Association of the Glutathione S-Transferase M1, T1 Polymorphisms with Cancer: Evidence from a Meta-Analysis

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Abstract

Background: Glutathione S-transferases (GSTs) are a family of multifunctional enzymes that are involved in the metabolism of many xenobiotics, including a wide range of environmental carcinogens. While the null genotypes in GSTM1 and GSTT1 have been implicated in tumorigenesis, it remains inconsistent and inconclusive. Herein, we aimed to assess the possible associations of the GSTM1 and GSTT1 null genotype in cancer risks.

Methods: A meta-analysis based on 506 case-control studies was performed. Odds ratios (OR) with corresponding 95% confidence intervals (CIs) were used to assess the association.

Results: The null genotypes of GSTM1 and GSTT1 polymorphisms were associated with a significantly increased risk in cancer (for GSTM1: OR = 1.17; 95%CI = 1.14–1.21; for GSTT1: OR = 1.16; 95%CI = 1.11–1.21, respectively). When the analysis was performed based on their smoking history, the risk associated of GSTM1 null and GSTT1 null genotypes with cancer is further increased (for GSTM1: OR = 2.66; 95%CI = 2.19–3.24; for GSTT1: OR = 2.46; 95%CI = 1.83–3.32, respectively).

Conclusions: These findings indicate that GSTM1 and GSTT1 polymorphisms may play critical roles in the development of cancer, especially in smokers.

Introduction

Glutathione S-transferases (GSTs) are a superfamily of phase II drug-metabolizing enzymes that are involved in the metabolism of many xenobiotics, including a variety of environmental carcinogens by catalyzing the conjugation of glutathione to electrophilic compounds [1]. GSTs also play an vital role in modulating the induction of other enzymes and proteins for cellular functions, for example DNA repair, and are therefore important in maintaining genomic integrity [1]. Cytoplasmic GSTs are classified into eight subfamilies: alpha, kappa, mu, omega, pi, sigma, theta, and zeta [2]. Previous studies showed that a homozygous deletion or null genotype, at either the GSTM1 locus or the GSTT1 locus resulted in enzyme function loss, and thus it was hypothesized to be related to the susceptibility to cancer [1,3]. Although some genetic variants in several of the GST gene families have been identified, most attentions have been focused on GSTM1 (encoding the mu class) and GSTT1 (encoding the theta class). GSTM1 and GSTT1 genes have a common variant of homozygous deletion (null genotype), which increases vulnerability to cytogenetic damage [4]. Over the past decades, an increasing number of studies have investigated the association between GSTM1 or GSTT1 polymorphisms and cancer risk in human. Given the biological function of GSTs, many epidemiological studies have focused on the association of GSTM1 and GSTT1 polymorphisms with cancer risk in human. However, the results from different studies are to some extent divergent, which may be attributing to limitations in individual studies [5–12]. Hence, we performed a meta-analysis with subgroup analysis of eligible studies to acquire more accurate estimation of the association of GSTM1 or GSTT1 with cancer risk.

Materials and Methods

Identification and Eligibility of Relevant Studies

All case-control studies on the association of the GSTM1 null or GSTT1 null polymorphisms with cancer risk published up to February 1, 2013 were identified through comprehensive searches using the PubMed database with the following terms and
keywords: “GSTM1”, “glutathione S-transferase M1”, “GSTT1”, “glutathione S-transferase T1” and “polymorphism”, “variation”, “mutation” and in combination with “cancer”, “tumor” and “carcinoma”. The search was limited to human studies and language in English.

Inclusion Criteria
The following criteria were used for the study selection: (a) a case–control study evaluating at least one of these two polymorphisms (GSTM1 and GSTT1) and cancer risk; (b) using a case-control design; (c) no overlapping data. For the same or overlapping data in the studies published by the same investigators, we selected the most recent study with a larger number of population; (d) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (95% CI). The exclusion criteria are as follows: (a) not for cancer research; (b) review articles; (c) reports without usable data; (d) duplicate publications.

Data Extraction
Information was carefully extracted from all the eligible publications independently by two researchers [F. S. and S. W] according to the inclusion criteria listed above. For conflicting evaluation, a consensus was reached by a third reviewer SLZ. The following data were collected from each study (Checklist S1), (Reference in File S1): first author’s name, publication date, country, ethnicity, cancer type, genotyping method, source of controls (population-based [PB] or hospital-based [HB] controls), total numbers of cases and controls and number of cases and controls for GSTM1 or GSTT1 polymorphism. Different ethnic descents were categorized as Caucasian, Asian, African and Mixed. Meanwhile, different case-control groups in one study were considered as independent studies.

Statistical Methods
The strength of association between either GSTM1 or GSTT1 polymorphisms and cancer risk was measured by ORs with 95% confidence intervals (CIs). The percentage weight determined by polymorphisms and cancer risk was measured by ORs with 95% confidence interval (95% CI). The exclusion criteria are as follows: (a) not for cancer research; (b) review articles; (c) reports without usable data; (d) duplicate publications.

Results

合格的 Studies and Meta-analysis Databases
There were 506 studies retrieved on the basis of the search criteria (Fig. 1). A total of 496 studies [113,631 cases and 155,007 controls] for GSTM1 polymorphism and 384 studies [94,740 cases and 126,414 controls] for GSTT1 polymorphism were selected in the meta-analysis. Study characteristics were summarized in Table S1. For GSTM1 polymorphism, there were a total of 254 Caucasians, 176 Asians, 4 Africans and 62 mixed descendants. Controls were selected with matched sex and age, including 348 hospital-based and 148 population-based studies. For GSTT1 polymorphism, here were 205 Caucasians, 123 Asians, 3 Africans and 53 mixed descendants. The sex and age matched controls include 261 hospital-based and 123 population-based studies. Cancers were clinically diagnosed and confirmed by histological or pathologically stated in the original article. Study characteristics are summarized in Table 1.

Quantitative Synthesis
The relationship between the GSTM1 or GSTT1 polymorphisms and the risk of different kinds of cancer are summarized in Table 1.

GSTM1
Overall, a significant increased risk of cancer is associated with the GSTM1 polymorphism (null vs. present: OR = 1.17, 95%CI = 1.14–1.21, p<0.001). In the subgroup analysis by ethnicity, the results indicated that individuals with GSTM1 null genotype had a significantly higher cancer risks among Caucasians (null vs. present: OR = 1.14, 95%CI = 1.09–1.18, p<0.001), Asians (null vs. present: OR = 1.26, 95%CI = 1.19–1.33, p<0.001) and the mixed descendants (null vs. present: OR = 1.14, 95%CI = 1.09–1.18, p<0.001).

Figure 1. Studies identified with criteria for inclusion and exclusion.

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null polymorphisms and smoking in the population. A 2-tailed P value less than 0.05 was considered as significant. All statistical analyses were performed with the Stata software (version 12.1; Stata Corp LP, College Station, TX, USA).
OR = 1.12, 95%CI = 1.03–1.23, p < 0.001), but not for Africans (null vs. present: OR = 0.93, 95%CI = 0.77–1.12, p = 0.42). This is possibly because that the sample numbers of Africans are relatively small. When restricting the analysis to the source of controls, significant associations were discovered both in the hospital-based source (null vs. present: OR = 1.23, 95%CI = 1.18–1.29, p < 0.001) and population-based source (null vs. present: OR = 1.07, 95%CI = 1.04–1.11, p < 0.001). In the stratified analysis by cancer types, significant associations (null vs. present) were found in prostate cancer (OR = 1.34, 95%CI = 1.17–1.54, p < 0.001), colorectal cancer (OR = 1.11, 95%CI = 1.04–1.19, p = 0.001), breast cancer (OR = 1.12, 95%CI = 1.06–1.18, p < 0.001), bladder cancer (OR = 1.38, 95%CI = 1.26–1.51, p < 0.001), lung cancer (OR = 1.13, 95%CI = 1.06–1.20, p < 0.001), acute lymphocytic leukemia (OR = 1.38, 95%CI = 1.08–1.76, p = 0.001), gastric cancer (OR = 1.24, 95%CI = 1.08–1.41, p < 0.001), head and neck cancer (OR = 1.32, 95%CI = 1.17–1.47, p < 0.001) and nasopharyngeal carcinoma (OR = 1.33, 95%CI = 1.13–1.56, p < 0.001).

### Table 1. Stratification analyses of the GSTM1 and GSTT1 polymorphism on cancer.

| Variables                      | Sample size   | GSTM1 null vs. GSTM1 present | Sample size   | GSTT1 null vs. GSTT1 present |
|--------------------------------|---------------|------------------------------|---------------|------------------------------|
|                                | N*            | OR (95% CI)                  | N*            | OR (95% CI)                  |
| **Total**                      |               | 1.17 (1.14–1.21)             | 1.16 (1.11–1.21) | < 0.001                      |
| **Tumor type**                 |               |                              |               |                              |
| Hodgkin lymphoma               | 4             | 0.54 (0.17–1.74)             |               |                              |
| Prostate cancer                | 34            | 1.34 (1.17–1.54)             | 27            | 1.05 (0.90–1.22)             |
| Colorectal cancer              | 40            | 1.11 (1.04–1.19)             | 32            | 1.13 (1.02–1.27)             |
| Breast cancer                  | 58            | 1.12 (1.06–1.16)             | 42            | 1.10 (1.02–1.19)             |
| Bladder cancer                 | 41            | 1.38 (1.26–1.51)             | 32            | 1.12 (0.98–1.29)             |
| Ovarian cancer                 | 8             | 1.08 (0.90–1.29)             | 6             | 1.00 (0.86–1.15)             |
| Chronic myelogenous leukemia   | 4             | 0.93 (0.66–1.32)             | 4             | 1.57 (0.90–2.74)             |
| Lung cancer                    | 87            | 1.13 (1.06–1.20)             | 52            | 1.11 (1.01–1.22)             |
| Acute myeloblastic leukemia     | 7             | 1.15 (0.84–1.57)             | 7             | 1.24 (0.96–1.61)             |
| Melanoma                       | 4             | 0.93 (0.79–1.10)             | 4             | 1.08 (0.87–1.35)             |
| Acute lymphoid leukemia         | 11            | 1.38 (1.08–1.76)             | 8             | 1.07 (0.82–1.39)             |
| Renal cell carcinoma           | 7             | 0.98 (0.84–1.14)             | 8             | 1.17 (0.88–1.53)             |
| Gastric cancer                 | 29            | 1.24 (1.08–1.41)             | 25            | 1.26 (1.04–1.49)             |
| Leukemia                       | 5             | 1.12 (0.82–1.54)             | 5             | 1.29 (0.88–1.91)             |
| Head and Neck cancer           | 59            | 1.32 (1.17–1.47)             | 46            | 1.16 (1.02–1.33)             |
| Endometrial cancer             | 4             | 0.96 (0.68–1.34)             | 4             | 1.07 (0.69–1.66)             |
| Nasopharyngeal carcinoma       | 5             | 1.33 (1.13–1.56)             |               |                              |
| Cervical cancer                | 12            | 1.28 (0.97–1.70)             | 11            | 1.38 (0.99–1.93)             |
| Esophageal cancer              | 21            | 1.12 (0.92–1.36)             | 15            | 0.95 (0.81–1.11)             |
| Hepatocellular carcinoma       | 13            | 1.07 (0.77–1.49)             | 10            | 1.23 (0.87–1.74)             |
| Pancreatic cancer              | 4             | 0.94 (0.78–1.13)             |               |                              |
| Thyroid cancer                 | 9             | 1.04 (0.85–1.28)             | 8             | 1.24 (0.82–1.89)             |
| Brain tumor                    | 6             | 1.05 (0.85–1.30)             | 6             | 1.10 (0.92–1.32)             |
| Others<sup>b</sup>             | 24            | 1.13 (0.98–1.31)             | 32            | 1.41 (1.12–1.77)             |
| **Ethnicity**                  |               |                              |               |                              |
| Caucasian                      | 254           | 1.14 (0.99–1.18)             | 205           | 1.19 (1.12–1.25)             |
| Asian                          | 176           | 1.26 (1.19–1.33)             | 123           | 1.14 (1.07–1.23)             |
| Mixed                          | 62            | 1.12 (1.03–1.23)             | 53            | 1.10 (0.99–1.21)             |
| African                        | 4             | 0.93 (0.77–1.12)             | 3             | 0.94 (0.53–1.67)             |
| **Control source**             |               |                              |               |                              |
| Hospital based                 | 348           | 1.23 (1.18–1.29)             | 261           | 1.20 (1.14–1.27)             |
| Population based               | 148           | 1.07 (1.04–1.11)             | 123           | 1.08 (1.03–1.14)             |
| **Sample size (both cases and controls)** | | | | |
| ≤ 500                          | 331           | 1.24 (1.19–1.30)             | 248           | 1.18 (1.12–1.25)             |
| > 500                          | 165           | 1.09 (1.05–1.14)             | 136           | 1.13 (1.07–1.19)             |

<sup>a</sup> Number of studies.
<sup>b</sup> Cancer less than 3 case-control studies.

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GSTT1

Similar to GSTM1, a dramatic increase in the cancer risk is associated with the GSTT1 polymorphism (null vs. present: OR = 1.16, 95%CI = 1.11–1.21, p = 0.001). We also performed a subgroup analysis stratified by ethnicity, source of control and cancer type. By ethnicity, statistically significant association was detected in Caucasians (null vs. present: OR = 1.19, 95%CI = 1.12–1.25, p < 0.001) and Asians (null vs. present: OR = 1.14, 95%CI = 1.07–1.23, p = 0.001). By the source of controls, both hospital-based (null vs. present: OR = 1.20, 95%CI = 1.14–1.27, p = 0.001) and population-based control (null vs. present: OR = 1.00, 95%CI = 1.03–1.14, p < 0.001) had a statistical significance. In the subgroup analysis stratified by cancer type, significant associations (null vs. present) were found in colorectal cancer (OR = 1.13, 95%CI = 1.02–1.27, p < 0.001), breast cancer (OR = 1.10, 95%CI = 1.02–1.19, p < 0.001), lung cancer (OR = 1.11, 95%CI = 1.01–1.22, p < 0.001), gastric cancer (OR = 1.26, 95%CI = 1.10–1.44, p = 0.002), head and neck cancer (OR = 1.16, 95%CI = 1.02–1.33, p < 0.001), and others cancer (OR = 1.41, 95%CI = 1.12–1.77, p < 0.001).

Smoking

Since smoking has been considered as a risk factor for some types of cancers, we asked whether the GSTM1 or GSTT1 null genotype further facilitates cancer risk in the population of smokers. To answer this question, we performed an analyses stratified for smoking in order to assess whether the GSTM1 or GSTT1 null genotype influence on cancer differently for smokers. Study characteristics were summarized in Table S2. The meta-analysis and pooled analysis indicated that both GSTM1 null genotype (null vs. present: OR = 2.66; 95%CI = 2.19–3.14) and GSTT1 null genotype (null vs. present: OR = 2.46; 95%CI = 1.83–3.32) were associated with an increased cancer risk in smokers (Table 2). These results indicate that smoking should be considered to influence the effect of both GSTM1 and GSTT1 null genotypes on tumor development.

Heterogeneity Analysis

There was significant heterogeneity for GSTM1 allele contrast (null vs. present: P < 0.001). Therefore, we used a meta-regression analysis to explore the source of heterogeneity for homoyzogate comparison (null vs. present) by Ethnicity, cancer types, source of controls and sample size. We found that the sample size (t = –3.32, P = 0.001) as well as the source of control (t = –3.88, P < 0.001) contributed to substantial altered heterogeneity. However, we did not find cancer types (t = –1.4, P = 0.162), or ethnicity (t = –0.06, P = 0.951) contributed to source of heterogeneity. Similarly, we found the source of control (t = –2.03, P = 0.043) contributed to substantial heterogeneity in GSTT1.

Publication Bias

Begg’s funnel plot and Egger’s test were performed to assess the publication bias. As shown in the Fig. 2, the shapes of the funnel plots seems asymmetrical in both GSTM1 and GSTT1 genotypes (GSTM1: P < 0.001; GSTT1: P = 0.003). Thus, the Egger’s test was used to provide statistical evidence of funnel plot symmetry. The both genotypes showed significant publication bias (GSTM1: t = 4.97, P < 0.001; GSTT1: t = 2.88, P = 0.004). To adjust this bias, a trim-and-fill method developed by Duval and Tweedie was used to both identify and correct for funnel plot asymmetry arising from publication bias. We filled in the asymmetric outlying part of the funnel after estimating how many studies were in the asymmetric part with the help of Stata software. Results in figure 2 showed that 60 studies should be filled after iterations. We then estimated the true center of the funnel, the true mean, and its 95%CI, based on the filled funnel plot. The OR estimates and 95%CI of GSTM1 in fixed-effect model before and after trim-and-fill were 1.132, (1.114–1.150) and 1.081, (1.065–1.098). Also, for random-effect model, the results were 1.173, (1.138–1.209) and 1.085, (1.050–1.122). Meta-analysis with or without the trim-and-fill method did not yield any different conclusions, indicating that our results in GSTM1 were statistically robust. In GSTT1, no studies were filled, as a consequence, no changes were observed before or after trim-and-fill method, which also indicates high reliability.

In conclusion, this meta-analysis demonstrates that GSTM1 and GSTT1 null genotypes are risk factors in multiple types of cancers. We also identified that smoking further increases the cancer risk, interestingly not only to lung cancers, in people with either GSTM1 or GSTT1 null genotypes.

Discussion

GSTs are the most important parts of phase II superfamily of metabolism enzymes. In humans, there are several GST classes that were encoded by distinct gene families [2]. Among them, GSTM1 and GSTT1 should be pointed out because a polymorphic deletion of these genes may influence the enzyme activity, and eventually increased vulnerability to genotoxic damage [15]. GSTs play a major role in cellular antimutagen and antioxidant defense mechanisms, and these enzymes may regulate pathways that prevent damage from several carcinogens. High levels of GSTs have been shown to detoxify several chemical carcinogens efficiently and to protect tissues against DNA damage [16,17]. Individuals with homozygous deletions of GSTM1 or GSTT1 lack GSTs and therefore may be unable to eliminate electrophilic carcinogens efficiently, which may increase the risk of somatic mutations that lead to tumor formation. Based on these backgrounds, the association between GSTM1 and GSTT1 has been intensively investigated polymorphisms and risk of a variety of cancer, but the results remain contradictory. The individual studies might have been underpowered to detect the overall effect of polymorphisms on the susceptibility of cancer. Meta-analysis has been considered to be a relative powerful tool to solve this problem by combining the results from independent studies together. To the best of our knowledge, this is the first meta-analysis with the largest and most comprehensive assessment for the relationship between the GSTM1 and GSTT1 polymorphisms and the cancer risk.

Table 2. Odds ratios for cancer with smoking status combinations of GST genotypes.

| Variables    | Smoking status | Cases | Controls | OR(95%CI) |
|--------------|----------------|-------|----------|-----------|
| GSTM1 present | Non-smokers    | 2830  | 6013     | 1(Reference) |
|              | Smokers        | 5377  | 6597     | 2.14(1.80–2.55) |
| GSTM1 null   | Non-smokers    | 2916  | 5512     | 1.28(1.16–1.41) |
|              | Smokers        | 5719  | 6304     | 2.66(2.19–3.24) |
| GSTT1 present| Non-smokers    | 4009  | 6707     | 1(Reference) |
|              | Smokers        | 7440  | 8093     | 2.16(1.72–2.70) |
| GSTT1 null   | Non-smokers    | 1575  | 2314     | 1.14(0.94–1.40) |
|              | Smokers        | 2501  | 2919     | 2.46(1.83–3.32) |

Begg’s funnel plot and Egger’s test were performed to assess the publication bias. As shown in the Fig. 2, the shapes of the funnel plots seem asymmetrical in both GSTM1 and GSTT1 genotypes (GSTM1: P < 0.001; GSTT1: P = 0.003). Thus, the Egger’s test was used to provide statistical evidence of funnel plot symmetry. The both genotypes showed significant publication bias (GSTM1: t = 4.97, P < 0.001; GSTT1: t = 2.88, P = 0.004). To adjust this bias, a trim-and-fill method developed by Duval and Tweedie was used to both identify and correct for funnel plot asymmetry arising from publication bias. We filled in the asymmetric outlying part of the funnel after estimating how many studies were in the asymmetric part with the help of Stata software. Results in figure 2 showed that 60 studies should be filled after iterations. We then estimated the true center of the funnel, the true mean, and its 95%CI, based on the filled funnel plot. The OR estimates and 95%CI of GSTM1 in fixed-effect model before and after trim-and-fill were 1.132, (1.114–1.150) and 1.081, (1.065–1.098). Also, for random-effect model, the results were 1.173, (1.138–1.209) and 1.085, (1.050–1.122). Meta-analysis with or without the trim-and-fill method did not yield any different conclusions, indicating that our results in GSTM1 were statistically robust. In GSTT1, no studies were filled, as a consequence, no changes were observed before or after trim-and-fill method, which also indicates high reliability.

In conclusion, this meta-analysis demonstrates that GSTM1 and GSTT1 null genotypes are risk factors in multiple types of cancers. We also identified that smoking further increases the cancer risk, interestingly not only to lung cancers, in people with either GSTM1 or GSTT1 null genotypes.

Discussion

GSTs are the most important parts of phase II superfamily of metabolism enzymes. In humans, there are several GST classes that were encoded by distinct gene families [2]. Among them, GSTM1 and GSTT1 should be pointed out because a polymorphic deletion of these genes may influence the enzyme activity, and eventually increased vulnerability to genotoxic damage [15]. GSTs play a major role in cellular antimutagen and antioxidant defense mechanisms, and these enzymes may regulate pathways that prevent damage from several carcinogens. High levels of GSTs have been shown to detoxify several chemical carcinogens efficiently and to protect tissues against DNA damage [16,17]. Individuals with homozygous deletions of GSTM1 or GSTT1 lack GSTs and therefore may be unable to eliminate electrophilic carcinogens efficiently, which may increase the risk of somatic mutations that lead to tumor formation. Based on these backgrounds, the association between GSTM1 and GSTT1 has been intensively investigated polymorphisms and risk of a variety of cancer, but the results remain contradictory. The individual studies might have been underpowered to detect the overall effect of polymorphisms on the susceptibility of cancer. Meta-analysis has been considered to be a relative powerful tool to solve this problem by combining the results from independent studies together. To the best of our knowledge, this is the first meta-analysis with the largest and most comprehensive assessment for the relationship between the GSTM1 and GSTT1 polymorphisms and the cancer risk.
In the present study, we examined the association between *GSTM1* and *GSTT1* null genotypes and cancer risk and assessed the multiplicative interactions among *GSTM1*, *GSTT1*, and smoking status. Our results demonstrated that these two polymorphisms are significant associated with cancer risk when all studies were pooled together. Stratified analysis by cancer type for these two polymorphisms indicated that the *GSTM1* null genotype was significantly associated with increased cancer risks for prostate cancer, colorectal cancer, breast cancer, bladder cancer, lung cancer, ALL, gastric cancer, head and neck cancer, and nasopharyngeal carcinoma. These results are in agreement with the previous meta-analysis [11,18–25]. Meanwhile, our results indicated that the *GSTT1* null genotype may be a risk factor for colorectal cancer, breast cancer, lung cancer, gastric cancer, head and neck cancer, “others cancers”, and not for prostate cancer, bladder cancer and ALL. But Yang et al [26] and Gong at al [7] results indicated that *GSTT1* null genotype was significantly increased prostate cancer and bladder cancer risk, respectively. Conflicting results might be owing to that our studies with relative small sample sizes may be underpowered for detecting the real association. Larger studies are needed to testify whether the *GSTM1* or *GSTT1* polymorphisms could truly impact on different types of cancer.

Figure 2. Begg’s funnel plot of publication bias test. (Each point represents a separate study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line, mean effect size. doi:10.1371/journal.pone.0078707.g002
In the subgroup analysis by ethnicity suggested that a possible association between the null genotype of GSTM1 and GSTT1 with higher risk of cancer in Asians and Caucasians but not in Africans. But some studies [6,7,18,27,28] indicated that there was an obviously difference between either GSTM1 or GSTT1 polymorphisms and ethnicity, especially in Asians and Caucasians. For some cancer, the different susceptibility in cancer in Asians and Caucasians perhaps exist, but unlikely for total cancer. In African group, the sample size and numbers of researches were not adequate to assess the association. Other factors such as selection bias may contribute to it. Hence, the results should be interpreted with caution.

We reviewed here published papers where an estimate of gene–smoking interaction between GSTM1 or GSTT1 polymorphisms and cancer risk was available. Our study suggests that the GSTM1 and GSTT1 null genotype significantly increase the carcinogenic effect in patients with smoking. Tobacco products contain over 3000 compounds, including many carcinogens and procarcinogens [29]. The effect of these compounds on tobacco-related cancer might be mediated by genetic polymorphisms encoding tobacco metabolizing enzymes such as GSTM1, GSTT1 [30]. Wallstrom et al. [31] examined the association of plasma autotoxins against the oxidized DNA base derivative 5-hydroxymethyl-2'-deoxuryridine as a biomarker of oxidative stress with the risk factors smoking, related to the genetic state of GSTM1 and GSTT1 in a cross-sectional sample (264 men and 280 women) from the population-based Swedish. They found that the current smokers lacking GSTM1 had higher auto-toxins titers, compared with non-smokers or persons expressing GSTM1, indicating that smoking increase the production of oxidative stress, especially in people carrying GSTM1 null genotype. Consequently, these populations tend to be more susceptible to gene damage and thus increase the cancer susceptibility.

The strengths of our meta-analysis included: first, a huge number of cases and controls as many as one hundred thousand people were pooled from different studies, which significantly increased statistical power of the analysis; second, studies included in our present meta-analysis strictly met our selection criteria; third, smoking, an important environment factor, was incorporated into to our study, our results demonstrate that smoking may increase cancer susceptibility with GSTM1, GSTT1 null genotype.

Several limitations might be included in this study. Since most of the included studies have conducted on Asians, Caucasians, and a few on Africans, the results must be interpreted with caution. Additionally, a possible publication bias might have been introduced as only published studies written in English that could be searched from Medline database were included. Moreover, our results were just concerned with smoking without adjustment for other risk factors such as age, dietary habit, and drinking status, environmental factors and other variables, which might have caused serious confounding bias. Finally, we should put smoking more detailed analysis. Smoking can be divided into packages per day or active and passive smokers, which may reflect more accurately.

Conclusions

In conclusion, this meta-analysis demonstrates that GSTM1 and GSTT1 null genotypes seem to be risk factors. Nevertheless, large scales, more rigorous designs, especially studies stratified for gene–gene and gene–environment interactions on these two polymorphisms and cancer risk are needed to research, which may eventually lead to better comprehensive understanding of the possible roles in tumorigenesis.

Supporting Information

Table S1 The genotype frequencies on each studies. A generalized distribution of genotype frequencies on each included studies are listed. (XLSX)

Table S2 The genotype frequencies on studies of smoking. A generalized distribution of genotype frequencies on each included studies are listed. (XLSX)

Checklist S1 PRISMA 2009 Checklist. (DOC)

File S1 The list of references included in this meta-analysis. (DOCX)

Author Contributions

Conceived and designed the experiments: JZF JZW. Performed the experiments: SQW JZF JBG RZ SLZ. Analyzed the data: HQC YZ YFD PCL. Wrote the paper: JZF SFS ZJW.

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