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Original Article

GSTT1 and gastric cancer susceptibility in the Chinese population: an updated meta-analysis and review

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Abstract: Aim: To assess the effects of GSTT1 null genotype on the risk of gastric cancer (GC), an updated meta-analysis was performed in the Chinese population. Methods: 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) to up 5th March 2015. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of the associations. Results: A total of 19 case-control studies including 2861 GC cases and 5064 controls were involved in this meta-analysis. Overall, significantly increased GC risk was associated with the null GSTT1 with OR of 1.20 (95% CI: 1.04-1.38) in the Chinese population. In subgroup analyses stratified by geographic area and source of controls, the significant results were found in South China and population-based studies. We also undertook gene-gene interaction analysis between GSTT1 and GSTM1 genes for GC risk, and the results indicated that the dual null genotypes of GSTT1 and GSTM1 might elevate the risk of GC (OR = 2.02, 95% CI: 1.63-12.51). Conclusion: This meta-analysis suggests that GSTT1 null genotype is associated with elevated GC risk in Chinese, but these associations vary in different geographic location.

Keywords: Meta-analysis, GSTT1, polymorphism, lung cancer, gene-gene interaction

Introduction

Although gastric cancer (GC) is among the leading causes of cancer-related death worldwide [1], and is currently the sixth most common cancer with 989,600 newly confirmed cases and 738,000 deaths in 2008, accounting for 8% of total cases and 10% of total cancer-related deaths [2]. The vast majority of these new cases occurred in China [2]. Epidemiologic evidence implicates *Helicobacter pylori* infection in the etiology of GC, which is classified as a group I carcinogen by the World Health Organization [3]. However, only 1% of infected individuals develop malignancy, suggesting that genetic variations and other environmental factors influence individual differences in susceptibility [4, 5].

Recently, several common, low-penetrant genes have been identified as potential GC susceptibility genes. Among these are genes encoding the five distinct families of glutathione S-transferases [6], of which the gene encoding glutathione S-transferase θ1 (*GSTT1*) has been extensively examined in association with risk of various diseases [7]. The most common *GSTT1* genotype is the homozygous deletion (null genotype), which is associated with loss of enzymatic activity, increased vulnerability to cytogenetic and oxidative DNA damage, and results in susceptibility to cancer [7, 8].

An association between *GSTT1* polymorphism and GC was first reported in the British population by Deakin *et al* [9] in 1996. Many studies have subsequently analyzed the influence of *GSTT1* polymorphisms on GC risk, with no clear consensus. Meta-analyses of related studies in other ethnic groups have also produced conflicting results [10-17]. In order to investigate the effect of *GSTT1* genotypes on GC risk in a Chinese population, a meta-analysis was performed including stratification by geographic area and the source of the control population. Moreover, a gene-gene interaction analysis was conducted to explore the relationship between *GSTT1* and glutathione S-transferase μ1 (*GSTM1*) genotypes with respect to GC risk.

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

Ref.	Control-source	Geographic area	Cases, *n*	Controls, *n*	Case genotype, *n*		Control genotype, *n*		Quality score[1]
					Null	Non-null	Null	Non-null	
Setiawan et al [25], 2000	PB	Jiangsu	81	418	44	37	190	228	8
Cai et al [26], 2001	PB	Fujian	95	94	41	54	47	47	8
Qian et al [27], 2001	PB	Jiangsu	85	96	51	34	46	50	7
Shen et al [28], 2002	PB	Jiangsu	110	675	43	67	309	366	6
Wu et al [29], 2002	HB	Taiwan	356	278	181	175	130	148	8
Zheng et al [30], 2002	PB	Fujian	92	92	49	43	38	54	7
Gao et al [31], 2002	PB	Jiangsu	153	223	71	82	119	104	8
Zhang et al [32], 2003	PB	Hubei	127	114	76	51	55	59	7
Zheng et al [33], 2003	HB	Fujian	313	192	180	133	115	77	8
Zhou et al [34], 2003	PB	Henan	19	72	10	9	28	44	6
Ye et al [35], 2003	HB	Hubei	56	56	34	22	26	30	7
Roth et al [36], 2004	PB	Henan	90	454	43	47	243	211	8
Mu et al [37], 2005	PB	Jiangsu	196	393	93	103	192	201	8
Shen et al [38], 2005	HB	Jiangsu	121	121	64	57	54	67	8
Xie et al [39], 2008	PB	Guangxi	70	100	48	22	50	50	6
Moy et al [40], 2009	PB	Shanghai	170	735	97	73	415	320	8
Luo et al [41], 2011	PB	Hunan	123	129	77	46	63	66	7
Zhang et al [42], 2011	PB	Guangdong	194	412	114	80	198	214	8
Jing et al [43], 2012	PB	Sichuan	410	410	236	174	202	208	8

HB: Hospital-based; PB: Population-based. [1]Newcastle-Ottawa Scale.

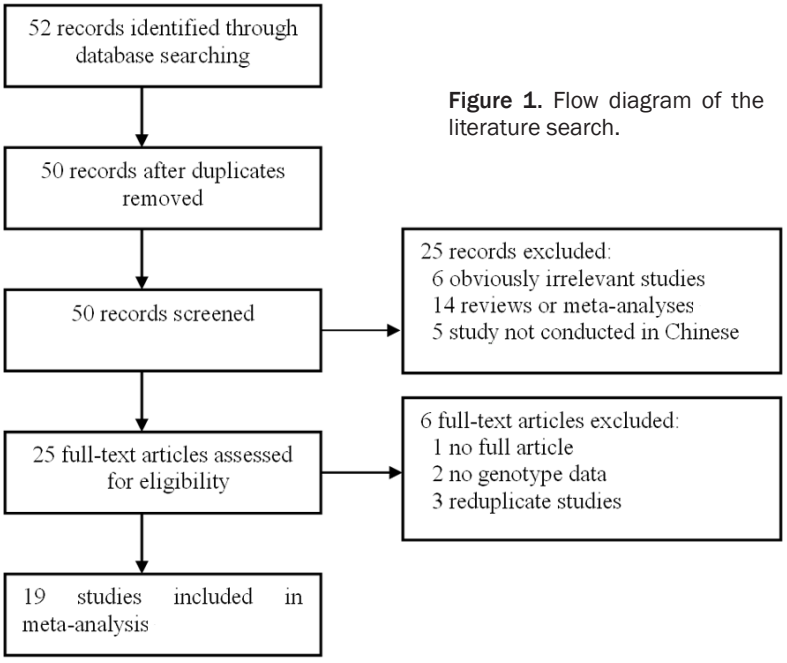

Figure 1. Flow diagram of the literature search.

Materials and methods

Search strategy and study selection

A systematic literature search was conducted for published articles concerning the association of *GSTT1* polymorphisms and GC risk. The search included PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine databases for articles published through March 5, 2015 using a combination of the following terms: GSTT1 or GST T1; gastric cancer or gastric neoplasm or stomach tumor; polymorphism or variant or variation; and Chinese or China or Taiwan. The search was performed without any restrictions on language and focused on studies conducted in humans. All reference lists of retrieved articles were manually reviewed to identify additional articles. Criteria for inclusion in the meta-analysis were: (1) case-control or cohort studies describing the association of *GSTT1*-null genotype and GC; (2) GC diagnoses were confirmed by pathologic

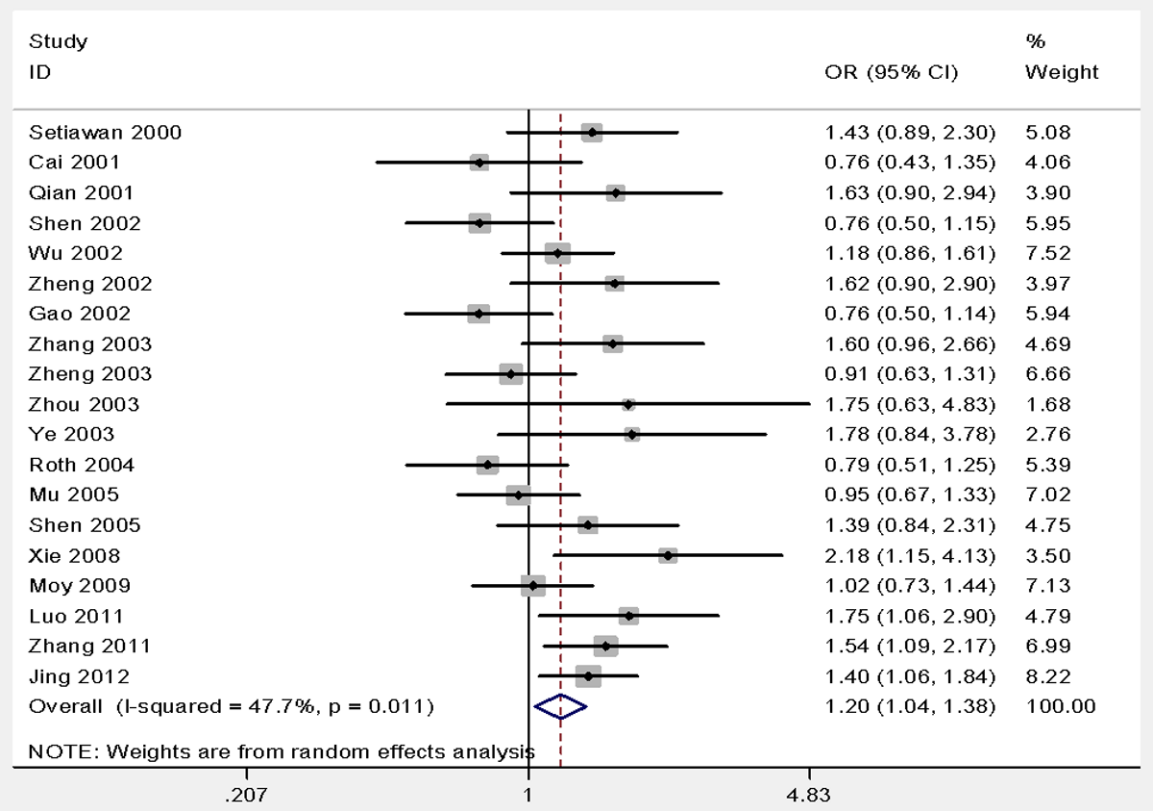

Figure 2. Forest plots of all selected studies on the association between GSTT1 polymorphism and GC risk in Chinese.

or histologic examinations; (3) studies with a clear description of *GSTT1* polymorphisms in GC patients and controls; (4) all participants were Chinese. The reasons for exclusion of studies were: (1) duplicate publications; (2) incomplete data; (3) lack of controls; (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. Information from all eligible publications was independently extracted by two authors. Discrepancies between the two authors were resolved by discussion, and if a consensus was not achieved, a decision was made by all the reviewers. The following data were extracted: the first author, publication year, source of controls, geographic area, sample size, *GSTT1* polymorphism in cases and controls, and the number of subjects with *GSTT1*-*GSTM1* interaction. If data from any category were not reported in the primary study, we did not contact the author to request the information. In this meta-analysis, the quality of individual studies was assessed according to the nine-star Newcastle-Ottawa Scale [18]. For articles including different source of controls, data were extracted separately (**Table 1**).

Statistical analysis

The strength of the association between the *GSTT1*-null allele and risk of GC was measured by odds ratios (ORs) with 95% confidence intervals (95% CIs). The significance of the pooled OR was determined by the *Z* test. Cochran's *Q*-statistic was used to assess heterogeneity, indicated by a $P < 0.10$. The random-effects model was chosen to pool the ORs when significant heterogeneity was observed; otherwise the fixed-effects model was used. Subgroup analyses were performed to test whether the effect size varied by the geographic area and the source of the control population. In order to evaluate the presence of an interaction between *GSTT1* and *GSTM1* polymorphisms,

Table 2. Main results in the total and subgroup analyses

Subgroup	*n*	Random-effects model	Fixed-effects model	Heterogeneity	
		OR (95% CI)	OR (95% CI)	χ^2	*P* value
Total analysis	19	1.20 (1.04-1.38)	1.17 (1.07-1.30)	34.39	0.011
Source of control					
Population-based	15	1.21 (1.01-1.43)	1.18 (1.06-1.32)	30.81	0.006
Hospital-based	4	1.16 (0.92-1.46)	1.15 (0.93-1.41)	3.52	0.318
Geographic area					
South China	16	1.19 (1.03-1.38)	1.17 (1.06-1.30)	28.50	0.019
North China[1]	3	1.27 (0.70-2.32)	1.18 (0.86-1.62)	5.89	0.053

CI: Confidence interval; OR: Odds ratio. [1]Including: Henan and Hunan.

Table 3. Combined genotype analysis of GSTT1 and GSTM1 on risk of gastric cancer in Chinese

Genotype		Cases	Controls	OR (95% CI)	*P* value
GSTM1	GSTT1				
Non-null	Non-null	213	510	1.00	
Non-null	Null	258	486	1.19 (0.94-1.49)	0.144
Null	Non-null	318	530	1.45 (1.16-1.81)	0.001
Null	Null	395	457	2.02 (1.63-12.51)	< 0.001

CI: Confidence interval; GSTM1: Glutathione S-transferase μ1; GSTT1: Glutathione S-transferase q1; OR: Odds ratio.

an additional gene-gene interaction analysis was performed using the individuals with genotypes positive for both genes as reference groups. Publication bias was investigated with a funnel plot, where the standard error of the log of the OR of each study was plotted against its OR. Funnel-plot asymmetry was further assessed by the method of Egger's linear regression test. All statistical analyses were conducted using Stata version 10.0 (Stata Corp, College Station, Texas, United States). A two-sided $P < 0.05$ was considered statistically significant.

Results

Description of included studies

A total of 52 articles that examined the association between *GSTT1* polymorphisms and risk of GC were identified. After screening the titles and abstracts of these articles, 27 were excluded. Of the remaining 25 potentially relevant articles [19-43], the full text of one article [19] could not be retrieved, two articles [20, 21] were excluded due to a lack of genotype data, and three [22-24] articles were excluded because they concerned subjects included in an expanded series [27, 25, 38]. The flow chart of study selection is shown in **Figure 1**. Finally, 19 case-control studies [25-43] published between 2000 and 2012 comprising 2861 GC cases and 5064 controls met the inclusion criteria. The characteristics of the included studies are summarized in **Table 1**.

Overall analysis

There was evidence of between-study heterogeneity among all included studies ($\chi^2 = 34.39$; $P = 0.011$). Therefore, the random-effects model was used in the overall analysis. The results showed that the pooled OR for GC was 1.20 (95% CI: 1.04-1.38) in Chinese patients with *GSTT1*-null genotype (**Figure 2**).

Subgroup analyses

In the subgroup analysis based on source of control, the results showed that the *GSTT1*-null polymorphism was significantly related to GC risk in population-based studies ($P = 0.006$), but not in hospital-based studies (**Table 2**). With respect to geographic location, significant risk was associated with populations based in south China ($P = 0.019$).

GSTT1-GSTM1 interaction analysis

GC risk was calculated based on *GSTT1-GSTM1* genotype interactions (**Table 3**). Relevant data was extracted from eight studies [26-28, 30, 32, 39, 42, 43]. The non-null genotypes were designated as the reference. There was a significant interaction for Chinese individuals with combined deletion mutations of *GSTT1* and *GSTM1* with respect to GC risk ($P < 0.001$), but also for individuals null for only *GSTM1* ($P = 0.001$).

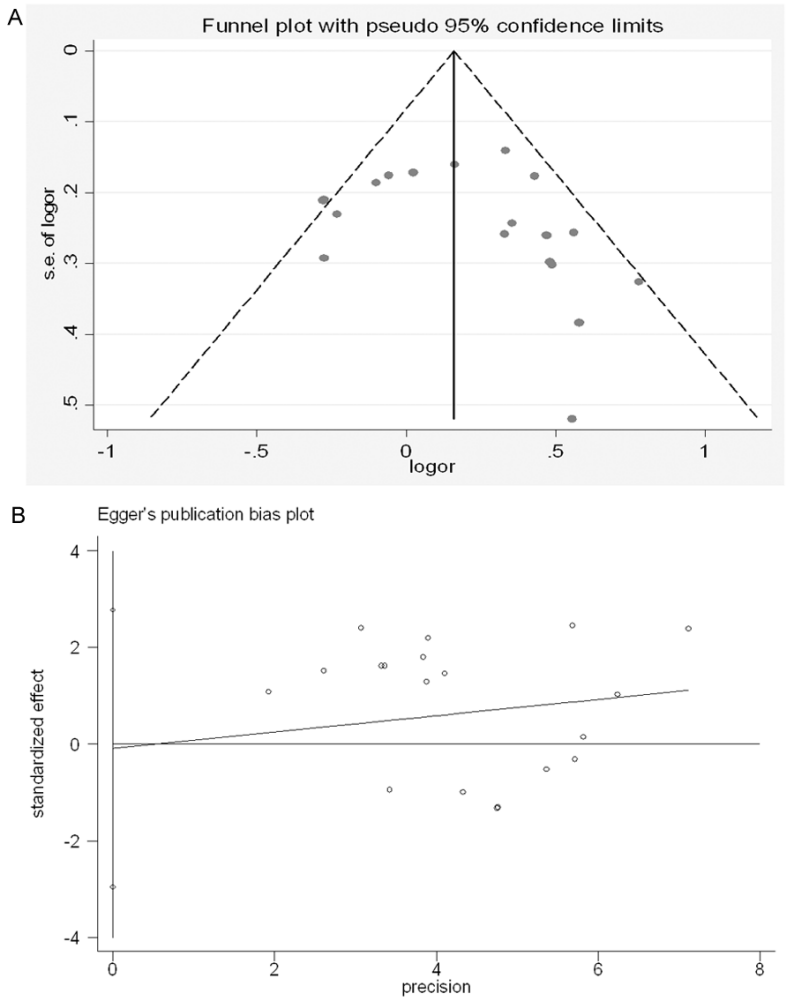

Figure 3. Publication bias evaluations on the association between GSTT1 polymorphism and GC risk in Chinese. A: Funnel plot; B: Egger's test.

Sensitivity analysis and bias

To validate the credibility of the outcomes of this meta-analysis, a sensitivity analysis was performed by comparing results of random-effects and fixed-effects models. None of the results were substantially different with respect to the model type (**Table 2**), indicating that they were relatively stable and credible.

A Begg's funnel plot was constructed and an Egger's test was performed to assess the publication bias of the included studies. As shown in **Figure 3A**, the shape of the funnel plot did not indicate obvious asymmetry. Similarly, the Egger's test indicated no publication bias in the 19 reviewed studies (t = -0.07, P = 0.946) (**Figure 3B**).

Discussion

Previous meta-analyses investigating the role of *GSTT1* polymorphisms in the development of GC in various ethnic groups have led to conflicting or inconclusive results [10-17]. One recent meta-analysis [44] focused on the Chinese population, however, it included three studies [22-24] containing overlapping data. Therefore, the present meta-analysis was conducted by critically reviewing 19 individual studies on *GSTT1* polymorphisms and GC within a Chinese population, and confirms that the *GSTT1*-null genotype is associated with an elevated risk of GC. Moreover, the present study includes subgroup analysis by geographic region. This is an important factor, as previous research has indicated that the distribution of *GSTT1* in populations from northern and southern China is different [45]. Additionally, environment-specific carcinogens may contribute to the enhanced risk afforded by the *GSTT1*-null genotype. Indeed, a significant association with GC development was found among south Chinese study populations.

The results of this meta-analysis also indicate a significant association between the *GSTT1*-null genotype in GC among population-based studies, but not hospital-based studies. This may be due to biases within hospital-based studies as the controls represent an ill-defined reference population, rather than the general population. Importantly, there was significant heterogeneity among the included studies. Additional factors that may have contributed to this include dietary habits, alcohol drinking, smoking status, *H. pylori* infection, family history of cancer, other genetic-related respiratory

diseases, and other related genetic polymorphisms.

As the effect of any single gene likely has a limited impact on GC risk, it is possible that combinations of certain genotypes may be more discriminatory. Thus, the possible interaction between *GSTT1* and *GSTM1* status and GC risk was investigated in this meta-analysis. Eight of the included studies investigated the interaction of *GSTT1-GSTM1* polymorphisms. Results of the meta-analysis show that there is a significant twofold-increased risk for GC in individuals null for both genotypes compared with those with the positive genotypes. This finding is consistent with three previously published meta-analyses by Wang et al [12], Boccia et al [17], and Lao et al [46].

Some limitations of this meta-analysis should be addressed. Firstly, it was not possible to perform subgroup analyses based on smoking status, alcohol drinking or *H. pylori* infection due to the lack of sufficient data. Secondly, the results presented here are based on unadjusted estimates. More precise analyses could be conducted if individual data were available, which would allow for the adjustment by other covariates including age, sex, race, and other factors. Thirdly, the presence of heterogeneity may interfere with the interpretation of the results. However, a careful search of published studies and subgroup analyses were conducted to minimize this.

The findings from this meta-analysis indicate that the *GSTT1*-null polymorphism increases the risk for GC in the Chinese population, especially among individuals living in south China. However, the multifactorial etiology of GC dictates that additional, larger studies in select populations are needed to further evaluate gene-gene and gene-environment interactions with respect to *GSTT1* polymorphisms and GC.

Disclosure of conflict of interest

None.

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