GSTMI 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 GSTMI null genotype and gastric cancer in People’s Republic of China, this association remains elusive and controversial. To clarify the effects of the GSTMI 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 GSTMI 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 GSTMI 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, GSTMI, 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 GSTMI plays an important role in the detoxification of xenobiotics. The most common genotype of GSTMI 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...
susceptibility to cancer. An association between the GSTM1 null genotype and gastric cancer was first reported by Strange et al in 1991 among Britain’s population. As a consequence, many studies analyzed the influence of the GSTM1 null genotype on gastric cancer risk; however, no clear consensus was reached. Meta-analyses of studies of the GSTM1 null genotype in other ethnic groups have been reported elsewhere and produced conflicting results. 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.

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. 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 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 (χ²=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 Null genotype | Non-null | Control Null genotype | Non-null | Quality score |
|-------------|--------------------|------|-------------|----------------|--------------------|----------|-----------------------|----------|---------------|
| Cai et al14 | PB                 | Fujian | 95          | 94             | 60                 | 35       | 43                    | 51       | 6             |
| Gao et al17 | PB                 | Jiangsu | 153         | 223            | 90                 | 63       | 133                   | 90       | 7             |
| Gong et al18| PB                 | Anhui | 32          | 88             | 25                 | 7        | 50                    | 38       | 7             |
| Huang et al19| PB                 | Guangxi | 121         | 138            | 66                 | 55       | 54                    | 84       | 8             |
| Jiang et al20| HB                | Liaoning | 41          | 41             | 24                 | 17       | 14                    | 27       | 6             |
| Jing et al21| PB                 | Sichuan | 410         | 410            | 240                | 170      | 207                   | 203      | 8             |
| Lai et al22 | PB                 | Taiwan | 123         | 121            | 73                 | 50       | 55                    | 66       | 7             |
| Li et al23  | HB                 | Shandong | 100        | 62             | 67                 | 33       | 26                    | 36       | 6             |
| Liu et al24 | PB                 | Liaoning | 99          | 364            | 63                 | 36       | 186                   | 178      | 8             |
| Luo et al25 | PB                 | Hunan | 123         | 129            | 93                 | 30       | 71                    | 58       | 7             |
| Moy et al26 | PB                 | Shanghai | 170       | 735            | 98                 | 72       | 415                   | 320      | 7             |
| Mu et al27  | PB                 | Jiangsu | 196         | 393            | 127                | 69       | 235                   | 158      | 8             |
| Qian et al28| PB                 | Jiangsu | 89          | 94             | 55                 | 34       | 44                    | 50       | 7             |
| Roth et al29| PB                 | Henan | 89          | 454            | 23                 | 66       | 145                   | 309      | 8             |
| Setiawan et al30| PB        | Jiangsu | 87          | 419            | 42                 | 45       | 212                   | 207      | 8             |
| Shen et al31| PB                 | Jiangsu | 112         | 675            | 71                 | 41       | 361                   | 314      | 8             |
| Shen et al32| HB                 | Jiangsu | 121         | 121            | 54                 | 67       | 41                    | 80       | 6             |
| Wang et al33| PB                 | Hainan | 129         | 138            | 39                 | 90       | 26                    | 112      | 8             |
| Wu et al34  | HB                 | Taiwan | 356         | 278            | 173                | 183      | 136                   | 142      | 7             |
| Zhang et al35| PB                 | Guangdong | 194       | 412            | 105                | 89       | 194                   | 218      | 6             |
| Zhang et al36| PB                 | Hubei | 127         | 114            | 78                 | 49       | 53                    | 61       | 8             |
| Zheng et al37| PB                 | Fujian | 92          | 92             | 64                 | 28       | 48                    | 44       | 8             |
| Zheng et al38| HB                | Fujian | 313         | 192            | 145                | 168      | 86                    | 106      | 7             |
| Zhou et al39| PB                 | Henan | 19          | 72             | 7                  | 12       | 28                    | 44       | 6             |
| Zhou et al40| PB                 | Shandong | 100       | 62             | 67                 | 33       | 26                    | 36       | 6             |

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

Table 2 Main results in the total and subgroup analysis

| Subgroups                        | n   | Random-effect model OR (95% CI) | Fixed-effect model OR (95% CI) | Heterogeneity |
|----------------------------------|-----|--------------------------------|--------------------------------|---------------|
| 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.

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.
null variant with gastric cancer in the Chinese population. To our knowledge, our study represented the first meta-analysis with a large sample size on the interaction of this update meta-analysis by critically reviewing 25 individual studies on the association between the null genotype and gastric cancer risk. Therefore, we conducted this update meta-analysis by critically reviewing 25 individual studies on the association between the null genotype and gastric cancer risk. 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.

**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.

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. 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, 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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