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Null Genotypes of *GSTM1* and *GSTT1* Contribute to Risk of Cervical Neoplasia: An Evidence-Based Meta-Analysis

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Abstract

Background and Objectives: Glutathione S-transferases (GSTs) are multifunctional enzymes that play a key role in the detoxification of varieties of both endogenous products of oxidative stress and exogenous carcinogens.

Methods: In this meta-analysis, twenty-five studies were identified by searching PubMed, EMBASE, ISI Web of Science and CBM databases: 23 evaluated *GSTM1* and 19 evaluated *GSTT1*. Crude odds ratios with corresponding 95% confidence intervals were used to estimate the association between *GSTM1* and *GSTT1* polymorphisms and risk of cervical neoplasia. Subgroup analyses were conducted by pathological history, ethnicity, source of DNA for genotyping, quality score, and matching variable.

Results: The null genotypes of *GSTM1* and *GSTT1* polymorphisms were associated with a significantly increased risk of cervical neoplasia (for *GSTM1*: OR = 1.40; 95%CI, 1.19–1.65; for *GSTT1*: OR = 1.30; 95%CI, 1.05–1.62, respectively). Subgroup analyses showed that the null genotype of *GSTM1* increased the risk of cervical neoplasia in Asians, studies with DNA isolation from white blood cells and tissue samples, both high and low quality studies, and matched studies. In *GSTM1-GSTT1* interaction analysis, individuals with dual null genotype were associated with a significantly increased risk of cervical neoplasia (OR = 1.72; 95%CI, 1.18–2.51).

Conclusion: These findings indicate that *GSTM1* and *GSTT1* polymorphisms, particularly *GSTM1-GSTT1* interaction, may play critical roles in the development of cervical neoplasia. A conservative manner should be adopted to interpret these results because of obvious heterogeneity between-study, unadjusted data, and relatively small sample size in this meta-analysis. Well designed studies with larger sample size are of great value to confirm these results.

Introduction

Cervical cancer is the second most frequent cancer among women worldwide, with approximately 493,000 new cases diagnosed and 274,000 deaths occurring each year (2002 estimates) [1]. Despite substantial declines in the incidence and mortality of cervical cancer in developed countries, more than 80% of all cervical cancer occurs in developing countries [1,2]. The burden of cervical cancer is not only the high incidence rates in women in some developing countries, but also the societal impact because a fraction of patients who suffered from the disease in their 30's or 40's are still raising or supporting families.

It is well established that human papilloma virus (HPV) infection is a necessary but insufficient event for the development of cervical cancer [3–6], because not all HPV-infected patients do develop cervical cancer. Therefore, many research efforts were taken to identify cofactors for cervical cancer development. To date, the major risk cofactors have been confirmed by large meta-analysis, including smoking, multiple sexual partners, increasing parity, earlier age at first intercourse (≤20 years), and long duration of oral contraceptive use [7–9]. However, it is currently accepted that the development of cervical cancer is the result of complex interaction of both environmental and genetic factors [10]. Epidemiological evidence has shown that there is a significant familial clustering among biological relatives. The familial relative risk for individuals with biological full-sisters of cervical cancer cases is almost twice as high as those with biological full-sisters of controls [11–13]. Recently, several meta-analysis studies revealed that a polymorphic variant of the tumor suppressor *P53* (Pro72Arg) may represent a genetic marker for cervical carcinogenesis [14–17].

Over the past decades, glutathione S-transferases (GSTs) genetic variants have been explored extensively as a predictive factor for cancer prognosis [18]. GSTs are a family of enzymes with a crucial function in the detoxification of a variety of both endogenous products of oxidative stress and exogenous carcinogens [19,20]. In humans, GST super-family consists of many cytosolic, mitochondrial, and microsomal proteins. The cytosolic family has been assigned to eight distinct classes: alpha, kappa, mu, omega, pi, sigma, theta, and zeta [21]. The mu class of GSTs, encoded by the GSTM1 gene, is located on the short arm of chromosome 1 (1p13.3) [22]. The theta class of GSTs, encoded by the GSTT1 gene, is locate on the long arm of chromosome 22 (22q11.23) [23]. Both GSTM1 and GSTT1 gene exhibit an inherited homozygous deletion polymorphism (null genotype) that is associated with an absence of enzyme activity. Individuals with homozygous deletion polymorphism are considered to be at increased risk for malignancies due to reduced efficiency in protection against environmental carcinogens [18,24].

In 1994, Warwick et al. explored for the first time the association between GSTM1 and GSTT1 polymorphisms and the risk of cervical neoplasia, and found that the combination of three factors (i.e., GSTM1 or GSTT1 null, CYP2D6 EM, and smoking) appeared significantly different frequency in cases and controls [25,26]. Subsequently, a large number of epidemiological studies have been addressed to evaluate the association between GSTM1 and GSTT1 homozygous deletion polymorphisms and risk of cervical neoplasia in diverse ethnicities [25–49]. However, this issue remains controversial because of inconsistent results among different studies. The possibilities for this discrepancy may be that some positive results might occur by chance and some negative findings might be caused by insufficient statistical power with small sample size. Additionally, different experimental design and selection bias should also be considered.

In order to provide strong evidence of the effects of GSTM1 and GSTT1 polymorphisms on cervical neoplasia risk, we carried out a quantitative meta-analysis by combining data from all published case-control studies. Additionally, gene-gene and gene-environment interactions have also been examined in this meta-analysis.

Materials and Methods

Selection of Published Studies

We identified all publications by conducting computer-based searches of PubMed, EMBASE, ISI Web of Science, and CBM databases without language restrictions, using the following search algorithm: ("cervical cancer" or "cervical carcinoma" or "uterine cervix cancer" or "CC" or "cervical neoplasia") and ("glutathione S-transferase" or "GST" or "GSTM" or "GSTM1" or "GSTT" or "GSTT1") and ("polymorphism" or "polymorphisms" or "variant"). The literature search was performed up to Aug 2010. The inclusion criteria were: (a) case-control studies that investigated the association between GSTM1 and/or GSTT1 polymorphism and risk of cervical neoplasia; (b) presenting original data for the calculation of odds ratios (ORs) with corresponding 95% confidence intervals (95%CIs).

One hundred and fifty-four articles were identified by searching PubMed, EMBASE, ISI Web of Science and CBM databases. Eighty-four studies were excluded after screening the title or abstract (67 were not cervical cancer; eight were no polymorphism; six were not human studies; three were not case-control studies). Then full-text articles were retrieved for assessment in detail. Forty-three were excluded with reasons for not cervical cancer (n = 23), no GSTM1 and/or GSTT1 polymorphism (n = 13), no available data (n = 5) and review articles (n = 2). Additionally, we excluded two

studies because the results were duplicated in subsequent publications [50,51]. Finally, a total of 25 studies were included in this meta-analysis (Figure S1). Of the 25 studies, 23 studies investigated the association between GSTM1 polymorphism and risk of cervical neoplasia and 19 studies investigated the association between GSTT1 polymorphism and risk of cervical neoplasia.

The groups of pathologic type were set according to the report by Klug et al. [17]. Briefly, the selected studies in this analysis were composed of unclear type of cervical cancer, squamous cell carcinoma (SCC), adenocarcinoma (AC), adenosquamous carcinoma, high-grade lesions (HGL, containing high-grade squamous intraepithelial lesions and cervical intraepithelial lesions grades 2 and 3) and low-grade lesions (LGL, containing low-grade squamous intraepithelial lesions and cervical intraepithelial lesions grade 1).

This study was approved by the ethics committee of Sichuan University. The data included in this study was taken from literatures, and thus written consent given by the patients was not needed.

Data Extraction

Two independent researchers (Gao and Pan) extracted raw data according to the inclusion criteria. The following information was collected from each study using a data extraction form: the surname of the first author, date of publication, country of origin, year of sample collection, ethnicity, characteristics of cases and controls, DNA source for genotyping, matching variables, number of cases and controls, genotype distribution of cases and controls, and quality control for genotyping assay. Additionally, we extracted, if available, the genotype frequency of cases and controls based on age (>40 or ≤40 years), smoking status (smoking or non-smoking) and HPV infection status (HPV positive or HPV negative). Given that there was no distribution of null/present heterozygote in each single study selected, the Hardy-Weinberg equilibrium (HWE) test could not be conducted. To ensure the accuracy of data extraction, the original extraction information was checked by Li, and discordant results were settled through discussion among the three authors.

Quality Score Evaluation

Three investigators (Gao, Pan, and Li) independently assessed the quality of included studies based on a predetermined rating scale (Table S1) that was amended from previous studies [52–54]. Any discrepancies were resolved by consultation with the other authors in the team group, and an ultimate decision was made by the majority of the votes cast. A numerical score ranging from 0 to 12 was assigned as a quantitative measure of literature quality. Studies were categorized as "high quality" if the quality score was ≥7; otherwise, studies were categorized as "low quality".

Statistical Analysis

We used crude ORs with corresponding 95% CIs as a measure of the association between GSTM1 and GSTT1 polymorphisms and risk of cervical neoplasia. Study-specific ORs comparing null genotype versus present genotype were combined using random-effects model (the DerSimonian and Laird) or fixed-effects model (the Mantel–Haenszel method), which was determined by the Q-test and I^2 statistics [55,56]. If the P value for heterogeneity was ≤0.10 or $I^2≥50\%$, indicating a high extent of heterogeneity between studies, we used the DerSimonian and Laird method to evaluate the summary ORs. In contrast, if the P value for heterogeneity was >0.10 and $I^2<50\%$, indicating an absence of heterogeneity between studies [57,58], we used the Mantel–Haenszel method to evaluate the summary ORs.

Subgroup analyses were conducted by pathological history (squamous cell cervical carcinoma, adenocarcinoma and adeno-

squamous carcinoma, cervical cancer of unknown type, HGL, LGL, and mixed), ethnicity (Asian, Caucasian, and mixed), source of DNA for genotyping (white blood cells, exfoliated cervical cells, tissue sample, and mixed), quality score (high versus low), matching according to age (matched versus unmatched), smoking status (smoking versus non-smoking) and HPV infection status (HPV positive versus HPV negative). Additionally, we evaluated the effect of the *GSTM1-GSTT1* interaction on cervical neoplasia compared with null/null versus present/present, null/null versus present/null, null/null versus null/present, null/present versus present/null, null/present versus present/present, and present/null versus present/present.

Logistic meta-regression was used to investigate possible sources of heterogeneity across studies. To determine the reliability of the outcomes in the meta-analysis, a sensitivity analysis was performed by exclusion an individual study each time. An evaluation of publication bias was carried out with funnel plot for visual inspection and Egger's regression asymmetry test [59]. All analyses were conducted in STATA software, version 10.0 (STATA Corp., College Station, TX).

Results

Characteristics of Studies

The baseline characteristics of the included studies are shown in Tables S2 and S3.

GSTM1 Polymorphism. Totally, 23 studies met the inclusion criteria and were selected in this meta-analysis with 2,610 cases and 3,084 controls. Cases consisted of 32.5% patients with cervical cancer (histology not specified), 31.9% patients with SCC, 14.2% patients with HGL, 8.6% patients with LGL, 5.0% patients with SIL (unknown grade), 4.7% patients with both ICC and HGL and 3.0% patients with AC. Most of the controls (86.8%) were normal participants. There were sixteen studies of Asians, six studies of Caucasians, and two studies of mixed ethnicities that included more than one ethnicity. DNA used for *GSTM1* genotyping was extracted from white blood cells in 15 studies (62.5%). 17 studies (70.8%) mentioned genotyping quality control methods, mainly using an internal control. However, only six studies (25.0%) reported smoking status and only four studies (16.7%) detected HPV infection status.

GSTT1 Polymorphism. A total of 19 studies were included in the meta-analysis with 2,092 cases and 2,054 controls. Cases consisted of 27.1% patients with cervical cancer (histology not specified), 30.5% patients with SCC, 15.9% patients with HGL, 8.6% patients with LGL, 6.3% patients with SIL (unknown grade), 5.9% patients with both ICC and HGL and 5.8% patients with AC. Most of the controls (85.5%) were normal participants. Twelve studies were conducted in Asia; four in Europe; two in America and one in South America. Similar to *GSTM1* polymorphism, most studies (68.4%) mentioned genotyping quality control methods, but only about 20% studies reported smoking status and HPV infection status.

Meta-analysis of GSTM1 Polymorphism and Cervical Neoplasia

The evaluations of the association between *GSTM1* polymorphism and cervical neoplasia risk are summarized in Table S4.

The null genotype of *GSTM1* polymorphism was associated with a significantly increased risk of cervical neoplasia when compared with present genotype (OR = 1.40; 95%CI, 1.19–1.65). When stratified by pathologic types, significantly elevated risks were observed in unknown type of cervical cancer (OR = 1.54; 95%CI, 1.16–2.04) and mixed group (OR = 1.98; 95%CI,

1.46–2.68) but not in groups of SCC, HGL, LGL and AC. In the subgroup analysis by ethnicity, significantly increased risks were observed in Asian population (OR = 1.60; 95%CI, 1.29–1.98) but not in Caucasian and mixed populations (Figure S2). Subgroup analysis on the basis of DNA source showed that the increased risks were found in studies that DNA was extracted from white blood cells (OR = 1.29; 95%CI, 1.08–1.55) or tissue sample (OR = 3.14; 95%CI, 1.90–5.19). No excess risk was found in studies that DNA was extracted from exfoliated cervical cells. Subgroup analysis was also performed according to quality criteria. The combined results showed that the null genotype was associated with an increased risk of cervical neoplasia in studies whether the quality score was high (OR = 1.31; 95%CI, 1.06–1.62) or low (OR = 1.49; 95%CI, 1.16–1.91). The increased risks were also found in studies in which controls were frequency matched to cases by age (OR = 1.54; 95%CI, 1.22–1.95), but not in studies in which controls were unmatched to cases by age. Additionally, subgroup analysis by age presented the results that the null genotype was associated with an increased risk of cervical neoplasia in studies with patients of age ≤40 years (OR = 2.02; 95%CI, 1.30–3.14).

Meta-analysis of GSTT1 Polymorphism and Cervical Neoplasia

The evaluations of the association of *GSTT1* polymorphism and cervical neoplasia risk are listed in Table S5.

The null genotype of *GSTT1* polymorphism was associated with a significantly increased risk of cervical neoplasia (OR = 1.30; 95%CI, 1.05–1.62) and unknown type of cervical cancer (OR = 1.49; 95%CI, 1.02–2.19), while the association was not observed in subgroup analyses according to ethnicity, DNA source, and quality criteria (Figure S3).

Meta-analysis of GSTM1-GSTT1 Interaction with Cervical Neoplasia

The evaluations of the association between *GSTM1-GSTT1* interaction and cervical neoplasia risk are shown in Table S6.

The dual null genotype was associated with a significantly increased risk of cervical neoplasia when compared with the dual present genotype (OR = 1.72; 95%CI, 1.18–2.51) (Figure S4). No significantly increased risk was detected in any other comparison group.

Interaction between GSTM1 and GSTT1 and Environmental Exposure

There were six literatures which investigated the impact of interaction between *GSTM1* polymorphism and smoking on cervical neoplasia, and there were four literatures which investigated the impact of interaction between *GSTT1* polymorphism and smoking on cervical neoplasia. The effect of interaction between *GSTM1* polymorphism and HPV infection status on cervical neoplasia was reported in four studies, and the effect of interaction between *GSTT1* polymorphism and HPV infection status on cervical neoplasia was reported in five studies. No increased risks were found in the interaction between *GSTM1* and *GSTT1* polymorphisms and environmental exposure (i.e., smoking status and HPV infection status) (Tables S4 and S5).

Heterogeneity Analysis

The findings of Q-tests and I^2 statistics were shown in Tables S4, S5, and S6. Significant heterogeneity across studies was present in overall analyses (for *GSTM1*, I^2 = 53.3%; for *GSTT1*, I^2 = 59.1%) and subgroup analyses. We explored several possible

sources of the between-study heterogeneity, including cancer type, ethnicity, sample size, DNA source for genotyping and quality score. However, none of these variables could explain the heterogeneity.

Sensitivity Analysis and Publication Bias

To assess the effect of individual study on the overall meta-analysis estimate, we excluded one study at a time, and the exclusion of any single report did not alter the significance of the final decision, suggesting that the outcomes were robust. Funnel plot and Egger's test were used to assess publication bias of literatures on cervical neoplasia. No evidence of publication bias was observed in all comparison groups ($P > 0.05$).

Discussion

The glutathiones S-transferases (GSTs) are the most important parts of phase II superfamily of metabolism enzymes. In humans, there are several GST classes that were encoded by distinct gene families [21]. Among them, GSTM1 and GSTT1 should be pointed out because a polymorphic deletion of these genes may influence the enzyme activity, and eventually increased vulnerability to genotoxic damage [60,61]. Based on these backgrounds, the association has been intensively investigated between GSTM1 and GSTT1 polymorphisms and risk of cervical neoplasia [25–49]. Unfortunately, most of the studies have only a few hundred of participants, even less, which is too small to evaluate the overall effects precisely. Meta-analysis has been considered to be a powerful tool to overcome this problem by combining the results from independent studies together. In this meta-analysis, we found that the null genotypes of GSTM1 and GSTT1 polymorphisms were associated with a significantly increased risk of cervical neoplasia, suggesting that GSTM1 and GSTT1 polymorphisms may be involved in the development of cervical neoplasia. Notably, the between-study heterogeneity was observed in both overall analyses and some subgroup analyses, further studies therefore are warranted to confirm these findings.

After subgroup analysis according to ethnicity, significantly increased risks were observed in Asian population but not in Caucasian and mixed populations. The possibilities of the conflicting results among diverse ethnicities may be that the GSTM1 and GSTT1 polymorphisms have different effects on the risk of cervical neoplasia in different genetic backgrounds and environment which they exposed to. The major difference in the distribution of GSTM1 and GSTT1 polymorphisms has been reported among control groups in 2001. The frequency of GSTM1 null genotype was 53.1% (42.0–60.0%) in Caucasians, 52.9% (42.0–54.0%) in Asians, and 26.7% (16.0–36.0%) in Africans. The frequency of GSTT1 null genotype was 19.7% (13.0–26.0%) in Caucasians and 47.0% (35.0–52.0%) in Asians [62]. Additionally, the small sample size should also be taken into consideration because limited sample size may have not enough statistical power to detect a real effect or generate a fluctuated estimation. At present, limited studies investigated the association between GSTM1 and GSTT1 polymorphisms and the risk of cervical neoplasia in Caucasian and mixed populations. Therefore, well-designed studies with thousands of sample size are of great value to confirm this finding in Caucasians and other ethnic populations.

When stratified based on the source of DNA for GSTM1 and GSTT1 genotyping, the null genotype of GSTM1 significantly increased the cervical neoplasia risk in studies that the polymorphism was determined from white blood cells rather than from exfoliated cervical cells. The difference of studies with DNA isolation from exfoliated cervical cells tended to be significant

($P = 0.057$). It is likely that the potentially negative results were caused by small sample size with only 299 cases and 405 controls available in this meta-analysis. Another important issue is the source of cell used for DNA analysis. DNA isolation from different cell types may influence performance of genotyping, and eventually, lead to the conflicting results.

It is absolutely pivotal for a meta-analysis to assess the quality of literatures included. Currently, no standard quality score method was developed to evaluate observational case-control studies. We used a self-made rating scale for quality assessment, which was modified from previous studies [52–54]. Studies included in this meta-analysis were classified into high quality (≥ 7) or low quality (< 7) according to the quality score. The combined results showed that the null genotype of GSTM1 polymorphism was associated with an increased risk of cervical neoplasia in both high quality studies and low quality studies. However, there was lack of association between GSTT1 polymorphism and cervical neoplasia risk either in high quality studies or in low quality studies. These findings denote that GSTM1 plays much more important roles than GSTT1 in the development of cervical neoplasia.

The hypothesis of cigarette smoking being a risk factor for cervical cancer was originally presented in 1977 [63]. Subsequently, amounts of epidemiological studies reported the support for this hypothesis [7,64–69]. Despite the mechanism that tobacco smoking increase the risk of uterine cervical cancer remains unknown, it is believed that the occurrence of tobacco-initiated DNA damage in the cervical epithelium may be responsible for malignant transformation [70]. Tobacco smoke contains over fifty known carcinogens, such as polynuclear aromatic hydrocarbons, aromatic amines, nicotine, and nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl) -1-butanone (NNK) [70–73]. The concentrations of NNK in cervical mucous of cigarette smoking women were three times higher than those in non-smokers [70]. Such carcinogens may promote cancer through the stimulation of cell division or impairment of local immunosurveillance in the cervical epithelial tissue [67,74]. In view of the crucial role that the smoking play in the etiology of cervical cancer, the effect of the interaction of GSTM1 and GSTT1 polymorphisms and smoking on the development of cervical neoplasia has been conducted in several studies [31–33,37,38,46]. Therefore, it is necessary to analyze quantitatively the association between gene-environment interaction and the risk of cervical neoplasia using a meta-analysis. However, no evidence of correlation was observed between GSTM1 and GSTT1 polymorphisms and cervical neoplasia in combination with smoking habit. There may be a high risk of false negative results due to insufficient statistical power with very limited subjects eligible in this meta-analysis (for GSTM1 polymorphism: 737 cases and 704 controls; for GSTT1 polymorphism: 403 cases and 373 controls).

Persistent HPV infections are known to be the major cause of cervical cancer [5,6]. Therefore, HPV infection status was also examined in subgroup analysis. Nevertheless, we failed to find any association between GSTM1 and GSTT1 polymorphisms and cervical neoplasia risk in either HPV positive women or HPV negative women. The null result may be owing to limited relevant studies included in this meta-analysis. Thus, large-scale prospective cohort studies are needed to provide the best evidence for the impact of interaction of gene-environment on the risk of cervical neoplasia.

Over the past decades, a large number of meta-analyses have been done to investigate the association between GSTM1 and GSTT1 polymorphisms and various cancers, including brain tumors [75], hepatocellular carcinoma [76,77], colorectal cancer [78,79],

gastric cancer [80–84], breast cancer [85–90], bladder cancer [91–93], lung cancer [94–99], esophageal cancer [100,101], prostate cancer [102,103], nasopharyngeal carcinoma [104], head and neck cancer [105], oral and laryngeal cancer [106–108], and acute leukaemia [109,110]. During revision of the manuscript, a similar report investigating the association between GSTM1 and GSTT1 polymorphisms and cervical cancer risk was published [111]. In the report, Economopoulos et al. identified publications by a search of Medline database (last search: August 3, 2009) and found that the GSTM1 polymorphism but not GSTT1 polymorphism was associated with the risk of cervical cancer [111]. In this meta-analysis, the eligible studies were identified by computer-based searches of three additional databases (i.e., EMBASE, ISI, and CBM) besides Medline, and the last search was performed up to August 2010. Moreover, studies examining the association between GSTM1 and GSTT1 polymorphisms and cervical intraepithelial neoplasia were also selected. Much more eligible studies, therefore, were included in this meta-analysis. Consistent with the results reported by Economopoulos et al., we found that the null genotype of GSTM1 polymorphism was associated with a significantly increased risk of cervical neoplasia. Inconsistent with the results reported by Economopoulos et al., we found an evidence of an association between GSTT1 polymorphism and the risk of cervical neoplasia with a borderline statistical significance. Larger sample size in this study may be responsible for the positive results. Our findings were in agreement with several previous reports. For example, Wang et al. reported that both GSTM1 and GSTT1 polymorphisms are associated with increased risk of hepatocellular carcinoma [77]. Economopoulos et al. reported that both GSTM1 and GSTT1 null genotype carriers exhibited higher colorectal cancer risk in Caucasian population [78]. In contrast, some researchers reported that GSTM1 and GSTT1 polymorphisms did not increase a substantial risk of breast cancer [88] and prostate cancer [102]. Taken together, these results indicate that GSTM1 and GSTT1 homozygous deletion polymorphisms may yield different effects on different types of cancers.

Our study has some limitations. Firstly, the between-study heterogeneity is a major problem in this meta-analysis because obvious heterogeneity was detected in overall analyses and also subgroup analyses. We explored several possible sources of heterogeneity, including cancer type, ethnicity, sample size, DNA source for genotyping and quality score. Unfortunately, we failed to find a bright reason for this variation, indicating that unknown confounding variables in single studies may have biased the findings. A conservative manner should, therefore, be adopted to interpret these results. Secondly, some potential confounding factors, such as age, sexual habits, and menopausal status can not be ruled out due to unadjusted data used. Finally, the sample size is relatively small in the meta-analysis, especially in some subgroup analyses.

In summary, this meta-analysis indicates that the null genotypes of GSTM1 and GSTT1 polymorphisms were associated with a significantly increased risk of cervical neoplasia. In GSTM1-GSTT1 interaction analysis, individuals with dual null genotype were associated with a significantly increased risk of cervical neoplasia. In gene-environment interaction analysis, neither smoking status nor HPV infection status was associated with GSTM1 and GSTT1 polymorphisms. To ensure a precise estimate of the effect of GSTM1 and GSTT1 polymorphisms on cervical neoplasia risk, additional unbiased studies with larger sample size are needed. Such studies will not only elucidate the pivotal roles GSTM1 and GSTT1 polymorphisms playing in the development of cervical neoplasia, but also increase our understanding the etiology of cervical neoplasia.

Supporting Information

Figure S1 Flow diagram of the literature search.
(TIF)

Figure S2 Forest plot of cervical neoplasia risk of GSTM1 polymorphism in subgroup analysis according to ethnicity.
(TIF)

Figure S3 Forest plot of association between GSTT1 polymorphism and risk of cervical neoplasia.
(TIF)

Figure S4 Forest plot of GSTM1-GSTT1 interaction (null/null versus present/present).
(TIF)

Table S1 Quality assessment for the included studies.
(DOC)

Table S2 Overview of literatures included in the meta-analysis.
(DOC)

Table S3 Characteristics of the included studies.
(DOC)

Table S4 Summary odds ratios with confidence intervals between the GSTM1 polymorphism and cervical neoplasia risk.
(DOC)

Table S5 Summary odds ratios with confidence intervals between the GSTT1 polymorphism and cervical neoplasia risk.
(DOC)

Table S6 Summary odds ratios with confidence intervals between the GSTM1-GSTT1 interaction and cervical neoplasia risk.
(DOC)

Author Contributions

Conceived and designed the experiments: L-BG X-MP LZ. Performed the experiments: X-MP L-JL W-BL PB. Analyzed the data: X-MP TW. Contributed reagents/materials/analysis tools: LR X-WS. Wrote the paper: L-BG LZ. Helped edit the manuscript: BZ Y-GW.

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