Polymorphic variants conferring genetic risk to cervical lesions support GSTs as important associated loci

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Abstract
To analyze the association between glutathione S-transferases polymorphisms and the risk of cervical lesions.

Case-control studies focusing on the association between glutathione S-transferase polymorphisms and the risk of cervical lesions were collected from the PubMed, Web of Science, Cochrane Library, Embase, Medline, CNKI, VIP and Wanfang databases from inception to August 2018. Pooled odds ratios and 95% confidence intervals were employed to evaluate the strength of the association. Subgroup analysis and sensitivity analysis were used to test the potential discrepancy and robustness, respectively.

A total of 30 studies comprising 3961 patients and 4726 healthy controls satisfied the inclusion criteria. Of these, 6 studies contained information about GSTP1, 27 studies contained information about GSTM1, and 22 studies contained information about GSTT1. Our results supported that there was no statistical association between GSTP1 polymorphism and the risk of cervical lesions (odds ratio [OR] = 1.08, P = .40). The GSTM1 null variant showed increased susceptibility to cervical lesions (OR = 1.45, P < .001). Subgroup analysis revealed that the GSTM1 null variant caused cervical lesions among HPV infection cases (OR = 1.69, P = .02) and among the Chinese and Indian populations (OR = 2.24 and OR = 1.87, respectively, P < .001). The GSTT1 null variant increased the risk of cervical lesions in smokers (OR = 1.52, P = .03). The GSTT1 null genotype was also related to high-grade intraepithelial neoplasia (HSIL) and cervical cancer risk (OR = 1.30 and OR = 1.78, respectively, P < .05).

The GSTM1 null variant caused cervical lesions, especially among HPV infection cases and among the Chinese and Indian populations. The GSTT1 null variant increased the risk of cervical lesions in smokers and was also related to HSIL and cervical cancer risk.

Abbreviations: CI = confidence interval, CIN = cervical intraepithelial neoplasia, GST = Glutathione S-transferase, HDI = human development index, HPV = human papillomavirus, HSIL = high-grade squamous intraepithelial neoplasia, LSIL = low-grade squamous intraepithelial neoplasia (LSIL), OR = odds ratio.

Keywords: cervical lesions, GSTM1, GSTP1, GSTT1, polymorphisms

1. Introduction
Cervical cancer ranks fourth for both incidence and mortality rates in women, with an estimated 770,000 cases and 311,000 deaths in 2018 worldwide. In lower human development index (HDI) regions, it is the second most frequently diagnosed cancer and the second leading cause of cancer death.[1] In China, the results indicated that an estimated 98,900 new cases and 30,500 cancer deaths occurred in 2015.[2] Human papillomavirus (HPV) is considered a major factor in cervical cancer. Other co-factors are also important in cervix carcinogenesis, including immune suppression, cigarette smoking, parity, and oral contraceptive use.

Glutathione S-transferases (GSTs) are a family of phase II enzymes that are responsible for the metabolism of various xenobiotics and carcinogens by catalyzing the conjugation of glutathione to electrophilic compounds.[3] Studies have shown that genetic variations in GSTs affect human phase II detoxification enzymes, thereby altering their ability to detoxify various exogenous and endogenous active species.[4] Previous studies revealed that the GST genetic variants were related to the risk of several cancers, such as breast, lung, prostate, bladder, and nasopharyngeal cancer risk.[5] However, the results were controversial regarding whether GST polymorphisms would lead to the development of cervical lesions, so we conducted this meta-analysis about the relationship between GST genetic variants and cervical lesions risk.

2. Material and methods
2.1. Literature search strategy
We searched the Cochrane Library, Embase, Medline, PubMed, Web of Science, CNKI, Wanfang, and VIP databases by the
following search terms: Glutathione Transferase[Mesh] or GST*, glutathione S-transferase [p][Mesh] or GSTP1, glutathione S-transferase M1[Mesh] or GSTM1, glutathione S-transferase T1 [Mesh] or GSTT1, polymorphism*/variant*/mutation*/SNP, Uterine Cervical Neoplasm [Mesh]/cervix cancer/cervical cancer/cervical neoplasm*/cervical carcinoma*, and the combinations of these. In addition, we searched the reference lists of all identified articles manually to acquire more data.

2.2. Inclusion and exclusion criteria
Studies included needed to meet the following criteria: regarding on the association between GST gene polymorphisms (GSTP1/ GSTM1/GSTT1) and the risk to cervical lesions; human study subjects; case-control studies; available and sufficient genotype distribution data to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs); and diagnoses based on cervical biopsy pathology or cytology. Besides, if there were duplicate studies, the most complete one was reserved. Otherwise, the article was excluded if it did not satisfy the criteria above.

2.3. Data extraction and synthesis
Two investigators extracted relevant data from all the eligible studies independently. A third reviewer was invited to participate in the work when some disagreement occurred; consensus was ultimately reached by discussion. According to the 4th WHO Women’s Genital Tumor Classification Guidelines, we defined cervical lesions as cervical cancer, high-grade intraepithelial neoplasia (HSIL), and low-grade intraepithelial neoplasia (LSIL). LSIL was equivalent to cervical intraepithelial neoplasia (CIN) grade 1, and HSIL included most amount of CIN2 and all CIN3 cases. We gathered characteristics from all satisfied records: the first author, publication year, ethnicity, total numbers of cases and controls, source of controls, genotyping method.

2.4. Statistical analysis
Using the ORs and 95% CIs to assess the degree of association between GSTs polymorphic variants and cervix lesions. A Z-test revealed statistical significance when \(P < .05\). \(I^2\) and \(Q\) statistic were applied to detect heterogeneity among different studies. There was no heterogeneity if \(I^2 < 50\%\) and \(P > .1\) and a fixed effect model was used, otherwise we thought heterogeneity existed in the incorporated populations and a random effect model was used instead. Subsequently, we conducted a subgroup analysis according to HPV infection status, cigarette smoking, degree of cervical lesions, and ethnicity. Hardy-Weinberg equilibrium (HWE) was evaluated by chi-square test with \(P < .05\) indicating a deviation from HWE. Sensitivity analysis was employed to estimate stability of the meta-analysis results by deleting all the studies one by one. Additionally, a Begg funnel plot and an Egger test were used to evaluate publication bias. The statistical analyses were performed using RevMan 5.3 (Cochrane Collaboration) and STATA 12.0 (StatCorp., College Station, TX, USA) software.

3. Results

3.1. Characteristics of included studies
By searching the electronic databases systematically, we initially retrieved 300 articles. After excluding duplicate studies, 207 articles remained. Further reviewing of the titles and abstracts of the identified studies allowed the removal of 169 articles. Of those removed, 141 were clearly irrelevant to GST polymorphisms, 20 were review papers or meta-analyses, 8 records were deleted for other reasons. We downloaded the remaining 38 articles as full-text reports and reviewed them carefully. Four records were excluded for containing duplicate samples, and the data were not available in other 4 studies. Finally, 30 case-control studies containing 3961 cases and 4726 controls were included, among which 6 studies were about GSTP1, 27 articles were on GSTM1, and 22 studies focused on GSTT1 (Fig. 1). The characteristics of included studies were presented at Table 1.

3.2. Meta-analysis results
There were 6 studies on the GSTP1 variant that included 897 cases and 1387 healthy controls. The meta-analysis results did not show a statistical association between GSTP1 polymorphism and the risk of cervical lesions in the dominant genetic model (\(OR = 1.08, P = .40\)) (Fig. 2).

A total of 27 case-control studies were included in the meta-analysis of GSTM1 involving 3383 cases and 3652 controls. The results showed that the GSTM1 null allele was related to an increased risk of cervical lesions (\(OR = 1.45, P < .001\)) (Fig. 3). Great heterogeneity existed in the GSTM1 studies (\(I^2 = 63\%), thus, a random-effect model was employed. In addition, we conducted subgroup analysis based on HPV infection status, smoking status, degree of cervical lesions, ethnicity. The results presented in Table 2. The GSTM1 null variant was related to an increased risk of cervical lesions among HPV positive cases (\(OR = 1.69, P = .02\)) (Fig. 4), nonsmokers (\(OR = 1.73, P < .001\)), and Chinese and Indian populations (\(OR = 2.24\) and \(OR = 1.87\), respectively, \(P < .001\)), but was not related to the degree of cervical lesions (Table 2).

For the GSTT1 genotype, there were 2680 cases and 2971 controls incorporated in the study. The pooled OR suggested that the GSTT1 null genotype might not be related to cervical lesions (\(P = .06\)) (Fig. 5). Considering the heterogeneity, we performed a subgroup analysis stratified by HPV infection status, cigarette smoking, degree of cervical lesions, and ethnicity. The results revealed that the GSTT1 null variant increased cervical lesions in smokers (\(OR = 1.52, P = .03\)) and nonsmokers (\(OR = 1.78\), respectively, \(P < .05\)) but was not related to LSIL (Fig. 6). HPV infection status and ethnicity did not modify the association between GSTT1 polymorphism and cervical lesions (Table 3).

3.3. Detection for heterogeneity and sensitivity analysis
As presented in Tables 2 and 3, there was great heterogeneity among studies relating to GST genetic variants (\(I^2 > 50\%), \(P < .1\)). In consideration of this, we used a random effect model for the meta-analysis. Additionally, subgroup analysis stratified by HPV infection status, cigarette smoking, degree of cervical lesions, and ethnicity was performed to eliminate heterogeneity. Heterogeneity was clearly decreased in the ethnicity subgroup. This indicated that ethnicity might be a confounding factor and heterogeneity source, while the pooled ORs were substantially robust.
300 records identified through database searching

0 additional study identified through other sources

207 articles remaining after duplicates removed

169 articles excluded after scanning titles and abstracts:
- 141 records were irrelevant;
- 20 were review or meta-analysis;
- 8 records were for other reasons.

38 records for full-text reading

4 articles had duplicated study subject;
4 studies’ data were not available.

30 studies were further assessed

30 records included in qualitative synthesis

Figure 1. Flow diagram of searching procedure.

| Study           | Country | Number (case/control) | Source of controls | Genotyping method     |
|-----------------|---------|-----------------------|--------------------|-----------------------|
| Agorastos 2007  | Greece  | 166/114               | Hospital           | PCR                   |
| Chagas 2017     | Brazil  | 175/266               | Hospital           | TaqMan RT-PCR         |
| Chen 1999       | America | 190/206               | Population         | PCR                   |
| Cseh 2011       | Hungary | 117/136               | Hospital           | PCR                   |
| de Carvalho 2008| Brazil  | 43/86                 | Hospital           | PCR                   |
| Goodman 2001    | America | 131/180               | Population         | PCR                   |
| Hasan 2013      | Pakistan| 50/50                 | Population         | PCR                   |
| Jee 2002        | Korea   | 342/707               | Hospital           | PCR                   |
| Kim 2000        | Korea   | 181/181               | Population         | PCR                   |
| Kiran 2010      | Turkey  | 46/52                 | Hospital           | PCR                   |
| Lee 2004        | Korea   | 81/86                 | Hospital           | PCR-RFLP              |
| Ma 2009         | China   | 43/45                 | Hospital           | PCR-RFLP              |
| Natphopsuk 2015 | Thailand| 198/198               | Hospital           | PCR                   |
| Nishino 2008    | Japan   | 124/125               | Population         | PCR                   |
| Nwa 2005        | Japan   | 131/320               | Hospital           | PCR                   |
| Nunobiki 2015   | Japan   | 140/52                | Hospital           | PCR                   |
| Palma 2010      | Italy   | 81/111                | Population         | PCR                   |
| Salinder 2017   | India   | 150/150               | Hospital           | PCR-RFLP              |
| Sethreetham-Ishida 2009 | Thailand | 90/94               | Population         | PCR                   |
| Sharma 2015     | India   | 160/457               | Hospital           | PCR                   |
| Sharma 2004     | India   | 142/96                | Hospital           | PCR                   |
| Sierra-Torres 2003 | America | 69/72                | Population         | PCR                   |
| Sierra-Torres 2006 | Colombia | 91/02                 | Population         | PCR                   |
| Singh 2008      | India   | 150/168               | Population         | PCR                   |
| Soobi 2006      | India   | 103/103               | Hospital           | PCR                   |
| Song 2006       | China   | 130/130               | Hospital           | PCR                   |
| Stotic 2014     | Serbia  | 97/50                 | Population         | PCR                   |
| Ueda 2010       | Japan   | 298/158               | Population         | PCR                   |
| Wang 2018       | China   | 116/116               | Hospital           | PCR                   |
| Zhou 2006       | China   | 129/125               | Hospital           | PCR                   |

PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism.
Sensitivity analysis was utilized to evaluate the stability of the meta-analysis by deleting all the studies one by one. The pooled ORs did not change significantly in any of the GST variants, indicating that the meta-analysis was robust and stable (Fig. 7).

3.4. Publication bias

To detect publication bias, Begg funnel plot and Egger test were performed. The results indicated that no significant evidence of publication bias for GSTP1, GSTM1, and GSTT1 variant was observed in our study ($P > .05$) (Fig. 8).

4. Discussion

Cervical cancer is an outcome of virus-induced carcinogenesis. HPV is the primary etiology of cervical carcinogenesis but all HPV infections do not result in cervical cancer. Tobacco use, immune system function, use of oral contraceptive, number of sexual partners all modify the outcome of cervix lesions.

GSTs play an important role in protecting cells from oxidative damage and in modulating the induction of other enzymes and proteins in response to DNA damage, therefore, they are

![Figure 2](image-url) Forest plots of the association between GSTP1 polymorphism and susceptibility of cervical lesions in dominant genetic model.

![Figure 3](image-url) Forest plots of the association between GSTM1 polymorphism and susceptibility of cervical lesions.
## Table 2

Meta-analysis results of GSTM1 polymorphism.

| GSTM1 | OR (95% CI) | P value | I² (%) | P value | Effects model |
|-------|-------------|---------|--------|---------|---------------|
| Overall | 1.45[1.23, 1.71] | <.001 | 63 | <.00001 | R |
| HPV subgroup | Overall | 1.51[1.11, 2.05] | .009 | 40 | .06 | R |
| HPV positive | 1.69[1.10, 2.61] | .02 | 32 | .19 | R |
| HPV negative | 1.37[0.87, 2.15] | .18 | 40 | .07 | R |
| Smoking subgroup | Overall | 1.56[1.27, 1.91] | <.0001 | 10 | .35 | R |
| Smoking | 1.29[0.92, 1.66] | .14 | 0 | .50 | R |
| Non-smoking | 1.73[1.34, 2.22] | <.0001 | 17 | .30 | R |
| Degree of lesions subgroup | Overall | 1.27[1.07, 1.50] | .006 | 0 | .66 | F |
| Cervical cancer | 1.30[0.87, 1.96] | .20 | 0 | .77 | F |
| HSIL | 1.24[0.97, 1.59] | .08 | 23 | .26 | F |
| LSL | 1.28[0.96, 1.71] | .09 | 0 | .57 | F |
| Ethnicity subgroup | Overall | 1.65[1.44, 1.88] | <.0001 | 64 | .0009 | F |
| China | 2.24[1.70, 2.96] | <.0001 | 34 | .21 | F |
| Japan | 1.15[0.91, 1.44] | .24 | 48 | .12 | F |
| India | 1.87[1.52, 2.30] | <.0001 | 43 | .14 | F |

95% CI = 95% confidence interval, F = fixed-effect model, HSIL = high-grade intraepithelial neoplasia, LSL = low-grade intraepithelial neoplasia, OR = odds ratio, R = random-effect model.

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### Study or Subgroup | Case Events | Case Total | Control Events | Control Total | Odd Ratio M-H | Odd Ratio Random | 95% CI M-H | 95% CI Random |
|-----------------|-------------|------------|----------------|---------------|---------------|----------------|------------|---------------|
#### 3.2.1 HPV Positive

| Study or Subgroup | Case Events | Case Total | Control Events | Control Total | Odd Ratio M-H | Odd Ratio Random | 95% CI M-H | 95% CI Random |
|-----------------|-------------|------------|----------------|---------------|---------------|----------------|------------|---------------|
| Goodman 2001 | 52 | 95 | 8 | 17 | 5.8% | 2.22 [0.76, 6.48] |
| Lee 2004 | 17 | 25 | 14 | 34 | 5.7% | 3.04 [1.03, 8.96] |
| Ma 2009 | 24 | 35 | 6 | 8 | 3.1% | 1.31 [0.26, 6.48] |
| Nunoaki 2015 | 32 | 57 | 4 | 10 | 4.0% | 1.92 [0.49, 7.55] |
| Sharma 2015 | 58 | 95 | 35 | 91 | 11.3% | 2.51 [1.39, 4.53] |
| Sierra-Torres 2006 | 33 | 83 | 18 | 36 | 8.5% | 0.66 [0.30, 1.45] |
| Wang 2018 | 54 | 76 | 26 | 42 | 8.4% | 1.51 [0.68, 3.35] |
| Subtotal (95% CI) | 466 | 238 | 46.8% | 1.69 [1.10, 2.61] |
| Total events | 270 | 108 |

Heterogeneity: Tau² = 0.10; Chi² = 8.76, df = 6 (P = 0.19); I² = 32%
Test for overall effect: Z = 2.39 (P = 0.02)

#### 3.2.2 HPV Negative

| Study or Subgroup | Case Events | Case Total | Control Events | Control Total | Odd Ratio M-H | Odd Ratio Random | 95% CI M-H | 95% CI Random |
|-----------------|-------------|------------|----------------|---------------|---------------|----------------|------------|---------------|
| Goodman 2001 | 22 | 36 | 92 | 163 | 9.2% | 1.21 [0.58, 2.54] |
| Lee 2004 | 25 | 56 | 28 | 52 | 8.9% | 0.69 [0.32, 1.48] |
| Ma 2009 | 5 | 8 | 10 | 37 | 3.1% | 4.50 [0.90, 22.39] |
| Nunoaki 2015 | 42 | 83 | 24 | 42 | 9.0% | 0.77 [0.36, 1.62] |
| Sharma 2015 | 31 | 65 | 125 | 366 | 12.2% | 1.76 [1.03, 2.99] |
| Sierra-Torres 2006 | 3 | 8 | 20 | 56 | 3.3% | 1.08 [0.23, 5.00] |
| Wang 2018 | 15 | 40 | 12 | 74 | 7.4% | 3.10 [1.27, 7.55] |
| Subtotal (95% CI) | 296 | 790 | 53.2% | 1.37 [0.87, 2.15] |
| Total events | 143 | 311 |

Heterogeneity: Tau² = 0.17; Chi² = 11.80, df = 6 (P = 0.07); I² = 49%
Test for overall effect: Z = 1.36 (P = 0.18)

### Figure 4

Subgroup analysis of the association between GSTM1 polymorphism and cervical lesions stratified by HPV infection status. HPV = human papillomavirus.
GSTs catalyzed the conjugation of glutathione to electrophilic substrates, which resulted in the enhanced renal clearance and reduced carcinogenic load from the cell.\[38\] The \textit{GSTP1} G/A single nucleotide polymorphism caused valine (Val) to take the place of isoleucine (Ile) at codon 105, resulting in decreased enzymatic activity and low ability to metabolize certain xenobiotics and carcinogens.\[39\] Biochemical studies indicated that the \textit{GSTP1} AA genotype was 2 to 3 times less stable\[40\] and might be associated with the risk of gynecological cancer. However, our results supported that \textit{GSTP1} AA genetic variant was not associated with the risk of cervix lesions, which was consistent with Zhao\'s finding.\[38\] This might be attributed to an insufficient sample size.

With regard to the \textit{GSTM1} and \textit{GSTT1} genotypes, some studies indicated that the \textit{GSTM1} null or \textit{GSTT1} null variants contributed to cervical cancer susceptibility, while some studies showed that the 2 variants were not associated with cervical carcinogenesis. Our results supported that the \textit{GSTM1} null variant increased the risk of cervical lesions in smokers. The \textit{GSTT1} null genotype was also related to HISL and cervical cancer risk. The \textit{GSTM1} null variant increased susceptibility to cervical carcinogenesis. Subgroup analysis revealed that the \textit{GSTM1} null variant caused cervical lesions among HPV infection cases and among the Chinese and Indian populations. This implied that there were differences in ethnicity and environment. In addition, it elevated the risk of cervical lesions among women who were not smoking, which implied that the \textit{GSTM1} null genotype might be a risk factor independent of cigarette smoking.

A previous study demonstrated that the GST null genotype resulted in complete loss of the ability of the enzyme to bind genotoxic substrates. This led to decreased detoxification ability, a reduction in the metabolic rate of intracellular toxic substances, and increased malignant transformation of cells, which thereby promoted tumorigenesis.\[40\] Several studies on the relationship between GST polymorphisms and cervical cancer risk were conducted. Compared with those studies, our meta-analysis included additional qualified studies to evaluate the association and therefore obtained more persuasive conclusions. Additionally, the study included the association of \textit{GSTP1}, \textit{GSTM1}, and \textit{GSTT1} genetic variants on cervical lesion risk, while previous studies were based on only one or two of the three variants. Moreover, to eliminate the effects of co-factors, we performed subgroup analysis stratified by HPV infection status, cigarette smoking, degree of cervical lesion and ethnicity. Thus, our findings provide stronger evidence for the association between GST genetic variants and cervical lesions.

There are some limitations to our study. First, the small sample size was insufficient to support our results regarding the \textit{GSTP1} genetic variant. Second, the incidence of cervical cancer is highest in sub-Saharan Africa, Latin America, the Caribbean, and Melanesia, where people of African origin account for the majority of the population.\[1\] However, there were no statistics and studies of interest focused on women of African descent. This caused bias in the relationship, which is concerning. Additionally, although we considered the effect of age on our conclusions and attempted to perform a subgroup analysis, inconsistent age grouping of the included studies prevented us from conducting a subgroup analysis stratified by age. Last but not least, \textit{GSTP1}, \textit{GSTM1}, and \textit{GSTT1} all belonged to the glutathione S-transferase family, playing an important role in protecting cells from oxidative damage and in metabolizing...
2.4.1 Cervical cancer

| Study or Subgroup | Case | Control | Odds Ratio | Odds Ratio |
|-------------------|------|---------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Palma 2010        | 8     | 25     | 8      | 25    | 1.90  | [0.73, 4.98] |
| Stosis 2010       | 12    | 32     | 12     | 32    | 0.90  | [0.36, 2.24] |
| Ueda 2010         | 58    | 83     | 58     | 83    | 2.26  | [1.29, 3.97] |
| Subtotal (95% CI) | 140   | 319    | 140    | 319    | 1.78  | [1.17, 2.72] |

Heterogeneity: $Ch^2 = 2.86$, df = 2 ($P = 0.24$); $I^2 = 30$
Test for overall effect: $Z = 2.67$ ($P = 0.008$)

2.4.2 HSIL

| Study or Subgroup | Case | Control | Odds Ratio | Odds Ratio |
|-------------------|------|---------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Agorstinos 2007   | 39    | 97     | 39     | 97    | 0.81  | [0.46, 1.42] |
| Cseh 2011        | 47    | 117    | 47     | 117    | 1.94  | [1.14, 3.30] |
| Nunobiki 2015    | 25    | 41     | 25     | 41     | 1.69  | [0.74, 3.87] |
| Palma 2010       | 7     | 30     | 7      | 30     | 1.23  | [0.47, 3.24] |
| Sierra-Torres 2006 | 25  | 91    | 25     | 91    | 0.96  | [0.50, 1.84] |
| Stosis 2010      | 12    | 33     | 12     | 33     | 0.86  | [0.35, 2.12] |
| Ueda 2010        | 33    | 49     | 33     | 49     | 2.01  | [1.03, 3.94] |
| Subtotal (95% CI) | 458   | 698    | 458    | 698    | 1.30  | [1.01, 1.68] |

Total events: 188/253
Heterogeneity: $Ch^2 = 8.52$, df = 6 ($P = 0.20$); $I^2 = 30$
Test for overall effect: $Z = 2.01$ ($P = 0.04$)

2.4.3 LSIL

| Study or Subgroup | Case | Control | Odds Ratio | Odds Ratio |
|-------------------|------|---------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Agorstinos 2007   | 23    | 51     | 23     | 51    | 0.99  | [0.50, 1.94] |
| Nunobiki 2015    | 50    | 90     | 50     | 90    | 1.35  | [0.68, 2.68] |
| Palma 2010       | 8     | 26     | 8      | 26     | 1.80  | [0.69, 4.67] |
| Stosis 2010      | 14    | 32     | 14     | 32     | 1.17  | [0.47, 2.87] |
| Ueda 2010        | 76    | 167    | 76     | 167    | 0.81  | [0.53, 1.26] |
| Subtotal (95% CI) | 366   | 470    | 366    | 470    | 1.03  | [0.77, 1.37] |

Total events: 171/192
Heterogeneity: $Ch^2 = 3.11$, df = 4 ($P = 0.54$); $I^2 = 0$
Test for overall effect: $Z = 0.18$ ($P = 0.86$)

Total (95% CI) 964/1487 100.0% 1.26 [1.06, 1.50]
Total events 437 567
Heterogeneity: $Ch^2 = 18.90$, df = 14 ($P = 0.17$); $I^2 = 26$
Test for overall effect: $Z = 2.59$ ($P = 0.010$)
Test for subgroup differences: $Ch^2 = 4.54$, df = 2 ($P = 0.10$); $I^2 = 56$

Figure 6. Subgroup analysis of the association between GSTT1 polymorphism and cervical lesions stratified by degree of lesions.

Table 3
Meta-analysis results of GSTT1 polymorphism.

| GSTT1   | OR (95% CI) | P value | $I^2$ (%) | P value | Effects model |
|---------|-------------|---------|-----------|---------|---------------|
| Overall | 1.21[0.99, 1.47] | .06     | 61        | <.0001  | R             |
| HPV subgroup | Overall | 1.27[0.85, 1.90] | .24     | 56        | .009          | R             |
| HPV positive | Overall | 1.39[0.67, 2.89] | .37     | 67        | .009          | R             |
| HPV negative | Overall | 1.16[0.73, 1.86] | .53     | 46        | .10           | R             |
| Smoking subgroup | Overall | 1.05[0.76, 1.46] | .77     | 35        | .11           | R             |
| Smoking | Overall | 1.52[1.03, 2.23] | .03     | 0         | .98           | R             |
| Non-smoking | Overall | 0.76[0.46, 1.26] | .29     | 51        | .07           | R             |
| Degree of lesion subgroup | Overall | 1.26[1.06, 1.50] | .01     | 26        | .17           | F             |
| Cervical cancer | Overall | 1.78[1.17, 2.72] | .008    | 30        | .24           | F             |
| HSIL | Overall | 1.30[0.91, 1.86] | .04     | 30        | .20           | F             |
| LSL | Overall | 1.03[0.77, 1.37] | .86     | 0         | .54           | F             |
| Ethnicity Subgroup | Overall | 1.15[0.84, 1.56] | .38     | 66        | .003          | R             |
| Japan | Overall | 1.13[0.90, 1.42] | .28     | 0         | .86           | R             |
| India | Overall | 1.16[0.61, 2.22] | .66     | 82        | .0001         | R             |

95% CI = 95% confidence interval, F = fixed-effect model, HSIL = high-grade intraepithelial neoplasia, LSL = low-grade intraepithelial neoplasia, OR = odds ratio, R = random-effect model.
various carcinogens. As reported, the combination of the \textit{GSTM1} null, \textit{GSTT1} null, and \textit{GSTP1} AA genotypes was associated with an increased risk of gynecological cancer, while the \textit{GSTs} alone were not.\textsuperscript{[23]} Therefore, gene–gene interactions are likely more appropriate to assess disease risk than individual genes. In our meta-analysis, there was no association study between gene–gene interactions and the risk of cervical lesions. Future studies containing more comprehensive information are needed to obtain more reliable conclusions.

\begin{figure}[h]
\begin{center}
\hspace{0.5cm}
\includegraphics[width=\textwidth]{sensitivity_analysis.png}
\end{center}
\caption{Sensitivity analysis of the association between \textit{GST} SNPs and risk of cervical lesions. (A) \textit{GSTP1}; (B) \textit{GSTM1}; (C) \textit{GSTT1}.}
\end{figure}
5. Conclusion

In general, the GSTP1 AA genotype was not associated with the risk of cervical lesions. The GSTM1 null variant caused cervix lesions, especially among HPV infection cases and among the Chinese and Indian populations. GSTT1 null variant increased the risk of cervical lesions in smokers and was also related to HISL and cervical cancer risk. Additional large, well-designed case-control studies are needed to authenticate these results.

Author contributions

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Figure 8. Publication bias of GST polymorphisms. (A, B). GSTP1, Begg test, \( P = .452 \), Egger test, \( P = .448 \); (C, D). GSTM1, Begg test, \( P = .144 \), Egger test, \( P = .122 \); (E, F). GSTT1, Begg test, \( P = .778 \), Egger test, \( P = .502 \).
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