The MDM2 SNP309T>G Polymorphism Increases Bladder Cancer Risk among Caucasians: a Meta-analysis

Huai-Gao Wang, Qing-Yun Wu, Hui Zhou, Xin-Sheng Peng, Meng-Jie Shi, Jie-Mei Li, Yan-Fang Zhou

Abstract

Published studies have evaluated associations between the MDM2 SNP309T>G polymorphism and bladder cancer susceptibility. However, these generated inconsistent results. The aim of the present investigation was to quantify the strength of association between MDM2 SNP309T>G polymorphism and bladder cancer risk by conducting a meta-analysis. We searched PubMed and Embase for related studies that had been published in English before April 1, 2014 and associations were assessed by summarizing the odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). Five case-control studies with a total of 972 cases and 1,012 controls were finally identified to be eligible for the meta-analysis. Overall, the results indicated that there was no significant association between the MDM2 SNP309T>G polymorphism and bladder cancer risk (for the allele model G vs. T: OR=1.08, 95% CI 0.85-1.36, p=0.54; for the co-dominant model GG vs. TT: OR=1.20, 95% CI 0.74-1.93, p=0.46; for the dominant model GG+GT vs. TT: OR=0.98, 95% CI 0.80-1.20, p=0.83; for the recessive model GG vs. GT+TT: OR=1.20, 95% CI 0.83-1.74, p=0.33). However, on subgroup analysis by ethnicity, significant associations were found in Caucasians in three models (for the allele model G vs. T: OR=1.41, 95% CI 1.10-1.81, p=0.006; for the co-dominant model GG vs. TT: OR=2.16, 95% CI 1.28-3.63, p=0.004; for the recessive model GG vs. GT+TT: OR=2.06, 95% CI 1.31-3.22, p=0.002). In summary, the present meta-analysis provides evidence that the genotype for the MDM2 SNP309T>G polymorphism may be associated with genetic susceptibility to bladder cancer among Caucasians.

Keywords: Bladder cancer - MDM2 - polymorphism - meta-analysis - ethnic variation

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Introduction

According to the GLOBOCAN 2012 report from the World Health Organization’s International Agency for Research on Cancer (IARC), bladder cancer is the ninth most common cancer in the world and there are nearly 429,793 new cases and 165,068 deaths die of bladder cancer in 2012 (GLOBOCAN2012, IARC). The majority of bladder cancer occurs in males and the highest incidence rates are found in the countries of Europe, North America, and Northern Africa (Jemal et al. 2011). Although the development of bladder cancer is associated smoking, occupational exposure and chronic infection with Schistosoma hematobium, not all of these populations will ever develop bladder cancer (Mommersn and Aagaard 1983; Olffer et al. 2006; Murta-Nascimento et al. 2007). The genetic susceptibility, environmental and lifestyle factors also play an important role in the development of the disease (McConkey et al. 2010).

P53 tumor suppressor pathway plays an important role in cell cycle, apoptosis and inhibition of angiogenesis. The mutation that inactivates the p53 gene has been found in at least half of all human cancers (Greenblatt et al. 1994). The human mouse double minute 2 (MDM2) gene located on chromosome 12q13 to 14 with a genomic length of 34 kb is a major negative regulator of the p53 network (Kubbutat et al. 1997). The over expression of MDM2 can decrease the level of p53 protein and eventually results in the dysfunction of the P53 pathway, in turn, contribute to the development of cancers. A functional T to G polymorphism at nucleotide 309 in the promoter region of the MDM2 gene has been identified (Whibley et al. 2009). The G allele of SNP309 confers an increased binding affinity to the Sp1 transcriptional activator which can increase transcription of the MDM2 gene (Pietsch et al. 2006). Thus the SNP309 GG and TG genotypes seem to express higher levels of MDM2 protein than those with the TT genotypes, eventually causes a relative decrease of p53 protein. This highly suggests that MDM2 variant may be a potential modulator of cancer susceptibility.

Published studies have evaluated the association between MDM2 SNP309T>G polymorphism and bladder...
cancer susceptibility (Onat et al. 2006; Horikawa et al. 2008; Wang et al. 2008; Gangwar and Mittal 2010; Hitzenbichler et al. 2014). However, these studies showed inconsistent results. To derive a more precise estimation of this association, a meta-analysis was performed to estimate the effect of MDM2 SNP309T>G polymorphism on bladder cancer risk.

Materials and Methods

Identification and eligibility of relevant studies

Electronic searches of PubMed and Embase databases (up to October 2013) were performed for all possible publications on the association between MDM2 SNP309T>G polymorphism and bladder cancer risk. The initial search terms were “MDM2,” “rs2279744,” “T309G,” “polymorphism,” “variant,” “mutation,” “bladder,” “cancer” and “carcinoma.” The search was limited to English-language studies. In addition, the reference lists of identified studies were manually checked to include other potentially eligible studies.

Inclusion and exclusion criteria

Studies were selected according to the following inclusion criteria: case-control studies in design; investigating the association between MDM2 SNP309T>G polymorphism and bladder cancer risk; with genotype distribution data to calculate combined ORs and 95% CIs. The major exclusion criteria were: no control population; abstract, comment, and review; duplicate of earlier publication and no usable genotype frequency data.

Data extraction

Two investigators (Huai-Gao Wang and Qing-Yun Wu) independently extracted the data according to the listed inclusion and exclusion criteria above. Disagreements were resolved by discussion among the investigators. The following information was extracted from each eligible study: name of the first author, year of publication, country of origin, ethnicity, numbers of genotyped cases and controls and genotype frequency in cases and controls. Different ethnic descents were categorized as Asian and Caucasian.

Table 1. Association Between Individual Study Characteristics and MDM2 T309G Polymorphism

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Area</th>
<th>Ethnicity</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
<th>HWE(control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gangwar et al.</td>
<td>2010</td>
<td>India</td>
<td>Asian</td>
<td>212</td>
<td>250</td>
<td>70</td>
<td>89</td>
<td>53</td>
</tr>
<tr>
<td>Hitzenbichler et al.</td>
<td>2014</td>
<td>Germany</td>
<td>Caucasians</td>
<td>224</td>
<td>140</td>
<td>75</td>
<td>101</td>
<td>48</td>
</tr>
<tr>
<td>Horikawa et al.</td>
<td>2008</td>
<td>Japan</td>
<td>Asian</td>
<td>227</td>
<td>266</td>
<td>44</td>
<td>116</td>
<td>67</td>
</tr>
<tr>
<td>Onat et al.</td>
<td>2006</td>
<td>Turkey</td>
<td>Caucasians</td>
<td>75</td>
<td>103</td>
<td>13</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2008</td>
<td>China</td>
<td>Asian</td>
<td>234</td>
<td>253</td>
<td>62</td>
<td>121</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 2. Meta-analysis of MDM2 T309G Polymorphism and Bladder Cancer Risk in Each Subgroup

<table>
<thead>
<tr>
<th>Category</th>
<th>G vs. T</th>
<th>GG vs. TT</th>
<th>TT</th>
<th>GT+TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnictiy</td>
<td>OR (95%CI)</td>
<td>P (%)</td>
<td>OR (95%CI)</td>
<td>P (%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0.92 (0.79,1.06)</td>
<td>0.26</td>
<td>0.85 (0.64,1.14)</td>
<td>0.28</td>
</tr>
<tr>
<td>Caucasian.1.41 (1.10,1.81)</td>
<td>0.006</td>
<td>0.45</td>
<td>2.16 (1.28,3.63)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*CI 95% confidence intervals, OR odds ratio

Statistical analysis

In this meta-analysis, the association strength between MDM2 SNP309T>G polymorphism and bladder cancer risk was measured by the pooled odds ratios (ORs) with 95% confidence intervals (CIs). The alleles model (G vs. T), the co-dominant model (GG vs. TT), the dominant model (GG+GT vs. TT), and the recessive model (GG vs. GT+TT) were performed respectively. Subgroup analysis by ethnicity was also performed. The Z-test was performed to assess the significance of the pooled ORs and p<0.05 was considered as statistically significant. The Q test and F test were performed to assess the heterogeneity between studies. According to the heterogeneity, the fixed-effect or random-effect model would be used to calculate the pooled odds ratios (ORs) with 95% confidence intervals (CIs). If $P<0.10$ and I²>50%, indicating the presence of heterogeneity, the random-effects model (the DerSimonian and Laird method) was used to calculate the pooled OR. Otherwise, the fixed-effects model (Mantel-Haenszel) was selected. The Hardy-Weinberg equilibrium (HWE) was determined in the control groups. Sensitivity analyses were performed to identify one single study’ effect on pooled results and test the reliability of results. Publication bias among the included studies was investigated by Begger’s funnel plots and Egger’ linear regression test, and a p<0.05 was considered as statistically significant. Data analysis was performed using the software STATA (version 12.0) and Review Manager (version 5.0).

Results

Characteristics of published studies

Based on the inclusion and exclusion criteria, five studies (972 cases and 1012 controls) published from 2006 to 2014 were identified to be eligible studies (Onat et al. 2006; Horikawa et al. 2008; Wang et al. 2008; Gangwar and Mittal 2010; Hitzenbichler et al. 2014). All of the studies were published in English. The characteristics of all the studies that were included in the meta-analysis were listed in Table 1. There were two studies on Caucasians, three studies on Asians. Among them, one study was from Turkey (Onat et al. 2006), one study was from Japan (Horikawa et al. 2008), one study was from China (Wang et al. 2008), one study was from India (Gangwar and Mittal 2010).
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Overall, the combined results indicated that MDM2 SNP309T>G polymorphism was not significantly associated with bladder cancer risk in all genetic models (for the allele model G vs. T: OR=1.08, 95% CI 0.85-1.36, \(p=0.54\); for the co-dominant model GG vs. TT: OR=1.20, 95% CI 0.74-1.93, \(p=0.46\); for the dominant model GG+GT vs. TT: OR=0.98, 95% CI 0.80-1.20, \(p=0.83\); for the recessive model GG vs. GT+TT: OR=1.20, 95% CI 0.83-1.74, \(p=0.33\)) (Figure 1). Subgroup analyses by ethnicity further showed that there was also no significant association between MDM2 SNP309T>G polymorphism and susceptibility to bladder cancer in Asians (for the allele model G vs. T: OR=0.92, 95% CI 0.79-1.06, \(p=0.26\); for the co-dominant model GG vs. TT: OR=0.85, 95% CI 0.64-1.14, \(p=0.28\); for the dominant model GG+GT vs. TT: OR=0.87, 95% CI 0.68-1.11, \(p=0.25\); for the recessive model GG vs. GT+TT: OR=0.92, 95% CI 0.73-1.16, \(p=0.48\)) (Table 2). However, significant associations were found in Caucasians in three models (for the allele model G vs. T: OR=1.41, 95% CI 1.10-1.81, \(p=0.006\); for the co-dominant model GG vs. TT: OR=2.16, 95% CI 1.28-3.63, \(p=0.004\); for the recessive model GG vs. GT+TT: OR=2.06, 95% CI 1.31-3.22, \(p=0.002\)) (Table 2). In the sensitivity analysis, we excluded one single study from the overall pooled analysis each time to check the influence of the removed data set to the overall ORs. The pooled ORs and 95% CIs were not significantly changed when any part of the study was omitted, which indicated that omission of any single study did not have significant impact on the combined ORs (Figure 2).

Publication bias

Begg’s funnel plot and Egger’s linear regression
null
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References


