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Original Article

Association of *GSTP1* Ile105Val polymorphism with risk of esophageal cancer: a meta-analysis of 21 case-control studies

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Abstract: Background: The association of *glutathione s-transferase P1* (*GSTP1*) Ile105Val polymorphism with risk of esophageal cancer (EC) has been evaluated in many studies; however, the results from these studies are controversial. Thus, further analysis on association between *GSTP1* Ile105Val polymorphism and risk of EC is needed among a larger study population. Method: We searched the relevant electronic databases and performed a meta-analysis based on 21 published case-control studies. The Chi-square based I^2-statistic test was performed to evaluate possible heterogeneity across the studies. Additionally, random-effects models were used to calculate crude pooled odds ratios (ORs) with 95% confidence intervals (CIs). Results: Overall, this meta-analysis did support a significant association between *GSTP1* Ile105Val polymorphism and risk of EC (pooled OR 1.25, 95% CI, 1.05-1.49). Furthermore, the stratified analysis showed that, in comparison to *GSTP1* Ile105Val Ile/Ile genotype, the Val/Val genotype was significantly associated with risk of esophageal squamous cell carcinoma (ESCC) (pooled OR 1.45, 95% CI, 1.07-1.96), particularly in the Caucasian population (pooled OR 1.41, 95% CI, 1.01-1.95). Such a significant association was not observed for esophageal adenocarcinoma (EAC) patients or subjects of an Asian ethnicity. Moreover, substantial evidence of heterogeneity among the studies was not observed. Conclusion: The results from this meta-analysis support a significant association between the *GSTP1* Ile105Val polymorphism and risk of EC, particularly in a subgroup with ESCC and in the Caucasian population. Further studies with larger sample sizes are needed to validate our findings.

Keywords: Esophageal cancer, GSTP1, polymorphism, meta-analysis, cancer risk

Introduction

Esophageal cancer (EC) is one of the most common malignancies in the world, with obvious geographical characteristics of its pathogenesis [1]. The development of EC is a multifactorial process. For example, tobacco smoking and alcohol consumption are well-recognized etiological factors for EC [2, 3]. However, not every smoker and/or alcohol consumer develops EC, suggesting that individual susceptibility factors might also be involved in the development of this malignancy.

Evidence indicates that genetic polymorphisms in certain carcinogen-metabolizing genes play an important role in modifying the risk for EC [4]. Sequence variations in these genes can alter the expression, function and activity of the encoded enzymes and may consequently increase or decrease carcinogen activation or detoxification. Among them, the glutathione-s-transferases (GSTs) represent a superfamily of phase II enzymes which catalyze the conjugation reactions between reduced glutathione and reactive intermediates of a variety of endogenous and exogenous electrophilic compounds. Some of these compounds have carcinogenic potential, thereby making them more water-soluble for easy elimination from the body. GSTP1 has a high level of esophageal expression and plays a central role in the inacti-

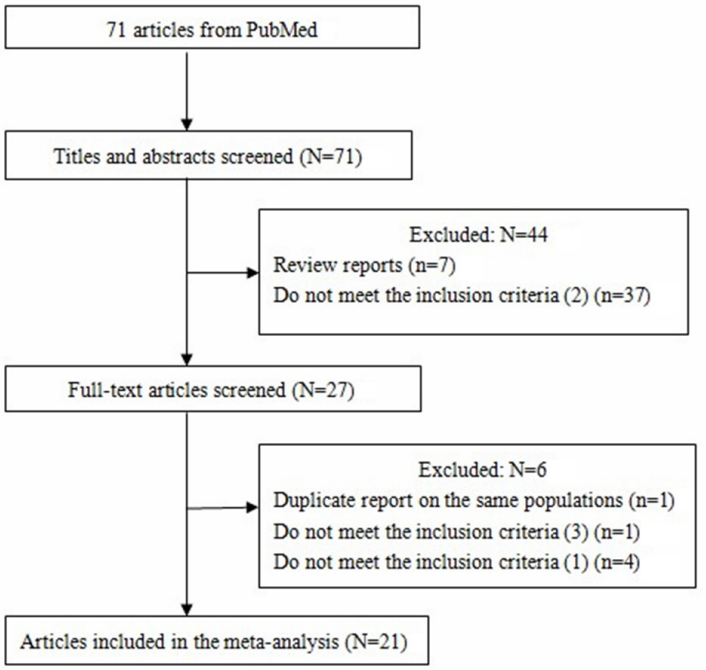

Figure 1. Flow diagram of study identification.

vation of toxic and carcinogenic compounds [5, 6]. The tendency of *GST* polymorphisms to alter carcinogen metabolization is well established, with *GSTP1* polymorphisms having been extensively studied in human population.

The *GSTP1* gene is located on chromosome 11q13 and consists of seven exons. There are two known *GSTP1* polymorphic sites, which are characterized by an A-to-G transition at nucleotide 313 (codon 105, exon 5), causing an isoleucine-to-valine change (Ile105Val), and a C-to-T transition at nucleotide 341 (codon 113, exon 6), causing an alanine-to-valine substitution (Ala114Val) [7]. Four allele genotypes are composed of these two polymorphic sites: the wild type *GSTP1*A* (Ile105, Ala114), *GSTP1**B (Val105, Ala114), *GSTP1**C (Val105, Val114), and *GSTP1**D (Ile105, Val114) [7, 8]. The GSTP1 enzyme having Val105 shows a catalytic efficiency for the diol epoxides of polycyclic aromatic hydrocarbons that is seven-fold higher than the isoenzymes having Ile105. In contrast, the catalytic efficiency for 1-chloro-2,4-dinitrobenzene was reduced approximately three-fold in *GSTP1*/Val105 compared to *GSTP1*/Ile105 [7, 9, 10]. The *GSTP1*/Val105 variant was found to be 2-3 times less stable than the Ile105 variant [11] and was associated with a higher hydrophilic DNA adduct level [12].

The association between *GSTP1* polymorphism and risk of EC is unclear, with some studies reporting increased EC risk in subjects carrying *GST1/Val105* variant [13-17]; some reporting decreased risk [18]; and others reporting no association [19-28]. A previous meta-analysis investigated the association between EC risk and *GSTP1* polymorphism [29]; however, this study also included a limited number of published studies, and new results have since been published. In the current meta-analysis, we gave a more comprehensive overview of risk effect of *GSTP1* Ile05-Val polymorphism on EC occurrence, including journal articles published up to September 1, 2013.

Materials and methods

Identification of eligible studies

We conducted a literature search through September 1, 2013 using the key words search in the PubMed, Web of Knowledge, MEDLINE, Embase, and Google Scholar electronic databases and search engines. The language of publication was restricted to English. The following search terms were used: glutathione s-transferase p or GST or GSTP1 or glutathione S-transferase P1, and polymorphism or single nucleotide polymorphism or SNP, and esophageal cancer or esophagus or esophageal squamous cell carcinoma or ESCC or esophageal adenocarcinoma or EAC.

Inclusion and exclusion criteria

The following inclusion criteria were used to select studies: (1) case-control study methodology; (2) association of EC with *GSTP1* polymorphisms; (3) reported sample size, odds ratios (ORs) and 95% confidence intervals (CIs); and (4) EC cases confirmed using histopathology. The exclusion criteria were as follows: (1) rationale and study design obviously different from our research objectives; (2) not case-control study; (3) malignant tumor cases included in controls; and (4) duplicated studies, reviews, case reports. If duplicate data were presented in more than one study, only the most informative and recent one was included.

Table 1. Characteristics of studies on the association of *GSTP1* Ile105Val and the risk of esophageal cancer

Study	Study area	Ethnicity	Cases/ controls	OR[#] (95% CI)	OR[&] (95% CI)	OR[%] (95% CI)
Morita 1998 [18]	Japan	Asian	66/164	0.19 (0.07-0.51)	-	0.18 (0.07-0.48)
Lin 1998 [19]	China	Asian	42/36	0.83 (0.31-2.22)	0.25 (0.03-2.60)	0.7 (0.3-1.8)[a]
Van Lieshout 1999 [6, 13]	Caucasian	Caucasian	34/247	3.45 (1.55-7.65)	3.65 (0.88-15.07)	3.47 (1.60-7.57)
Tan 2000 [20]	China	Asian	150/150	0.89 (0.55-1.44)	1.47 (0.50-4.29)	1.0 (0.8-1.3)[a]
Lee 2000 [21]	China	Asian	90/270	-	-	0.66 (0.39-1.11)
Casson 2003 [14]	Canada	Caucasian	45/45	2.5 (1.0-6.3)	0.8 (0.2-3.1)	1.8 (0.8-4.3)[a]
Wang 2003 [15]	China	Asian	62/38	1.91 (0.82-4.45)	2.48 (0.24-25.44)	5.37 (2.50-11.50)
Ribeiro Pinto 2003 [16]	Brazilian	Mixed	34/68	-	-	4.09 (1.29-13.00)
Abbas 2004 [22]	France	Caucasian	70/124	1.12 (0.61-2.07)	1.27 (0.41-3.90)	1.02 (0.55-1.89)[a]
Jain 2006 [23]	India	Indian	100/137	0.80 (0.47-1.39)	1.29 (0.48-3.45)	0.87 (0.52-1.46)
Cai 2006 [24]	China	Asian	218/415	0.93 (0.64-1.35)	0.46 (0.13-1.67)	0.88 (0.61-1.27)
Casson 2006 [25]	Canada	Caucasian	56/95	1.36 (0.65-2.84)	2.22 (0.81-6.06)	1.54 (0.77-3.07)
Murphy 2007 [26]	Ireland	Caucasian	207/223	0.93 (0.62-1.39)	1.00 (0.53-1.88)	0.94 (0.62-1.41)
Wideroff 2007 [27]	U.S	Caucasian	67/206	0.71 (0.38-1.32)[a]	1.73 (0.75-4.02)[a]	0.87 (0.50-1.50)
Rossini 2007 [17]	Brazil	Mixed	162/252	1.66 (1.04-2.66)	1.78 (0.89-3.54)	2.12 (1.37-3.29)[a]
Zendehdel 2009 [28]	Sweden	Caucasian	175/471	1.21 (0.83-1.75)	1.41 (0.76-2.62)	1.24 (0.87-1.77)
Liu 2010 [30]	China	Asian	97/97	0.896 (0.478-1.678)[a]	-	0.825 (0.447-1.52)[a]
Moaven 2010 [31]	Iran	Mixed	148/137	0.83 (0.50-1.36)	1.672 (0.678-4.119)[a]	1.100 (0.688-1.757)[a]
Li 2010 [32]	South African	Mixed	245/288	1.01 (0.68-1.48) [a]	1.21 (0.71-2.07)[a]	1.00 (0.70-1.43)
Malik 2010 [4]	Kashmir Valley	Indian	135/195	1.00 (0.62-1.6)[a]	2.48 (1.03-6.02)[a]	1.16 (0.74-1.80)
Matejcic 2011 [33]	South African	Mixed	554/902	1.02 (0.79-1.32)	1.03 (0.77-1.38)	1.02 (0.81-1.30)

[#]OR of esophageal cancer associated with GSTP1 Ile105Val: Ile/Val vs. Ile/Ile. [&]OR of esophageal cancer associated with GSTP1 Ile105Val: Val/Val vs. Ile/Ile. [%]OR of esophageal cancer associated with GSTP1 Ile105Val: Ile/Val + Val/Val vs. Ile/Ile. [a]adjusted for potential confounding variables. OR, odds ratio and CI, confidence interval.

Data extraction

Three investigators (Song, Zhou, and Du) reviewed and extracted information independently from selected publications in accordance with the above mentioned inclusion and exclusion criteria. Any conflicts over study/data inclusion were settled by a discussion between the investigators. Following the criteria above, 21 articles [4, 13-28, 30-33] were included in the present analyses. The steps taken towards article selection are shown below (**Figure 1**). The following data were extracted from included studies: authors of study, study area and period, the number of cases and controls, OR and 95% CIs. If crude and adjusted ORs and 95% CIs were both offered, we extracted the results that were adjusted for the most potential confounding variables. When the ORs were not presented, we calculated unadjusted ORs from the exposure data given in the articles. The details of each study are shown in **Table 1**.

Statistical analysis

Deviations from Hardy--Weinberg equilibrium (HWE) were tested using Fisher's exact test to evaluate the genetic equilibrium of each study [34]. For all studies, we evaluated the risk of the hetero- and homozygous carriers of the variant Val allele, both together and separately, compared with the wild type Ile allele. Then, we calculated the overall ORs of the polymorphisms.

Tests for heterogeneity were made among studies using the Cochran's Q and I2 test statistic [35]. For the Cochran's Q test statistic, a *P* value < 0.10 was accepted as statistically significant heterogeneity. Random-effects models were used to estimate summary ORs and 95% CIs [36]. To examine potential sources of heterogeneity, we also conducted subgroup analyses by histological types (EAC and ESCC) and by ethnicity (Asian and Caucasian population). Meta regression analysis was also performed to identify sources of heterogeneity according to several variables, such as number of cases, source of controls, covariates adjusted, and publication time.

Sensitivity analyses were conducted to assess the strength of our findings by excluding one study at a time. Begg's funnel plot and Egger's regression test [37] were used to evaluate publication bias. In Egger's test, when *P* value <

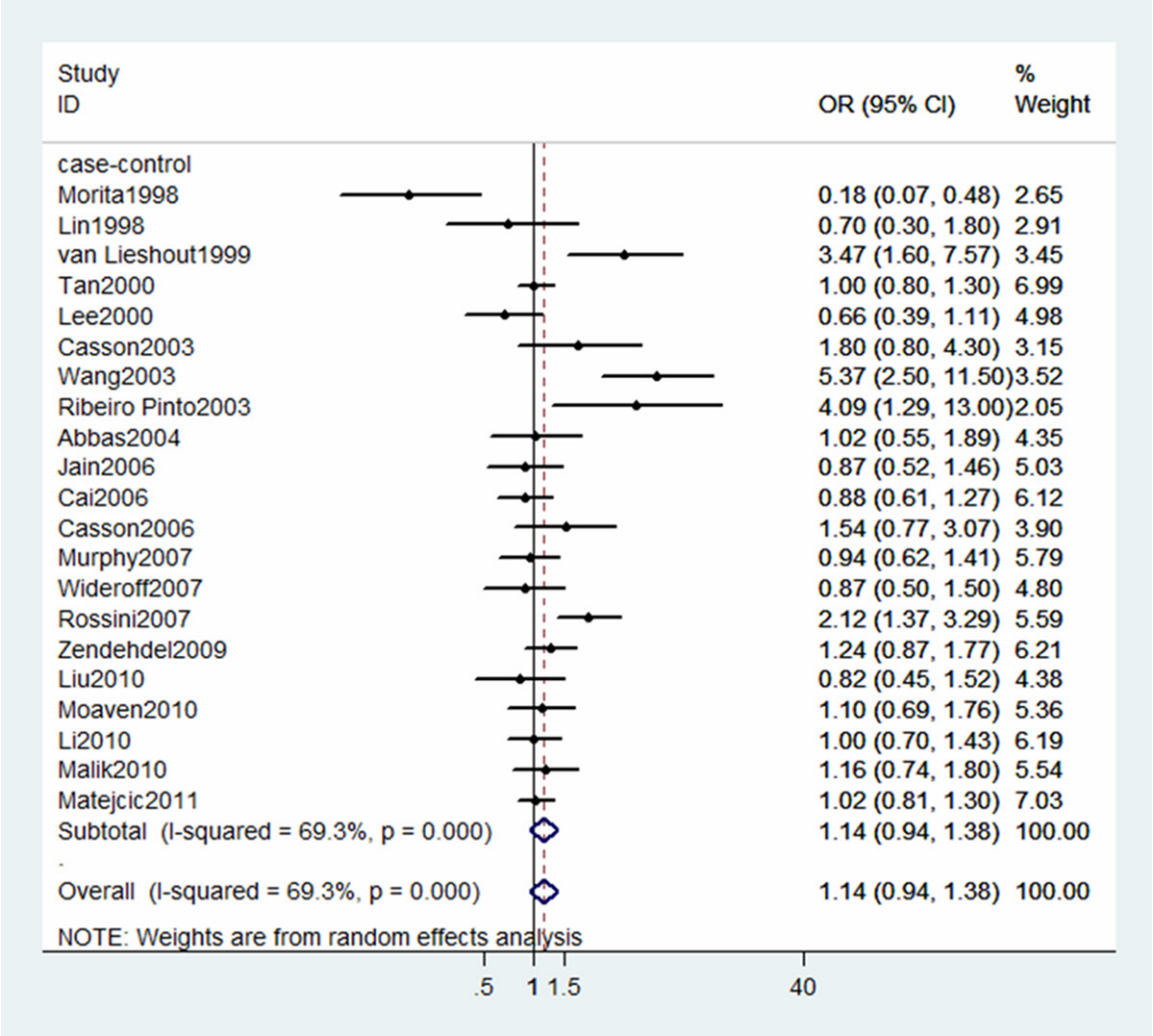

Figure 2. Forest plot for association between *GSTP1 Ile105Val* and risk of ESCC (Ile/Val + Val/Val vs Ile/Ile). A random-effects model was used. The *squares* and *horizontal lines* represent the study-specific OR and 95% CI. The *diamond* corresponds to the summary OR and 95% CI.

0.10, it was considered statistically significant publication bias. All analyses were conducted using Stata v.12 (StataCorp LP, TX) statistical software.

Results

Literature search and studies' characteristics

Our keyword search identified 71 papers, from which 44 papers [7 reviews and 37 did not meet criteria (2)] were excluded after review of the abstracts. After reading the full texts of the remaining 27 papers, we eliminated an additional 6 papers, including 1 duplicated report, 4 failure to meet inclusion criterion (1) and 1 failure to meet inclusion criterion (3) (**Figure 1**). In summary, a total of 21 case-control studies evaluating the association between *GSTP1* Ile105Val polymorphism and risk of EC were identified, with 2,757 cases and 4,560 controls included [4, 13-28, 30-33]. Among these 21 studies, 9 were performed in Asian populations, 7 in Caucasians, and 5 in mixed ethnicity populations. Controls in 7 studies were population-based and controls in the other 14 studies were hospital-based. The study characteristics are shown in **Table 1**.

Meta-analysis results

The summary OR for Ile/Val + Val/Val vs. Ile/Ile, Ile/Val vs. Ile/Ile and Val/Val vs. Ile/Ile was 1.14 (95% CI 0.94-1.38), 1.05 (95% CI 0.88-1.24), 1.25 (95% CI 1.05-1.49), respectively. (**Figures 2-4**).

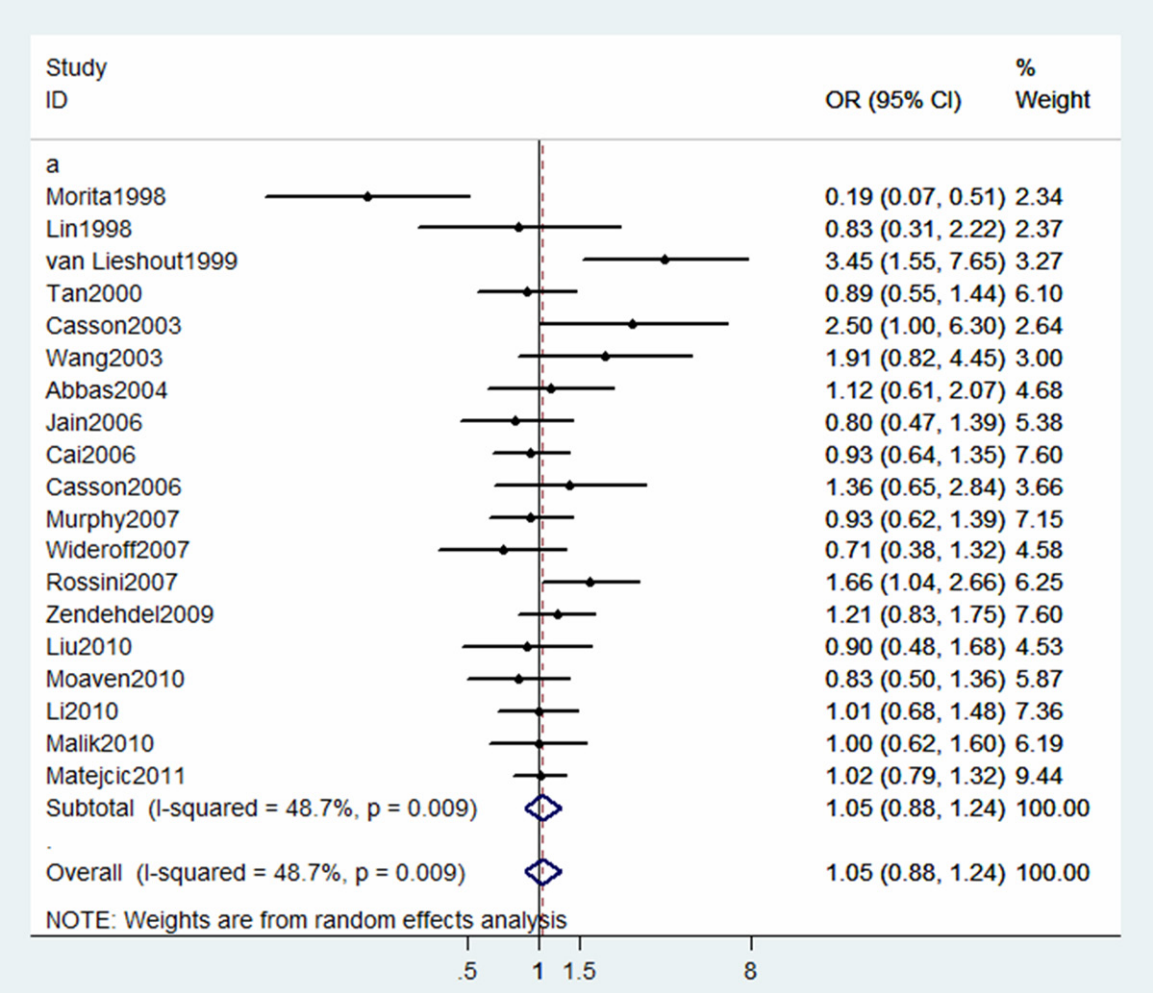

Figure 3. Forest plot for association between *GSTP1 Ile105Val* and risk of ESCC (Ile/Val vs Ile/Ile). A random-effects model was used. The *squares* and *horizontal lines* represent the study-specific OR and 95% CI. The *diamond* corresponds to the summary OR and 95% CI.

Subgroup analyses

Subgroup analyses according to histological types are shown in **Table 2**. Compared with wild-type (Ile/Ile), variant homozygote (Val/Val) of *GSTP1* Ile105Val was associated with a significantly increased risk of ESCC (Val/Val vs. Ile/Ile: OR = 1.45, 95% CI = 1.07-1.96; P = 0.134 for heterogeneity test). However, we failed to find any significant association for *GSTP1* Ile105Val with risk of EAC in different genetic models. We also performed stratified analysis by ethnicity (Asian and Caucasian group). As shown in **Table 2**, a significant association between *GSTP1* Ile105Val polymorphism and risk of EC among the Caucasian population was found (OR = 1.41, 95% CI = 1.01-1.95; P = 0.602 for heterogeneity test). Such a significant association was not observed in the Asian study population.

Meta-regression analyses

We performed meta-regression analyses regarding the number of cases, ethnicity, adjusted covariates, and the publication time. We found that all of these variables did not appear to be main causes of heterogeneity, with *P* values equal to 0.542, 0.453, 0.992, and 0.873, respectively.

Sensitivity analyses

We performed sensitivity analyses by removing one study at a time and then estimating summary OR of the remaining studies. We found the results to be stable (data not shown).

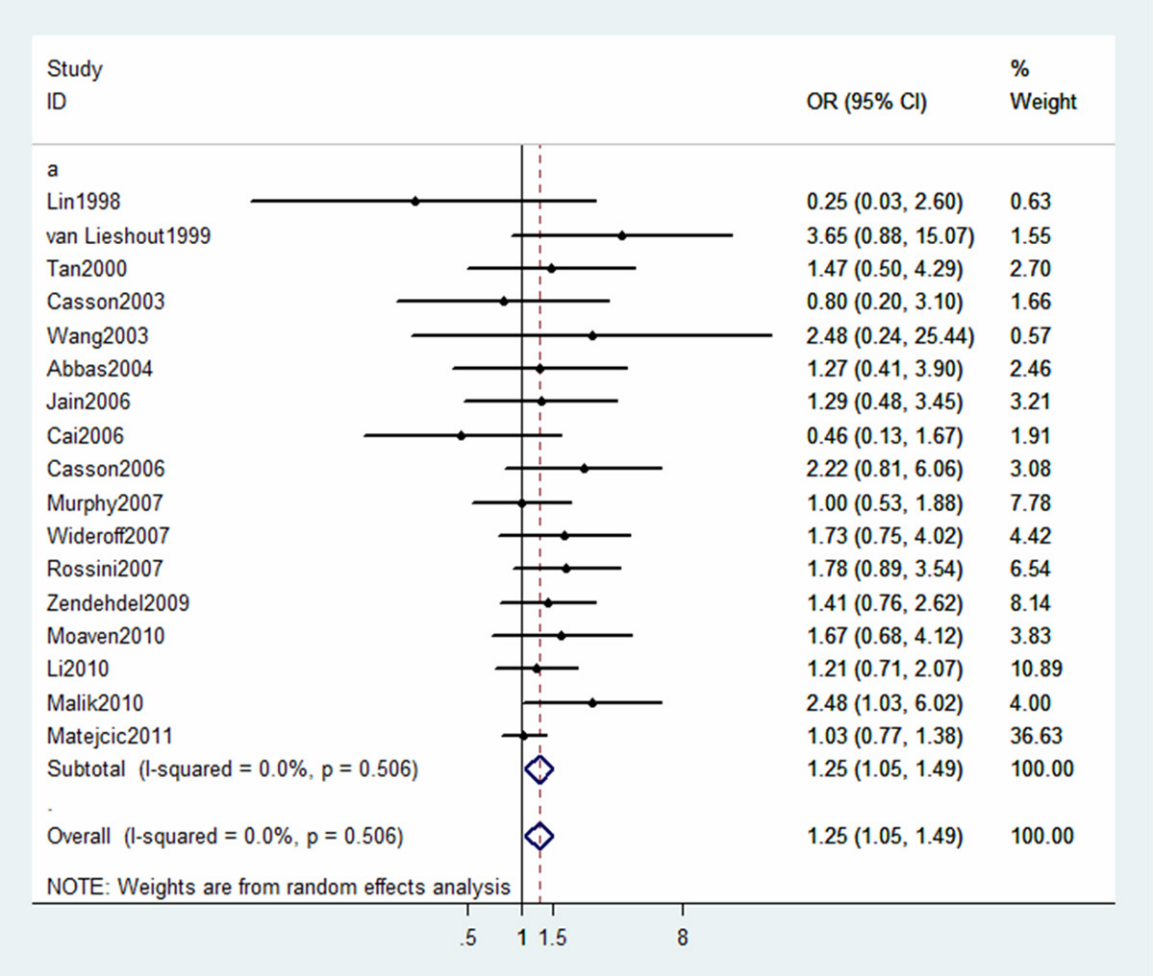

Figure 4. Forest plot for association between *GSTP1 Ile105Val* and risk of ESCC (Val/Val vs Ile/Ile). A random-effects model was used. The *squares* and *horizontal lines* represent the study-specific OR and 95% CI. The *diamond* corresponds to the summary OR and 95% CI.

Assessment for publication bias

A Begg's funnel plot was generated, showing nearly symmetrical pattern (**Figure 5**), indicating low possibility of publication bias. Egger's test was also used to quantitatively evaluate publication bias, which confirmed no evidence of bias (p = 0.570).

Discussion

GSTP1 Ile105Val polymorphism has been evaluated as a potential susceptibility factor contributing to the risk of developing various cancers including cancer of the breast, prostate and lung, with the variant Val105 genotype more likely to be associated with increased risk of cancer [38-40]. Using a meta-analytic approach, we consistently found a statistically significant association between variant homozygote (Val/Val) of *GSTP1* Ile105Val and increased risk of EC. A previous meta-analysis of 13 published case-control studies found no significant general main effects for *GSTP1* Ile105Val polymorphism on EC risk [29]. In the present study, we analyzed data from 2,757 cases and 4,560 controls in 21 studies to have the statistical power to detect differences and provide more precise risk estimates than the previous meta-analysis and individual studies, the majority of which suffered from limited sample size [4, 13-28, 30-33].

Results from our meta-analysis stratified by histological types of EC indicate that individuals carrying variant homozygous Val/Val genotype had significantly higher risk of ESCC than individuals carrying wild-type Ile/Ile genotype. However, such a significant association was not

Table 2. Subgroup analyses for the association of *GSTP1* Ile105Val polymorphism and esophageal cancer

Subgroups	No of studies	OR (95% CI)	I^2 statistics (%)	Test for heterogeneity* (*p* value)
Histological subtype				
ESCC				
Ile/Val + Val/Val vs. Ile/Ile	13	1.19 (0.93-1.51)	68.6	< 0.001
Ile/Val vs. Ile/Ile	12	1.06 (0.91-1.24)	14.4	0.303
Val/Val vs. Ile/Ile	11	1.45 (1.07-1.96)	33.1	0.134
EAC				
Ile/Val + Val/Val vs. Ile/Ile	9	1.18 (0.90-1.55)	29.9	0.179
Ile/Val vs. Ile/Ile	9	1.21 (0.88-1.67)	43.9	0.075
Val/Val vs. Ile/Ile	9	1.29 (0.90-1.84)	0	0.84
Ethnicity				
Asian				
Ile/Val + Val/Val vs. Ile/Ile	7	0.88 (0.55-1.42)	82.4	<0.001
Ile/Val vs. Ile/Ile	6	0.83 (0.55-1.27)	59.9	0.029
Val/Val vs. Ile/Ile	4	0.75 (0.33-1.68)	75.6	0.006
Caucasian				
Ile/Val + Val/Val vs. Ile/Ile	8	1.36 (0.99-1.88)	53.8	0.034
Ile/Val vs. Ile/Ile	7	1.28 (0.91-1.79)	55.8	0.035
Val/Val vs. Ile/Ile	7	1.41 (1.01-1.95)	0	0.602

*Test for heterogeneity: random effect modeling was used.

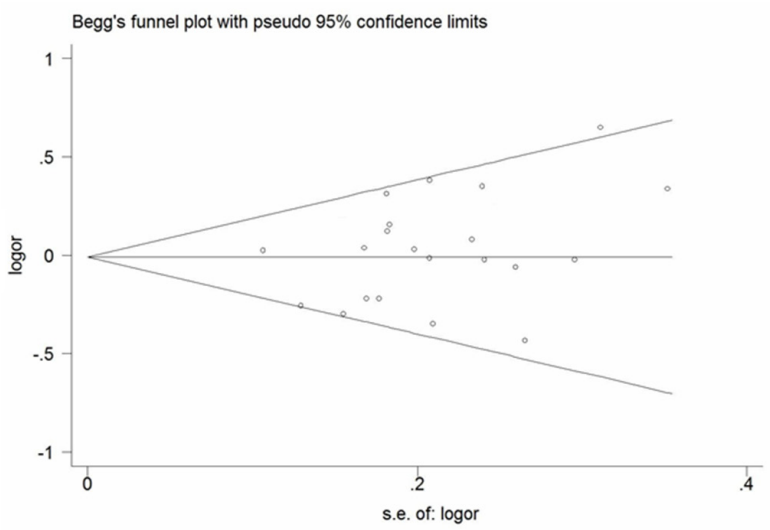

Figure 5. Begg's funnel plot for publication bias assessment.

observed with EAC. GSTP1 is known to metabolize tobacco-related carcinogens and eliminate the oxidative products of thymidine or uracil propenal [41]. GSTP1 has an effect upon benzo(α)pyrene and its major metabolites [9], which are the major components of cigarette smoke [42]. Moreover, epidemiological studies have shown that *GSTP1* polymorphisms seem to be more associated with tobacco-related cancers [19]. ESCC and EAC have significant divergence in etiology while sharing a few etiological factors. Smoking is generally accepted as a risk factor for both ESCC and EAC, but the effect is much stronger in ESCC than in EAC [43]. Thus, the difference in main effects of *GSTP1* variant genotype in these two histological types of EC is biologically plausible.

Our stratified analyses by ethnicity revealed a significant association between *GSTP1* Ile105Val polymorphism and EC in Caucasians, while the association was not significant in the Asian subgroup. This appears to contradict the above stratification analysis by histological type because ESCC is the major type of EC in the Asian population. However, the result in the Asian subgroup was based on 4 studies in Chinese populations showing a high level of between-study heterogeneity, suggesting that

the studies do not estimate the same effect due to different degree of bias. In addition, there are significant differences regarding etiological profiles between high and low incidence areas within China [44]. This difference may also be responsible for variation in EC risk in these studies and the overall non-significance. More large studies are warrant to determine the effect of *GSTP1* Ile105Val polymorphism on EC risk in Asians.

Although no significant association between *GSTP1* Ile105Val polymorphism and EC risk was observed in dominant model (Ile/Val + Val/Val vs Ile/Ile) or in pair comparison between Ile/Val and Ile/Ile genotype, we cannot exclude that we may fail to detect the effect because of between-study heterogeneity ($p < 0.001$ for heterogeneity test for both meta-analyses). Although we conducted subgroup analyses by ethnicity and histological type to explore potential sources of heterogeneity, other possible sources such as publication year, case-control matching, and sample size were unable to be examined in our analyses. Uncontrolled confounding factors could be a major source of between-study heterogeneity because most studies used crude ORs and 95% CI. Additionally, the design of some studies was not optimal, some having small sample sizes [14-16, 19], and some including populations with highly heterogeneous ethnic backgrounds or of unclear ethnicity [16, 17, 31-33]. Case-control study design is prone to selection bias, which could be a source of heterogeneity. Furthermore, because *GSTP1* polymorphisms might contribute to susceptibility to non-cancer disease, using hospital-based controls may introduce heterogeneity to the meta-analysis. Therefore, more optimal and well-designed studies are required to evaluate the genetic association between *GSTP1* Ile105Val polymorphism and EC risk in the future.

Considerable effort was made to test for possible associations between *GSTP1* Ile105Val polymorphism and risk of EC, and a significant effect of *GSTP1* variant homozygous (Val/Val) genotype on EC risk was found with no significant between-study heterogeneity. However, there are still some limitations to the meta-analysis. First, we cannot control for confounding factors that were not adjusted for in individual studies, such as age, sex, family history of cancer, smoking, alcohol consumption, and other potential risk factors. These factors might modify or even change the direction of observed effect. Second, *GSTP1* may interact with environmental factors or interact with other genes in creating susceptibility for EC. However, due to lack of these data in individual data, we were unable to explore potential gene-gene or gene-environment interactions. Thirdly, although we did not find evidence of publication bias, it is possible as we do not have information on unpublished studies.

In conclusion, this meta-analysis demonstrates that *GSTP1* Ile105Val significantly modified the risk of EC, especially ESCC, and that the effect of modification was particularly pronounced in the Caucasian population. To confirm our findings, more, well-designed large-scale studies in diverse ethnic populations are warranted.

Abbreviations

GSTP1, glutathione *s*-transferase P1; EC, esophageal cancer; ORs, odds ratios; CIs, confidence intervals; SNP, single-nucleotide polymorphism; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

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