Original Article
TERT rs2736098 polymorphism and bladder cancer risk: a meta-analysis

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Abstract: Background: Numerous studies have evaluated the relationship between the human telomerase reverse transcriptase (TERT) gene variant rs2736098 polymorphism and bladder cancer risk, but the sample size has been small and the results were conflicting. This meta-analysis was conducted to comprehensively evaluate the overall association. Methods: Pubmed, Web of science, Embase, China biology medical literature database (CBM), China National Knowledge Infrastructure (CNKI), WanFang and Weipu databases were searched before Jun 30, 2018. The strength of associations was assessed using Odds ratios (ORs) and 95% confidence intervals (CIs). All of the statistical analyses were conducted using Review Manager 5.3 and Stata 14.0. Results: Six studies involved 1974 cases and 2887 controls. Overall, significant association was observed between the TERT gene variant rs2736098 polymorphism and bladder cancer (A vs. G: OR = 1.22, 95% CI = 1.11-1.33; AA vs. GG: OR = 1.53, 95% CI = 1.25-1.87; AA vs. AG+GG: OR = 1.44, 95% CI = 1.20-1.74; AA+AG vs. GG: OR = 1.22, 95% CI = 1.08-1.38). In subgroup analysis by ethnic groups, a statistically significant association was observed in Asians (A vs. G: OR = 1.29, 95% CI = 1.07-1.55), but not in Caucasians (A vs. G: OR = 1.13, 95% CI = 0.98-1.31). Sensitivity analysis confirmed the reliability and stability of the meta-analysis. Conclusion: Meta-analysis supports that the TERT gene variant rs2736098 polymorphism might contribute to individual susceptibility to bladder cancer in Asians.

Keywords: Bladder cancer, TERT, polymorphism, meta-analysis

Introduction

Bladder cancer, the ninth most frequently-diagnosed cancer worldwide, is the leading cause of cancer-related morbidity and mortality among urological cancers [1]. United States estimates suggest that approximately 76,960 new BC cases have been diagnosed, and 16,390 patients died of bladder cancer in 2016 [2]. At present, the etiology of bladder cancer largely unknown, but multiple factors such as smoking, alcoholic consumption, genetic mutation, family history, and occupational exposure to carcinogens are risk factors for bladder cancer, and play essential roles in the pathogenesis and progression [3-6]. In addition, current evidence indicates that the TERT gene variant rs2736098 polymorphism is associated with the risk of bladder cancer [7, 8].

The TERT gene is located in chromosome 5 at 5p15.33, and TERT complex is a ribonucleoprotein polymerase, involved in DNA telomere elongation and plays an essential role in maintenance of telomere DNA length [9, 10]. Telomeres are special structures at the end of eukaryotic chromosomes that help to synthesize the sequence of DNA, to offset or postpone the continuously shortening of the telomere during mitosis [11, 12], which is mediated by TERT [13]. Mutations in the TERT gene can affect telomerase activity and telomere length, thus may promote the incidence and progression of cancer [13-15].

TERT rs2736098, which is located on exon 2 of the TERT gene, was recently identified as a risk factor for bladder cancer [7, 16]. Although a number of studies have focused on the TERT gene variant rs2736098 and polymorph TERT gene variant rs2736098 polymorphisms with respect to bladder cancer, they have small sample sizes and yielded contradictory results. Therefore, meta-analysis was performed on all
published case-control studies to derive a more precise estimation of TERT gene variant rs2736098 polymorphism with bladder cancer risk.

**Materials and methods**

**Publication search**

The databases of Pubmed, Web of science, Embase, CBM, CNKI, WanFang and Weipu databases were searched for studies examining the relation between TERT gene variant rs2736098 polymorphism and bladder cancer risk up to Jun 30, 2018. The search terms were as follows: "telomerase reverse transcriptase", "TERT", "rs2736098", "bladder cancer", "bladder carcinoma", "bladder tumor", and "bladder neoplasm". In addition, the reference lists of relevant studies were also reviewed to identify other potential studies missed by the initial search.

**Inclusion and exclusion criteria**

Only studies meeting the following inclusive selection criteria were eligible: (1) case-control study investigating the association of TERT gene variant rs2736098 polymorphism and bladder cancer susceptibility; (2) the genotypes in cases and controls were available, (3) sufficient raw data to calculate odd ratio (OR) with 95% confidence interval (CI). Exclusion criteria: 1) study with incomplete data; 2) editorial articles, review articles, case reports, and meeting abstracts; 3) duplicate publications with overlapping data.

**Data extraction**

Two authors extracted the relevant data using a standardized data extraction form independently. Discrepancies were resolved by discussion with a third investigator. The following information was extracted from each study: first author, year of publication, country, ethnicity, genotyping method, sample size, genotype frequencies of TERT gene variant rs2736098 polymorphism.

**Quality assessment**

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies by two authors [17]. This scale assesses the quality of case-control studies included three areas: selection, comparability, and exposure. A star rating system was used to judge methodological quality. Scores range from 0 stars (worst) to 9 stars (best), and studies with a score ≥7 were defined as high quality. Discrepant opinions were resolved by discussion and consensus.

**Statistical analysis**

Odds ratios (OR) with 95% CI were used to assess the strength of association between TERT gene variant rs2736098 polymorphism and bladder cancer risk. The pooled ORs were performed for TERT gene variant rs2736098 polymorphism under the allele comparison model (A vs. G), additive model (AA vs. GG), recessive model (AA vs. AG+GG) and dominant model (AA+AG vs. GG), respectively. The significance of the pooled OR was analyzed by the Z test, and P<0.05 was considered statistically significant. Chi-square-based Q-test and I² statistics were used to calculate heterogeneity among included studies. The P>0.05 for Q test or I²<50% indicated a statistically significant degree of heterogeneity among studies, thus, a fixed effect model was used. In contrast, the random-effects model was used. All statistical analyses were performed by using Review Manager 5.3 and Stata 14.0. Publication bias was investigated with the funnel plot, Begg’s test, and Egger's test. Sensitivity analysis was conducted to assess the stability of the results by sequentially omitted individual studies.

**Results**

**Description of included studies**

A total of 146 results were retrieved after first search in the selected databases, as shown in Figure 1. Of these studies, after the first screening, 140 studies were excluded based on inclusion and exclusion criteria. Finally, 6 case-control studies considering 1,974 cases and 2,887 controls were included in the meta-analysis [7, 8, 18-20]. The publication years of the assessed studies ranged from 2011 to 2016. Of these, there were two studies of Caucasian descendants and four studies of Asian descendants. The countries of these studies were USA, Austria, India, and China. The characteristics of each of the included studies are shown in Table 1.
Meta-analysis of TERT gene variant rs2736098 polymorphism in bladder cancer susceptibility

Six studies involving a total of 4,861 individuals evaluated the influence of the TERT gene variant rs2736098 polymorphism on the risk of bladder cancer. Figures 2-5 show meta-analysis results for the allele model, additive model, recessive model, and dominant model, for which the I² value was 43%, 36%, 13%, and 49%, respectively. Thus, the fixed effect model was used to synthesize the data. Overall, pooled risk estimates indicated that TERT gene variant rs2736098 polymorphism was associated with an increased risk of bladder cancer (A vs. G: OR = 1.22, 95% CI = 1.11-1.33; AA vs. GG: OR = 1.53, 95% CI = 1.25-1.87; AA vs. AG+GG: OR = 1.44, 95% CI = 1.20-1.74; AA+AG vs. GG: OR = 1.22, 95% CI = 1.08-1.38).

Subgroup analysis based on ethnicity indicated that the TERT gene variant rs2736098 polymorphism was associated with increased susceptibility to bladder cancer in Asians (A vs. G: OR = 1.22, 95% CI = 1.11-1.33; AA vs. GG: OR = 1.53, 95% CI = 1.25-1.87; AA vs. AG+GG: OR = 1.44, 95% CI = 1.20-1.74; AA+AG vs. GG: OR = 1.22, 95% CI = 1.08-1.38), however, no association was found between TERT gene variant...
TERT rs2736098 polymorphism and bladder cancer

Table 1. Characteristics of studies included in meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Region</th>
<th>Genotyping method</th>
<th>Case (GG)</th>
<th>Control (GG)</th>
<th>Case (AG)</th>
<th>Control (AG)</th>
<th>Case (AA)</th>
<th>Control (AA)</th>
<th>HWE</th>
<th>NOS</th>
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<tbody>
<tr>
<td>Gago-Dominguez 1</td>
<td>2011</td>
<td>USA</td>
<td>TaqMan</td>
<td>449</td>
<td>531</td>
<td>217</td>
<td>189</td>
<td>43</td>
<td>278</td>
<td>&gt;0.05</td>
<td>7</td>
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<tr>
<td>Gago-Dominguez 2</td>
<td>2011</td>
<td>China</td>
<td>TaqMan</td>
<td>499</td>
<td>527</td>
<td>178</td>
<td>236</td>
<td>85</td>
<td>203</td>
<td>&lt;0.05</td>
<td>7</td>
</tr>
<tr>
<td>Jaworowska</td>
<td>2011</td>
<td>Australia</td>
<td>TaqMan</td>
<td>426</td>
<td>428</td>
<td>239</td>
<td>168</td>
<td>19</td>
<td>260</td>
<td>&gt;0.05</td>
<td>8</td>
</tr>
<tr>
<td>Lu</td>
<td>2016</td>
<td>China</td>
<td>PCR-RFLP</td>
<td>201</td>
<td>200</td>
<td>58</td>
<td>95</td>
<td>48</td>
<td>80</td>
<td>&gt;0.05</td>
<td>6</td>
</tr>
<tr>
<td>Ma</td>
<td>2013</td>
<td>China</td>
<td>MassARRAY</td>
<td>174</td>
<td>961</td>
<td>71</td>
<td>75</td>
<td>28</td>
<td>373</td>
<td>&gt;0.05</td>
<td>7</td>
</tr>
<tr>
<td>Singh</td>
<td>2014</td>
<td>India</td>
<td>TaqMan</td>
<td>225</td>
<td>240</td>
<td>77</td>
<td>106</td>
<td>42</td>
<td>117</td>
<td>&gt;0.05</td>
<td>6</td>
</tr>
</tbody>
</table>

Figure 2. Forest plot of studies assessing association between TERT rs2736098 polymorphism and bladder cancer. (Allelic model: A vs. G).

Figure 3. Forest plot of studies assessing association between TERT rs2736098 polymorphism and bladder cancer. (Additive model: AA vs. GG).

Figure 4. Forest plot of studies assessing association between TERT rs2736098 polymorphism and bladder cancer. (Dominant model: AA+AG vs. GG).

rs2736098 polymorphism and bladder cancer risk in Caucasians (A vs. G: OR = 1.22, 95% CI = 1.11-1.33; AA vs. GG: OR = 1.53, 95% CI = 1.25-1.87; AA vs. AG+GG: OR = 1.44, 95% CI = 1.20-1.74; AA+AG vs. GG: OR = 1.22, 95% CI = 1.08-1.38) (Table 2).
Publication bias and sensitivity

Funnel plot, Begg's test, and Egger test were used to analyze potential publication bias. No significant publication bias was observed under all the genetic models, as shown in Figure 6 and Table 3. Sensitivity analyses were performed to assess the effect of each individual
TERT rs2736098 polymorphism and bladder cancer

Table 3. Publication bias test for TERT rs2736098 polymorphism

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Egger test</th>
<th>Begg test</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>P value</td>
</tr>
<tr>
<td>TERT rs2736098</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A vs. G</td>
<td>3.817</td>
<td>0.304</td>
</tr>
<tr>
<td>AA vs. GG</td>
<td>-1.095</td>
<td>0.777</td>
</tr>
<tr>
<td>AA+AG vs. GG</td>
<td>4.109</td>
<td>0.214</td>
</tr>
<tr>
<td>AA vs. AG+GG</td>
<td>-3.560</td>
<td>0.215</td>
</tr>
</tbody>
</table>

Figure 7. Sensitivity analysis diagram for each study used to assess relative risk estimates for TERT rs2736098 polymorphism and bladder cancer in all included studies. (A. Allelic model: A vs. G; B. Additive model: AA vs. GG; C. Dominant model: AA+AG vs. GG, D. Recessive model: AA vs. AG+GG).

study on the pooled ORs by sequentially excluding individual studies, and the results showed no individual study influenced the overall pooled ORs (Figure 7), indicating that the results of this meta-analysis are relatively stable.

Discussion

This meta-analysis was conducted to provide a clear understanding of TERT gene variant rs-2736098 polymorphism and risk of bladder cancer. The results of this meta-analysis suggest that genetic variations of TERT gene rs-2736098 may contribute to susceptibility to bladder cancer in Asians, but not in Caucasians. The etiology of bladder cancer is complicated, and several risk factors are involved in the development and progression [21]. In addition to environmental and lifestyle risk factors, genetic causes, such as single gene mutations, also play essential roles in bladder cancer [22-25]. The rs2736098 (G>A) polymorphism is one of the most commonly investigated SNPs in the TERT gene, which is located in the second exon of TERT [26]. The SNP can affect the activity of telomerase and shorten telomere length, which may promote the occurrences and progression of cancer [13, 14]. In the present study, the overall results showed that TERT gene rs2736098 polymorphism could increase
the risk of bladder cancer (A vs. G: OR = 1.22, 95% CI = 1.11-1.33; AA vs. GG: OR = 1.53, 95% CI = 1.25-1.87; AA vs. AG+GG: OR = 1.44, 95% CI = 1.20-1.74; AA+AG vs. GG: OR = 1.22, 95% CI = 1.08-1.38). It reveals that individuals with the variant A allele may have a higher risk for bladder cancer than those carrying G homozygote. Nevertheless, in the subgroup analysis of ethnicity, the TERT gene rs2736098 polymorphism had an effect on increase in the bladder cancer risk in Asians, while the susceptibility to bladder cancer was not observed in Caucasian population. In this study, there was no evidence of heterogeneity across studies, even though populations from 4 different countries were included.

There is increasing evidence investigating the association between TERT gene rs2736098 polymorphism and risk of different type of cancers [27-29]. Several studies have evaluated the relationship of TERT gene rs2736098 polymorphism and bladder cancer, and the results remain inconclusive rather than consistent. Singh et al. reported that TERT gene rs2736098 polymorphism confirmed high risk for bladder cancer in North Indian population. A case-control study conducted by Lu et al. found the TERT gene rs2736098 polymorphism is associated with risk of bladder cancer in Chinese population. However, Jaworowska et al. reported that no association was observed between TERT gene rs2736098 polymorphism and bladder cancer in the Polish Population. Similarly, Ma et al. found that the TERT gene rs2736098 polymorphism is not a major risk factor for bladder cancer in the Chinese population. In addition, a Genome-wide association study conducted by Gago-Dominguez et al. revealed an association between TERT gene rs2736098 polymorphism and bladder cancer in Chinese population, and no significant association was found in America population. The difference between the studies could arise from race, geographic, or genetic background differences of the study population. In the present study, a significant association was observed between the TERT gene rs2736098 polymorphism and bladder cancer in the overall population. In a sub-group analysis based on nationality, a significant association between the TERT gene rs2736098 polymorphism and bladder cancer risk in Asians was found, but not in Caucasian population. Only two studies reported the relationship between the TERT gene rs2736098 polymorphism and bladder cancer risk in Caucasians and four studies for Asian population were included in the present meta-analysis. The sample size was small, thus studies with larger sample sizes are needed to further investigate the potential relationships of TERT gene rs2736098 polymorphism with bladder cancer risk.

When interpreting the results of the current study, there are still several limitations should be taken with cause. First, only six studies were included in the meta-analysis, the sample size of included published articles was small, and so sufficient data was unavailable. Second, subgroup analysis was not conducted based on pathological patterns, due to the lack of information. Third, potential interactions among gene-gene, gene-environment, were not estimated as the studies enrolled lacked of information. Finally, the OR values were non-adjusted data, due to the lack of data of smoking, alcoholic consumption, family history, age, and other environmental exposure factors.

Conclusions

This meta-analysis result suggests that the TERT gene variant rs2736098 polymorphism may increase the risk of bladder cancer, especially in Asians. However, large sample size, well-designed, and population-based studies are necessary to comprehensively verify the association between TERT gene variant rs2736098 polymorphism and bladder cancer risk.

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Disclosure of conflict of interest

None.

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References


