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Review

Glutathione S-Transferase Mu1 polymorphisms and environmental factors in cervical cancer susceptibility: a systematic review and meta-analysis

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Abstract

Cervical cancer is a multifactorial disease like any other human cancer. Among these factors, genetic polymorphisms of Glutathione S-Transferase Mu1 (*GSTM1*) have been incriminated, but the study results remain controversial. The objective of this meta-analysis was to assess the association between *GSTM1* polymorphisms and cervical cancer, and to examine potential interactions with Human Papillomavirus (HPV) infection and tobacco smoke exposure. A meta-analysis was conducted on studies published up to June 12, 2025, from six databases: ScienceDirect, Embase, Scopus, PubMed, Google Scholar and Web of Science. Eligible studies included all case-control investigations that assessed the association between *GSTM1* polymorphisms and the risk of cervical cancer. Odds ratios and confidence intervals from the studies were used to estimate the combined effect size. Statistical analyses were conducted using both the DerSimonian and Laird random-effects model and Mantel and Haenszel fixed-effect model with a 95% confidence interval. Subgroup analyses were performed to identify potential sources of variability. A significant association was observed between the *GSTM1-null* and an increased risk of Cervical Cancer (ORCC=1.47, P=0.011) and Squamous Intraepithelial Lesions (ORSIL=1.50, P=0.020) compared with the *GSTM1-present*. Overall, carriers of the *GSTM1-null* had a higher likelihood of developing Cervical Cancer compared to carriers of the **GSTM1-present**. In subgroup analyses, an increased risk associated with the *GSTM1-null* was found among Asian populations (ORCC=1.54, P=0.002) and, according to sample type, in blood DNA extracts (ORMix=1.31, P=0.006). Furthermore, the *GSTM1-null* was associated with increased risk in HPV+ women (ORMix=2.40, P=0.003), but without no association in women exposed to tobacco smoke (ORCC=1.30, P=0.072). According to histological type, *GSTM1-null* was also associated with the development of Squamous Cell Carcinoma (ORSCC=1.52, P=0.020). In conclusion, the *GSTM1-null* genotype is associated with an increased risk of cervical cancer in women, especially in HPV+ women and not those exposed to tobacco smoke.

Keywords: *GSTM1* polymorphism, Cervical cancer, Environmental factors.

1. Introduction

In 2022, cervical cancer ranked eighth worldwide in terms of incidence (662,301 cases) and ninth in terms of cancer-related mortality (348,874 cases). [1]. The development of cervical cancer, like other malignancies, results from a complex interplay between genetic susceptibility and environmental exposures.

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Genetic factors such as polymorphism in glutathione S-transferase (*GST*) genes have been implicated in several pathologies including cervical cancer. The *GST* genes family encode for enzymes catalyze the conjugation of reactive xenobiotics to the endogenous, water-soluble substrate glutathione (GSH), thereby facilitating their detoxification. Through this mechanism, GST enzymes protect cells from environmental insults, oxidative stress [2] and the deleterious effects of reactive oxygen and nitrogen species (ROS/RNS) [3]. In humans, GSTs are classified into three main families based on their cellular localization and genetic origin, cytosolic, mitochondrial, and membrane-associated GSTs, each encoded by genes located on different chromosomes [4, 5]. Human GST enzymes include alpha, zeta, theta, mu, pi, sigma and omega classes [6]. The mu class contains five genes (*GSTM1*, *GSTM2, GSTM3, GSTM4, GSTM5*). The *GSTM1* polymorphism (1p13.3) has been implicated in susceptibility to cervical cancer [7, 8].

Among environmental factors, infection with human papillomavirus (HPV) and exposure to tobacco smoke are the most frequently implicated in the development of cervical cancer [9–11]. Tobacco smoke contains more than 9,500 chemical compounds, including 79 carcinogens [12]. The best-known carcinogenic components are tar (benzo[α]pyrene, hydrocarbon) and nicotine. Exposure to tobacco smoke has been associated with an increased risk of several malignancies, including cancers of the lung [13], nasopharynx [14], liver [15], kidney [16] and cervix [9], etc.

Furthermore, infection with HPV has been identified as the primary cause of cervical cancer, particularly high-risk oncogenic genotypes [17]. However, because cancer is a multifactorial disease, not all cervical HPV infections progress to carcinogenesis, as most infections are naturally cleared by the host immune system. The persistence of HPV infection, and consequently the development of cervical cancer, requires the involvement of additional genetic and/or environmental cofactors [18, 19].

According to the literature, the *GSTM1-null* genotype and exposure to tobacco smoke are among the main cofactors influencing cervical carcinogenesis. Several studies have investigated the association between the *GSTM1* polymorphism and cervical cancer risk in women, both in the general population and among subgroups such as HPV, infected individuals and active or passive smokers, but the results have remained controversial [8, 20–23]. A meta-analysis of the data from the different studies would therefore be necessary for an overall evaluation.

Previous meta-analyses have been conducted to elucidate the relationship between the *GSTM1-null* genotype and the risk of developing cervical cancer [24, 25]. However, the limited amount of available data and the emergence of new studies highlight the need for updated analyses. It is therefore necessary to perform a new meta-analysis that incorporates recently published data and considers specific sub-environmental factors such as HPV infection and exposure to tobacco smoke.

The objective of the present meta-analysis was therefore to select and analyze case-control studies examining the association between the *GSTM1* polymorphism and cervical cancer in women. Data were pooled and analyzed by cluster and subgroup to assess the association between *GSTM1* polymorphisms and cervical cancer risk and to evaluate potential effect modification by HPV infection status and tobacco smoke exposure.

2. Materials and methods

2.1. Literature search strategy

The data search for this meta-analysis was performed in six databases using the following keyword equation : ("GSTM1" OR "glutathione s-transferase M1" OR "glutathione s-transferase mu1") AND ("polymorphism" AND "gene variant" OR "genotype" OR "mutation") AND ("cervical cancer" OR "cervical carcinoma" OR "uterine cervix cancer" OR "cervical tumor" OR "cervical neoplasia" OR "uterine cervical neoplasms") in Web of Science, Embase, Scopus, PubMed, Google Scholar and ("GSTM1" OR "glutathione s-transferase M1" OR "glutathione s-transferase mu1") AND ("cervical cancer" OR "cervical carcinoma" OR "uterine cervix cancer" OR "cervical tumor" OR "cervical neoplasia" OR "uterine cervical neoplasms") in ScienceDirect. The search for published articles was performed without restriction, including all studies available up to June 12, 2025.

2.2. Selection criteria

The present meta-analysis was conducted according to the PRISMA guidelines. The databases have been selected so as to have the maximum possible number of articles. The keywords have been discussed to refine the search for articles without missing the objective of the study. The inclusion criteria and exclusion criteria were set to remain focused on the case-control studies presenting original data that examined the association between *GSTM1* polymorphism and cervical cancer acquisition. We have included in the present meta-analysis any case-control study on the polymorphism of *GSTM1* and cervical cancer or cervical precancerous lesions risk. Duplicates, synthetic studies (meta-analysis and systematic review), studies that did not present cases and controls distinctly, studies that only had unusable data (OR, CI) or an inaccessible full text, those that did not report statistical data on the frequency of genotype null for *GSTM1* in cases and controls, studies in languages other than French and English were excluded from this meta-analysis.

2.3. Data extraction and synthesis

All references identified were organized using Zotero bibliographic management software, and study selection was performed in Microsoft Excel (version 2016) through a multi-step process. Only studies with extractable data were included in this meta-analysis. Two independent reviewers initially screened the studies based on the relevance of their titles and abstracts. Full-text articles meeting the predefined eligibility criteria were then carefully reviewed. From each selected publication, the following information was extracted: year of publication, first author name, country or region of the study, type of study, mean age of participants, type of biological samples, methodology used for polymorphism detection, total samples size, the number of cases and controls, HPV status, tobacco use or exposure and the frequency of the *GSTM1-null* genotype. Heterozygous individuals were classified as *GSTM1-present.*

2.4. Statistical analysis

Data were analyzed using the Meta-essential_1.5

software (2 Meta-Essentials Differences between independent groups - binary data 1.5) by following the procedures described in the user manual.

Data analysis was performed using both the random-effects model [26] and the fixed-effect model [27] with a 95% confidence interval [28]. The inverse variance method and odds ratio (OR) were selected as model options. The statistical significance of the pooled estimates was assessed using the Z-value with significance set at a two-tailed p-value < 0.05. An increased risk was inferred when $OR > 1$, and no risk was considered when $OR \leq 1$. Between-study heterogeneity was assessed using Cochran's Q test [29] and the I^2 statistic [30] to provide a quantitative measure of variability [31]. Heterogeneity was categorized as low when $I^2 < 0.25$, moderate when I^2 was between 0.25 and 0.5, and substantial when $I^2 > 0.5$ [32].

However, heterogeneity was considered significant when the $P_{Q\text{-statistic}} \leq 0.10$ and/or the $I^2_{\text{-statistic}} > 50\%$. In such cases, the random-effects model was applied. Conversely, the fixed-effect model was used.

In the included studies, the variance between the observed effects, denoted as Tau-squared (τ^2) was also evaluated. Tau^2 quantifies the extent of dispersion of the true effect sizes across studies. When Tau^2 close to zero, this indicates that the true effect sizes are similar among studies. Conversely, $Tau^2 > 0$ suggested the presence of variability in the true effects of the included studies.

Publication bias was assessed using a funnel plot, which visually represents the distribution of included studies. In addition, the Trim and Fill method [33–35], the Begg rank correlation test [36], and the Egger regression test [37] were applied to statistically evaluate potential asymmetry. The presence of publication bias was considered significant when $p < 0.05$. Subgroup analyses were conducted according to several variables, including geographical region, DNA source, and histological classification (cervical cancer, squamous cervical cancer, adenocarcinoma or adenosquamous carcinoma, unknown cervical cancer, SIL, HSIL, LSIL), as well as HPV infection status and smoking status. Sensitivity analyses were performed by sequentially excluding one study at a time and recalculating the pooled effect size to assess the robustness and stability of the overall results.

3. Results

A total of 1533 studies were initially identified through the search strategy. After removing duplicates, meta-analyses, systematic reviews, and studies excluded during abstract screening, 57 articles remained for full-text evaluation. Based on eligibility criteria, including case–control design, accessibility of the full text (PDF), availability of histological data for participants, and extractable information on *GSTM1* polymorphisms, 36 scientific publications were ultimately included in this meta-analysis (Fig. 1). These studies encompassed a total of 10,202 samples, comprising 4,774 cases and 5,188 controls.

Among the 36 studies, authors from 8 studies investigated *GSTM1*/HPV status [8, 20, 23, 38–42] and 11 studies on *GSTM1*/passive and active smoker [7, 21, 22, 42–49]. The studies included in this meta-analysis are summarized in Table S1. They originated from various countries, which were classified into four geographical regions (Africa, America, Asia, and Europe). Some studies did not report the mean age of participants. Three types of biological samples, blood cells, cervical cells, and tissue, were used for polymorphism identification across the included studies. The methods used for detecting the *GSTM1* polymorphism and the corresponding genotype frequencies in cases and controls are presented in Table S1

Table S2 summarizes the results of the analyses performed to assess the association between *GSTM1* polymorphisms and the development of cervical lesions and cervical cancer. Analyses were first carried out in all cases combined and controls (Mix), without distinction of histology subtype and then specifically according to the confirmed histology: Low-grade Squamous Intraepithelial Lesions or LSIL, High-grade Squamous Intraepithelial Lesions or HSIL, Squamous Cell Carcinoma or SCC, Adenosquamous Carcinoma or ASC, Adenocarcinoma or AC. However, some analyses could not be performed in Africa and in certain subgroups because of insufficient data (HSIL and LSIL in America, CC in cell samples). Additional analyses could not be performed on the relationship between *GSTM1-null* carriage and the development of low-grade lesions according to HPV status (LSIL_HPV), as well as the association between smoking status (passive and active) and HPV infection.

3.1. Group analyses on cancer and intraepithelial squamous lesions

Figure 2 presents the analysis of all the studies (36 articles) selected for this meta-analysis examining the association between *GSTM1-null* genotype and the risk of cervical cancer (CC) and cervical lesions (SIL) in the overall study population (Mix group). Specifically, Figure 3 shows the analysis results of 24 studies assessing the association between *GSTM1-null* and CC, while Figure 4 displays the results of 15 studies evaluating *GSTM1-null* and SIL. A significant association was observed between *GSTM1-null* and an increased risk of both CC and SIL compared with *GSTM1-present* in the Mix analysis (OR_{Mix}

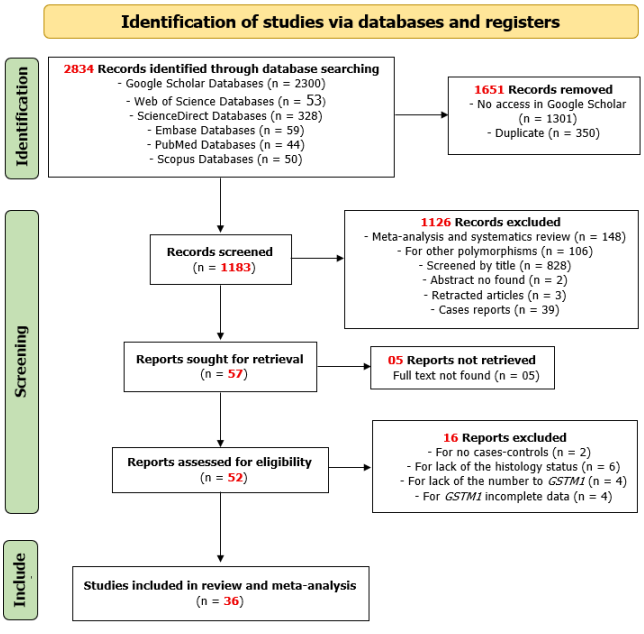


Fig. 1. PRISMA diagram of the selected articles. Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/

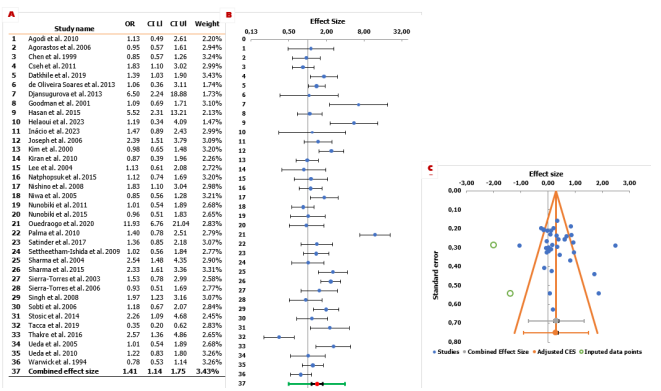


Fig. 2. Association between *GSTM1-null* and cervical cancer risk in Mix group. (**A**) Statistic analysis results of association between *GSTM1-null* and cervical cancer risk (OR = Odds Ratio, CI = Confiance Intervalle, Ll = Lower limit, Ul = Upper limit); (**B**) Forest plot of the meta-analysis of association between and cervical cancer risk in Mix group; (**C**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and cervical cancer risk in Mix group.

= 1.41, 95%CI = 1.14–1.75, P = 0.001) (Fig. 2 A & B). This association remained significant when analyzed separately in histologically confirmed CC samples (OR_{CC} = 1.47, 95%CI = 1.07-2.03, P = 0.011) (Fig. 3 A & B) and SIL samples (OR_{SIL} = 1.50, 95%CI = 1.03-2.18, P = 0.020) (Fig. 4 A & B). The studies exhibited substantial heterogeneity (Q = 160.51, P_Q < 0.001, I^2 = 78.20%) with similar true effect sizes or similar in terms of results (Tau^2 = 0.25). The lowest odds ratio was reported by Warwick *et al.* (OR_{Mix} = 0.78, 95%CI = 0.53-1.14) [43], while the highest was observed in Ouedraogo *et al.* (OR_{Mix} = 11.93, 95%CI = 6.76-21.04) [8] (Fig. 2 A & B). The study by Ouedraogo *et al.*, exerted the greatest influence on the overall Mix effect size (difference in OR_{CC} = 0.17), whereas six studies had minimal influence (difference in OR_{CC} = 0.01).

The Funnel plots showed symmetric (Fig. 2C, 3C) and asymmetric (Fig. 4C) distributions. Visual inspection identified eight studies (Fig. 2C), five studies (Fig. 3C) and one study (Fig. 4C) lying outside the funnel boundaries. However, the Egger's regression test for small-study effects and the Begg's rank correlation test both indicated no significant publication bias (p > 0.1), thereby confirming the absence of publication bias in the meta-analysis.

3.2. Subgroup analyses

3.2.1. Association between GSTM1-null genotype and the risk of squamous cell carcinoma and adenocarcinoma

Analyses stratified by histological type revealed a significant association between squamous cell carcinoma (SCC) and the *GSTM1-null* genotype compared with *GSTM1-present* (OR_{SCC} = 1.52, 95%CI = 1.02-2.26, P = 0.020). The studies demonstrated substantial heterogeneity (Q = 46.39, PQ < 0.001, I^2 = 76.29%), with similar true effect sizes (Tau^2 = 0.20) and no evidence of publication bias in the cancer subgroup analysis (Table S2). In contrast, no significant association was observed for adenocarcinoma (P= 0.399).

3.2.2. Association between GSTM1-null genotype and the risk of low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL)

Although the forest plot for SIL the cases indicated an

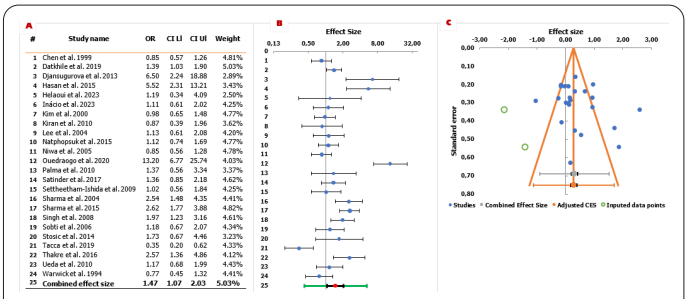


Fig. 3. Association between *GSTM1-null* and risk of squamous cell carcinoma or Adenocarcinoma; (**A**) Statistic analysis results of association between *GSTM1-null* and squamous cell carcinoma or Adenocarcinoma risk (OR = Odds Ratio, CI = Confiance Intervalle, Ll = Lower limit, Ul = Upper limit) (**B**) Forest plot of the meta-analysis of association between *GSTM1-null* and squamous cell carcinoma or Adenocarcinoma risk; (**C**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and squamous cell carcinoma or Adenocarcinoma risk.

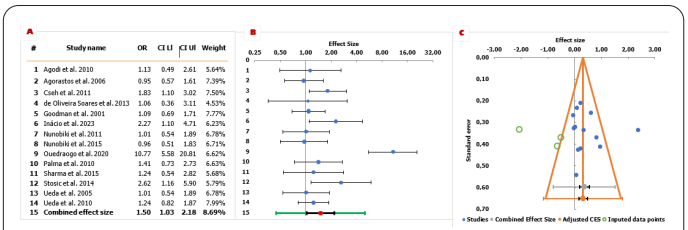


Fig. 4. Association between *GSTM1-null* and Squamous Intraepithelial Lesion (SIL) risk; (**A**) Statistic analysis results of association between *GSTM1-null* and SIL risk (OR = Odds Ratio, CI = Confiance Intervalle, Ll = Lower limit, Ul = Upper limit) (**B**) Forest plot of the meta-analysis of association between *GSTM1-null* and SIL risk; (**C**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and SIL risk.

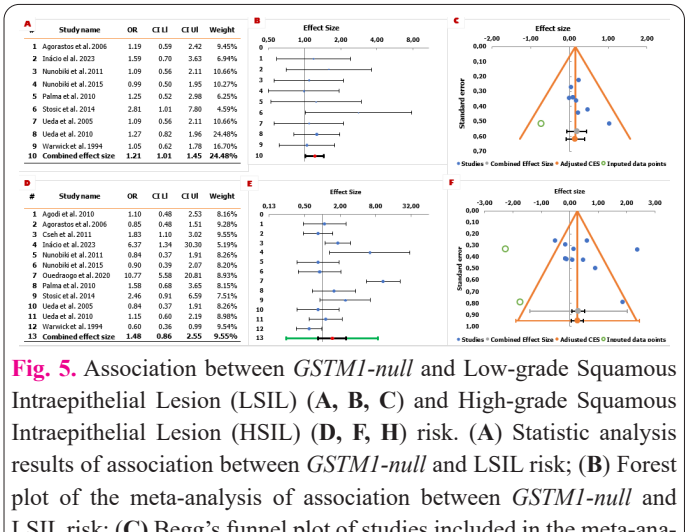


Fig. 5. Association between *GSTM1-null* and Low-grade Squamous Intraepithelial Lesion (LSIL) (**A, B, C**) and High-grade Squamous Intraepithelial Lesion (HSIL) (**D, F, H**) risk. (**A**) Statistic analysis results of association between *GSTM1-null* and LSIL risk; (**B**) Forest plot of the meta-analysis of association between *GSTM1-null* and LSIL risk; (**C**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and LSIL risk; (**D**) Statistic analysis results of association between *GSTM1-null* and HSIL risk; (**E**) Forest plot of the meta-analysis of association between *GSTM1-null* and HSIL risk; (**F**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and HSIL risk.

increased risk of developing SIL among women carrying the *GSTM1-null* genotype compared with those with the *GSTM1-present* genotype; the association was not statistically significant for either LSIL or HSIL (P = 0.081, P = 0.116 respectively) (Fig. 5, Table S2). The studies exhibited substantial heterogeneity (Q = 57.27, PQ < 0.001, I^2 = 75.56%) with similar true effect sizes (Tau^2 = 0.28).

The Funnel plots (Fig. 5C, 5F) displayed asymmetric distributions of studies around the mean. However, both the Egger's test and the Begg's test were not statistically significant (p > 0.1) confirming the absence of publication bias in this analysis

3.2.3. Distribution into subgroups according to geographic regions

Subgroup distribution across geographic regions showed no significant difference in the association between *GSTM1-null* and the occurrence of cervical cancer or lesions in America (OR_{Mix} = 0.87, 95%CI = 0.51-1.46, P = 0.477) and Europe (OR_{Mix} = 1.28, 95%CI = 0.90-1.81, P = 0.087). In contrast, a significant association was observed in Asia Mix group (OR_{Mix} = 1.49, 95%IC = 1.18-1.86, P = 0.000) and in CC group (OR_{CC} = 1.54, 95%CI = 1.15-2.06, P = 0.002) (Table S2 and 1). This distribution across geographic areas was heterogeneous, but no publication bias was detected. No significant association was found between *GSTM1-null* carriage and the occurrence of cervical lesions across the different regions. Due to insufficient data, analyses could not be conducted for Africa.

3.2.4. Distribution of subgroups by source of DNA extracts

Table 2 shows the distribution of studies according to the source of DNA used for the determination of polymorphisms. A significant association between the *GSTM1-null* genotype and the risk of cervical cancer was observed in samples where DNA was extracted from blood cells in Mix group (OR_{Mix} = 1.31, 95%CI = 1.07-1.61, P = 0.006). For samples in which DNA was extracted from cervical cells, no confirmed cancer cases were reported; however, the analysis of cervical lesions showed no significant association (OR_{SIL} = 1.19, 95%CI = 0.82-1.73, P = 0.203). The studies included in blood cells Mix group were heterogeneous (Q = 87.62, P_Q = 0.000, I^2 = 68.04%), but showed no statistically significant publication bias (p = 0.139 and 0.115) and no similar true effect sizes (Tau^2 = 0.15 > 0) (Table 2). Due to insufficient data, analyses could not be conducted for the tissue sample. Overall, no significant association was found between *GSTM1-null* carriage and the occurrence of cervical lesions.

3.2.5. Distribution of subgroups by HPV status

Analyses of data on HPV infection produced a forest plot showing an overall increased risk of cervical cancer acquisition among HPV+ women carrying the *GSTM1-null* genotype compared with HPV+ women with the *GSTM1-present* genotype in Mix group (OR_{Mix} = 2.40, 95%CI = 1.20-4.82, P = 0.003), (Fig. 6 A & B and Table S2). Heterogeneity among studies was significant (Q = 23.87, P_Q = 0.001, I^2 = 70.67%) with similar true effect sizes (Tau^2 = 0.41) (Table S2). The funnel plot showed a symmetric distribution of studies, although Egger's (p = 0.545) and Begg's test (p = 0.621) indicated no significant publication bias (Fig. 6C et Table S2). However, because fewer than ten studies were included, these results should be interpreted with caution and do not allow firm conclusions to be drawn. In contrast, the analysis among HPV- women with *GSTM1-null* genotype did not show statistically significant association with cervical cancer compared with women with *GSTM1-present*/HPV- women (OR_{Mix} = 1.74, 95%CI = 0.65-4.68, P = 0170) (Fig. 6 D & E, Table S2).

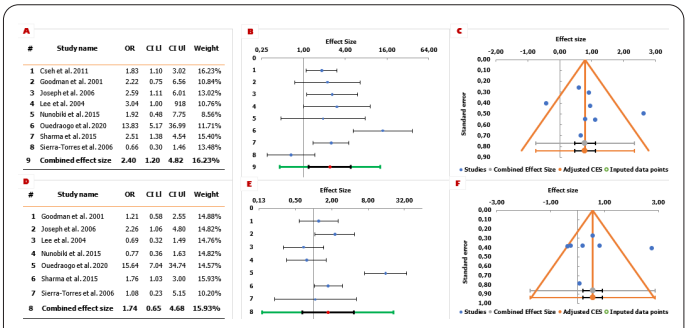


Fig. 6. Association between *GSTM1-null* and cervical cancer risk in HPV positive (**A, B, C**) and HPV negative group (**D, E, F**) in Mix group. (**A**) Statistic analysis results of association between *GSTM1-null* and cervical cancer risk in HPV positive; (**B**) Forest plot of the meta-analysis of association between *GSTM1-null* and cervical cancer risk in HPV positive; (**C**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and cervical cancer risk in HPV positive; (**D**) Statistic analysis results of association between *GSTM1-null* and cervical cancer risk in HPV negative; (**E**) Forest plot of the meta-analysis of association between *GSTM1-null* and cervical cancer risk in HPV negative; (**F**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and cervical cancer risk in HPV negative.

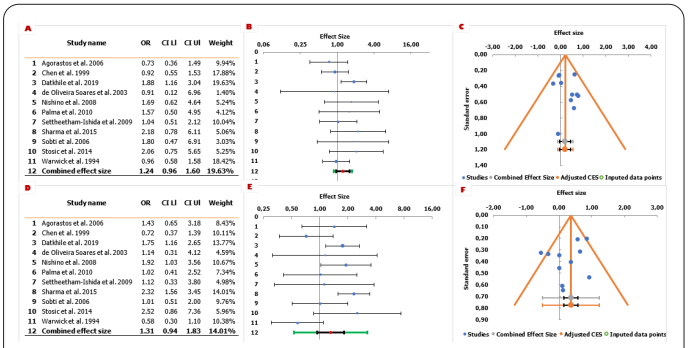


Fig. 7. Association between *GSTM1-null* and cervical cancer risk in smoking (**A, B, C**) or non-smoking group (**D, E, F**) in Mix group. (**A**) Statistic analysis results of association between *GSTM1-null* and cervical cancer risk in smoking group; (**B**) Forest plot of the meta-analysis of association between *GSTM1-null* and cervical cancer risk in smoking group; (**C**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and cervical cancer risk in smoking group; (**D**) Statistic analysis results of association between *GSTM1-null* and cervical cancer risk in non-smoking group; (**E**) Forest plot of the meta-analysis of association between *GSTM1-null* and cervical cancer risk in non-smoking group; (**F**) Begg's funnel plot of studies included in the meta-analysis of association between *GSTM1-null* and cervical cancer risk in non-smoking group.

3.2.6. Distribution of subgroups tobacco smoke exposure status

Analyses evaluating tobacco smoke exposure in *GSTM1-null* women and its relation to cervical cancer risk are shown in (Fig. 7). The combined effects estimates indicated an no increased risk of cervical cancer among smoking women carrying the *GSTM1-null* genotype in Mix group (OR_{Mix} = 1.23, 95%CI = 0.96-1.58, P = 0.060) and in CC subgroup (OR_{CC} = 1.30, 95%CI = 0.87-1.93, P = 0.072) compared with *GSTM1-present* smokers (Fig. 7 A & B). Heterogeneity was low in CC subgroup (Q = 5.73, P_Q = 0.334, I^2 = 12.67%) with similar true effect sizes (Tau^2 = 0.02). The funnel plot exhibited symmetry (Fig. 7C), and Egger's and Begg's tests were not significant (p = 0.632, p

Table 1. Meta-analysis of the association between *GSTM1-null* genotype and cervical cancer risk by region in Mix group.

Study name / Subgroup name	Odds Ratio	CI Lower limit	CI Upper limit	Weight	Q	p_Q	I^2	T^2	T	PI Lower limit	PI Upper limit
America											
Chen et al. 1999	0.85	0.57	1.26	21.40%							
de Oliveira Soares et al. 2013	1.06	0.36	3.11	9.04%							
Goodman et al. 2001	1.09	0.69	1.71	20.05%							
Sierra-Torres et al. 2003	1.53	0.78	2.99	15.23%							
Sierra-Torres et al. 2006	0.93	0.51	1.69	16.85%							
Tacca et al. 2019	0.35	0.20	0.62	17.41%							
Combined effect size	**0.87**	**0.51**	**1.46**	**25.22%**	**13.84**	**0.017**	**63.88%**	**0.14**	**0.38**	**0.29**	**2.61**
Asia											
Datkhile et al. 2019	1.39	1.03	1.90	6.44%							
Djansugurova et al. 2013	6.50	2.24	18.88	2.29%							
Hasan et al. 2015	5.52	2.31	13.21	3.01%							
Joseph et al. 2006	2.39	1.51	3.79	5.35%							
Kim et al. 2000	0.98	0.65	1.48	5.68%							
Kiran et al. 2010	0.87	0.39	1.96	3.29%							
Lee et al. 2004	1.13	0.61	2.08	4.35%							
Natphopsuk et al. 2015	1.12	0.74	1.69	5.69%							
Nishino et al. 2008	1.83	1.10	3.04	5.02%							
Niwa et al. 2005	0.85	0.56	1.28	5.71%							
Nunobiki et al. 2011	1.01	0.54	1.89	4.23%							
Nunobiki et al. 2015	0.96	0.51	1.83	4.16%							
Satinder et al. 2017	1.36	0.85	2.18	5.29%							
Settheetham-Ishida et al. 2009	1.02	0.56	1.84	4.46%							
Sharma et al. 2004	2.54	1.48	4.35	4.81%							
Sharma et al. 2015	2.33	1.61	3.36	6.02%							
Singh et al. 2008	1.97	1.23	3.16	5.28%							
Sobti et al. 2006	1.18	0.67	2.07	4.64%							
Thakre et al. 2016	2.57	1.36	4.86	4.17%							
Ueda et al. 2005	1.01	0.54	1.89	4.23%							
Ueda et al. 2010	1.22	0.83	1.80	5.87%							
Combined effect size	**1.49**	**1.18**	**1.86**	**40.39%**	**58.49**	**0.000**	**65.81%**	**0.12**	**0.35**	**0.69**	**3.20**
Europe											
Agodi et al. 2010	1.13	0.49	2.61	8.88%							
Agorastos et al. 2006	0.95	0.57	1.61	15.36%							
Cseh et al. 2011	1.83	1.10	3.02	15.90%							
Inácio et al. 2023	1.47	0.89	2.43	15.92%							
Palma et al. 2010	1.40	0.78	2.51	13.76%							
Stosic et al. 2014	2.26	1.09	4.68	10.72%							
Warwick et al. 1994	0.78	0.53	1.14	19.46%							
Combined effect size	**1.28**	**0.90**	**1.81**	**34.39%**	**12.24**	**0.057**	**50.97%**	**0.08**	**0.28**	**0.59**	**2.77**
All Combined effect size	1.23	0.90	1.68	0.40%	102.36	0.000	67.76%	0.14	0.38	0.75	2.03

Legend: PI= Prediction Interval, CI= Confidence Interval.

Table 2. Meta-analysis results of association between *GSTM1-null* and cervical cancer risk by DNA source.

Study name / Subgroup name	Odds Ratio	CI Lower limit	CI Upper limit	Weight	Q	p_Q	I^2	T^2	T	PI Lower limit	PI Upper limit
Blood cell											
Chen et al. 1999	0.85	0.57	1.26	4.27%							
Datkhile et al. 2019	1.39	1.03	1.90	4.68%							
de Oliveira Soares et al. 2013	1.06	0.36	3.11	1.82%							
Djansugurova et al. 2013	6.50	2.24	18.88	1.82%							
Goodman et al. 2001	1.09	0.69	1.71	4.00%							
Hasan et al. 2015	5.52	2.31	13.21	2.36%							
Helaoui et al. 2023	1.19	0.34	4.09	1.49%							
Inácio et al. 2023	1.47	0.89	2.43	3.79%							
Joseph et al. 2006	2.39	1.51	3.79	3.98%							
Kim et al. 2000	0.98	0.65	1.48	4.19%							
Kiran et al. 2010	0.87	0.39	1.96	2.56%							
Lee et al. 2004	1.13	0.61	2.08	3.30%							
Natphopsuk et al. 2015	1.12	0.74	1.69	4.20%							
Nishino et al. 2008	1.83	1.10	3.04	3.76%							
Niwa et al. 2005	0.85	0.56	1.28	4.21%							
Nunobiki et al. 2015	0.96	0.51	1.83	3.17%							
Palma et al. 2010	1.40	0.78	2.51	3.42%							
Satinder et al. 2017	1.36	0.85	2.18	3.94%							
Settheetham-Ishida et al. 2009	1.02	0.56	1.84	3.38%							
SHarma et al. 2004	2.54	1.48	4.35	3.62%							
Sierra-Torres et al. 2003	1.53	0.78	2.99	3.06%							
Sierra-Torres et al. 2006	0.93	0.51	1.69	3.38%							
Singh et al. 2008	1.97	1.23	3.16	3.93%							
Sobti et al. 2006	1.18	0.67	2.07	3.51%							
Stosic et al. 2014	2.26	1.09	4.68	2.85%							
Tacca et al. 2019	0.35	0.20	0.62	3.49%							
Thakre et al. 2016	2.57	1.36	4.86	3.19%							
Ueda et al. 2010	1.22	0.83	1.80	4.32%							
Warwick et al. 1994	0.78	0.53	1.14	4.32%							
Combined effect size	**1.31**	**1.07**	**1.61**	**65.57%**	**87.62**	**0.000**	**68.04%**	**0.15**	**0.38**	**0.58**	**2.96**
Cervical cell											
Agodi et al. 2010	1.13	0.49	2.61	10.27%							
Agorastos et al. 2006	0.95	0.57	1.61	25.91%							
Cseh et al. 2011	1.83	1.10	3.02	27.86%							
Nunobiki et al. 2011	1.01	0.54	1.89	17.98%							
Ueda et al. 2005	1.01	0.54	1.89	17.98%							
Combined effect size	**1.19**	**0.81**	**1.73**	**34.43%**	**4.06**	**0.398**	**1.47%**	**0.00**	**0.04**	**0.80**	**1.76**
All Combined effect size	1.27	1.15	1.40	0.66%	91.82	0.000	64.06%	0.13	0.36	1.15	1.40

Legend: PI= Prediction Interval, CI= Confidence Interval.

= 0.573 respectively).

Conversely, in non-smoking women carrying the *GSTM1-null* genotype, no significant association with cervical cancer risk was observed in Mix group (OR_{Mix} = 1.31, 95%CI = 0.94-1.83, P = 0.065) and in CC subgroup (OR_{CC} = 1.11, 95%CI = 0.53-2.35, P = 0.720) (Fig. 7 D & E and Table S2). Heterogeneity was substantial in CC subgroup (Q = 25.03, P_Q = 0.000, I^2 = 80.02%) with similar true effect sizes Tau^2 = 0.38). Although the funnel plot showed slight asymmetry (Fig. 7F), Egger's and Begg's tests remained non-significant (p = 0.093; p = 0.348, respectively), confirming the absence of publication bias in this analysis.

4. Discussion

Since the publication of the first studies on the link between the GSTM1-null genotype and the risk of cervical cancer and SIL (Mix) by Warwick et al. (1994) [43], several meta-analyses have been published, eleven (11) of which focused specifically on cervical cancer. Nevertheless, the limited data concerning environmental factors and geographical variations continue to justify the need for additional, updated meta-analyses. The objectives of this meta-analysis were to compile case-control studies on the GSTM1 genetic factor and the epigenetic cofactors HPV infection and exposure to tobacco smoke, in order to analyze the data and draw a more accurate conclusion using Meta-Essentials 1.5 software.

In this meta-analysis, we found a significant association between *GSTM1-null* genotype carriage and the risk of cervical cancer. The Mix odds ratio value (OR=1.41; 95%CI=1.14-1.75) calculated from 36 studies included supports an increased risk of developing cervical cancer and precancerous lesions, regardless of HPV status or tobacco exposure. Previous meta-analyses have also reported similar associations between the *GSTM1-null* genotype and cervical cancer risk [24, 25, 68–76]. This finding suggests that the *GSTM1-null* genotype may act as a genetic cofactor contributing to cervical carcinogenesis and could potentially serve as a biomarker of genetic susceptibility to cervical cancer and squamous intraepithelial lesions. Nevertheless, other etiological factors, particularly persistent infection with high-risk oncogenic HPV types, are also likely to play a major role in the progression of cervical lesions.

In general, *GSTM1-null* appears to be associated with an increased risk of cervical cancer. However, specific genetic predispositions that vary among populations according to geographical location may influence these findings. The present meta-analysis revealed a significant association between *GSTM1-null* carriage and cervical cancer risk in the Asian population, whereas no significant associations were observed in other regions. In Africa, the available data were insufficient to allow meaningful analysis. Similar findings were reported by Ye *et al*., who observed a significant increase in cervical cancer risk among Asian populations (OR = 1.44, 95%CI = 1.18-1.75) and in India (OR = 1.96, 95%CI = 1.51-2.55) [25]. Several other meta-analyses have also reported significant associations in Asian cohorts [69, 72, 74]. This regional difference may be explained by the predominance of Asian studies in the literature, which could influence the combined effects, or by genetic and environmental factors specific to Asian populations. Indeed, Garte *et al*., using data from the International Project on Genetic Susceptibility to Environmental Carcinogens (GSEC), reported variations in the frequency of the *GSTM1-null* genotype among different ethnic groups [77]. Thus, the genetic background of populations, along with environmental factors such as nutrition and lifestyle, may together contribute to the regional variability in the association between *GSTM1-null* genotype and cervical cancer risk. On the other hand, in Africa, two articles were published on *GSTM1null* and the occurrence of cancer, but analysis was not possible due to the difference in nature of case and control samples in one of the articles (cells and tissues).

According to histological type, a significantly increased risk was observed in the association analysis between *GSTM1-null* genotype carriage and the development of cervical cancer, particularly squamous cell carcinoma, compared with carriers of the *GSTM1-present* genotype. Similarly, Liu *et al*. reported a significant combined effect for cervical cancer (OR = 1.57, 95%CI = 1.25-1.98, P < 0.00001) [76]. In contrast, both the present analysis and that of Wang *et al.* (OR = 1.26, 95%CI = 0.64-2.48) [71] did not reveal a significant association between *GSTM1-null* carriage and the risk of developing adenocarcinoma. This lack of association may be attributable to the small and non-representative sample size (30 cases and 253 controls), which limited the statistical power to produce reliable estimates and conclusions regarding adenocarcinoma risk among *GSTM1-null* women. Further investigations focusing on the potential role of the *GSTM1-null* genotype in the pathogenesis of adenocarcinomas are therefore warranted.

We observed a significant association between *GSTM1-null* genotype carriage and the overall risk of SIL. However, no significant association was found between *GSTM1-null* genotype carriage and the development of HSIL or LSIL when analyzed separately in the present study. The absence of a significant association between the *GSTM1-null* genotype and the development of HSIL and LSIL was also reported in the analyses conducted by Gao *et al*. [69].

Consistent with the findings of Zhen *et al.* (OR = 22.51, 95%CI = 16.27-31.15, P = 0.023) [74] and Liu *et al*. (OR = 2.59, 95%CI = 1.57-4.27, P = 0.0002) [76], our analyses also revealed a significant between *GSTM1-null* genotype carriage and an increased risk of cervical cancer among HPV+ women in Mix subgroup, compared with HPV+ women carrying the *GSTM1-present* genotype. The hypothesis that the *GSTM1-null* genotype acts as a cofactor in the development of cervical cancer among HPV-infected women is supported by its biological role in xenobiotic detoxification. *GSTs* catalyze the conjugation of electrophilic compounds, including carcinogens, toxins, and products of oxidative stress, to glutathione (GSH), thereby increasing their solubility and facilitating their elimination from the body. In addition, *GSTs* are involved in DNA repair through the modulation of enzyme and protein induction [78]. Among the GST isoenzymes, mu-class GSTs (GSTM) are particularly efficient in catalyzing reactions with substrates containing unsaturated carbonyl or oxirane groups. *GSTM1* specifically metabolizes benzo[a]pyrene and polycyclic aromatic hydrocarbons [79, 80]. An upregulation of *GSTM1* expression has been observed as part of the body's protective response to oxidative stress, such as in chronic kidney failure [81]. Conversely, a combined *GSTM1-null–GSTP1A105G* (GG) genotype has been

associated with severe gastrointestinal toxicity in patients undergoing chemotherapy for cervical cancer [82]. The absence of *GSTM1* activity thus leads to a detoxification deficit, resulting in oxidative stress and genotoxic damage, which may contribute to the persistence of HPV infection and promote carcinogenesis. Since oxidative stress is recognized as a cofactor in infection progression, the lack of antioxidant and detoxification capacity caused by the *GSTM1-null* genotype could play a key role as a cofactor in HPV persistence and, consequently, in the development of cervical cancer.

A no significant increase in cervical cancer risk was observed among women carrying the *GSTM1-null* genotype who were exposed to tobacco smoke, compared with women carrying the *GSTM1-present* genotype. This result was the same among non-smoking women. In constrast, the analyses conducted by Liu and Xu demonstrated an increased risk of cervical cancer in *GSTM1-null* women who were smokers, whereas no elevated risk was observed among *GSTM1-null* non-smokers [72]. In general, tobacco smoke is recognized as a major risk factor for several cancers, including those of the lung, oral cavity, bladder, pancreas, liver, kidney, colon-rectum, ovary and leukemia, etc. The main carcinogenic constituents of tobacco smoke include tar, particularly (benzo[α]pyrene, hydrocarbon) and other polycyclic aromatic hydrocarbons, as well as nicotine. At the level of the cervix uteri, tobacco exposure has been linked to early carcinogenic alterations and to immune system impairment, which may hinder the clearance of HPV infection and thereby promote viral persistence and cervical carcinogenesis [65]. Indeed, a decrease in local immunosurveillance has been observed in the cervical transformation zone of women who smoke, characterized by a decrease in Langerhans and T-helper lymphocytes [85]. Acute exposure to cigarette smoke extracts has been shown to enhance the expression of oncogenic proteins when cervical epithelial cells harbor HPV in episomal form [86]. Experimental studies have demonstrated that elevated concentrations of benzo[α]pyrene increased the in vitro virion production rate [87] and that nicotine promotes the expression of the HPV16 oncogenic proteins E6 and E7 [88]. Moreover, in HPV-infected non-tumoral cervical cells, exposure to tobacco smoke activates p53 functional activity, which is normally suppressed by the HPV E6 oncoprotein, thereby amplifying DNA damage and facilitating carcinogenesis [86]. The present meta-analysis could not specifically evaluate the association between *GSTM1-null* genotype carriage and cervical cancer risk in HPV+ smokers because of insufficient data, our findings not revealed a significant increase in risk between *GSTM1-null* carriage cervical cancer development among women who smoke. The discrepancies between Lui and Xu's analyses and ours could be explained by the number of included studies, thus related to the statistical power of the analyses or the intensity of exposure not taken into account. Similary to our analyses Lui *et al*., had not obtained statistically significant results [76]. Additional studies including a larger number of publications focusing on *GSTM1-null* status in smokers group and HPV+ smokers group, are therefore needed to confirm this association.

Wood smoke, other than tobacco, would be implicated in the occurrence of cancer [53], but an analysis could not be performed due to a lack of data. Investigating the relationship between wood smoke and cervical cancer in Africa would be of great importance due to the common and daily use of firewood for cooking. Although the presence of HPV is documented in sub-Saharan Africa among sexually active women [89, 90], pregnant women [91], newborns [92], and patients high-grade cervical lesions and cervical cancer [10, 11, 93], some grey areas remain. Complementary research integrating genetic predispositions and environmental factors such as exposure to smoke would allow a better understanding of the evolution of lesions and refine strategies for combating this cancer at the regional level.

Furthermore, other genes could interact with *GSTM1* in the elimination of xenobiotics, such as cytochrome 450. A polymorphism of this gene could have an effect that influences xenobiotic elimination despite the presence of the *GSTM1* gene. Cancer being multifactorial pathologies, it would be interesting to explore through cohort studies several polymorphisms and several environmental factors simultaneously in the determination of biomarkers for cervical cancer. Furthermore, several genes involved in apoptotic regulation have been implicated in the occurrence of cervical cancer and could be subject to simultaneous meta-analysis.

The heterogeneity of studies in this meta-analysis was remarkable in most analyses. This heterogeneity could be due to several reasons including sample size, ethnic origin, HPV status (oncogenic or non-oncogenic types), study design (case-control, cohorts), etc. Our analysis Mix group a total of 5014 cases and 5188 controls. In the different publications included in this analysis, 3 studies had a sample size of 100, 11 studies had a sample size between 101 and 200, and 14 studies had a sample size of < 300. Heterogeneity could be due to the presence of small and large studies. The analysis also grouped several geographical areas, Africa, Asia, America and Europe. Since the genetic distribution is different, such a grouping may be a factor of heterogeneity. Moreover, the different analyses carried out grouped studies by authors who had inclusion criteria that varied from one study to another such as environmental factors (exposure to tobacco smoke, HPV infection status, alcohol status...), the divergence in the choice of controls (without cancer, no cancer history, normal cytology, normal histology, healthy women, normal cytology and LSIL, ...), the nature of the sampling (blood, cervical cell, tissue), the methodological differences for polymorphism search, all of which can be factors of heterogeneity in the analysis. In the present meta-analysis, we conducted a univariate and multivariate binary meta-regression analysis according to histological status, nature of samples, origin of controls, geographical area, the HPV status and exposure to smoke but we did not find a factor associated with heterogeneity; the results were indeterminate. (supplement file).

One of the limitations of this meta-analysis is that there are not enough data to verify if the distribution of the control groups were in accordance with the Hardy-Weinberg equilibrium (HWE). Only, the publication bias was analyzed. Publication bias analyses were performed considering the significance of the Egger test and the Begg & Mazumdar test ($p < 0.05$). We found publication bias in the HSIL_Blood_cell subgroup ($p_{egger's\ test} = 0.008$, $p_{Begg\ \&\ Mazumdar\ test} = 0.015$). Indeed, the patients or controls of the articles included in this meta-analysis came from both non-hospital and hospital environments (with many

pathologies), which could be sources of heterogeneity and bias, because these controls might not suffer from cancer but other pathologies that would influence genotypic analyses. Biases could also be explained by the selection of types of controls [94], which varies from one author to another. Then, the isolation of DNA in various types of samples could affect the performance of genotype detection, leading to contradictory results and causing bias. Furthermore, the biases could be related to the selection of publications because the English-only publications in specific sites had been made, with factors not considered in the analysis such as age, diet, alcoholism, etc., hence the selection biases.

Like all meta-analyses, our study has certain limitations. The data analyzed were derived exclusively from published studies. Some research with unexpected or non-significant results may not have been published and thus could not be included in our analyses. Moreover, participant selection criteria and methodologies used to detect polymorphisms varied among the included studies. Such variations could influence not only the degree of heterogeneity but also the pooled effect estimates. Another limitation lies in the lack of consistent data regarding environmental factors, including age, parity, HPV infection status in women exposed and unexposed to tobacco smoke, exposure to wood smoke, and other potential cofactors that may influence cancer risk. Consequently, their effects could not be assessed in our meta-analysis. Furthermore, the included studies extracted nucleic acids from biological samples of different types, such as blood, cervical exfoliated cells, biopsy tissues, and formalin-fixed paraffin-embedded (FFPE) tissues. Differences in results were observed depending on the nature of the sample. In studies using exfoliated cervical cells, cases were specifically defined as LSIL and HSIL. We did not observe a significant association between the *GSTM1-null* genotype and the acquisition of LSIL or HSIL, regardless of sample type. However, analyses based on DNA derived from blood cells revealed a statistically significant increase in risk of cervical cancer among *GSTM1-null* carriers in mix group. In a previous analysis Gao *et al.*, reported a significant association between the *GSTM1-null* genotype and cancer susceptibility in DNA from blood samples (OR = 1.29; 95% CI = 1.08-1.55) as well as in tissue samples (OR = 3.14; 95% CI = 1.90-5.19) [69]. In contrast, we were unable to perform tissue-based analyses due to insufficient available data. We also observed that odds ratios were markedly higher in the study that used formalin-fixed paraffin-embedded (FFPE) tissues as case samples and cervical cells as controls. This discrepancy may be attributed to the chemical processing of FFPE samples, which can cause nucleic acid degradation because of the fixation with formalin or paraffin embedding. In effect, formaldehyde leads to the denaturation DNA, creates chemical interactions (addition reactions, methylations, hydrolyses) [95], protein-protein bonds, and protein-nucleic acid cross-links that make it difficult to separate the DNA from the histones and obtain pure nucleic acids by extraction [96, 97]. As for the treatment with the Bouin, it degrades both DNA and RNA [98]. On the other hand, conservation in paraffin leads to nucleic acid fragmentation inducing less satisfactory PCR [99] as well as the DNA extraction method from FFPE tissues using Xylene [100, 101]. In addition, the significant degradation of DNA from FFPE tissues is observed after a duration of 4 to 6 years [102].

In addition to these limitations, the study has notable strengths, including a substantial sample size of 10,202 participants (5,014 cases and 5,188 controls), which enhances the statistical power of the analysis. The analyses of the mixed groups, as well as the specific subgroup analyses, were carried out, which clearly highlighting the consistency and clarity of the results. Only publications in English have been included to avoid language bias.

Cancer is a multifactorial disease that can involve genetic and environmental factors. In addition to the GST, polymorphisms of other genes would be involved in the acquisition of cancer, such as gene polymorphisms involved in apoptosis, elimination of carcinogens and environmental factors. These genes could be analyzed simultaneously to highlight their interaction in the acquisition of cervical cancer. There are few studies on the search for polymorphisms, particularly those that may be cofactors for cervical cancer in Africa, and they merit further study.

Conclusion

The *GSTM1-null* genotype is significantly associated with an increased risk of cervical cancer in women. The polymorphism was primarily linked to squamous cell carcinoma, whereas data on adenocarcinoma were limited. Although the *GSTM1* polymorphism may be associated with cervical lesions overall, no significant relationship was observed when high-grade (HSIL) and low-grade (LSIL) lesions were analyzed separately. In addition, HPV-positive women carrying the *GSTM1-null* genotype had a higher risk of developing cervical lesion and cancer in global analysis. Most of the included studies were conducted in Asian populations, where the regional analysis revealed a notable increase in cervical cancer risk associated with the *GSTM1-null* genotype. However, due to a lack of sufficient data, no meaningful analysis could be performed for African populations. Further studies in Africa and other underrepresented regions are needed to explore the interactions between genetic polymorphisms and environmental exposures in cervical cancer acquisition.

Conflict of Interests

The authors declare that they have no conflict of interest.

Authors' contributions

T-WCO and BVEJTB designed and performed the research, collected and analyzed data, and wrote the manuscript. AS designed and performed the research and revised the manuscript. WAS, MS, and TEY collected data. YDK analyzed data. AKO collected data and revised the manuscript. RAO, LT, ARZ, TS, TMZ, FWD, DSK, and JS critically revised the manuscript.

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