### Introduction

Esophageal cancer is one of the most common cancers and causes a large number of cancer-related deaths in the world (Mao et al., 2011). Apart from the environmental factors including dietary habits, smoking and alcohol drinking, genetic susceptibility has been shown to contribute to the variation in individual susceptibility to esophageal cancer (Hiyama et al., 2007; Lin et al., 2011; Kogo et al., 2011).

Glutathione-S-transferase T1 (GSTT1) plays a crucial role in detoxification and elimination of electrophilic carcinogens by conjugating them to glutathione (Wang et al., 2006). GSTT1 is genetically polymorphic, and deletion polymorphism (homozygous deletion of the gene) of the GSTT1 loci results in the loss of functional activity. Individuals with GSTT1 null genotype are more susceptible to chemical carcinogens and thus have a higher risk of developing malignant tumors. 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 previous studies have been published to estimate the association between GSTT1 polymorphism and esophageal cancer risk, but the available evidence for the genetic association is still weak because of disagreements among studies (Jain et al., 2006; Liu et al., 2010). Differences among study designs, methodology and insufficient power may be responsible for the inconsistent findings among those studies. Meta-analysis by combining data from all eligible studies has the advantage of reducing random error and obtaining a more precise estimate for some potential genetic associations (Attia et al., 2003). Thus, we presented the results of a meta-analysis of published data investigating the association between GSTT1 polymorphism and esophageal cancer risk to shed some light on these contradictory results.

### Materials and Methods

**Literature search**

We conducted a comprehensive search of the PubMed, Embase and Wanfang databases from the inception up to August 2012. Search terms for GSTT1 polymorphism and esophageal cancer included GSTT1, Glutathione-S-Transferase T1, gene polymorphism, gene polymorphisms and esophageal cancer, esophageal carcinoma. No language restrictions were imposed. All references cited in the studies were also reviewed to identify additional...
Table 1. Characteristics of 15 Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Publication Country</th>
<th>Year</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds Ratio (OR) (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao P et al. 2012</td>
<td>China</td>
<td>2012</td>
<td>22</td>
<td>18</td>
<td>2.89 (2.23, 3.88)</td>
<td>4.20</td>
</tr>
<tr>
<td>Malik MA et al. 2010</td>
<td>India</td>
<td>2010</td>
<td>25</td>
<td>110</td>
<td>1.23 (0.95, 1.59)</td>
<td>9.72</td>
</tr>
<tr>
<td>Liu R et al. 2010</td>
<td>China</td>
<td>2010</td>
<td>98</td>
<td>94</td>
<td>0.88 (0.70, 1.11)</td>
<td>6.03</td>
</tr>
<tr>
<td>Zhang LW et al. 2009</td>
<td>China</td>
<td>2009</td>
<td>77</td>
<td>54</td>
<td>1.43 (0.45, 4.73)</td>
<td>0.40</td>
</tr>
<tr>
<td>Deng J et al. 2008</td>
<td>China</td>
<td>2008</td>
<td>51</td>
<td>36</td>
<td>1.27 (0.15, 1.11)</td>
<td>0.59</td>
</tr>
<tr>
<td>Wang Z et al. 2006</td>
<td>China</td>
<td>2006</td>
<td>28</td>
<td>37</td>
<td>12.02 (3.72, 3.97)</td>
<td>7.06</td>
</tr>
<tr>
<td>Jain M et al. 2005</td>
<td>India</td>
<td>2005</td>
<td>46</td>
<td>60</td>
<td>1.09 (0.92, 1.24)</td>
<td>6.30</td>
</tr>
<tr>
<td>Yi LH et al. 2004</td>
<td>India</td>
<td>2004</td>
<td>46</td>
<td>60</td>
<td>1.05 (0.89, 1.24)</td>
<td>6.34</td>
</tr>
<tr>
<td>Roth MJ et al. 2003</td>
<td>China</td>
<td>2003</td>
<td>98</td>
<td>94</td>
<td>0.82 (0.49, 1.42)</td>
<td>8.64</td>
</tr>
<tr>
<td>Wang LD et al. 2002</td>
<td>China</td>
<td>2002</td>
<td>77</td>
<td>54</td>
<td>1.20 (0.94, 1.54)</td>
<td>8.40</td>
</tr>
<tr>
<td>Lin DX et al. 1998</td>
<td>China</td>
<td>1998</td>
<td>122</td>
<td>146</td>
<td>1.20 (0.84, 1.74)</td>
<td>3.93</td>
</tr>
<tr>
<td>Overall (Random)</td>
<td></td>
<td></td>
<td>100.00</td>
<td>100.00</td>
<td>1.29 (1.05, 1.52)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*A HWE, Hardy-Weinberg equilibrium; +, Hardy-Weinberg equilibrium of genotypes of controls was confirmed; -, Hardy-Weinberg equilibrium of genotypes of controls was not confirmed.

Selection criteria

Studies were included in the meta-analysis if: (1) Case-control studies which evaluated associations between GSTT1 polymorphism and esophageal cancer risk in Asian populations; (2) Odds ratio (OR) with its 95% confidence interval (95%CI) or other data for estimating OR (95% CI) were available; (3) Providing information on genotype frequency of GSTT1 polymorphism. In addition, review papers, case-only studies, or studies containing overlapping data were all excluded.

Data extraction

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 I² 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>Total studies 15(1,626/2,216)</td>
<td>OR [95%CI]*</td>
<td>P_{OR}</td>
<td>F (%)</td>
</tr>
<tr>
<td></td>
<td>Subgroup analyses by sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Studies (case sample sizes&gt;100) 8(1,107/1,587)</td>
<td>1.10(0.93-1.29)</td>
<td>0.265</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>Studies (case sample sizes≤100) 7(519/631)</td>
<td>1.61(1.26-2.05)</td>
<td>&lt;0.001</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>Subgroup analyses by different country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>China 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></td>
<td>India 2(235/332)</td>
<td>0.83(0.56-1.23)</td>
<td>0.351</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>Iran 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) and 5 Chinese language ones (Yi et al., 2005; Jain et al., 2006; Wang et al., 2006; Liu 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., 2010).

**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 ≤ 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 test 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 22ql1.23 with 8146 base pairs, 5 exons and 4 introns in all (McElwain 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...
exploring the association between GSTT1 polymorphism can be deduced that interactions of gene-gene and gene-environmental factors should be treated with caution when exploring the association between GSTT1 polymorphism 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.

Acknowledgements

The author(s) declare that they have no competing interests.

References


Gao P, Tian Y, Ye XF, et al (2012). Study of CTPIA1, GSTT1, GSTM1 affected the susceptibility to esophageal cancer (Moaven et al., 2010). Besides, Genotyping analysis of GSTP1 together with assessment of smoking seems to be important in determining the risk of esophageal cancer in the Iranian population (Moaven et al., 2010). It can be deduced that interactions of gene-gene and gene-environmental factors should be treated with caution when exploring the association between GSTT1 polymorphism 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.

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Stuck AE, Rubenstein LZ, Wieland D (1998). Bias in meta-analysis detected by a simple, graphical test. Asymmetry detected in funnel plot was probably due to true heterogeneity. BMJ, 316, 469; author reply 70-1.


