Glutathione S-transferase gene polymorphism and lung cancer in Indian population: a meta-analysis of case-control studies

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Among the respiratory diseases, lung cancer is one of the most critical in terms of mortality. In India, more than half a million people die every year because of lung cancer. Tobacco smoke along with polymorphism of glutathione S-transferase gene is considered to be one of the most important factors for lung cancer. Here a review has been carried out to find the association of gene polymorphism and lung cancer, especially in the Indian population. This article deals with reviews on the effect of GSTTI and GSTMI polymorphism on lung cancer specifically from case-control studies of the Indian population. In the overall population, from the pooled odds ratio, a significant association of GSTMI (null versus present) was found with lung cancer, whereas the association of GSTTI (null versus present) genotype was found to be statistically insignificant. From the null test (two-tailed), GSTMI (null versus present genotype; \( P \text{ value} = 0.035, \chi^2 = 4.058\% \)) was found to be significantly associated with lung cancer. Begg’s funnel plot analysis showed no publication bias for both gene polymorphisms. Thus this review shows that GSTMI polymorphism is a significant risk factor for lung cancer in the Indian population.

Keywords: Gene polymorphism, glutathione S-transferase, lung cancer, meta-analysis.

Lung cancer is one of the leading causes of death due to disease worldwide. Males compared to females are more prone to death due to lung cancer. According to the World Health Organization (WHO) World Cancer Report 2014 (ref. 1), about 20% of total cancer deaths that occurred worldwide during 2012 was due to lung cancer.

The most vital factor considered for 70% of global lung cancer deaths is the use of tobacco products¹. Along with the tobacco smoke, there are also other several factors which are directly or indirectly associated with the development of lung cancer. These include viruses, UV radiation or adverse occupational environment. The malfunctioning of the enzymes that are involved in the detoxification process of the xenobiotic compounds seems to be an important phenomenon linked to the occurrence of lung cancer due to tobacco smoke and other related exposures.

Glutathione S-transferase (GST) enzymes are the phase-II metabolic enzymes. The main function of these enzymes is to conjugate the non-polar xenobiotic compounds with the highly charged glutathione (antioxidant) to make it polar, so that those compounds can easily be excreted out from the body with the help of phase-III metabolic enzymes²,³. The GST genes are a superfamily arising from three different origins such as cytosolic, mitochondrial and membrane-bound microsomal⁴. The phase-I and phase-II metabolic enzymes are found to be associated with different disorders related to the lungs⁵-⁸.

The genes coding for phase-II metabolic enzymes such GSTTI and GSTMI were found to be associated with lung cancer in different ethnic groups⁹-¹². However, there are also some studies where no significant relation between the GSTTI/GSTMI and lung cancer risk was observed¹³,¹⁴. Considering the fact that using the results of a single study to draw a conclusive statistical analysis has certain limitations, a meta-analysis is needed to come to an effective conclusion. Despite India having the second largest population in the world, there is no meta-analysis report related to GST and lung cancer risk in the Indian population. Though there are only a few studies related to the respective genes reported as case- control studies on the Indian population, we have done an extensive statistical analysis to draw an effective conclusion from those studies in the form of a meta-analysis. The current meta-analysis contains 16 studies considered independently for both GSTTI and GSTMI in combination to investigate the susceptibility to lung cancer risk due to polymorphism of GSTTI and GSTMI genes¹²,¹⁵-²¹.
**Methods**

**Search strategies**

A comprehensive web search was performed on PubMed, Web of Science (WoS) and HuGENet databases using the terms ‘GSTT1 polymorphism and lung cancer’, ‘GSTM1 polymorphism and lung cancer’, ‘lung cancer in India’ and ‘lung cancer case-control studies’. The criteria for selection of suitable reported studies were set as follows: (i) the study should be entirely on GSTT1 polymorphism and lung cancer; (ii) it should be entirely on GSTM1 polymorphism and lung cancer risk; (iii) it should include male and female subjects from the Indian population. The mere published ‘abstracts and review articles’ were not included in this meta-analysis. We have also gone through the cross references of suitable articles to get the entire relevant articles based on the above criteria.

**Data extraction**

Three of the authors of the present study independently reviewed the literature. The information extracted from the suitable reported studies was as follows: first author, publication year, Indian population, age, gender, smoking history, genotyping methods, total number of case and control subjects, and genotyping population size.

**Statistical analysis**

The association of GSTT1 and GSTM1 polymorphism with lung cancer was assessed with 95% confidence interval (CI) and odds ratio (OR). In this meta-analysis null variant was compared with wild type (null vs present). Pooled OR was estimated by both fixed-effects model as well as random-effects model. Heterogeneity was estimated through Q-test and considered statistically significant if \( P < 0.05 \). Publication bias was analysed using Begg’s funnel plot and Egger’s test. All statistical analyses were performed using comprehensive meta-analysis 2.0 (CMA) (Biostat Inc, USA) and GraphPad Prism 5 (GraphPad Software, Inc, USA) software.

**Results**

**Characteristics of included studies**

After performing a comprehensive search on PubMed, WoS and HuGENet, 181 research articles relevant to the search criteria were selected, out of which 165 studies were excluded for being not relevant to GSTT1 and GSTM1 polymorphism in the Indian population. Gene polymorphism analysis of both GSTT1 and GSTM1 was carried out independently in the 16 articles selected. The studies included in this meta-analysis have been performed in different geographical locations of India (Table 1).

**Meta-analysis of lung cancer association with GSTT1 and GSTM1 gene polymorphism**

In the present meta-analysis, after pooling all the data together, both random-effects model as well as fixed-effects model were studied depending on the significance of heterogeneity. A summary of GSTT1 and GSTM1 gene polymorphism with lung cancer in the Indian population is given in Figure 1.

**Analysis of the overall population**

Eight studies with a total population of 1347 cases and 1855 control subjects were included in the GSTT1 polymorphism study. Similarly, eight studies with a total

<table>
<thead>
<tr>
<th>Mean age (case)</th>
<th>GSTM1 (null/present)</th>
<th>Percentage of GSTM1 null genotype</th>
<th>GSTT1 (null/present)</th>
<th>Percentage of GSTT1 null genotype</th>
<th>Method</th>
<th>Geographic location</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>55.50 ± 11.30</td>
<td>62/38</td>
<td>52/24</td>
<td>64.77</td>
<td>82/18</td>
<td>65/11</td>
<td>83.52</td>
<td>Multiplex PCR</td>
</tr>
<tr>
<td>58.17 ± 10.95</td>
<td>46/100</td>
<td>39/107</td>
<td>29.11</td>
<td>32/114</td>
<td>13/133</td>
<td>15.41</td>
<td>Multiplex PCR</td>
</tr>
<tr>
<td>42.60 ± 6.30</td>
<td>44/49</td>
<td>99/154</td>
<td>41.33</td>
<td>24/69</td>
<td>56/197</td>
<td>23.12</td>
<td>Multiplex PCR</td>
</tr>
<tr>
<td>60.41 ± 10.56</td>
<td>66/122</td>
<td>113/177</td>
<td>37.45</td>
<td>33/155</td>
<td>73/217</td>
<td>22.17</td>
<td>Multiplex PCR</td>
</tr>
<tr>
<td>56.14 ± 11.91</td>
<td>82/136</td>
<td>58/180</td>
<td>30.70</td>
<td>84/134</td>
<td>90/148</td>
<td>38.16</td>
<td>Multiplex PCR</td>
</tr>
<tr>
<td>56.14 ± 11.91</td>
<td>84/134</td>
<td>90/148</td>
<td>38.16</td>
<td>82/136</td>
<td>58/180</td>
<td>30.70</td>
<td>PCR</td>
</tr>
<tr>
<td>59.16 ± 9.95</td>
<td>57/97</td>
<td>66/88</td>
<td>39.94</td>
<td>22/132</td>
<td>42/112</td>
<td>20.78</td>
<td>Real-Time PCR</td>
</tr>
<tr>
<td>59.02 ± 13.02</td>
<td>116/114</td>
<td>168/292</td>
<td>41.16</td>
<td>113/117</td>
<td>193/267</td>
<td>44.35</td>
<td>Multiplex PCR</td>
</tr>
</tbody>
</table>

*Total population = Case + control. Percentage of GSTM1 (null genotype) in overall population is 40.33. Percentage of GSTT1 (null genotype) in overall population is 34.78.

% Null genotypes of both GSTT1 and GSTM1 genes is lowest among South Indian population compared to the rest of India.

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**Table 1. Comparison of polymorphism of glutathione S-transferase genes reported in various studies in different geographic locations of India**

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GSTT1 and GSTM1 gene polymorphism and their susceptibility to lung cancer reported in different studies. a, Forest plot analysis of GSTT1 gene polymorphism and lung cancer, where relative weights are measured by random effects analysis (P > 0.05). b, Forest plot analysis of GSTM1 gene polymorphism and lung cancer, where relative weights are measured by random effects analysis (P < 0.05). OR, Odds ratio; 95%CI, 95% confidence interval.

Figure 1. Comparison of odds ratio (OR) and relative weight of GSTT1 and GSTM1 gene polymorphism and their susceptibility to lung cancer in the Indian population. The pooled results showed a significant association of GSTM1 polymorphism (null versus present, OR = 1.173; 95% CI: 1.011–1.361; P = 0.03; I² = 40.58%) with incidence of lung cancer in the Indian population. However, the GSTT1 gene polymorphism (null versus present, OR = 1.278; 95% CI: 0.914–1.796; P = 0.157; I² = 82.25%) was found to be not significantly associated with lung cancer in the Indian population.

Publication bias

Publication bias was evaluated using Begg’s funnel plot and Egger’s test. It can be observed from the test results shown in Figure 2 that there is no significant publication bias for both GSTM1 (t = 0.68, P = 0.52) polymorphism as well as GSTT1 polymorphism (t = 0.67, P = 0.53) in the published literatures.

Discussion

In this meta-analysis, an extensive study was done on the data collected from 16 studies based on GSTT1 and GSTM1 gene polymorphism to find their association with the occurrence of lung cancer among the Indian population. In the present meta-analysis study, a significant association of GSTM1 (homologous deletion) polymorphism with the elevated risk of lung cancer has been observed. The study involved more than 2500 cases and control subjects to find a strong correlation of candidate genes with the risk of lung cancer. However, there was no significant association in the case of GSTT1 (homologous deletion) gene polymorphism with elevated risk of lung cancer.

The association of GST genes with increase in the risk of lung cancer has long been studied, but the results are inconsistent. Saarikoski et al. did not find any significant association of GSTT1 and GSTM1 genes with lung cancer. The results of some studies were found to be consistent with those of Saarikoski et al. However, results of the present study are similar to those of Matakova et al. and Nazar-Stewart et al., who found significant association of GSTM1 (null genotype) with elevated risk of lung cancer. Results of the present study also predict that GSTT1 (null genotype) is not significantly associated with lung cancer, similar to the results of Malats et al.

Comparing the gene polymorphism and susceptibility to lung cancer across the world population, it was found that association of GSTM1 gene polymorphism and lung cancer is highly prevalent in most of the Asian population. However, results of the present study are in contrast with those of Yang et al., who reported significant correlation of GSTT1 (null genotype) (OR = 1.28, 95% CI = 1.10–1.49; heterogeneity, P < 0.001 and I² = 62.0%) with lung cancer in the Asian population.

The GST enzymes are well known for their detoxifying properties. Most of the carcinogenic chemicals of cigarette smoke that enter the human body are metabolised by the GST enzymes. The polymorphism of μ-class (Mu) and β-class (theta) of GST enzymes is the most studied enzymes for different types of respiratory diseases. Polymorphism of these two genes has been considered as the potentially important marker for environmentally induced lung cancer. Although there are considerable number of studies relating polymorphism of these genes with lung cancer among different ethnicities across the world, there are only a few reported studies on the Indian population. Therefore, the present meta-analysis of these reported studies was done specifically on the Indian population. Results of the present study indicate that GSTM1 gene (null versus present) (OR = 1.173; 95% CI: 1.011–1.361) is associated with elevated risk of lung cancer in the overall population.

There have been certain limitations in the present study. The number of published results is less, which limits a comprehensive meta-analysis on the Indian population. The data required for stratified analysis of gene–smoking, gene–ethnicity, gene–age interactions are not

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sufficient. Although all the relevant publications were taken into consideration in the present study, the number of reported studies is less; hence, publication bias may exist.

Thus in conclusion, it can be summarized that GSTM1 (null genotype) gene polymorphism is significantly associated with elevated risk of lung cancer in the Indian population. Further, case-control studies on larger populations are required to elucidate the effect of gene polymorphism on lung cancer in the Indian population. Studies relating the GST enzymes profile and their interaction with cigarette smoke compounds will be useful.

8. Ma, Z., Guo, W., Gong, T., Niu, H. J., Wang, R. W. and Jiang, Y. G., CYP1A2 rs762551 polymorphism contributes to risk of lung...

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