RESEARCH ARTICLE

# Association Between GSTM1 Polymorphism and Nasopharyngeal Cancer Susceptibility: a Meta-analysis

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## Abstract

**Background/Aims: Glutathione S-transferase M1 (GSTM1) is a multifunctional enzyme that plays a critical role in the detoxification of varieties of carcinogenic metabolites. Many studies have been conducted to investigate the association between GSTM1 polymorphism and nasopharyngeal cancer (NPC) risk, but the findings among those studies are inconsistent. To assess this relationship more precisely, we performed a meta-analysis of all available studies on the subject. Methods: Case-control studies were identified by searching Pubmed, Embase, ISI Web of Science, and Wanfang databases through September 6, 2012. We used the pooled odds ratio (OR) with its corresponding 95% confidence interval (95%CI) to evaluate the association of GSTM1 polymorphism with NPC susceptibility. Subgroup analyses by pathological types, sex and smoking status were performed to further identify the association. Results: Overall, 11 published studies with 1,513 cases and 2,802 controls were finally included into this meta-analysis according to the inclusion criteria. Meta-analysis of total studies showed that the null genotype of GSTM1 was significantly associated with increased risk of NPC, when comparing with the non-null genotype (OR=1.51, 95%CI=1.33-1.72, POR<0.001). The association was still statistically significant in subgroup analysis of patients with nasopharyngeal squamous cell carcinoma (OR=1.73, 95%CI=1.24-2.42, POR=0.001). Males with the null genotype of GSTM1 were more likely to subject to NPC than females. In addition, the association between the null genotype of GSTM1 and NPC risk was strongest in individuals with exposure to smoking. Sensitivity analysis by sequential omission of any individual studies one at a time further demonstrated the significant association. Conclusions: The findings suggest that the null genotype of GSTM1 is a risk factor for NPC, and there is a gene- smoking interaction in this association.**

**Keywords:** Nasopharyngeal cancer - polymorphism - glutathione S-transferase M1 - meta-analysis

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## Introduction

Nasopharyngeal cancer (NPC) is one of the most common otolaryngological cancers, characterized by a high frequency of nodal and distant metastasis at diagnosis (Chan, 2011). Although it is rare in many areas of the world, NPC still causes serious damage to public health (Chan, 2011). The exact pathogenesis of NPC has not yet been understood up till now. Apart from epstein-barr virus (EBV) infection and endogenous/exogenous carcinogens, genetic susceptibility seems to be a risk factor playing an crucial role in the development of NPC (O'Neil et al., 2008). Many published studies have revealed that polymorphisms of carcinogen-metabolizing genes encoding detoxifying enzymes contribute to the variation of individual susceptibility to NPC (Chang et al., 2006; Guo et al., 2008; Zhuo et al., 2009).

Glutathione S-transferase M1 (GSTM1) is a detoxifying enzyme, which plays a critical role in the detoxification of varieties of carcinogenic metabolites (Moaven et al., 2010). Genetic variation of GSTM1 results in loss of its enzymatic activity and consequently affects an individual's susceptibility to carcinogens and toxins. Previous evidence has demonstrated that the GSTM1 polymorphism is associated with susceptibility to a number of malignant cancers, such as pancreatic cancer and renal cell carcinoma (Vrana et al., 2009; Ahmad et al., 2012). A recent meta-analysis indicated that the null genotype of GSTM1 was a risk factor for NPC, but the sample size of this meta-analysis was not big enough to give a confirmed conclusion (Zhuo et al., 2009). Several previous studies (Guo et al., 2008; Jiang et al., 2011) on the association of GSTM1 polymorphism with NPC risk gave inconsistent results due to several factors, such as environmental factors, family history and different genetic backgrounds. Furthermore, a single study might not be powered sufficiently to detect a small effect of the genetic polymorphisms on NPC risk, particularly in studies with small sample size. Meta-analysis by pooling data from all available studies takes the advantage of reducing random error and obtaining a more precise estimate for the association between GSTM1 polymorphism and NPC susceptibility (Attia et al., 2003). Thus, we performed the present meta-analysis of all eligible case-control studies to

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clarify the effect of GSTM1 polymorphism on the risk of NPC and to shed some light on the contradictory findings.

## Materials and Methods

*Search strategy*

All case-control studies assessing the association of GSTM1 polymorphism with NPC risk published up to September 6, 2012 were identified by searching Pubmed, Embase, ISI Web of Science, and Wanfang databases. There was no language limitation. The following search terms were used: Glutathione-S-Transferase M1, GSTM1, polymorphism, polymorphisms, mutation, variation, nasopharyngeal cancer, nasopharyngeal carcinoma and NPC. For each article retrieved, manual search of the relevant references was simultaneously performed to identify additional published articles.

*Inclusion criteria*

Studies were included in this meta-analysis if they satisfied with the inclusion criteria as follow: (1) Case-control studies; (2) Studies assessing the association of GSTM1 polymorphism with NPC risk; (3) Providing sufficient information for estimating Odds ratio (OR) with its 95% confidence interval (95%CI); (4) Providing available data to acquire genotype frequency of GSTM1 polymorphism. If studies with overlapping cases or controls, the most recent and/or the largest study with available data was included into the meta-analysis.

*Data extraction*

Essential data were carefully extracted from all eligible studies independently by two investigators, and discrepancies were finally resolved by consensus between the two authors. The extracted data included the first author's name, the year of publication, ethnicity, countries, clinical status of controls, genotyping method, source of controls, and the genotype distribution of cases and controls.

*Statistical methods*

We pooled the unadjusted OR with its 95% CI to assess the strength of the association between GSTM1 polymorphism and NPC risk. Subgroup analyses by pathological typing of NPC, sex and exposure to smoking were performed to further identify the correlation. Heterogeneity analysis was assessed by the chi-square-based Q statistic test (Cochran's Q statistic) and the $I^2$ statistic (Cochran, 1950; Higgins et al., 2003). A P value larger than 0.05 indicated that there was lack of heterogeneity among the included studies. The random-effects model was conducted using the DerSimonian and Laird's method (DerSimonian et al., 1986), while the fixed-effects model was conducted using the Mantel-Haenszel's method (Mantel et al., 1959) according to the results of heterogeneity analysis. Sensitivity analysis was performed by sequential omission of any individual studies one at a time to validate the credibility of the outcomes in this meta-analysis (Md et al., 1999). Publication bias was investigated by funnel plot, Begg's funnel plot and Egger's linear regression test (Egger et al., 1997; Stuck et al., 1998). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas), and the significance level was set at 0.05.

## Results

*Description of studies*

A total of 34 potentially relevant publications up to September 6, 2012 were systematically identified by searching Pubmed, Embase, ISI Web of Science, and Wanfang databases. According to the inclusion criteria, 11 published case-control studies with 1,513 cases and 2,802 controls were included into this meta-analysis (Nazar-Stewart et al., 1999; Da et al., 2002; Cheng et al., 2003; Liu et al., 2003; Deng et al., 2004; Deng et al., 2005; Tiwawech et al., 2005; Bendjemana et al., 2006; Guo et al., 2008; Jiang et al., 2011; Wei et al., 2012), while the other 23 ones were finally excluded because they did not examine the relationship of GSTM1 polymorphism with NPC risk or they were reviews. Two of the 11 publications (Deng et al., 2004; Deng et al., 2005) had the same first author, however, the both were considered as two separate study because they were not based on the same participants with NPC. There were 8 English literatures (Nazar-Stewart et al., 1999; Cheng et al., 2003; Deng et al., 2005; Tiwawech et al., 2005; Bendjemana et al., 2006; Guo et al., 2008; Jiang et al., 2011; Wei et al., 2012) and 3 Chinese ones (Da et al., 2002; Liu et al., 2003; Deng et al., 2004).

The characteristics of these 11 case-control studies were briefly presented in Table 1. There were 7 studies from China, one from Tunisie, one from Thailand, one

**Table 1. Characteristics of Total 11 Available Studies in the Meta-analysis**

| First Author | Publication Year | Country | Ethnicity | Cases | | Controls | |
|---|---|---|---|---|---|---|---|
| | | | | Null (%) | Present (%) | Null (%) | Present (%) |
| Wei YP | 2012 | China | Asians | 78(61.9) | 48(38.1) | 305(47.6) | 336(52.4) |
| Jiang Y | 2011 | China | Asians | 97(53.3) | 85(46.7) | 157(42.2) | 215(57.8) |
| Guo X | 2008 | China | Asians | 204(59.8) | 137(40.2) | 328(55.6) | 262(44.4) |
| Bendjemana K | 2006 | Tunisie | Africans | 23(51.1) | 22(48.9) | 33(33.0) | 67(67.0) |
| Tiwawech D | 2005 | Thailand | Asians | 50(64.1) | 28(35.9) | 74(51.0) | 71(49.0) |
| Deng ZL | 2005 | China | Asians | 78(61.4) | 49(38.6) | 95(45.9) | 112(54.1) |
| Deng ZL | 2004 | China | Asians | 56(61.5) | 35(38.5) | 64(47.4) | 71(52.6) |
| Liu ZG | 2003 | China | Asians | 28(60.9) | 18(39.1) | 18(34.0) | 35(66.0) |
| Cheng YJ | 2003 | Taiwan | Asians | 173(55.1) | 141(44.9) | 169(50.1) | 168(49.9) |
| Da SJ | 2002 | China | Asians | 48(60.0) | 32(40.0) | 36(45.0) | 44(55.0) |
| Nazar-Stewart V | 1999 | USA | Mixed | 45(54.2) | 38(45.8) | 63(44.4) | 79(55.6) |

**Table 2. Summary Meta-analyses Results for Association of GSTM1 Polymorphism with Nasopharyngeal Cancer Susceptibility**

| Null vs. Present* | Studies ( Cases / Controls) | Odds Ratio | | Model† | Heterogeneity | |
|---|---|---|---|---|---|---|
| | | OR[95%CI]* | $P_{OR}$ | | $I^2$ (%) | ‡PH |
| Total studies | 11(1,513/2,802) | 1.51[1.33-1.72] | <0.001 | Fixed | 9.2 | 0.357 |
| Subgroup analysis by pathological types | 4(227/502) | 1.73[1.24-2.42] | 0.001 | Fixed | 0.0 | 0.958 |
| Subgroup analysis by sex | | | | | | |
| Males | 3(332/393) | 1.36[1.01-1.83] | 0.044 | Fixed | 0.0 | 0.505 |
| Females | 3(169/484) | 1.20[0.84-1.71] | 0.312 | Fixed | 37.1 | 0.204 |
| Subgroup analysis by smoking or not | | | | | | |
| Smokers | 2(111/124) | 2.02[1.19-3.42] | 0.009 | Fixed | 0.0 | 0.355 |
| Nonsmokers | 2(51/98) | 1.06[0.54-2.10] | 0.861 | Fixed | 0.0 | 0.625 |

*OR=Odds Ratio; 95%CI=95% Confidence Interval; †Fixed=fixed-effects model; ‡PH, the P value of heterogeneity analysis

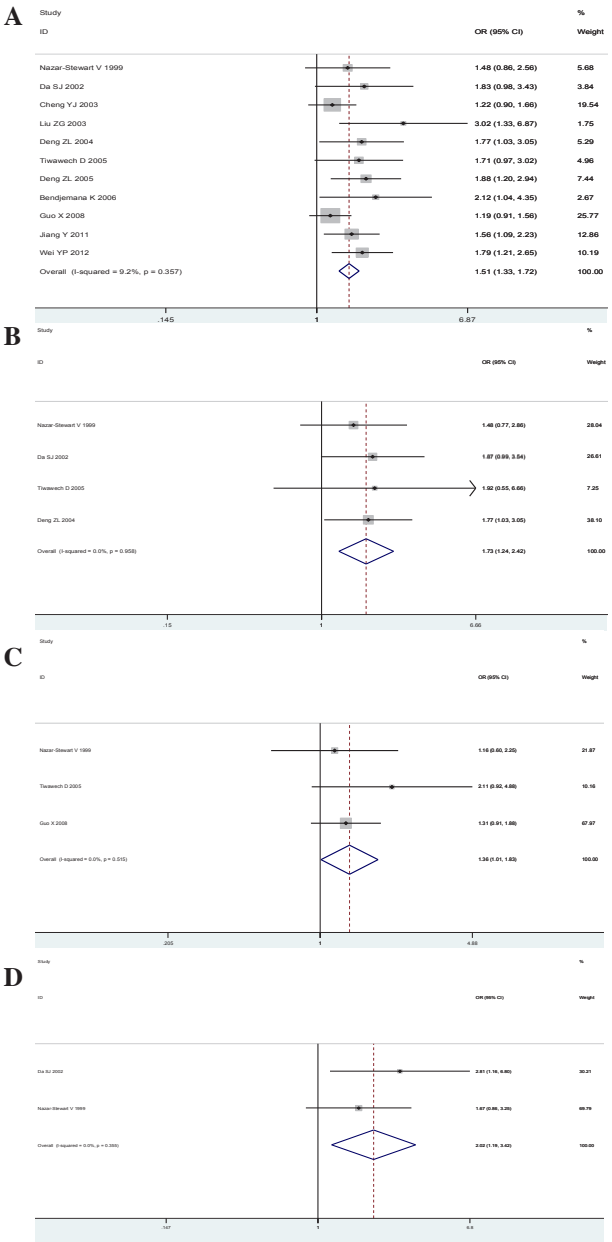


**Figure 1. Forest Plots of Pooled ORs with 95% CIs for Association Between GSTM1 Polymorphism and Nasopharyngeal Cancer Risk** (A. Analysis of total studies; B. Subgroup analysis by pathological typing; C. Subgroup analysis by sex; D. Subgroup analysis by smoking or not) (Results of individual and summary ORs, 95% CIs and weights of each study were shown in the forest plots. Horizontal lines represented 95% CI and dotted vertical lines represent the value of the summary ORs)

from Taiwan and still one from USA. The ethnicity among these 11 studies was as follow: 9 publications from Asian, one from Africa, and the last one from mixed populations. The genotype distributions were showed in great details in Table1. Four case-control studies of the 11 included studies (Nazar-Stewart et al., 1999; Da et al., 2002; Deng et al., 2004; Tiwawech et al., 2005) made stratified analysis by pathological types. Three out of the total 11 studies (Nazar-Stewart et al., 1999; Tiwawech et al., 2005; Guo et al., 2008) examined the association between the null genotype of GSTM1 and NPC risk in stratified analysis by gender (males and females). In addition, two of the 11 studies (Nazar-Stewart et al., 1999; Da et al., 2002) explored the association in stratified analysis by smoking status (smokers and nonsmokers).

*Meta-analysis of association between GSTM1 polymorphism and NPC risk*

Total included studies: The pooled OR of total 11 studies estimating the relationship of GSTM1 polymorphism with NPC susceptibility suggested that the null genotype of GSTM1 was strongly associated with increased risk of NPC, while comparing with the present genotype (OR=1.51, 95%CI=1.33-1.72, $P_{OR}$<0.001) (Table 2 and Figure 1A). Sensitivity analysis by sequential omission of any individual studies further identified the significant association (data were not shown). Heterogeneity was not found in meta-analysis of total studies with an $I^2$ equal to 9.2% (PH=0.357) (Table 2).

*Subgroup analyses*

Subgroup analysis by pathological types: In the stratified analysis by pathological types, the risk for nasopharyngeal squamous cell carcinoma was higher in individuals carrying the null genotype of GSTM1 (OR=1.73, 95%CI=1.24-2.42, $P_{OR}$=0.001, $I^2$= 0.0%) (Table 2 and Figure 1B). Sensitivity analysis indicated that the result was stable (data were not shown). There were lack of sufficient data reported on the associations between GSTM1 null genotype and the other pathological types of NPC risk.

Subgroup analysis by sex: A stratified analysis was conducted by sex. Interestingly, the pooled OR for three studies with 332 cases and 393 controls was modestly significant in the male population, indicated males with the null genotype of GSTM1 were more likely to have NPC than females (OR=1.36, 95%CI=1.01-1.83, $P_{OR}$=0.044,

$I^2$= 0.0%) (Table 2 and Figure 1C).

Subgroup analyses by smoking or not: Two of the 11 studies had explored the association of the null genotype of GSTM1 with NPC risk in stratified analysis by smoking status (smokers and nonsmokers) (Table 2). Significantly increased risk of NPC associated with the null genotype of GSTM1 was observed for smokers (OR=2.02, 95%CI=1.19-3.42, $P_{OR}$=0.009, $I^2$= 0.0%), whereas no such association was observed for nonsmokers (OR=1.06, 95%CI=0.54-2.10, $P_{OR}$=0.861, $I^2$= 0.0%) (Table 2 and Figure 1D).

*Publication bias*

Begg's funnel plot and Egger's test were performed to identify the publication bias of the included studies on association of GSTM1 polymorphism with NPC susceptibility. Funnel plots' shape of all contrasts did not reveal obvious evidence of asymmetry. The results of Egger's tests also suggested there was no publication bias in this meta-analysis.

## Discussion

To our knowledge, Glutathione S-Transferase (GST) is one of the most common members of phase II isoenzymes playing crucial role in detoxifying kinds of electrophilic compounds, including carcinogens, chemotherapeutic drugs, and environmental toxins (Moaven et al., 2010). The absence of a homozygous allele of GSTM1 gene (the GSTM1 null genotype) yields a complete loss of enzyme activity (Moaven et al., 2010). Previous studies have demonstrated that the GSTM1 polymorphism is associated with susceptibility to a number of malignant cancers (Vrana et al., 2009; Ahmad et al., 2012). The molecule mechanism on how the null genotype of GSTM1 affects the development of cancers has not been defined till now. Many case-control studies were published to assess the association between the polymorphism of GSTM1, located on chromosome 1p13.3, and NPC risk, but the existing evidence was still weak due to limited sample size, ethnic difference or disagreements among the published studies (Tiwawech et al., 2005; Bendjemana et al., 2006; Guo et al., 2008). Therefore, the present meta-analysis of all available case-control studies was conducted to shed some light on those inconsistent results.

Similar to the meta-analytic results of Zhuo et al. (Zhuo et al., 2009), significant association of GSTM1 polymorphism and NPC risk was demonstrated. In our meta-analysis, 11 individual case-control studies with 1,513 cases and 2,802 controls were included (Nazar-Stewart et al., 1999; Da et al., 2002; Cheng et al., 2003; Liu et al., 2003; Deng et al., 2004; Deng et al., 2005; Tiwawech et al., 2005; Bendjemana et al., 2006; Guo et al., 2008; Jiang et al., 2011; Wei et al., 2012). Meta-analysis of total studies showed that the null genotype of GSTM1 was strongly associated with increased risk of NPC without apparent heterogeneity (OR=1.51, 95%CI=1.33-1.72, $P_{OR}$<0.001, $I^2$=9.2%) (Table 2 and Figure 1A). Subgroup analyses by pathological typing, gender and exposure to smoking further identified the association between the null genotype of GSTM1 and susceptibility to NPC. The results of sensitivity analyses by sequential omission of individual studies one at a time suggested the significant association was highly unlikely due to chance.

Our meta-analysis firstly suggested that the null genotype of GSTM1 may increase susceptibility to nasopharyngeal squamous cell carcinoma (OR=1.73, 95%CI=1.24-2.42, $P_{OR}$=0.001) (Table 2 and Figure 1B). Furthermore, the results of subgroup analysis by sex did show that males were at a higher risk for NPC than females(Table 2 and Figure 1C), which were in agreement with the findings of a study by Tiwawech et al. in Thailand population (Tiwawech et al., 2005). However, Nazar-Stewart et al. found that females with the null genotype of GSTM1 were more susceptible to NPC than males (Nazar-Stewart et al., 1999), inversely. Worthy of note, our meta-analysis had enlarged the sample size by combining data from all eligible studies, and thus had the advantage of obtaining a more precise estimate for the potential genetic association between the null genotype of GSTM1 and NPC risk in males. GSTM1 was involved in the metabolism of tobacco and alcohol carcinogens (Ho et al., 1999). It has been demonstrated that smoking and alcohol consumption are considered to be risk factors for NPC (Ho et al., 1999; Nazar-Stewart et al., 1999). Our subgroup meta-analysis by smoking or not revealed that an increasing risk of NPC associated with GSTM1 null genotype was observed in smokers (OR=2.02, 95%CI=1.19-3.42, $P_{OR}$=0.009), but not in nonsmokers (OR=1.06, 95%CI=0.54-2.10, $P_{OR}$=0.861) (Table 2 and Figure 1D), which indicated that smoking was a risk factor for NPC in GSTM1 null genotype carrying individuals.

Some limitations of our meta-analysis should be considered when interpreting the results. Firstly, the results may be affected by additional confounding factors, such as EBV infection status, tumor staging and age. However, most studies did not estimate the relationship of GSTM1 polymorphism with NPC susceptibility on these aspects, making it impossible to include them in the meta-analysis. Further studies with large sample size are needed to identify this relationship in different tumor staging of NPC or provide the baseline data of EBV infection status and age in details. Secondly, the sample sizes of subgroup analyses by pathological typing, sex and smoking status were still not large enough to give a comprehensive analysis and a confirmed conclusion. Thus, more studies with large sample size are encouraged to evaluate the association of GSTM1 polymorphism with NPC susceptibility in future. Finally, Guo et al. found that the combined null genotype of GSTM1/GSTT1 was associated with increased risk of NPC (Guo et al., 2008). It can be deduced that the gene-gene interactions should be taken into account when exploring the association between GSTM1 polymorphism and NPC risk. However, the effect of GSTM1 polymorphism combined with other genes including GSTT1 on NPC susceptibility was not fully addressed in our meta-analysis due to insufficient data. Future studies are expected to further estimate the possible association of combined genetic polymorphisms with NPC risk.

In conclusion, our meta-analysis shows that the null genotype of GSTM1 is a risk factor for NPC, and there

is a gene-smoking interaction in this association. Future studies may further explore the possible gene-gene interactions in the association of GSTM1 polymorphism with NPC risk.

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

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