an increased risk for prostate cancer (OR, 1.7; 95% CI, 1.0–3.0). Interestingly, the association with the A2 allele was strongest for men diagnosed at an earlier age (OR, 2.3; 95% CI, 1.0–5.4 for men ≤ 64 years). A subsequent study from Austria (9) also found an increased risk estimate of 2.8 (95% CI, 1.0–77.8) in men with the A2/A2 genotype, with the highest risk noted among men aged 66 and older (OR, 8.9; 95% CI, 1.8–49.2). Another study from Japan (10) reported an OR of 2.4 (95% CI, 1.04–5.46) in men homozygous for the A2 allele compared with those with the A1/A1 genotype. The largest study reported to date was from the United States Physicians' Health Study cohort and included 590 prostate cancer cases and 782 controls (11). This study found a borderline significant association between the A2 allele (A1/A2 or A2/A2 genotypes) and prostate cancer risk (OR, 1.2; 95% CI, 0.99–1.5). These four studies provide some evidence that the A2 allele may be associated with an elevated risk of prostate cancer.

Our results do not confirm earlier studies that reported an overall association between the homozygous state of the *CYP17* A2 allele and risk of prostate cancer (8–10). However, we observed several subgroups in which prostate cancer risk was increased among white men with the A2/A2 genotype. In our investigation, white men with a first-degree relative(s) with prostate cancer who had the A2/A2 genotype exhibited a particularly high risk (OR, 19.2) relative to those with no family history who had the A1/A1 genotype (test for interaction, P = 0.0005). Among white men homozygous for the A2 allele, the risk associated with having a family history of prostate cancer was 26.1 (95% CI, 3.41–199.6) relative to men without a family history of the disease. It is interesting that a previous study that found an increased risk of breast cancer associated with the *CYP17* A2 allele detected the highest risk estimate in the subgroup of women who had a family history of breast cancer

Table 3 Associations between *CYP17* genotype and prostate cancer stratified by selected characteristics among white subjects

Characteristic	Genotype			P^a
	A1/A1	A1/A2	A2/A2	
First-degree family history of prostate cancer				
No	1.00[b]	0.78 (0.59–1.03)	0.69 (0.47–1.03)	0.0005
Yes	1.36 (0.79–2.35)	1.19 (0.57–2.50)	19.2 (2.23–157.4)	
BMI				
18–23	1.00[c]	0.84 (0.49–1.43)	0.46 (0.20–1.09)	0.048
24–26	0.78 (0.47–1.28)	1.17 (0.59–2.33)	2.35 (0.83–6.64)	
27–29	0.69 (0.40–1.20)	1.01 (0.47–2.16)	1.47 (0.47–4.59)	
≥30	0.91 (0.48–1.73)	0.51 (0.21–1.23)	3.54 (0.99–12.6)	
Physical activity, times per week				
None	1.00[c]	0.88 (0.45–1.72)	1.14 (0.41–3.13)	0.75
≤1	0.79 (0.42–1.46)	0.73 (0.31–1.70)	0.91 (0.27–3.12)	
2–3	0.86 (0.48–1.56)	1.02 (0.45–2.28)	0.83 (0.26–2.68)	
≥4	0.94 (0.50–1.75)	0.93 (0.40–2.17)	0.49 (0.14–1.79)	
Smoking habits				
Never	1.00[c]	0.81 (0.53–1.25)	0.95 (0.53–1.71)	0.51
Former	1.12 (0.73–1.72)	1.04 (0.59–1.86)	0.77 (0.35–1.72)	
Current	1.23 (0.70–2.15)	0.76 (0.35–1.67)	1.52 (0.48–4.78)	
Number alcohol drinks/week				
Nondrinker	1.00[c]	0.62 (0.26–1.49)	0.54 (0.15–1.99)	0.82
≤3	1.40 (0.64–3.07)	1.19 (0.42–3.36)	2.05 (0.46–9.11)	
4–13	1.35 (0.65–2.83)	1.30 (0.50–3.41)	1.34 (0.33–5.45)	
≥14	1.36 (0.61–3.01)	1.51 (0.54–4.22)	2.40 (0.51–11.3)	

[a] *P* for interaction of genotype with selected characteristic.
[b] ORs are adjusted for age; 95% CI are in parentheses.
[c] ORs are adjusted for age and family history of prostate cancer.

(18). Our results also suggest that there may be a relationship between BMI, *CYP17* genotype, and risk of prostate cancer. The OR for prostate cancer among obese (BMI ≥ 30) men with the A2/A2 genotype was 3.54 (95% CI, 0.99–12.6) compared with lean men with the A1/A1 genotype. Furthermore, among the subset of white men homozygous for the A2 allele, the OR for prostate cancer was 3.14 (95% CI, 0.97–10.2) in men with a BMI of ≥30.

The *CYP17* A2 allele is hypothesized to enhance promoter activity resulting in an increased rate of transcription and, thus, increased production of androgens and estrogens, which may affect prostate cancer risk (4, 8, 19, 20). The mechanism by which this is accomplished is not clear. Whereas the generation of an Sp-1 binding site has been hypothesized to increase transcription of the associated gene, Kristensen *et al.* (21) report that, when assayed by mobility shift assays, the T to C polymorphism does not influence binding to the putative Sp-1 site in this region. It is equally likely that the polymorphism serves as a marker for another gene with a biological effect, particularly because an association with the A2 allele has been reported for multiple hormone related phenotypes. An excess number of carriers of the A2 allele has been demonstrated in women with polycystic ovaries and men with male pattern baldness compared with controls, and both of these phenotypes are characterized clinically by elevated levels of serum androgens (3). The A2 allele also has been associated with advanced stage (22) and early onset breast cancer (18) in women, and with breast cancer (23) and prostate cancer (8–10) in men. Feigelson *et al.* (4) measured serum hormones in healthy nulliparous women and found elevated levels of estradiol and progesterone in women with the A2/A2 genotype. However, two recent studies of men without a history of cancer found no association between *CYP17* genotype and total or free serum testosterone levels (11, 24). On the basis of these data, the potential biological significance of the A2 allele on *CYP17* expression remains uncertain.

The observation of a significant *CYP17*-family history interaction on prostate cancer risk, in the absence of an overall association between *CYP17* genotype and risk, suggests that the A2 variant may play a role in familial disease. It may be acting independently or interacting with independently segregating alleles associated with other gene(s). Examples to consider include genetic variants in other genes involved in the androgen pathway such as *HSD3B2* or *SRD5A2*, which may result in an increase in androgen bioavailability and thereby alter risk.

Studies of high-risk prostate cancer families have identified six chromosomal locations that may contains genes linked to the hereditary form of prostate cancer (25, 26). However, none of these studies has reported strong significant results at 10q24.32 where *CYP17* is located. In addition, a recent study of 159 hereditary prostate cancer families that examined this locus, specifically, found no evidence for linkage (27). This is surprising given the strong positive association reported here for men with a family history of prostate cancer. However, the high-risk family cohorts collected to date are extremely heterogeneous in terms of race, age at diagnosis, and clinical presentations (25, 26). Once highly penetrant genes for hereditary prostate cancer are cloned and specific disease-associated mutations are identified, it will be possible to partition the existing data sets and determine the association of *CYP17* variants both in the presence and absence of rare highly penetrant alleles. In the meantime, it may be particularly useful to examine families that have multiple cases of both prostate and breast cancer, because an association of the A2 allele has been reported for breast cancer as well (18, 22). In addition, it may be useful for researchers to consider a meta-analysis of exclusively families with an early mean age at prostate cancer diagnosis, because the case-control study analyzed here was restricted to men diagnosed before age 65 years. Finally, because the observations reported here are the most significant for individuals who are homozygotes for the A2 allele, it may be most appropriate to

analyze family linkage data using either a recessive model of inheritance or, alternatively, by nonparametric methods.

Our study had several strengths and limitations to consider when interpreting the results. To our knowledge, this is the second largest and the only population-based study of the *CYP17* polymorphism and prostate cancer relationship reported to date. Despite the overall number of men studied, sample size was limited for exploring the combined effects of genotype with personal characteristics, lifestyle factors, or environmental exposures. In this study, there were only 163 (15.1% of 1083) white men with the A2/A2 genotype. Thus, much larger population-based studies will be necessary to fully investigate the associations suggested by our data. Genotyping results were only available for 78% of cases and 77% of controls for whom interview data were available. However, there were no significant differences in the distributions of age, race, family history of prostate cancer, BMI, or socioeconomic factors between interviewed and genotyped cases or controls. Furthermore, it seems unlikely that genotype would have determined participation in the interview or blood draw components of the study.

Another potential concern is misclassification of disease status among controls, given the high prevalence of asymptomatic prostate cancer. In our study, only 5.9% of the control men reported that they had never been screened for prostate cancer. As part of another substudy, we completed PSA testing on serum from a random sample of 400 controls included in this genotyping study. Exclusion of the 38 controls with elevated serum PSA values did not substantially alter our results.

In summary, our findings suggest that the *CYP17* genotype may be a marker of prostate cancer susceptibility in white men with a first-degree family history of the disease. It is possible that a gene-gene interaction between *CYP17* and another gene(s), which influences development of prostate cancer, may account for these results. Larger studies of the *CYP17* polymorphism will be required to confirm these results and to determine whether *CYP17* genotyping may be clinically useful for identifying the subset of men with a family history of prostate cancer who are at highest risk.

Acknowledgments

We thank Dr. John Potter for his helpful advice on the paper. We are grateful for the cooperation and time contributed by the men who participated in the study.

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Cancer Epidemiol Biomarkers Prev 2002;11:243-247.