RESEARCH ARTICLE

Genetic Polymorphisms of Glutathione S-transferase M1 and Prostate Cancer Risk in Asians: A Meta-analysis of 18 Studies

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Abstract

Background: Many studies have investigated associations between the glutathione S-transferase M1 (GSTM1) null polymorphism and risk of prostate cancer, but the impact of GSTM1 in people who live in Asian countries is still unclear owing to inconsistencies across results. Methods: We searched the PubMed, Web of Science, Scopus, Ovid and CNKI databases for studies of associations between the GSTM1 null genotype and risk of prostate cancer in people who live in Asian countries, and estimated summary odds ratios (ORs) with 95% confidence intervals (95% CIs). Results: A total of 18 case-control studies with 2,172 cases and 3,258 controls were included in this meta-analysis, which showed the GSTM1 null genotype to be significantly associated with increased risk of prostate cancer in people who live in Asian countries (random-effects OR=1.74, 95% CI:1.44-2.09, \( P<0.001 \)). Similar results were found in East Asians (OR=1.41; 95% CI: 1.12–1.78; \( P=0.004 \)) and Caucasians in Asia (OR=2.19; 95% CI: 1.85-2.60; \( P<0.001 \)). No evidence of publication bias was observed. Conclusions: This meta-analysis of available data suggested that the GSTM1 null genotype does contribute to increased risk of prostate cancer in people who live in Asian countries.

Keywords: Glutathione-S-transferase M1 - prostate cancer - gene polymorphism - meta-analysis

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Introduction

Prostate cancer (PCa) is the most common malignancy among men in industrialized countries and with a worldwide incidence of 25.3 per 100,000 (Jemal et al., 2008). The reported incidence in Asia is much lower than that in Western countries. For example, the incidence in the African-American population is 60 times that of the Chinese population of Han nationality, so the research of pathogenesis of PCa from genetic and geographic aspects has important significance (Quinn et al., 2002; Bono, 2004; Pu et al., 2004).

Glutathione S-transferases (GSTs) are generally detoxifying enzymes, active in the detoxification of a wide variety of potentially toxic and carcinogenic electrophiles by conjugating them to glutathione. The GSTM1 gene, a member of the \( \mu \) class of the GST gene family, catalyzes the detoxification of certain carcinogenic polycyclic aromatic hydrocarbon compounds. Thus its inactive form will cause lower detoxification, and that maybe the risk for cancer. For this reason GSTM1 is one of the most extensively studied genes concerning polymorphism and cancer risk. GSTM1 null genotype has been reported to be associated with cancers of the gastric (Masoudi et al., 2009; Garcia-Gonzalez et al., 2012; Zhu et al., 2012), colorectum (Ye et al., 2003), bladder (Garcia-Closas et al., 2005; McGrath et al., 2006), lung (Ada et al., 2012; Lopez-Cima et al., 2012), breast (Oliveira et al., 2010; de Aguiar et al., 2012), head and neck (Suzen et al., 2007; Nosheen et al., 2010).

Many studies have investigated the association between GSTM1 null genotype and risk of prostate cancer, but the impact of GSTM1 null genotype on prostate cancer in people who live in Asian countries was still unclear owing to the obvious inconsistence among those studies. We present herein the results of a meta-analysis of published data investigating the association between GSTM1 null genotype and risk of prostate cancer to shed some light on these contradictory results and to decrease the uncertainty of the effect size of the estimated risk.

Materials and Methods

Literature search

We performed a systematic search of the PubMed, Web of Science, Scopus, Ovid and CNKI databases to identify studies on GSTM1 null genotype and prostate cancer published before Oct 2012. The following search strategy was performed by consecutively entering the combined free words: ‘GSTM1’ or ‘Glutathione S-transferases’, ‘prostate’, ‘carcinoma’ or ‘cancer’ or ‘tumor’, ‘PCa’. The reference lists of reviews and retrieved articles were
Study eligibility

Eligibility criteria included the following: (1) case–control design with the genotyping of men with and without prostate cancer, concentrating upon polymorphisms in GSTM1; (2) an appropriate description of GSTM1 polymorphisms in prostate cancer cases and prostate cancer-free controls, provided information on genotype frequency; (3) cases with prostate cancer were eligible regardless of whether they had a first-degree relative with prostate cancer or not, regardless of tumor stage; (4) controls were eligible if they were male, with or without BPH, or other diseases; (5) results expressed as odds ratio (OR); (6) studies with a 95% CI for OR, or sufficient data to calculate these numbers; (7) the population is in Asia. While for the exclusion criteria, we provided as follows: (1) review articles and editorial; (2) case reports; (3) preliminary result was not on GSTM1 or outcome was not prostate cancer; (4) studies that used GSTM1 polymorphisms to predict survival in prostate cancer; (5) if multiple publications from the same study group occurred, we selected only the most complete paper for our final analysis.

Data Extraction

Two investigators independently extracted data, and disagreements were resolved through consensus. The extracted data included first author’s name, year of publication, the country of origin, ethnicity, characteristics of cases and controls, source of controls, demographics, genotyping method, and the genotype distribution of cases and controls for the GSTM1 polymorphism. The frequency of GSTM1 null genotype was extracted or calculated for cases and controls. All data were extracted from published articles, and we did not contact individual authors for further information.

Statistical Analyses

The odds ratio (OR) was used as thematic of choice. Based on the individual ORs, the pooled OR was estimated. We did not pool the adjusted ORs because studies either did not adjust for confounders, or the adjustments were not comparable among them. To determine whether to use the fixed- or random-effects model, we measured statistical heterogeneity between and within groups using the Q

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**Table 1. Characteristics of Studies Included in the Meta-analysis**

<table>
<thead>
<tr>
<th>Study (author, year)</th>
<th>Study period</th>
<th>Population (country)</th>
<th>Genotyping method</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Null of cases</th>
<th>Null of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murata, 2001</td>
<td>1995-1996</td>
<td>East Asians (Japan)</td>
<td>PCR</td>
<td>115</td>
<td>200 (BPH)</td>
<td>57</td>
<td>85</td>
</tr>
<tr>
<td>Nakazato, 2003</td>
<td>DNR</td>
<td>East Asians (Japan)</td>
<td>PCR</td>
<td>81</td>
<td>105 (Hospital)</td>
<td>38</td>
<td>53</td>
</tr>
<tr>
<td>Guan, 2005</td>
<td>2001-2003</td>
<td>East Asians (China)</td>
<td>PCR</td>
<td>83</td>
<td>115 (Hospital)</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Aktas, 2004</td>
<td>1999-2002</td>
<td>Caucasian (Turkey)</td>
<td>PCR</td>
<td>100</td>
<td>107 (BPH)</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Komiya, 2005</td>
<td>1992-2002</td>
<td>East Asians (Japan)</td>
<td>PCR-RFLP</td>
<td>190</td>
<td>294 (Healthy)</td>
<td>93</td>
<td>157</td>
</tr>
<tr>
<td>Lai, 2005</td>
<td>DNR</td>
<td>East Asians (Taiwan, China)</td>
<td>PCR</td>
<td>96</td>
<td>121 (Hospital)</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>Wang, 2005</td>
<td>DNR</td>
<td>East Asians (China)</td>
<td>PCR</td>
<td>81</td>
<td>50 (Hospital)</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Vijayalakshmi, 2005</td>
<td>DNR</td>
<td>Caucasian (India)</td>
<td>PCR</td>
<td>75</td>
<td>100 (Hospital)</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Srivastava, 2005</td>
<td>2001-2004</td>
<td>Caucasian (India)</td>
<td>PCR</td>
<td>127</td>
<td>144</td>
<td>70</td>
<td>51</td>
</tr>
<tr>
<td>Yang, 2006</td>
<td>2003-2005</td>
<td>East Asians (China)</td>
<td>PCR</td>
<td>163</td>
<td>202 (Hospital)</td>
<td>99</td>
<td>112</td>
</tr>
<tr>
<td>Silig, 2006</td>
<td>2002</td>
<td>Caucasian (Turkey)</td>
<td>PCR-RFLP</td>
<td>152</td>
<td>169 (Hospital)</td>
<td>98</td>
<td>52</td>
</tr>
<tr>
<td>Mittal, 2006</td>
<td>2003-2005</td>
<td>Caucasian (India)</td>
<td>PCR</td>
<td>54</td>
<td>105 (BPH)</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Li, 2008</td>
<td>2001-2004</td>
<td>East Asians (China)</td>
<td>PCR</td>
<td>208</td>
<td>230 (BPH)</td>
<td>121</td>
<td>96</td>
</tr>
<tr>
<td>Kwon, 2011</td>
<td>DNR</td>
<td>East Asians (South Korea)</td>
<td>PCR</td>
<td>166</td>
<td>327</td>
<td>90</td>
<td>125</td>
</tr>
<tr>
<td>Ashtiani, 2011</td>
<td>DNR</td>
<td>Caucasian (Iran)</td>
<td>PCR</td>
<td>110</td>
<td>100(Healthy)+99(BPH)</td>
<td>50</td>
<td>10(Healthy)+47(BPH)</td>
</tr>
<tr>
<td>Kumar, 2011</td>
<td>DNR</td>
<td>Caucasian (India)</td>
<td>PCR</td>
<td>57</td>
<td>53(Healthy)+46(BPH)</td>
<td>34</td>
<td>15(Healthy)+21(BPH)</td>
</tr>
<tr>
<td>Thakur, 2011</td>
<td>2003-2006</td>
<td>Caucasian (India)</td>
<td>PCR</td>
<td>150</td>
<td>172(Healthy)+150(BPH)</td>
<td>87</td>
<td>62(Healthy)+82(BPH)</td>
</tr>
<tr>
<td>Safarinejad, 2011</td>
<td>DNR</td>
<td>Caucasian (Iran)</td>
<td>PCR</td>
<td>168</td>
<td>336 (Healthy)</td>
<td>72</td>
<td>94</td>
</tr>
</tbody>
</table>

DNR, data not reported; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism
Table 2. Summary of Odds Ratios (OR) with Confidence Interval (CI) in the Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>OR (95 % CI)</th>
<th>Odds ratio</th>
<th>Model</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total studies</td>
<td>1.74(1.44–2.09)</td>
<td>Random</td>
<td>60</td>
<td>0.001</td>
</tr>
<tr>
<td>Subgroup analyses by ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasians</td>
<td>2.19(1.85–2.60)</td>
<td>Fixed</td>
<td>22.2</td>
<td>0.246</td>
</tr>
<tr>
<td>East Asians</td>
<td>1.41(1.12–1.78)</td>
<td>Random</td>
<td>55.1</td>
<td>0.023</td>
</tr>
<tr>
<td>Subgroup analyses by control source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>2.33(1.21–4.49)</td>
<td>Random</td>
<td>88.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital</td>
<td>1.81(1.41–2.32)</td>
<td>Random</td>
<td>59.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPH</td>
<td>1.37 (1.09–1.73)</td>
<td>Random</td>
<td>31.5</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Figure 1. Forest Plots Showed Associations Between GSTM1 Null Genotype and Risk of Prostate Cancer

Figure 2. Forest Plots Showed Results of the Cumulative Meta-analysis (The random effects pooled odds ratio with the corresponding 95% confidence interval at the end of each information step was shown)

Results

Characteristics of included studies

Excluding overlapping data, we identified 18 eligible reports. All reports selected prostate cancer patients based on a histologic diagnosis from biopsy or prostatectomy. Among the eligible studies, three articles contained separate data on two different control groups (Ashtiani et al., 2011; Kumar et al., 2011; Thakur et al., 2011). One article provided data on both blood and tissue samples from the same subjects (Mittal et al., 2006), to avoid overlapping, only the data of blood samples were included. Thus, a total of 18 case-control studies with 2172 cases and 3258 controls were included into this meta-analysis. All included studies were English language literature except for two Chinese language literatures (Guan et al., 2005; Wang et al., 2005). Of these studies, 9 reported on Caucasians, and 9 reported on East Asians. Studies were carried out in Japan (Murata et al., 2001; Nakazato et al., 2003; Komiya et al., 2005), China (Guan et al., 2004; Guan et al., 2005; Lai et al., 2005; Yang et al., 2006; Li et al., 2008), India (Vijayalakshmi et al., 2005; Mittal et al., 2006), South Korea (Kwon et al., 2011), Iran (Ashtiani et al., 2011; Safarinejad et al., 2011), and Turkey (Aktas et al., 2004; Silig et al., 2006). A list of details abstracted from the studies included in the meta-analysis is provided through Table 1.

Main results

There was obvious heterogeneity among in the meta-analysis of total 18 studies ($I^2=60\%$), thus the random-effects model was used. Meta-analysis showed GSTM1 null genotype was associated increased risk of prostate cancer (OR=1.74, 95% CI 1.44–2.09, $P<0.001$) (Figure 1).

This analysis is based on pooling of data from a number of different ethnic groups (Table 2). Subgroups analyses in the different ethnic groups were therefore conducted. Similar results were found in East Asians (OR=1.41; 95% CI: 1.12–1.78; $P=0.004$) and Caucasians (OR=2.19; 95% CI: 1.85–2.60; $P<0.001$). By considering control source subgroups in healthy controls, the OR was 2.33 (95% CI: 1.21–4.49; $P<0.001$), compared to 1.81 (95% CI: 1.41–2.32; $P<0.001$) in hospital controls, and 1.37 (95% CI: 1.09–1.73; $P=0.007$) in BPH controls.

The cumulative meta-analyses for total 18 studies showed a trend of more obvious association as information accumulated (Figure 2).

Sensitivity Analyses and Publication Bias

Sensitivity analyses by sequential omission of individual studies did not significantly alter the overall combined ORs (Figure 3). In the funnel plot analysis of publication bias (contrast of null genotype plotted against the present), the shape of the funnel plot seems symmetrical, both Begg’s test ($P=0.65$) (Figure 4) and Eggar’s test ($P=0.51$) showed no evidence of publication bias.

Discussion

Many studies have investigated the association between GSTM1 null genotype and risk of prostate cancer, but the impact of GSTM1 null genotype on prostate cancer risk in people who live in Asian countries is unclear owing to the obvious inconsistence among those studies. Our meta-analysis of 2172 prostate cancer cases and 3258 controls from 18 case–control studies provides evidence that the GSTM1 null genotype is associated with a increase in the risk of prostate cancer in Asian population.

GSTM1 null genotype also has been extensively studied for many other cancers. To explore the exact association between GSTM1 polymorphisms and gastric cancer risk, Zhu et al. conducted a meta-analysis of 38 published genetic association studies including 6605 gastric cancer cases and 11,311 controls. This meta-analysis indicated that GSTM1 null genotype might be associated with increased gastric cancer risk in Asians, while it did not provide an evidence of confirming association between GSTM1 polymorphism and gastric cancer in Caucasians (Zhu et al., 2012).

GSTM1 have broad and overlapping substrate specificities, and the genetic polymorphisms of these enzymes are attractive candidates for cancer susceptibility, as reduced ability to remove potential carcinogens may result in mutation in key tumor suppressor genes. Earlier molecular epidemiologic studies have suggested that allelic (deletion or null) variants of GSTM1 genes are associated with failure to express GST proteins, which may lead to less effective detoxification of potential carcinogens and increased susceptibility to cancer (Board, 1981; Pemble et al., 1994, Spurdle et al., 2001). Mavis et al. examined Gst gene expression and Gst promoter DNA methylation in normal murine prostates and Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) tumors, and demonstrate that reduced Gst gene expression is a common event in primary tumors arising in the TRAMP model, reminiscent of human prostate cancer (Mavis et al., 2009).

Our results showed GSTM1 null genotype was associated with increased risk of prostate cancer in people who live in Asian countries. In subgroup analysis of Caucasians and East Asians, there were also obvious associations between GSTM1 null genotype and increased risk of prostate cancer.

Similar results were found in different control source subgroups (healthy, in the hospital and BPH). However, compared to the subgroups of healthy controls (OR 2.33) and hospital controls (OR 1.81), the BPH controls’ estimate magnitude was drown down (OR 1.37). One possible reason was that BPH may be also affected by the same polymorphism, but susceptibility to prostate enlargement is a different issue than susceptibility to prostate cancer.

Cumulative meta-analysis and sensitivity analysis were also performed. Sensitivity analyses by sequential omission of individual studies did not materially alter the significance of pooled ORs. Sensitivity analysis and publication bias analysis suggest that it is highly unlikely that the findings may be due to chance (Type 1 error) or bias favoring publication of ‘positive’ studies. Thus, these
findings support the concept of GSTM1 null genotype as a genetic susceptibility factor of PCa in people who live in Asian countries.

Wei et al. (2012) evaluated the association between GSTM1 null polymorphism and PCa risk from 36 Case-Control studies and drew a conclusion that GSTM1 null allele was a low-penetrant risk factor for PCa among East Asians (Chinese, Japanese, and Korean). Their article mainly discussed the possible role of ethnic differences in genetic backgrounds, while we want to investigate the situation in the region of Asia, so to explore the association between the gene polymorphism and PCa risk in this region is also significant.

As with all meta-analyses, our analysis has limitations that must be considered when interpreting the findings. Firstly, most eligible studies were published papers written in English, only two were Chinese. Thus, some inevitable publication bias may exist in the results, although the funnel plots as well as Egger’s linear regression tests indicated no remarkable publication bias in the meta-analysis. Secondly, only published studies were included in the meta-analysis; therefore, publication bias may have occurred. Further studies should search thoroughly to obtain as many papers as possible, especially the unpublished ones in remote countries. Thirdly, no prospective studies have addressed this association between GSTM1 null genotype and prostate cancer risk, and all included studies followed a retrospective case-control design. Thus, owing to the limitations of case-control design, we can not exclude the possibility of undetected bias. Future prospective studies can investigate whether routine screening for the presence of the GSTM1 null genotype may improve prediction of prostate cancer risk. Finally, gene-gene and gene-environmental factors interactions were not addressed in this meta-analysis for the lack of sufficient data.

In conclusion, this present meta-analysis supports a significant association between GSTM1 null genotype and risk of prostate cancer in Asians. Larger and more rigorous analytical studies will be required to generate a more robust result in the future.

Acknowledgements

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Mittal RD, Mishra DK, Mandhani A (2006). Evaluating the association between the gene polymorphism and PCa risk in this region is also significant.

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