Original Article

GSTM1 null genotype is a risk factor for laryngeal cancer

Xuejun Liu, Qijun Fan, Liyan Ni, Fanli Liu, Saiyu Huang, Jinjian Gao, Bobei Chen

The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China
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Abstract: It remains unclear whether the Glutathione S-transferase M1 (GSTM1) null genotype influence laryngeal cancer development. This study aimed to investigate the interactions among GSTM1 genotype with regard to laryngeal cancer development. We searched online electronic databases (PubMed, EMBASE and CNKI). The strength of association between the GSTM1 genotype and laryngeal cancer risk was assessed by calculating OR with 95% CI. Finally, a total of 25 case-control studies with 2999 cases and 4942 controls on the association between GSTM1 genotype and laryngeal cancer risk were included in this meta-analysis. The overall result showed that the GSTM1 null genotype was related to increased risk of laryngeal cancer (OR = 1.34; 95% CI, 1.09-1.63). Subgroup analysis was performed according to ethnicity. The results showed that Asians had increased risk of laryngeal cancer (OR = 1.90; 95% CI, 1.40-2.57), while no significant increased risk was observed in Caucasians (OR = 1.15; 95% CI, 0.97-1.36). In conclusion, this meta-analysis suggested that GSTM1 null genotype was significantly associated with increased laryngeal cancer risk.

Keywords: Laryngeal cancer, GSTM1, meta-analysis, polymorphism

Introduction

Laryngeal cancer is fourteenth most common cancer in the world and it is the most common cancer in the head and neck [1]. Approximately 13,000 men and women will be diagnosed with laryngeal cancer in the United States in 2012. Tobacco smoking and alcohol drinking are the two major risk factors for the laryngeal carcinoma in the developed countries [2]. However, it was reported that genetic was also play an important role in the laryngeal cancer development.

Oxidative stress has been implicated in the pathogenesis of laryngeal cancer. The glutathione S-transferases (GSTs) are a family of enzymes that have the general function of detoxifying xenobiotics that are capable of generating free radicals, by conjugating them with glutathione. GSTM1 has been extensively studied because its locus is polymorphic with a common null allele that produces a complete lack of the enzyme. The association between the GSTM1 null genotype and laryngeal cancer development is not well established in the current literature. Several studies have demonstrated an increased risk of laryngeal cancer risk in subjects with the GSTM1 null genotype, whereas other studies have reported no association between the GSTM1 genotype and laryngeal cancer [3-27]. Therefore, we performed this meta-analysis.

Materials and methods

Search for publications

We searched online electronic databases (PubMed, EMBASE and CNKI) using terms: (Glutathione S-transferase M1 or GSTM1) and (polymorphism or variant or variation) and (“laryngeal cancer”). Additional studies were identified by a hand search from reference of original studies or review articles on this topic. There was no language restriction.

Inclusion and exclusion criteria

The major inclusion criteria were: (1) case-control studies or cohort studies; (2) report the association between GSTM1 genotype and
laryngeal cancer; (3) available genotype distribution data in cases and controls or odds ratio (OR) with its 95% confidence intervals (CIs). Exclusion criteria included the following: duplicate publications; case reports; insufficient data; lack of a control group; and abstracts, reviews, talks, and review class documentations.

**Data extraction**

Data were independently abstracted by two investigators using a standard protocol and data-collection form in accordance to the criteria stated above. Differences among evaluators were resolved by discussion and rereading with the third investigator. The following information was extracted from each included study using a standardized data collection protocol: first author, year of publication, ethnicity of participants, numbers of cases and controls, and genotype number in cases and controls.

**Statistical analysis**

The strength of association between the GSTM1 genotype and laryngeal cancer risk was assessed by calculating OR with 95% CI. A statistical test for heterogeneity was performed based on the Q statistic. The $P > 0.10$ of the Q-test indicated a lack of heterogeneity among studies. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled OR (the DerSimonian and Laird method). Otherwise, the fixed-effects model was adopted (the Mantel-Haenszel method). Stratified analysis was performed by ethnicity. Sensitivity analysis was conducted through sequentially excluded individual studies to assess the stability of the results. Potential publication bias was examined visually in a funnel plot and Egger’s test. All statistical tests were performed with the software STATA version 11.0 (Stata Corporation, College Station, TX, USA).

Table 1. Characteristics of the studies included in this meta-analysis

<table>
<thead>
<tr>
<th>First author/Year</th>
<th>Ethnicity</th>
<th>No. of case</th>
<th>No. of control</th>
<th>Case Present</th>
<th>Case Null</th>
<th>Control Present</th>
<th>Control Null</th>
</tr>
</thead>
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<td>118</td>
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<td>18</td>
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<td>180</td>
<td>142</td>
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<td>32</td>
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<td>178</td>
<td>114</td>
<td>151</td>
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<td>164</td>
<td>39</td>
<td>30</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
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<tr>
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<td>117</td>
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<td>104</td>
<td>100</td>
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<td>234</td>
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</tbody>
</table>
GSTM1 and laryngeal cancer

Discussion

There are several studies of the relationship of GSTM1 null genotype and cancers. For example, Gong et al. suggested that GSTM1 null genotype was associated with high risks of prostate cancer [28]. Song et al. indicated that GSTM1 null genotype may slightly increase the risk of hepatocellular carcinoma [29]. Zhang et al. found a significant association between GSTM1 allelic variant and head and neck squamous cell carcinoma [30]. In addition, GSTM1 null genotype also associated with coronary artery disease risk [31] and asthma risk [32].

In this study, we found that GSTM1 null genotype was significantly associated with laryngeal cancer risk. In the subgroup analysis by ethnicity, we found that Asians carrying GSTM1 null genotype had an increased laryngeal cancer risk, while Caucasians did not have an increased laryngeal cancer risk.

The etiology of laryngeal cancer is quite unclear by now. In general, it is a disease caused by both genetic and environmental factors. By now, several genetically polymorphic enzymes like cytochrome P450 1A1 are reported to be related with laryngeal cancer [33]. Besides, several other kinds of environmental factors,
such as alcohol intake [34], human papillomavirus infection [35] and silica exposure [36] are also reported to be associated with risk of laryngeal cancer.

This study has several limitations that need to be addressed. First, the overall sample size was not large enough. We need to perform more original studies to enhance the reliability and accuracy of our conclusions. In addition, the majority of the subjects included in the studies were Caucasian. To explain the discrepancy in the results caused by the different races of the subjects, more studies in other ethnic groups are needed. Second, some important information was unavailable and was not reported in the included studies, e.g., pathological sub-types and smoking status. Therefore, the effects of pathological status, environmental exposure or lifestyle on the association between GSTM1 variant and laryngeal cancer could not be determined in this meta-analysis.

In conclusion, this meta-analysis suggested that GSTM1 null genotype was significantly associated with increased laryngeal cancer risk.

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Disclosure of conflict of interest

None.

Address correspondence to:
Bobei Chen, The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China. Tel: 86-0577-88002817; E-mail: chenbobei224@126.com

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