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ORIGINAL RESEARCH

GSTM1 null genotype and gastric cancer risk in the Chinese population: an updated meta-analysis and review

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Abstract: Although a number of studies have been conducted on the association between the *GSTM1* null genotype and gastric cancer in People's Republic of China, this association remains elusive and controversial. To clarify the effects of the *GSTM1* null genotype on the risk of gastric cancer, an updated meta-analysis was performed in the Chinese population. Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to November 5, 2014. A total of 25 studies including 3,491 cases and 5,921 controls were included in this meta-analysis. Overall, a significant association (odds ratio [OR] =1.47, 95% CI: 1.28–1.69) was found between the null *GSTM1* and gastric cancer risk when all studies in Chinese population were pooled into the meta-analysis. In subgroup analyses stratified by quality score, geographic area, and source of controls, the same results were observed. Additionally, a significant association was found both in smokers and non-smokers. This meta-analysis showed that the null *GSTM1* may be a potential biomarker for gastric cancer risk in Chinese, and further studies with gene–gene and gene–environment interactions are required for definite conclusions.

Keywords: meta-analysis, *GSTM1*, polymorphism, gastric cancer

Introduction

The incidence and mortality of gastric cancer have declined dramatically over the past several decades. Nonetheless, gastric cancer remains a major public health issue as the fourth most common cancer and the second most frequent cause of cancer death worldwide.[1] A total of 989,600 new stomach cancer cases and 738,000 deaths are estimated to have occurred in 2008, accounting for 8% of the total cases and 10% of total deaths.[1] Over 70% of new cases and deaths occur in developing countries, with the majority in People's Republic of China.[1] The mechanism of gastric carcinogenesis is still not fully understood. It has been suggested that low-penetrance susceptibility genes combining with environmental factors may be important in the development of cancer.[2] In recent years, several common low-penetrant genes have been identified as potential gastric cancer susceptibility genes. An important one is glutathione *S*-transferase (*GST*), which consists of five distinct classes, namely alpha (*GSTA*), sigma (*GSTS*), mu (*GSTM*), pi (*GSTP*), and theta (*GSTT*).[3] Located on the chromosome 1p13.3, the *GSTM1* plays an important role in the detoxification of xenobiotics. The most common genotype of *GSTM1* gene is a homozygous deletion (null genotype), which has been suggested to be associated with the loss of enzyme activity and increased vulnerability to cytogenetic damage that resulted in the increased

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susceptibility to cancer.[4,5] An association between the *GSTM1* null genotype and gastric cancer was first reported by Strange et al in 1991 among Britain's population.[6] As a consequence, many studies analyzed the influence of the *GSTM1* null genotype on gastric cancer risk; however, no clear consensus was reached. Meta-analyzes of studies of the *GSTM1* null genotype in other ethnic groups have been reported elsewhere and produced conflicting results.[7–13] In order to lessen the impact of different genetic backgrounds, we performed this update meta-analysis to assess the relationship of the *GSTM1* null genotype with risk of gastric cancer in Chinese population.

Materials and methods

Search strategy

The studies were searched in PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to November 5, 2014. The keywords used were combinations of the following terms: (1) *GSTM1* or *GST M1*; (2) gastric cancer or gastric neoplasm or stomach tumor; (3) polymorphism or variant or variation; and (4) Chinese or China or Taiwan. The search was performed without any restrictions on language and focused on studies conducted in humans. Besides, the references from retrieved articles were also searched.

Inclusion and exclusion criteria

The criteria used to select studies for this meta-analysis were as follows: (1) independent cohort or case–control studies for human; (2) all patients with the diagnosis of gastric cancer confirmed by pathological or histological examinations; (3) the distribution of the *GSTM1* null genotype in patients and controls provided; and (4) all participants were Chinese. The reasons for exclusion of studies were: (1) duplicate publications; (2) incomplete data; (3) no control; and (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Relevant data were extracted from all the eligible studies independently by the two reviewers according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. The following data were extracted from the identified studies: the first author, publication year, source of controls, geographic area, sample size, and the number of subjects with two *GSTM1* genotypes. In this meta-analysis, the quality assessment of individual study was conducted according to the nine-star Newcastle–Ottawa Scale.[14]

Statistical analysis

We examined the association between the *GSTM1* null genotype and gastric cancer risk by calculating pooled odds ratio (OR), with 95% confidence intervals (CIs). The significance of the pooled OR was determined by the *Z*-test. Given that there was distribution of null/present heterozygote in only one study selected, the Hardy–Weinberg equilibrium (HWE) test could not be conducted. Cochrane's *Q*-test was performed to test the between-study heterogeneity. If there was heterogeneity, then the random-effects model was chosen to pool the ORs with 95% CIs, otherwise the fixed-effects model was used. Moreover, subgroup analyses were performed to test whether the effect size varied by the smoking status, quality score, geographic area, and the source of control population. Publication bias was investigated with the funnel plot, in which the standard error (SE) of log OR of each study was plotted against its OR. Funnel plot asymmetry was further assessed by the method of Egger's linear regression test.[15] All the *P*-values were two sided. *P*-value less than 0.05 was considered statistically significant. All statistical analysis was conducted by using Stata version 10.0 (Stata Corp, College Station, Texas, USA).

Results

Study selection

According to the inclusion criteria, 25 case–control studies[16–40] were included and 54 articles were excluded. The publication year of involved studies ranged from 2000 to 2012. The flowchart of study selection is shown in Figure 1. In total, 3,491 gastric cancer cases and 5,921 controls were involved in this meta-analysis, which evaluated the relationship between *GSTM1* polymorphism and gastric cancer risk. The source of controls was mainly based on a healthy population. The characteristics of the included studies are summarized in Table 1.

Overall analysis

There was evidence of between-study heterogeneity in all included studies (χ^2=49.62, *P*=0.002). Therefore, the random-effects model was used in overall analysis. The results showed that the pooled OR with 95% CI for gastric cancer in Chinese with the *GSTM1* null genotype was 1.47 (1.28–1.69) (Figure 2).

Subgroup analysis

In the subgroup analysis based on smoking status, the results showed that the *GSTM1* null genotype was significantly

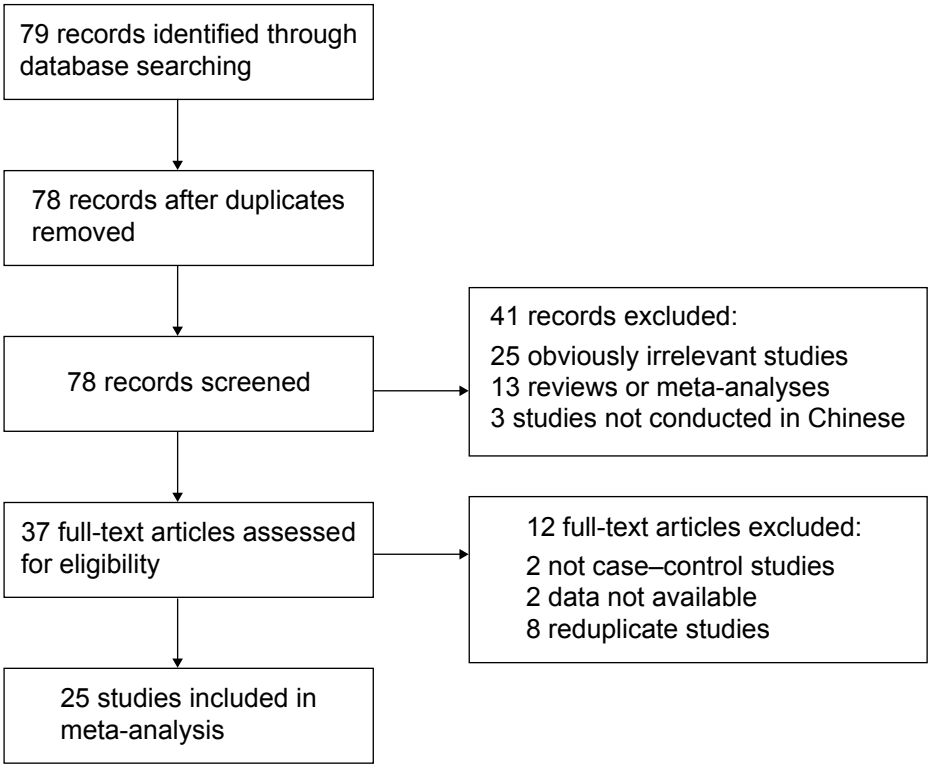

Figure 1 Flow diagram of the literature search process.

Table 1 Characteristics of studies included in the meta-analysis

Reference	Source of controls	Area	Case number	Control number	Case		Control		Quality score
					Null genotype	Non-null	Null genotype	Non-null	
Cai et al[16]	PB	Fujian	95	94	60	35	43	51	6
Gao et al[17]	PB	Jiangsu	153	223	90	63	133	90	7
Gong et al[18]	PB	Anhui	32	88	25	7	50	38	7
Huang et al[19]	PB	Guangxi	121	138	66	55	54	84	8
Jiang et al[20]	HB	Liaoning	41	41	24	17	14	27	6
Jing et al[21]	PB	Sichuan	410	410	240	170	207	203	8
Lai et al[22]	PB	Taiwan	123	121	73	50	55	66	7
Li et al[23]	HB	Shandong	100	62	67	33	26	36	6
Liu et al[24]	PB	Liaoning	99	364	63	36	186	178	8
Luo et al[25]	PB	Hunan	123	129	93	30	71	58	7
Moy et al[26]	PB	Shanghai	170	735	98	72	415	320	7
Mu et al[27]	PB	Jiangsu	196	393	127	69	235	158	8
Qian et al[28]	PB	Jiangsu	89	94	55	34	44	50	7
Roth et al[29]	PB	Henan	89	454	23	66	145	309	8
Setiawan et al[30]	PB	Jiangsu	87	419	42	45	212	207	8
Shen et al[31]	PB	Jiangsu	112	675	71	41	361	314	8
Shen et al[32]	HB	Jiangsu	121	121	54	67	41	80	6
Wang et al[33]	PB	Hainan	129	138	39	90	26	112	8
Wu et al[34]	HB	Taiwan	356	278	173	183	136	142	7
Zhang et al[35]	PB	Guangdong	194	412	105	89	194	218	6
Zhang et al[36]	PB	Hubei	127	114	78	49	53	61	8
Zheng et al[37]	PB	Fujian	92	92	64	28	48	44	8
Zheng[38]	HB	Fujian	313	192	145	168	86	106	7
Zhou et al[39]	PB	Henan	19	72	7	12	28	44	6
Zhou et al[40]	PB	Shandong	100	62	67	33	26	36	6

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

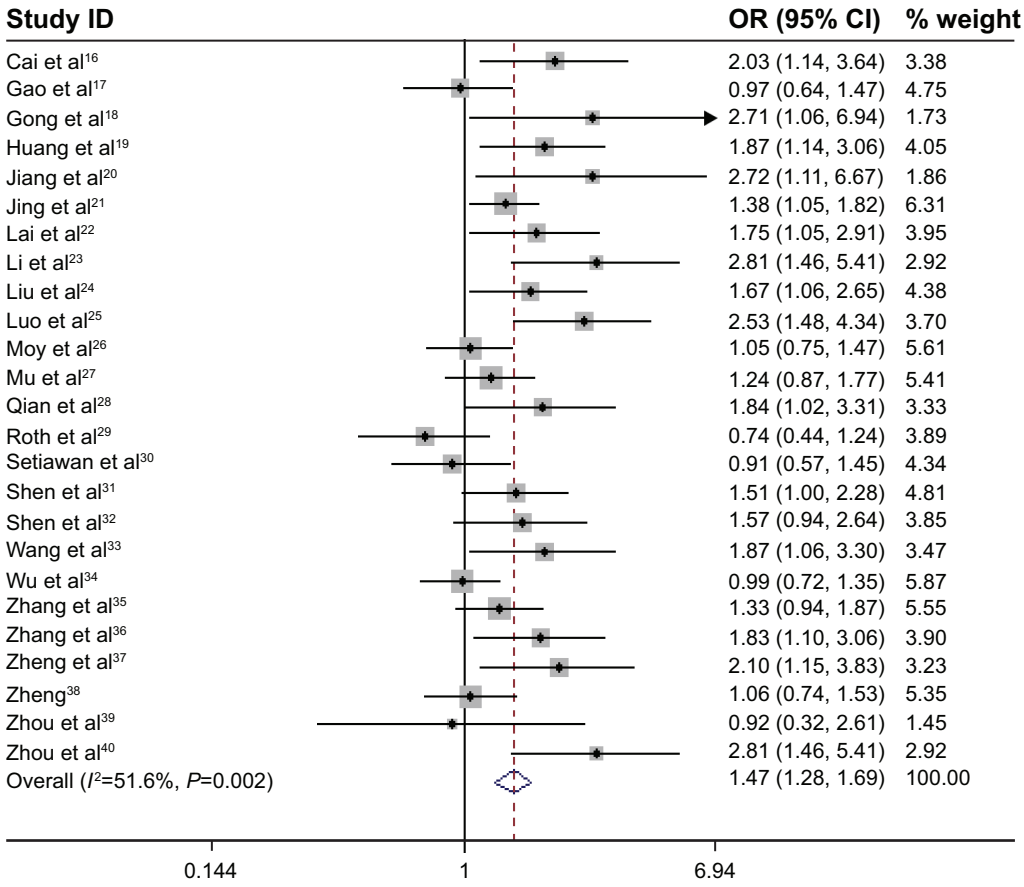

Figure 2 The forest plot of all selected studies on the association between *GSTM1* polymorphism and gastric cancer risk in Chinese.
Note: Weights are from random effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval.

related to gastric cancer risk among smokers (OR =1.98, 95% CI: 1.28–3.06), as well as among non-smokers (OR =1.42, 95% CI: 1.11–1.81) (Table 2). In addition, we also performed stratified analysis based on the source of control, quality score, and geographic area. It revealed similar results with all the studies (Table 2).

Sensitive analysis

To evaluate the stability of the results, we performed a sensitivity analysis by a different model. All the results were not materially altered (Table 2). Hence, the results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible.

Table 2 Main results in the total and subgroup analysis

Subgroups	n	Random-effect model	Fixed-effect model	Heterogeneity	
		OR (95% CI)	OR (95% CI)	χ^2	P
Total analysis	25	1.47 (1.28–1.69)	1.39 (1.27–1.52)	49.62	0.002
Source of control					
Population-based	20	1.48 (1.28–1.72)	1.42 (1.29–1.58)	35.90	0.011
Hospital-based	5	1.48 (1.01–2.19)	1.26 (1.03–1.53)	12.48	0.014
Quality score					
8	10	1.41 (1.18–1.70)	1.40 (1.22–1.60)	15.39	0.081
7	8	1.35 (1.04–1.74)	1.23 (1.06–1.43)	17.94	0.012
6	7	1.84 (1.38–2.45)	1.74 (1.47–2.15)	9.38	0.155
Area					
South People's Republic of China	17	1.35 (1.19–1.53)	1.32 (1.19–1.46)	23.76	0.095
North People's Republic of China	8	1.88 (1.27–2.79)	1.78 (1.43–2.21)	19.77	0.006
Smoking					
Smokers	8	1.98 (1.28–3.06)	1.71 (1.30–2.25)	14.75	0.039
Non-smokers	7	1.42 (1.06–1.91)	1.42 (1.11–1.81)	8.20	0.224

Abbreviations: OR, odds ratio; CI, confidence interval.

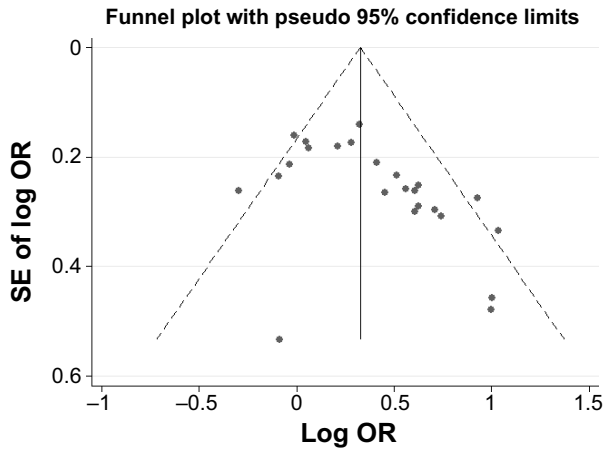

Figure 3 The funnel plot of all selected studies on the association between *GSTM1* polymorphism and gastric cancer risk in Chinese.
Abbreviations: OR, odds ratio; SE, standard error.

Bias diagnosis

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. As shown in Figure 3, the shape of the funnel plots did reveal obvious asymmetry. Similarly, the Egger's test indicated some publication bias in the 25 reviewed studies (t=–2.65, P=0.014).

Discussion

The *GSTM1* enzyme is responsible for the metabolism of reactive electrophilic intermediates, including environmental pollutants and other polycyclic aromatic hydrocarbons, which are potent carcinogenic agents. Thus, impaired *GSTM1* function may lead to serious DNA damage and carcinogenesis. Considering that null genotype causes a complete loss of *GSTM1* enzyme activity, it is biologically plausible that the *GSTM1* null genotype may increase risk of gastric cancer. Up to this time, a series of studies in People's Republic of China have focused on the relation between the *GSTM1* null genotype and gastric cancer risk. Nevertheless, the results were inconclusive and inconsistent. Some papers have reported that a statistically significant correlation was found between null *GSTM1* and gastric cancer risk. Conversely, the results from other studies suggested that the null *GSTM1* was not associated with gastric cancer risk. Therefore, we conducted this update meta-analysis by critically reviewing 25 individual studies on the *GSTM1* null genotype with gastric cancer risk in the Chinese population. In the meta-analysis, we found that the *GSTM1* null variant was significantly associated with gastric cancer risk in overall and subgroup analyses by source of control, quality score, and geographic area. To our knowledge, our study represented the first meta-analysis with a large sample size on the interaction of *GSTM1* variant with gastric cancer in the Chinese population.

Furthermore, the interaction between the *GSTM1* null genotype and tobacco smoking as a risk factor for gastric cancer has been evaluated by several studies with inconsistent results, possibly because of small sample size.[41] Thus, we performed a stratified analysis by smoking status to ascertain the interaction by pooling all available studies. We found that the *GSTM1* null genotype significantly increases the risk of gastric cancer, both in smokers and non-smokers. However, the risk conferred by null genotype is higher among smokers (OR =1.98, 95% CI: 1.28–3.06) than in non-smokers (OR =1.42, 95% CI: 1.11–1.81). Smoking habit was quite heterogeneous among eligible studies. It might make attributions for other unknown factors, such as dietary habits, drinking status, other environmental exposures, family history of cancer, other genetic-related respiratory diseases, as well as other related genetic polymorphisms. Moreover, the association between the extent of smoke exposure and gastric cancer risk was not clear; further studies with larger sample sizes are needed to provide insights into the interaction association.

The pathways of carcinogen metabolism are complex, mediated by the activity of multiple enzymes. The effect of any single gene might have a limited impact on gastric cancer risk than have so far been anticipated. The knowledge of environmental determinants and large studies with detailed exposure information are crucial to evaluate reliably any moderate genetic effects. Many controversial data are present in literature. Positive associations were found in certain populations and not confirmed in others. In addition to an expected interethnic variability in allele frequencies, variability has also been found within ethnic groups,[42] resulting in heterogeneity in association studies. Gene–environment interactions could be a confounding factor in these studies, with controversial findings on cancer risk.

This study has some limitations. First, only published studies were included in the meta-analysis; therefore, publication bias may have occurred probably due to the exclusion of negative studies. It is evident that positive results had a greater probability of being published with respect to negative ones, even though unpublished studies are generally of lesser quality with respect to published ones. Second, we could not obtain information from most studies regarding infection with *Helicobacter pylori*, a strong risk factor for gastric cancer, and other several factors like salt intake, age, alcohol drinking, etc. Third, our results were based on unadjusted estimates.

Conclusion

In conclusion, this meta-analysis suggests that the *GSTM1* null genotype is associated with gastric cancer among Chinese populations. The null genotype increased susceptibility to

gastric cancer both in smokers and non-smokers. The risk conferred by the null genotype is higher among smokers than in non-smokers. Further studies analyzing gene–gene and gene–environment interactions are required. Such studies may eventually lead to have a better, comprehensive understanding of the association between the *GSTM1* null genotype and gastric cancer risk.

Disclosure

The authors report no conflicts of interest in this work.

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