RESEARCH ARTICLE

Null Genotype of GSTT1 Contributes to Esophageal Cancer Risk in Asian Populations: Evidence from a Meta-analysis

Sheng-Ming Yi, Gui-Yuan Li*

Abstract

Background/Aims: Glutathione S-transferase T1 (GSTT1), a phase-II enzyme, plays an important role in detoxification of carcinogen electrophiles. Many studies have investigated the association between GSTT1 polymorphism and esophageal cancer risk in Asian populations, but its actual impact is not clear owing to apparent inconsistencies among those studies. Thus, a meta-analysis was performed to explore the effect of GSTT1 polymorphism on the risk of developing esophageal cancer. Methods: A literature search of PubMed, Embase, and Wanfang databases up to August 2012 was conducted and 15 eligible papers were finally selected, involving a total of 1,626 esophageal cancer cases and 2,216 controls. We used the pooled odds ratio (OR) with its corresponding 95% confidence interval (95%CI) to estimate the association of GSTT1 polymorphism with esophageal cancer risk. Subgroup analyses and sensitivity analyses were performed to further identify the association. Results: Meta-analysis of total studies showed the null genotype of GSTT1 was significantly associated with an increased risk of esophageal cancer in Asians (OR=1.26, 95%CI=1.05-1.52, P_{OR}=0.015, I^2=42.7%). Subgroup analyses by sample size and countries also identified a significant association. Sensitivity analysis further demonstrated a relationship of GSTT1 polymorphism to esophageal cancer risk in Asians. Conclusions: The present meta-analysis of available data showed a significant association between the null genotype of GSTT1 and an increased risk of esophageal cancer in Asians, particularly in China.

Keywords: Esophageal cancer - gene polymorphism - glutathione S-transferase T1 - meta-analysis

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Introduction

Esophageal cancer is one the most common cancers and causes a large number of cancer-related deaths in the world (Mao et al., 2011). Apart from the environmental factors including dietary habits, smoking and alcohol drinking, genetic susceptibility has been shown to contribute to the variation in individual susceptibility to esophageal cancer (Hiyama et al., 2007; Lin et al., 2011; Kogo et al., 2011).

Glutathione S-transferase T1 (GSTT1) plays a crucial role in detoxification and elimination of electrophilic carcinogens by conjugating them to glutathione (Wang et al., 2006). GSTT1 is genetically polymorphic, and deletion polymorphism (homozygous deletion of the gene) of the GSTT1 loci results in the loss of functional activity. Individuals with GSTT1 null genotype are more susceptible to chemical carcinogens and thus have a higher risk of developing malignant tumors. Recent studies have found that GSTT1 null genotype is strongly associated with susceptibility to a number of cancers, such as colorectal, renal and esophageal cancers (Wang et al., 2003; Xu et al., 2011; Cheng et al., 2012). Many previous studies have been published to estimate the association between GSTT1 polymorphism and esophageal cancer risk, but the available evidence for the genetic association is still weak because of disagreements among studies (Jain et al., 2006; Liu et al., 2010). Differences among study designs, methodology and insufficient power may be responsible for the inconsistent findings among those studies. Meta-analysis by combining data from all eligible studies has the advantage of reducing random error and obtaining a more precise estimate for some potential genetic associations (Attia et al., 2003). Thus, we presented the results of a meta-analysis of published data investigating the association between GSTT1 polymorphism and esophageal cancer risk to shed some light on these contradictory results.

Materials and Methods

Literature search

We conducted a comprehensive search of the PubMed, Embase and Wanfang databases from the inception up to August 2012. Search terms for GSTT1 polymorphism and esophageal cancer included GSTT1, Glutathione-S-TransferaseT1, gene polymorphism, gene polymorphisms and esophageal cancer, esophageal carcinoma. No language restrictions were imposed. All references cited in the studies were also reviewed to identify additional

*Department of Oncology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China *For correspondence: guiyuanli2012@163.com*

Table 1. Characteristics of 15 Studies Included in the Meta-analysis

Study	Publication	Country	Cases		Controls	
(Reference)	Year		Null	Present	Null	Present
Gao P et al.	2012	China	22	18	25	55
Moaven O et al.	2010	Iran	36	112	31	105
Malik MA et al.	2010	India	25	110	49	146
Liu R et al.	2010	China	63	34	40	57
Ji R et al.	2010	China	98	91	94	122
Zhang LW et al.	2009	China	57	31	33	39
Deng J et al.	2008	China	51	36	87	75
Wang Z et al.	2006	China	46	61	33	74
Jain M et al.	2006	India	28	72	37	100
Yi LH et al.	2005	China	46	60	51	55
Roth MJ et al.	2004	China	77	54	243	211
Wang LD et al.	2003	China	34	28	20	18
Gao CM et al.	2002	China	74	67	119	104
Tan W et al.	2000	China	60	90	59	91
Lin DX et al.	1998	China	26	19	22	23

*HWE, Hardy-Weinberg equilibrium; +, Hardy-Weinberg equilibrium of genotypes of controls was confirmed; -, Hardy-Weinberg equilibrium of genotypes of controls was not confirmed

published articles not indexed in the common database.

Selection criteria

Studies were included in the meta-analysis if: (1) Case-control studies which evaluated associations between GSTT1 polymorphism and esophageal cancer risk in Asian populations; (2) Odds ratio (OR) with its 95% confidence interval (95%CI) or other data for estimating OR (95% CI) were available; (3) Providing information on genotype frequency of GSTT1 polymorphism. In addition, review papers, case-only studies, or studies containing overlapping data were all excluded.

Data extraction

We performed a meta-analysis to investigate the association between the null genotype of GSTT1 and esophageal cancer risk. Two investigators independently extracted data, and disagreements were resolved through consensus finally. The extracted information contained: year of publication, first author, ethnicity, research designs, number of cases and controls, genotyping method, and characteristics of cases and controls. All data were extracted accurately from published articles.

Statistical analysis

The strength of the association between GSTT1 polymorphism and esophageal cancer risk was measured by the pooled OR with its 95%CI. Both the chi-square based Q statistic test and the I^2 statistic were calculated to examine whether the results of studies were homogeneous, and the significance level was set at 0.05 (Cochran, 1950; Higgins et al., 2003). Data were combined by using the DerSimonian and Laird random-effects model or Mantel and Haenszel fixed-effects model (Mantel et al., 1959; DerSimonian et al., 1986) according to results of heterogeneity analysis. Sensitivity analysis was performed by sequential omission of individual studies to validate the credibility of outcomes in the meta-analysis (Md et al., 1999). In addition, subgroup analyses according to sample size in cases and countries were also conducted to estimate the association between GSTT1 polymorphism and esophageal cancer risk. Both Begg's funnel plot and Egger's regression asymmetry test were used to assess the publication bias (Stuck et al., 1998). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas).

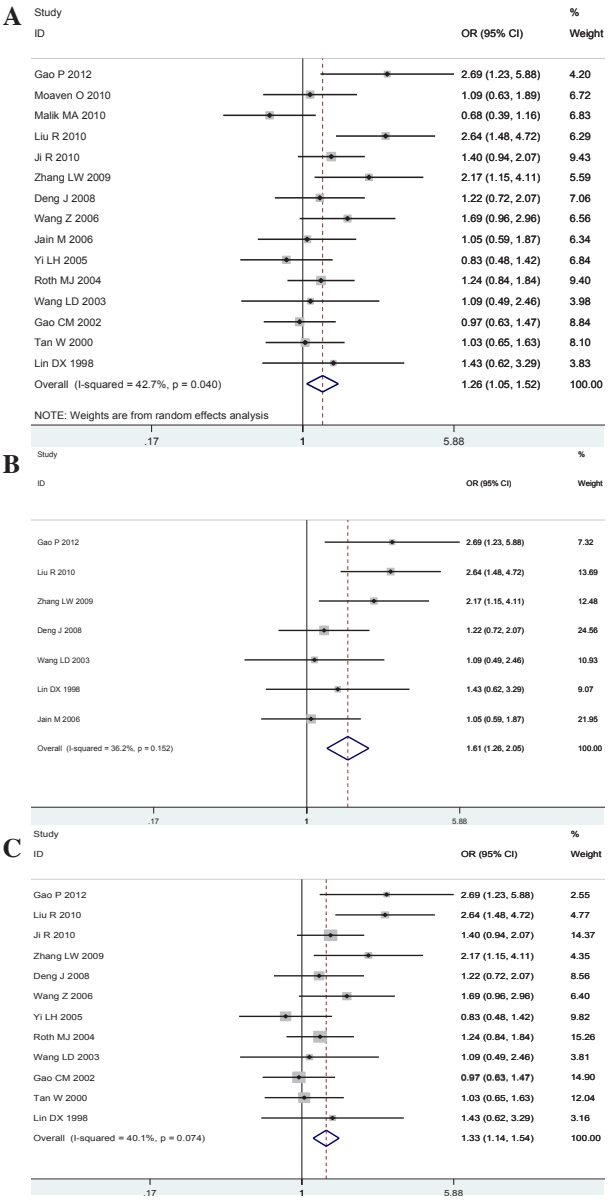

Figure 1. Forest Plots of Pooled OR with 95% CI for Associations Between GSTT1 Polymorphism and Esophageal Cancer Risk (A. Analysis of pooling total 15 studies; B. Subgroup analysis of pooling studies (case sample size≤100); C. Subgroup analysis of pooling studies in Chinese population) (Results of individual and summary OR, 95% CI and weights of each study were shown. Horizontal lines represented 95% CI and dotted vertical lines represent the value of the summary OR)

Results

Characteristics of included studies

With our search criterion, 15 individual case-control publications with 1,626 cases and 2,216 controls were

Table 2. Summary of Pooled Odds Ratios (ORs) and Heterogeneity Results for Association Between GSTT1 Polymorphism and Esophageal Cancer Risk

Null vs. Present*	Studies (Cases/Controls)	Odds Ratio		Model†	Heterogeneity	
		OR [95%CI]*	P_{OR}		I^2 (%)	‡P_H
Total studies	15(1,626/2,216)	1.26(1.05-1.52)	0.015	R	42.70%	0.04
Subgroup analyses by sample size						
Studies (case sample size>100)	8(1,107/1,587)	1.10(0.93-1.29)	0.265	F	19.00%	0.28
Studies (case sample size≤100)	7(519/631)	1.61(1.26-2.05)	<0.001	F	36.20%	0.152
Subgroup analyses by different country						
China	12(1,243/1,075)	1.33(1.14-1.54)	<0.001	F	40.10%	0.074
India	2(235/332)	0.83(0.56-1.23)	0.351	F	15.70%	0.276
Iran	1(148/136)	1.09(0.63-1.89)	0.762	NA	NA	NA

*OR, Odds Ratio; 95%CI, 95% Confidence Interval; †R, random-effects model; F, fixed-effects model; ‡PH, the P value of heterogeneity; NA, data not available

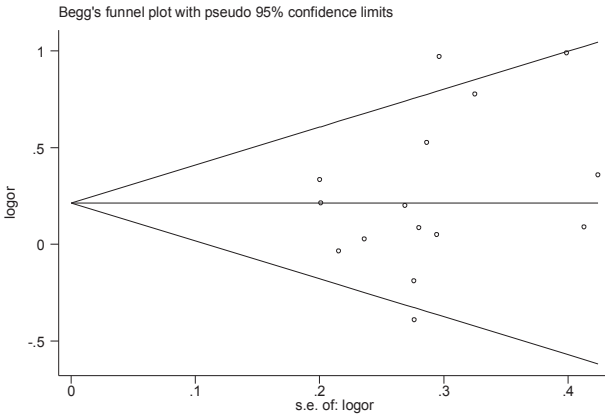

Figure 2. Begg's Funnel Plot for Estimating the Publication Bias (P_{Egger} = 0.270)

finally included into this 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; Jain et al., 2006; Wang et al., 2006; Deng et al., 2008; Zhang et al., 2009; Ji et al., 2010; Liu et al., 2010; Malik et al., 2010; Moaven et al., 2010; Gao et al., 2012). There were 10 English language literatures (Lin et al., 1998; Tan et al., 2000; Gao et al., 2002; Wang et al., 2003; Roth et al., 2004; Jain et al., 2006; Wang et al., 2006; Liu et al., 2010; Malik et al., 2010; Moaven et al., 2010) and 5 Chinese language ones (Yi et al., 2005; Deng et al., 2008; Zhang et al., 2009; Ji et al., 2010; Gao et al., 2012). Table 1 presented a brief description of these 15 case-control studies. There were 12 studies from China, 2 from India and one from Iran. The number of cases varied from 40 to 189, with a mean of 108.4, and the numbers of controls varied from 38 to 454, with a mean of 147.9. There were 8 studies with case sample size more than one hundred (Tan et al., 2000; Gao et al., 2002; Roth et al., 2004; Yi et al., 2005; Wang et al., 2006; Ji et al., 2010; Malik et al., 2010; Moaven et al., 2010) and 7 ones with case sample size less than one hundred (Lin et al., 1998; Wang et al., 2003; Jain et al., 2006; Deng et al., 2008; Zhang et al., 2009; Liu et al., 2010; Gao et al., 2012).

GSTT1 polymorphism and esophageal cancer risk

Table 2 showed the main results of meta-analysis of the association between GSTT1 polymorphism and esophageal cancer risk. The pooled OR of total studies by the random-effects model revealed that the null genotype of GSTT1 was modestly associated with increased risk of esophageal cancer in Asians (OR=1.26, 95%CI=1.05-1.52, P_{OR}=0.015, I^2=42.7%) (Table 2, Figure 1). Sensitivity analyses by sequential omission of any individual studies also did not materially alter the overall combined ORs (data were not shown).

There was no obvious heterogeneity found in subgroups (Table 2). Meanwhile, the association between GSTT1 polymorphism and esophageal cancer risk was still statistically significant in subgroup of studies with case sample size ≤ 100 (OR=1.61, 95%CI=1.26-2.05, P_{OR}<0.001, I^2=36.2%), but not in subgroup of studies with case sample size > 100 (Table 2, Figure 1). The subgroup analyses by different countries showed that the null genotype of GSTT1 was significantly associated with an increased risk of esophageal cancer in Chinese population, but not in Indian or Iran (Table 2).

The shape of Begg's funnel plot did not reveal obvious evidence of asymmetry. Besides, the P value of Egger's tests was 0.270, providing statistical evidence of funnel plot' symmetry (Figure 2). Thus, there was no risk of publication bias in this meta-analysis.

Discussion

GSTT1, a significant candidate gene implicated in several cancers, is located on 22q11.23 with 8146 base pairs, 5 exons and 4 introns in all (McIlwain et al., 2006). It plays an important role in the detoxification and elimination of electrophilic carcinogens by catalyzing the conjugation of electrophiles to detoxicate glutathione (Wang et al., 2006). Deletion polymorphism of GSTT1 results in the loss of its functional activity. It is conceivable that individuals with GSTT1 null genotype may become susceptible to chemical carcinogens and thus develop kinds of cancers at high risks. Recent studies have found that GSTT1 null genotype is strongly associated with susceptibility to a number of cancers, such as colorectal, renal and esophageal cancers (Wang et al., 2003; Xu et al., 2011; Cheng et al., 2012).

Many published studies have assessed the association between GSTT1 polymorphism and esophageal cancer risk, but the findings were controversial (Jain et al., 2006; Liu et al., 2010). A recent study by Ji et al. explored the association between GSTT1 polymorphism and risk of esophageal cancer, but reported contradictory

conclusion compared with our study (Ji et al., 2010). Worthy of note, the null genotype of GSTT1 alone was not associated with increased risk of esophageal cancer in Chinese population, but a significant association was found between the combined null genotype of GSTT1 and Glutathione S-transferase M1 (GSTM1) and esophageal cancer risk (Ji et al., 2010). Since then, many case-control studies have investigated the association between GSTT1 polymorphism and esophageal cancer risk in Asian populations, but the impact of GSTT1 polymorphism on esophageal cancer risk is not clear owing to the apparent inconsistence among those studies. Thus, there was a need to perform a meta-analysis of published data to shed some light on these contradictory results. The present meta-analysis investigating the relationship between GSTT1 polymorphism and esophageal cancer risk was based on the large amount of available data giving greater information to detect significant differences. There were 15 case-control studies with 1,626 cases and 2,216 controls included. Significant association of the null genotype of GSTT1 and esophageal cancer risk was demonstrated. Meta-analyses of total studies and studies with case sample size less than 100 showed that GSTT1 polymorphism was associated with an increasing risk of esophageal cancer (Table 2 and Figure 1). Subgroup analyses by different countries and sensitivity analyses further identified the significant association. Interestingly, our study shows no association between the GSTT1 polymorphism and esophageal cancer risk in Indian and Iran, but in Chinese population (Table 2). Several factors such as environmental factors and different genetic backgrounds might contribute to the difference. Conclusively, our meta-analyses of available data shed some light on these contradictory results and suggest the null genotype of GSTT1 is obviously associated with increased risk of esophageal cancer in Asians, particularly China.

Some limitations must be considered while interpreting the findings in the meta-analysis. Firstly, we could not exclude the possibility of undetected bias owing to the limitations of case-control design. More prospective studies are expected to investigate the relationship of the null genotype of GSTT1 with esophageal cancer risk. Secondly, the association between GSTT1 polymorphism and esophageal cancer risk may be influenced by different histological types or tumor staging of esophageal cancer. However, little data on these aspects were reported in previous studies, and we were unable to make subgroup analyses by the different histological types or tumor staging of esophageal cancer. Further studies are encouraged to identify this association in different histological types or tumor staging of esophageal cancer. Finally, Moaven et al. found that combinations of different genotypes including GSTT1, Glutathione S-transferase P1 (GSTP1) and GSTM1 affected the susceptibility to esophageal cancer (Moaven et al., 2010). Besides, Genotyping analysis of GSTP1 together with assessment of smoking seems to be important in determining the risk of esophageal cancer in the Iranian population (Moaven et al., 2010). It can be deduced that interactions of gene-gene and gene-environmental factors should be treated with caution when exploring the association between GSTT1 polymorphism and esophageal cancer risk. However, gene-gene and gene-environmental interactions were not fully addressed in this meta-analysis owing to lack of sufficient data. Future studies are expected to further explore the possible effects of gene-gene and gene-environmental interactions on esophageal cancer risk.

In conclusion, the present meta-analysis shows a significant association between the null genotype of GSTT1 and risk of esophageal cancer in Asians. In addition, future studies may further assess the possible gene-gene and gene-environmental interactions in this association.

Acknowledgements

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

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