

# *GSTM1* polymorphism is related to risks of nasopharyngeal cancer and laryngeal cancer: a meta-analysis

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**Background:** Accumulating data have reported that *GSTM1* polymorphism may be related to nasopharyngeal cancer (NPC) and laryngeal cancer (LC). This meta-analysis was performed to investigate the relationship between *GSTM1* polymorphism and risks of NPC and LC.

**Methods:** Pubmed, Embase, and China National Knowledge Infrastructure (CNKI) databases were searched for potential articles. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the relationship of *GSTM1* polymorphism with the risks of NPC and LC.  $P > 50%$  or  $P < 0.05$  indicates significant heterogeneity. When heterogeneity existed, the random-effects model was used to pool data, otherwise, the fixed-effects model was adopted. Publication bias was detected by Begg's funnel plot and Egger's regression. Quality of each study was evaluated by Newcastle-Ottawa Scale.

**Results:** Thirty-two eligible articles were included. Pooled outcome suggested the significant relationship of *GSTM1* null genotype with increased risk of LC (OR = 1.28, 95% CI = 1.05–1.54). Compared with hospital-based (HB) population, *GSTM1* null genotype was also related to increased risk of LC (OR = 1.38, 95% CI = 1.06–1.80). Positive relationship of *GSTM1* null genotype with enhanced risk of NPC was observed (OR = 1.43, 95% CI = 1.26–1.63). A similar trend was also observed in the subgroup analysis by source of control (population-based [PB]: OR = 1.39, 95% CI = 1.18–1.63; HB: OR = 1.52, 95% CI = 1.22–1.89).

**Conclusion:** *GSTM1* null genotype is related to increased risk of NPC and LC.

**Keywords:** *GSTM1*, polymorphism, NPC, LC

## Introduction

Nasopharyngeal cancer (NPC) is a fast-growing tumor which features distant metastasis and frequent nodal at diagnosis time.<sup>1</sup> Epstein-Barr virus (EBV) infection has been demonstrated as a major risk factor for NPC.<sup>2</sup> Besides, alcohol consumption and cigarette smoking could also increase the risk of NPC.<sup>3</sup> Laryngeal cancer (LC) is a common malignancy in the head and neck region.<sup>4</sup> Evidences have indicated that cigarette smoking and alcohol consumption play important roles in the development of the cancer.<sup>5</sup> Recent studies indicate that carcinogen-metabolizing genes could modulate individual susceptibility to cancers. Polymorphisms of these genes may influence carcinogen activation/detoxification by altering the expression and function of the genes.

Xenobiotics could be detoxified by the *GSTM1* and *GSTT1* enzymes. These phase II enzymes are involved in the detoxification of benzopyrene and polycyclic aromatic hydrocarbons (PAHs).<sup>6</sup> In addition, *GSTM1* and *GSTT1* serve as important factors in metabolizing carcinogens derived from tobacco smoke.<sup>7</sup> It has been observed

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that homozygous deletions of *GSTM1* and *GSTT1* genes bring about phenotypic absence of glutathione S-transferases (GSTs) activity.<sup>8,9</sup> *GSTM1* and *GSTT1* null genotypes show an association with susceptibility to lung cancer or bladder cancer, which are induced by environmental factors.<sup>10,11</sup>

*GSTM1* products are responsible for catalyzing the conjugation of glutathione to epoxide derivatives of PAHs, which are the major carcinogens in tobacco smoke.<sup>12</sup> Three different polymorphisms are observed in *GSTM1* gene.<sup>13</sup> Among them, the most important polymorphism (*GSTM1* null genotype) causes the inactivation of GSTM1 enzyme. The frequency of the null genotype ranges from 23% to 62% among different populations.<sup>14</sup>

This present meta-analysis aimed to investigate the association of *GSTM1* polymorphism with NPC and LC. The obtained outcome contributes to uncovering the pathogenesis of the cancers. Meanwhile, it contributes to clinical diagnosis of high-risk individuals for NPC and LC.

## Methods

### Article search

Pubmed, Embase, and China National Knowledge Infrastructure (CNKI) databases were searched for potential articles without language limitation. The search date was limited to May 2017. The keywords used in the search were: *GSTM1*, polymorphism or mutation or variant, nasopharyngeal carcinoma or nasopharynx cancer, LC or laryngocarcinoma. The references of obtained articles were also checked for additional articles.

### Inclusion and exclusion criteria

The eligible articles had to meet the following criteria: (1) case-control studies; (2) articles investigating the relationship of *GSTM1* polymorphism with NPC or LC; (3) articles providing the genotype data in case and control groups. The articles would be excluded if they were: (1) review articles; (2) animal or in vitro experiments; (3) *GSTM1* polymorphism and risk of other cancers rather than NPC or LC.

### Data extraction

Two authors were responsible for data extraction. The work was performed independently and any disagreements were resolved by discussion with a third author. The extracted information included: name of first author, publication year, country, ethnicity, experimental method, sample size, and genotypes' distribution in case and control groups. Quality of each study was evaluated by the method of Newcastle-Ottawa Scale (NOS).

## Statistical analysis

All the analyses were performed with Stata 12.0 software. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the relationship of *GSTM1* polymorphism with NPC or LC.  $I^2$  and  $P$ -value were used to assess the inter-study heterogeneity.  $I^2 > 50\%$  or  $P < 0.05$  indicates the presence of heterogeneity. If heterogeneity existed, the random-effects model was performed to pool data, otherwise, the fixed-effects model was used. Subgroup analyses based on ethnicity and source of control were initiated as well. Sensitivity analysis was conducted to assess the robustness of pooled results. Begg's funnel plot and Egger's regression analysis were used to evaluate the potential publication bias.

## Results

### Article selection

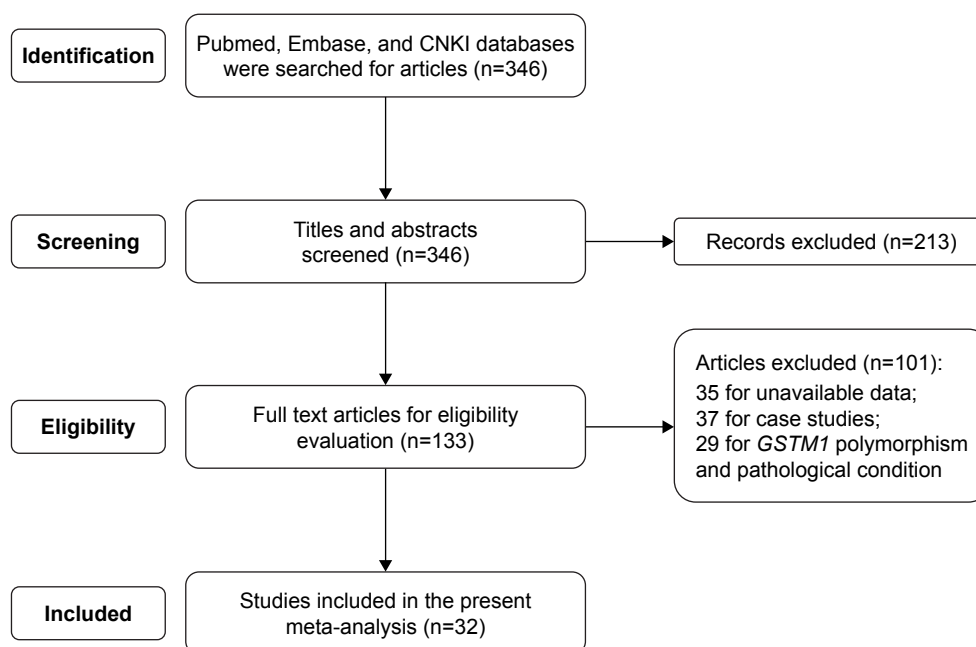
During the search, a total of 346 relevant articles were obtained. After screening the titles and abstracts, 213 records were excluded for review articles ( $n=82$ ), *GSTM1* polymorphism and other cancers ( $n=67$ ), and other genes and NPC or LC ( $n=64$ ). The remaining 133 articles were evaluated for eligibility. During the evaluation, 101 articles were excluded for unavailable data ( $n=35$ ), case studies ( $n=37$ ), *GSTM1* polymorphism and pathological condition ( $n=29$ ). Finally, 32 eligible articles were selected for the present meta-analysis.<sup>15-46</sup> The detailed selection process was shown in Figure 1. The basic information of included articles was listed in Table 1. The results about the quality assessment was shown in Table 1 as well.

### Relationship of *GSTM1* polymorphism with LC

Random-effects model was used to analyze the association between *GSTM1* polymorphism and risk of LC ( $P=0.000$ ). The pooled results indicated that *GSTM1* null genotype was related to increased risk of LC (OR =1.28, 95% CI =1.05–1.54). Subgroup analyses by ethnicity and source of control were performed as well (Table 2). The outcome indicated that *GSTM1* null genotype was correlated with enhanced risk of LC, compared with hospital-based (HB) population (OR =1.38, 95% CI =1.06–1.80) (Figure 2). No positive results were observed in the analysis of ethnicity.

### Relationship of *GSTM1* polymorphism with NPC

Fixed-effects model was adopted to analyze the relationship of *GSTM1* polymorphism with NPC ( $P=0.417$ ). Overall results indicated that *GSTM1* null genotype could increase the risk of NPC (OR =1.43, 95% CI =1.26–1.63). In the



**Figure 1** Article selection process. 32 eligible articles were included into the present meta-analysis.

**Abbreviation:** CNKI, China National Knowledge Infrastructure.

**Table 1** Basic information of included articles

Cancers	Author	Year	Country	Method	Score	Case		Control	
						Present	Null	Present	Null
LC	Unal et al <sup>26</sup>	2004	Turkey	Real-time PCR	5	23	19	57	32
	Gajecka et al <sup>27</sup>	2005	Poland	PCR-RFLP	7	152	140	157	164
	Acar et al <sup>28</sup>	2006	Turkey	PCR	8	53	57	123	74
	To-Figueras et al <sup>29</sup>	2002	Spain	PCR-RFLP	8	108	96	103	100
	Hong et al <sup>30</sup>	2000	Korean	PCR	8	26	56	30	33
	Charzimichalis et al <sup>31</sup>	2010	Greece	PCR	8	14	74	14	88
	Jourenkova et al <sup>32</sup>	1998	France	PCR	9	51	78	82	90
	Tian et al <sup>33</sup>	2011	China	PCR	8	117	116	80	22
	Lourenco et al <sup>34</sup>	2011	Brazil	PCR-RFLP	7	23	14	76	66
	Yan and Zhou <sup>35</sup>	2003	China	PCR	7	12	30	56	52
	Li et al <sup>36</sup>	2004	China	PCR	7	39	50	95	69
	Morita et al <sup>37</sup>	1999	Japan	PCR	7	39	81	30	83
	Kihara et al <sup>38</sup>	1997	Japan	PCR	8	70	86	242	230
	Bardacki et al <sup>39</sup>	2003	Turkey	PCR	8	11	25	19	16
	Gattas et al <sup>40</sup>	2006	Brazil	PCR-RFLP	8	12	10	63	39
	Lei et al <sup>41</sup>	2003	China	PCR	7	17	45	28	28
	Matthias et al <sup>42</sup>	2003	German	PCR	7	114	151	83	95
	Risch et al <sup>43</sup>	2003	German	PCR-RFLP	9	118	127	116	135
	Gronau et al <sup>44</sup>	2003	German	PCR	8	107	80	71	68
	Jahnke et al <sup>45</sup>	1997	German	PCR-RFLP	8	118	51	104	112
NPC	Biselli et al <sup>46</sup>	2006	Brazil	PCR	8	15	7	31	29
	Deng et al <sup>15</sup>	2004	China	PCR	7	35	56	71	64
	Jiang et al <sup>16</sup>	2011	China	PCR	7	85	97	215	157
	Cheng et al <sup>17</sup>	2003	China	PCR	8	141	173	168	169
	Guo et al <sup>18</sup>	2008	China	PCR	8	137	204	262	328
	Zhang <sup>19</sup>	2012	China	PCR-CTPP	7	18	27	19	11
	Da et al <sup>20</sup>	2002	China	PCR	8	32	48	44	36
	Wei et al <sup>21</sup>	2010	China	PCR	7	48	48	336	305
	Deng et al <sup>22</sup>	2005	China	PCR	7	49	78	112	95
	Tiwawech et al <sup>23</sup>	2005	Japan	PCR	7	28	50	71	74
Liao et al <sup>24</sup>	2005	China	PCR	7	30	50	40	32	
Nazar-Stewart et al <sup>25</sup>	1999	America	PCR	8	38	45	79	63	

**Note:** Quality assessment of each study was performed by the method of Newcastle-Ottawa Scale and the score was calculated.

**Abbreviations:** PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-CTPP, polymerase chain-reaction with the confronting-two-pair primer; NPC, nasopharyngeal cancer; LC, laryngeal cancer.

**Table 2** Pooled results of the present meta-analysis

Cancers	Subgroup	Types	OR	95% CI	P-value for heterogeneity
LC	Ethnicity	Caucasian	1.27	0.99–1.56	0.000
		Asian	1.36	0.96–1.93	0.053
	Source of control	PB	1.13	0.86–1.48	0.022
		HB	1.38	1.06–1.80	0.000
	Total	–	1.28	1.05–1.54	0.000
NPC	Source of control	PB	1.39	1.18–1.63	0.309
	HB	1.52	1.22–1.89	0.423	
	Total	–	1.43	1.26–1.63	0.417

**Abbreviations:** LC, laryngeal cancer; NPC, nasopharyngeal cancer; OR, odds ratio; CI, confidence interval; PB, population-based; HB, hospital-based.

subgroup analysis by source of control, we found that *GSTM1* null genotype was still related to increased risk of NPC (population-based: OR = 1.39, 95% CI = 1.18–1.63; HB: OR = 1.52, 95% CI = 1.22–1.89) (Figure 3).

## Sensitivity analysis

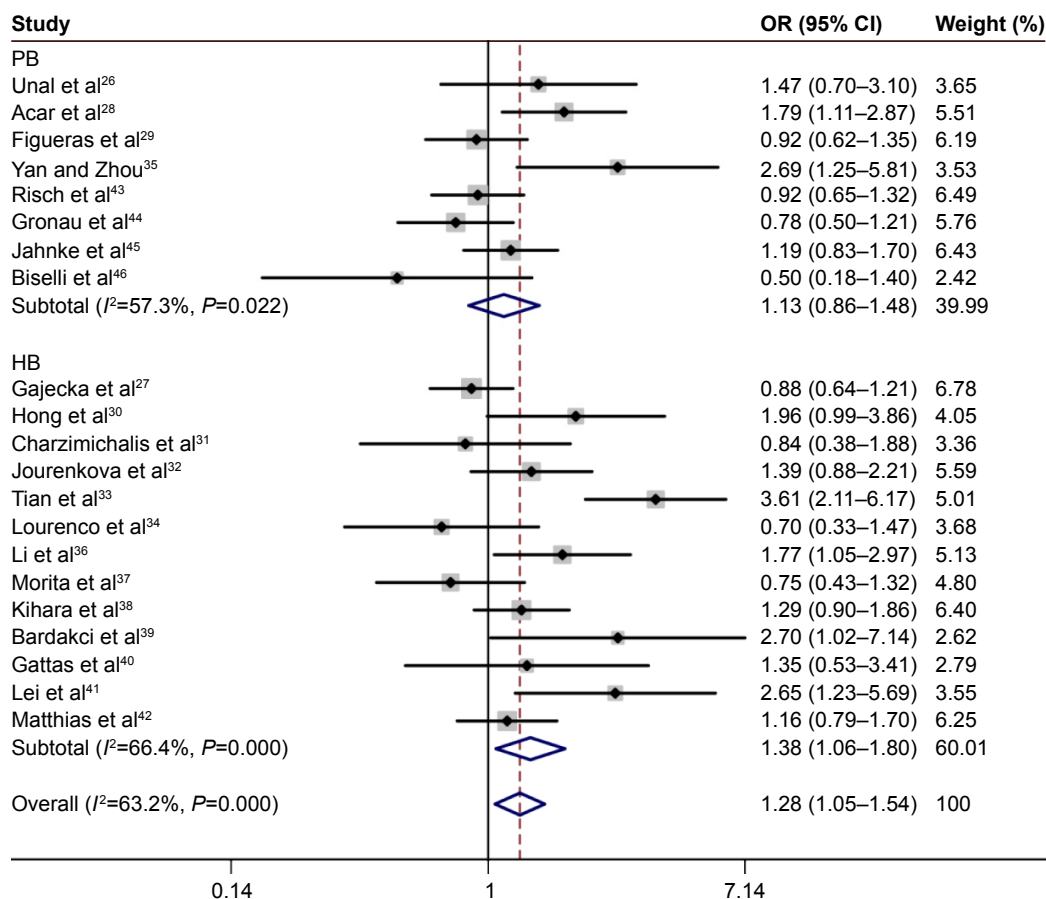
Sensitivity analysis was performed by deleting one study at a time. The analysis indicated that the pooled results were robust.

## Publication bias detection

Begg's funnel plot and Egger's regression analysis were performed to detect the potential publication bias. The funnel plot seemed to be symmetrical ( $P=0.436$ ) (Figure 4). Egger's analysis also suggested the absence of publication bias ( $P=0.097$ ).

## Discussion

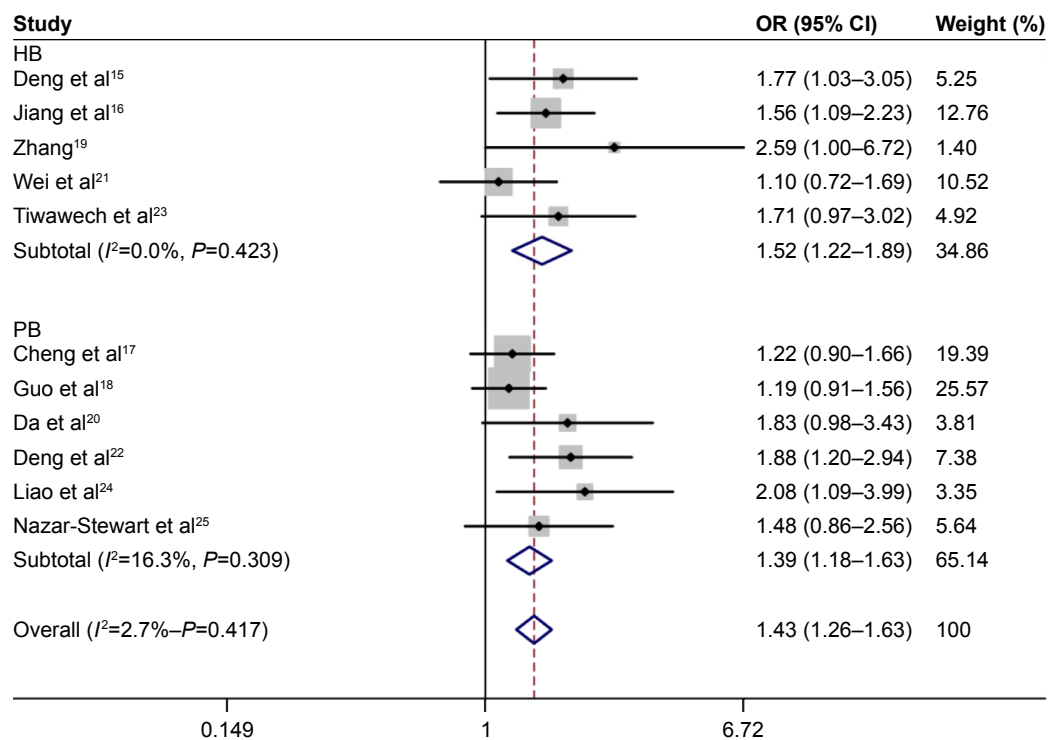
GSTs, member of a super-family of detoxification enzymes, show important effects in resisting various environmental toxicants and chemical carcinogens. For the phase II detoxification enzymes, more than five classes ( $\mu$ ,  $\sigma$ ,  $\pi$ ,  $\alpha$ ,  $\theta$ ) of GSTs have been confirmed. Among these enzymes, only enzymes of GST-M ( $\mu$ ), GST-T ( $\theta$ ) and GST-P ( $\pi$ ) play important roles in the detoxification of carcinogenic electrophiles. Null mutations of *GSTM1* are linked with complete loss of enzyme activities for binding with genotoxic substrates, such as epoxides.<sup>47</sup> Cumulative data have confirmed that individuals with null genotype of *GSTM1* are more likely to develop various cancers such as colorectal cancer, prostate cancer, gastric cancer, lung cancer,



**Figure 2** Subgroup analysis by source of control about the association between *GSTM1* null genotype and risk of LC.

**Note:** Weights are from random effects analysis.

**Abbreviations:** LC, laryngeal cancer; OR, odds ratio; CI, confidence interval; PB, population-based; HB, hospital-based.



**Figure 3** Subgroup analysis by source of control about the association between *GSTM1* null genotype and risk of NPC.

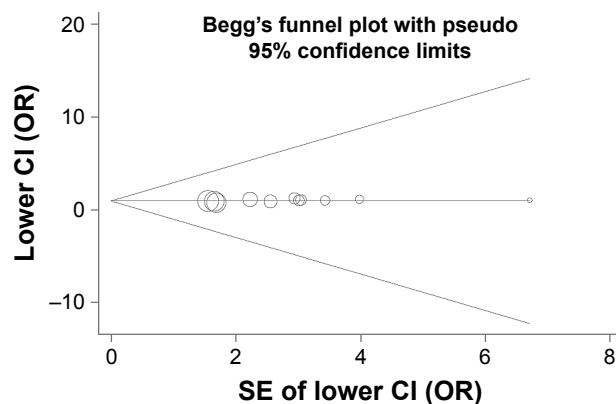
**Abbreviations:** NPC, nasopharyngeal cancer; OR, odds ratio; CI, confidence interval; PB, population-based; HB, hospital-based.

liver cancer, bladder cancer, breast cancer, ovarian cancer, skin cancer, oral cancer, NPC, and LC.<sup>25,27,48–57</sup>

Accumulating data suggest that EBV infection, carcinogen exposure, and genetic susceptibility play an important role in NPC tumorigenesis. EBV infection is confirmed as a causal factor.<sup>58</sup> However, not all EBV-infected individuals would develop NPC, which indicates that other factors may be involved in the pathogenesis of the cancer, such as tumor promotion, lifestyle, and exposure to carcinogens.<sup>59–61</sup> Besides, susceptibility genes such as interferon-alpha, HLA-regions and *p53* alleles, and certain polymorphic genes encoding

enzymes involved in metabolic activation and detoxification of xenobiotics have been regarded as risk factors.<sup>62,63</sup> The null genotype of *GSTM1* is linked with the loss of enzyme activity for binding with genotoxic substrates, therefore, the individuals with *GSTM1* null are believed to be more likely to suffer NPC than individuals with normal genotype of *GSTM1*. The fact is that frequency of *GSTM1* null genotype is different among different ethnic groups, such as 45%–56% in Asians, 40%–58% in Caucasians, and 29%–30% in African-Americans.<sup>64–67</sup> In addition, the opinions on the relationship of *GSTM1* null genotype with risk of NPC were inconsistent among the published studies. Therefore, this meta-analysis was initiated to obtain a more accurate outcome. The outcome indicated that *GSTM1* null genotype could increase the risk of NPC (OR=1.43, 95% CI=1.26–1.63). A similar outcome was also observed in the subgroup analysis by source of control.

As for LC, smoking tobacco has been regarded as its main risk factor and only 1% of LC occurs among nonsmokers. However, not all smokers would develop LC. The incidence of LC is different among different countries and ethnic groups. Besides, LC cases exhibit geographic variations in distribution. These evidences indicate the important role of genetic susceptibility in the pathogenesis of LC. Tobacco contains aldehydes, nitrosamines, aromatic amines, and PAHs. These components can cause genetic mutations. There are many protective enzymes functioning in the deactivation or degradation of



**Figure 4** Begg's funnel plot (NPC). The funnel plot seemed to be symmetrical ( $P=0.436$ ).

**Abbreviations:** NPC, nasopharyngeal cancer; OR, odds ratio; CI, confidence interval; SE, standard error.

carcinogenic compounds, such as phase I enzymes (cytochrome p450, alcohol dehydrogenase) and phase II enzymes (N-acetyl transferases, GSTs). These enzymes, known as xenobiotic-metabolizing enzymes, commonly exist in the liver and have been found in the mucosa of the upper aerodigestive tract.<sup>68</sup> Phase II enzymes are involved in most metabolic detoxification processes of chemical carcinogens. Products of *GSTM1* gene contribute to conjugating glutathione to epoxide derivatives of PAHs. The associations of *GSTM1* null genotypes with tobacco-related cancers have been extensively reported, however, the role of *GSTM1* polymorphism in LC is still controversial. Our results, based on a meta-analysis, suggested that *GSTM1* null genotype was related to increased risk of LC (OR =1.28, 95% CI =1.05–1.54). The subgroup analysis by source of control also indicated that *GSTM1* null genotype was correlated with enhanced risk of LC.

This meta-analysis was performed with 32 eligible articles. The sample size was 10,185. The outcome showed certain priority in accuracy compared with other studies. However, several limitations existed in the analysis. Only *GSTM1* genetic polymorphism was analyzed, phase I and other phase II enzymes were not considered. Future analysis should focus much more on genes encoding these enzymes, which will contribute to uncovering the pathogenesis of NPC and LC. In addition, the occurrences of NPC and LC involve many risk factors. The analysis only considered the genetic factor and other environmental factors and genes should be investigated to get a much more complete outcome. Besides, significant heterogeneity existed in the analysis of LC, which might affect the accuracy of pooled results.

Subgroup analyses based on ethnicity and source of control were performed to identify the source of heterogeneity.

## Conclusion

*GSTM1* null genotype was related to increased risk of NPC and LC. The outcome will contribute to screening high-risk populations for NPC and LC.

## Acknowledgment

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## Disclosure

The authors report no conflicts of interest in this work.

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