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Original Article

Association between glutathione S-transferase M1 polymorphism and esophageal cancer: a pooled analysis based on Chinese individuals

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Abstract: Many studies have analyzed the association between between glutathione S-transferase M1 (GSTM1) polymorphism and esophageal cancer, however, the results are inconsistent. This meta-analysis updated and re-evaluated the possible associations between GSTM1 polymorphism and susceptibility to esophageal cancer based on Chinese individuals. The PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure and Chinese Biology Medicine were searched up to February 2017. A total of 20 case-control studies including 2113 esophageal cancer cases and 2848 relevant controls were screened out. Overall, the meta-analysis demonstrated significant associations between the GSTM1 null genotype and increased risk for esophageal cancer in the Chinese population. In subgroup analyses, it indicated the similar results in population-based and hospital-based studies, as well as in North China and South China. As for subgroup analysis by histological type, a non-significant association was found in esophageal squamous cell carcinoma. Our study suggested that GSTM1 null genotype might contribute to increased risk of esophageal cancer in Chinese population.

Keywords: Genes, GSTM1, polymorphism, esophageal cancer, Chinese

Introduction

Esophageal cancer is one of the most common malignancy and the six leading cause of cancer-related deaths in the world [1]. A growing body of epidemiological evidence has evident regional characteristics. The morbidity and mortality rates of esophageal cancer in China are the highest in the world, and over 50% of patients have locally advanced or metastatic disease at presentation [1, 2]. The major risk factors for esophageal cancer include alcohol consumption, smoking tobacco, and micronutrient deficiency [3]. Various factors and multiple processes lead to esophageal cancer development. In addition to the above mentioned factors, genetic factors also account for esophageal cancer cases. Several common low-penetrance genes have been identified as potential leukemia susceptibility genes. An important one is Glutathione S-transferase M1 (GSTM1) gene, has been extensively examined in association with risk of various diseases [4]. The most common variant of GSTM1 gene is homozygous deletion (null genotype), which has been suggested to be associated with the loss of enzyme activity, increased vulnerability to cytogenetic damage, and oxidative DNA damage and resulted in the susceptibility to cancer [4, 5]. In 1998, Lin et al. firstly investigated the association between GSTM1 polymorphism and esophageal cancer in Chinese [6]. Subsequently, a number of studies were conducted to investigate the influence of GSTM1 polymorphism on esophageal cancer risk in Chinese population; however, no clear consensus was reached. Differences in results may be related to the regional and individual differences in China, as well as a limited number of patients in each study. In order to reduce the influence of these factors, we performed a meta-analysis to assess the relationship of GSTM1 polymorphism with risk of esophageal cancer in Chinese population. In addition, we

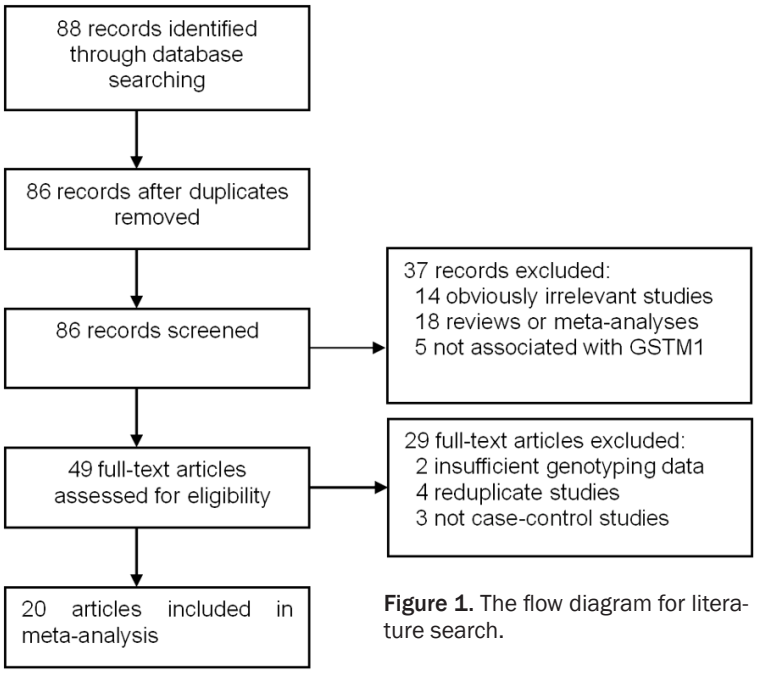

Figure 1. The flow diagram for literature search.

performed subgroup analysis stratified by geographic area and the source of control population to explore their possible effects on GSTM1 polymorphism and esophageal cancer.

Materials and methods

Search strategy and selection criteria

We conducted a comprehensive literature search of studies published through February 2017, without language restrictions. The database includes PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure and Chinese Biology Medicine. The search keywords were (glutathione S-transferase M1 or GSTM1) and (esophageal cancer or esop-hageal adenocarcinoma) and (polymorphism or variant). Additional eligible studies were identified through references that were cited in the relevant articles.

Inclusion criteria: (1) The articles clearly described the association of esophageal cancer with GSTM1 polymorphism, (2) The study design should be case-control or cohort studies, (3) Sufficient genetypes data for calculating the odds ratio (OR) with 95% confidence intervals (95% CIs) were present, (4) All participants were Chinese. For studies with reduplicate data, we selected the study with the most recent or the largest data.

Data extraction

Two authors extracted information from all eligible publications independently according to the inclusion criteria. Disagreements were resolved by a discussion. The following data were collected: first author's surname, publication year, source of controls (categorized as population-based studies [PB] and hospital-based studies [HB]), geographic areas (South China and North China), histological type, sample size, and available genotype information from GSTM1 polymorphism.

Statistical analysis

An OR with the corresponding 95% CI was used to assess the strength of the relationship between GSTM1 polymorphism and esophageal cancer susceptibility. The pooled ORs were evaluated for null vs non-null genotypes. The between-study heterogeneity was assessed by Chi-square based Q-test. When there is apparent heterogeneity between studies, the OR was pooled using the random-effects model; otherwise, the fixed-effects model was used. The significance of the pooled OR was evaluated by a Z-test. Sensitivity analysis was assessed by omitting one study at a time to test the effect of a single study on the pooled OR. Begg's funnel plot and Egger's linear regression test were employed to evaluate the publication bias. All statistical analyses were conducted using the Stata, version 12 (StataCorp LP, College Station, TX). A *P* value less than 0.05 was considered to be statistically significant.

Results

Description of included studies

After searching the databases and reading the full-text articles, twenty studies [6-25] were included and 68 articles were excluded (**Figure 1**). The publication year of involved studies ranged from 1998 to 2015. In total, 2113 cases and 2848 controls were included in this meta-analysis. The source of controls was based on a healthy population in ten studies.

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

First author and publication year	Source of controls	Histological type	Geographic areas	Case number	Control number	Case		Control	
						Null genotype	Non-null	Null genotype	Non-null
Lin 1998 [6]	PB	NR	Henan	45	45	20	25	21	24
Shao 2000 [7]	HB	ESCC	Guangdong	107	111	68	39	55	56
Tan 2000 [8]	PB	ESCC	Henan	150	150	46	104	76	74
Gao 2002 [9]	PB	NR	Jiangsu	141	223	106	35	133	90
Shi 2002 [10]	HB	NR	Hubei	98	120	67	31	51	69
Wang 2003 [11]	PB	ESCC	Henan	62	38	27	35	19	19
Roth 2004 [12]	Nest	ESCC	Henan	131	454	41	90	145	309
Wang 2004 [13]	HB	NR	Shanxi	127	101	74	53	44	57
Han 2005 [14]	HB	ESCC	Shanxi	89	99	46	43	48	51
Lu 2005 [15]	PB	ESCC	Xinjiang	104	104	36	68	4	100
Yin 2005 [16]	HB	NR	Jiangsu	106	106	69	37	61	45
Dong 2007 [17]	HB	NR	Gansu	120	120	76	44	51	69
Deng 2008 [18]	PB	NR	Hebei	87	162	45	42	73	89
Li 2008 [19]	PB	NR	Guangdong	125	125	77	48	55	70
Ji 2010 [20]	PB	ESCC	Gansu	189	225	111	78	98	127
Liu 2010 [21]	PB	ESCC	Jiangsu	97	97	54	43	32	65
Gao 2012 [22]	HB	ESCC	Ningxia	40	80	22	18	45	35
Chen 2012 [23]	HB	NR	Xinjiang	99	186	68	31	90	96
Liu 2013 [24]	HB	ESCC	Ningxia	110	220	47	63	74	146
Zeng 2015 [25]	PB	NR	Xinjiang	86	82	70	16	40	42

PB: Population-based study; HB: Hospital-based study; ESCC: Esophageal squamous cell carcinoma; NR: Not reported.

One case-control study was nested within a cohort study, and 10 studies provided data of the histological type of the esophageal cancer cases. The characteristics of these included studies are provided in **Table 1**.

Meta-analysis results

There was evidence of between-study heterogeneity in all included studies (χ^2 = 81.76, P = 0.000). Therefore, the random-effects model was used to calculate the pooled ORs for the GSTM1 null vs non-null genotypes in overall analysis. Individuals with GSTM1 null genotype were significantly associated with an increased risk for esophageal cancer compared those carrying non-mull genotype (OR = 1.66, 95% CI: 1.29-2.15, **Figure 2**). In the sensitivity analysis, individual studies were sequentially removed. The results indicated that no individual study significantly affected the pooled OR, suggesting that these results were statistically robust (**Figure 3**).

In the subgroup analysis based on source of controls and geographic area, the results showed that the GSTM1 polymorphism was significantly related to esophageal cancer in studies with population-based controls and hospital-based controls, as well as in North China and South China (OR = 1.77, 95% CI: 1.09-2.88; OR = 1.76, 95% CI: 1.47-2.10; OR = 1.52, 95% CI: 1.07-2.16; OR = 2.05, 95% CI: 1.65-2.54) (**Table 2**). In addition, we also performed stratified analysis based on the histological type, it revealed the significant results in studies which not reported histological type (OR = 2.01, 95% CI: 1.69-2.38) (**Table 2**).

Publication bias diagnosis

The Begg's funnel plot and Egger's test were performed to assess the publication bias. As showed in **Figure 4A**, the shape of the funnel plot did not reveal some asymmetry. Moreover, the Egger's test indicated that there was no evidence of obvious publication bias in the 20 reviewed studies (t = 0.83, *P* = 0.415, **Figure 4B**).

Discussion

GSTM1 is one member of the glutathione S-transferase family, which are phase II me-

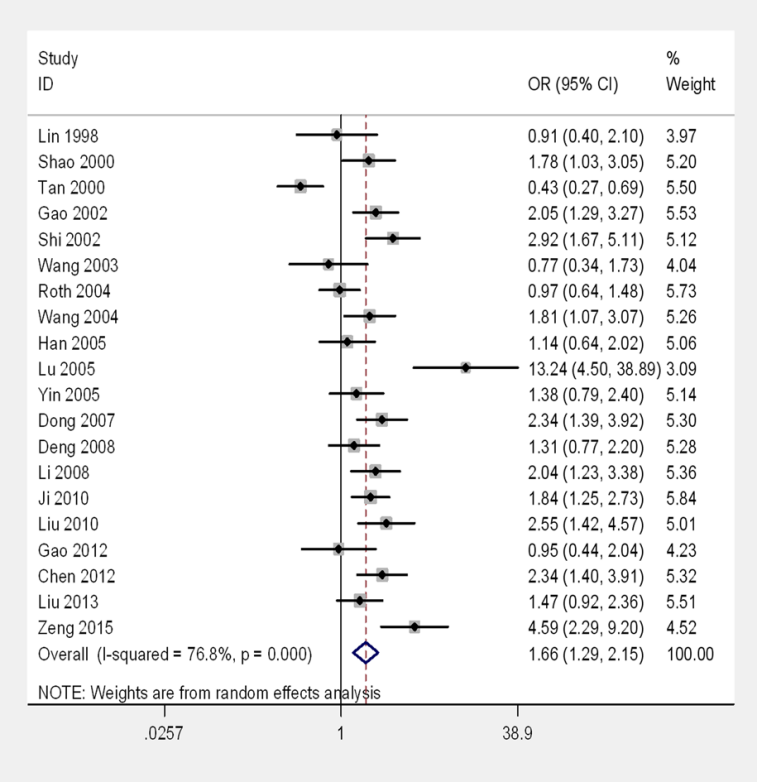

Figure 2. The forest plots of all selected studies on the association between GSTM1 polymorphism and esophageal cancer susceptibility.

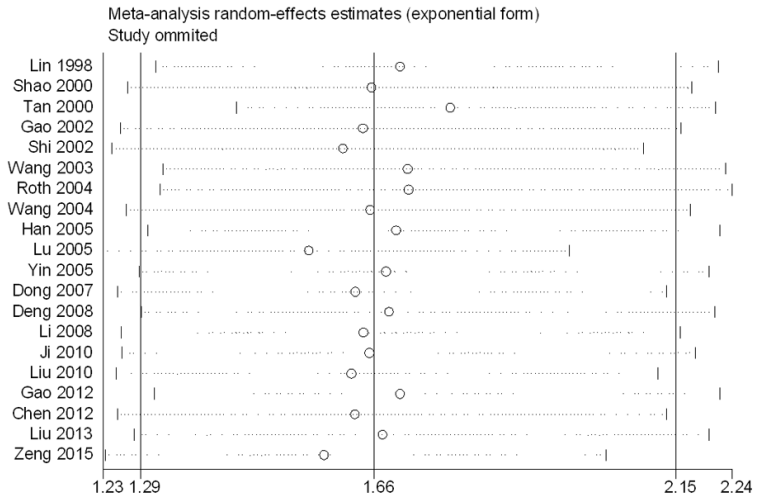

Figure 3. The sensitivity analysis on the association between GSTM1 polymorphism and esophageal cancer.

tabolizing enzymes. These enzymes play an important role in the detoxification of electrophilic carcinogens through conjugation with glutathione [4, 5]. Though a number of studies have reported the potential role of GSTM1 polymorphism in esophageal cancer development, results were discrepant and inconsistent. Up to this time, there are several published meta-analyses regarding GSTM1 polymorphism and esophageal cancer risk [26-33]. Six meta-analyses which were published between 2004 to 2009 did not support the association between GSTM1 null genotype and esophageal cancer [28-33]. One meta-analysis published in 2016 suggested the GSTM1 null polymorphism might be associated with an increased risk for esophageal cancer in Asian but not Caucasian populations [26]. Therefore, we conducted this updated meta-analysis to derive a more precise estimation of GSTM1 polymorphism and esophageal cancer. Our meta-analysis involved 20 studies with 2113 cases and 2848 controls. The overall results suggested GSTM1 null genotype might be a potential biomarker of esophageal cancer susceptibility in Chinese population. It was consistent with the previously published meta-analysis in Chinese population [27]. Furthermore, in the subgroup analysis by source of controls and geographic area, we detected a significant association between the GSTM1 polymorphism and esophageal cancer risk in population-based and hospital-based studies, as well as in North China and South China.

Another major finding of this meta-analysis was the different associations of GSTM1 polymorphism with the risk of esophageal cancer according to the histological type. Our study found that GSTM1 null genotype might be associated with an increased risk of esophageal cancer in studies which not reported histological type; no signifi-

Table 2. Association of the GSTM1 polymorphism on esophageal cancer susceptibility

Subgroups	n	OR_r (95% CI)	OR_f (95% CI)	Heterogeneity	
				χ^2	P
Total analysis	20	1.66 (1.29-2.15)	1.62 (1.44-1.82)	81.76	0.000
Source of control					
Population-based	10	1.77 (1.09-2.88)	1.64 (1.39-1.94)	63.80	0.000
Hospital-based	9	1.74 (1.40-2.17)	1.76 (1.47-2.10)	11.56	0.172
Geographic area					
North China	14	1.52 (1.07-2.16)	1.46 (1.27-1.68)	70.01	0.000
South China	6	2.05 (1.65-2.54)	2.05 (1.65-2.54)	4.35	0.500
Histological type					
ESCC	10	1.40 (0.92-2.15)	1.33 (1.13-1.57)	53.05	0.000
Not reported	10	2.00 (1.58-2.52)	2.01 (1.69-2.38)	15.86	0.070

OR_r: Odd ratio for random-effects model; OR_f: Odd ratio for fixed-effects model; South China included Hubei, Jiangsu, Guangdong; North China included Xinjiang, Ningxia, Henan, Hebei, Gansu, Shanxi.

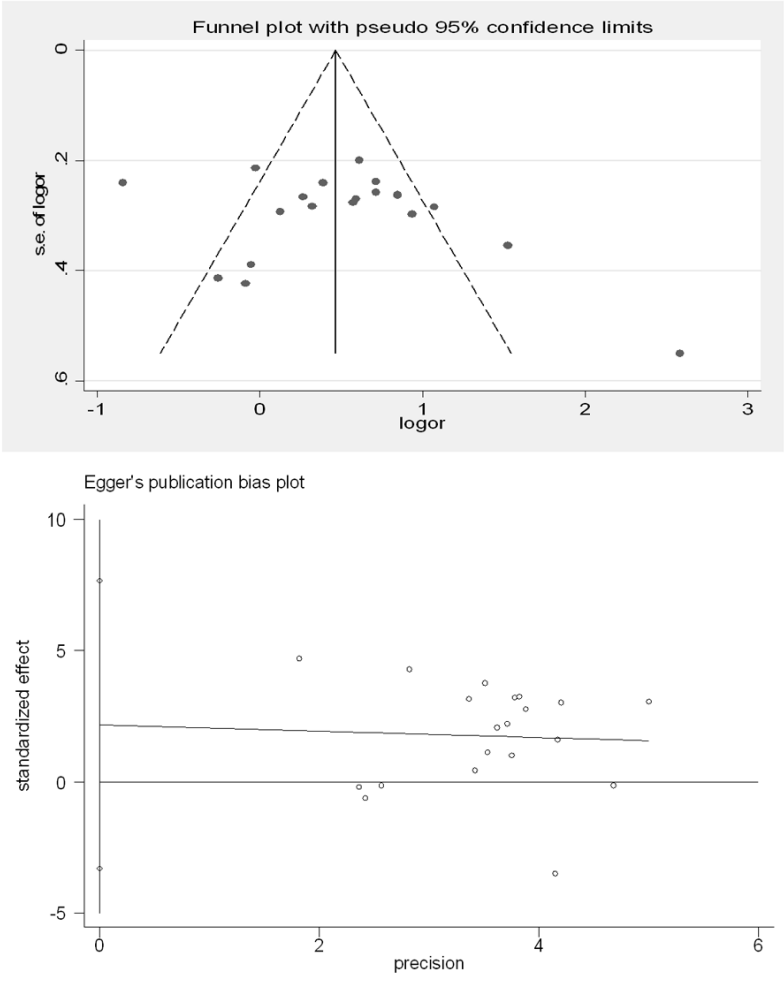

Figure 4. Publication bias assessment (A: Begg's funnel plot; B: Egger's linear regression).

cant association was detected between the GSTM1 polymorphism and esophageal squamous cell carcinoma risk. The discrepancies indicated that histological type might affect the statistical correlation between the GSTM1 polymorphism and esophageal cancer. Similar results have been reported in the previous meta-analysis [26], indicating that further clarification of the histological type might avoid the interference of some confounding factors.

This meta-analysis is strengthed by investigating the influence of geographic area and histological type on the risk of esophageal cancer and GSTM1 polymorphism. The findings provide an evidence for the association between GSTM1 null genotype and risk of esophageal cancer in Chinese population including the northerner and the southerner. The histological types of esophageal cancer may confer different risks associated with the GSTM1 null genotype. In this meta-analysis, only 10 studies had the data of GSTM1 null genotype and esophageal squamous cell carcinoma, ten studies didn't provide information on histological types of esophageal cancer. Therefore, further studies are needed to assess the influence of GSTM1 null genotype on different histological types of esophageal cancer. In addition, the association between GSTM1 null genotype and risk of esophageal cancer in other population is still

unclear, and more case-control studies with large sample size are needed.

In conclusion, this meta-analysis concluded that GSTM1 null genotype might contribute to increased risk of esophageal cancer in Chinese population. To further evaluate gene-gene and gene-environment interactions on GSTM1 polymorphism and esophageal cancer, larger studies in a single population with different environmental background and histological types of esophageal cancer are required.

Disclosure of conflict of interest

None.

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