The association of XRCC3 Thr241Met genetic variant with risk of prostate cancer: a meta-analysis

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Abstract
Background: Previous studies suggest that the X-ray repair cross-complementing group 3 gene (XRCC3) Thr241Met genetic variant could be potentially associated with the risk of prostate cancer. However, results from these published studies were conflicting rather than conclusive.

Objectives: This meta-analysis aimed to conduct a better understanding of the effects of XRCC3 Thr241Met genetic variant on prostate cancer risk.

Methods: We identified three eligible studies, 499 prostate cancer cases and 571 controls.

Results: Overall, significant associations were detected in the heterozygote comparison genetic model (CT versus (vs.) CC: OR = 0.71, 95% CI 0.53-0.94, Z = 2.38, p = 0.017), and the dominant genetic model (TT/CT vs. CC: OR = 0.74, 95% CI 0.57-0.98, Z = 2.11, p = 0.035). In the subgroup analysis by ethnicities, we found that this genetic variant was significantly associated with the decrease risk of prostate cancer in Caucasians for heterozygote comparison genetic model (CT vs. CC: OR = 0.66, 95% CI 0.44-0.98, Z = 2.04, p = 0.042). No publication bias was found in this study.

Conclusions: Results from this meta-analysis indicate that the XRCC3 Thr241Met genetic variant is associated with prostate cancer risk.

Keywords: Prostate cancer; XRCC3 gene; Genetic variant; Meta-analysis

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Introduction
Prostate cancer is the most common malignancy of men in the world, accounting for 10% of men cancer-related mortality. The etiology of prostate cancer is largely unknown, although genetic and environmental factors might increase risk of prostate cancer. The X-ray repair cross-complementing group 3 (XRCC3) is one of the DNA repair genes, and is an important candidate gene for mediating the genetic influence on prostate cancer. The C18067T genetic variant in XRCC3 gene at exon 7 (C>T, rs861539), one of the most studied functional genetic variants, results from a C to T mutation and causes the substitution of Threonine (Thr) to Methionine (Met) at codons 241 (p.Thr241Met), has been potentially associated with the risk of prostate cancer. However, results from published studies were conflicting rather than conclusive. Therefore, to clarify the effects of XRCC3 Thr241Met genetic variant on prostate cancer risk, we conducted a meta-analysis of all available published studies to date.

Materials and methods
Publication search
Pubmed, Excerpta Medica Database (EMBASE), and Chinese National Knowledge Infrastructure (CNKI) databases were searched using the search terms: “prostate cancer/neoplasm”, “XRCC3”, “Thr241Met”, and “rs8761539” (the last search was updated on June 2014). Publication searching was utilized without limitation on language and publication date. Two investigators searched the publication literature and extracted data independently.

Inclusion, exclusion criteria and Data extraction
For inclusion criteria in the present meta-analysis, the selected eligible articles had to provide informa-
Statistical analysis

The strength of the association of XRCC3 Thr241Met genetic variant with the risk of prostate cancer was assessed by the pooled ORs with their 95% CIs. Subgroup analyses were evaluated by ethnicities.

The significance of pooled ORs was determined by the Z-test. The heterogeneity assumption was evaluated by the chi-square-based Q-test and/or I² > 50% for Q-test indicated a lack of heterogeneity among the studies. The fixed effect model (the Mantel-Haenszel method) was used when P-value > 0.10; otherwise fixed effect model was used.

Table 1. The characteristics of eligible studies included in this meta-analysis.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Genotyping methods</th>
<th>No. (cases/controls)</th>
<th>Case (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritchey</td>
<td>2005</td>
<td>USA</td>
<td>Caucasians</td>
<td>MALDI-TOF</td>
<td>159/241</td>
<td>139/17</td>
<td>214/31</td>
</tr>
<tr>
<td>Mandal</td>
<td>2010</td>
<td>India</td>
<td>Asians</td>
<td>PCR-RFLP</td>
<td>224/192</td>
<td>137/78</td>
<td>197/77</td>
</tr>
<tr>
<td>Dhillon</td>
<td>2011</td>
<td>Australia</td>
<td>Caucasians</td>
<td>PCR-RFLP</td>
<td>116/132</td>
<td>68/44</td>
<td>124/72</td>
</tr>
</tbody>
</table>

MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; PCR-RFLP: Polymerase Chain Reaction Restriction Fragment Length Polymorphism

Meta-analysis

Table 2 summarized the association strength between XRCC3 Thr241Met genetic variant and the risk of prostate cancer. In the overall, significant associations were detected in heterozygote comparison genetic model (CT versus CC): OR = 0.71, 95% CI 0.53-0.94, Z = 2.38, P = 0.017, Table 2, Figure 1), and dominant genetic model (TT/CT versus CC: OR = 0.74, 95% CI 0.57-0.98, Z = 2.11, P = 0.035, Table 2).
The XRCC3 Thr241Met genetic variant was significantly associated with the decrease risk of prostate cancer in Caucasians for heterozygote comparison genetic model (CT vs. CC: OR = 0.66, 95% CI 0.44-0.98, Z = 2.04, P = 0.042, Table 2). Our data indicated that there were no significant associations between XRCC3 Thr241Met genetic variant and prostate cancer risk in other genetic models (All P-values >0.05, Table 2). No evidence of publication bias was found in all comparison genetic models (All P-values > 0.05).

The funnel plot (Figure 2) demonstrated a potential publication bias which was not statistically significant (Egger’s test, P = 0.15). The pooled ORs for the XRCC3 Thr241Met genetic variant with prostate cancer risk in the Caucasian subpopulation were 0.66 (95% CI 0.44-0.98, Z = 2.04, P = 0.042). Another subgroup analysis of the enrolled African-American, Asian, and Mediterranean populations did not produce significant results. However, the results for the enrichment of the XRCC3 Thr241Met genetic variant showed no significant results in South Asian populations.

In the subgroup analysis by ethnicities, we found that the XRCC3 Thr241Met genetic variant was negatively associated with the decrease risk of prostate cancer in Caucasians. Ritchey and colleagues reported that XRCC3 Thr241Met genetic variant showed no significance with the risk of prostate cancer, and several studies have carried out to investigate the potential association of XRCC3 Thr241Met genetic variant with prostate cancer risk in other ethnic groups. Ritchey and colleagues reported that XRCC3 Thr241Met genetic variant showed no significance with the risk of prostate cancer. Ritchey and colleagues reported that XRCC3 Thr241Met genetic variant was significantly associated with the decrease risk of prostate cancer only in Caucasians population. Ritchey and colleagues reported that XRCC3 Thr241Met genetic variant was significantly associated with the decrease risk of prostate cancer in Caucasians population. 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