Glutathione S-transferase pi 1 variant and squamous cell carcinoma susceptibility: a meta-analysis of 52 case-control studies

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Abstract
Background: There are several meta-analyses on the genetic relationship between the rs1695 polymorphism within the GSTP1 (glutathione S-transferase pi 1) gene and the risk of different SCC (squamous cell carcinoma) diseases, such as ESCC (oesophageal SCC), HNSCC (head and neck SCC), LSCC (lung SCC), and SSCC (skin SCC). Nevertheless, no unified conclusions have been drawn.

Methods: Herein, an updated meta-analysis was performed to evaluate the probable impact of GSTP1 rs1695 on the susceptibility to different SCC diseases under six genetic models (allele, carrier, homozygote, heterozygote, dominant, and recessive). Three online databases, namely, PubMed, WOS (Web of Science), and Embase (Excerpta Medica Database), were searched.

Results: Initially, we obtained a total of 497 articles. Based on our selection criteria, we eventually included 52 case-control studies (9763 cases/15,028 controls) from 47 eligible articles. As shown in the pooling analysis, there was no difference in the risk of overall SCC disease between cases and controls [allele, \( P_a = 0.601 \); carrier, \( P_a = 0.587 \); homozygote, \( P_a = 0.689 \); heterozygote, \( P_a = 0.167 \); dominant, \( P_a = 0.289 \); dominant, \( P_a = 0.548 \)]. Similar results were obtained after stratification by race (Asian/Caucasian), genotyping, control source, and disease type (ESCC/HNSCC/LSCC/SSCC) (all \( P_a > 0.05 \)).

Conclusion: The rs1695 polymorphism within the GSTP1 gene is not associated with the risk of overall SCC or a specific SCC type, including ESCC, HNSCC, LSCC, and SSCC.

Keywords: GSTP1, Polymorphism, Squamous cell carcinoma, Susceptibility

Background
SCC (squamous cell carcinoma), also termed “epidermal carcinoma,” is a malignant tumour that takes part in epidermis or adnexal cells and exhibits distinct degrees of keratosis [1–3]. SCC exists in the squamous epithelium of several places, e.g., skin, mouth, lung, lips, oesophagus, cervix, and vagina [4–6]. Based on GWAS (genome-wide association study) data, more and more reported genetic polymorphisms are believed to contribute to the aetiologies of different SCC types. For instance, a series of genes, including CADM1 (cell adhesion molecule 1), AHR (aryl hydrocarbon receptor), and SEC16A (SEC16 homolog A, endoplasmic reticulum export factor), may be related with the risk of SCC [7]. Two variants within the KLF5 (Kruppel-like factor 5) gene on chromosome 13q22.1, namely, rs1924966 and rs115797771, may be relevant to ESCC (oesophageal SCC) susceptibility [8]. Herein, we determined whether GSTP1 (glutathione S-transferase pi 1) gene polymorphism is associated with the susceptibility to different SCC patterns.

GSTP1, a member of the GST (glutathione S-transferase) family in humans, is associated with the biological detoxification or biotransformation process through catalysing the conjugation of many hydrophobic and electrophilic compounds with reduced glutathione [9, 10]. The GSTP1 gene, which is located on human chromosome 11q13, comprises seven exons and six introns [11]. Two common polymorphisms, namely, rs1695 A/G polymorphism in exon five
(p.Ile105Val) and rs1138272 C/T polymorphism in exon six (p.Ala114Val), have been reported [12, 13].

Several SCC/GSTP1 rs1695-associated meta-analyses with conflicting conclusions have been reported. For instance, in 2009, Zendehdel et al. enrolled three case-control studies [14–16], performed a meta-analysis to assess the association between GSTP1 rs1695 and ESCC risk in Caucasian populations, and found a borderline significant association [16]. In 2014, Song et al. enrolled 21 case-control studies to perform a meta-analysis concerning the role of the GSTP1 rs1695 polymorphism in the risk of oesophageal cancers, including EAC (oesophageal adenocarcinoma) and ESCC [17]. The subgroup meta-analysis of ESCC containing thirteen case-control studies showed a positive correlation, particularly in the Caucasian population [17]. However, in 2015, Tan et al. performed another meta-analysis with twenty case-control studies on overall oesophageal cancer and reported negative results in both ESCC and EAC subgroups [18]. Accordingly, we performed an updated meta-analysis with a relatively larger sample size to reevaluate the potential impact of the GSTP1 rs1695 A/G polymorphism on the susceptibility to SCC diseases, mainly including ESCC, SSCC, HNSCC (head and neck SCC), and LSCC (lung SCC).

Methods

Electronic database retrieval

We reviewed three on-line databases, including PubMed, WOS (Web of Science), and Embase (Excerpta Medica Database), through January 2018 using the following main search keywords: Carcinoma, Squamous Cell; Carcinomas, Squamous Cell; Squamous Cell Carcinomas; Squamous Cell Carcinoma; Carcinoma, Squamous; Carcinomas, Squamous; Squamous; Squamous Carcinoma; Squamous Carcinomas; Carcinoma, Epidermoid; Carcinomas, Epidermoid; Epidermoid Carcinoma; Epidermoid Carcinomas; Carcinoma, Planocellular; Carcinomas, Planocellular; Planocellular Carcinoma; Planocellular Carcinomas; SCC; GSTP1; Glutathione S-Transferase pi; Glutathione S Transferase pi; GST Class-phi; Class-phi, GST; GST Class phi; Glutathione Transferase P1–1; Glutathione Transferase P1 1; Transferase P1–1, Glutathione; GSTP1 Glutathione D-Transferase; D-Transferase, GSTP1 Glutathione; GSTP1 Glutathione D Transferase; Glutathione D-Transferase, GSTP1; Polymorphism; Polymorphism, Genetic; Polymorphisms, Genetic; Genetic Polymorphisms; Genetic Polymorphism; Polymorphism (Genetics); Polymorphisms (Genetics); and Polymorphism; Polymorphisms.

Eligible article screening

We performed a literature search and screened the retrieved articles as per the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines [19]. Selection criteria included duplicated articles; data from animal or cell experiments; meeting abstract or meta-analysis; review, trials or case reports; data of GSTP1 expression; not SCC or GSTP1; lack confirmed histopathological data; combined GA + AA genotype frequency; without the control data; and P value of HWE (Hardy-Weinberg equilibrium) less than 0.05. Eligible case-control studies provided sufficient genotype frequency data of the GSTP1 gene rs1695 polymorphism in each case and control group.

Data extraction

Two investigators independently extracted the data and evaluated the methodological quality of each article by means of the NOS (Newcastle-Ottawa Scale) system. One table contains the following basic information: first author, publication year, region, race, genotyping assay, genotype frequency, disease type, control source, P values of HWE, study number, and sample size of the case/control.

Data synthesis

We utilized STATA software (StataCorp LP, College Station, TX, USA) for the following statistical analyses. The allele (allele G vs. A), carrier (carrier G vs. A), homozygote (GG vs. AA), heterozygote (AG vs. AA), dominant (GG + GG vs. AA), and recessive (GG vs. AA+AG) models were utilized to target the GSTP1 gene rs1695 G/A polymorphism. We calculated the OR (odds ratio), 95% CIs (confidence intervals) and $P_S$ ($P$ value of association test) values to estimate the association. When the $P_S$ ($P$ value of heterogeneity) was > 0.1 or $I^2$ was < 50.0%, a fixed-effects model was adopted. Otherwise, a random-effects model was selected.

Considering the factors of race, genotyping assay, control source, and disease type, we performed the corresponding subgroup meta-analyses. We also carried out Egger’s/Begg’s tests to determine a potential publication bias. The presence of a publication bias was considered when $P_E$ ($P$ value of Egger’s test) and $P_B$ ($P$ value of Begg’s test) were below 0.05. Sensitivity analysis was applied to assess data stability and robustness.

Results

Article retrieval and screening

The article retrieval and selection processes during our meta-analysis were conducted as described in the flow chart shown in Fig. 1. After our literature search, a total of 497 articles were obtained. Then, 168 articles with duplicated data and 214 articles meeting the exclusion criteria were excluded. Next, we assessed the eligibility of the remaining 115 full-text articles. After the exclusion of 68 ineligible articles, a total of 47 articles containing 52 case-control studies [14–16, 20–63] were ultimately
recruited for our meta-analysis. Table 1 summarizes the extracted basic information.

**Overall meta-analysis**

First, we performed the overall meta-analysis, which included 52 case-control studies with 9763 cases and 15,028 controls (Table 2). The fixed-effects model was applied in all meta-analyses, because no substantial between-study heterogeneity was detected [Table 2, $I^2$ value < 50.0%, $P_h > 0.1$]. As shown in Table 2, no altered susceptibility to SCC disease in cases was observed compared with controls [allele, $P_a = 0.601$; carrier, $P_a = 0.587$; homozygote, $P_a = 0.689$; heterozygote, $P_a = 0.167$; dominant, $P_a = 0.289$; dominant, $P_a = 0.548$]. These data suggest that the rs1695 polymorphism within the *GSTP1* gene does not contribute to the risk of overall SCC.

**Subgroup analysis**

Next, we performed additional subgroup meta-analyses according to the factors of race (Asian/Caucasian), genotyping assay (PCR-RFLP), control source (PB/HB), and disease type (ESCC/HNSCC/LSCC/SSCC). As shown in Tables 3 and 4, there were no significant associations in any subgroup analysis for all genetic models tested (all $P > 0.05$). The forest plot of the subgroup analysis by disease type under the allele model is shown in Fig. 2.

Furthermore, we included all case-controls studies regarding the specific SCC type and conducted a series of subgroup analyses by race and control source. However, similar results were obtained (data not shown). As a result, the *GSTP1* gene rs1695 polymorphism is not likely related to the genetic susceptibility of a specific SCC type, including ESCC, HNSCC, LSCC, and SSCC.

**Publication bias and sensitivity analysis**

The publication bias analysis data obtained from Egger’s and Begg’s tests are shown in Table 2. There was no remarkable publication bias in most genetic models ($P_E > 0.05$, $P_B > 0.05$), except for the heterozygote ($P_E = 0.022$, $P_B = 0.049$) and dominant ($P_E = 0.036$) models. The funnel plot (allele model) is displayed in Fig. 3a-b. Moreover, our sensitivity analysis led us to consider the stability of the data. Figure 4 shows a representative example of the sensitivity analysis (allele model).

**Discussion**

In the current meta-analysis, we first focused on the genetic relationship between the *GSTP1* rs1695 A/G
| First author | Year | Region | Race | Assay       | Case | Disease type | Control | Control source | \( P_{\text{HWE}} \) |
|-------------|------|--------|------|-------------|------|--------------|---------|----------------|----------------|
| Abbas       | 2004 | France | Caucasian | PCR-RFLP | 21   | ESCC         | 59      | PB             | 0.38           |
| Cabelguennie | 2001 | France | Caucasian | PCR-RFLP | 89   | HNSCC       | 146     | HB             | 0.31           |
| Cai         | 2006 | China | Asian | PCR-RFLP | 143  | ESCC         | 265     | PB             | 0.87           |
| Cho         | 2006 | Korea | Asian | Gene sequencing | 201 | HNSCC | 211     | HB             | 0.29           |
| Dura        | 2013 | Netherlands | Caucasian | PCR   | 48   | ESCC         | 246     | PB             | 0.27           |
| Dzian       | 2012 | Netherlands | Caucasian | PCR-RFLP | 56   | LSCC        | 153     | PB/HB          | 0.95           |
| Evans       | 2004 | USA | Caucasian | PCR-RFLP | 123  | HNSCC       | 97      | PB             | 0.42           |
| Fryer       | 2005 | Australia | Caucasian | PCR-RFLP | 59   | SSCC         | 95      | HB             | 0.60           |
| Harth       | 2008 | Germany | Caucasian | PCR-melting-curve | 145 | HNSCC | 130     | HB             | 0.62           |
| Jain        | 2006 | India | Asian | PCR-RFLP | 46   | ESCC         | 72      | HB             | 0.67           |
| Jourenkova  | 1999a | France | Caucasian | PCR-RFLP | 49   | HNSCC       | 86      | HB             | 0.07           |
| Jourenkova  | 1999b | France | Caucasian | PCR-RFLP | 62   | HNSCC       | 86      | HB             | 0.07           |
| Jourenkova  | 1998 | France | Caucasian | PCR-RFLP | 46   | LSCC        | 86      | HB             | 0.07           |
| Kelders     | 2002 | Netherlands | Caucasian | PCR-RFLP | 36   | HNSCC       | 26      | HB             | 0.20           |
| Khara       | 1999 | Japan | Asian | PCR-RFLP | 84   | LSCC        | 184     | HB             | 0.45           |
| Larsen      | 2006 | Australia | Caucasian | PCR-RFLP | 230  | LSCC        | 161     | HB             | 0.66           |
| Leichsenring | 2006 | Brazil | Mixed | PCR-RFLP | 30   | HNSCC       | 30      | PB             | 0.95           |
| Leite       | 2007 | Brazil | Mixed | PCR-RFLP | 14   | SSCC        | 60      | PB             | 0.07           |
| Lewis       | 2002 | UK | Caucasian | PCR-RFLP | 14   | LSCC        | 64      | HB             | 0.19           |
| Li          | 2010 | South African | Black African | PCR-RFLP | 56   | ESCC        | 76      | PB             | 0.58           |
| Li          | 2007 | USA | Caucasian | PCR-RFLP | 336  | HNSCC       | 333     | PB             | 0.57           |
| Liang       | 2005 | China | Asian | diASA-AMP | 58   | LSCC       | 132     | HB             | 0.27           |
| Liu         | 2010 | China | Asian | PCR-RFLP | 66   | ESCC         | 61      | PB             | 1.00           |
| Malik       | 2010 | India | Asian | PCR-RFLP | 53   | ESCC        | 111     | PB             | 0.41           |
| Matejcic    | 2011 | South African | Black African | TaqMan genotyping | 79 | ESCC    | 100    | PB             | 0.57           |
| McWilliams  | 2000 | USA | Mixed | PCR-RFLP | 60   | HNSCC       | 58      | PB             | 0.47           |
| Miller      | 2006 | USA | Caucasian | PCR-RFLP | 190  | LSCC        | 579     | PB             | 0.16           |
| Moaven      | 2010 | Iran | Asian | PCR-RFLP | 84   | ESCC         | 74      | PB             | 0.65           |
| Nazar       | 2003 | USA | Mixed | PCR-RFLP | 35   | LSCC        | 199     | PB             | 0.23           |
| Olshan      | 2000 | USA | Mixed | PCR-RFLP | 40   | HNSCC       | 68      | PB             | 0.63           |
| Oude        | 2003 | Netherlands | Caucasian | PCR-RFLP | 116  | HNSCC       | 125     | PB             | 0.27           |
| Peters      | 2006 | USA | Mixed | PCR-RFLP | 303  | HNSCC       | 333     | PB             | 0.73           |
| Ramsay      | 2001 | UK | Caucasian | SSCP | 10   | SSCC        | 53      | HB             | 0.36           |
| Risch       | 2001 | Germany | Caucasian | SSCP | 76   | LSCC        | 167     | HB             | 0.92           |
| Rossini      | 2007 | Brazil | Mixed | PCR-RFLP | 42   | ESCC        | 116     | PB             | 0.71           |
| Ruwali      | 2009 | India | Caucasian | PCR-RFLP | 224  | HNSCC       | 199     | PB             | 0.06           |
| Ruwali      | 2011 | India | Caucasian | PCR-RFLP | 316  | HNSCC       | 285     | PB             | 0.06           |
| Ryberg      | 1997 | Norway | Caucasian | PCR-RFLP | 20   | LSCC        | 153     | PB             | 0.50           |
| Schneider    | 2004 | Germany | Caucasian | PCR-melting-curve | 81   | LSCC    | 298    | PB/HB          | 0.16           |
polymorphism and the risk of overall SCC and then conducted subgroup analyses by the specific histological status. After rigorous screening, four main types of SCC, namely, ESCC, HNSCC, ESCC, and SSCC, were targeted. ESCC, a type of squamous epithelium differentiation of a malignant tumour within the oesophagus, accounts for the vast majority of oesophageal cancers [64, 65]. ESCC often presents in physiological or pathological stenosis of the oesophagus, and genetic factors, carcinogens, and/or chronic irritants may contribute to the pathogenesis of ESCC [64, 65]. The GSTP1 rs1695 A/G polymorphism is significantly related to the risk of ESCC in the Kashmiri population [42]. Similarly, GSTP1 rs1695 may be an independent risk factor for ESCC in Western populations [53]. Nevertheless, different associations were detected in other reports. For instance, no difference between unrelated controls and ESCC cases was observed in a French population [14] or a Chinese population [61]. Therefore, a meta-analysis was required to comprehensively evaluate the role of the GSTP1 rs1695 A/G polymorphism in ESCC risk. Herein, we recruited 15 case-control studies involving 1934 cases and 3951 controls and performed a new meta-analysis to examine the association between the GSTP1 rs1695 A/G polymorphism and ESCC susceptibility. The carrier (carrier G vs. A) model, as well as the allele, homozygote, heterozygote, dominant and recessive genetic models, was used. Our results in the stratified analysis of specific ESCCs are consistent with the data of Tan et al. [18].

Table 1 Basic information of the eligible articles in the meta-analysis (Continued)

| First author | Year | Region      | Race    | Assay                        | Case  | Disease type | Control | Control source | $P_{HWE}$ |
|--------------|------|-------------|---------|------------------------------|-------|--------------|---------|----------------|-----------|
| Soucek       | 2010 | Czech/Polish | Caucasian | TaqMan drug metabolism genotyping | 56    | 53          | 7       | HNSCC          | 57       |
| Soya         | 2007 | India       | Asian   | PCR-RFLP                     | 219   | 162          | 27      | LADTSCC     | 120       |
| Stücker      | 2002 | France      | Caucasian | PCR-RFLP                     | 54    | 46          | 15      | LSCC         | 124       |
| Tan          | 2000 | China       | Asian   | PCR-RFLP                     | 93    | 48          | 9       | ESCC         | 91        |
| To           | 2002 | Spain       | Caucasian | PCR-RFLP                     | 101   | 84          | 19      | HNSCC        | 100       |
| To           | 1999 | Spain       | Caucasian | PCR-RFLP                     | 29    | 20          | 3       | LSCC         | 64        |
| van          | 1999 | Netherlands | Caucasian | PCR-RFLP                     | 5     | 6           | 2       | ESCC         | 146       |

$\text{PCR}$ polymerase chain reaction, $\text{PCR-RFLP}$ polymerase chain reaction-restriction fragment length polymorphism, diASA-AMP di-allele-specific-amplification with artificially modified primers assay, SSCP single-stranded conformational polymorphism, ESCC oesophageal squamous cell carcinoma, HNSCC head and neck squamous cell carcinoma, LSCC lung squamous cell carcinoma, SSCC skin squamous cell carcinoma, OSCC oral squamous cell carcinoma, UADTSCC upper aerodigestive tract squamous cell carcinoma, PB population-based, HB hospital-based, $P_{HWE}$ P value of hardy-weinberg equilibrium

Table 2 Meta-analysis of the GSTP1 rs1695 A/G polymorphism

| Statistical analysis | Index | Allele | Carrier | Heterozygote | Dominant | Recessive |
|----------------------|-------|--------|---------|--------------|----------|----------|
| Association          | OR    | 0.99   | 1.02    | 0.96         | 0.97     | 1.03     |
| 95% CIs              | 0.95−1.03 | 0.94−1.03 | 0.93−1.12 | 0.91−1.02 | 0.92−1.03 | 0.94−1.12 |
| $P_a$                | 0.601 | 0.587  | 0.689   | 0.167        | 0.289    | 0.548    |
| Sample size          | case  | 9763   | 9763    | 9763         | 9763     | 9763     |
|                      | control | 15,028 | 15,028  | 15,028       | 15,028   | 15,028   |
|                      | study  | 52     | 52      | 52           | 52       | 52       |
| Heterogeneity        | $\tau^2$ | 15.5%  | 0.0%    | 9.7%         | 7.7%     | 11.8%    | 1.2%     |
|                      | $P_h$  | 0.174  | 0.999   | 0.278        | 0.318    | 0.239    | 0.450    |
|                      | Model  | Fixed  | Fixed   | Fixed        | Fixed    | Fixed    |
| Egger’s test         | $t$    | 1.14   | 1.38    | 0.13         | 2.36     | 2.16     | -0.31    |
|                      | $P_t$  | 0.259  | 0.175   | 0.899        | 0.022    | 0.036    | 0.760    |
| Begg’s test          | $z$    | 0.53   | 0.84    | 0.77         | 1.96     | 1.82     | 1.29     |
|                      | $P_z$  | 0.597  | 0.398   | 0.444        | 0.049    | 0.068    | 0.198    |

$OR$ odds ratio, CIs confidence intervals, $P_a$ P value of association test, $P_h$ P value of heterogeneity test, $P_t$ P value of Egger’s test, $P_z$ P value of Begg’s test
### Table 3: Subgroup analysis of the GSTP1 rs1695 A/G polymorphism by race, genotyping assay and control source

| Factor          | Subgroup | Index | Allele Carrier | Homozygote | Heterozygote | Dominant | Recessive |
|-----------------|----------|-------|----------------|------------|--------------|----------|-----------|
| Race            | Asian    | OR (95% CIs) | 1.00 (0.89~1.12) | 0.98 (0.86~1.11) | 1.29 (0.94~1.76) | 0.90 (0.78~1.04) | 0.94 (0.82~1.08) | 1.35 (0.99~1.83) |
|                 |          | $P_a$  | 0.948           | 0.716      | 0.114        | 0.139    | 0.361     | 0.058     |
|                 |          | Case/control | 1696/2139 | 1696/2139 | 1696/2139 | 1696/2139 | 1696/2139 | 1696/2139 |
|                 |          | Study number | 10         | 10        | 10          | 10       | 10         | 10         |
| Race            | Caucasian| OR (95% CIs) | 0.98 (0.93~1.03) | 0.98 (0.82~1.04) | 1.00 (0.89~1.12) | 0.94 (0.87~1.01) | 0.95 (0.89~1.02) | 1.02 (0.91~1.14) |
|                 |          | $P_a$  | 0.358           | 0.447      | 0.984        | 0.099    | 0.153     | 0.716     |
|                 |          | Case/control | 5968/9719 | 5968/9719 | 5968/9719 | 5968/9719 | 5968/9719 | 5968/9719 |
|                 |          | Study number | 30         | 30        | 30          | 30       | 30         | 30         |
| genotyping      | PCR-RFLP | OR (95% CIs) | 0.99 (0.94~1.03) | 0.99 (0.93~1.04) | 1.01 (0.91~1.12) | 0.96 (0.90~1.03) | 0.97 (0.91~1.03) | 1.01 (0.91~1.12) |
|                 |          | $P_a$  | 0.542           | 0.579      | 0.874        | 0.260    | 0.351     | 0.824     |
|                 |          | Case/control | 8008/11,342 | 8008/11,342 | 8008/11,342 | 8008/11,342 | 8008/11,342 | 8008/11,342 |
|                 |          | Study number | 42         | 42        | 42          | 42       | 42         | 42         |
| control source  | PB       | OR (95% CIs) | 0.98 (0.94~1.03) | 0.98 (0.93~1.04) | 1.00 (0.90~1.12) | 0.96 (0.89~1.03) | 0.96 (0.90~1.03) | 1.02 (0.92~1.13) |
|                 |          | $P_a$  | 0.519           | 0.572      | 0.943        | 0.214    | 0.287     | 0.751     |
|                 |          | Case/control | 6697/10,170 | 6697/10,170 | 6697/10,170 | 6697/10,170 | 6697/10,170 | 6697/10,170 |
|                 |          | Study number | 31         | 31        | 31          | 31       | 31         | 31         |
| control source  | HB       | OR (95% CIs) | 0.98 (0.91~1.06) | 0.98 (0.90~1.07) | 1.00 (0.84~1.20) | 0.95 (0.86~1.06) | 0.96 (0.87~1.07) | 1.01 (0.85~1.19) |
|                 |          | $P_a$  | 0.586           | 0.638      | 0.977        | 0.377    | 0.461     | 0.044     |
|                 |          | Case/control | 2771/3946 | 2771/3946 | 2771/3946 | 2771/3946 | 2771/3946 | 2771/3946 |
|                 |          | Study number | 19         | 19        | 19          | 19       | 19         | 19         |

$P_a$, $P$ value of association test

PCR-RFLP polymerase chain reaction-restriction fragment length polymorphism, PB population-based, HB hospital-based, OR odds ratio, CIs confidence intervals

### Table 4: Subgroup analysis of the GSTP1 rs1695 A/G polymorphism by SCC type

| Subgroup | Index | Allele Carrier | Homozygote | Heterozygote | Dominant | Recessive |
|----------|-------|----------------|------------|--------------|----------|-----------|
| ESCC     | OR (95% CIs) | 1.05 (0.96~1.15) | 1.03 (0.93~1.14) | 1.15 (0.95~1.39) | 1.00 (0.88~1.14) | 1.03 (0.92~1.17) | 1.13 (0.95~1.34) |
|          | $P_a$  | 0.263           | 0.568      | 0.155        | 0.970    | 0.575     | 0.160     |
|          | Case/control | 1934/3951 | 1934/3951 | 1934/3951 | 1934/3951 | 1934/3951 | 1934/3951 |
|          | Study number | 15         | 15        | 15          | 15       | 15         | 15         |
| HNSCC    | OR (95% CIs) | 0.95 (0.89~1.10) | 0.96 (0.89~1.03) | 0.94 (0.82~1.09) | 0.94 (0.87~1.02) | 0.93 (0.86~1.01) | 0.95 (0.83~1.09) |
|          | $P_a$  | 0.112           | 0.247      | 0.408        | 0.131    | 0.102     | 0.459     |
|          | Case/control | 4671/4961 | 4671/4961 | 4671/4961 | 4671/4961 | 4671/4961 | 4671/4961 |
|          | Study number | 18         | 18        | 18          | 18       | 18         | 18         |
| LSCC     | OR (95% CIs) | 1.00 (0.93~1.08) | 1.00 (0.92~1.09) | 1.04 (0.88~1.24) | 0.97 (0.87~1.07) | 0.98 (0.89~1.09) | 1.06 (0.90~1.25) |
|          | $P_a$  | 0.940           | 0.973      | 0.616        | 0.526    | 0.741     | 0.485     |
|          | Case/control | 2574/5421 | 2574/5421 | 2574/5421 | 2574/5421 | 2574/5421 | 2574/5421 |
|          | Study number | 15         | 15        | 15          | 15       | 15         | 15         |
| SSCC     | OR (95% CIs) | 0.91 (0.70~1.19) | 0.94 (0.69~1.28) | 0.83 (0.46~1.49) | 0.94 (0.64~1.36) | 0.91 (0.64~1.30) | 0.86 (0.49~1.51) |
|          | $P_a$  | 0.493           | 0.688      | 0.532        | 0.728    | 0.605     | 0.597     |
|          | Case/control | 177/475 | 177/475 | 177/475 | 177/475 | 177/475 | 177/475 |
|          | Study number | 3         | 3        | 3          | 3       | 3         | 3         |

ESCC oesophageal squamous cell carcinoma, HNSCC head and neck squamous cell carcinoma, LSCC lung squamous cell carcinoma, SSCC skin squamous cell carcinoma, OR odds ratio, CIs confidence intervals, $P_a$, $P$ value of association test
### Table

| Study ID | SCC Type | Allele G vs. A | OR (95% CI) | % Weight |
|----------|-----------|----------------|-------------|----------|
| A        |           |                | 1.01 (0.90, 1.12) | 60.60 |
| C        |           |                | 0.85 (0.62, 1.19) | 17.77 |
| D        |           |                | 0.90 (0.67, 1.25) | 1.66 |
| E        |           |                | 0.97 (0.55, 1.71) | 0.68 |
| F        |           |                | 1.11 (0.81, 1.53) | 1.57 |
| G        |           |                | 0.89 (0.55, 1.44) | 0.96 |
| H        |           |                | 0.81 (0.47, 1.40) | 0.63 |
| I        |           |                | 1.44 (0.26, 2.10) | 0.67 |
| J        |           |                | 0.94 (0.77, 1.15) | 4.34 |
| K        |           |                | 1.07 (0.95, 1.24) | 3.12 |
| L        |           |                | 1.03 (0.71, 1.50) | 1.18 |
| M        |           |                | 1.41 (0.33, 1.52) | 0.82 |
| N        |           |                | 1.12 (0.69, 1.90) | 1.74 |
| O        |           |                | 2.11 (0.03, 4.77) | 0.15 |
| P        |           |                | 1.45 (0.02, 2.05) | 1.10 |
| Q        |           |                | 1.05 (0.98, 1.15) | 21.74 |

### Figure 2

Data of subgroup analysis by SCC type (allele model)

### Figure 3

Funnel plot of publication bias analysis.

**A** Egger's test; **B** Begg's test
Similarly, inconsistent results regarding an association between the GSTP1 rs1695 A/G polymorphism and LSCC risk have been reported in different races and geographical locations [24, 31, 33, 34, 37, 40, 45, 47, 52, 56, 57, 60, 63]. Here, we failed to detect a positive correlation between GSTP1 rs1695 and LSCC susceptibility, consistent with the prior meta-analysis of Feng in 2013 [66] and Xu in 2014 [67].

Head and neck cancer comprises cancers of the mouth, nose, sinuses, salivary glands, throat, and lymph nodes in the neck, and HNSCC is the major pathologic type [68]. In 2012, Lang et al. enrolled 28 case-control studies to perform a meta-analysis regarding the genetic effect of the GSTP1 rs1695 A/G polymorphism on overall head and neck cancer [69]. The authors were unable to identify a positive association between the GSTP1 rs1695 A/G polymorphism and the risk of overall head and neck cancer. Nevertheless, the potential role of GSTP1 rs1695 in the susceptibility to HNSCC was not assessed. Therefore, we performed a subgroup meta-analysis of HNSCC involving 18 case-control studies, but did not identify an association between GSTP1 rs1695 and HNSCC risk.

SSCC, SBCC (skin basal cell carcinoma) and (MM malignant melanoma) are the three main types of cutaneous cancer [4]. Herein, we did not identify an association between the GSTP1 rs1695 A/G polymorphism and SSCC risk, consistent with the prior meta-analyses regarding the correlation between GSTP1 rs1695 and the susceptibility to cutaneous cancer in 2015 [70, 71].

Human GST family genes, mainly including GSTA (glutathione S-transferase alpha), GSTM1 (glutathione S-transferase mu 1), GSTT1 (glutathione S-transferase theta 1) and GSTP1, encode phase II enzymes and are thus important for the body defence, metabolic detoxification of mutagens or chemical drugs, or cellular elimination of carcinogens [9, 10]. The rs1695 A/G polymorphism within the GSTP1 gene can result in the substitution of Ile (isoleucine) for Val (valine) at amino acid position 105, which may lower the cytosolic enzyme activity of GSTP1 protein [72, 73]. Although significant associations were not
obtained in our overall meta-analysis or subgroup analyses by pathological type, we cannot rule out the potential genetic effect of the GSTP1 rs1695 A/G polymorphism.

There are still some limitations to our meta-analysis that should be clarified. Even though our findings were considered reliable by our sensitivity analysis and publication bias assessment, more eligible investigations are still warranted to further enhance the statistical power. We note that population-based controls were not utilized in each case-control study. The currently available data of genotypic and allelic frequency from the on-line databases led us to only target the rs1695 polymorphism of the GSTP1 gene. Other possible functional polymorphisms of the GSTP1 gene, such as rs1138272, or relative haplotypes will be important to examine in the future. We should also pay attention to the genetic relationship between GSTP1/GSTM1/GSTT1 polymorphisms and the risk of SCC.

Conclusion
In general, based on the currently published data, the GSTP1 gene rs1695 polymorphism is not associated with the susceptibility to overall SCC diseases, including ESCC, HNSCC, LSCC, and skin SCC. The confirmation or refutation of this conclusion merits further evidence.

Abbreviations
AHR: Aryl hydrocarbon receptor; CADM1: Cell adhesion molecule 1; diASA-AMP: Di-allele-specific amplification with artificially modified primers assay; Embase: Excerpta Medica Database; ESCC: Oesophageal squamous cell carcinoma; GST: Glutathione S-transferase; GSTA: Glutathione S-transferase alpha; GSTM1: Glutathione S-transferase mu 1; GSTP1: Glutathione S-transferase pi 1; GSTT1: Glutathione S-transferase theta 1; GWAS: Genome-wide association study; HB: Hospital-based; HNSCC: Head and neck squamous cell carcinoma; HWE: Hardy-Weinberg equilibrium; KLF5: Kruppel-like factor 5; LSCC: Lung squamous cell carcinoma; MM: Malignant melanoma; OSCP: Oral squamous cell carcinoma; PB: Population-based; PCR: Polymerase chain reaction; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; SBCC: Skin basal cell carcinoma; OSCC: Oral squamous cell carcinoma; PB: Population-based; HNSCC: Head and neck squamous cell carcinoma; ESCC, HNSCC, LSCC, and skin SCC. The confirmation or refutation of this conclusion merits further evidence.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
SW and ZB designed the study. SW, JZ and FJ extracted, analyzed, and interpreted the data. SW and ZB drafted the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
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The authors declare that they have no competing interests.

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