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REVIEW

Glutathione S-Transferase T1 (*GSTT1*) Gene Polymorphism and Gastric Cancer Susceptibility: A Meta-Analysis of Epidemiologic Studies

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Abstract
Purpose Studies investigating the association between genetic polymorphism of glutathione S-transferase T1 (*GSTT1*) and gastric cancer risk have reported conflicting results. Therefore, we conducted this meta-analysis to provide more precise evidence.
Methods We searched the databases Medline, PubMed, Embase, and China National Knowledge Infrastructure up to July 30, 2009. Thirty-six studies with 4,357 gastric cancer cases and 9,796 controls were selected. Odds ratio (OR) and 95% confidence intervals (CI) were calculated based on fixed- and random-effects models.
Results The combined results based on all studies showed there was a significant link between *GSTT1* null genotype and gastric cancer risk (OR = 1.14, 95%CI = 1.01–1.28). In subgroup analysis stratified on the basis of ethnic group, we also observed positive association between *GSTT1* polymorphism and gastric cancer risk among Caucasians (non-Europeans + non-Americans), but not among East Asians. When stratifying by control source, the overall ORs for population- and hospital-based studies were 1.09 (95%CI = 0.94–1.28) and 1.17 (95%CI = 1.03–1.34), respectively. Subjects with both *GSTM1* and *GSTT1* negative genotypes had increased gastric cancer risk compared with those who had nonnull genotypes of both GST genes. Subgroup analyses for *Helicobacter pylori* infection and smoking habit did not reveal any significant association between *GSTT1* polymorphism and gastric cancer development.
Conclusions This meta-analysis suggests that *GSTT1* gene polymorphism may be not associated with increased gastric cancer risk among Europeans, Americans, and East Asians. More large-scale studies based on the same racial group are needed.

Keywords Glutathione S-transferase T1 · Gene polymorphism · Gastric cancer · Meta-analysis

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Introduction

Gastric cancer (GC), the fourth most common cancer and the second most frequent cause of cancer death globally, remains an important public health problem [1, 2]. Although the incidence and mortality rates of GC have declined over the past several decades, it is reported that the number of GC cases globally will increase up to the year 2050 [3]. Previous research data also showed that the incidence rates of GC varied across different geographic regions. At present, 38% of worldwide cases occur in China, and there is also rising incidence in both Eastern Europe and the USA [4, 5]. Therefore, early screening of risk factors may be an effective means of primary prevention for GC.

It is widely accepted that gastric carcinogenesis is a multilevel multifactorial process. Genetic factors are believed to play an important role in the development of GC. Interindividual variations in the genetic and cellular

mechanisms of activation and detoxification of cancer-causing chemicals could confer different degrees of susceptibility to GC [6].

Glutathione S-transferases (GSTs), a supergene family of phase II detoxification enzymes, appear to form a protection mechanism against chemical carcinogenesis [7]. Human cytosolic GSTs are involved in metabolism of many xenobiotics, including an array of environmental carcinogens, chemotherapeutic agents, and endogenously derived reactive oxygen species [8–11]. They have been grouped into at least seven classes called α (alpha), μ (mu), π (pi), σ (sigma), ω (omega), θ (theta), and ζ (zeta) [6, 8]. Glutathione S-transferase T1 (*GSTT1*), a member of the θ class gene family, has been shown to be polymorphic. It has a functional and a nonfunctional allele. Homozygous deletion of *GSTT1* gene (null genotype) causes absence of GSTT1 enzyme activity [9]. In human populations, the frequency of *GSTT1* deficiency is 13–26% and 36–52% in Caucasian and Asian individuals, respectively [10]. Subjects with *GSTT1* null genotype may be genetically predisposed for increased cancer risk.

Over the last two decades, a great number of studies have been carried out to clarify the relation between *GSTT1* polymorphism and GC risk in human. However, previous studies reported conflicting results. In order to clarify the effect of *GSTT1* genotype on the risk of developing GC, we performed an updated meta-analysis of published case-control and cohort studies to better compare results between studies. In this study, we included several additional epidemiologic studies which allowed for a greater number of subjects and hence more detailed and accurate risk estimation than in prior meta-analysis, for which the literature ended in 2005 [6].

Materials and Methods

Literature Search Strategy

We searched the following electronic databases: Medline (1966 to July 2009), PubMed (1950 to July 2009), Embase (1950 to July 2009), and China National Knowledge Infrastructure (CNKI) (1979 to July 2009). The following key words were used: ("glutathione S-transferase" or "GST") and ("gastric" or "stomach") and ("adenocarcinoma*" or "carcinoma*" or "cancer*" or "tumour*" or "neoplasm*"). The search was conducted on human subjects, without restriction on language. The reference lists of reviews and retrieved articles were hand-searched manually at the same time. If more than one article was published by the same author using the same case series, we selected the research with larger sample size [11].

Inclusion and Exclusion Criteria

The following criteria were used to include published case-control and cohort studies: (1) an appropriate description of *GSTT1* status in GC cases and controls; (2) an accurate and explicit quantitative assessment of the relationship between *GSTT1* status and GC; (3) independent studies for human. The reasons for exclusion of studies were: (1) duplicates; (2) not human studies; (3) no raw data available; (4) no controls. We did not consider unpublished reports or abstracts.

Data Extraction

All the available data were extracted from each study by two of the authors (B.C. and L.C.) independently, the data were cross-checked by the research team. All extracted data are presented in Table 1.

Statistical Analysis

Statistical analysis was performed by use of RevMan 5.0.21, which was provided by Cochrane Collaboration. In this meta-analysis, $P < 0.05$ was considered statistically significant. Dichotomous data were presented as odds ratio (OR) with 95% confidence intervals (95%CI). Statistical heterogeneity was checked by use of the χ^2 test ($P < 0.10$ was considered to be representative of statistically significant heterogeneity) [11]. Meta-analysis was performed with the fixed-effects model when there was no heterogeneity of the results of the studies. Otherwise, the random-effects model was used. To establish the effect of clinical heterogeneity between researches on the results of the systematic review, subgroup analysis was performed on the basis of ethnicity, control source, smoking behavior, and so on. Additionally, two methods were used to assess the publication bias: (1) visual inspection of asymmetry in funnel plots; and (2) calculating the number of fail-safes (N_{fs}).

Results

Study Characteristics

There were 656 articles relevant to the search terms. Thirty-six studies were identified for further evaluation after the steps of screening title, scanning the abstract, and reading the entire article [12–47]. The studies had been carried out in China, Japan, Korea, Italy, America, the UK, and so on. Most of the study populations were Asian (Table 1).

Table 1 Characteristics of studies included in the meta-analysis

First author	Year	Source of controls	Ethnicity	Country	*GSTT1* active		*GSTT1* null		Ref.
					Cases	Controls	Cases	Controls	
Agudo A	2006	Population-based	Caucasians	10 European countries	205	801	37	131	12
Al-Moundhri MS	2009	Population-based	Caucasians	Oman	88	87	19	20	13
Boccia S	2007	Hospital-based	Caucasians	Italy	68	197	39	57	14
Cai L	2001	Population-based	Asians	China	54	47	41	47	15
Choi SC	2003	Population-based	Asians	Korea	37	83	43	94	16
Colombo J	2004	Population-based	Caucasians + Negroid	Brazil	83	122	17	28	17
Deakin M	1996	Hospital-based	Caucasians	UK	93	415	21	94	18
Gao CM	2002	Population-based	Asians	China	82	104	71	119	19
Hong SH	2006	Hospital-based	Asians	Korea	63	119	45	119	20
Katoh T	1996	Hospital-based	Asians	Japan	73	70	66	56	21
Lan Q	2001	Population-based	Caucasians	Poland	233	352	60	66	22
Martínez C	2006	Population-based	Caucasians	Spain	49	253	38	76	23
Masoudi M	2009	Hospital-based	Caucasians	Iran	42	96	25	38	24
Moy KA	2009	Population-based	Asians	China	73	320	97	415	25
Mu LN	2005	Population-based	Asians	China	103	201	93	192	26
Nan HM	2005	Hospital-based	Asians	Korea	229	367	171	247	27
Palli D	2005	Population-based	Caucasians	Italy	134	455	41	91	28
Qian Y	2001	Population-based	Asians	China	38	48	51	46	29
Roth MJ	2004	Population-based	Asians	China	47	211	43	243	30
Ruzzo A	2007	Population-based	Caucasians	Italy	67	86	12	26	31
Saadat I	2001	Population-based	Caucasians	Iran	27	90	15	41	32
Setiawan VW	2000	Population-based	Asians	China	37	228	44	190	33
Sgambato A	2002	Hospital-based	Caucasians	Italy	8	82	0	18	34
Shen J	2002	Population-based	Asians	China	67	366	43	309	35
Shen XB	2004	Hospital-based	Asians	China	23	34	37	26	36
Tamer L	2005	Hospital-based	Caucasians	Turkey	49	151	21	53	37
Torres MM	2004	Hospital-based	Caucasians	Colombia	38	82	8	14	38
Tripathi S	2008	Population-based	Caucasians	India	46	77	30	23	39
Wang KY	1998	Hospital-based	Asians	China	47	38	36	45	40
Wideroff L	2007	Population-based	Caucasians	USA	95	173	21	35	41
Wu MS	2002	Hospital-based	Asians	China	175	148	181	130	42
Ye M	2003	Hospital-based	Asians	China	22	30	34	26	43
Zendehdel K	2009	Population-based	Caucasians	Sweden	111	394	13	76	44
Zhang YC	2003	Hospital-based	Asians	China	51	59	76	55	45
Zheng TR	2002	Population-based	Asians	China	43	54	49	38	46
Zhou Q	2003	DNR	Asians	China	9	44	10	28	47

GSTT1 glutathione S-transferase T1; *DNR* data not reported; *Ref* Reference

Overall Analysis

The 36 studies involving 4,357 GC cases and 9,796 controls satisfied the inclusion criteria; 27 were in English, 8 in Chinese, and 1 in Spanish. The combined results based on all studies showed that there was a statistically significant link between *GSTT1* null genotype and GC risk (OR = 1.14, 95%CI = 1.01–1.28, $P = 0.03$). Because the test for heterogeneity among studies was significant ($P = 0.004$, $I^2 = 43\%$), the random-effects model was conducted for the meta-analysis (Fig. 1). Additionally, the funnel plot provided evidence of publication bias (Fig. 2). However, the fail-safe number was large ($N_{fs0.01} = 279$), suggesting that the publication bias probably had little effect on the summary estimates.

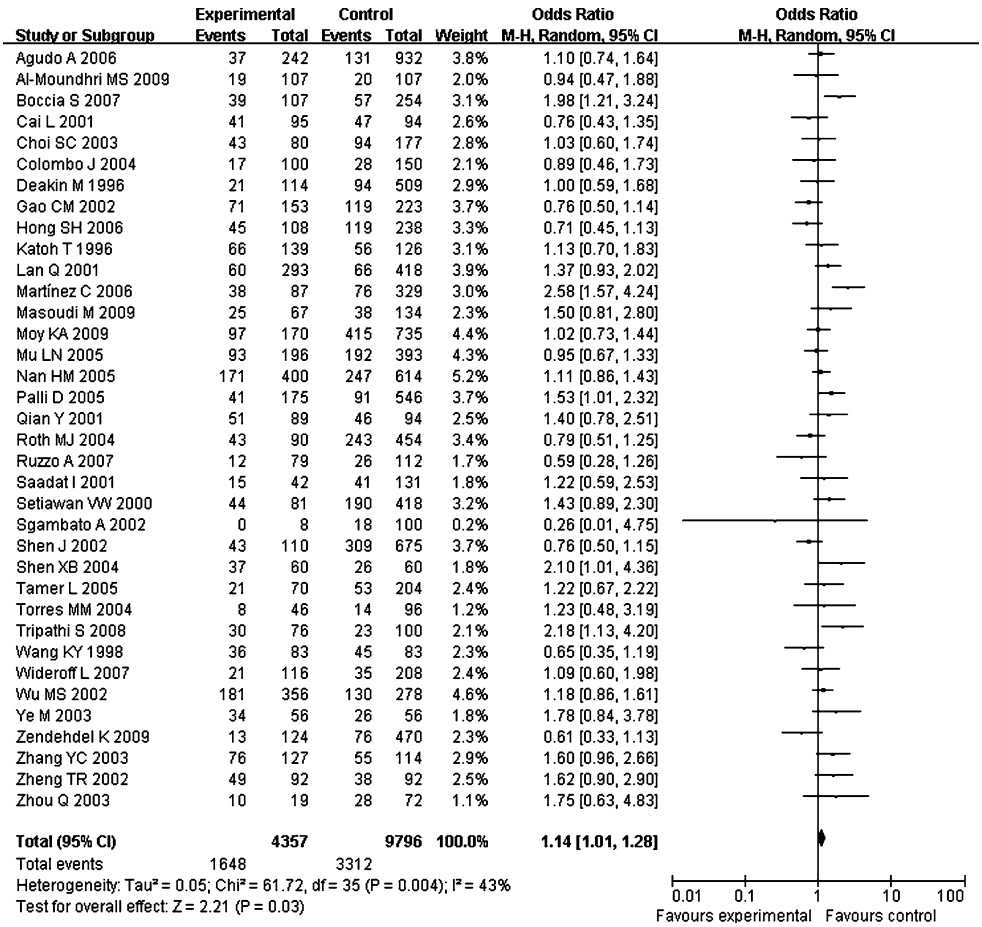

Fig. 1 Meta-analysis of glutathione S-transferase T1 gene polymorphism and gastric cancer risk

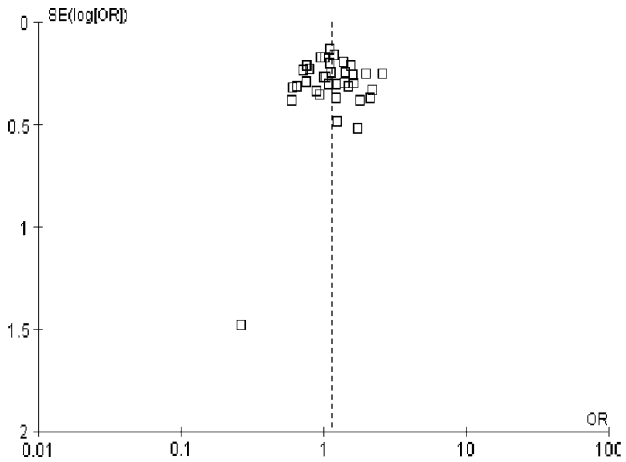

Fig. 2 Funnel plot of the reported studies considered in this meta-analysis

Ethnic Origin (Asians and Caucasians)

When stratifying for race, the pooled result showed there was no significant difference in genotype distribution between GC cases and controls among Asians (OR = 1.05, 95%CI = 0.92–1.20, $P = 0.43$). On the contrary, the OR of 17 studies was 1.27 (95%CI = 1.05–1.53, $P = 0.02$) in the analysis among Caucasians. In addition, very interestingly, we did not observe any significant increase in GC risk among Europeans, Americans, and East Asians with *GSTT1* null genotype.

Control Sources (Hospital- and Population-Based)

Stratifying this meta-analysis by control source, the overall ORs for population-based studies and hospital-based studies were 1.09 (95%CI = 0.94–1.28, $P = 0.26$) and 1.17 (95%CI = 1.03–1.34, $P = 0.02$), respectively. Therefore, with different study designs, we also found statistically significant differences between the GC case and control groups for association between *GSTT1* status and GC risk.

Smoking Status (Ever-Smokers and Nonsmokers)

When stratifying by the smoking status, we noted that there was no increase in risk for ever-smokers (OR = 1.06, 95%CI = 0.76–1.47, $P = 0.74$) or nonsmokers (OR = 1.15, 95%CI = 0.81–1.64, $P = 0.44$) with *GSTT1* null genotype.

Helicobacter pylori (*H. pylori*) Infected and Noninfected

The summary ORs were 0.97 (95%CI = 0.64–1.49, $P = 0.90$) and 1.14 (95%CI = 0.32–4.08, $P = 0.84$) for *H. pylori* infected and noninfected subjects, respectively.

Others

Thirteen studies reported combination genotypes of glutathione S-transferase M1 (*GSTM1*) and *GSTT1* in GC cases and controls. In this subgroup analysis, subjects with both *GSTM1* and *GSTT1* negative genotypes had increased GC risk (OR = 1.96, 95%CI = 1.42–2.70) compared with those who had nonnull genotypes of both GST genes. When stratifying by Lauren's classification of GC, we also noted that no statistically significant results were observed for all analyses. All results are presented in Table 2.

Discussion

The exact mechanisms of human gastric tumorigenesis remain unknown. It is currently accepted that the development of GC results from a complex interaction of both environmental and genetic factors [48, 49]. Genetic predisposition has been suggested to correlate with GC tumorigenesis by epidemiological studies [50, 51]. Until recently, most investigations on genetic polymorphisms and cancer have concerned polymorphisms of xenobiotic-metabolizing enzymes [52]. Most of these studies were based on small sample sizes. Moreover, there are still some conflicting results. A systematic meta-analysis, therefore, may assist in estimating population-wide effects of genetic risk factors in GC tumorigenesis and provide more reliable outcomes [6, 53].

As a powerful statistical method, meta-analysis can provide a quantitative approach for pooling the results of different research on the same topic, and for estimating and explaining their diversity [54, 55]. Based on the accumulated evidence, we performed an updating meta-analysis on 36 case-control and cohort studies.

We found that *GSTT1* null genotype conferred a 1.14-fold statistically significant increased risk of GC in this meta-analysis, and this finding is consistent with prior studies [6, 53]. Another major finding of this study was the different associations of *GSTT1* gene polymorphism with the risk of GC according to race. Differences in the distribution of various ethnicities between cases and controls may be a source of confounding when pooling studies [56, 57]. In this subanalysis, the frequency of *GSTT1* null genotype showed distinct differences among Asians and Caucasians. The pooled OR associated with *GSTT1* gene polymorphism was statistically significant among Caucasians (non-Europeans + non-Americans), but not in East Asians. The discrepancy might be due to genetic background and/or environmental exposure differences. Differences between ethnic groups were also reported in prior

Table 2 Meta-analysis of glutathione S-transferase T1 polymorphism and risk of gastric cancer

Groups	No. of studies	OR (95% CI)	Statistical method	*P*
All studies	36	1.14 (95%CI = 1.01–1.28)	Random	0.03
Caucasians	17	1.27 (95%CI = 1.05–1.53)	Random	0.02
Europeans + Americans	10	1.22 (95%CI = 0.92–1.62)	Random	0.16
Non-Europeans + non-Americans	7	1.31 (95%CI = 1.01–1.70)	Fixed	0.04
Asians	19	1.05 (95%CI = 0.92–1.20)	Random	0.43
Asian countries	24	1.09 (95%CI = 0.97–1.24)	Random	0.15
East Asian countries (East Asians)	19	1.05 (95%CI = 0.92–1.20)	Random	0.43
Non-East Asian countries (Non-East Asians)	5	1.37 (95%CI = 1.02–1.83)	Fixed	0.03
Hospital-based studies	14	1.17 (95%CI = 1.03–1.34)	Fixed	0.02
Population-based studies	21	1.09 (95%CI = 0.94–1.28)	Random	0.26
Nonsmokers	8	1.15 (95%CI = 0.81–1.64)	Random	0.44
Ever-smokers	8	1.06 (95%CI = 0.76–1.47)	Random	0.74
H. pylori infected	2	0.97 (95%CI = 0.64–1.49)	Fixed	0.90
H. pylori non-infected	2	1.14 (95%CI = 0.32–4.08)	Random	0.84
Combination of genotypes[a]	13	1.96 (95%CI = 1.42–2.70)	Random	<0.0001
Intestinal type	4	0.57 (95%CI = 0.20–1.60)	Random	0.28
Diffuse type	4	0.97 (95%CI = 0.64–1.47)	Fixed	0.89

OR odds ratio; *CI* confidence interval; *H. pylori Helicobacter pylori*

[a] Both *GSTM1* and *GSTT1* null genotypes versus nonnull genotypes of both *GSTM1* and *GSTT1*

studies concerning GST genotypes at risk of GC [6, 11, 48, 53]. It should be noted that: (1) The Caucasian reports in the subgroup analysis included a mixture of populations; and (2) The *VacA* and *CagA* genotypes of *H. pylori* and the prevalence of *H. pylori* infection vary between different populations and ethnic groups [58]. Also, other environment factors may affect the GC risk. In this context, the true association between the risk of GC and *GSTT1* null genotype may be masked. Therefore, these findings must be interpreted with caution.

Results of meta-analyses often depend on control selection procedures [59]. *GSTT1* null genotype frequency might have differed between the two control sources (hospital-based and population-based) (Table 1). In subgroup analysis stratified on the basis of different study designs, we found that use of hospital-based controls resulted in a significantly stronger association between *GSTT1* null genotype and development of GC than did use of population-based controls.

It is now widely accepted that cigarette smoking and *H. pylori* infection are obvious risk factors for development of GC. By pooling the available data from eight articles that evaluated associations and interaction between *GSTT1* genotype and smoking on GC risk, the *GSTT1* null genotype was not associated with increased risk of GC in either ever-smokers or nonsmokers. This finding was similar to that of a recent meta-analysis which focused on colorectal cancer risk [60]. Regarding *H. pylori* infection, unfortunately, there were only two studies that mentioned the *H. pylori* infection status of their subjects. In previous studies, conflicting results had been reported on the possible effect of *H. pylori* status in modifying the contribution of polymorphisms to GC risk [61–64]. In this meta-analysis, we also found that *GSTT1* null genotype was not significantly associated with GC risk in either *H. pylori*(+) or *H. pylori*(−) groups. However, because of the limited study sample size, these results should be considered with care.

Because both *GSTM1* and *GSTT1* are expressed in normal stomach tissue, the effects of their overlapping substrate specificities and detoxification of carcinogens involved in GC susceptibility might be additive [28, 48, 65–67]. Therefore, we conducted an evaluation of combination effect of the two genes. Pooling data from 13 articles showed that subjects with combined deletion mutations in *GSTM1* and *GSTT1* genotypes had an OR of 1.96 ($P < 0.0001$) for GC in comparison with individuals carrying nonnull genotypes of both GST genes (*GSTM1* and *GSTT1*).

There are several limitations to this meta-analysis: (1) As carcinogenesis is influenced by a multitude of genes, any single genetic polymorphism affecting GC risk is expected to make a small contribution at the level of the individual [52]. (2) Because many environmental factors may affect the GC risk (e.g., geographic variation in *H. pylori* strain types and infection rates, eating habit differences), all our findings may be due to the context of the gene within other factors. (3) This study encountered difficulties that are common to most meta-analyses (e.g., not searching for unpublished studies, the relatively small sample size in some subgroup analyses). (4) Some results should be interpreted with care, because the populations from different countries and controls were not uniform. (5) Because of the lack of individual patient data, we could not conduct an adjustment estimate (by age, gender and dietary information). (6) This meta-analysis was based on studies with obvious heterogeneity, and homogeneous studies might provide more precise evidence.

In summary, this meta-analysis suggests that *GSTT1* gene polymorphism may be not associated with increased gastric cancer risk among Europeans, Americans, and East Asians. Stratified analysis according to hospital-based controls showed positive association. Additional analysis based on combined genotypes demonstrated that there was a more significant relationship between the *GSTM1* null, *GSTT1* null genotype polymorphisms and GC susceptibility. Because more than half of the included studies provided a small number of participants, and obvious heterogeneity among included studies was observed, more large-scale and well-designed epidemiological studies based on the same racial group are needed.

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