Lack of Association Between CYP17 MspA1 Polymorphism and Prostate Cancer Risk: A Meta-Analysis of 14 494 Cases and 15 971 Controls

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Key Words: CYP17 MspA1 polymorphism; meta-analysis; prostate cancer.

Summary. Background and Objective. A T-to-C polymorphism that creates a recognition site for the MspA1 restriction enzyme in the 5’ promoter region of CYP17 has been implicated as a risk factor for prostate cancer. To date, many studies have evaluated associations between the CYP17 MspA1 polymorphism and prostate cancer risk; however, the results were controversial. Therefore, the aim of this study was to perform a meta-analysis to investigate the association between the CYP17 MspA1 polymorphism and the risk of prostate cancer.

Material and Methods. By searching the Pubmed, Web of Science, ScienceDirect, and EBSCO databases, 36 studies including 14 494 cases and 15 971 controls were collected. Odds ratios (ORs) with their 95% confidence intervals (CIs) were used to assess the strength of the association.

Results. The overall results showed no significant association between the CYP17 MspA1 polymorphism and the risk of prostate cancer (OR, 1.07; 95% CI, 0.92–1.25 for A2/A2 vs. A1/A1; OR, 1.02; 95% CI, 0.92–1.12 for A1/A2 vs. A1/A1; OR, 1.07; 95% CI, 0.94–1.22 for A2/A2 vs. A1/A2+A1/A1; OR, 1.03; 95% CI, 0.93–1.14 for A1/A2+A2/A2 vs. A1/A1). In the stratified analysis according to ethnicity, no significant associations were observed in Asian, European, and African populations in all genetic models. In the stratified analysis by the source of controls and inpatients were found to have an increased risk of prostate cancer in all genetic models.

Conclusions. The meta-analysis suggests that the CYP17 MspA1 polymorphism is unlikely to increase the risk of prostate cancer in a wide population.

Introduction

Prostate cancer (PCA) is the most common cancer among men, accounting for 10% of male cancer-related mortality (1). The major risk factors for the development of PCA are advanced age, familial predisposition, ethnicity, and environmental factors (2, 3). The role of steroid hormones in the etiology of PCA has been reported, and several molecules encoded by polymorphic genes (hormones, their receptors, and enzymes involved in hormone biosynthesis and metabolism) have recently been shown to be associated with the risk of PCA (4). The CYP17 gene maps to chromosome 10q24.3 (5) that encodes the cytochrome P450c17α enzyme mediating both 17α-hydroxylase and 17, 20-lyase activities at key points in the testosterone biosynthesis in gonads and adrenals (6). It is conceivable that changes in the activity of the CYP17 enzyme may have an impact on androgen biosynthesis and, thus, influence susceptibility to the risk of PCA. The 5’-untranslated region of CYP17 contains a single T-to-C base transition at position 1931 (rs743572) that creates a recognition site for the MspA1 restriction enzyme that has been used to designate 2 alleles: A1 (wild allele) and A2 (variant allele) (7). This polymorphism may enhance the transcription of the CYP17 gene and, thus, increases enzyme activity.

A few studies have indicated that the A2 allele may be associated with an increased risk of PCA (8–13). However, other investigations have apparently been inconclusive (14, 15) or have even reported that the A1 allele may increase the risk of PCA (16, 17). To clarify the effect of the CYP17 MspA1 polymorphism on the risk of PCA, we conducted a meta-analysis of all available studies.

Material and Methods

Literature Search. The PubMed, Web of Science, ScienceDirect, and EBSCO databases (the last search was updated on November 5, 2010) were searched with the following key words and terms: cytochrome P450c17α, CYP17 polymorphism, and prostate cancer. All eligible articles were retrieved, and their references were checked for other relevant articles. When more than one publication involved the same patient population, only the most recent or
complete study was included in this meta-analysis. Inclusion Criteria. The study was included into our meta-analysis only if it met the following criteria: 1) available data on the risk of PCa and the MspA1 polymorphism; 2) published in English or Chinese; 3) case-control studies; 4) sources of cases clearly described; 5) sufficient data to estimate an odds ratio (OR) with its 95% confidence interval (CI); and 6) available genotype frequency. When the publication reported results for more than one population, we considered it as two separate studies.

Information was carefully extracted from all the eligible publications independently by 2 of the authors according to the inclusion criteria listed above. The following information was extracted from the study: the first author’s last name, year of publication, ethnicity of subjects, number of patients and controls, source of controls, and genotype frequency.

Statistical Analysis. The strength of association between the CYP17 MspA1 polymorphism and the risk of PCa was assessed by ORs with 95% CIs. The pooled ORs were estimated for codominant (A2/A2 vs. A1/A1; A1/A2 vs. A1/A1), dominant (A2/A2+ A1/A2 vs. A1/A1), and recessive (A2/A2 vs. A1/A2+A1/A1) models. Stratified analyses were performed by ethnicity and the source of controls. Firstly, the Pearson χ² test was used to determine whether the distribution of genotypes in controls was in agreement with the Hardy-Weinberg equilibrium (18). Secondly, the heterogeneity among the studies was evaluated with the Cochrane Q test; it was considered significant when P<0.05. The data were combined using both fixed- and random-effects models. The random-effects model was more appropriate when heterogeneity existed (19); otherwise, the fixed-effects model was utilized (20). Finally, publication bias was checked. Publication bias was assessed graphically by using funnel plots and statistically by using the Egger’s test (21). Statistical analysis was performed with STATATA11.1 and SPSS13.0, and all the P values were two-sided.

Results

Study Characteristics. Based on our search criteria, a total of 53 studies were preliminarily eligible. All the papers were reviewed according to the crite-

### Table 1. The Main Characteristics of Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Ethnicity</th>
<th>No. of Patients With PCa</th>
<th>No. of Controls</th>
<th>Source of Controls</th>
<th>A2 allele</th>
<th>$P_{\text{meta}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu (22)</td>
<td>2009</td>
<td>Asian</td>
<td>85</td>
<td>82</td>
<td>HB</td>
<td>0.52</td>
<td>0.49</td>
</tr>
<tr>
<td>Sobti (23)</td>
<td>2009</td>
<td>Asian</td>
<td>157</td>
<td>170</td>
<td>HB</td>
<td>0.30</td>
<td>0.01</td>
</tr>
<tr>
<td>Sobti (24)</td>
<td>2008</td>
<td>Asian</td>
<td>157</td>
<td>170</td>
<td>HB</td>
<td>0.31</td>
<td>0.01</td>
</tr>
<tr>
<td>Dos Santos (25)</td>
<td>2008</td>
<td>African</td>
<td>43</td>
<td>50</td>
<td>HB</td>
<td>0.28</td>
<td>0.45</td>
</tr>
<tr>
<td>Sarma (26)</td>
<td>2008</td>
<td>African</td>
<td>126</td>
<td>322</td>
<td>PB</td>
<td>0.39</td>
<td>0.00</td>
</tr>
<tr>
<td>Setiawan (27)</td>
<td>2007</td>
<td>European</td>
<td>7948</td>
<td>8834</td>
<td>PB</td>
<td>0.40</td>
<td>0.90</td>
</tr>
<tr>
<td>Gunes (28)</td>
<td>2007</td>
<td>Asian</td>
<td>148</td>
<td>102</td>
<td>HB</td>
<td>0.28</td>
<td>0.71</td>
</tr>
<tr>
<td>Cussenot (29)</td>
<td>2007</td>
<td>European</td>
<td>998</td>
<td>777</td>
<td>PB</td>
<td>0.41</td>
<td>0.10</td>
</tr>
<tr>
<td>Onen (30)</td>
<td>2007</td>
<td>Asian</td>
<td>100</td>
<td>105</td>
<td>PB</td>
<td>0.43</td>
<td>0.91</td>
</tr>
<tr>
<td>Hamada (31)</td>
<td>2007</td>
<td>European</td>
<td>222</td>
<td>83</td>
<td>PB</td>
<td>0.39</td>
<td>0.44</td>
</tr>
<tr>
<td>Sobti (32)</td>
<td>2006</td>
<td>Asian</td>
<td>100</td>
<td>100</td>
<td>HB</td>
<td>0.30</td>
<td>0.63</td>
</tr>
<tr>
<td>Guli (33)</td>
<td>2006</td>
<td>Asian</td>
<td>31</td>
<td>104</td>
<td>HB</td>
<td>0.45</td>
<td>0.49</td>
</tr>
<tr>
<td>Yang (34)</td>
<td>2006</td>
<td>Asian</td>
<td>163</td>
<td>202</td>
<td>HB</td>
<td>0.59</td>
<td>0.54</td>
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<tr>
<td>Okugi (35)</td>
<td>2006</td>
<td>Asian</td>
<td>102</td>
<td>117</td>
<td>HB</td>
<td>0.47</td>
<td>0.75</td>
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<tr>
<td>Vesovic (36)</td>
<td>2005</td>
<td>European</td>
<td>174</td>
<td>89</td>
<td>NR</td>
<td>0.39</td>
<td>0.09</td>
</tr>
<tr>
<td>Forrest (37)</td>
<td>2005</td>
<td>European</td>
<td>262</td>
<td>425</td>
<td>PB</td>
<td>0.36</td>
<td>0.35</td>
</tr>
<tr>
<td>Antognelli (38)</td>
<td>2005</td>
<td>European</td>
<td>384</td>
<td>360</td>
<td>NR</td>
<td>0.44</td>
<td>0.06</td>
</tr>
<tr>
<td>Antognelli (39)</td>
<td>2004</td>
<td>European</td>
<td>96</td>
<td>18</td>
<td>NR</td>
<td>0.44</td>
<td>0.67</td>
</tr>
<tr>
<td>Cicik (40)</td>
<td>2004</td>
<td>African</td>
<td>38</td>
<td>38</td>
<td>FB</td>
<td>0.33</td>
<td>0.17</td>
</tr>
<tr>
<td>Cicik (40)</td>
<td>2004</td>
<td>European</td>
<td>397</td>
<td>436</td>
<td>FB</td>
<td>0.40</td>
<td>0.61</td>
</tr>
<tr>
<td>Madigan (41)</td>
<td>2003</td>
<td>Asian</td>
<td>174</td>
<td>274</td>
<td>PB</td>
<td>0.61</td>
<td>0.22</td>
</tr>
<tr>
<td>Lin (42)</td>
<td>2003</td>
<td>Asian</td>
<td>93</td>
<td>121</td>
<td>HB</td>
<td>0.36</td>
<td>0.02</td>
</tr>
<tr>
<td>Stanford (13)</td>
<td>2002</td>
<td>European</td>
<td>560</td>
<td>523</td>
<td>PB</td>
<td>0.40</td>
<td>0.59</td>
</tr>
<tr>
<td>Stanford (13)</td>
<td>2002</td>
<td>African</td>
<td>30</td>
<td>15</td>
<td>PB</td>
<td>0.37</td>
<td>0.99</td>
</tr>
<tr>
<td>Santos (43)</td>
<td>2002</td>
<td>African</td>
<td>8</td>
<td>72</td>
<td>PB</td>
<td>0.34</td>
<td>0.38</td>
</tr>
<tr>
<td>Santos (43)</td>
<td>2002</td>
<td>European</td>
<td>84</td>
<td>128</td>
<td>PB</td>
<td>0.34</td>
<td>0.22</td>
</tr>
<tr>
<td>Chang (14)</td>
<td>2001</td>
<td>European</td>
<td>225</td>
<td>182</td>
<td>PB</td>
<td>0.36</td>
<td>0.43</td>
</tr>
<tr>
<td>Latil (15)</td>
<td>2001</td>
<td>European</td>
<td>226</td>
<td>156</td>
<td>PB</td>
<td>0.42</td>
<td>0.20</td>
</tr>
<tr>
<td>Kittles (12)</td>
<td>2001</td>
<td>African</td>
<td>71</td>
<td>111</td>
<td>PB</td>
<td>0.30</td>
<td>0.93</td>
</tr>
<tr>
<td>Haiman (11)</td>
<td>2001</td>
<td>European</td>
<td>590</td>
<td>782</td>
<td>PB</td>
<td>0.39</td>
<td>0.12</td>
</tr>
<tr>
<td>Yamada (10)</td>
<td>2001</td>
<td>Asian</td>
<td>101</td>
<td>200</td>
<td>HB</td>
<td>0.45</td>
<td>0.00</td>
</tr>
<tr>
<td>Habuchi (17)</td>
<td>2000</td>
<td>Asian</td>
<td>252</td>
<td>333</td>
<td>NR</td>
<td>0.44</td>
<td>0.42</td>
</tr>
<tr>
<td>Guoqi Song, Ling Gu, Fuliang Tian, et al.</td>
<td>2013</td>
<td>European</td>
<td>988</td>
<td>984</td>
<td>RB</td>
<td>0.36</td>
<td>0.09</td>
</tr>
</tbody>
</table>

PCa, prostate cancer; HWE, Hardy-Weinberg equilibrium; FB, family-based; HB, hospital-based; PB, population-based; NR, not reported.
We excluded 3 reviews, 3 repeated articles, and 15 papers that did not offer full information or were irrelevant to our study. Four studies analyzed different populations. Finally, 36 studies were included in our analysis. There were 16 studies of European, 13 studies of Asian, and 7 studies of African populations.

Table 1 summarizes their main characteristics. In the majority of the analyzed studies, genotype distributions were in agreement with the Hardy-Weinberg equilibrium with the exception of 5 studies (10, 23, 24, 26, 42).

Table 2 lists the main results of the meta-analysis. When all the 36 studies were pooled into the meta-analysis, there was no evidence for a significant association between the CYP17 MspA1 polymorphism and the risk of PCa. In the subgroup analyses by ethnicity and the source of controls, significant associations were found only in inpatients subjects in all genetic models (Table 2).

For heterogeneity, there was significant heterogeneity across the studies in overall comparisons. In order to clarify the source of the heterogeneity, stratified analyses by the source of controls and ethnicity were performed. As a result, the source of controls was found to contribute to the heterogeneity for dominant (\( P_{\text{heterogeneity}} < 0.001 \)), recessive (\( P_{\text{heterogeneity}} = 0.006 \)), and codominant (A2/A2 vs. A1/A2, \( P_{\text{heterogeneity}} = 0.001 \); A2/A1 vs. A1/A1, \( P_{\text{heterogeneity}} = 0.002 \); A1/A2 vs. A1/A1, \( P_{\text{heterogeneity}} = 0.001 \)) models. However, ethnicity was not the source of heterogeneity.

Publication bias was assessed using Begg's funnel plot and the Egger's test. As shown in Fig. 1, the shapes of the funnel plot did not reveal any obvious asymmetry. The Egger's test was used to provide the statistical evidence of funnel plot symmetry. The results did not show any publication bias. The\( \left( r^2 = 27, P = 0.213, \text{for A2/A2 vs. A1/A1} \right) \)
Discussion
The present meta-analysis of 36 studies, including 14,494 cases and 15,971 controls, provided the most comprehensive analysis on the association of the CYP17 MspA1 polymorphism with the risk of PCa. The results indicated that the CYP17 MspA1 polymorphism was not associated with an increased risk of PCa in the overall studied population. These findings were consistent with most of the studies that were included into our meta-analysis.

A study by Zmuda et al. reported that white men with the A2/A2 genotype had a higher bioavailable testosterone level than men with the A1/A1 genotype. A1/A2 heterozygotes had intermediate testosterone values (44). However, there was no evidence of a consistently increased androgen concentration in A2 allele carriers demonstrated. Additionally, the CYP17 genotype was not reported to be associated with the different levels of testosterone, other androgens and their metabolites (dehydrotestosterone, androstanediol glucuronide) (11, 45). Furthermore, genome scans had typically not identified significant linkage to the 10q24.32 chromosomal region where the CYP17 gene was located (46, 47).

In the stratified analysis according to ethnicity, no significant associations were observed in Asian, European, and African populations in all genetic models suggesting that ethnic differences in genetic backgrounds and the environment they lived did not play an obvious role in the association between the CYP17 MspA1 polymorphism and the risk of PCa.

Between-study heterogeneity may be attributed to many factors including the selection of publications and differences in population characteristics, sample sizes, and source of controls. We also explored the ethnicity and source of controls as the possible causes of heterogeneity. First, controls in the studies were not uniformly defined. Although most of the controls were mainly selected from healthy populations, a few controls had benign prostatic hyperplasia. Nondifferential misclassification bias was possible because these studies might have included controls that had different risks for developing PCa. Second, the detailed information on patients’ age, smoking habits, and environmental factors could not be traced. Therefore, our unadjusted estimates should be confirmed by further studies. Third, we should also admit the possibility of publication bias. Some studies on the relationship between the CYP17 MspA1 polymorphism and the risk of PCa may not have been indexed online or may be unpublished so far.

In summary, this meta-analysis did not provide the evidence of an association between the CYP17 MspA1 polymorphism and the risk of PCa in a pooled worldwide population. Future studies should use standardized, unbiased, homogenous groups of cancer patients and well-matched controls. Studies of the combined effects of gene and environment contribution would lead to more comprehensive understanding of the association between the CYP17 MspA1 polymorphism and the risk of PCa.

Conclusions
The meta-analysis demonstrated that the CYP17 MspA1 polymorphism was not associated with an increased risk of prostate cancer in a worldwide population.

Statement of Conflicts of Interest
The authors state no conflict of interest.

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