Association between the combined effects of \textit{GSTM1} present/null and \textit{CYP1A1} MspI polymorphisms with lung cancer risk: an updated meta-analysis

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Background: Many studies have been performed to explore the combined effects of glutathione-S-transferase M1 (\textit{GSTM1}) present/null and cytochrome P4501A1 (\textit{CYP1A1}) MspI polymorphisms with lung cancer (LC) risk, but the results are contradictory. Two previous meta-analyses have been reported on the issue in 2011 and 2014. However, several new articles since then have been published. In addition, their meta-analyses did not evaluate the credibility of significantly positive results.

Objectives: We performed an updated meta-analysis to solve the controversy following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Methods: False-positive report probability (FPRP), Bayesian false discovery probability (BFDP), and the Venice criteria were used to verify the credibility of meta-analyses.

Results: Twenty-three publications including 5734 LC cases and 7066 controls met the inclusion criteria in the present study. A significantly increased risk of LC was found in overall analysis, Asians and Indians. However, all positive results were considered as ‘less-credible’ when we used the Venice criteria, FPRP, and BFDP test to assess the credibility of the positive results.

Conclusion: These positive findings should be interpreted with caution and results indicate that significant associations may be less-credible, there are no significantly increased LC risk between the combined effects of \textit{GSTM1} present/null and \textit{CYP1A1} MspI polymorphisms.

Background

Lung cancer (LC) is one of the most common malignancies and it is the leading cause of cancer deaths in both men and women [1-3]. It is an extremely complex disease because it is the result of the combined effects of genes, environment, and lifestyle [4-6]. As an example, smoking has been confirmed to be associated with increased LC risk [7]. However, not all smokers will get LC, therefore, other factors, such as genetic susceptibility, may play an important role in LC susceptibility [8,9].

Glutathione-S-transferase M1 (\textit{GSTM1}) and cytochrome P4501A1 (\textit{CYP1A1}) have been reported to be involved in the detoxification and bioactivation of chemical carcinogen in habitual smokers, which might lead to LC susceptibility [10,11]. The above two genes play an important role in the metabolism of polycyclic aromatic hydrocarbons (PAHs) [12]. \textit{CYP1A1} including two genetic polymorphisms has been reported: one is Ile462Val (\textit{CYP1A1}*2C) polymorphism and the other is MspI (\textit{CYP1A1}*2A) polymorphism [13,14], which may result in an increased activity. \textit{GSTM1} gene shows deletion polymorphisms (null genotype) [15], which cause the absence of expression and enzyme activity loss [16] and is located on chromosome 1 (1p13.3) [17]. As the preservation of genomic integrity is essential in the prevention of
Figure 1. Flow diagram for identifying and including studies in the current meta-analysis

Tumor initiation and progression, mutations and variations, especially in genes of enzymes in carcinogen metabolism, may play a role in the genetic predisposition to cancer. Therefore, genetic polymorphisms leading to altered activity in phase I enzymes may cause variations in the levels of DNA damage and cancer susceptibility [12].

Two large-scale meta-analyses [18,19] have been published in 2011 and 2014 that confirmed the combined effects of CYP1A1 MspI and GSTM1 present/null genotypes to be significant risk factors for LC. However, several new articles have been published. Moreover, results of previous original studies [20–47] on the combined effects of the two genes were inconsistent or even contradictory, and individual studies may be underpowered to detect the effect of polymorphism on the susceptibility of LC. Furthermore, previous two meta-analyses did not evaluate the credibility of significantly positive results on the issue. Hence, the association of this issue remains unknown. It is very important to identify the genotype distribution for predicting the risk of LC and understanding the pathogenesis of LC. Hence, an updated meta-analysis was performed to provide a more precise evaluation on such association. In addition, to minimize random errors and strengthen the robustness of the results, we performed a trial sequential analysis (TSA). Moreover, we used false-positive report probability (FPRP) [48], Bayesian false discovery probability (BFDP) [49], and the Venice criteria [50,51] to evaluate the credibility of significantly positive results in the present study.

Materials and methods

The present meta-analysis was performed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [52].
Figure 2. Forest plot of the association between the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk in Asians (all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1)

Search strategy
PubMed, China National Knowledge Infrastructure (CNKI), and Wan Fang were used to search eligible studies. The latest date was 8 May 2020. We used the following keywords: (GSTM1 OR Glutathione S-transferase M1 OR Glutathione S-transferase Mu 1) AND (Cytochrome P450 1A1 OR CYP1A1) AND lung. The corresponding authors were contacted when some studies were not available in full-text. If necessary, some reference lists of selected articles were carefully examined by hand searching.

Inclusion and exclusion criteria
Publications will be selected if they met the following inclusion criteria: (1) publications regarding the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk; (2) case–control or cohort studies; (3) selecting the maximum sample size when data of one study was duplicated with another study; (4) providing the combined genotype data or ORs and their 95% CIs. Articles will be excluded if they met the following criteria: (1) original data not shown, (2) only cases, and (3) reviews, conference abstracts, letters and editorials.

Data extraction
Data were independently extracted by two authors. Each eligible study includes the following data: (1) first author’s name, (2) publication year, (3) country, (4) ethnicity, (5) source of controls, (6) matching, (7) sample size, and (8) genotype distribution of cases and controls. The individuals from China and Japan were regarded as ‘Asians’, from Spain, Russia, Greece and other Western countries were regarded as ‘Caucasian’, and from India were as ‘Indians’. If one study did not state race or sample included several races, ‘Mixed populations’ was used.
Quality score evaluation

The quality of the selected studies was evaluated independently by two authors. Table 1 lists the literature quality assessment criteria. The criteria were designed by previous meta-analyses about molecular epidemiology studies [53,54]. The highest value was 21 score in the quality assessment; studies scoring ≥12 were considered as high quality. Inconsistent scores were adjudicated by a third author.

TSA

TSA was conducted as described by a previous meta-analysis [55]. Briefly, α (type I error) and β (type II error) adopted a level of significance of 0.05 and 0.2, respectively. Information size was calculated using accrued information size (AIS), and TSA monitoring boundaries were also built.

Credibility analysis

To evaluate the credibility of statistically significant results, FPRP, BFDP, and the Venice criteria were applied. Significant association was considered as ‘noteworthy’ when the results of FPRP and BRDP were less than 0.05 and 0.2, respectively. Concerning the Venice criteria, we assessed the criteria of amount of evidence by statistical power: A: ≥80%, B: 50–79%, and C: <50%. For replication, we applied the I² recommended by Ioannidis et al. [50]: A: <25%, B: 25–50%, and C: >50%. For avoiding biases, we considered using the criteria proposed by Ioannidis et al. [50].

Statistical analysis

The association between the combined effects of the GSTM1 present/null and CYP1A1 MspI polymorphisms and LC risk was assessed using pooled crude ORs and 95% CIs. The following eight genetic models were used: GSTM1 null/CYP1A1 m1/m1 vs. GSTM1 present/CYP1A1 m1/m1, GSTM1 present/CYP1A1 m1/m2 vs. GSTM1 present/CYP1A1 m1/m1, GSTM1 null/CYP1A1 m1/m2 vs. GSTM1 present/CYP1A1 m1/m1, GSTM1 present/CYP1A1 m2/m2 vs. GSTM1 present/CYP1A1 m1/m1, GSTM1 null/CYP1A1 m1/m1 vs. GSTM1

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**Figure 3.** Forest plot of the association between the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk in Indians (all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1)

| Study                         | Odds Ratio (95% CI) | Weight |
|-------------------------------|--------------------|--------|
| Groth [41]2016                | 1.32 (0.86, 2.04)  | 24.37  |
| Shah [25]2006                 | 2.49 (1.64, 3.73)  | 25.52  |
| Sreeja [31]2005               | 1.79 (1.11, 2.86)  | 22.34  |
| Poddinady [17]2016            | 2.84 (1.83, 3.82)  | 27.77  |
| Overall (I² = 56.8%, p = 0.074) | 2.01 (1.46, 2.76)  | 100.00 |
Table 1 Scale for quality assessment of molecular association studies of LC

| Criterion                                                                 | Score |
|---------------------------------------------------------------------------|-------|
| Source of case                                                             |       |
| Selected from population or cancer registry                               | 3     |
| Selected from hospital                                                    | 2     |
| Selected from pathology archives, but without description                 | 1     |
| Not described                                                             | 0     |
| Source of control                                                          |       |
| Population-based                                                          | 3     |
| Blood donors or volunteers                                                 | 2     |
| Hospital-based                                                            | 1     |
| Not described                                                             | 0     |
| Ascertainment of cancer                                                   |       |
| Histological or pathological confirmation                                  | 2     |
| Diagnosis of LC by patient medical record                                 | 1     |
| Not described                                                             | 0     |
| Ascertainment of control                                                  |       |
| Controls were tested to screen out LC                                     | 2     |
| Controls were subjects who did not report LC, no objective testing         | 1     |
| Not described                                                             | 0     |
| Matching                                                                  |       |
| Controls matched with cases by age                                        | 1     |
| Not matched or not described                                              | 0     |
| Genotyping examination                                                    |       |
| Genotyping done blindly and quality control                               | 2     |
| Only genotyping done blindly or quality control                           | 1     |
| Unblinded and without quality control                                     | 0     |
| Specimens used for determining genotypes                                  |       |
| Blood cells or normal tissues                                             | 1     |
| Tumor tissues or exfoliated cells of tissue                               | 0     |
| HWE                                                                       |       |
| HWE in the control group                                                  | 1     |
| Hardy–Weinberg disequilibrium in the control group                        | 0     |
| Association assessment                                                    |       |
| Assess association between genotypes and breast cancer with appropriate statistics and adjustment for confounders | 2     |
| Assess association between genotypes and breast cancer without adjustment for confounders | 1     |
| Inappropriate statistics used                                              | 0     |
| Total sample size                                                         |       |
| >1000                                                                     | 3     |
| 500–1000                                                                  | 2     |
| 200–500                                                                   | 1     |
| <200                                                                      | 0     |

Abbreviation: HWE, Hardy–Weinberg equilibrium.

present/CYP1A1 m1/m1, GSTM1 present/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1, GSTM1 null/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1, and all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1. Heterogeneity was estimated by the Cochran’s $Q$ [56] and $I^2$ value [57]. Significant heterogeneity was considered if $P<0.10$ and/or $I^2 > 50\%$. A fixed-effects model (Mantel–Haenszel method) was applied if no heterogeneity [58]; otherwise, a random-effects model (DerSimonian and Laird method) was used [59]. Hardy–Weinberg equilibrium (HWE) was detected according to chi-square goodness-of-fit test, and significant deviation was considered in controls when $P<0.05$. Sensitivity analysis was performed by the following methods: (1) each time that a single study was removed, and (2) a dataset was used that comprised only high-quality and controls in HWE studies. Begg’s funnel [60] and Egger’s test [61] were used to assess the publication bias. In addition, we estimated the heterogeneity source by meta-regression analysis. All statistical analyses were calculated using STATA version 12.0 (STATA Corporation, College Station, TX).
Figure 4. Begg’s funnel plot to assess publication bias on the combined effects of GSTM1 and CYP1A1 with LC risk in overall population (all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1)

Results

Study characteristics

A total of 178, 35, and 42 studies were identified from PubMed, CNKI, and Wanfang databases (Figure 1), respectively. In total, 227 studies were excluded when titles and abstracts were appraised by review articles, case reports, and meta-analyses. In addition, the data of the five publications [21,31,37,38,42] were included in another four articles [27,35,45,58]. Therefore, 23 publications were included in the current study, as shown in Table 2. Of these publications, four studies were from Caucasians, four were from Indian populations, thirteen were from Asians, and two were from mixed populations. Furthermore, there were ten high-quality studies and thirteen low-quality studies (as also shown in Table 2). Table 3 lists the genotype frequencies of the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk.

Meta-analysis results

The results of pooled analyses were shown in Table 4. The individuals carrying the GSTM1 null/CYP1A1 m1/m1, GSTM1 present/CYP1A1 m1/m2, GSTM1 null/CYP1A1 m1/m2, GSTM1 null/CYP1A1 m2/m2, GSTM1 present/CYP1A1 m*, GSTM1 null/CYP1A1 m*, and all risk genotypes, the pooled ORs with their 95% CIs for all populations were 1.13 (1.03–1.24), 1.36 (1.01–1.83), 1.48 (1.07–2.06), 2.16 (1.62–2.89), 1.33 (1.08–1.63), 1.69 (1.32–2.16), and 1.43 (1.22–1.67) when compared with GSTM1 present/CYP1A1 m1/m1, respectively. Then, we performed a sub-group analysis by ethnicity, significantly increased LC risk was observed in Asians (GSTM1 null/CYP1A1 m2/m2 vs. GSTM1 present/CYP1A1 m1/m1: OR = 2.05, 95% CI = 1.42–2.95; GSTM1 present/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1: OR = 1.32, 95% CI = 1.09–1.61; GSTM1 null/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1: OR = 1.85, 95% CI = 1.44–2.38; all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1: OR = 1.55, 95% CI = 1.33–1.82, Figure 2) and Indians (GSTM1 null/CYP1A1 m1/m1 vs. GSTM1 present/CYP1A1 m1/m1: OR = 1.68, 95% CI = 1.20–2.35; GSTM1 present/CYP1A1 m1/m2 vs. GSTM1 present/CYP1A1 m1/m1: OR = 2.37, 95% CI = 1.12–5.01; GSTM1 null/CYP1A1 m1/m2 vs. GSTM1 present/CYP1A1 m1/m1: OR = 2.76, 95% CI = 1.60–4.75; GSTM1 present/CYP1A1 m2/m2 vs. GSTM1 present/CYP1A1 m1/m1: OR = 3.24, 95% CI = 1.72–6.08; GSTM1 null/CYP1A1 m2/m2 vs. GSTM1 present/CYP1A1 m1/m1: OR = 3.59, 95% CI = 1.82–7.09; GSTM1 present/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1: OR = 2.28, 95% CI = 1.48–3.51; GSTM1
null/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1: OR = 3.44, 95% CI = 2.34–5.06; all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1: OR = 2.01, 95% CI = 1.46–2.77, Figure 3).

Heterogeneity and sensitivity analyses
A meta-regression analysis was performed to explore the heterogeneity source. Current study indicated that ethnicity, source of controls, type of controls, matching, HWE, quality score, and sample size were not heterogeneity source. The results did not change if a single study was deleted each time (results not shown). In addition, the results also did not change when studies only including controls in HWE and high quality were pooled, as shown in Table 5.

Publication bias
Obvious publication bias was found by Egger’s test in all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1 (P=0.030) and Begg’s funnel plots (Figure 4). Results changed (all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1: OR = 1.09, 95% CI: 0.91–1.30) in overall analysis after using the nonparametric ‘trim and fill’ method (Figure 5).

TSA and credibility of the positive results
Figure 6 lists the TSA for the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk in overall population (all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1 model). The result indicated the cumulative evidence is sufficient. Then, we applied FPRP, BFDP, and the Venice criteria to assess the credibility of statistically significant results. All positive results were considered as ‘less-credible’ (Tables 4 and 5).
Table 3 Genotype frequencies of the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms and LC risk

| First author/year | Present/m1/m1 | Null/m1/m1 | Present/m1/m2 | Null/m1/m2 | Present/m2/m2 | Null/m2/m2 | Present/m* | Null/m* | HWE for CYP1A1 |
|-------------------|--------------|------------|--------------|------------|--------------|------------|------------|--------|----------------|
|                   | Case | Control | Case | Control | Case | Control | Case | Control | Case | Control | Case | Control | Case | Control |
| Peddireddy et al. (2016) [20] | 74     | 133     | 31    | 40       | 84   | 44       | 32    | 19       | 21    | 12       | 4     | 2       | 105  | 56       |
| Girdhar et al. (2016) [44] | 71     | 101     | NA    | NA       | NA   | NA       | 71    | 56       | NA    | NA       | 15    | 9       | NA   | NA       |
| López-Cima et al. (2012) [22] | 283    | 286     | 90    | 70       | NA   | NA       | NA    | NA       | NA    | NA       | NA    | NA       | 308  | 332      |
| Li et al. (2011) [45] | 12     | 40      | 15    | 33       | 24   | 33       | 39    | 21       | 3     | 4        | 9     | 7       | 27   | 37       |
| Jin et al. (2010) [25] | 27     | 40      | 52    | 40       | NA   | NA       | NA    | NA       | NA    | NA       | NA    | NA       | 28   | 31       |
| Zhu et al. (2010) [24] | 29     | 38      | 26    | 30       | 23   | 36       | 45    | 30       | 15    | 14       | 22    | 12      | 38   | 50       |
| Chang et al. (2009) [23] | 82     | 100     | 80    | 88       | NA   | NA       | NA    | NA       | NA    | NA       | NA    | NA       | 29   | 37       |
| Shah et al. (2008) [28] | 60     | 103     | 46    | 34       | 41   | 44       | 32    | 12       | 10    | 5        | 11    | 2       | 51   | 49       |
| Xia et al. (2008) [46] | 7      | 21      | 10    | 19       | 20   | 30       | 16    | 28       | 1     | 6        | 4     | 12      | 21   | 36       |
| Hou et al. (2008) [47] | 16     | 19      | 19    | 21       | 15   | 4        | 19    | 20       | 1     | 6        | 7     | 7       | 16   | 10       |
| Gu et al. (2007) [27] | 34     | 154     | 57    | 149      | NA   | NA       | NA    | NA       | NA    | NA       | NA    | NA       | 81   | 205      |
| Belogubova et al. (2008) [32] | 49     | 183     | 55    | 174      | 17   | 48       | 18    | 42       | 1     | 0        | 1     | 3       | 18   | 48       |
| Wang et al. (2008) [36] | 16     | 19      | 16    | 16       | 10   | 9        | 13    | 21       | 9     | 12       | 27    | 14      | 19   | 21       |
| Sreeja et al. (2005) [34] | 48     | 68      | 23    | 24       | NA   | NA       | NA    | NA       | NA    | NA       | NA    | NA       | 52   | 40       |
| Wang et al. (2004) [39] | 19     | 28      | 13    | 25       | 7    | 19       | 16    | 27       | 9     | 18       | 27    | 21      | 16   | 37       |
| Vnec et al. (2004) [35] | 560    | 573     | 653   | 640      | 102  | 112      | 127   | 145      | 8     | 6        | 16    | 12      | 110  | 118      |
| Dialyna et al. (2003) [40] | 40     | 57      | 49    | 73       | 17   | 23       | 11    | 22       | 2     | 2        | 3     | 1       | 19   | 25       |
| Cheng et al. (2000) [41] | 35     | 12      | 24    | 11       | NA   | NA       | NA    | NA       | NA    | NA       | NA    | NA       | 4    | 4        |
| Song et al. (2000) [33] | 23     | 95      | 10    | 66       | NA   | NA       | NA    | NA       | NA    | NA       | NA    | NA       | 74   | 146      |
| Le Marchand et al. (1998) [29] | 50     | 101     | 76    | 147      | NA   | NA       | NA    | NA       | NA    | NA       | NA    | NA       | 50   | 81       |
| Hong et al. (1996) [30] | 14     | 11      | 21    | 15       | 21   | 18       | 22    | 16       | 3     | 1        | 4     | 2       | 24   | 19       |
| García-Closas et al. (1997) [26] | 174    | 155     | 195   | 182      | 38   | 32       | 35    | 43       | NA    | NA       | NA    | NA       | NA   | NA       |
| Khara and Noda (1995) [43] | 18     | 48      | 18    | 64       | 21   | 54       | 24    | 51       | 3     | 25       | 13    | 16      | 24   | 79       |

Abbreviation: NA, not available.
### Table 4 The results of the pooled analysis between the combined effects of GSTM1 present/null and CYP1A1 Msp1 and LC risk

| Variable | n    | Cases/controls | Test of association | Test of heterogeneity | Prior probability of 0.001 | Venice criteria |
|----------|------|----------------|---------------------|-----------------------|---------------------------|----------------|
|          |      |                | OR (95% CI)         | P                     | P<sub>h</sub> | I<sup>2</sup> (%) | Power | FPRP | BFDP |
| GSTM1 null/CYP1A1 m1/m1 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 22 | 324/9425 | **1.13** (1.03, 1.24) | 0.013 | 0.401 | 4.5 | 1.000 | 0.908 | 0.998 | AAB |
|          | Ethnicity | Asian | 13 | 693/122 | 1.18 (0.97, 1.44) | 0.101 | 0.534 | 0.0 | - | - | - |
|          |          | Indian | 3 | 282/402 | **1.68** (1.20, 2.35) | 0.002 | 0.337 | 8.2 | 0.254 | 0.906 | 0.981 | CAB |
|          |          | Caucasian | 4 | 1779/2056 | 1.08 (0.95, 1.24) | 0.236 | 0.665 | 0.0 | - | - | - |
|          |          | Mixed | 2 | 495/585 | 0.98 (0.77, 1.26) | 0.883 | 0.738 | 0.0 | - | - | - |
| GSTM1 present/CYP1A1 m1/m2 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 14 | 1,528/1,934 | **1.36** (1.01, 1.83) | 0.045 | 0.001 | 62.6 | 0.741 | 0.983 | 0.998 | BCB |
|          | Ethnicity | Asian | 8 | 272/427 | 1.27 (0.92, 1.74) | 0.143 | 0.127 | 37.9 | - | - | - |
|          |          | Indian | 2 | 259/324 | **2.37** (1.12, 5.01) | 0.024 | 0.034 | 77.8 | 0.116 | 0.995 | 0.997 | CCB |
|          |          | Caucasian | 3 | 785/996 | 1.00 (0.77, 1.28) | 0.973 | 0.612 | 0.0 | - | - | - |
|          |          | Mixed | 1 | 212/187 | 1.06 (0.63, 1.78) | 0.83 | - | - | - | - | - |
| GSTM1 null/CYP1A1 m1/m2 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 15 | 1679/2082 | **1.48** (1.07, 2.06) | 0.019 | <0.001 | 73.5 | 0.532 | 0.974 | 0.997 | BCB |
|          | Ethnicity | Asian | 8 | 325/438 | 1.49 (0.93, 2.38) | 0.095 | 0.021 | 57.4 | - | - | - |
|          |          | Indian | 3 | 340/424 | **2.76** (1.60, 4.75) | <0.001 | 0.088 | 58.8 | 0.014 | 0.947 | 0.911 | CCB |
|          |          | Caucasian | 3 | 805/1022 | 0.95 (0.75, 1.20) | 0.657 | 0.198 | 38.2 | - | - | - |
|          |          | Mixed | 1 | 209/198 | 0.73 (0.44, 1.19) | 0.204 | - | - | - | - | - |
| GSTM1 present/CYP1A1 m2/m2 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 13 | 1000/1384 | **1.32** (0.82, 2.14) | 0.255 | 0.067 | 40.0 | - | - | - |
|          | Ethnicity | Asian | 8 | 175/310 | 0.83 (0.53, 1.29) | 0.411 | 0.354 | 9.8 | - | - | - |
|          |          | Indian | 2 | 165/253 | **3.24** (1.72, 6.08) | <0.001 | 0.899 | 0.0 | 0.008 | 0.968 | 0.928 | CAB |
|          |          | Caucasian | 3 | 660/821 | 1.65 (0.68, 3.99) | 0.271 | 0.474 | 0.0 | - | - | - |
| GSTM1 null/CYP1A1 m2/m2 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 14 | 1148/1494 | **2.16** (1.62, 2.89) | <0.001 | 0.735 | 0.0 | 0.007 | 0.030 | 0.014 | CAB |
|          | Ethnicity | Asian | 8 | 244/315 | **2.05** (1.42, 2.95) | <0.001 | 0.831 | 0.0 | 0.046 | 0.705 | 0.791 | CAB |
|          |          | Indian | 3 | 235/350 | **3.59** (1.82, 7.09) | <0.001 | 0.061 | 15.6 | 0.006 | 0.975 | 0.934 | CCB |
|          |          | Caucasian | 3 | 669/829 | 1.52 (0.77, 3.00) | 0.224 | 0.842 | 0.0 | - | - | - |
| GSTM1 present/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 21 | 2610/3590 | **1.33** (1.08, 1.63) | 0.006 | <0.001 | 61.6 | 0.877 | 0.872 | 0.993 | ACB |
|          | Ethnicity | Asian | 13 | 733/1337 | **1.32** (1.09, 1.61) | 0.005 | 0.121 | 32.7 | 0.896 | 0.873 | 0.993 | AAB |
|          |          | Indian | 3 | 390/449 | **2.28** (1.48, 3.51) | <0.001 | 0.102 | 56.1 | 0.029 | 0.864 | 0.863 | CCB |
|          |          | Caucasian | 4 | 1387/1622 | 0.98 (0.83, 1.15) | 0.777 | 0.682 | 0.0 | - | - | - |
|          |          | Mixed | 1 | 100/182 | 1.25 (0.77,2.03) | 0.376 | - | - | - | - | - |
| GSTM1 null/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 21 | 2505/3251 | **1.69** (1.32, 2.16) | <0.001 | <0.001 | 71.3 | 0.170 | 0.140 | 0.516 | CCB |
|          | Ethnicity | Asian | 13 | 915/1268 | **1.85** (1.44, 2.38) | <0.001 | 0.069 | 39.8 | 0.051 | 0.032 | 0.077 | CAB |
|          |          | Indian | 3 | 284/353 | **3.44** (2.34, 5.06) | <0.001 | 0.266 | 24.4 | <0.001 | 0.027 | <0.001 | CAB |
|          |          | Caucasian | 4 | 1197/1408 | 1.01 (0.84, 1.22) | 0.887 | 0.456 | 0.0 | - | - | - |
|          |          | Mixed | 1 | 109/222 | 0.99 (0.62, 1.56) | 0.949 | - | - | - | - | - |
| All risk genotypes vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 23 | 5734/7066 | **1.43** (1.22, 1.67) | <0.001 | <0.001 | 68.5 | 0.727 | 0.008 | 0.243 | BCC |
|          | Ethnicity | Asian | 13 | 1692/2512 | **1.55** (1.33, 1.82) | <0.001 | 0.206 | 23.5 | 0.344 | <0.001 | 0.006 | CAB |

Continued over
Table 4 The results of the pooled analysis between the combined effects of GSTM1 present/null and CYP1A1 MspI and LC risk (Continued)

| Variable | n  | Cases/controls | Test of association | Test of heterogeneity | Prior probability of 0.001 Venice criteria |
|----------|----|----------------|---------------------|---------------------|---------------------------------------------|
|          |    |                | OR (95% CI)         | $P$                 | $P_h$ | $I^2$ (%) | Power | FPRP | BFDPP |
| Indian   | 4  | 741/781        | 2.01 (1.46, 2.77)   | <0.001              | 0.074 | 56.8     | 0.037 | 0.350 | 0.448 | CCB   |
| Caucasian| 4  | 2518/2905      | 1.03 (0.92, 1.15)   | 0.584               | 0.717 | 0.0      | -     | -     | -     | -     |
| Mixed    | 2  | 783/868        | -                   | -                   | 0.015 | 83.3     | -     | -     | -     | -     |

*Random-effects model was used in the pooled data.
Note: The bold values indicate significant results.

Figure 5. The Duval and Tweedie nonparametric ‘trim and fill’ method’s funnel plot of the combined effects of GSTM1 and CYP1A1 with LC risk (all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1)

Discussion
In 1994, Alexandrie et al. [21] first investigated the combined effects between GSTM1 present/null and CYP1A1 MspI polymorphisms and LC risk. Since then, many studies have been published. However, the results of these studies were contradictory. In addition, two published meta-analyses did not assess the credibility of significantly positive results. Therefore, an updated meta-analysis was calculated to investigate the association between the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk.

In the present study, we observed that the individuals carrying GSTM1 null/CYP1A1 m1/m1, GSTM1 present/CYP1A1 m1/m2, GSTM1 null/CYP1A1 m1/m2, GSTM1 null/CYP1A1 m2/m2, GSTM1 present/CYP1A1 m*, GSTM1 null/CYP1A1 m*, and all risk genotypes were associated with LC risk. In addition, statistically significant increased LC risk was also found in Asians and Indians. Moreover, when we restrained only high-quality and HWE studies, statistically significant increased LC risk still be observed in overall population, Asians, and Indians. Then, we performed a TSA in the present study and the results indicated that the cumulative evidence is sufficient. Actually,
Table 5 The results of sensitivity analysis between the combined effects of GSTM1 present/null and CYP1A1 MspI and LC risk

| Variable | n  | Cases/controls | Test of association | Test of heterogeneity | Prior probability of 0.001 | Venice criteria |
|----------|----|----------------|---------------------|-----------------------|---------------------------|-----------------|
|          |    |                | OR (95% CI)         | P         | I² (%) | Power | FPRP | BFDP |
| GSTM1 null/CYP1A1 m1/m1 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 10 | 2615/3094 | **1.20 (1.01, 1.42)** | 0.035 | 0.088 | 40.5 | 0.995 | 0.971 | 0.999 | AAB |
|          | Ethnicity | Asian | 3 | 274/429 | 1.15 (0.67, 1.96) | 0.622 | 0.095 | 57.6 | - | - | - | - |
|          |          | Indian | 3 | 282/402 | **1.68 (1.20, 2.35)** | 0.002 | 0.337 | 8.2 | 0.254 | 0.906 | 0.981 | CAB |
|          |          | Caucasian | 3 | 1690/1926 | 1.09 (0.95, 1.25) | 0.002 | 0.337 | 8.2 | - | - | - | - |
|          |          | Mixed | 1 | 369/337 | 0.95 (0.71, 1.28) | 0.758 | - | - | - | - | - | - |
| GSTM1 present/CYP1A1 m1/m2 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 5 | 1199/1427 | - | - | <0.001 | 82.6 | - | - | - | - | - |
|          | Ethnicity | Indian | 2 | 259/324 | - | - | 0.034 | 77.8 | - | - | - | - |
|          |          | Caucasian | 2 | 728/916 | **1.68 (1.20, 2.35)** | 0.002 | 0.337 | 8.2 | 0.254 | 0.906 | 0.981 | CAB |
|          |          | Caucasian | 2 | 728/916 | **1.68 (1.20, 2.35)** | 0.002 | 0.337 | 8.2 | 0.254 | 0.906 | 0.981 | CAB |
|          |          | Mixed | 1 | 212/187 | 1.05 (0.63, 1.78) | 0.831 | - | - | - | - | - | - |
| GSTM1 null/CYP1A1 m1/m2 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 5 | 1161/1408 | - | - | <0.001 | 86.8 | - | - | - | - | - |
|          | Ethnicity | Indian | 2 | 198/267 | **3.63 (2.25, 5.86)** | <0.001 | 0.404 | 0.0 | <0.001 | 0.469 | 0.020 | CAB |
|          |          | Caucasian | 2 | 754/943 | 1.11 (0.64, 1.92) | 0.707 | 0.099 | 63.3 | - | - | - | - |
|          |          | Mixed | 1 | 209/187 | 0.73 (0.44, 1.19) | 0.204 | - | - | - | - | - | - |
| GSTM1 present/CYP1A1 m2/m2 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 4 | 783/1015 | **2.68 (1.58, 4.56)** | <0.001 | 0.448 | 0.0 | 0.016 | 0.945 | 0.916 | CAB |
|          | Ethnicity | Indian | 2 | 165/253 | **3.24 (1.72, 6.08)** | <0.001 | 0.899 | 0.0 | 0.008 | 0.968 | 0.928 | CAB |
|          |          | Caucasian | 2 | 618/943 | 1.11 (0.64, 1.92) | 0.707 | 0.099 | 63.3 | - | - | - | - |
|          |          | Mixed | 1 | 209/187 | 1.05 (0.63, 1.78) | 0.831 | - | - | - | - | - | - |
| GSTM1 null/CYP1A1 m2/m2 vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 4 | 775/1011 | **2.26 (1.27, 4.04)** | 0.006 | 0.135 | 46.0 | 0.083 | 0.986 | 0.991 | CAB |
|          | Ethnicity | Indian | 2 | 149/240 | **6.49 (2.11, 19.99)** | 0.001 | 0.409 | 0.0 | 0.005 | 0.995 | 0.991 | CAB |
|          |          | Caucasian | 2 | 626/771 | 1.35 (0.66, 2.77) | 0.410 | 0.941 | 0.0 | - | - | - | - |
| GSTM1 present/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 10 | 2061/2620 | - | - | <0.001 | 76.6 | - | - | - | - | - |
|          | Ethnicity | Asian | 3 | 263/449 | **1.44 (1.03, 2.01)** | 0.034 | 0.140 | 49.1 | 0.595 | 0.982 | 0.998 | BBB |
|          |          | Indian | 3 | 390/449 | **2.28 (1.49, 3.51)** | <0.001 | 0.102 | 56.1 | 0.029 | 0.864 | 0.863 | CCB |
|          |          | Caucasian | 3 | 1328/1540 | 0.97 (0.82, 1.15) | 0.732 | 0.492 | 0.0 | - | - | - | - |
|          |          | Mixed | 1 | 100/182 | 1.25 (0.76, 2.03) | 0.376 | - | - | - | - | - | - |
| GSTM1 null/CYP1A1 m* vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 10 | 1827/2294 | - | - | <0.001 | 79.7 | - | - | - | - | - |
|          | Ethnicity | Asian | 3 | 291/391 | **2.12 (1.53, 2.93)** | <0.001 | 0.668 | 0.0 | 0.018 | 0.228 | 0.204 | CAB |
|          |          | Indian | 3 | 284/353 | **3.44 (2.34, 5.06)** | <0.001 | 0.266 | 24.4 | <0.001 | 0.027 | <0.001 | CAB |
|          |          | Caucasian | 3 | 1143/1328 | 1.02 (0.84, 1.24) | 0.813 | 0.295 | 18.1 | - | - | - | - |
|          |          | Mixed | 1 | 109/222 | 0.99 (0.62, 1.56) | 0.949 | - | - | - | - | - | - |
| All risk genotypes vs. GSTM1 present/CYP1A1 m1/m1 | Overall | 10 | 4010/4539 | - | - | <0.001 | 81.6 | - | - | - | - | - |
|          | Ethnicity | Asian | 3 | 580/804 | **1.59 (1.23, 2.05)** | <0.001 | 0.442 | 0.0 | 0.327 | 0.515 | 0.911 | CAB |
|          |          | Indian | 3 | 592/796 | **2.34 (1.85, 2.97)** | <0.001 | 0.413 | 0.0 | <0.001 | <0.001 | <0.001 | CAB |
|          |          | Caucasian | 3 | 2396/2727 | 1.04 (0.92, 1.16) | 0.553 | 0.527 | 0.0 | - | - | - | - |
|          |          | Mixed | 1 | 442/442 | 0.93 (0.71, 1.22) | 0.601 | - | - | - | - | - | - |

*Random-effects model was used in the pooled data.
Note: The bold values indicate significant results.

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Figure 6. TSA for the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk in overall population (all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1 model)

it may be common that the same polymorphism played different roles in cancer risk among different ethnic populations, because cancer is a complicated multigenetic disease, and different genetic backgrounds may contribute to the discrepancy [12]. Five [25,27,33,45,47] and three [20,28,34] studies indicated that the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk in Asians and Indians, respectively. However, eight different genetic models were used in this meta-analysis to explore the association. In this case, the P-value must be adjusted to make multiple comparisons clear [62]. In addition, a lot of evidence was required to ensure statistical power to reach more stringent levels of statistical significance or lower false-discovery rate for detecting associations, especially in molecular epidemiological studies [63]. Therefore, we used FPRP, BFDP, and the Venice criteria to assess the credibility of these positive results, and found that all significant associations were considered as 'less-credibility'.

Significant publication bias was found by Begg’s funnel plots and Egger’s test in all risk genotypes vs. GSTM1 present/CYP1A1 m1/m1 (P=0.030). Random error and bias were common in the studies with small sample sizes, and the results may be unreliable in molecular epidemiological studies. Furthermore, small sample studies were easier to accept if there was a positive report as they tend to yield false-positive results because they may be not rigorous and are often of low quality. Figure 4 indicates that the asymmetry of the funnel plot was caused by a study with low-quality small samples. In addition, at any case, the association between between the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms with LC risk in Indians (n=4) and Caucasians (n=4) remain an open field, because the number of studies are considerably smaller than that needed for the achievement of robust conclusions [64]. Therefore, a huge population-based case–control study is required to confirm these associations in Indians and Caucasians.

Two meta-analyses have been published on the association between the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms and LC risk. Li et al. [18] only examined seven studies (809 LC cases and 935 controls) and their meta-analysis indicated that the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms were significantly associated with an increased LC risk. Li et al. [19] selected 21 studies including 3896 LC cases and 4829 controls for investigation, and results were same as Li et al. [18]. However, their studies did not exclude the quality studies to further perform a meta-analysis. In addition, their studies did not calculate HWE of
the controls for CYP1A1 MspI genotypes. There may be selection bias or genotyping errors if the control group did not meet HWE. It can lead to misleading results. Moreover, their studies did not assess the credibility of the positive results. The present study has quite a few advantages over the two previous meta-analyses [18,19]: (1) the sample size was much larger, which consists of 23 studies including 5734 cases and 7066 controls; (2) a meta-regression analysis was performed to explore the heterogeneity source; (3) eight genetic models were used; (4) the Venice criteria, FPRP, and BFDP tests were applied to assess the credibility of the positive results. Therefore, our findings should be more credible and convincing.

However, there are still some limitations in the present study. First, language bias could not be avoided because the included studies were written in both English and Chinese. Second, we were not able to perform several important subgroup analyses, such as cancer type, gender, smoking status, and so on. Third, only published articles were selected. Therefore, publication bias may be found as shown in Figure 4. Four, confounding factors did not be controlled such as age, gender, smoking, drinking, and so on, were closely related to affect the results. These positive findings should be interpreted with caution and results indicate that significant associations may be less-credible, there are no significantly increased LC risk between the combined effects of GSTM1 present/null and CYP1A1 MspI polymorphisms.

Data Availability
All relevant data are presented within the paper.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution
Wen-Ping Zhang: performed research, collected data, and wrote original manuscript. Xiao-Feng He: performed and designed research, collected data, analyzed data and revised manuscript. Xiang-Hua Ye: designed research and revised manuscript.

Abbreviations
BFDP, Bayesian false discovery probability; CI, confidence interval; CNKI, China National Knowledge Infrastructure; CYP1A1, cytochrome P4501A1; FPRP, false-positive report probability; GSTM1, glutathione-S-transferase M1; HWE, Hardy–Weinberg equilibrium; LC, lung cancer; OR, odds ratio; TSA, trial sequential analysis.

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