

## Association of the *CYP17* Gene Polymorphism with the Risk of Prostate Cancer: A Meta-Analysis

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### Abstract

**A T-to-C polymorphism in the 5' promoter region of the *CYP17* gene that encodes the cytochrome P450c17 $\alpha$  has been implicated as a risk factor for prostate cancer, but individual studies have been inconclusive or controversial. Therefore we performed a meta-analysis of 10 studies (12 comparisons) with *CYP17* genotyping on 2404 patients with prostate cancer and 2755 controls. Overall, the random effects odds ratio (OR) for the A2 (C) versus A1 (T) allele was 1.08 [95% confidence interval (CI), 0.95–1.22], with some between-study heterogeneity ( $P = 0.04$ ). There was no suggestion of an overall effect either in recessive or dominant modeling of A2 effects, and the comparison of A2/A2 versus A1/A1 also showed no differential susceptibility to prostate cancer (OR, 1.15; 95% CI, 0.91–1.46). No effect of A2 was seen in subjects of European descent (7 comparisons, OR, 1.04; 95% CI, 0.92–1.18, no significant between-study heterogeneity) or Asian descent (2 comparisons, OR, 1.06; 95% CI, 0.66–1.71;  $P = 0.02$  for heterogeneity), whereas A2 increased susceptibility to prostate cancer in subjects of African descent (3 comparisons, OR, 1.56; 95% CI, 1.07–2.28; no between-study heterogeneity). Smaller studies unilaterally showed more prominent genetic effects for A2 than larger studies ( $P = 0.038$ ). The meta-analysis suggests that the *CYP17* polymorphism is unlikely to increase considerably the risk of sporadic prostate cancer on a wide population basis, especially in subjects of European descent. Previously reported associations may reflect publication bias, although it is also possible that the polymorphism may be important in subjects of African descent.**

### Introduction

High levels of endogenous androgens have long been considered as risk factors for prostate cancer (1, 2). Therefore, it has

been postulated that variants in the genes of the enzymes involved in androgen biosynthesis and metabolism may be associated with the development of prostate cancer. Among these genes, *CYP17* is located on chromosome 10 and encodes the cytochrome P450c17 $\alpha$  enzyme (3). This cytochrome mediates both 17 $\alpha$ -hydroxylase and 17,20-lyase activities at key points in the testosterone biosynthesis in gonads and adrenals (3). The 5'-untranslated promoter region of the *CYP17* gene contains a polymorphic T-to-C substitution that gives rise to A1 (T) and A2 (C) alleles (4). There is controversy on whether the A2 allele may change the binding characteristics of the promoter region and lead to increased transcription of *CYP17* mRNA (4, 5). Molecular epidemiological studies have also presented seemingly contradictory results concerning a potential role of *CYP17* in prostate cancer. Some studies have indicated that the A2 allele may be associated with an increased risk of prostate cancer (6–11). However, other investigations have been apparently inconclusive (12, 13) or have even reported that the A1 allele may increase the risk of prostate cancer (14, 15). Single studies may have been underpowered to detect dose-response relationships or even overall effects. Given the amount of accumulated data, a quantitative synthesis of the evidence using rigorous methods was deemed important to perform. To address these issues, we conducted a comprehensive meta-analysis of all available studies relating the *CYP17* polymorphism to the risk of prostate cancer. We aimed to obtain summary estimates for the strength of the postulated genetic association, estimate the between-study heterogeneity, and find possible explanations for the presence of heterogeneity between studies.

### Materials and Methods

**Identification and Eligibility of Relevant Studies.** We considered all studies that examined the association of the *CYP17* polymorphism with prostate cancer. Sources included Medline and Embase (last search update 6/2002). The search strategy was based on combinations of prostate cancer, *CYP17*, androgens, polymorphism, allele, and genetics. The references of retrieved articles were also screened.

Case-control studies were eligible if they had determined the distribution of *CYP17* genotypes in prostate cancer cases and in a concurrent control group of prostate cancer-free subjects using a molecular method for genotyping. We excluded studies or subgroups thereof with familial linkage designs. We accepted disease-free controls regardless of whether they had BPH<sup>2</sup> or not. Cases with prostate cancer were eligible regardless of whether they had a first-degree relative with prostate cancer or not. However, we excluded family-based studies of

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<sup>2</sup> The abbreviations used are: BPH, benign prostatic hyperplasia; OR, odds ratio; CI, confidence interval.

pedigrees with several affected cases per family because their analysis is based on linkage considerations.

**Data Extraction.** Two investigators independently extracted the data and reached consensus on all items. The following information was sought from each study: authors; journal and year of publication; country of origin; selection and characteristics of prostate cancer cases and controls; demographics; racial descent of the study population (categorized as European, African, and Asian descent); eligible and genotyped cases and controls; and number of cases and controls for each *CYP17* genotype. For studies where subjects of different racial descent were included, data were extracted separately for each race. Furthermore, we examined whether matching had been used, whether there was specific mention of blinding of the personnel who performed the genotyping to the clinical status of the subjects, and whether the genotyping method had been validated. Whenever complete information on distribution of genotypes in cases and controls was missing in a published report, we obtained the pertinent data directly from primary study investigators.

**Meta-Analysis.** The primary analysis compared prostate cancer patients against controls for the contrast of *A2 versus A1* alleles. This analysis aims to detect overall differences. We also examined the contrast of extremes (homozygotes) *A2/A2 versus A1/A1*. Finally, we examined the contrast of *A2/A2 versus (A1/A2 + A1/A1)* and *(A1/A2 + A2/A2) versus A1/A1*. These contrasts correspond to recessive and dominant effects, respectively, of the *A2* allele.

Because case-control studies were involved, the OR was used as the metric of choice. Studies with subjects of different races were split into separate race-specific comparisons. For each genetic contrast, we estimated the between-study heterogeneity across all eligible comparisons using the  $\chi^2$ -based Q statistic (16). Heterogeneity was considered significant for  $P < 0.10$ . Data were combined using both fixed effects (Mantel-Haenszel) and random effects (DerSimonian and Laird) models (17). Random effects incorporate an estimate of the between-study variance and tend to provide wider CIs when the results of the constituent studies differ among themselves. In the absence of between-study heterogeneity, the two methods provide identical results. Random effects are more appropriate when heterogeneity is present (17).

Subgroup analyses estimated race-specific ORs for the *A2 versus A1* contrast. Beyond race, studies were not consistent about adjusting for other parameters such as age, smoking, or family history and presented different genetic contrasts for the adjusted analyses. Therefore, we examined whether the unadjusted analyses yielded similar OR estimates as the adjusted/stratified analyses whenever reported.

We also performed cumulative meta-analysis (18) and recursive cumulative meta-analysis (19, 20) to evaluate whether the summary OR for the *A2 versus A1* contrast changed over time as more data accumulated. Inverted funnel plots and the Begg-Mazumdar publication bias diagnostic (nonparametric  $\tau$  correlation coefficient; Ref. 21) evaluated whether the magnitude of the observed association was related to the variance of each study.

Analyses were conducted in SPSS 10.0 (SPSS, Inc., Chicago, IL), StatXact (Cytel, Inc., Boston, MA), and Meta-Analyst (Joseph Lau, Boston, MA). All *P* values are two-tailed.

## Results

**Eligible Studies.** Ten studies probing the relationship between the *CYP17* polymorphism and prostate cancer susceptibility

were identified (6–15). One of the two comparisons in one report pertained to a family-based linkage study, so this comparison was excluded (12). Two of the eligible studies (6, 11) contained subjects of two different racial descents, thus a total of 12 separate comparisons were considered (Table 1). There was a considerable diversity of ethnic groups. Six studies (6–8, 11, 13, 15) selected prostate cancer patients based on a histological diagnosis from biopsy and/or prostatectomy, whereas the other four (9, 10, 12, 14) did not clarify the exact criteria used for the diagnosis of prostate cancer. Two studies (11, 14) mentioned that they included a small proportion of patients with a first-degree relative with prostate cancer, one study (13) specifically excluded such patients, whereas the remaining did not clarify the background of family history. Controls did not have a clinical diagnosis of prostate cancer, but the amount of additional screening [with digital rectal examination, prostate-specific antigen (<4 ng/ml), needle biopsy or prostate resection] to exclude prostate cancer differed substantially across studies (Table 1).

With one exception (10) where the mean age of controls and cases differed by 9 years, the mean or median age of cases and controls was very similar (difference < 2 years), and specific matching for age was described in five studies (7–9, 11, 14). One study also matched for smoking status (9). Three studies (9, 11, 15) mentioned specifically blinding of the personnel who performed the genotyping. Appropriate molecular methods for genotyping were used. All studies used PCR, and three studies used also sequencing (9–11).

**Meta-Analysis Database.** The eligible studies included a total of 2442 patients with prostate cancer and 2816 controls of whom 2404 and 2755, respectively, had genotype data. Allele and genotype frequencies per group are shown in Table 2. The *A2* allele was more highly represented among controls of Asian descent [44% (95% CI, 41–47)] than in controls of European descent [39% (95% CI, 37–40)] or African descent [31% (95% CI, 25–37)]. Overall, the prevalence of *A2/A2* homozygosity was 18, 15, and 10% in control subjects of Asian, European, and African descent, respectively. The respective prevalence rates of *A1/A2* heterozygosity were 52, 48, and 42%, and the respective rates for *A1/A1* homozygosity were 30, 37, and 48%. The distribution of genotypes in control groups was consistent with Hardy-Weinberg equilibrium in all studies, with the exception of Yamada *et al.* (8), where there was a significant deficit of both homozygote genotypes ( $P = 0.01$ ). A sensitivity analysis was thus performed excluding this study.

**Overall Effects for Alleles.** There was no strong evidence that the *A2* allele conferred increased susceptibility to prostate cancer (Fig. 1). The summary OR was 1.08 by random effects ( $P = 0.24$ ) and 1.04 by fixed effects ( $P = 0.29$ ). However, there was significant heterogeneity between the 12 study comparisons ( $P = 0.04$ ). Excluding the one study where Hardy-Weinberg equilibrium was violated in the controls (8) brought the results even closer to the null (OR, 1.05; 95% CI, 0.93–1.19;  $P = 0.43$  by random effects and OR, 1.03; 95% CI, 0.95–1.11;  $P = 0.53$  by fixed effects), but there was still some between-study heterogeneity ( $P = 0.053$ ).

In subgroup analyses, we documented a significant association of the *A2* allele with the risk of prostate cancer ( $P = 0.022$ ) in subjects of African descent without any between-study heterogeneity, although data were limited (Table 3). On the contrary, no differences were observed in allele distribution between prostate cancer patients and controls in European and Asian descent subgroups (Table 3). There was no significant between-study heterogeneity in comparisons of subjects of Eu-

Table 1 Characteristics of studies included in the meta-analysis

First author, yr	Country	Selection/characteristics of cases and controls (age range [mean])		Racial descent	Eligible subjects <sup>a</sup>	
		Prostate cancer	Controls		Prostate cancer	Controls
Lunn, 1999	USA	Prostatectomy-documented cancer [63]	Men presenting with BPH or impotence, without history of cancer other than nonmelanoma skin cancer [64]	European	96	159
				African	12	8
Wadelius, 1999	Sweden	Not clarified. Family history in 12% (51–79 [71])	Randomly selected from the county population register, no screening for prostate cancer (50–79 [71])	European	178	160
Gsur, 2000	Austria	Histologically documented cancer by TRUS-guided biopsy after a suspicious finding on DRE, elevated serum PSA, or both [66]	Patients with BPH symptoms. Prostate cancer was excluded by negative DRE and not elevated serum PSA (50.5%), by TRUS-guided biopsy (16.5%), or by transurethral resection of the prostate (33%) [67]	European	63	126
Habuchi, 2000	Japan	Histologically documented cancer by transrectal needle biopsy or transurethral resection of the prostate [72]	BPH on DRE without elevated serum PSA or negative transrectal biopsy ( $n = 202$ ); nonurological admissions without BPH on DRE and not elevated serum PSA or negative transrectal biopsy ( $n = 131$ ) [72]	Asian	252	333
Haiman, 2001	USA	Not clarified (40–84)	Physicians participating in Physicians' Health Study Cohort with negative clinical history for cancer who returned blood samples (40–84)	European	600	804
Kittles, 2001	USA	Not clarified [66]	Not elevated serum PSA and normal DRE [57]	African	71	111
Yamada, 2001	Japan	Histologically documented cancer by TRUS-guided biopsy or by radical prostatectomy [72]	No cancer seen in retropubic prostatectomy ( $n = 136$ ) or not elevated serum PSA or a negative biopsy ( $n = 74$ ) [72]	Asian	105	210
Chang, 2001	USA	Not clarified [59]	Normal DRE and not elevated serum PSA [58]	European	225	182
Latil, 2001	France	Histologically documented cancer. Excluded patients with family history (46–98 [71])	Negative DRE and not elevated serum PSA for at least 7 years (51–92 [72])	European	226	156
Stanford, 2002	USA	Histologically documented cancer. First-degree family history in 19% (40–64 [58])	Random digit telephone dialing. 59% have had negative DRE screening, and 35% have had negative DRE and PSA screening. BPH in 18% (40–64 [58])	European	560	523
				African	30	15

<sup>a</sup> All eligible subjects were genotyped with the exception of 10 cancer patients and 22 controls in Haiman *et al* (9), and 4 cancer patients and 10 controls in Yamada *et al* (8).

<sup>b</sup> TRUS, transrectal ultrasound; DRE, digital rectal examination; PSA, prostate-specific antigen.

Table 2 Distribution of CYP17 alleles among prostate cancer cases and controls in the included studies

First author, yr	Racial descent	A2/A2		A2/A1		A1/A1	
		Cancer	Control	Cancer	Control	Cancer	Control
Lunn, 1999	European	13	18	54	73	29	68
	African	2	1	6	3	4	4
Wadelius, 1999	European	34	26	74	88	70	46
Gsur, 2000	European	15	12	27	67	21	47
Habuchi, 2000	Asian	46	69	111	157	95	107
Haiman, 2001	European	98	127	290	350	202	305
Kittles, 2001	African	11	10	38	46	22	55
Yamada, 2001	Asian	19	29	68	120	14	51
Chang, 2001	European	31	26	106	79	88	77
Latil, 2001	European	35	24	116	84	75	48
Stanford, 2002	European	84	79	248	256	228	188
	African	2	2	18	7	10	6

ropean descent ( $P = 0.15$ ), whereas there was significant heterogeneity ( $P = 0.02$ ) between the two studies performed in subjects of Asian descent, with a trend for an association between A2 and prostate cancer seen only in the study without Hardy-Weinberg equilibrium in the control group.

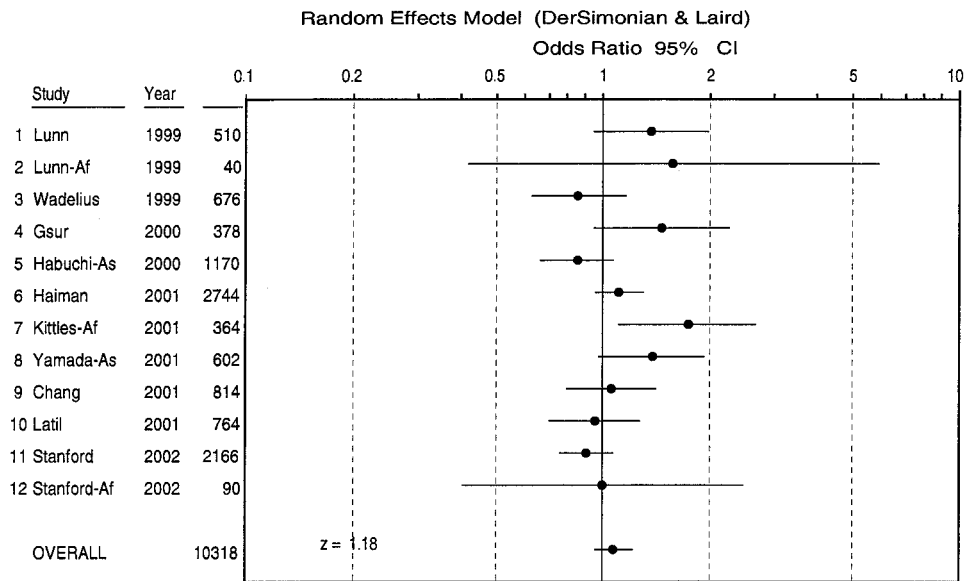
**Other Contrasts.** We found no evidence of an association of the A2/A2 genotype with the risk of prostate cancer relative to the A1/A1 genotype. There was no significant between-study heterogeneity ( $P = 0.11$  for heterogeneity), and the 95% CI excluded a large effect (Table 3). No evidence for an association with prostate cancer was discerned also when recessive and dominant models were examined for the effect of A2. There was no between-study heterogeneity in the recessive model contrast,

whereas significant heterogeneity ( $P = 0.003$ ) was seen for the dominant model contrast (Table 3).

#### Adjusted/stratified Analyses for Age and Other Factors.

Three studies (10, 13, 14) provided only unadjusted analyses. The other studies provided some estimates taking also age into account [either by stratification (6–8) or as a continuous adjusting variable (9, 11, 12, 15)]. Smoking status was also considered in one study (9) and having a relative with prostate cancer in another (11). In four studies (8, 9, 11, 12), the adjusted and unadjusted estimates practically coincided (difference in ORs  $< 0.03$ ). In the other three studies (6, 7, 15), the adjusted OR was slightly smaller than the unadjusted OR for the effects of either A2/A2 or A1/A2+A2/A2 versus A1/A1. In Gsur *et al*.

Fig. 1. Meta-analysis for the effect of A2 versus A1 allele on the risk of prostate cancer. Each comparison is presented by the name of the first author, the year of publication, and the number of alleles. Af signifies subjects of African descent, As signifies subjects of Asian descent; all other comparisons are in subjects of European descent. For each comparison, the point estimate of the OR and the accompanying 95% CI are shown. Also shown is the summary random effects estimate for the comparison along with the respective 95% CI as well as final z-statistic for the summary OR. The studies are ordered according to year of publication. Values >1 denote an increased risk for prostate cancer with A2.



(7), adjusted and unadjusted OR for the contrast A2/A2 versus A1/A1 were 2.65 and 2.80, respectively. In the comparison of prostate cancer versus non-BPH controls in Habuchi *et al.* (15), the adjusted and unadjusted OR for the contrast of A2/A2 versus A1/A1 were 0.39 and 0.44, respectively. Finally, in Lunn *et al.* (6), adjusted and unadjusted OR for the contrast A1/A2 + A2/A2 versus A1/A1 were 1.66 versus 1.75, respectively. Therefore, the adjusted analyses would probably bring the summary OR for the comparison of A2 versus A1 alleles (1.08 based on unadjusted data) closer toward the null.

In two stratified analyses (6, 8), A2/A2 and A1/A2 seemed to confer a significant susceptibility to prostate cancer in younger subjects (subgroups  $\leq 64$  and  $< 72$  years old, respectively). Conversely, in another stratified analysis (7), A2/A2 and A1/A2 conferred susceptibility to prostate cancer in older patients (subgroup  $> 66$  years old), whereas a protective trend was seen in the younger group. Thus, there was no consistent evidence for a greater susceptibility in younger or older patients.

**Other Bias Diagnostics.** In cumulative meta-analysis and recursive cumulative meta-analysis, the magnitude of the summary OR had been stable and not changing in the same direction over time (by random effects, summary OR for A2 versus A1: 1.10 at the end of 1999, 1.07 at the end of 2000, 1.12 at the end of 2001, and 1.08 in 2002). However, the inverted funnel plot was potentially asymmetric. There was a significant correlation between the variance of each study and the magnitude of the OR ( $\tau = 0.52$ ,  $P = 0.038$  considering the 10 studies;  $\tau = 0.44$ ,  $P = 0.046$  considering the 12 comparisons with racial subgroups considered separately), suggesting that a relationship between A2 and prostate cancer was seen unilaterally in the smaller studies.

## Discussion

This meta-analysis includes data from 12 case-control comparisons with  $> 5000$  genotyped prostate cancer patients and controls. The overall data demonstrate that the CYP17 polymorphism is unlikely to be a major risk factor for susceptibility to prostate cancer on a wide population basis. There has been

some heterogeneity between the results of various studies. Heterogeneity may be because of bias, in particular publication bias (22, 23), because the published smaller studies suggest increased susceptibility to prostate cancer with the A2 allele, whereas this has not been documented in studies with larger sample sizes. Genuine heterogeneity may also be present and it may relate to racial differences, with a genetic effect limited to subjects of African descent.

For subjects of European descent, the meta-analysis excludes any clinically meaningful overall effect of this polymorphism on prostate cancer risk. No overall effect is seen among Asian descent subjects, but data seem heterogeneous and one study lacks Hardy-Weinberg equilibrium in the control group. Conversely, the polymorphism may play a role in susceptibility to prostate cancer among subjects of African descent. If the association between this polymorphism and prostate cancer holds true, especially in subjects of African descent, this may be because of gene by gene or gene by environment interactions or may be a reflection of a pattern of linkage disequilibrium with other more important polymorphisms, which is unique to men of African descent. However, the currently available data on men of African descent are still very limited and thus should be interpreted with caution. A few more studies may be required in African Americans or other African-derived groups. African Americans have a higher incidence of prostate cancer, present with more advanced disease and at younger ages, and have a worse prognosis than subjects of other ethnicities (24–27). This differential profile is not entirely explained by lifestyle, dietary, socioeconomic, or clinical factors (25–27), thus genetic parameters may be important. In the meta-analysis database, the A2 allele was slightly less frequent in subjects of African versus European descent, whereas an opposite trend has been observed in a different study (28). Overall, these two racial groups may exhibit little difference in A2 frequency.

The meta-analysis findings may be interpreted against the postulated biological context of the CYP17 polymorphism. One study has shown that white men with the A2/A2 genotype have 0.5 SDs higher bioavailable testosterone than men with the A1/A1 genotype, and A1/A2 heterozygotes have intermediate

Table 3 Summary ORs for various contrasts

Contrast	Comparisons (n)	Random effects OR (95% CI)	Fixed effects OR (95% CI)
<i>A2 versus A1</i> alleles	12 (10,318)	1.08 (0.95–1.22) <sup>a</sup>	1.04 (0.96–1.13)
European	7 (8,052)	1.04 (0.92–1.18)	1.03 (0.94–1.13)
Asian	2 (1,772)	1.06 (0.66–1.71) <sup>a</sup>	0.99 (0.82–1.20)
African	3 (494)	1.56 (1.07–2.28)	1.56 (1.07–2.28)
<i>A2/A2 versus A1/A1</i>	12 (2,673)	1.15 (0.91–1.46)	1.09 (0.92–1.29)
<i>A2/A2 versus (A1/A2+A1/A1)</i>	12 (5,159)	1.08 (0.92–1.24)	1.07 (0.92–1.24)
<i>(A1/A2+A2/A2) versus A1/A1</i>	12 (5,159)	1.11 (0.90–1.38) <sup>b</sup>	1.05 (0.93–1.18)

<sup>a</sup> Heterogeneity,  $0.01 < P < 0.10$ .<sup>b</sup> Heterogeneity,  $P < 0.01$ .

values (29). However, other studies have found no differences in the levels of testosterone or other androgens and metabolites thereof (dehydrotestosterone, androstanediol glucuronide) according to *CYP17* genotypes in men (9, 30). Most studies in women also do not suggest major influences on hormonal levels (31–33). An early study suggested that the *A2* allele creates an additional Sp1-binding site in the *CYP17* promoter region (4). Subsequently, Nedelcheva Kristensen *et al.* (5) did not document Sp1 binding at this polymorphic site or within the promoter region of *CYP17* in general, whereas Lin *et al.* (34) found that Sp1 is an essential factor for *CYP17* transcription in human adrenal NCI-H295A cells. Overall, evidence that the *A2* allele increases androgen levels is weak and inconsistent. The exact role of androgens in prostate cancer is a contentious issue (1, 35, 36). If androgens participate in the causal pathway of prostate cancer (1, 35, 36), a null effect of the *CYP17* polymorphism on androgen levels would be consistent with the results of the meta-analysis.

The *CYP17* polymorphism may not be an important population-wide risk factor for prostate cancer. Genome scans have typically not identified significant linkage in the 10q24.32 chromosomal region where the *CYP17* gene is located (37, 38). A recent meta-analysis of 15 comparisons (39) also concluded that this polymorphism does not seem to play a significant role in susceptibility to breast cancer in women, another type of cancer where hormonal influences are considered to be important. Data on other conditions potentially affected by endogenous sex hormone levels such as endometrial cancer (32, 40), ovarian cancer (41, 42), hepatocellular carcinoma (43), and polycystic ovaries (44) are more limited and don't always show consistent associations. A larger number of studies and many more genotyped subjects are required to clarify these postulated associations.

The meta-analysis was consistently based on unadjusted estimates, but we took care to account for racial effects. Moreover, the reported adjusted estimates taking age into consideration suggest that the overall results would probably shift even closer to the null, if age-adjusted analyses were consistently available. We should acknowledge that the meta-analysis could not address conclusively familial prostate cancer. One study with pedigrees of  $\geq 3$  prostate cancer cases/family (mean, 5.08; Ref. 12) has suggested a possible link of prostate cancer with the *CYP17* gene region, but the LOD score was only 1.3. However, hereditary forms of prostate cancer with many members affected per family are not very common (38). Associations limited to strictly hereditary forms are unlikely to have a substantial population attributable fraction for prostate cancer. Conversely, it is common to encounter families where two first-degree relatives or one first-degree relative and at least two second-degree relatives are affected. This pattern may account

for 10–20% of all cases of the disease (38). Future studies should explore specifically whether the *CYP17* polymorphism may have any effect on the risk of prostate cancer specifically in this setting.

Attention should also be given to the design of individual studies. The results of meta-analyses may be affected by methodological problems and potential biases in the designs of the constituent studies. Quality deficiencies may sometimes affect the magnitude of the observed association. Nondifferential misclassification errors may dilute the strength of an observed association. In the *CYP17* studies, genotyping was performed with appropriate methods, thus genotype errors are unlikely to have influenced the results substantially. However, controls were not screened consistently across studies to exclude subclinical, latent prostate cancer. Control groups of the different studies were also not equally well characterized as to the extent of inclusion of subjects with BPH. The inclusion or not of subjects with BPH in the control group may affect the results if the *CYP17* polymorphism affects BPH. One study found a difference between controls with *versus* without BPH in the frequency of the *A2* allele (15), but another study has shown no effect of this polymorphism on prostate volume (45). Moreover, some young control subjects may have developed prostate cancer at older ages. The lifetime risk of prostate cancer in American men is estimated at 16% (46), therefore the dilution of the OR would not be very large. The choice of an appropriate age-window for assessing a postulated genetic risk factor for prostate cancer is difficult. Studies of younger subjects may be more suitable for identifying risk factors that result in early carcinogenesis. Conversely, selection of younger subjects may be less appropriate, if hormonal or other influences regulated by the postulated risk factor are more important in later ages (35).

Cases of prostate cancer included in most of these studies are those brought to therapeutic attention, and this may differ from cases diagnosed from population screening. However, there is no reason why the *CYP17* genotype distribution would be affected by this selection. Moreover, cases and controls may have been recruited through different sources, but they were ethnically matched and with one exception, they were also well matched for age. Finally, even among cases with prostate cancer, some misclassification might be unavoidable, if cases were unconfirmed by histology. However, this potential misclassification should not have affected a considerable proportion of the cancer cases.

Notwithstanding these considerations, one should not overemphasize subgroup analyses of age or other factors. For *CYP17*, age subgroup analyses in different studies have reached opposite conclusions, perhaps as a result of chance and multiple comparisons. The summary results do not support a strong overall effect. A very large number of subjects are needed to

establish or refute a genetic association of modest magnitude (47) and even larger numbers are needed to validate subgroup differences, let alone more subtle associations such as gene-gene and gene-environment interactions. Given the large number of potential genetic risk factors that may be probed, several initial observations may not be validated by subsequent evidence (47).

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