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Meta-Analysis

Null genotype of GSTT1 may be associated with esophageal cancer risk: a meta-analysis in Chinese individuals

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Abstract: Many studies have analyzed the association between between GSTT1 polymorphism and esophageal cancer, however, the results remained inconclusive. We therefore performed an updated meta-analysis based on Chinese individuals. PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure and Chinese Biology Medicine were searched up to December 2016. An OR with the corresponding 95% CI was used to assess the strength of the association. This meta-analysis included 12 studieswith 1246 cases and 1863 controls. Overall, GSTT1 null genotype was associated with an increased esophageal cancer risk when all studies in Chinese populations pooled into this meta-analysis. In stratified studies with geographical location, significantly increased risk was found in North China (OR = 1.45, 95%CI: 1.11–1.91) and in studies with population-based control (OR = 1.29, 95%CI: 1.07–1.55). This study suggested that GSTT1 null genotype may be potential biomarkers for esophageal cancer in China, especially in North China. Studies with larger sample sizes and wider spectrum of populations are warranted to verify this finding.

Key words: Genes; GSTT1; Polymorphism; Esophageal cancer; Meta-analysis.

Introduction

Esophageal cancer is one of the most most common malignancy and the six leading cause of cancer-related deaths in the world with a rising incidence (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). It is well-known that the carcinogenesis of various cancers is associated with interaction between environmental carcinogens and individuals' genetic background. Polymorphisms in cancer-related genes have been suggested to be the genetic basis of individuals' susceptibility to esophageal cancer. In recent years, several common low-penetrance genes have been identified as potential esophageal cancer susceptibility genes. An important one is Glutathione S-transferase T1 (GSTT1) gene, has been extensively examined in association with risk of various diseases (3). The most common variant of GSTT1 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 (3, 4). In 1998, Lin et al. firstly investigated the association between GSTT1 polymorphism and esophageal cancer in Chinese (5). Subsequently, a number of studies were conducted to investigate the influence of GSTT1 polymorphism on esophageal cancer risk in different ethnic groups; however, no clear consensus was reached. Differences in results may be related to the racial and regional differences in patients who have been studied, as well as a limited number of patients in each study. In order to reduce the influence of the diverse genetic backgrounds, we performed a meta-analysis to assess the relationship between GSTT1 polymorphism and esophageal cancer risk based on Chinese individuals.

Materials and Methods

Search strategy and selection criteria

Literature search was performed using the PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure and Chinese Biology Medicine through December 2016. The search keywords were (glutathione S-transferase T1 or GSTT1) and (esophageal cancer or esophageal adenocarcinoma) and (polymorphism or variant). The search was conducted without language restrictions. Additional articles were located manually through the references of the related reports.

Inclusion criteria: (1) studies describing the association between GSTT1 polymorphism and the risk of esophageal cancer, (2) case-control or cohort studies, (3) including sufficient genetypes data for calculating the odds ratio (OR) with 95% confidence intervals (95% CIs). Exclusion criteria: (1) repeated literatures, (2) incomplete data, (3) no controls, (4) review articles and abstracts.

Data extraction

The following data were extracted independently

and entered into separate databases by two authors from each qualified study: first author's name, publication year, source of controls, geographic location, sample size, and available genotype information from GSTT1 polymorphism. Titles and abstracts of all potentially relevant articles were screened firstly. Full articles were then scrutinized if the title and abstract were ambiguous. Any encountered discrepancies were adjudicated by a discussion and a consensus was reached.

Statistical analysis

An OR with the corresponding 95% CI was used to assess the strength of the association between the GSTT1 null genotype and esophageal cancer risk. The between-study heterogeneity was assessed by Chi-squarebased 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 performed by comparing the results of fixed- and random-effects models. 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

Figure 1 illustrates the literature search process with a flow chart. Eighty-nine articles relevant to the searching words were identified. According to the inclusion and exclusion criteria, twelve articles (5-16) were included and 77 articles were excluded. The publication year of involved studies ranged from 1998 to 2013. In total, 1246 cases and 1863 controls were included in this meta-analysis, which evaluated the relationship between GSTT1 polymorphism and esophageal cancer risk. The source of controls was mainly based on a healthy population. The characteristics of these included studies are provided in Table 1.

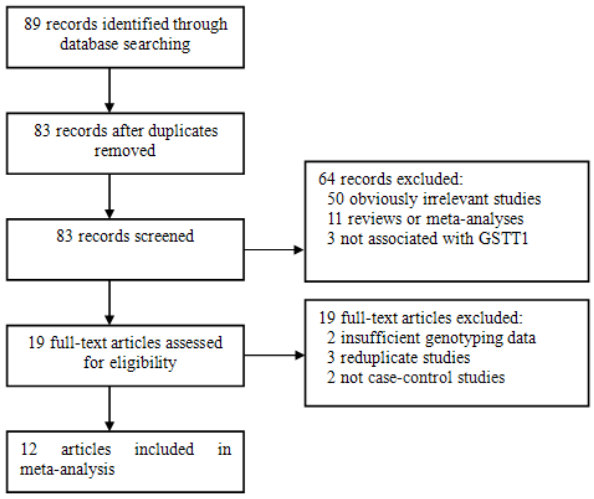

Figure 1. Flow diagram of the literature search.

Overall analysis

There was evidence of between-study heterogeneity in all included studies (χ^2=27.83, p=0.003). Therefore, the random-effects model was used in overall analysis. The results showed that the pooled OR with 95% CI for esophageal cancer risk in Chinese with null GSTT1 was 1.40 (1.09–1.79) (Figure 2). In addition, the finding from cumulative meta-analysis showed that there was a trend of more obvious association between GSTT1 null genotype and risk of esophageal cancer in Chinese as data accumulated by publication year (Figure 3).

Subgroup analysis

In the subgroup analysis based on source of control, the results showed that the GSTT1 polymorphism was significantly related to esophageal cancer among population-based population (OR = 1.29, 95%CI: 1.07–1.55), but not among hospital-based studies (OR = 1.88, 95%CI: 0.78–4.50) (Table 2). In addition, we also performed stratified analysis based on the geographic area, it revealed the significant results in North China (OR = 1.45, 95%CI: 1.11–1.91) (Table 2).

Sensitivity analysis and publication bias diagnosis

In order to compare the difference and evaluate the

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

First author and publication year	Source of controls	Geographic area	Case number	Control number	Case		Control	
					Null genotype	Non-null	Null genotype	Non-null
Lin 1998	PB	Henan	45	45	19	26	23	22
Tan 2000	PB	Henan	150	150	60	90	59	91
Gao 2002	PB	Jiangsu	141	223	74	67	119	104
Wang 2003	PB	Henan	62	38	34	28	20	18
Roth 2004	Nest	Henan	131	454	77	54	243	211
Yin 2005	HB	Jiangsu	106	106	46	60	51	55
Deng 2008	PB	Hebei	87	162	51	36	87	75
Zhang 2009	PB	Xinjiang	88	72	57	31	33	39
Ji 2010	PB	Gansu	189	216	98	91	94	122
Liu 2010	PB	Jiangsu	97	97	63	34	40	57
Gao 2012	HB	Ningxia	40	80	23	17	24	56
Liu 2013	HB	Ningxia	110	220	34	76	31	189

HB, hospital-based; PB, population-based.

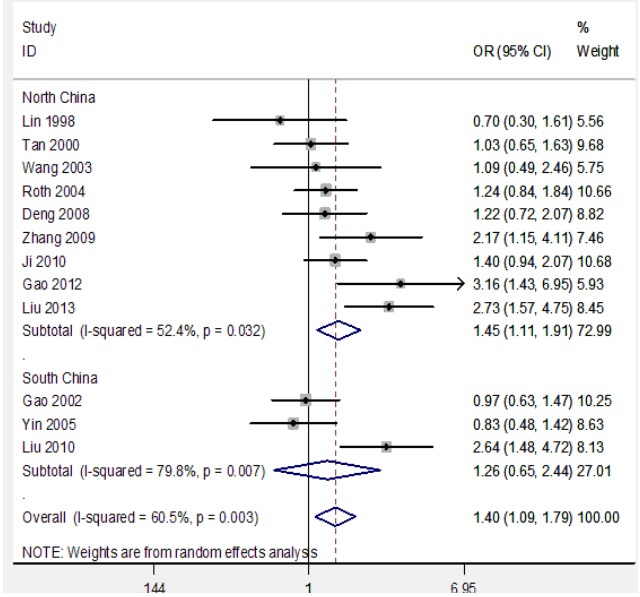

Figure 2. The forest plots of all selected studies on the association between GSTT1 polymorphism and esophageal cancer susceptibility.

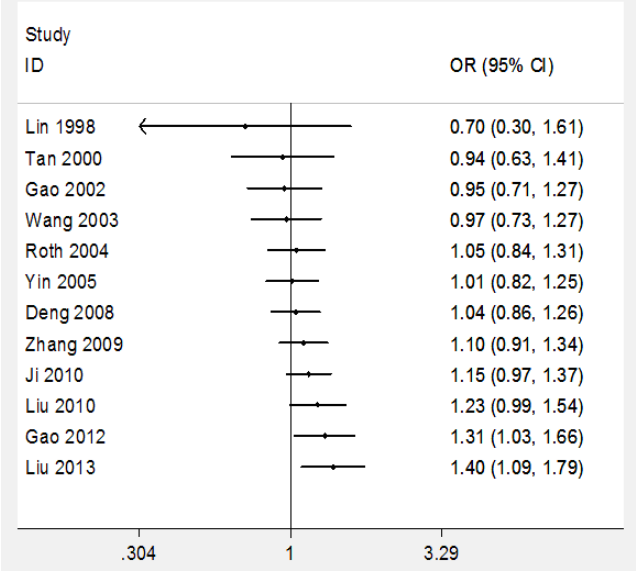

Figure 3. The cumulative meta-analysis on the association between GSTT1 polymorphism and esophageal cancer.

sensitivity of the meta-analysis, we used both models (the fixed- and random-effects models) to evaluate the stability of the meta-analysis. All the significant results were not materially altered except the population-based analysis (Table 2). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. The Begg's funnel plot and Egger's test were performed to assess the publication bias. As showed in Figure 4, the shape of the funnel plot did reveal some asymmetry. However, the Egger's test indicated that there was no evidence of obvious publication bias in the 12 reviewed studies (t=1.05, p=0.320).

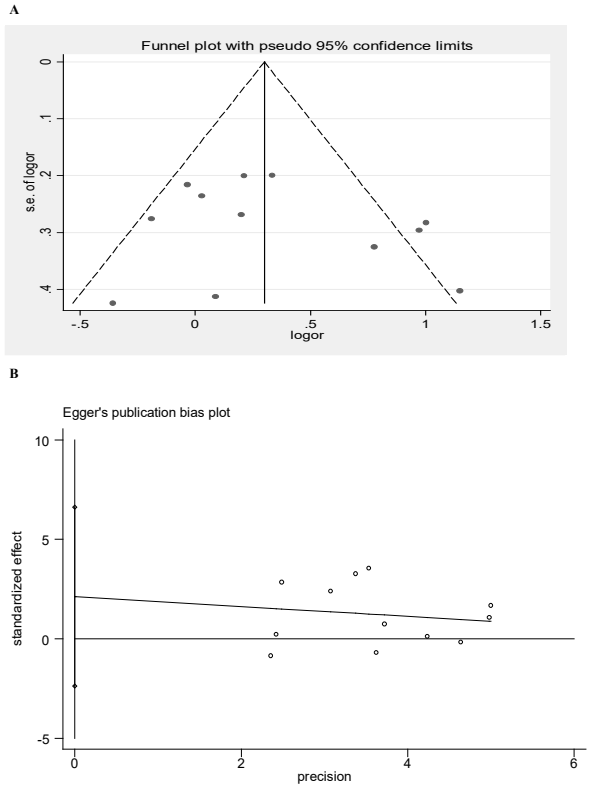

Figure 4. Publication bias assessment (A: Begg's funnel plot; B: Egger's linear regression).

Discussion

Although many studies analyzing the association between GSTT1 polymorphism and esophageal cancer, definite conclusions cannot be drawn. Up to this time, there are several published meta-analyses regarding GSTT1 polymorphism and esophageal cancer risk (17-22). Nevertheless, the results were inconclusive and inconsistent. Three meta-analyses were published to assess the associations between GSTs polymorphisms and esophageal cancer risk, but failed to find a significant association between GSTT1 null genotype and esophageal cancer risk (17-19). Three meta-analyses showed

Table 2. Association of the GSTT1 polymorphism on esophageal cancer susceptibility.

Subgroups	n	OR_r(95%CI)	OR_f(95%CI)	Heterogeneity	
				χ^2	P
Total analysis	12	1.40 (1.09–1.79)	1.35(1.16–1.57)	27.83	0.003
Source of control					
Population-based	8	1.30 (0.99–1.70)	1.29 (1.07–1.55)	13.59	0.059
Hospital-based	3	1.88 (0.78–4.50)	1.69 (1.20–2.38)	11.98	0.003
Geographic area					
North China	9	1.45 (1.11–1.91)	1.41 (1.19–1.69)	16.82	0.032
South China	3	1.26 (0.65–2.44)	1.19 (0.89–1.58)	9.92	0.007

ORr: Odd ratio for random-effects model; ORf: Odd ratio for fixed-effects model; South China included Jiangsu; North China included Xinjiang, Ningxia, Henan, Hebei, Gansu.

there was an obvious association between GSTT1 null genotype and increased risk of esophageal cancer in East Asians (particularly in China), and a race-specific effect may exist in this association (20-22). Therefore, we conducted this updated meta-analysis to derive a more precise estimation of GSTT1 polymorphism and esophageal cancer in Chinese population. Our meta-analysis involved 12 studies with 1246 cases and 1863 controls. The meta-results showed a significantly increased association between GSTT1 null genotype and risk of esophageal cancer in Chinese individuals.

The exact mechanism for the ethnic discrepancy is uncertain but differences in underlying genetic backgrounds and social factors among different populations studied may be important. Ethnically diverse subjects may have unique cultures and lifestyles that can contribute to different genetic characteristics and susceptibility to specific cancer. Furthermore, the distribution of GSTT1 genotype may be different in various areas in China. In this meta-analysis stratified by geographical location, significantly increased risk of esophageal cancer with the GSTT1 null genotype was found in Chinese individuals from North China, whereas was not found in South China. Therefore, the relationship between GSTT1 polymorphism and esophageal cancer might be susceptible in different regions and nationalities. We didn't perform subgroup analysis on other ethnicity history, because of the lack of sufficient data.

This study has some limitations. First, this ethnic-specific meta-analysis only included data from a single ethnic group, and thus, our results are only applicable to this ethnic group. Second, because the papers searched in our study were limited to those openly published, it is possible that some non-published literature that may meet the inclusion criteria were missed. Third, significant heterogeneity between different studies still existed in the subgroup analysis, thus might introduce some bias. Fourth, due to the relative small sample size of some studies or lack of necessary information, we did not perform further subgroup analyses. In spite of these limitations, our meta-analysis also had some advantages. First, we have followed the inclusion and exclusion criteria strictly to reduce possible selection bias. Second, a funnel plot and Egger's linear regression test were used to assess publication bias. Third, the sensitivity analysis had been performed to confirm the reliability and stability of this meta-analysis. Most of the important, impact of different geographical background was minimized by performing the analysis in North and South China respectively. Therefore, our results would appear to be more meaningful and shed new light on the further research.

In conclusion, this meta-analysis finds a significantly increased association between GSTT1 null genotype and esophageal cancer risk in China, especially in North China.. To further evaluate gene-gene and gene–environment interactions on GSTT1 polymorphism and esophageal cancer, larger studies in a single population with different environmental background or other risk factors are required.

Declaration of Interest

The authors report no conflicts of interest.

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