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Role of *GSTT*1 Polymorphisms in Cervical Cancer Risk: Influence of Human Papillomavirus Infection and Tobacco Smoke Exposure

—A Systematic Review and Meta-Analysis

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Abstract

Polymorphisms in certain human genes may contribute to the development of gynecological cancers. While infection with human papillomavirus (HPV) is considered the main cause, studies suggest that deletion of the Glutathione

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S-Transferase Thêta1 (*GSTT*1) gene is associated with an increased risk of cervical cancer. The objective of this meta-analysis was to investigate the relationship between *GSTT*1*-null* genotype and cervical cancer, and to assess the influence of HPV infection and exposure to tobacco smoke. Our analyses targeted articles published up to June, 13, 2025 in the Web of Science, ScienceDirect, Embase, Scopus, PubMed and Google Scholar databases. We included only case-control studies that evaluated the association between *GSTT*1 polymorphisms and cervical cancer risk. Summary odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using Meta-Essentials software, applying both fixed-effect model and random-effect models. Subgroup analyses were performed to explore potential sources of heterogeneity and the influence of environmental factors, such as HPV status and tobacco smoke exposure. Thirty-five studies were included in the meta-analyses. Overall, the *GSTT*1*-null* genotype was associated with a significantly increased risk of cervical cancer (OR = 1.35; 95%CI = 1.03 - 1.77, p = 0.022) and high-grade intraepithelial lesions (OR = 1.50, 95%CI = 1.15 - 1.96, p = 0.001). In subgroup analysis, significant increased risk was observed, in the pooled subgroup of HPV-positive women (OR = 1.54, 95%CI = 1.09 - 2.16, p = 0.004) and in women exposed to tobacco smoke (OR = 1.31, 95%CI = 1.01 - 1.69, p = 0.019). For high-grade lesions specifically, significant associations were found in Asian populations (OR = 2.23, 95%CI = 1.18 - 4.22, p = 0.000). An association was also observed of HPV-positive infection status. Conversely, no conclusive risk was observed among women not exposed to tobacco smoke and among DNA source (OR < 1 or CI including null value). Altogether, this meta-analysis indicates that the *GSTT*1*-null* genotype is associated with a significant increase in the risk of cervical cancer and high-grade.

Keywords

*GSTT*1 Polymorphism, Cervical Cancer, HPV Infection, Tobacco Smoke

1. Introduction

Cancer is a multifactorial disease involving both genetic and environmental factors. In 2022, Cervical cancer (CC) was the fourth most common cancer among women worldwide [1]. The geographic areas most affected by cervical cancer are Asia and Africa [1]. In Burkina Faso, CC ranks as the fifth most common cancer overall and the second most frequent among women, with an estimated 14,538 new cases and 10,998 deaths [1]. The primary environmental driver of CC is persistent infection with the human papillomavirus (HPV), a well-established causal factor [2], Consequently, several studies have focused on HPV epidemiology among sexually active women with cervical lesions or CC in Burkina Faso. Their findings reveal a wide variation in HPV prevalence, ranging from 20.6% to 87.2% across different study populations [3]-[7]. Although persistent HPV infection is the primary cause of cervical cancer, the majority of sexually active women clear

the virus spontaneously. This variation in viral clearance has led to extensive research into host genetic factors and other environmental co-factors that may influence progression to cancer. Among these, tobacco smoke, both active and passive, is a well-documented environmental risk factor due to its numerous carcinogenic compounds [8]-[10]. The proposed mechanism involves tobacco-induced immunosuppression, for instance Poppe *et al*. observed a decrease in local immunosurveillance, marked by decreased Langerhans and T-helper cells in the cervical transformation zone of women who smoke [11]. Consequently, tobacco smoke has been directly associated with both persistent HPV infection and the early stages of cervical carcinogenesis [12] [13]. In addition to external factors such as HPV infection and tobacco smoke, intrinsic genetic factors such as such as polymorphisms in genes involved in xenobiotic detoxification, are also implicated in cervical cancer susceptibility. One key candidate is the *GSTT*1 *gene*, whose deletion has been associated with cervical cancer risk in several studies [14]-[16].

The *GSTT*1 gene is located on chromosome 22q11.23 [17] and belongs to the GST-theta class, which comprised two (02) genes, *GSTT*1, *GSTT2*. This gene encodes the *GSTT*1 enzyme, a critical component of Phase II detoxification. *GSTT*1 conjugates reduced glutathione (GSH) to a range of toxic compounds, including monohaloethanes, ethylene oxide, propylene oxide, and butylene oxide, thereby solubilizing them for elimination from the body. Polymorphisms in *GSTT*1 are known to influence the metabolic capacity against exogenous genotoxins and have been linked to the baseline rate of sister chromatid exchanges [18]. Consequently, an impaired ability to regulate such compounds due to *GSTT*1 polymorphisms may contribute to various pathologies, including head and neck cancer [19], as well as cancers of the urinary system, and prostate [20], etc. However, findings regarding the specific association between *GSTT*1 polymorphisms and cervical cancer risk remain inconsistent in the literature. This controversy necessitates a comprehensive synthesis of the existing evidence. Therefore, the present meta-analysis aims to aggregate case-control studies to evaluate the overall risk of cervical cancer and pre-cancerous lesions associated with the *GSTT*1-*null* genotype. Furthermore, it will conduct subgroup analyses to assess how this risk is modulated by HPV status and exposure to tobacco smoke.

2. Methodology

2.1. Literature Search Strategy

A systematic literature search was conducted for the present meta-analysis. Data were retrieved from six electronic databases: ScienceDirect, Embase, Scopus, PubMed, Google Scholar, and Web of Science. No restrictions on language or publication date were applied; all studies published up to June 12, 2025, were considered for inclusion. The search strategy employed the following key terms and Boolean operators. For Web of Science, Embase, Scopus, PubMed, and Google Scholar, the search equation was: ("*GSTT*1" OR "glutathione s-transferase T1" OR "glutathione s-transferase teta1") 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"). A modified strategy was used for the ScienceDirect database to optimize results: ("*GSTT*1" OR "glutathione s-transferase T1" OR "glutathione s-transferase teta1") AND ("cervical cancer" OR "cervical carcinoma" OR "uterine cervix cancer" OR "cervical tumor" OR "cervical neoplasia" OR "uterine cervical neoplasms").

2.2. Selection Criteria

The present analysis included original case-control studies that evaluated the association between *GSTT*1 polymorphism and cervical cancer or pre-cancerous lesions. Studies were excluded if they did not provide separate genotype distributions for cases and controls, were duplicate publications, lacked extractable statistical data on the *GSTT*1-null genotype, or were not case-control in design (e.g., reviews, commentaries, or animal studies).

2.3. Data Extraction and Synthesis

All identified references were collated using the Zotero reference management software, and a selection process was conducted in Microsoft Excel 2016 (**Figure 1**). Two authors independently screened titles and abstracts for relevance. The full texts of potentially eligible studies were then retrieved and reviewed. Studies were included only if they contained extractable data for quantitative synthesis. The following information was systematically extracted from each selected study: first author, publication year, country or region, study design, participants' mean age, sample type, genotyping method, total sample size, number of cases and controls, frequencies of the *GSTT*1-null genotype in cases and controls, and data on environmental factors such as HPV status and tobacco exposure. In the few articles that reported heterozygote data separately, such individuals were classified as *GSTT*1-present for consistency in the analysis.

2.4. Statistical Analysis

The extracted data were analyzed using Meta-essential version 1.5 software [21] [22]. Both fixed-effect [23] and random-effects [24] models were applied, employing the inverse variance method to calculate pooled odds ratios (ORs) and 95% CIs [25].

Heterogeneity across studies was assessed using Cochran's Q test [26] and the I^2 statistic, [27] interpreted as follows: low ($I^2 < 25\%$), moderate ($I^2 = 25\text{-}50\%$), or high ($I^2 > 50\%$) [28]. In cases of significant heterogeneity (Cochran's Q *p* < 0.10 and/or $I^2 > 50\%$), the "Random-effects" model was selected; otherwise (Cochran's Q *p* > 0.10 and $I^2 < 50\%$), the "Fixed-effect" model was used. However, in case of contradictory results between the confidence intervals and the p-value, we used both models. Between-study variance was further quantified by Tau^2 (τ^2), where a value close to zero indicates homogeneity in true effect sizes, and $\tau^2 > 0$ reflects variability across studies.

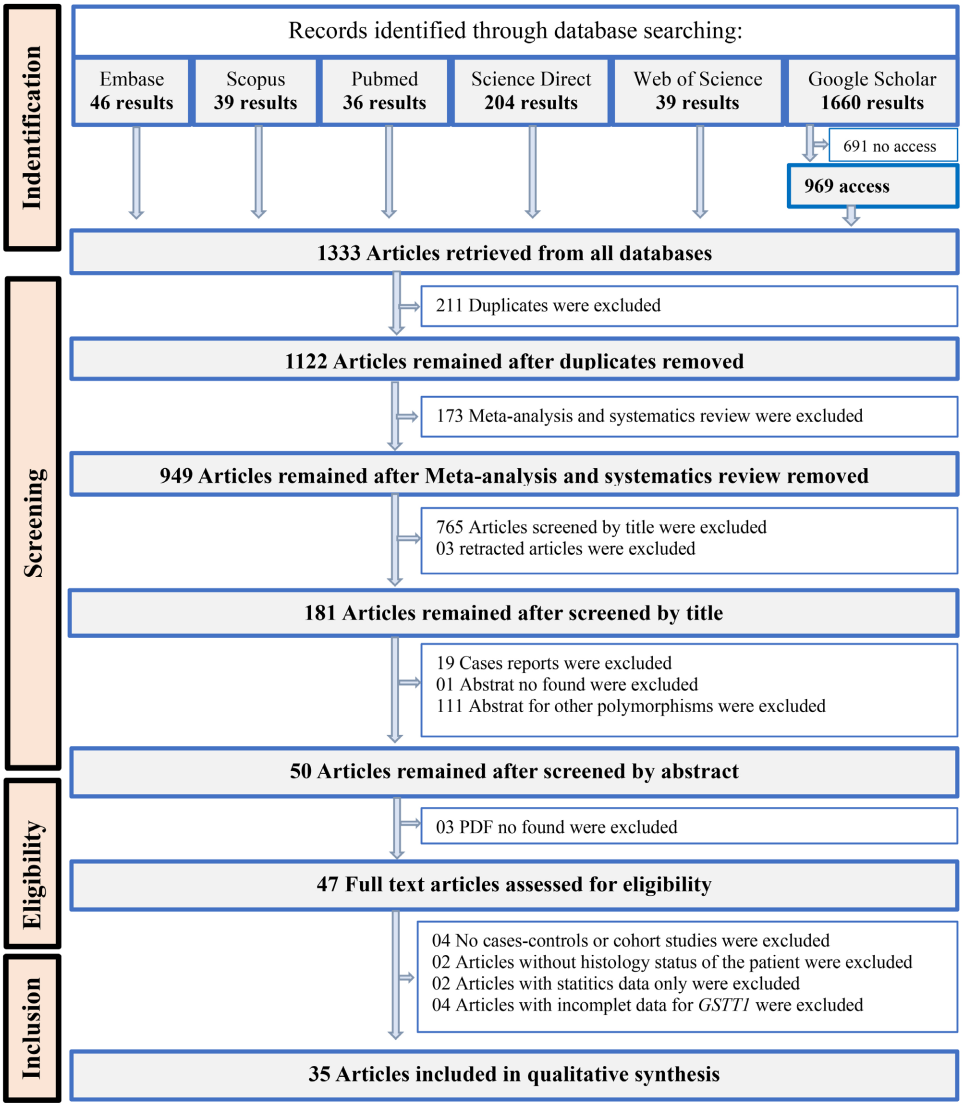


Figure 1. PRISMA diagram of article selection.

Subgroup analyses were performed to explore potential sources of heterogeneity and to assess effect modification by the following factors: study country/region, sample type (e.g., tissue vs. blood), HPV infection status, and tobacco smoke exposure.

2.5. Sensitivity and Publication Bias Analysis

Publication bias was assessed using multiple complementary methods. Visual inspection of funnel plot asymmetry was performed, followed by quantitative tests, including the Begg rank correlation test [29], and the Egger linear regression test [29] [30]. For both statistical tests, a *p*-value < 0.05 was considered indicative of significant publication bias. Furthermore, the non-parametric Trim and Fill method was applied to estimate and adjust for the potential effect of missing studies [31]-[33].

To evaluate the robustness and stability of the pooled results, a sensitivity analysis was conducted using the leave-one-out method. This involved iteratively removing each individual study from the meta-analysis and recalculating the summary effect size to determine whether any single study disproportionately influenced the overall findings [34]-[45].

3. Results

Our systematic search across six databases yielded 1333 using the formulated search equations. Following the removal of duplicates, meta-analyses, systematic reviews, and screening based on both titles and abstracts, 47 articles remained eligible for full-text review. After applying our inclusion criteria, restricting to case-control studies with confirmed histological status of participants and available *GSTT*1 polymorphism data, we ultimately included 35 published articles in the final meta-analysis (**Figure 1**). These studies comprised a total of 10,690 samples including 5,107 cases and 5,583 controls. The characteristics of the selected studies, including mean age, sample type, genotyping method, and genotype frequencies, are summarized in **Table 1**.

Table 1. Studies included in the meta-analysis accessing the association between *GSTT*1 -*null* and cervical cancer risk.

Auteurs	Countries	Mean age cases/controls	Source of controls	Type of sample	Methode	Cases/ controls	*GSTT*1 -*null* cases/ controls	All sample
Ângela Inácio *et al*. 2023 [46]	Portugual	NA	Population	Blood cell	PCR	308/552	30/29	860
Ahlem Helaoui *et al*. 2023 [47]	Tunisia	45.26 ± 10.12/ 45 ± 11.34	Hospital	Blood cell	PCR	71/100	10/4	171
Wannapa Settheetham-Ishida *et al*. 2020 [48]	Northeast Thailand,	NA	Hospital	Blood cell	PCR	198/198	64/71	396
Kailas D. Datkhile *et al*. 2019 [49]	Maharashtra, India	48.67 ± 13.78/ 46.37 ± 13.90	NC	Blood cell	PCR	350/400	94/80	350
A.L.M. Tacca *et al*. 2019 [16]	Brezil	49.6 ±14.3/ 54.3 ±15.1	Hospital	Blood cell	PCR	135/100	65/56	235
Sophida Phuthong *et al*. 2018 [50]	Thailand	NA	Hospital	Blood cell	PCR	204/204	64/71	408
K. Satinder *et al*. 2017 [51]	North-Indian	48.5 ± 9.4/ 46.1 ± 11.2	Hospital	Blood cell	PCR	150/150	22/37	300
Tulsi Rani Thakre *et al*. 2016 [15]	India	47.49 ± 10.95/ 47.6 ± 10.98	Hospital	Blood cell	PCR	230/230	80/52	460
Anita Sharma *et al*. 2015 [52]	India	41.1 ± 8.9/40.7 ± 9.5/42.1 ± 11.7	Hospital	Tissue	PCR	160/457	30/65	617
Osamu Nunobiki *et al*. 2015 [53]	Japan	NA	Hospital	Blood cell	PCR	140/52	75/25	192
Sarah Hasan *et al*. 2015 [54]	Pakistan	NA	Hospital	Blood cell	PCR	50/50	14/18	100
Ivana Stosic *et al*. 2014 [55]	Serbia	44.54 ± 12.19/ 42.98 ± 8.26	NC	Blood cell	PCR	97/50	38/20	147
Adriano José de Oliveira Soares *et al*. 2013 [56]	Brezil	NA	Hospital	Blood cell	PCR	100/120	2/20	220

Continued

Leyla B. Djansugurova *et al*. 2013 [57]	Kazakhstan	NA	NC	Blood cell	PCR	207/160	129/43	367
József Cseh *et al*. 2011 [58]	Hungary	NA	Hospital	Cervical cell	PCR	117/136	47/35	253
Osamu Nunobiki *et al*. 2011 [59]	Japan	NA	Hospital	Cervical cell	PCR	144/54	69 /24	198
Antonella Agodi *et al*. 2010 [60]	Sicily	NA	Hospital	Cervical cell	PCR	27/162	4/17	189
Masatsugu Ueda *et al*. 2010 [61]	Japan	NA	Hospital	Blood cell	PCR	299/158	167/80	457
Beray Kiran *et al*. 2010 [62]	Turkish	53.73 ± 10.35/ 51.32 ± 8.86	Hospital	Blood cell	PCR	46/52	15/16	98
Selena Palma *et al*. 2010 [63]	Italy	41.7 ± 12.3/ 36.3 ± 10.1	Hospital	Blood cell	PCR	81/111	23/22	192
Wannapa Settheetham-Ishida *et al*. 2009 [64]	Thailand	NA	Hospital	Blood cell	PCR	90/94	42/38	184
Hariom Singh *et al*. 2008 [64]	India	45.2 ± 8.8/ 50.3 ± 8.3	Population	Blood cell	PCR	150/168	40/18	318
Koji Nishino *et al*. 2008 [66]	Japan	41.6 ± 8/ 40.6 ± 10.5	Hospital	Blood cell	PCR + sequence	124/125	56/58	249
C.R. Nogueira de Carvalho *et al*. 2008 [14]	Brazil	52.48	Hospital	Tissue	PCR	43/86	22/16	144
Carlos H. Sierra-Torres *et al*. 2006 [67]	Colombia	44.53 ± 14.62/ 42.34 ± 10.56	Hospital	Blood cell	PCR	91/92	25/26	183
Thomas Joseph *et al*. 2006 [68]	India	46 ± 10.3/ 47 ± 9.2	Hospital	Blood cell	PCR	147/165	24/16	312
Theodoros Agorastos *et al*. 2007 [69]	Greece	NA	Hospital	Cervical cell	PCR	166/114	62/43	280
R.C. Sobti *et al*. 2006 [70]	India	48.6 ± 6 9.9; 48.0 ± 6 11.3	NC	Blood cell	PCR	103/103	16/26	206
Yoshimitsu Niwa *et al*. 2005 [71]	Japan	47.2 ± 12.2/ 56.2 ± 11.8	Hospital	Blood cell	PCR	131/320	63/145	451
Masatsugu Ueda *et al*. 2005 [72]	Japan	NA	Hospital	Cervical cell	PCR	144/54	69/24	198
A.Sharma *et al*. 2004 [73]	India	49.2 ± 8.8/ 41.4 ± 8.4	NC	Blood cell	PCR	142/96	28/12	238
Sang-Ah Lee *et al*. 2004 [74]	Korea	NA	Hospital	Blood cell	PCR	81/86	38/54	215
Marc T. Goodman, *et al*. 2001 [75]	Hawaii	32.3/39.1	Hospital	Blood cell	PCR	131/180	44/56	621
Jin W. Kim *et al*. 2000 [76]	Korea	46.5 ± 10.1/ 46.5 ± 10.1	Population	Blood cell	PCR	181/181	120/92	362
Adrian Warwick *et al*. 1994 [77]	United Kingdom	NA	Hospital	Blood cell	PCR	233/168	31/27	401

NA: No available; NC: No clarified.

The different analyses carried out in the present study on *GSTT*1 polymorphisms related to the acquisition of cervical lesions (SIL, LSIL, HSIL) or cervical cancer (CC) in the population of studies, according to histological status and in particular regions, the nature of the sample, HPV status, and smoking status were

summarized in Table 2. Nevertheless, the lack of available data did not allow certain subgroup analyses to be conducted (these subgroups are: Africa, HSIL, and LSIL in the American region, CC in the Cervical cell sample, SIL and HSIL in the Tissue sample, Smoking status/HPV status).

Table 2. Summary of statistic results in the meta-analysis.

Studies (cases/controls)	Article (n)	OR(IC)	Z_{test}	p-value	Q	Heterogeneity P_Q	Heterogeneity I^2	τ^2	$P_{egger's\ test}$	$P_{Begg\ \&\ Mazumdar\ test}$	$P_{hi\text{-}square\ test}$
***GSTT*1-null and cervical lesions and cancer**											
Lesions & cancer (SIL & CC)	**35**	**1.26** (1.05 - 1.52)	2.54	**0.011***	108.76	0.000 [r]	68.74% [r]	0.17	0.890	0.989	0.000
***GSTT*1-null and histology status**											
All CC	**24**	**1.35** (1.03 - 1.77)	2.30	**0.022***	101.27	0.000 [r]	77.29% [r]	0.27	0.975	0.785	0.000
SCC	13	1.25 (0.85 - 1.82)	1.27	0.203	59.51	0.000 [r]	79.83% [r]	0.29	0.526	0.583	0.000
ADC & AD	03	1.14 (0.04 - 33.93)	0.16	0.871	10.86	0.004 [r]	81.58% [r]	1.89	0.149	0.602	0.000
Unknow CC	10	1.36 (0.88 - 2.10)	1.62	0.106	31.13	0.000 [r]	71.09% [r]	0.22	0.944	0.531	0.000
All SIL	14	1.15 (0.96 - 1.39)	1.64	0.100	10.32	0.667 [f]	0.00% [f]	0.00	0.959	0.381	0.022
LSIL	09	0.97 (0.74 - 1.27)	-0.23	0.815	4.56	0.804 [f]	0.00% [f]	0.00	**0.011#**	**0.005#**	0.125
HSIL	**11**	**1.50** (1.15 - 1.96)	3.41	**0.001***	15.27	0.123 [f]	34.49% [f]	0.08	0.623	0.533	0.000
***GSTT*1-null and source of controls**											
Hospital-based	27	1.12 (0.94 - 1.34)	1.32	0.187	53.24	0.001 [r]	51.16% [r]	0.09	0.644	0.602	0.000
Population-based	03	**2.29** (1.18 - 4.43)	5.39	**0.000***	1.63	0.441 [f]	0.00% [f]	0.00	0.192	0.117	0.000
Unclarified-based	05	1.44 (0.57 - 3.61)	1.10	0.270	27.81	0.000 [r]	85.62% [r]	0.44	0.510	1	0.000
***GSTT*1-null and geographic region subgroups**											
Africa											
Africa	01	3.93 (1.17 - 13.22)	---	---	---	---	---	---	---	---	---
America											
CC & SIL	05	1.16 (0.42 - 3.19)	0.41	0.681	16.03	0.003 [r]	75.04% [r]	0.34	0.853	1	0.001
All CC	02	1.78 (0.00 - 208245.54)	0.63	0.530	14.06	0.000 [r]	92.89% [r]	1.57	---	0.317	0.000
All SIL	02	1.03 (0.05 - 20.20)	0.12	0.905	1.39	0.239 [f]	27.98% [f]	0.13	---	0.317	0.136
HSIL	00	---	---	---	---	---	---	---	---	---	---
LSIL	00	---	---	---	---	---	---	---	---	---	---
Asia											
CC/SIL	22	1.23 (0.98 - 1.55)	1.88	0.060	75.96	0.000 [r]	72.36% [r]	0.18	0.312	0.446	0.000
All CC	17	1.27 (0.94 - 1.73)	1.66	0.097	76.75	0.000 [r]	79.15% [r]	0.25	0.366	0.537	0.000
SCC	11	1.21 (0.80 - 1.84)	1.02	0.306	53.25	0.000 [r]	81.22% [r]	0.29	0.460	0.436	0.000
ADC	02	0.48 (0.00 - 587.50)	−1.32	0.188	0.29	0.589 [f]	0.00% [f]	0.00	---	0.317	0.092
SIL	05	1.10 (0.75 - 1.60)	0.69	0.493	0.43	0.980 [f]	0.00% [f]	0.00	0.191	0.462	0.358

Continued

HSIL	**04**	**2.23** (1.18 - 4.22)	3.99	**0.000***	1.06	0.787 [f]	0.00% [f]	0.00	0.574	0.308	0.000
LSIL	04	0.86 (0.54 - 1.37)	−1.04	0.300	0.65	0.884 [f]	0.00% [f]	0.00	0.600	0.089	0.202
Europe											
CC & SIL	07	1.33 (0.88 - 2.01)	1.71	0.087	12.28	0.056 [r]	51.15% [r]	0.11	0.910	0.881	0.001
All CC	04	1.41 (0.52 - 3.81)	1.11	0.266	7.09	0.069	57.66% [r]	0.24	0.473	1	0.005
SCC	02	1.49 (0.00 - 4895.03)	0.62	0.534	5.55	0.018 [r]	82.00% [r]	0.67	---	0.317	0.003
ADC	01	4,58 (2,03 - 10,36)	---	---	---	---	---	---	---	---	---
All SIL	07	1.25 (0.91 - 1.71)	1.73	0.085	7.74	0.258 [f]	22.50% [f]	0.04	0.684	0.453	0.010
HSIL	07	1.21 (0.84 - 1.74)	1.31	0.191	8.28	0.218 [f]	27.53% [f]	0.06	0.859	0.293	0.014
LSIL	05	1.20 (0.71 - 2.03)	0.96	0.339	1.96	0.742 [f]	0.00% [f]	0.00	0.094	0.142	0.173
***GSTT*1-null and DNA source subgroups**											
Blood cell											
CC & SIL	28	1.21 (0.98 - 1.5)	1.85	0.064	94.87	0.000 [r]	71.54% [r]	0.19	0.475	0.797	0.000
All CC	22	1.29 (0.98 - 1.70)	1.89	0.059	92.28	0.000 [r]	77.24% [r]	0.27	0.712	0.866	0.000
All CC	**22**	**1.32** (1.17 - 1.49)	4.69	**0.000***	92.28	0.000 [f]	77.24% [f]	0.27	0.712	0.866	0.000
All SIL	08	1.09 (0.84 - 1.42)	0.79	0.432	5.78	0.566 [f]	0.00% [f]	0.00	0.982	0.458	0.070
HSIL	06	1.35 (0.86 - 2.13)	1.70	0.090	6.43	0.267 [f]	22.21% [f]	0.06	0.713	0.851	0.011
LSIL	06	1.02 (0.71 - 1.48)	0.16	0.869	3.75	0.586 [f]	0.00% [f]	0.00	**0.022#**	**0.039#**	0.116
Cervical cell											
All CC	00	---	---	---	---	---	---	---	---	---	---
All SIL	04	1.26 (0.85 - 1.86)	1.62	0.104	3.93	0.416 [f]	0.00% [f]	0.00	0.986	0.462	0.040
HSIL	**05**	**1.72** (0.91 - 3.27)	2.36	0.018	8.19	0.085 [r]	51.18% [r]	0.15	0.583	0.806	0.000
HSIL	**05**	**1.64** (1.05 - 2.56)	3.07	**0.002***	8.19	0.085 [f]	51.18% [f]	0.15	0.583	0.806	0.000
LSIL	03	0.88 (0.38 - 2.07)	−0.62	0.534	0.45	0.799 [f]	0.00% [f]	0.00	**0.000#**	0.296	0.238
Tissue											
CC & SIL	02	2.41 (0.00 - 4578.13)	1.48	0.139	6.21	0.013 [r]	83.89% [r]	0.60	---	0.317	0.000
All CC	02	2.45 (0.00 - 3781.16)	1.55	0.120	5.70	0.017 [r]	82.47% [r]	0.55	---	0.317	0.000
All SIL	00	---	---	---	---	---	---	---	---	---	---
HSIL	00	---	---	---	---	---	---	---	---	---	---
***GSTT*1-null and HPV infection status subgroups**											
HPV+											
CC & SIL	**10**	**1.54** (1.09 - 2.16)	2.85	**0.004***	16.53	0.057	45.54%	0.20	0.859	0.721	0.000
All CC	04	1.79 (0.22 - 14.94)	0.88	0.381	16.71	0.001 [r]	82.04% [r]	1.20	0.580	0.497	0.000
All SIL	07	**1.60** (1.02 - 2.51)	2.57	**0.010***	1.81	0.937 [f]	0.00% [f]	0.00	0.096	0.368	0.035
HSIL	**06**	**2.02** (1.23 - 3.32)	3.64	**0.000***	3.40	0.638 [f]	0.00% [f]	0.00	0.522	0.452	0.000
LSIL	04	0.79 (0.27 - 2.26)	−0.73	0.468	0.74	0.865 [f]	0.00% [f]	0.00	0.115	0.734	0.265

Continued

HPV-											
CC & SIL	09	1.07 (0.79 - 1.44)	0.49	0.627	9.32	0.316 [f]	14.20% [f]	0.03	0.483	0.754	0.029
All CC	04	1.19 (0.38 - 3.75)	0.49	0.627	6.30	0.098 [r]	52.39% [r]	0.40	0.965	0.497	0.021
All SIL	06	1.05 (0.70 - 1.56)	0.30	0.768	4.09	0.537 [f]	0.00% [f]	0.00	**0.044[#]**	**0.024[#]**	0.116
HSIL	05	2.11 (0.86 - 5.20)	2.31	0.021	2.36	0.671 [f]	0.00% [f]	0.00	**0.028[#]**	0.086	0.015
HSIL	**05**	**2.11** (1.06 - 4.22)	3.01	**0.003***	2.36	0.671 [r]	0.00% [r]	0.00	**0.028[#]**	0.086	0.015
LSIL	04	0.92 (0.54 - 1.56)	−0.50	0.617	1.73	0.630 [f]	0.00% [f]	0.00	0.417	0.089	0.151
***GSTT*1-null and smoking status subgroups**											
Smoking											
CC & SIL	**11**	**1.31** (0.99 - 1.72)	2.16	**0.031***	8.54	0.577 [f]	0.00% [f]	0.00	0.746	0.815	0.006
CC & SIL	**11**	**1.31** (1.01 - 1.69)	2.34	**0.019***	8.54	0.577 [r]	0.00% [r]	0.00	0.746	0.815	0.006
All CC	07	1.25 (0.87 - 1.79)	1.52	0.127	7.82	0.252 [f]	23.23% [f]	0.05	0.530	0.293	0.008
All SIL	04	1.46 (0.64 - 3.34)	1.47	0.141	0.54	0.911 [f]	0.00% [f]	0.00	0.105	0.174	0.151
HSIL	02	1.31 (0.03 - 61.52)	0.89	0.374	0.07	0.788 [f]	0.00% [f]	0.00	---	0.317	0.199
Non-smoking											
CC & SIL	11	0.78 (0.52 - 1.15)	−1.43	0.153	21.50	0.018 [r]	53.49% [r]	0.17	0.066	0.139	0.000
All CC	07	0.89 (0.54 - 1.48)	−0.56	0.574	12.19	0.058	50.76%	0.13	0.087	0.099	0.004
All SIL	**03**	**0.50** (0.08 - 3.05)	−1.64	0.101	2.28	0.319 [f]	12.40% [f]	0.07	0.943	0.602	0.030
***GSTT*1-*null*_smoking status_HPV infection**	01	---	---	---	---	---	---	---	---	---	---

Legend: # = significant publication biais, * = significant associate; r = random effects model applied; f = fixed effects model applied; CC = cervical cancer; SIL = squamous intraepithelial lesions; LSIL = low-grade squamous intraepithelial lesions; HSIL = high-grade squamous intraepithelial lesions; SCC = squamous cell carcinoma; ADC = adenocarcinoma or adenosquamous carcinoma; HPV+ = positive infection of human papillomavirus; HPV− = negative infection of human papillomavirus.

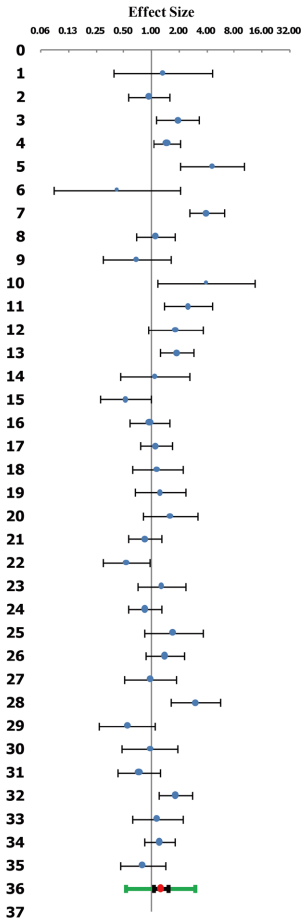
3.1. Analysis of the Association between *GSTT*1-Null Genotype and Cervical Cancer (CC) Acquisition as Well as the Low-Grade (LSIL) and High-Grade (HSIL) Intraepithelial Lesions

Figure 2 presents the pooled analysis of all studies included in this meta-analysis, valuating the association between *GSTT*1-null genotype and the risk of cervical cancer or cervical lesions (combined group) in the overall study population.

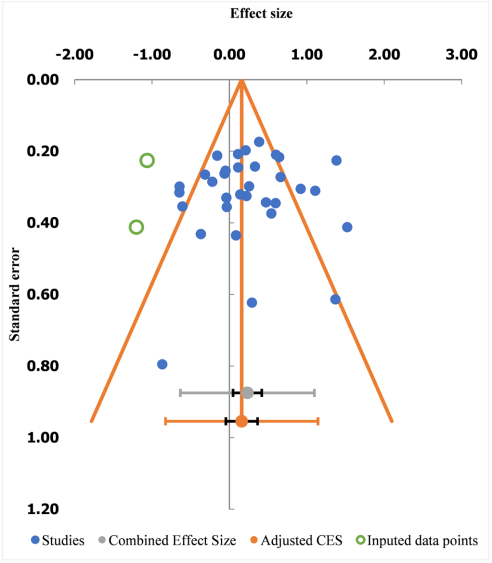
In this meta-analysis, a significant association was observed between the *GSTT*1-null genotype and an increased risk of CC or SIL compared to *GSTT*1-present carriers (OR = 1.26, 95%CI = 1.05 - 1.52, p = 0.011) (Figure 2(a) & Figure 2(b)). Significant heterogeneity was detected between studies (PQ = 0.000, I^2 = 68.74%) with moderate between-study variance (Tau^2 = 0.17). Visual inspection of the funnel plot suggested some asymmetry, indicating the possible absence of small or non-significant studies, as implied by the Trim and Fill method (Figure 2(c)). The initial and combined effects (OR = 0.23, 95%CI = 0.05 - 0.42) after adjustment had non-significant results (OR = 0.16, 95%CI = −0.05 - 0.36). which suggests a

#	Study name	OR	CI Lower limit	CI Upper limit	Weight
1	Agodi et al. 2010	1.34	0.39	4.57	1.38%
2	Agorastos et al. 2006	0.94	0.56	1.57	3.20%
3	Cseh et al. 2011	1.94	1.13	3.31	3.13%
4	Datkhile et al. 2019	1.47	1.04	2.07	3.81%
5	de Carvalho et al. 2008	4.58	2.03	10.36	2.26%
6	de Oliveira Soares et al. 2013	0.42	0.09	2.04	0.96%
7	Djansugurova et al. 2013	3.99	2.56	6.22	3.45%
8	Goodman et al. 2001	1.12	0.69	1.81	3.32%
9	Hasan et al. 2015	0.69	0.29	1.63	2.15%
10	Helaoui et al. 2023	3.93	1.17	13.22	1.41%
11	Inácio et al. 2023	2.51	1.38	4.58	2.91%
12	Joseph et al. 2006	1.82	0.92	3.58	2.65%
13	Kim et al. 2000	1.90	1.24	2.91	3.52%
14	Kiran et al. 2010	1.09	0.46	2.58	2.14%
15	Lee et al. 2004	0.52	0.28	0.98	2.84%
16	Nishino et al. 2008	0.95	0.58	1.57	3.25%
17	Niwa et al. 2005	1.12	0.74	1.68	3.58%
18	Nunobiki et al. 2011	1.15	0.61	2.16	2.80%
19	Nunobiki et al. 2015	1.25	0.66	2.37	2.77%
20	Palma et al. 2010	1.60	0.82	3.15	2.66%
21	Phuthong et al. 2018	0.85	0.56	1.30	3.55%
22	Satinder et al. 2017	0.52	0.29	0.94	2.95%
23	Settheetham-Ishida et al. 2009	1.29	0.72	2.32	2.95%
24	Settheetham-Ishida et al. 2020	0.85	0.56	1.30	3.55%
25	Sharma et al. 2004	1.72	0.82	3.59	2.47%
26	Sharma et al. 2015	1.39	0.86	2.24	3.33%
27	Sierra-Torres et al. 2006	0.96	0.50	1.84	2.74%
28	Singh et al. 2008	3.03	1.65	5.58	2.87%
29	Sobti et al. 2006	0.54	0.27	1.09	2.59%
30	Stosic et al. 2014	0.97	0.48	1.95	2.58%
31	Tacca et al. 2019	0.73	0.43	1.23	3.18%
32	Thakre et al. 2016	1.83	1.21	2.76	3.56%
33	Ueda et al. 2005	1.15	0.61	2.16	2.80%
34	Ueda et al. 2010	1.23	0.84	1.82	3.65%
35	Warwick et al. 1994	0.80	0.46	1.40	3.04%
36	**Combined Effect size**	**1.26**	**1.05**	**1.52**	**3.81%**

(a)



(b)



Observed: OR=0.23, 95%CI=0.05-0.42
Adjusted: OR=0.16, 95%CI=-0.05-0.36

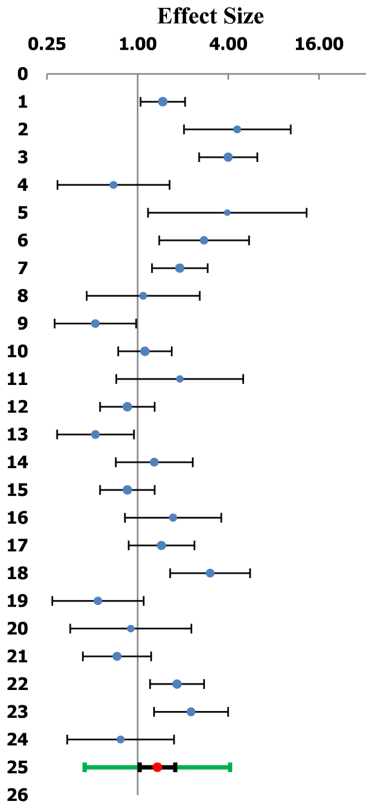
(c)

Figure 2. Association between *GSTT*1*-null* and cervical cancer risk or lesion. (a) Statistic analysis results of association between *GSTT*1*-null* and cervical cancer risk; (b) Forest plot of the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk; (c) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk.

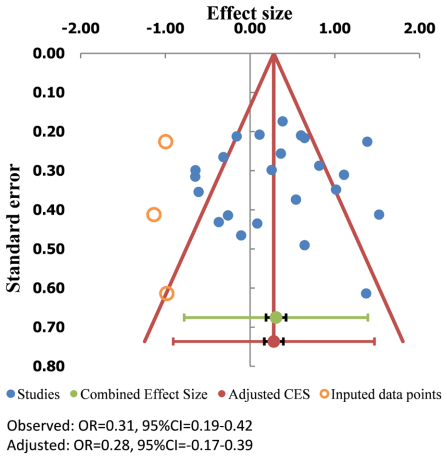
possible overestimation of the combined effect due to publication bias. However, neither the Egger regression test (*p* = 0.890) nor the Begg rank correlation test (*p* = 0.989) reached statistical significance, indicating no strong evidence of significant publication bias in the overall analysis.

	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Datkhile et al. 2019	1.47	1.04	2.07	5.19%
2	de Carvalho et al. 2008	4.58	2.03	10.36	3.55%
3	Djansugurova et al. 2013	3.99	2.56	6.22	4.86%
4	Hasan et al. 2015	0.69	0.29	1.63	3.42%
5	Helaoui et al. 2023	3.93	1.17	13.22	2.42%
6	Inácio et al. 2023	2.76	1.39	5.48	3.99%
7	Kim et al. 2000	1.90	1.24	2.91	4.92%
8	Kiran et al. 2010	1.09	0.46	2.58	3.40%
9	Lee et al. 2004	0.52	0.28	0.98	4.22%
10	Niwa et al. 2005	1.12	0.74	1.68	4.98%
11	Palma et al. 2010	1.90	0.72	5.02	3.06%
12	Phuthong et al. 2018	0.85	0.56	1.30	4.95%
13	Satinder et al. 2017	0.52	0.29	0.94	4.34%
14	Settheetham-Ishida et al. 2009	1.29	0.72	2.32	4.35%
15	Settheetham-Ishida et al. 2020	0.85	0.56	1.30	4.95%
16	Sharma et al. 2004	1.72	0.82	3.59	3.81%
17	Sharma et al. 2015	1.44	0.87	2.38	4.65%
18	Singh et al. 2008	3.03	1.65	5.58	4.26%
19	Sobti et al. 2006	0.54	0.27	1.09	3.95%
20	Stosic et al. 2014	0.90	0.36	2.27	3.21%
21	Tacca et al. 2019	0.73	0.43	1.23	4.58%
22	Thakre et al. 2016	1.83	1.21	2.76	4.97%
23	Ueda et al. 2010	2.26	1.28	3.98	4.43%
24	Warwick et al. 1994	0.77	0.34	1.74	3.54%
25	**Combinet effect size**	**1.35**	**1.03**	**1.77**	**5.19%**

(a)



(b)



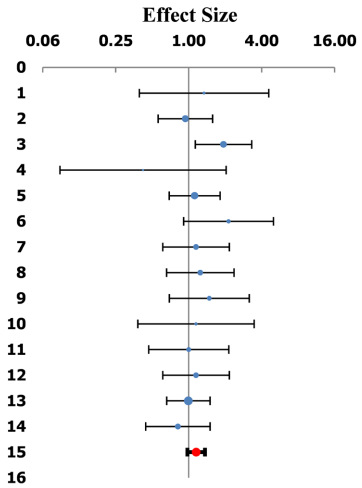
(c)

Figure 3. Association between *GSTT*1*-null* and squamous cell carcinoma or Adenosquamous carcinoma risk. (a) Statistic analysis results of association between *GSTT*1*-null* and squamous cell carcinoma or Adenosquamous carcinoma risk; (b) Forest plot of the meta-analysis of association between *GSTT*1*-null* and squamous cell carcinoma or Adenosquamous carcinoma risk; (c) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and squamous cell carcinoma or Adenosquamous carcinoma risk.

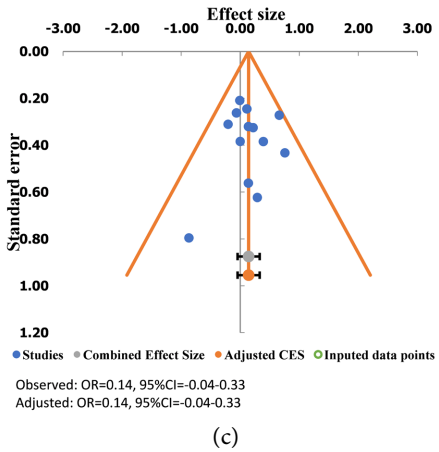
When analyzing the association of the *GSTT*1-null genotype with specific histological statuses, a significant increase in risk was observed for the pooled group of all cervical cancer cases (OR = 1.35, 95%CI = 1.03 - 1.77, p = 0.022) (Figure 3(a) & Figure 3(b)). The studies included in this analysis exhibited significant heterogeneity (PQ < 0.001, I^2 = 77.29%) with substantial between-study variance (Tau^2 = 0.27). Visual inspection of the funnel plot suggested asymmetry, with three (03) studies imputed on the left by the Trim and Fill method. The initial combined effect (OR = 0.31, 95%CI = 0.19 - 0.42) remains statistically significant after adjusting for the variation in OR (OR = 0.28, 95%CI = 0.17 - 0.39), (Figure 3(c)). Indeed, no statistically significant publication bias was detected by the Egger regression test (*p* = 0.975) or the Begg rank correlation test. Conversely, when analyzed by specific histological subtypes Squamous Cell Carcinoma (SCC), Adenocarcinoma/Adenosquamous Carcinoma (ADC/AD), or unspecified cervical cancer no statistically significant associations were found between the *GSTT*1-null genotype and cancer risk compared to the *GSTT*1-present genotype (Table 2).

	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Agodi et al. 2010	1.34	0.39	4.57	1.94%
2	Agorastos et al. 2006	0.94	0.56	1.57	10.92%
3	Cseh et al. 2011	1.94	1.13	3.31	10.16%
4	de Oliveira Soares et al. 2013	0.42	0.09	2.04	1.19%
5	Goodman et al. 2001	1.12	0.69	1.81	12.51%
6	Inácio et al. 2023	2.13	0.91	5.00	4.02%
7	Nunobiki et al. 2011	1.15	0.61	2.16	7.32%
8	Nunobiki et al. 2015	1.25	0.66	2.37	7.11%
9	Palma et al. 2010	1.48	0.69	3.16	5.09%
10	Sharma et al. 2015	1.15	0.38	3.46	2.38%
11	Stosic et al. 2014	1.00	0.47	2.14	5.10%
12	Ueda et al. 2005	1.15	0.61	2.16	7.32%
13	Ueda et al. 2010	0.99	0.66	1.50	17.16%
14	Warwick et al. 1994	0.81	0.44	1.50	7.78%
15	**Combined effect size**	**1.15**	**0.96**	**1.39**	**17.16%**

(a)



(b)



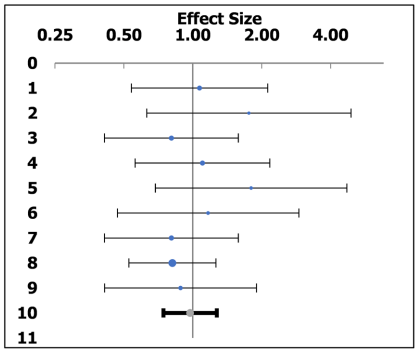
(c)

Figure 4. Association between *GSTT*1*-null* and Squamous Intraepithelial Lesion (SIL) risk. (a) Statistic analysis results of association between *GSTT*1*-null* and SIL risk; (b) Forest plot of the meta-analysis of association between *GSTT*1*-null* and SIL risk; (c) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and SIL risk.

We have also observed, at the level of cases of squamous intraepithelial lesions, an absence of risk in lesions in general (Figure 4) and in low-grade lesions particularly.

#	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Agorastos et al. 2006	1.07	0.54	2.12	11.30%
2	Inácio et al. 2023	1.76	0.63	4.91	5.02%
3	Nunobiki et al. 2011	0.81	0.41	1.58	11.70%
4	Nunobiki et al. 2015	1.10	0.56	2.17	11.57%
5	Palma et al. 2010	1.80	0.69	4.71	5.73%
6	Stosic et al. 2014	1.17	0.47	2.91	6.46%
7	Ueda et al. 2005	0.81	0.41	1.58	11.70%
8	Ueda et al. 2010	0.81	0.53	1.26	27.48%
9	Warwick et al. 1994	0.88	0.41	1.90	9.04%
10	**Combined effect size**	**0.97**	**0.74**	**1.27**	**27.48%**

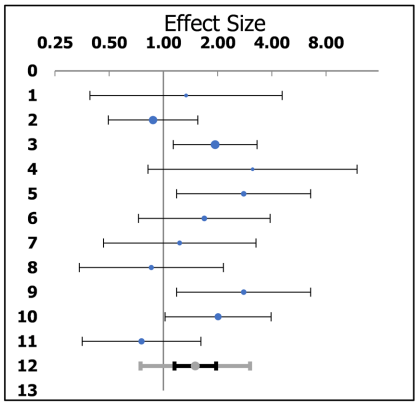
(a)



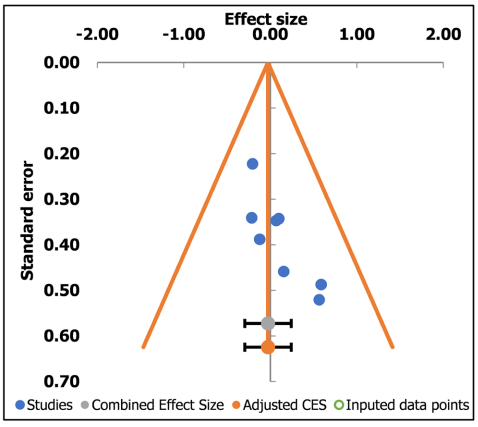
(b)

#	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Agodi et al. 2010	1.34	0.39	4.57	3.66%
2	Agorastos et al. 2006	0.88	0.49	1.55	16.90%
3	CSEH et al. 2011	1.94	1.13	3.31	19.17%
4	Inácio et al. 2023	3.13	0.82	11.90	3.10%
5	Nunobiki et al. 2011	2.79	1.18	6.57	7.61%
6	Nunobiki et al. 2015	1.69	0.73	3.92	7.90%
7	Palma et al. 2010	1.23	0.46	3.26	5.84%
8	Stosic et al. 2014	0.86	0.34	2.15	6.62%
9	Ueda et al. 2005	2.79	1.18	6.57	7.61%
10	Ueda et al. 2010	2.01	1.02	3.96	12.01%
11	Warwick et al. 1994	0.76	0.35	1.61	9.58%
12	**Combined effect size**	**1.50**	**1.15**	**1.96**	**19.17%**

(c)

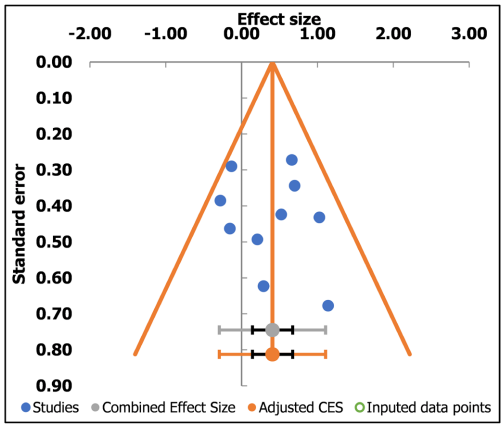


(d)



Observed: OR=-0.03, 95%CI=-0.30-0.24
Adjusted: OR=-0.03, 95%CI=-0.30-0.24

(e)



Observed: OR=-0.41, 95%CI=-0.14-0.67
Adjusted: OR=-0.41, 95%CI=-0.14-0.67

(f)

Figure 5. Association between *GSTT*1*-null* and low-grade squamous intraepithelial lesion (LSIL) (a, b, e) and high-grade squamous intraepithelial lesion (HSIL) (c, d, f)) risk. (a) Statistic analysis results of association between *GSTT*1*-null* and LSIL risk; (b) Forest plot of the meta-analysis of association between *GSTT*1*-null* and LSIL risk; (c) Statistic analysis results of association between *GSTT*1*-null* and HSIL risk; (d) Forest plot of the meta-analysis of association between *GSTT*1*-null* and HSIL risk; (e) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and LSIL risk; (f) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and HSIL risk.

For high-grade intraepithelial lesions (HSIL), the forest plot demonstrated a significant increase in risk (OR = 1.50, 95%CI = 1.15 - 1.96, p = 0.001) (**Figure 5(a)** & **Figure 5(d)**) among carriers of the *GSTT*1-null genotype compared to those with the *GSTT*1-present genotype. Heterogeneity between studies was low to moderate (PQ = 0.123, I^2 = 34.49%), with minimal variance in true effect sizes (Tau^2 = 0.08). The funnel plot showed mild symmetry (**Figure 5(f)**) with non-significant intervals before and after adjustment; however, neither the Egger regression test (*p* = 0.623) nor the Begg rank correlation test (*p* = 0.533) indicated significant publication bias.

3.2. Sub-Group Analysis by Geographical Region

We analyzed the association between the *GSTT*1-null genotype and the risk of cervical cancer (CC), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL) by geographical region. The distribution of studies across regions is shown in **Table 3**.

Table 3. Meta-analysis results of association between *GSTT*1-null and cervical cancer risk by region.

Study name/Subgroup name	OR	CI Ll	CI Ul	Weight	Q	p_Q	I^2	T^2	T	PI Ll	PI Ul
America											
de Carvalho *et al.* 2008 [14]	4.58	2.03	10.36	19.33%							
de Oliveira Soares *et al.* 2013 [56]	0.42	0.09	2.04	10.18%							
Goodman *et al.* 2001 [75]	1.12	0.69	1.81	24.57%							
Sierra-Torres *et al.* 2006 [67]	0.96	0.50	1.84	21.94%							
Tacca *et al.* 2019 [16]	0.73	0.43	1.23	23.97%							
Combined effect size_America	**1.16**	**0.42**	**3.19**	**6.01%**	**16.03**	**0.003**	**75.04%**	**0.34**	**0.59**	**0.17**	**7.91**
Asia											
Datkhile *et al.* 2019 [49]	1.47	1.04	2.07	5.64%							
Djansugurova *et al.* 2013 [57]	3.99	2.56	6.22	5.13%							
Hasan *et al.* 2015 [54]	0.69	0.29	1.63	3.22%							
Joseph *et al.* 2006 [68]	1.82	0.92	3.58	3.95%							
Kim *et al.* 2000 [76]	1.90	1.24	2.91	5.22%							
Kiran *et al.* 2010 [62]	1.09	0.46	2.58	3.19%							
Lee *et al.* 2004 [74]	0.52	0.28	0.98	4.23%							
Nishino *et al.* 2008 [66]	0.95	0.58	1.57	4.83%							
Niwa *et al.* 2005 [71]	1.12	0.74	1.68	5.31%							
Nunobiki *et al.* 2011 [59]	1.15	0.61	2.16	4.18%							
Nunobiki *et al.* 2015 [53]	1.25	0.66	2.37	4.13%							
Phuthong *et al.* 2018 [50]	0.85	0.56	1.30	5.26%							
Satinder *et al.* 2017 [51]	0.52	0.29	0.94	4.39%							
Settheetham-Ishida *et al.* 2009 [64]	1.29	0.72	2.32	4.40%							

Continued

Settheetham-Ishida *et al*. 2020 [48]	0.85	0.56	1.30	5.26%							
Sharma *et al*. 2004 [73]	1.72	0.82	3.59	3.69%							
Sharma *et al*. 2015 [52]	1.39	0.86	2.24	4.95%							
Singh *et al*. 2008 [65]	3.03	1.65	5.58	4.28%							
Sobti *et al*. 2006 [70]	0.54	0.27	1.09	3.86%							
Thakre *et al*. 2016 [15]	1.83	1.21	2.76	5.29%							
Ueda *et al*. 2005 [72]	1.15	0.61	2.16	4.18%							
Ueda *et al*. 2010 [61]	1.23	0.84	1.82	5.41%							
Combined effect size_Asia	**1.23**	**0.98**	**1.55**	**65.72%**	**75.96**	**0.000**	**72.36%**	**0.18**	**0.42**	**0.50**	**3.04**
Europe											
Agodi *et al*. 2010 [60]	1.34	0.39	4.57	6.26%							
Agorastos *et al*. 2006 [69]	0.94	0.56	1.57	17.61%							
Cseh *et al*. 2011 [58]	1.94	1.13	3.31	17.11%							
Inácio *et al*. 2023 [46]	2.51	1.38	4.58	15.49%							
Palma *et al*. 2010 [63]	1.60	0.82	3.15	13.81%							
Stosic *et al*. 2014 [55]	0.97	0.48	1.95	13.26%							
Warwick *et al*. 1994 [77]	0.80	0.46	1.40	16.45%							
Combined effect size_Europe	**1.33**	**0.88**	**2.01**	**28.27%**	**12.28**	**0.056**	**51.15%**	**0.11**	**0.33**	**0.54**	**3.28**
Combined effect size	1.25	1.18	1.33	0.66%	105.37	0.000	68.68%	0.17	0.41	1.18	1.33

Legend: OR = odds ratio, CI = confidence interval, PI = prediction interval, Ll = lower limit, UI = upper limit.

A statistically significant increase in risk was observed for the *GSTT*1-null genotype in the occurrence of HSIL cases in Asia compared to the *GSTT*1-present genotype (OR = 2.23, 95%CI = 1.18-4.22, $p < 0.001$). The included studies showed no significant heterogeneity (PQ = 0.787, $I^2 = 0.00\%$), with consistent true effect sizes across studies ($Tau^2 = 0.00$). No significant publication bias was detected for this subgroup (Table 2 & Table 3). No other statistically significant associations were observed in other geographical regions.

3.3. Subgroup Analysis by Sample Type

The distribution of studies by nucleic acid source is presented in Table 4. A statistically significant association was observed in the subgroup using DNA extracted from blood cells between the *GSTT*1-null genotype and the occurrence of cervical cancer (OR = 1.29, 95%CI = 0.98 - 1.70, p = 0.059 for the "Random effect" model and OR = 1.32, 95% (95%CI = 1.17 - 1.49), p = 0.000 for the "Fixed effect" model) (Table 2 & Table 4). Additionally, a statistically significant association was observed in the subgroup using cervical cell DNA extracts between the null genotype and the occurrence of HSIL (OR = 1.72, 95%CI = 0.91 - 3.27, p = 0.018 for the "Random effect" model and OR = 1.64, 95%CI = 1.05 - 2.56, p = 0.002 for

the "Fixed effect" model) (Table 2 & Table 4). However, the confidence intervals include the null value (1) for the "Random effect" model, indicating that the possibility of no effect cannot be excluded. Consequently, these findings are not conclusive in the context of a meta-analysis and should be interpreted with caution. Significant heterogeneity was evident in both subgroups (PQ < 0.001, I^2 = 77.24% for blood cells; PQ = 0.085, I^2 = 51.18% for cervical cells), with moderate between-study variance (Tau^2 = 0.27 and 0.15, respectively). No statistically significant publication bias was detected by either the Egger regression test (*p* = 0.583) or the Begg rank correlation test (*p* = 0.806) for these analyses.

Table 4. Meta-analysis results of association between *GSTT*1-null and cervical cancer risk by DNA source.

Study name/Subgroup name	OR	CI Ll	CI Ul	Weight	Q	p_Q	I^2	T^2	T	PI Ll	PI Ul
Blood											
Datkhile *et al.* 2019 [49]	1.47	1.04	2.07	4.62%							
de Oliveira Soares *et al.* 2013 [56]	0.42	0.09	2.04	1.23%							
Djansugurova *et al.* 2013 [57]	3.99	2.56	6.22	4.22%							
Goodman *et al.* 2001 [75]	1.12	0.69	1.81	4.07%							
Hasan *et al.* 2015 [54]	0.69	0.29	1.63	2.70%							
Helaoui *et al.* 2023 [47]	3.93	1.17	13.22	1.79%							
Inácio *et al.* 2023 [46]	2.51	1.38	4.58	3.59%							
Joseph *et al.* 2006 [68]	1.82	0.92	3.58	3.29%							
Kim *et al.* 2000 [76]	1.90	1.24	2.91	4.30%							
Kiran *et al.* 2010 [62]	1.09	0.46	2.58	2.68%							
Lee *et al.* 2004 [74]	0.52	0.28	0.98	3.52%							
Nishino *et al.* 2008 [66]	0.95	0.58	1.57	3.99%							
Niwa *et al.* 2005 [71]	1.12	0.74	1.68	4.36%							
Nunobiki *et al.* 2015 [53]	1.25	0.66	2.37	3.44%							
Palma *et al.* 2010 [63]	1.60	0.82	3.15	3.31%							
Phuthong *et al.* 2018 [50]	0.85	0.56	1.30	4.33%							
Satinder *et al.* 2017 [51]	0.52	0.29	0.94	3.64%							
Settheetham-Ishida *et al.* 2009 [64]	1.29	0.72	2.32	3.65%							
Settheetham-Ishida *et al.* 2020 [48]	0.85	0.56	1.30	4.33%							
Sharma *et al.* 2004 [73]	1.72	0.82	3.59	3.08%							
Sierra-Torres *et al.* 2006 [67]	0.96	0.50	1.84	3.40%							
Singh *et al.* 2008 [65]	3.03	1.65	5.58	3.55%							
Sobti *et al.* 2006 [70]	0.54	0.27	1.09	3.22%							
Stosic *et al.* 2014 [55]	0.97	0.48	1.95	3.21%							
Tacca *et al.* 2019 [16]	0.73	0.43	1.23	3.91%							

Continued

Thakre *et al*. 2016 [15]	1.83	1.21	2.76	4.35%							
Ueda *et al*. 2010 [61]	1.23	0.84	1.82	4.45%							
Warwick *et al*. 1994 [77]	0.80	0.46	1.40	3.75%							
Combined effect size_Blood	**1.21**	**0.98**	**1.50**	**63.35%**	**94.87**	**0.000**	**71.54%**	**0.19**	**0.44**	**0.48**	**3.03**
Cell											
Agodi *et al*. 2010 [60]	1.34	0.39	4.57	5.15%							
Agorastos *et al*. 2006 [69	0.94	0.56	1.57	29.01%							
Cseh *et al*. 2011 [58]	1.94	1.13	3.31	26.98%							
Nunobiki *et al*. 2011 [59]	1.15	0.61	2.16	19.43%							
Ueda *et al*. 2005 [72]	1.15	0.61	2.16	19.43%							
Combined effect size_Cell	**1.26**	**0.85**	**1.86**	**34.72%**	**3.93**	**0.416**	**0.00%**	**0.00**	**0.00**	**0.85**	**1.86**
Tissue											
de Carvalho *et al*. 2008 [14]	4.58	2.03	10.36	46.10%							
Sharma *et al*. 2015 [52]	1.39	0.86	2.24	53.90%							
Combined effect size_Tissue	**2.41**	**0.00**	**4578.13**	**1.93%**	**6.21**	**0.013**	**83.89%**	**0.60**	**0.77**	**0.00**	**572118.57**
Combined effect size	1.24	1.09	1.42		108.76	0.000	68.74%	0.17	0.42	1.09	1.42

Legend: OR = odds ratio, CI = confidence interval, PI = prediction interval, Ll = lower limit, UI = upper limit.

3.4. Subgroup Analysis by HPV Status

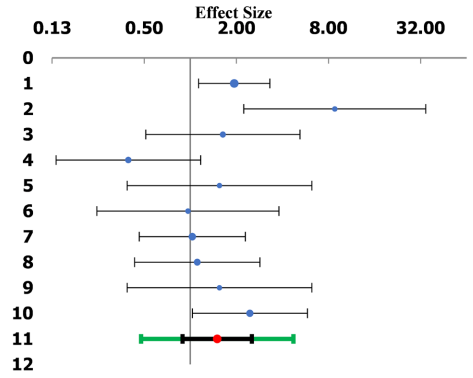
Figure 6 presents the forest plots and funnel plots for the association between the *GSTT*1-null genotype and cervical cancer/lesions in HPV-positive women (Figures 6(a) & Figures 6(b) & Figures 6(e)) and HPV-negative women (Figures 6(c) & Figures 6(d) & Figures 6(f)). A statistically significant increase in risk was observed among HPV-positive women for the combined cervical cancer/lesion group (OR = 1.54, 95%CI = 1.09 - 2.16, p = 0.004; Figure 6(a) & Figure 6(b)), as well as for the cervical lesion subgroup alone (OR = 1.60, 95%CI = 1.02 - 2.51, p = 0.010) (Table 2). Notably, this association was particularly strong for high-grade squamous intraepithelial lesions (HSIL) in HPV-positive women (OR = 2.02, 95%CI = 1.23-3.32, p = 0.000; Table 2). Interestingly, a similar trend was observed for HSIL in HPV-negative women, though the confidence interval included the null value (OR = 2.11, 95%CI = 0.86 - 5.20, p = 0.021) (Table 2). Both subgroups (HPV-positive and HPV-negative) showed negligible heterogeneity (I^2 = 0%, PQ > 0.1) and consistent effect sizes (Tau^2 = 0.00). No significant publication bias was detected for HPV-positive women, but potential bias was suggested by the Egger test for HPV-negative women (*p* = 0.028, Table 2).

3.5. Subgroup Analysis by Smoking Status

Figure 7 presents the forest plots and funnel plots for the association between the *GSTT*1-null genotype and cervical outcomes according to smoking status. An increased risk was observed among women exposed to tobacco smoke in the combined

#	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Cseh et al. 2011	1.94	1.13	3.31	17.25%
2	de Carvalho et al. 2008	8.80	2.24	34.60	7.10%
3	Joseph et al. 2006	1.63	0.51	5.21	8.74%
4	Lee et al. 2004	0.39	0.13	1.17	9.60%
5	Nunobiki et al. 2011	1.55	0.39	6.23	6.96%
6	Nunobiki et al. 2015	0.97	0.25	3.80	7.11%
7	Sharma et al. 2015	1.03	0.46	2.29	13.04%
8	Sierra-Torres et al. 2006	1.11	0.43	2.85	11.13%
9	Ueda et al. 2005	1.55	0.39	6.23	6.96%
10	Ueda et al. 2010	2.45	1.03	5.82	12.10%
11	**Combined Effect size**				

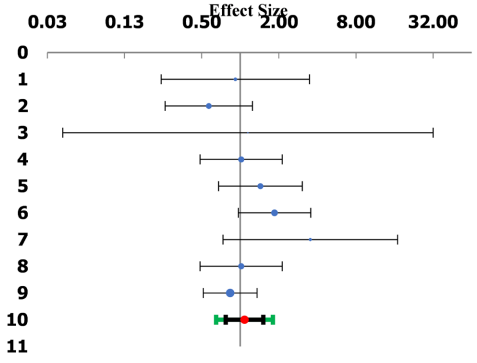
(a)



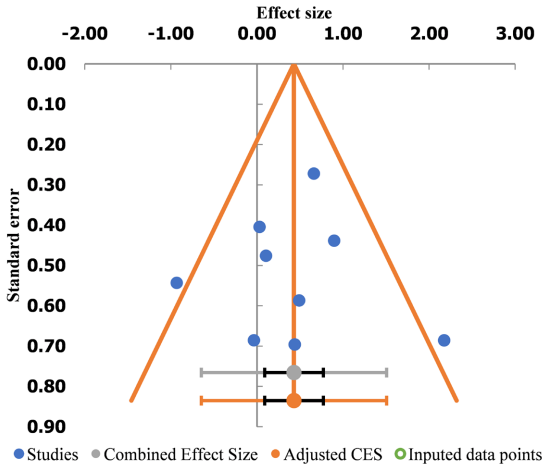
(b)

#	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Joseph et al. 2006	0.92	0.24	3.47	4.51%
2	Lee et al. 2004	0.57	0.26	1.25	11.83%
3	de Carvalho et al. 2008	1.15	0.04	31.98	0.78%
4	Nunobiki et al. 2011	1.02	0.49	2.13	13.07%
5	Nunobiki et al. 2015	1.44	0.68	3.05	12.66%
6	Sharma et al. 2015	1.85	0.97	3.55	15.89%
7	Sierra-Torres et al. 2006	3.52	0.73	16.88	3.39%
8	Ueda et al. 2005	1.02	0.49	2.13	13.07%
9	Ueda et al. 2010	0.83	0.51	1.35	24.79%
10	**Combined Effect size**				

(c)

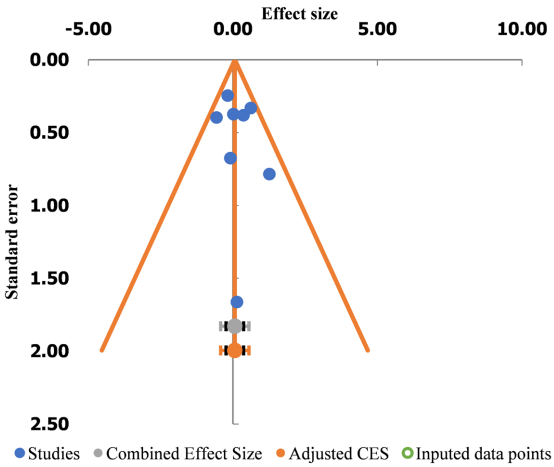


(d)



Observed: OR=0.43, 95%CI=0.09-0.77
Adjusted: OR=0.43, 95%CI=-0.09-0.77

(e)



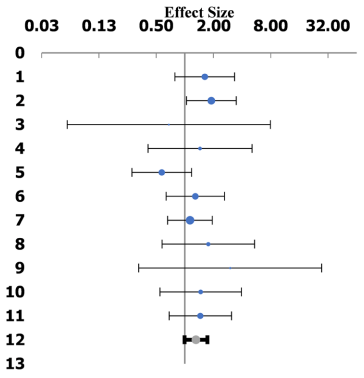
Observed: OR=0.06, 95%CI=-0.24-0.37
Adjusted: OR=0.06, 95%CI=-0.24-0.37

(f)

Figure 6. Association between *GSTT*1*-null* and cervical cancer risk in HPV positive (a, b, e) and HPV negative group (c, d, f); (a) Statistic analysis results of association between *GSTT*1*-null* and cervical cancer risk in HPV positive; (b) Forest plot of the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk in HPV positive; (c) Statistic analysis results of association between *GSTT*1*-null* and cervical cancer risk in HPV negative; (d) Forest plot of the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk in HPV negative; (e) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk in HPV positive; (f) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk in HPV negative.

#	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Agorastos et al. 2006	1.62	0.79	3.34	11.54%
2	Datkhile et al. 2019	1.90	1.04	3.46	16.51%
3	de Oliveira Soares et al. 2003	0.68	0.06	7.93	1.07%
4	Palma et al. 2010	1.44	0.41	5.09	3.89%
5	Phuthong et al. 2018	0.57	0.28	1.18	11.55%
6	Settheetham-Ishida et al. 2009	1.29	0.64	2.62	12.04%
7	Settheetham-Ishida et al. 2020	1.13	0.66	1.94	20.49%
8	Sharma et al. 2015	1.76	0.58	5.41	4.90%
9	Sobti et al. 2006	3.00	0.33	27.48	1.26%
10	Stosic et al. 2014	1.47	0.55	3.93	6.27%
11	Warwick et al. 1994	1.45	0.68	3.09	10.48%
12	**Combined Effect size**	1.31	0.99	1.72	20.49%

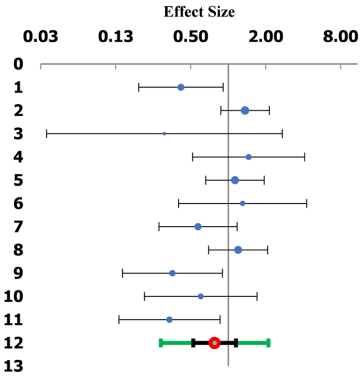
(a)



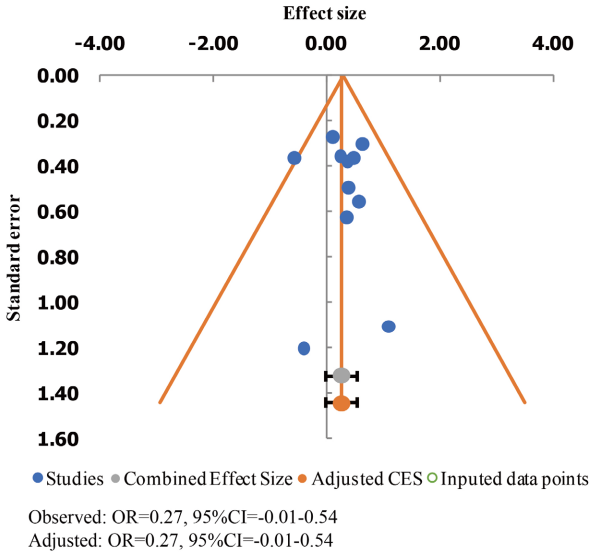
(b)

#	Study name	Odds Ratio	CI Lower limit	CI Upper limit	Weight
1	Agorastos et al. 2006	0.42	0.19	0.91	9.83%
2	Datkhile et al. 2019	1.36	0.87	2.14	14.42%
3	de Oliveira Soares et al. 2003	0.31	0.03	2.72	2.33%
4	Palma et al. 2010	1.46	0.52	4.11	7.24%
5	Phuthong et al. 2018	1.13	0.66	1.94	13.04%
6	Settheetham-Ishida et al. 2009	1.30	0.40	4.26	6.14%
7	Settheetham-Ishida et al. 2020	0.57	0.28	1.18	10.52%
8	Sharma et al. 2015	1.20	0.70	2.07	12.94%
9	Sobti et al. 2006	0.36	0.14	0.90	8.22%
10	Stosic et al. 2014	0.60	0.21	1.70	7.22%
11	Warwick et al. 1994	0.34	0.13	0.86	8.09%
12	**Combined Effect size**	0.78	0.52	1.15	14.42%

(c)

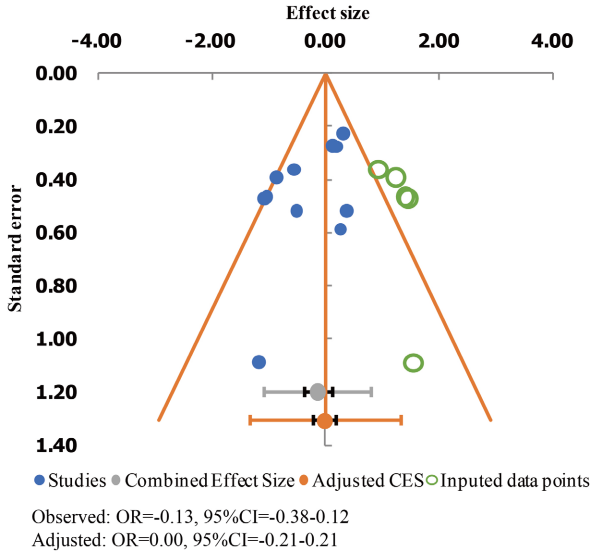


(d)



Observed: OR=0.27, 95%CI=-0.01-0.54
Adjusted: OR=0.27, 95%CI=-0.01-0.54

(e)



Observed: OR=-0.13, 95%CI=-0.38-0.12
Adjusted: OR=0.00, 95%CI=-0.21-0.21

(f)

Figure 7. Association between *GSTT*1*-null* and cervical cancer risk in smoking (a, b, e) or non-smoking group (c, d, f). (a) Statistic analysis results of association between *GSTT*1*-null* and cervical cancer risk in smoking group; (b) Forest plot of the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk in smoking group; (c) Statistic analysis results of association between *GSTT*1*-null* and cervical cancer risk in nonsmoking group; (d) Forest plot of the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk in nonsmoking group; (e) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk in smoking group; (f) Begg's funnel plot of studies included in the meta-analysis of association between *GSTT*1*-null* and cervical cancer risk in nonsmoking group.

cervical cancer/lesion group (OR = 1.31, 95%CI = 0.99 - 1.72, p = 0.031 for "Fixed effect" model, **Figure 7(a)** & **Figure 7(b)**; and OR = 1.31, 95%CI = 1.01 - 1.69, p = 0.019 for "Random effect"). A similar trend was noted specifically for low-grade lesions, though the confidence interval was extremely wide (OR = 2.08, 95% CI = 0.02 - 176.84, p = 0.036).

Conversely, no increased risk was observed among women not exposed to tobacco smoke.

4. Discussion

Cancer is a multifactorial disease arising from the complex interplay of genetic and environmental factors. Cervical carcinogenesis exemplifies this paradigm, where persistent infection with high-risk HPV acts as the necessary environmental driver, while host genetic susceptibility modulates individual risk. Among the candidate genetic modifiers, polymorphisms in GSTs genes, particularly the *GSTT*1-null genotype, have been extensively studied for their potential role in detoxifying carcinogens. However, the literature reports conflicting findings regarding the association between the *GSTT*1-null polymorphism and cervical cancer risk. Previous meta-analyses attempting to resolve this ambiguity have been limited by insufficient data or methodological constraints, underscoring the need for updated, comprehensive syntheses. The present meta-analysis was therefore conducted to provide a clearer assessment of this relationship and to evaluate the influence of key effect modifiers, namely HPV status and tobacco smoke exposure.

This meta-analysis identified a significant association between the *GSTT*1-null genotype and an increased risk of cervical cancer (OR = 1.35, 95%CI = 1.03 - 1.77, p = 0.022). This finding is consistent with previous meta-analyses by Liu *et al.* (OR = 1.44, 95% CI = 1.07 - 1.94, p = 0.02) and Tian *et al.* (OR = 1.78, $p < 0.05$) [34] [35]. Furthermore, in line with Tian *et al.* (OR = 1.30, $p < 0.05$) [35] we observed a significantly increased risk for HSIL (OR = 1.50, 95%CI = 1.15 - 1.96; p = 0.001), but not for low-grade lesions (p = 0.815). The biological plausibility of this association is well-established. The *GSTT*1 enzyme plays a critical role in Phase II detoxification, conjugating glutathione to a wide range of toxic and mutagenic substrates, including ethylene oxide, propylene oxide, butylene oxide [36], methyl chloride, dichloromethane [37], cumene hydroperoxide, 1,2-epoxy-3-(p-nitrophenoxy)propane, 4-nitrobenzyl chloride, ethylene diiodide [38], and various drug metabolites [39] [40]. Consequently, individuals carrying the *GSTT*1-null genotype have an impaired capacity to neutralize these genotoxic compounds, which may elevate susceptibility to DNA damage and carcinogenesis [41]. Thus, our results verify the hypothesis that the *GSTT*1-null polymorphism contributes to the development of cervical cancer and its high-grade precursors.

Subgroup analysis by geographical region revealed a notably strong association in Asia, where the *GSTT*1-null genotype was associated with a significantly increased risk of high-grade lesions (OR = 2.23, 95%CI = 1.18 - 4.22, p = 0.000). This specific regional finding, which was not highlighted in prior meta-analyses,

aligns with observations by Liu *et al*. (2017), who reported elevated risks in specific countries such as Kazakhstan (OR = 3.99, 95%CI = 2.56 - 6.21, p = 0.00001) and in Brazil (OR = 4.58, 95%CI = 2.04 - 10.28, p = 0.00002) [34]. Our updated analysis, which incorporated a more detailed consideration of participant characteristics and a broader dataset within these geographical subgroups, provides a clearer context for these previously noted regional disparities.

In the subgroup analysis by sample type, an increased risk for cervical cancer was observed among *GSTT*1-null carriers when using DNA extracted from blood (OR = 1.29, 95%CI = 0.98 - 1.70, p = 0.059, for the "Random effect" model and OR = 1.32, 95%(CI = 1.17 - 1.49), p = 0.000 for the "Fixed effect" model) and a risk for high-grade lesions in using the DNA from cervical cells (OR = 1.72, 95%CI = 0.91 - 3.27, p = 0.018 for the "Random effect" model and OR = 1.64, 95%CI = 1.05 -2.56, p = 0.002 for the "Fixed effect" model). These findings contrast with those of Goa *et al*., [42], who reported no significant association when stratifying by DNA source. This discrepancy may be attributed to key methodological differences between the studies. Specifically, Gao *et al*.'s analysis was limited to four databases and sixteen articles published up to 2010 within the Asian region, whereas the present meta-analysis incorporated six databases and twenty-two articles published up to 2025. The results were not significant in the tissues in present analysis. The expanded scope and updated dataset likely enhanced the statistical power and sensitivity to detect associations. Furthermore, the observed differences in risk estimates between blood and cervical cell samples may reflect variations in the biological relevance or detection sensitivity of the *GSTT*1 polymorphism across different tissue types. While blood DNA reflects the constitutional genotype, tumor DNA results from somatic alterations during carcinogenesis, including loss of heterozygosity (LOH), amplifications, deletions, or chromosomal rearrangements, which may introduce bias in genetic analysis. Tumor DNA extracted from paraffin blocks is also subject to DNA degradation related to formalin fixation and paraffin embedding (FFPE), which could further reduce extraction yield. These biological and methodological factors suggest that blood DNA is more suitable for polymorphism detection studies than tumor tissue DNA. However, it should be noted that the confidence intervals observed in our analyses encompassed the null value (1), and the p-value was close to 0.06 for the "Random effect" model; therefore, the results are not conclusive in the context of a meta-analysis, and the observed association may not exist according to this model.

In the subgroups of HPV status distribution, risk growth in the acquisition of high-grade lesions Analysis by HPV status revealed that the *GSTT*1-null genotype was associated with a significantly increased risk of high-grade lesions in both HPV-positive (OR = 2.02 95%CI = 1.23 - 3.32, p = 0.000) and HPV-negative women (OR = 2.11, 95%CI = 0.86 - 5.20, p = 0.021). While the point estimates are similar, the confidence interval in the HPV-negative subgroup crosses the null value, indicating less statistical precision. This suggests that HPV infection may potentiate the risk conferred by the *GSTT*1-null genotype. However, the relation-

ship appears complex, as other studies report varying risks depending on specific HPV genotypes [43] or even a protective association [44]. Given the limited number of studies (n = 5) and samples (559 HPV-positive, 369 HPV-negative) available for this subgroup analysis, these results should be interpreted cautiously, highlighting the need for further research to clarify this gene-virus interaction.

In contrast, among women exposed to tobacco smoke, a significant increase in risk was observed for the *GSTT*1-null genotype in the combined cervical cancer/lesion group (OR = 1.31, 95%CI = 0.99 - 1.72, p = 0.031 or OR = 1.31, 95%CI = 1.01 - 1.69, p = 0.019). This aligns with the findings of Tian *et al*. [35] and is biologically plausible, as tobacco smoke contains numerous carcinogens and induces local immunosuppression by reducing Langerhans and T-helper cells in the cervical transformation zone [11]. This impaired immune surveillance may facilitate HPV persistence and carcinogenic progression, suggesting that smoking substantively modifies the risk associated with the *GSTT*1-null genotype. However, consistent with the subgroup analyses according to DNA source, the confidence intervals obtained for this subgroup encompassed the null value (1), thereby precluding definitive conclusions within the framework of the meta-analysis.

Heterogeneity across studies was substantial and varied widely (PQ = 0.000 - 0.980 and I^2 = 0.000% - 92.89%), a common challenge in genetic association meta-analyses. This variability likely stems from differences in sample types (blood, tissue, cervical cells), ethnic backgrounds of study populations, and variations in participant characteristics such as histological status, smoking exposure, and HPV infection. Indeed, analyses according to histology precisely the subgroups of SIL in general, in Asia, in women HPV-positive, HPV-negative and the source of study controls in the general population have contributed the most to the reduction of heterogeneity. This could be compensated by the specificity of the relevant pathology, but also by the choice of controls in the general population avoiding biases in a hospital setting.

Evidence of significant publication bias was detected, particularly within analyses of cervical lesions. This bias may stem from several methodological factors: the selection of control groups, which can influence risk estimates as described by Wacholder *et al*. [45], the reliance solely on published literature, excluding potentially relevant unpublished data; language restrictions that omitted non-English studies; and the inherent limitations of the selected databases, some of which provided incomplete access to full-text articles. Indeed, we analyzed the data according to the source of controls (table II) hospital, non-hospital and not clarified. The controls coming from the hospital centers (OR = 1.12, 95%CI = 0.94 - 1.34, p = 0.187) and the unclarified ones (OR = 1.44, 95%CI = 0.57 - 3.61, p = 0.270) had a significant heterogeneity (51.16% and 85.62% respectively). The controls based on the population had a significant result with low heterogeneity: (OR = 2.29, 95% CI = 1.18 - 4.43, p = 0.000*)

Our meta-analysis has several notable limitations. First, heterogeneity was introduced by variability across the included studies in participant selection criteria and genotyping methodologies. Second, the available data were insufficient to an-

alyze the potential influence of key environmental and reproductive co-factors, such as parity and detailed HPV-infection status stratified by smoking exposure. The inability to account for these variables constrains the comprehensive assessment of gene-environment interactions in cervical carcinogenesis.

Notwithstanding its limitations, this meta-analysis possesses several significant strengths. The pooled analysis included a substantial sample size (10,690 individuals: 5,107 cases and 5,583 controls), which enhances the statistical power and precision of the findings. All analyses were performed using Meta-Essentials software (version 1.5), which provides robust tools for meta-regression and effect estimation. Furthermore, we conducted comprehensive mixed-effects models and detailed subgroup analyses to explore sources of heterogeneity and effect modification, thereby strengthening the validity and clarity of the conclusions. Finally, restricting the inclusion to English-language publications served to minimize potential linguistic bias in the study selection process.

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. AKO collected data and revised the manuscript. YDK analyzed data and wrote the manuscript. KMK, PB, PAS, MAET and IMAT collected data. RAO, LT, AAZ, TS, TMZ, FWD, CMRO, DSK, and JS critically revised the manuscript.

5. Conclusions

The results of this meta-analysis indicate that the *GSTT*1-null genotype is associated with a significantly increased risk of cervical cancer and high-grade squamous intraepithelial lesions (HSIL). Subgroup analyses revealed that this association was particularly pronounced for HSIL in Asian populations. Furthermore, the risk associated with the *GSTT*1-null genotype was amplified in the presence of established environmental co-factors. Specifically, a significantly elevated risk was observed in the combined subgroup of women exposed to tobacco smoke and in HPV-positive women.

When analyzed separately, the *GSTT*1-null genotype was strongly associated with HSIL in HPV-positive women. In contrast, no increased risk was observed in women not exposed to tobacco smoke. A notable limitation of this study is the insufficient data from Africa, a region with a high burden of cervical cancer mortality. Given the critical need for context-specific prognostic tools, future research should prioritize large-scale studies in African populations to investigate the interplay between genetic polymorphisms, such as *GSTT*1, and local environmental factors. Such research is essential for developing predictive biomarkers and tailored strategies in the global effort to reduce cervical cancer incidence and mortality.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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