Null Genotype of GSTT1 Contributes to Esophageal Cancer Risk in Asian Populations: Evidence from a Meta-analysis

Sheng-Ming Yi, Gui-Yuan Li*

Abstract

Background/Aims: Glutathione S-transferase T1 (GSTT1), a phase-II enzyme, plays an important role in detoxification of carcinogen electrophiles. Many studies have investigated the association between GSTT1 polymorphism and esophageal cancer risk in Asian populations, but its actual impact is not clear owing to apparent inconsistencies among those studies. Thus, a meta-analysis was performed to explore the effect of GSTT1 polymorphism on the risk of developing esophageal cancer.

Methods: A literature search of PubMed, Embase, and Wanfang databases up to August 2012 was conducted and 15 eligible papers were finally selected, involving a total of 1,626 esophageal cancer cases and 2,216 controls. We used the pooled odds ratio (OR) with its corresponding 95% confidence interval (95% CI) to estimate the association of GSTT1 polymorphism with esophageal cancer risk. Subgroup analyses and sensitivity analyses were performed to further identify the association.

Results: Meta-analysis of total studies showed the null genotype of GSTT1 was significantly associated with an increased risk of esophageal cancer in Asians (OR=1.26, 95% CI=1.05-1.52, \( P_{OR}=0.015, I^2=42.7\% \)). Subgroup analyses by sample size and countries also identified a significant association. Sensitivity analysis further demonstrated a relationship of GSTT1 polymorphism to esophageal cancer risk in Asians.

Conclusions: The present meta-analysis of available data showed a significant association between the null genotype of GSTT1 and an increased risk of esophageal cancer in Asians, particularly in China.

Keywords: Esophageal cancer - gene polymorphism - glutathione S-transferase T1 - meta-analysis
We performed a meta-analysis to investigate the association between the null genotype of GSTT1 and esophageal cancer risk. Two investigators independently extracted data, and disagreements were resolved through consensus finally. The extracted information contained: year of publication, first author, ethnicity, research designs, number of cases and controls, genotyping method, and characteristics of cases and controls. All data were extracted accurately from published articles.

Statistical analysis

The strength of the association between GSTT1 polymorphism and esophageal cancer risk was measured by the pooled OR with its 95% CI. Both the chi-square based Q statistic test and the I^2 statistic were calculated to examine whether the results of studies were homogeneous, and the significance level was set at 0.05 (Cochran, 1950; Higgins et al., 2003). Data were combined by using the DerSimonian and Laird random-effects model or Mantel and Haenszel fixed-effects model (Mantel et al., 1959; DerSimonian et al., 1986) according to results of heterogeneity analysis. Sensitivity analysis was performed by sequential omission of individual studies to validate the credibility of outcomes in the meta-analysis (Md et al., 1999). In addition, subgroup analyses according to sample size in cases and countries were also conducted to estimate the association between GSTT1 polymorphism and esophageal cancer risk. Both Begg’s funnel plot and Egger’s regression asymmetry test were used to assess the publication bias (Stuck et al., 1998). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas).

Results

Characteristics of included studies

With our search criterion, 15 individual case-control publications with 1,626 cases and 2,216 controls were
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Table 2. Summary of Pooled Odds Ratios (ORs) and Heterogeneity Results for Association Between GSTT1 Polymorphism and Esophageal Cancer Risk

<table>
<thead>
<tr>
<th>Null vs. Present</th>
<th>Studies (Cases/Controls)</th>
<th>Odds Ratio</th>
<th>Model†</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR [95%CI]*</td>
<td>(P_{OR})</td>
<td>(F) (%)</td>
</tr>
<tr>
<td>Total studies</td>
<td>15(1,626/2,216)</td>
<td>1.26(1.05-1.52)</td>
<td>0.015</td>
<td>R</td>
</tr>
<tr>
<td>Subgroup analyses by sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies (case sample size&gt;100)</td>
<td>8(1,107/1,587)</td>
<td>1.10(0.93-1.29)</td>
<td>0.265</td>
<td>F</td>
</tr>
<tr>
<td>Studies (case sample sizes&lt;100)</td>
<td>7(519/631)</td>
<td>1.61(1.26-2.05)</td>
<td>&lt;0.001</td>
<td>F</td>
</tr>
<tr>
<td>Subgroup analyses by different country</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>China</td>
<td>12(1,243/1,075)</td>
<td>1.33(1.14-1.54)</td>
<td>&lt;0.001</td>
<td>F</td>
</tr>
<tr>
<td>India</td>
<td>2(235/332)</td>
<td>0.83(0.56-1.23)</td>
<td>0.351</td>
<td>F</td>
</tr>
<tr>
<td>Iran</td>
<td>1(148/136)</td>
<td>1.09(0.63-1.89)</td>
<td>0.762</td>
<td>NA</td>
</tr>
</tbody>
</table>

*OR, Odds Ratio; 95%CI, 95% Confidence Interval; †R, random-effects model; F, fixed-effects model; ‡PH, the \(P\) value of heterogeneity; NA, data not available.

Figure 2. Begg’s Funnel Plot for Estimating the Publication Bias (\(P_{Egger} = 0.270\)) finally included into this meta-analysis (Lin et al., 1998; Tan et al., 2000; Gao et al., 2002; Wang et al., 2003; Roth et al., 2004; Yi et al., 2005; Jain et al., 2006; Wang et al., 2006; Deng et al., 2008; Zhang et al., 2009; Ji et al., 2010; Liu et al., 2010; Malik et al., 2010; Moaven et al., 2010; Gao et al., 2012). There were 10 English language literatures (Lin et al., 1998; Tan et al., 2000; Gao et al., 2002; Wang et al., 2003; Roth et al., 2004; Jain et al., 2006; Wang et al., 2006; Liu et al., 2010; Malik et al., 2010; Moaven et al., 2010) and 5 Chinese language ones (Yi et al., 2005; Deng et al., 2008; Zhang et al., 2009; Ji et al., 2010; Gao et al., 2012). Table 1 presented a brief description of these 15 case-control studies. There were 12 studies from China, 2 from India and one from Iran. The number of cases varied from 40 to 189, with a mean of 147.9. There were 8 studies with case sample size more than one hundred (Tan et al., 2000; Gao et al., 2002; Roth et al., 2004; Yi et al., 2005; Wang et al., 2006; Ji et al., 2010; Malik et al., 2010; Moaven et al., 2010) and 7 ones with case sample size less than one hundred (Lin et al., 1998; Wang et al., 2003; Jain et al., 2006; Deng et al., 2008; Zhang et al., 2009; Liu et al., 2010; Gao et al., 2012).

GSTT1 polymorphism and esophageal cancer risk

Table 2 showed the main results of meta-analysis of the association between GSTT1 polymorphism and esophageal cancer risk. The pooled OR of total studies by the random-effects model revealed that the null genotype of GSTT1 was modestly associated with increased risk of esophageal cancer in Asians (OR=1.26, 95%CI=1.05-1.52, \(P_{OR}=0.015, F=42.7\%\)) (Table 2, Figure 1). Sensitivity analyses by sequential omission of any individual studies also did not materially alter the overall combined ORs (data were not shown).

There was no obvious heterogeneity found in subgroups (Table 2). Meanwhile, the association between GSTT1 polymorphism and esophageal cancer risk was still statistically significant in subgroup of studies with case sample size \(\leq 100\) (OR=1.61, 95%CI=1.26-2.05, \(P_{OR}<0.001, F=36.2\%\)), but not in subgroup of studies with case sample size > 100 (Table 2, Figure 1). The subgroup analyses by different countries showed that the null genotype of GSTT1 was significantly associated with an increased risk of esophageal cancer in Chinese population, but not in Indian or Iran (Table 2).

The shape of Begg’s funnel plot did not reveal obvious evidence of asymmetry. Besides, the \(P\) value of Egger’s tests was 0.270, providing statistical evidence of funnel plot’ symmetry (Figure 2). Thus, there was no risk of publication bias in this meta-analysis.

Discussion

GSTT1, a significant candidate gene implicated in several cancers, is located on 22q11.23 with 8146 base pairs, 5 exons and 4 introns in all (McIlwain et al., 2006). It plays an important role in the detoxification and elimination of electrophilic carcinogens by catalyzing the conjugation of electrophiles to detoxicate glutathione (Wang et al., 2006). Deletion polymorphism of GSTT1 results in the loss of its functional activity. It is conceivable that individuals with GSTT1 null genotype may become susceptible to chemical carcinogens and thus develop kinds of cancers at high risks. Recent studies have found that GSTT1 null genotype is strongly associated with susceptibility to a number of cancers, such as colorectal, renal and esophageal cancers (Wang et al., 2003; Xu et al., 2011; Cheng et al., 2012). Many published studies have assessed the association between GSTT1 polymorphism and esophageal cancer risk, but the findings were controversial (Jain et al., 2006; Liu et al., 2010). A recent study by Ji et al. explored the association between GSTT1 polymorphism and risk of esophageal cancer, but reported contradictory

and esophageal cancer risk. However, gene-gene and gene-environmental interactions were not fully addressed in this meta-analysis owing to lack of sufficient data. Future studies are expected to further explore the possible effects of gene-gene and gene-environmental interactions on esophageal cancer risk.

In conclusion, the present meta-analysis shows a significant association between the null genotype of GSTT1 and risk of esophageal cancer in Asians. In addition, future studies may further assess the possible gene-gene and gene-environmental interactions in this association.

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References


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