

RESEARCH ARTICLE

Glutathione-S-Transferase T1 Polymorphism is Associated with Esophageal Cancer Risk in Chinese Han Population

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Abstract

Background: Glutathione-S-Transferase T1 (GSTT1) gene has been shown to be involved in the development of esophageal cancer. However, the results have been inconsistent. In this study, the authors performed a meta-analysis to clarify the association between GSTT1 polymorphism and esophageal cancer risk among Chinese Han population. **Methods:** Published literature from PubMed, the China National Knowledge Infrastructure and Wanfang Data were searched. Pooled odds ratio (OR) and 95% confidence interval (95% CI) was calculated using a fixed- or random-effects model. **Results:** Eleven studies with a total of 2779 individuals were included in the meta-analysis. The results showed that GSTT1 null genotype was significantly associated with esophageal cancer risk in Chinese (OR = 1.31, 95% CI 1.12 to 1.53, $p = 0.001$). Further sensitivity analyses confirmed the significant association. The cumulative meta-analysis showed a trend of an obvious association between GSTT1 null genotype and esophageal cancer risk as information accumulated by year. **Conclusions:** This meta-analysis suggests a significant association of GSTT1 null genotype with esophageal cancer risk in the Chinese Han population.

Keywords: Glutathione-S-transferase T1 - esophageal cancer - meta-analysis - Chinese

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Introduction

Esophageal cancer is one of the widespread and lethal cancers, ranked as sixth leading-cause of cancer related mortality in the world (Jemal et al., 2011; Thallinger et al., 2011). There is a wide-range variation of incidence in different regions, significantly higher in the esophageal cancer belt which is stretched from north-central China to Central Asia (Jemal et al., 2011). Besides, the large increases in the absolute number of deaths that resulted from the increasing and aging population are much more important in determining the future cancer burden than any changes due to change in risk, emphasizing the increasing importance of cancer as a health problem in the 21st century in China (Yang et al., 2003). Epidemiological studies have shown that smoking and alcohol are the major risk factors of esophageal cancer (Pera et al., 2005; Fang et al., 2011; Mao et al., 2011). However, emerging evidence has indicated the great contribution of genetic factors (Dong et al., 2008; Lao-Sirieix et al., 2010). Glutathione S-Transferases (GSTs) are the most important family of phase II isoenzymes known to detoxify a variety of electrophilic compounds and carcinogens, chiefly by conjugating them with glutathione (Strange et al., 2001; Hayes et al., 2005). The Glutathione S-Transferase T1 (GSTT1) is one of the genes encoding the Mzygous deletion (null genotype), which has been suggested to be associated with the loss of enzyme activity (Pearson et

al., 1993; Hayes et al., 2000). The most common variants of GSTT1 genes is homo with increased vulnerability to cytogenetic damage and oxidative DNA damage, and may result in the susceptibility to cancers (Pearson et al., 1993; Hayes et al., 2000). GSTT1 gene has been shown to be involved in the development of esophageal cancer, but the results have been inconsistent in Chinese (Lin et al., 1998; Tan et al., 2000; Gao et al., 2002; Wang et al., 2003; Roth et al., 2004; Liu et al., 2010). Therefore, we performed a meta-analysis to clarify the association between GSTT1 polymorphism and esophageal cancer risk among the Chinese Han population.

Materials and Methods

Literature and search strategy

We searched the literature databases including PubMed, the China National Knowledge Infrastructure (CNKI) and Wanfang databases. The search strategy to identify all possible studies involved the use of the following keywords: (GST, GSTT1, or glutathione S-transferase T 1); and (esophageal carcinoma, esophageal cancer, esophageal adenocarcinoma, or esophageal squamous cell carcinoma). All relevant studies were limited to ones published in the English and Chinese languages. The reference lists of retrieved articles were hand-searched. If more than one article was published using the same case series, only the study with the largest sample size was

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Table 1. Characteristics of the Studies Included in the Meta-analysis

Studies	Recruit time	Geography	Case group	Control group	Null genotype frequency (%)	
					Case	Control
Lin DX (1998) (Lin et al., 1998)	NG	Linxian of China	45 patients with esophageal cancer	46 non-cancer controls	42.20%	51.10%
Tan W (2000) (Tan et al., 2000)	1997-1998	Linxian of China	150 patients with ESCC	150 non-cancer controls	40.00%	39.30%
Gao CM (2002) (Gao et al., 2002)	1998-2000	Huaian of China	141 patients with esophageal cancer	223 healthy controls	52.50%	53.40%
Wang LD (2003) (Wang et al., 2003)	1998-1999	Linzhou of China	62 patients with ESCC	38 non-cancer controls	54.80%	52.60%
Roth MJ (2004) (Roth et al., 2004)	1991-1996	Linxian of China	131 patients with esophageal cancer	454 healthy controls	58.80%	53.50%
Yi LH (2005) (Yi et al., 2005)	NG	Huaian of China	106 patients with esophageal cancer	106 non-cancer controls	56.60%	51.90%
Deng J (2008) (Deng et al., 2008)	NG	Cixian of China	87 patients with esophageal cancer	162 healthy controls	58.60%	53.70%
Zhang LW (2009) (Zhang et al., 2009)	2003-2006	Xinjiang of China	88 patients with ESCC	72 healthy controls	64.80%	45.80%
Liu R (2010) (Liu et al., 2010)	2005	Huaian of China	97 patients with ESCC	97 healthy controls	64.90%	41.20%
Ji R (2010) (Ji et al., 2010)	2001-2007	Wuwei of Chins	189 patients with ESCC	216 healthy controls	51.90%	43.50%
Gao P (2012) (Gao et al., 2012)	2007-2010	Ningxia of China	40 patients with esophageal cancer	80 healthy controls	55.00%	31.30%

ESCC, esophageal squamous cell carcinoma; NG, data were not given

included. The literature search was updated on 20 May 2012.

Inclusion criteria and data extraction

The studies included in the meta-analysis must meet all the following inclusion criteria: (1) evaluating the association of GSTT1 polymorphism with esophageal cancer risk; (2) using case-control or cohort design; and (3) providing sufficient data for the calculation of odds ratio (OR) with 95% confidence interval (95%CI). The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) region; (4) sample size of cases and controls; and (5) GSTT1 polymorphism genotype distribution in cases and controls. Two authors independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements and reached a consistent decision.

Statistical analysis

The association of GSTT1 polymorphism with esophageal cancer risk was estimated by calculating the pooled OR and 95%CI. The significance of pooled OR was determined by Z test ($p < 0.05$ was considered statistically significant). A Q test was performed to evaluate whether the variation was due to heterogeneity or by chance (Cochran, 1954). A random- (DerSimonian-Laird method) (DerSimonian et al., 1986) or fixed- (Mantel-Haenszel method) (Mantel et al., 1959) was used to calculate the pooled OR in the presence ($p < 0.05$) or absence ($p > 0.05$) of heterogeneity, respectively. Sensitivity analysis, after removing one study at a time, was performed to evaluate the stability of the results. Cumulative meta-analysis was also performed to provide a framework for updating a genetic effect from all studies and to measure how much the genetic effect changes as evidence accumulates and find the trend in estimated risk effect (Lau et al., 1992). In cumulative meta-analysis, studies were chronologically ordered by publication year, and then the pooled ORs were obtained at the end of each year. Potential publication bias was estimated by constructing funnel plots and asymmetric funnel plot indicated a relationship between effect and study size, which suggested the possibility of either publication bias or a systematic difference between smaller and larger studies. Publication bias was also assessed by Egger's test ($p < 0.05$ was considered statistically significant) (Egger et al., 1997). Data analysis was performed using STATA version 11 (StataCorp LP, College Station, TX, USA).

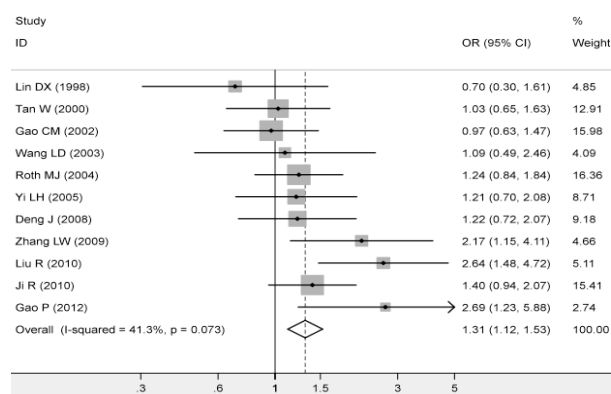


Figure 1. Forest Plot of the Association of GSTT1 Polymorphism with Esophageal Cancer Risk in Chinese Population

Results

Characteristics of the studies

The literature search identified a total of 87 potentially relevant papers. Sixty-two papers were excluded owing to overlapping records or obvious irrelevance to our study. In addition, 14 papers were excluded because they were duplicate publications, reviews, investigated association in other population or did not provide sufficient data for calculation OR with 95%CI. According to the inclusion criteria, eleven studies with a total of 2779 individuals were included in the meta-analysis (Lin et al., 1998; Tan et al., 2000; Gao et al., 2002; Wang et al., 2003; Roth et al., 2004; Yi et al., 2005; Deng et al., 2008; Zhang et al., 2009; Ji et al., 2010; Liu et al., 2010; Gao et al., 2012). The characteristics of the included studies are listed in Table 1. There were 6 studies published in English (Lin et al., 1998; Tan et al., 2000; Gao et al., 2002; Wang et al., 2003; Roth et al., 2004; Liu et al., 2010), while the five others were published in Chinese (Yi et al., 2005; Deng et al., 2008; Zhang et al., 2009; Ji et al., 2010; Gao et al., 2012). The number of cases varied from 40 to 189, with a mean of 103, and the numbers of controls varied from 38 to 454, with a mean of 149 (Table 1). Cases were patients with esophageal cancer in six studies, while the other five studies were patients with esophageal squamous cell carcinoma (Table 1). Seven studies selected controls from healthy subjects, while the other four studies selected controls from non-cancer patients (Table 1).

Meta-analysis results

There was no obvious heterogeneity ($p = 0.073$), thus

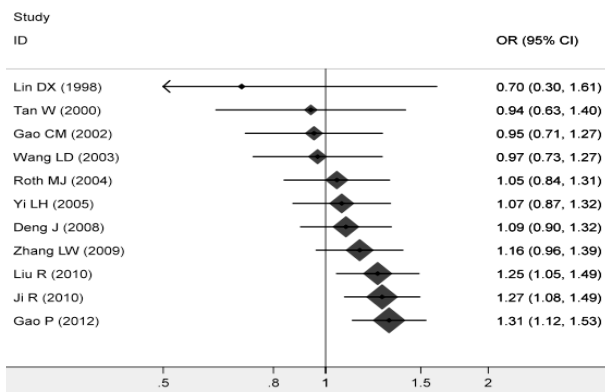


Figure 2. Cumulative Meta-analysis of the Association of GSTT1 Polymorphism with Esophageal Cancer Risk in Chinese Population

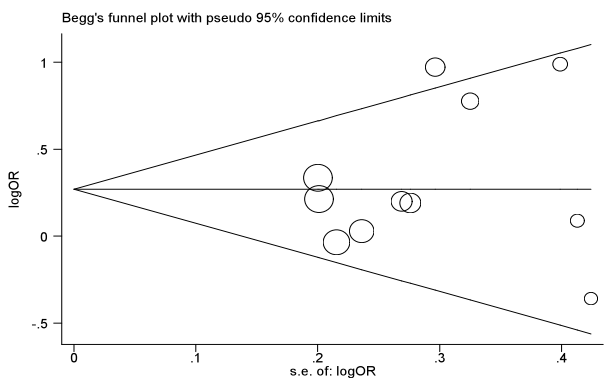


Figure 3. Begg's Funnel Plot to Assess the Risk of Publication Bias in this Meta-analysis

the fixed effects model was used to pool the data. The results showed that GSTT1 null genotype was significantly associated with esophageal cancer risk in Chinese Han population (OR = 1.31, 95%CI 1.12 to 1.53, $p = 0.001$) (Figure 1). Sensitivity analyses by removing one study at a time confirmed the significant association was stable. The cumulative meta-analysis showed a trend of an obvious association between GSTT1 null genotype and esophageal cancer risk in Chinese Han population as information accumulated by year (Figure 2).

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of this meta-analysis. The shape of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 3). Egger's test further suggested no evidence of publication bias ($p = 0.464$). Thus, there was no obvious risk of bias in this meta-analysis.

Discussion

To our knowledge, this is the first meta-analysis that comprehensively assessed the association between GSTT1 polymorphism and risk of esophageal cancer in the Chinese population. The meta-analysis indicated a significant association of GSTT1 null genotype with esophageal cancer risk in the Chinese population. Our findings were different from those based on the two previous meta-analyses that suggested no significant association in both Caucasians and Asians (Hiyama et al.,

2007; Zhuo et al., 2009).

The GSTs are one of the most important families of detoxifying enzymes in nature (Oakley, 2011; Raza, 2011). The classic activity of the GSTs is conjugation of compounds with electrophilic centers to the tripeptide glutathione (GSH), but many other activities are now associated with GSTs, including steroid and leukotriene biosynthesis, peroxide degradation, double-bond cis-trans isomerization, dehydroascorbate reduction, Michael addition, and noncatalytic "ligandin" activity (ligand binding and transport) (Oakley, 2011; Raza, 2011). GSTs play a major role in cellular antimutagen and antioxidant defense mechanisms, and these enzymes may regulate pathways that prevent damage from several carcinogens (Hayes et al., 2000; Strange et al., 2001). The null genotype of GSTT1 gene causes complete absence of GST enzymes activity, decreases the ability of detoxifying electrophilic compounds, and could increase the susceptibility to various cancers (Pearson et al., 1993; Hayes et al., 2000). Thus, there is obvious biochemical evidence for the relationship of GSTT1 polymorphism with esophageal cancer risk. Besides, GSTT1 polymorphism has also been studied extensively in terms of susceptibility for other malignancies. Previous studies have yielded significant associations of GSTT1 polymorphism with risk of gastric cancer, breast cancer, oral cancer, cervical cancer, laryngeal cancer and hepatocellular carcinoma (Qiu et al., 2010; Wang et al., 2010; Kumar et al., 2011; Qiu et al., 2011; Zhang et al., 2011; Zhang et al., 2012), which further suggest GSTT1 polymorphism plays an important role the carcinogenesis and can affect the individual susceptibility to common malignancies. Thus, there is high epidemiological evidence for the association between GSTT1 polymorphism and risk of common cancers.

Several limitations should be considered. Firstly, the present meta-analysis was based primarily on unadjusted effect estimates and the confounding factors were not controlled for. Secondly, the frequency of null type of GSTT1 among controls is about 50% among Han ethnicity in China, and the distribution of GSTT1 genotype may be different in various areas in China, which would cause high heterogeneity between those studies. In addition, it's obvious that many studies with small sample size had been included in this meta-analysis, which may result in a bias related to the conclusion. Therefore, more studies with large sample size and from different areas in China are needed to identify the association. Thirdly, the effect of gene-gene and gene-environment interactions was not addressed in this meta-analysis because most studies did not provide related data. The latter may be important for genes that code proteins with detoxifying function, but would require detailed information on exposures to various potential carcinogens and individual-level data and would be most meaningful only for common exposures that are found to be strong risk factors for the disease. Fourthly, some misclassification bias is possible. Most studies could not exclude latent prostate cancer cases in the control group. Finally, histological types of esophageal cancer may confer different risks associated with the GSTT1 null genotype. However, though several studies included in this meta-analysis studied the association

between GSTT1 null genotype and esophageal squamous cell carcinoma independently, most study didn't provide information on the subgroup analyses by histological types of esophageal cancer, so we were unable to make subgroup analysis by the histological types of esophageal cancer. In the future, studies with well-design are needed to further assess the different risks of the GSTT1 null genotype on different histological types of esophageal cancer.

In conclusion, this meta-analysis suggests a significant association of GSTT1 null genotype with esophageal cancer risk in the Chinese Han population. However, more studies with well-design and large sample size are needed to further assess the different risks of the GSTT1 null genotype on different histological types of esophageal cancer.

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