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Original Article

GSTM1 null genotype is a risk factor for laryngeal cancer

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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 an 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 an 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 identifed 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

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

First author/Year	Ethnicity	No. of case	No. of control	Case		Control	
				Present	Null	Present	Null
Jahnke/1996	Caucasian	269	216	118	151	104	112
Coutelle/1997	Caucasian	18	37	4	14	19	18
Jourenkova/1998	Caucasian	129	172	51	78	82	90
Jaskula-Sztul/1998	Caucasian	171	180	142	29	148	32
Matthias/1998	Caucasian	265	178	114	151	83	95
Morita/1999	Asian	69	164	39	30	81	83
Hong/2000	Asian	82	63	26	56	30	33
Hanna/2001	Caucasian	20	20	16	4	10	10
To-Figueras/2002	Caucasian	204	203	108	96	103	100
Gronau/2003	Caucasian	53	139	38	14	71	68
Risch/2003	Caucasian	245	251	118	127	116	135
Bardakci/2003	Caucasian	36	35	19	17	17	18
Unal/2004	Caucasian	42	47	23	19	57	32
Li/2004	Asian	89	164	39	50	95	69
Gajecka/2005	Caucasian	292	321	152	140	157	164
Gattas/2006	Caucasian	22	102	15	7	31	22
Biselli/2006	Caucasian	22	60	15	7	31	29
Peters/2006	Caucasian	135	753	54	81	349	404
Goloni-Bertollo/2006	Caucasian	16	45	10	6	23	22
Acar/2006	Caucasian	110	197	53	57	123	74
Chatzimichalis/2010	Caucasian	88	102	14	74	14	88
Ruwali/2011	Asian	148	500	70	78	340	160
Lourenco/2011	Caucasian	37	142	23	14	76	66
Tian/2011	Asian	233	102	117	116	80	22
Maurya/2014	Asian	204	749	104	100	515	234

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,

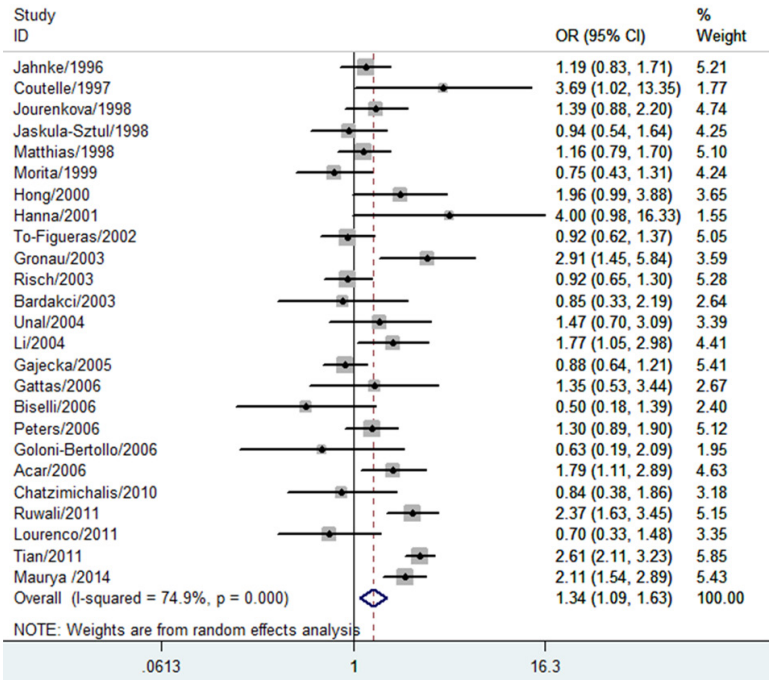

Figure 1. Meta-analysis for the association between GSTM1 null genotype and laryngeal cancer risk.

College station, TX, USA). A *P* value < 0.05 was considered statistically significant.

Results

Characteristics of studies

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. There were 6 studies of Asian population and 19 studies of Caucasian population. The characteristics of studies included in the meta-analysis are presented in **Table 1**.

Data synthesis and meta-analysis

The forest plot of the GSTM1 meta-analysis is shown in **Figure 1**. Heterogeneity was observed in the GSTM1 studies ($P < 0.001$, $I^2 = 75\%$), and therefore, a random-effects model was used. The overall result showed that the GSTM1 null genotype was related to an increased risk of laryngeal cancer (OR = 1.34; 95% CI, 1.09-1.63). Subgroup analyses were performed according to ethnicity. The results showed that Asians had an 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).

Sensitivity analyses were conducted to assess the influence of each individual study on the pooled OR by removing one study at a time. In the overall meta-analysis, no single study changed the pooled results, which indicates that the results were statistically stable and reliable (**Figure 2**).

Funnel plot and Egger's test were performed to assess the publication bias of the currently available literature. The shapes of the funnel plot appeared symmetrical (**Figure 3**). Egger's test was used to provide statistical evidence for funnel plot symmetry. The p-value of the Egger's test is 0.153, suggesting no evidence of publication bias.

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 cancinoma [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,

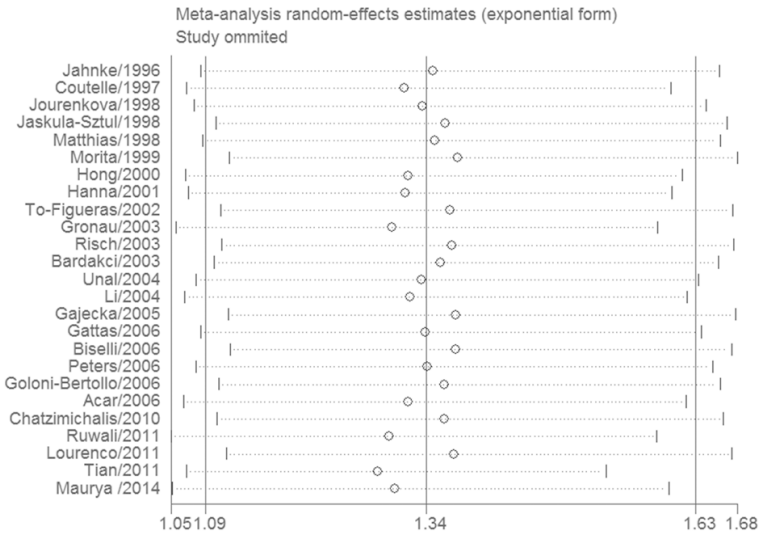

Figure 2. Sensitivity analysis of association between GSTM1 null genotype and laryngeal cancer risk.

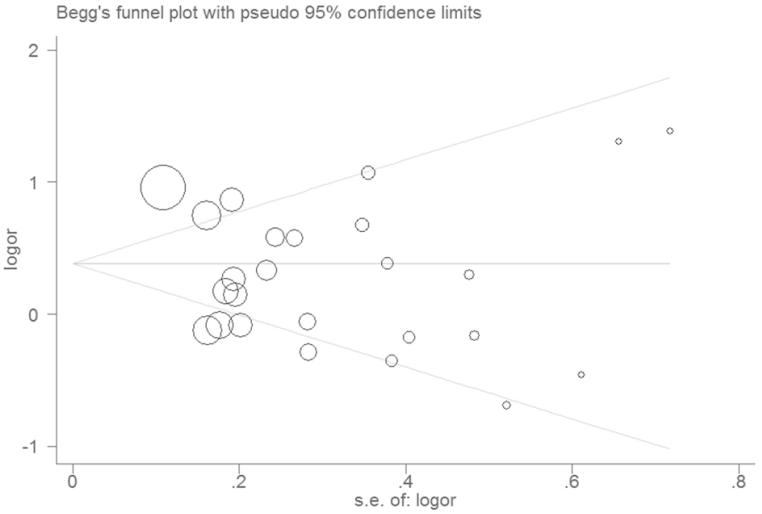

Figure 3. Funnel plot of associations between GSTM1 null genotype and laryngeal cancer risk.

such as alcohol intake [34], human papillomaviruses 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 subtypes 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.

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