SRD5A2 Gene Polymorphisms and the Risk of Prostate Cancer: A Meta-Analysis

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Abstract

Several polymorphisms in the 5α-reductase type 2 (SRD5A2) gene have been implicated as risk factors for prostate cancer. We performed a meta-analysis of 9 studies (12 comparisons) with V89L genotyping (2558 prostate cancer cases and 3349 controls), 7 studies (8 comparisons) with A49T genotyping (1594 cases and 2137 controls), and 4 studies with TA repeat genotyping (1109 cases and 1378 controls). The random effects odds ratio (OR) for the L versus V allele was 1.02 [95% confidence interval (CI), 0.94–1.11]. There was no suggestion of an overall effect either in recessive or dominant modeling, and comparison of L/L versus V/V also showed no differential prostate cancer susceptibility (OR, 1.03; 95% CI, 0.83–1.28). The random effects OR for the L versus A allele was 1.56 (95% CI, 0.93–2.62). However, excluding the first published study there was no evidence for any effect (OR, 1.08; 95% CI, 0.72–1.61). Moreover, the T allele had a low prevalence (0%, 1%, and 2% in Asian, African and European controls, respectively). The random effects OR for longer versus short TA alleles was 0.88 (95% CI, 0.74–1.05). Longer TA allele homozygotes were nonsignificantly under-represented among prostate cancer cases (OR, 0.53; 95% CI, 0.26–1.06). We exclude a role for the V89L polymorphism in conferring susceptibility to prostate cancer. The A49T and TA repeat polymorphisms may have a modest effect on prostate cancer susceptibility, but bias and chance findings cannot be excluded; any genuine genetic effects would account only for a small proportion of prostate cancer in the population.

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, SRD5A2 is located on chromosome 2 and encodes the steroid 5α-reductase type 2 enzyme expressed primarily in the androgen-sensitive cells of genital skin and the prostate gland (3, 4). This enzyme irreversibly converts testosterone into the main prostatic androgen, DHT. The binding affinity to the prostatic androgen receptor of DHT is five times higher than that of testosterone (5). Ross et al. (6) demonstrated that young Japanese men have lower 5α-reductase activity than young Caucasian-American and African-American men. Similarly, Wu et al. (7) reported that the DHT:testosterone ratio was highest in African-Americans, intermediate in Caucasians, and lowest in Asian-Americans, corresponding to the respective risk of developing prostate cancer in these groups.

Certain SRD5A2 polymorphisms may encode for 5α-reductase enzyme variants with different activities, probably because of altered mRNA stability (8). Makridakis et al. (9) reported a missense substitution in the SRD5A2 gene, which replaces valine at codon 89 with leucine (V89L). This substitution is associated with a reduced 5α-reductase activity both in vitro and in vivo (9). In another variant of the SRD5A2 gene (10), an alanine residue at codon 49 is replaced with threonine (A49T). This missense mutation increases steroid 5α-reductase activity 5-fold in vitro (10). Thus, these polymorphisms might alter DHT levels and consequently the risk of prostate cancer. A polymorphism in the 3′ untranslated region has also been reported, with different numbers of TA dinucleotide repeats (11).

Molecular epidemiological studies have presented seemingly contradictory results concerning a potential role of the V89L (12–20), A49T (10, 16–21), and TA repeat (17, 18, 20, 22) polymorphisms in prostate cancer susceptibility. 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 was deemed important to perform. In this meta-analysis we aimed to obtain summary estimates for the strength of the postulated genetic association, as well as to quantify and explain the potential between-study heterogeneity.

Materials and Methods

Identification and Eligibility of Relevant Studies. We considered all of the studies that examined the association of the V89L, A49T, and TA repeat polymorphisms with prostate cancer. Sources included MEDLINE and EMBASE (last search update January, 2003). The search strategy was based on combinations of “prostate cancer,” “SRD5A2,” “androgens,” “poly-
morphism,” “allele,” and “genetics.” References of retrieved articles were also screened.

Nonfamilial case-control studies were eligible if they had determined the distribution of genotypes for any of the three polymorphisms in prostate cancer cases and in a concurrent control group of prostate cancer-free subjects using a molecular method for genotyping. We accepted disease-free controls regardless of whether they had prostate cancer 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 pedigrees with several affected cases per family, because their analysis is different (based on linkage considerations).

Data Extraction. Two investigators independently extracted data and reached consensus on all of the items. The following information was sought from each report: 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 SRD5A2 genotype. For studies including subjects of different racial descent, data were extracted separately for each race, whenever possible. Furthermore, we examined whether matching had been used, whether there was specific mention of blinded of the personnel who performed the genotyping to the clinical status of the subjects, and whether the genotyping method had been validated. Whenever key information was missing in a published report, we obtained the pertinent data directly from primary study investigators.

Meta-Analysis. The primary analysis for the V89L polymorphism compared prostate cancer patients against controls for the contrast of L versus V alleles. This analysis aims to detect overall differences. We also examined the contrast of homozygotes (LL versus LV). Finally, we examined the contrast of L/L versus V/L+V/V and (V/L+L/L) versus V/V. These contrasts correspond to recessive and dominant effects, respectively, of the L allele. Similar contrasts were analyzed for the A49T polymorphism. For the TA repeat polymorphism, we contrasted the longer alleles [TA(9)] and the very rare TA(18) combined versus the short allele TA(0), as originally proposed (22). Genotype contrasts used the same longer versus short allele classification.

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 of the eligible comparisons using the \( \chi^2 \)-based Q statistic (23). Heterogeneity was considered significant for \( P < 0.10 \). Data were combined using both fixed effects (Mantel-Haenszel) and random effects (DerSimonian and Laird) models (23). Random effects incorporate an estimate of the between-study variance and provide wider CIs, when the results of the constituent studies differ among themselves. Random effects are more appropriate when heterogeneity is present (23). Subgroup analyses estimated race-specific ORs for each allele contrast.

We also performed cumulative meta-analysis (24) and recursive cumulative meta-analysis (25, 26) to evaluate whether the summary OR for the allele contrasts changed over time as more data accumulated. Inverted funnel plots and the Begg-Mazumdar publication bias diagnostic (nonparametric \( \tau \) correlation coefficient; Ref. 27) evaluated whether the magnitude of the observed association was related to the variance of each study. Finally, we evaluated whether the summary results were different when the analyses were limited to studies with rigorous selection of cases and controls (those that confirmed histologically all of the prostate cancer cases and specifically screened all of the controls to rule out prostate cancer).

Analyses were conducted in SPSS 11.0 (SPSS, Inc., Chicago, IL), StatXact (Cytel Inc., Boston, MA), and Meta-Analyst (Joseph Lau, Boston, MA). All of the \( P \) values are two-tailed.

Results

Eligible Studies

We identified 12 eligible reports (Refs. 10, 12–22; Table 1), 2 of which (13, 22) were derived from the same cohort, but presented complementary data on different polymorphisms. The number of studies with V89L (12–20), A49T (10, 16–21), and TA repeat data (16, 17, 19, 22) was 9, 7, and 4, respectively. After splitting data per racial descent in 3 studies (10, 14, 15), there were 12, 8, and 4 available comparisons for the three polymorphisms, respectively. There was a considerable diversity of ethnic groups.

Nine reports (12, 13, 15–20, 22) selected prostate cancer patients based on a histological diagnosis from biopsy or prostatectomy, whereas the other 3 (10, 14, 21) did not clarify the exact diagnostic criteria. One report (19) mentioned positive family history of prostate cancer in 11.9% of patients, 4 reports (10, 17, 20, 21) specifically included patients without a family history of prostate cancer, whereas the remaining did not clarify the background of family history. Controls did not have a clinical diagnosis of prostate cancer at entry, 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 5 years, the reported mean or median age of cases and controls was very similar (difference <2 years) and specific matching for age was described in 6 studies (13, 16–19, 22). Six reports (10, 12–14, 18, 22) mentioned specifically blinded of the personnel who performed the genotyping. Appropriate molecular methods for genotyping were used. All of the studies used PCR. Some studies performed in addition sequencing (13, 17, 22), single-strand conformational polymorphism analysis (10, 18, 20), or ASO-hybridization and sequencing (21). The distribution of genotypes in control groups was consistent with Hardy-Weinberg equilibrium for all three of the polymorphisms in all of the studies.

Meta-Analyses Databases (Table 2)

V89L. The eligible studies included 2662 patients with prostate cancer and 3573 controls of whom 2558 and 3349, respectively, had genotype data. The L allele was more highly represented among controls of Asian descent (50%; 95% CI, 48–52) than in controls of European descent (31%; 95% CI, 30–32) or African descent (25%; 95% CI, 22–28). Overall, the prevalence of L/L homozygosity was 25%, 10%, and 5% in control subjects of Asian, European, and African descent, respectively. The respective prevalence rates of V/L heterozygosity were 49%, 42%, and 39%.

A49T. The eligible studies included 1720 patients with prostate cancer and 2415 controls of whom 1594 and 2137, respectively, had genotype data. The prevalence of the T allele was 2% (95% CI, 1–3) and 1% (95% CI, 0.1–2) in control subjects of European and African descent, respectively. Overall, the
prevalence of $T/T$ homozygosity was 0.2% and 0.3% in control subjects of European and African descent, respectively. The respective prevalence rates of $A/T$ heterozygosity were 4% and 1%. The $T$ allele was not detected in any subjects of Asian descent, thus the 2 comparisons on Asian subjects were excluded from the quantitative synthesis.

**TA Repeats.** The eligible studies included 1192 patients with prostate cancer and 1574 controls of whom 1109 and 1378, respectively, had genotype data. The prevalence of longer $TA$ repeat alleles was 14% (95% CI, 12–15) and 9% (95% CI, 7–12) in control subjects of European and Asian descent, respectively. Overall the prevalence of homozygosity for longer $TA$ repeat alleles was 2.3% and 0.7%, in the two groups, respectively. No study included African descent subjects.

**Quantitative Synthesis (Table 3)**

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Selection/characteristics of cases and controls (age range [mean])</th>
<th>Racial descent</th>
<th>Eligible subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantoff, 1997 (Febbo, 1999)</td>
<td>USA</td>
<td>Review of medical records and pathology reports (40–84)</td>
<td>Physicians participating in Physicians’ Health Study. Cohort with negative clinical history of cancer who returned blood samples (40–84)</td>
<td>European</td>
</tr>
<tr>
<td>Lunn, 1999</td>
<td>USA</td>
<td>Prostatectomy-documented cancer [63]</td>
<td>Men presenting with BPH or impotence, without history of cancer other than nonmelanoma skin cancer [64]</td>
<td>European</td>
</tr>
<tr>
<td>Makridakis, 1999</td>
<td>USA</td>
<td>Not clarified. No history of prostate surgery. No family history of prostate cancer (45–75 [68.9])</td>
<td>No history of prostate surgery. Men who were selected as controls, but were subsequently found to have prostate cancer, were classified as controls (45–75 [63.6])</td>
<td>European</td>
</tr>
<tr>
<td>Margiotti, 2000</td>
<td>Italy</td>
<td>Histologically documented cancer. No family history of prostate cancer (60–80)</td>
<td>Normal DRE and serum PSA levels. Ambiguous results were checked by ultrasound and biopsy (70–110)</td>
<td>European</td>
</tr>
<tr>
<td>Nam, 2001</td>
<td>Canada</td>
<td>Histologically documented cancer by TRUS-guided prostate biopsy because of a PSA value &gt;3 ng/ml and an abnormal DRE [66]</td>
<td>TRUS-guided prostate biopsy because of a PSA value &gt;3 ng/ml and an abnormal DRE. Normal prostatic tissue (50%), evidence of inflammation, BPH or cellular atypia (22%), PIN (28%) [65.5]</td>
<td>European</td>
</tr>
<tr>
<td>Yamada, 2001</td>
<td>Japan</td>
<td>Histologically documented cancer by TRUS-guided biopsy [72]</td>
<td>No cancer seen in retroperitoneal prostatectomy (64.8%), not elevated serum PSA levels or negative biopsy (35.2%) [71.6]</td>
<td>Asian</td>
</tr>
<tr>
<td>Latil, 2001</td>
<td>France</td>
<td>Histologically documented cancer. No family history of prostate cancer (46–98 [70.5])</td>
<td>Negative DRE and not elevated serum PSA levels for at least 7 years (51–92 [71.7])</td>
<td>European</td>
</tr>
<tr>
<td>Hsing, 2001</td>
<td>USA</td>
<td>Histologically documented cancer. No history of any other cancer (50–94 [73])</td>
<td>No history of cancer. Normal DRE and not elevated serum PSA levels (66%) [71.9]</td>
<td>Asian</td>
</tr>
<tr>
<td>Mononen, 2001</td>
<td>Finland</td>
<td>Not clarified. No family history of prostate cancer</td>
<td>Healthy male blood donors (63.6%), BPH cases (27.5%), autopsies from cancer-free males aged &gt;65 years (8.9%)</td>
<td>European</td>
</tr>
<tr>
<td>Pearce, 2002</td>
<td>USA</td>
<td>Not clarified</td>
<td>Not elevated serum PSA levels</td>
<td>European</td>
</tr>
<tr>
<td>Soderstrom, 2002</td>
<td>Sweden</td>
<td>Histologically documented cancer. Family history in 11.9% (51–79 [71])</td>
<td>Randomly selected from the county population register. No screening for prostate cancer (50–79 [71])</td>
<td>European</td>
</tr>
</tbody>
</table>

*All eligible subjects were genotyped with the exception of 8 cancer patients and 8 controls in Febbo et al. (13), 11 controls in Lunn et al. (15), 13 cancer patients and 7 controls in Yamada et al. (16), 82 cancer patients and 192 controls (V98L), 98 cancer patients and 239 controls (A49T), 77 cancer patients and 191 controls (TA repeat) in Hsing et al. (18), 1 cancer patient and 2 controls (V98L), 1 cancer patient and 1 control (A49T) in Soderstrom et al. (19), and 5 controls (V98L), 2 cancer patients and 9 controls (A49T), 1 cancer patient and 10 controls (TA repeat) in Margiotti et al. (20).*

*Both reports are derived from the same cohort, but each targets different polymorphism.*

*V89L. There was no evidence that the L allele modified the risk of prostate cancer (Fig. 1). The summary OR was 1.02 by both random ($P = 0.61$) and fixed effects ($P = 0.64$). In subgroup analyses, no differences were observed in allele distribution between prostate cancer patients and controls of European, Asian, and African descent. We found no evidence of an association of the $L/L$ genotype with the risk of prostate cancer relative to the $V/V$ genotype. The 95% CIs excluded a large effect. No susceptibility effect was seen in either recessive or dominant models. There was no between-study heterogeneity in any of these analyses.*

*A49T. There was a trend suggesting that the $T$ allele may modify the risk of prostate cancer (Fig. 2). The summary OR was 1.56 by random effects ($P = 0.089$) and 1.44 by fixed effects ($P = 0.029$). However, no clear effect was seen in subjects of European descent. There was a trend for an association of the $T/T$ genotype with the risk of prostate cancer relative to the $A/A$ genotype, with an approximate doubling of the odds of cancer, but this was not formally statistically significant ($P = 0.25$ and $P = 0.13$, by random and fixed effects, respectively). No clear effect was seen in recessive or dominant models. There was no between-study heterogeneity in any of these analyses.*
**TA Repeats.** The contrast of alleles did not suggest any strong genetic effect ($P = 0.15$; Fig. 3). There was a suggestion that homozygotes for longer TA repeats may have a smaller risk for prostate cancer with almost a halving of the odds as compared with subjects with other genotypes. However, this association was not formally statistically significant ($P = 0.07$ by both random and fixed effects). There was no between-study heterogeneity in any of these analyses.

**Bias Diagnostics**

**V89L.** The magnitude of the summary OR had been stable over time (by random effects, summary OR for $L$ versus $V$: 0.96 at the end of 1999, 0.97 at the end of 2000, 1.01 at the end of 2001, and 1.02 at the end of 2002). Smaller studies did not show different results from larger studies. Analyses limited to studies with rigorous selection of cases and controls yielded similar results from larger studies. Analyses limited to studies with rigorous selection of cases and controls yielded similar results from larger studies.

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**Table 2** Distribution of $SRD5A2$ genotypes in cases and controls

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Racial descent</th>
<th>$L/L$ Cancer (%)</th>
<th>Control (%)</th>
<th>$V/L$ Cancer (%)</th>
<th>Control (%)</th>
<th>$V/V$ Cancer (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febbo, 1999</td>
<td>European</td>
<td>50 (8.6)</td>
<td>78 (9.8)</td>
<td>239 (40.9)</td>
<td>330 (41.3)</td>
<td>295 (50.5)</td>
<td>391 (48.9)</td>
</tr>
<tr>
<td>Lunn, 1999</td>
<td>European</td>
<td>7 (7.3)</td>
<td>13 (8.8)</td>
<td>47 (49)</td>
<td>58 (39.2)</td>
<td>42 (43.7)</td>
<td>77 (52)</td>
</tr>
<tr>
<td>Margiotti, 2000</td>
<td>European</td>
<td>3 (2.8)</td>
<td>9 (7.8)</td>
<td>51 (47.2)</td>
<td>40 (34.4)</td>
<td>54 (50)</td>
<td>67 (57.8)</td>
</tr>
<tr>
<td>Nam, 2001</td>
<td>European</td>
<td>11 (7)</td>
<td>21 (13)</td>
<td>67 (42.4)</td>
<td>69 (42.6)</td>
<td>80 (50.6)</td>
<td>72 (44.4)</td>
</tr>
<tr>
<td>Latil, 2001</td>
<td>European</td>
<td>23 (10.2)</td>
<td>8 (5.1)</td>
<td>98 (43.4)</td>
<td>64 (41)</td>
<td>105 (46.4)</td>
<td>84 (53.9)</td>
</tr>
<tr>
<td>Pearce, 2002</td>
<td>European</td>
<td>51 (12.1)</td>
<td>76 (12.7)</td>
<td>182 (43.1)</td>
<td>263 (43.8)</td>
<td>189 (44.8)</td>
<td>261 (43.5)</td>
</tr>
<tr>
<td>Soderstrom, 2002</td>
<td>European</td>
<td>23 (13.1)</td>
<td>16 (10.1)</td>
<td>74 (42.3)</td>
<td>66 (41.5)</td>
<td>78 (44.6)</td>
<td>77 (48.4)</td>
</tr>
<tr>
<td>Yamada, 2001</td>
<td>Asian</td>
<td>27 (29.4)</td>
<td>50 (24.6)</td>
<td>43 (46.7)</td>
<td>97 (47.8)</td>
<td>22 (23.9)</td>
<td>56 (27.8)</td>
</tr>
<tr>
<td>Hsing, 2001</td>
<td>Asian</td>
<td>60 (32.3)</td>
<td>105 (34.6)</td>
<td>86 (46.2)</td>
<td>136 (44.9)</td>
<td>40 (21.5)</td>
<td>62 (20.5)</td>
</tr>
<tr>
<td>Pearce, 2002</td>
<td>Asian</td>
<td>35 (21.6)</td>
<td>43 (15.2)</td>
<td>71 (43.8)</td>
<td>156 (54.9)</td>
<td>56 (34.6)</td>
<td>85 (29.9)</td>
</tr>
<tr>
<td>Lunn, 1999</td>
<td>African</td>
<td>1 (8.3)</td>
<td>1 (12.5)</td>
<td>6 (50)</td>
<td>5 (62.5)</td>
<td>5 (41.7)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Pearce, 2002</td>
<td>African</td>
<td>25 (7.4)</td>
<td>21 (5.1)</td>
<td>134 (39.8)</td>
<td>159 (38.7)</td>
<td>178 (52.8)</td>
<td>231 (56.2)</td>
</tr>
</tbody>
</table>

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**Table 3** Summary ORs and 95% CIs for various contrasts

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Comparisons (n)</th>
<th>Random effects OR (95% CI)</th>
<th>Fixed effects OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L$ vs. $V$ alleles</td>
<td>12 (11,814)</td>
<td>1.02 (0.94–1.11)</td>
<td>1.02 (0.94–1.10)</td>
</tr>
<tr>
<td>European descent</td>
<td>7 (7,818)</td>
<td>1.01 (0.89–1.15)</td>
<td>1.00 (0.91–1.10)</td>
</tr>
<tr>
<td>Asian descent</td>
<td>3 (2,460)</td>
<td>1.02 (0.87–1.21)</td>
<td>1.02 (0.87–1.21)</td>
</tr>
<tr>
<td>African descent</td>
<td>2 (1,536)</td>
<td>1.14 (0.91–1.43)</td>
<td>1.14 (0.91–1.43)</td>
</tr>
<tr>
<td>$L/A$ vs. $V/V$</td>
<td>12 (3,366)</td>
<td>1.03 (0.83–1.28)</td>
<td>1.02 (0.85–1.21)</td>
</tr>
<tr>
<td>($V/L+V/L$) vs. $V/V$</td>
<td>12 (3,507)</td>
<td>1.05 (0.85–1.29)</td>
<td>1.03 (0.88–1.21)</td>
</tr>
<tr>
<td>$T$ vs. $A$ alleles</td>
<td>6 (6,088)</td>
<td>1.56 (0.93–2.62)</td>
<td>1.44 (1.04–2.01)</td>
</tr>
<tr>
<td>European descent</td>
<td>5 (5,134)</td>
<td>1.19 (0.83–1.71)</td>
<td>1.22 (0.85–1.74)</td>
</tr>
<tr>
<td>$T/A$ vs. $A/A$</td>
<td>12 (5,907)</td>
<td>1.02 (0.92–1.14)</td>
<td>1.02 (0.92–1.14)</td>
</tr>
<tr>
<td>($T/T$+($T/T$) vs. $A/A$</td>
<td>6 (3,044)</td>
<td>1.87 (0.82–5.36)</td>
<td>2.51 (0.78–8.50)</td>
</tr>
<tr>
<td>Longer/Short TA alleles</td>
<td>4 (4,974)</td>
<td>0.88 (0.74–1.05)</td>
<td>0.88 (0.74–1.05)</td>
</tr>
<tr>
<td>European descent</td>
<td>3 (3,984)</td>
<td>0.91 (0.76–1.07)</td>
<td>0.91 (0.76–1.10)</td>
</tr>
<tr>
<td>Longer/Short vs. Short/Short</td>
<td>4 (1,959)</td>
<td>0.53 (0.26–1.05)</td>
<td>0.52 (0.26–1.05)</td>
</tr>
<tr>
<td>Longer/Longer vs. Short/Short</td>
<td>4 (2,487)</td>
<td>0.90 (0.75–1.03)</td>
<td>0.90 (0.75–1.09)</td>
</tr>
</tbody>
</table>

*Two studies on Asian populations are not included in the $A49T$ meta-analysis, since the $T$ allele was totally absent in both cases and controls.*
results [5 studies (3420 alleles), OR 1.03 (95% CI, 0.84–1.26), no significant between-study heterogeneity].

**A49T.** The magnitude of the summary OR had not been stable, and it had changed considerably in the last 2 years with an apparent dissipation of the postulated effect (by random effects, summary OR for T versus A: 2.67 at the end of 1999, 2.74 at the end of 2000, 1.66 at the end of 2001, and 1.56 at the end of 2002). Excluding the first study in the field (10) that may be considered to provide the hypothesis-generating data, the remaining studies did not suggest any strong association between the T allele and prostate cancer (random effects OR, 1.08; 95% CI, 0.72–1.61; \( P = 0.70 \)). The larger estimate of the association belonged to the smallest study, whereas the largest study had shown absolutely no effect. Analyses limited to studies with rigorous selection of cases and controls yielded similar results [2 studies (1200 alleles), OR 1.63 (95% CI, 0.26–10.2), no significant between-study heterogeneity].

**TA Repeats.** Data were very limited to apply meaningfully recursive cumulative meta-analysis and publication bias diagnostics. Analyses limited to studies with rigorous selection of cases and controls yielded similar results [3 studies (2190 alleles), OR 0.85 (95% CI, 0.64–1.12), no significant between-study heterogeneity].

### Discussion

This meta-analysis examined three well-characterized polymorphisms of the *SRD5A2* gene in their relationship to prostate cancer susceptibility. The current evidence definitively excludes any increased risk conferred by the V89L polymorphism. No additional studies are needed on this postulated association. One cannot exclude that the T allele in the A49T polymorphism may increase modestly the risk for prostate cancer, and homozygosity for the longer TA repeat alleles may decrease modestly this risk. Given the relative rarity of these two variants on a population basis, larger studies with many thousands of subjects would be needed to verify such effects. However, the meta-analysis clearly demonstrates that the contribution of these polymorphisms to prostate cancer at a population level is probably small, if at all present. Thus very large studies, if ever conducted, should be carefully designed to avoid dilution of the observed effects, and the cost of running such studies should be carefully weighted against the anticipated small gain of information. For A49T, the attributable fraction of prostate cancer in subjects of European descent is probably ≤1%, whereas the polymorphism is completely absent in subjects of Asian descent. Even the observed effect may be spurious, because it was largely driven by the first reported study in the field, i.e., from data that are mostly hypothesis-generating. Longer TA repeat homozygosity also occurs in only 2.3% of European descent subjects, and <1% of Asian subjects. No data have been generated on the association of this polymorphism with prostate cancer on African subjects, where the prevalence of longer TA repeat alleles may be higher (8).

The meta-analysis did not address whether these three polymorphisms may have an effect on the clinical behavior of prostate cancer or other clinicopathological attributes. A few studies have generated some relevant data, but their results have been contradictory. Nam et al. (12) claimed a 3.3-fold significantly increased risk of disease recurrence with the V/V and V/L genotypes. Conversely, Soderstrom et al. (19) claimed a significant 5.7-fold increased risk of metastatic disease with the...
L/L genotype, and Shibata et al. (28) also claimed a shorter time to biochemical failure for L/L subjects. Two other studies (17, 29) found no significant associations for the V89L polymorphism with clinicopathological correlates despite adequate sample sizes. Jaffe et al. (29) claimed that the T allele of the A49T polymorphism is associated with characteristics suggesting poor prognosis, and a younger age at diagnosis and a trend for more advanced stage were claimed by Soderstrom et al. (19), but no such associations were seen in 2 other studies (17, 21). Longer TA repeat homozygosity associations with stage have been probed on very limited data (17, 22). Definitions of clinicopathological correlates varied considerably across these studies, thus making difficult the comparison of their results. Given the multiplicity of possible comparisons and the unavoidable flexibility of choosing and defining these correlates, associations may have been detected by chance alone. The differences between studies are consistent with spurious findings, although some genuine association cannot be totally excluded.

The SRD5A2 gene may also have other polymorphisms that were not considered in the meta-analysis. One of them, the R227Q polymorphism, is already known, but is very rare: Q heterozygotes have a prevalence of only 0.2% in Asian descent subjects where this polymorphism has been studied (18). Nevertheless, we should note that linkage studies (30–32) based on genome scans have not identified overall any significant linkage of prostate cancer with the region of 2p23, the chromosomal location of the SRD5A2 gene.

The biochemical evidence for a putative relationship of SRD5A2 polymorphisms with androgen levels is also controversial. Hsing et al. (18) found that of all these polymorphisms, only the L allele had a statistically significant relationship with higher testosterone and lower 5α-androstan-3α,17β-diol glucuronide levels, but was not associated with apparent differences in DHT, estradiol, or steroid hormone binding globulin levels. A more marginal effect of the TA dinucleotide repeat polymorphism on DHT levels was also claimed (18). However, other investigators (33, 34) found actually lower testosterone levels with L/L, and in 2 studies (13, 33), the V89L polymorphism was not significantly associated with the levels of androstanediol glucuronide. Even if SRD5A2 is an important enzyme in androgen biosynthesis and even if the identified polymorphisms regulate its activity under certain experimental circumstances (8–11), there is no conclusive evidence that hormone levels are eventually affected in the serum, or more importantly, in the prostate tissue. Moreover, the exact role of androgens in the pathogenesis of prostate cancer has been a contentious issue (1, 35, 36), so serum hormone levels may not provide definitive proof for the presence or not of genetic predisposition to prostate cancer. Polymorphisms in genes coding for other enzymes of the androgen biosynthesis and metabolism pathway have also been postulated as prostate cancer determinants (2), but associations may also be refuted on scrutiny of the available evidence (37).

Postulated genetic associations for prostate cancer need to be carefully validated across several studies, because early and small genetic association studies may come up with spurious findings (38–40). Furthermore, genetic associations for such a multigenetic disease are likely to have relatively small ORs that would require large sample sizes to clarify. Some other limitations of this meta-analysis should be acknowledged. First, some nondifferential misclassification bias is possible. The majority of the considered studies could not exclude latent prostate cancer cases in the control group, and some controls may have developed prostate cancer during the subsequent years. However, the lifelong risk of prostate cancer among Americans is ~16% (41), so the OR dilution would probably be small. Furthermore, control groups included a large, often unknown proportion of subjects with BPH. BPH may be also androgen-dependent and affected by these same polymorphisms. However, one would then refer to a genetic factor conferring risk for prostate enlargement rather than cancer per se, a hypothesis with completely different connotations. Two (42, 43) of 3 studies (34, 42, 43) to date do not support this hypothesis. Finally, the meta-analysis did not address familial prostate cancer, i.e., the hereditary forms where several members of the same family may be affected. One study (21) has found no association between A49T and familial prostate cancer. Moreover, such hereditary forms account for a very small proportion of prostate cancer (31) and, thus, even strong genetic associations would have a limited impact on the incidence of prostate cancer at the population level.

Acknowledgments

We thank Drs. Alain Latil and Nina Mononen for providing additional data and clarifications on their studies.

References


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