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An Updated Meta-Analysis: Cervical Cancer Risk Conferred by GSTM1 and GSTT1 Polymorphisms

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Abstract Objective: To study the influence of GSTM1 and GSTT1 gene polymorphisms on cervical cancer (CC) risk, and explore genetic-environmental interactions. Methods: After a systematic literature search, all relevant studies entailing the association between GST polymorphisms and CC were included. The pooled odds ratio (OR) was used for analysis of the results and corresponding 95% confidence intervals (CI) were estimated. Results: A total of 23 case-control studies were included in the meta-analysis of GSTM1 (2,250 CC cases and 3,025 controls) and GSTT1 (1,704 CC cases and 2,460 controls) genotypes. For the GSTM1 polymorphisms, the null genotype of GSTM1 was associated with an increased CC risk for the total population (OR=1.57, 95% CI=1.25-1.98). A similar association was found in China (OR=2.34, 95% CI=1.56-3.52), India (OR=2.02, 95% CI=1.43-2.83), Pakistan (OR=5.52, 95% CI=2.34-13.07), Serbia (OR=1.73, 95% CI=0.68-4.39) and Kazakhstan (OR=6.5, 95% CI=2.25-18.81), but was not noted for others countries. Regarding human papilloma virus (HPV) infection, moderately but significantly increased risk of the null GSTM1 genotype was found in HPV-positive patients (OR=2.59, 95% CI=1.57-4.27). For the GSTT1 polymorphisms, the null GSTT1 genotype was associated with increased CC risk in the total population (OR=1.44, 95% CI=1.07-1.93). Regarding ethnic stratification, a significantly increased risk of the null GSTT1 genotype was found in Kazakhstan (OR=3.99, 95% CI=2.56-6.21) and Brazil (OR=4.58, 95% CI=2.04-10.28). With respect to smoking, the two aspects of the analysis above were not significantly associated with CC risk in smokers or non-smokers, respectively. For the GSTM1/GSTT1 interaction analysis, the dual null genotypes of GSTM1/GSTT1 were significantly associated with increased CC risk for the total population (OR=1.62, 95% CI=1.14-2.29). Conclusion: This meta-analysis provided sufficient evidence that the null genotype of GSTM1, or GSTT1 and the dual-null genotypes of GSTM1/GSTT1 are associated with CC.

Keywords: Cervical cancer, genetic polymorphism, glutathione S-transferase M1, glutathione S-transferase T1, meta-analysis

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Introduction

Cervical cancer (CC), which has an annual global incidence of 530,000 new cases, is the second most commonly diagnosed cancer and third leading cause of cancer death among females in less developed countries. Cervical cancer is predominantly attributed to infection accounting for 100% of cases worldwide [1]. Sub-Saharan Africa, Latin America and the Caribbean, and Melanesia have the highest incidence of CC. Nearly 90% of cervical cancer deaths occurred in developing parts of the world: 60,100 deaths in Africa, 28,600 in Latin America and the Caribbean, and 144,400 in Asia. India, the second most populous country in the world, accounted for 25% of cervical cancer deaths (67,500 deaths). In Eastern, Middle, and Southern Africa as well as in Melanesia, cervical cancer is the leading cause of cancer deaths in females [2]. The above data show that CC has a high morbidity and mortality in various racial groups and geographic regions. Thus, we concluded that CC may not be caused by one single factor; rather that genetic and environmental factors may play important roles in cervical cancer.

It is well known that human papilloma virus (HPV) infection is a necessary but insufficient cause for cervical cancer because not all CC patients are infected with HPV [3]. Previous studies have shown that DNA repair gene variants are associated with cervical cancer [4]. Indeed, functional variants of two xenobiotic metabolism genes, glutathione S-transferase mu 1 (GSTM1) and glutathione S-transferase theta 1 (GSTT1), were associated with several cancers including cervical cancer.

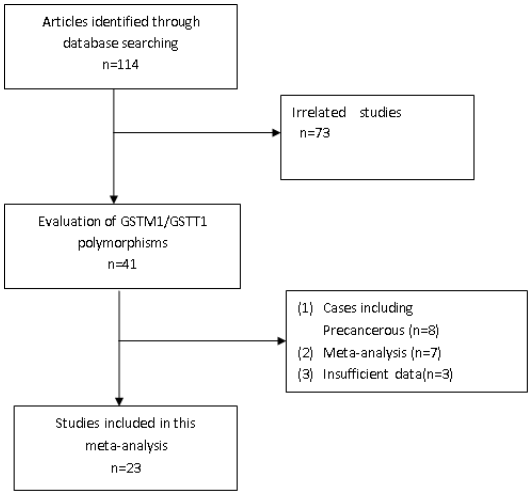

Fig. 1. Flow chart depicting the study selection procedure.

The null genotypes GSTM1 and GSTT1 may promote the development of cervical cancer by modulating the activity and detoxification of polycyclic hydrocarbons and other compounds that influence oxidative stress and DNA adduct formation [5]. There exist a large number of studies describing the association between GSTM1 and the GSTT1 and risk for cervical cancer; however, the results are inconsistent [6-8]. Although there were meta-analyses reported regarding the two gene polymorphisms and cervical cancer, these were not in the context of HPV infection. Therefore, we conducted a meta-analysis regarding the effects of GSTM1 and GSTT1 gene polymorphisms on cervical cancer risk, and further explored the interaction of genes and environment and their roles in the risk for cervical cancer.

Materials and Methods

Literature Search Strategy. We conducted a comprehensive systematic search to identify relevant studies from PubMed, CBM (Chinese Biomedicine Database), CNKI (China National Knowledge Infrastructure), Wan Fang data, and VIP databases using numerous terms without any restriction on language, including "cervical cancer" or "cervical adenocarcinoma" or "cervical neoplasms" or "uterine cervical neoplasms" or "GST" or "glutathione S-transferase" or "GSTM1" or "GSTT1" or "polymorphism" or "polymorphisms" or "gene variant" or "gene variants".

Inclusion Criteria and Data Extraction. Only studies that matched all of the following criteria were included: (1) case-control studies, (2) those studies entailing the association between GSTM1 or GSTT1 and CC risk, (3) cases in the population were not to include precancerous lesion patients, (4) the control population

was not to include malignant tumor patients, and (5) studies that provided the information on genotypic frequencies of GSTM1 and GSTT1 polymorphisms in both cases and controls. Exclusion criteria were the following: (1) precancerous lesions included in the cases, (2) insufficient data; and (3) reviews and Meta-analyses. The following information was extracted from each study: (1) name of the first author, (2) year of publication, (3) country and ethnicity, (4) sample size of cases and controls, (5) study design, and (6) genotyping methods used.

Statistical analysis. Statistical analyses were performed using software Review Manager 5.3 and STATA 11.0. The association between GSTM1 and GSTT1 polymorphisms and risk for CC were expressed as pooled odds ratios (OR), and the corresponding p value, $p<0.05$, was considered to be statistically significant. Heterogeneity among studies was determined using an a-based Q-statistic and I^2-statistic [9]. When there was some evidence of heterogeneity in the analysis ($P_{Q\text{-statistic}} \leq 0.10$ or I^2-statistic >50%), pooled ORs were determined using a random-effects model; otherwise, the fixed-effects model was assumed. Subgroup analyses were performed on the basis of ethnicity, smoking and HPV infection. Finally, Begg's funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detect bias. Publication bias was evaluated by Begg's test and Egger's test ($p>0.05$ was considered to be significant, and there was no publication bias found).

Results

Characteristics of the studies. As Fig. 1, a flow chart of 23 studies included in this meta-analysis is presented. 21 studies of GSTM1 polymorphisms (2,250 CC cases and 3,025 controls) [6, 8, 10-28], 17 studies of GSTT1 polymorphisms (1,704 CC cases and 2,060 controls) genotypes [6, 11-13, 15-17, 20-24, 26-30] , and 9 studies of GSTM1-GSTT1 interaction analyses (1,046 CC cases and 1,319 controls) [6, 11, 12, 15, 16, 24, 26, 28] were included in our meta-analysis. The characteristics of the studies are summarized in Table 1.

Meta-analysis results. The forest plot of the GSTM1 polymorphisms is shown in Fig. 2a. Since there was heterogeneity in studies of GSTM1 ($P_Q<0.001$, $I^2=71\%$), a random-effects model was used. The overall results showed that the null genotype of GSTM1 was related to increased risk of CC (OR=1.57, 95% CI=1.25-1.98, $p<0.00001$). In the subgroup analysis for ethnicity, the result showed that the null genotype of GSTM1 was associated with an increased CC risk in China (OR=2.34, 95% CI=1.56-3.52, $p<0.00001$), India (OR=2.02, 95% CI=1.43-2.83, $p=0.00001$), Pakistan (OR=5.52, 95% CI=2.34-13.07, $p=0.0001$), and Kazakhstan (OR=6.5, 95% CI=2.25-18.81, $p=0.0006$) (Fig. 3a). In the subgroup analysis for smoking, there was no statistical significance associated with CC risk in smokers (OR=1.89, 95% CI=0.97-3.69, $p=0.06$) or non-smokers (OR=1.48, 95% CI=0.72-3.07, $p=0.29$) (Fig. 3b). In the subgroup analysis for HPV infection, a significant association was found between cervical cancer and HPV infection (OR=2.59, 95% CI=1.57-4.27, $p=0.0002$) (Fig. 3c).

The forest plot of the GSTT1 polymorphisms is shown in Fig. 2b. There was heterogeneity in studies of GSTT1 ($P_Q<0.001$, $I^2=75\%$), and therefore a random-effects model was used. The overall results showed that the null genotype of GSTT1 was also associated with an increased cervical cancer risk (OR=1.44, 95% CI=1.07-1.94, $p=0.02$).

Table 1. Characteristics of Studies Included in the Meta-analysis.

First author	Year	Country	Case year（age）	Study design	Number of null genetypes (Cases/Controls)	Genotyping methods
GSTM1:						
Warwick AP	1994	UK	48.5	PCC	40/94	PCR
Sharam A	2004	India	49.2±8.8†	PCC	81/33	mPCR
Sharma	2015	India	42.1±11.7†	HCC	79/160	PCR
Kiran	2010	Turkish	53.73±10.35†	HCC	25/30	mPCR
Chen	1999	USA	NM	PCC	101/118	PCR
Singh	2008	India	45.2± 8.8†	PCC	64/46	mPCR
Stosic	2014	Serbia	44.54±12.19†	HCC	72/28	mPCR
Kim	2000	Korean	46.5±10.1†	PCC	95/96	PCR
Djansugurova	2013	Kazakhstan	NM	PCC	31/4	mPCR
Liu	2009	China	46.9	HCC	13/12	PCR
Ma	2009	China	47±l3	HCC	29/15	PCR
Ueda	2010	Janpan	NM	HCC	41/72	mPCR
Palma	2010	Italy	41.7±12.3†	PCC	15/58	PCR
Sobti	2006	India	48.6± 9.9†	PCC	42/38	mPCR
Lee	2004	Korean	NM	HCC	42/42	PCR
Hasan	2015	Pakistan	NM	PCC	37/17	mPCR
Natphopsuk	2015	Thailand	NM	HCC	130/125	PCR

Table 1. Characteristics of Studies Included in the Meta-analysis.

First author	Year	Country	Case year（age）	Study design	Number of null genetypes (Cases/Controls)	Genotyping methods
Song	2008	China	49.05	PCC	77/57	mPCR
Settheetham-Ishida	2009	Thailand	NM	HCC	54/56	PCR
Niwa	2005	Janpan	47.2±12.2†	HCC	70/184	PCR
Zhou	2006	China	50.66	HCC	73/54	mPCR
GSTT1:						
Sharam A	2004	India	49.2±8.8†	PCC	28/12	mPCR
Warwick A	1994	UK	49	HCC	9/27	PCR
Sharma	2015	India	42.1±11.7†	HCC	26/65	PCR
Kiran	2010	Turkish	53.73±10.35†	HCC	15/16	mPCR
de Carvalho	2008	Brazil	NM	HCC	22/16	PCR
Singh	2008	India	45.2±8.8†	PCC	40/18	mPCR

Stosic	2014	Serbia	44.54±12.19†	HCC	38/20	mPCR
Kim	2000	Korean	46.5±10.1†	PCC	120/92	PCR
Djansugurova	2013	Kazakhstan	NM	PCC	129/43	mPCR
Palma	2010	Italy	41.7±12.3†	PCC	8/22	PCR
Sobti	2006	India	48.6±9.9†	PCC	16/26	mPCR
Lee	2004	Korean	NM	HCC	38/54	PCR
Hasan	2015	Pakistan	NM	PCC	14/18	mPCR
Settheetham-Ishida	2009	Thailand	NM	HCC	42/38	PCR
Niwa	2005	Janpan	47.2±12.2	HCC	63/145	PCR
Zhou	2006	China	50.66	HCC	67/55	mPCR
GSTM1+GSTT1:						
Sharam A	2004	India	49.2±8.8†	PCC	27/11	mPCR
Sharma	2015	India	42.1±11.7†	HCC	23/53	PCR
Singh	2008	India	45.2±8.8†	PCC	23/2	mPCR
Stosic	2014	Serbia	44.54±12.19†	HCC	38/20	mPCR
Kim	2000	Korean	46.5±10.1†	PCC	62/48	PCR
Sobti	2006	India	48.6±9.9†	PCC	8/9	mPCR
Hasan	2015	Pakistan	NM	PCC	3/5	mPCR
Settheetham-Ishida	2009	Thailand	NM	HCC	26/18	PCR
Zhou	2006	China	50.66	HCC	39/27	mPCR

HCC: hospital-based case-control study; PCC: population-based case-control study.

NM: not mentioned; † mean±SD

PCR: polymerase chain reaction; mPCR: multiple polymerase chain reaction.

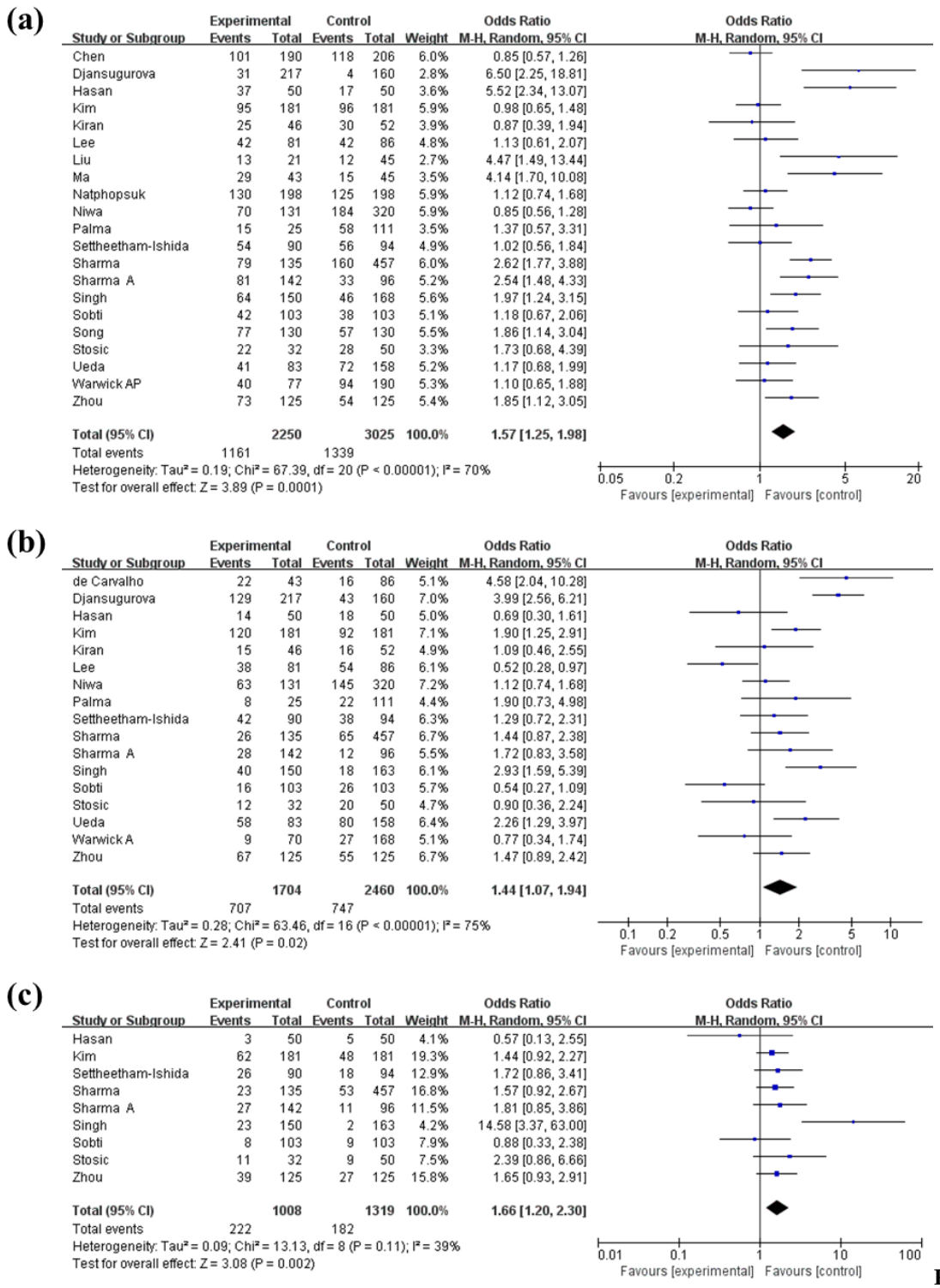

Fig. 2. Forest plots of the association between GSTM1/GSTT1 genotypes and cervical cancer. (a) Forest plot of the association between GSTM1-null genotype and CC. (b) Forest plot of the association between GSTT1-null genotype and CC. (C) Forest plot of the association between dual-null GSTM1/GSTT1 and CC.

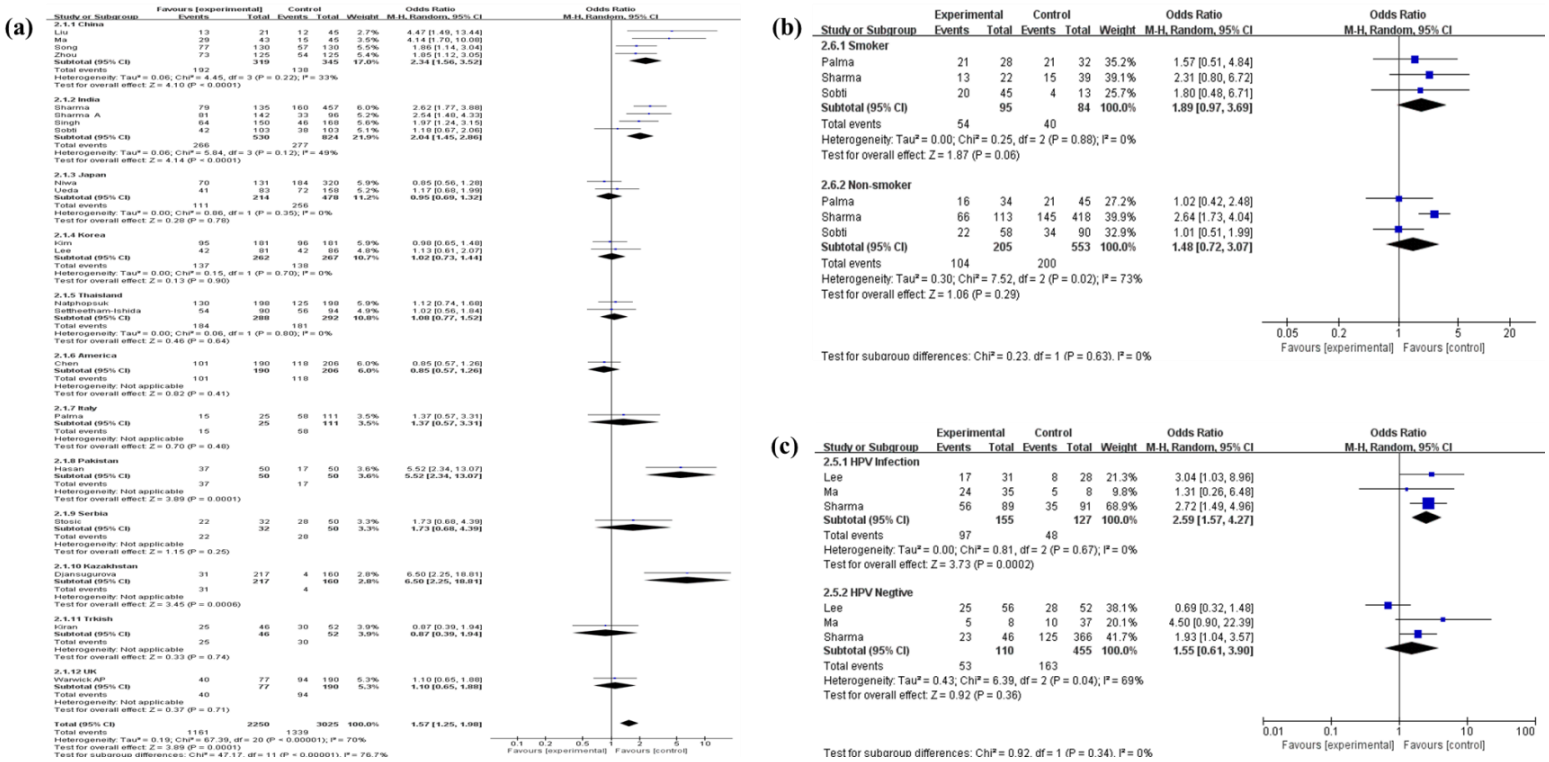

Fig. 3. Forest plots of the association between GSTM1/GSTT1 genotypes and cervical cancer. (a) Forest plot of the association between GSTM1-null genotype and CC. (b) Forest plot of the association between GSTT1-null genotype and CC. (c) Forest plot of the association between dual-null GSTM1/GSTT1 and CC.

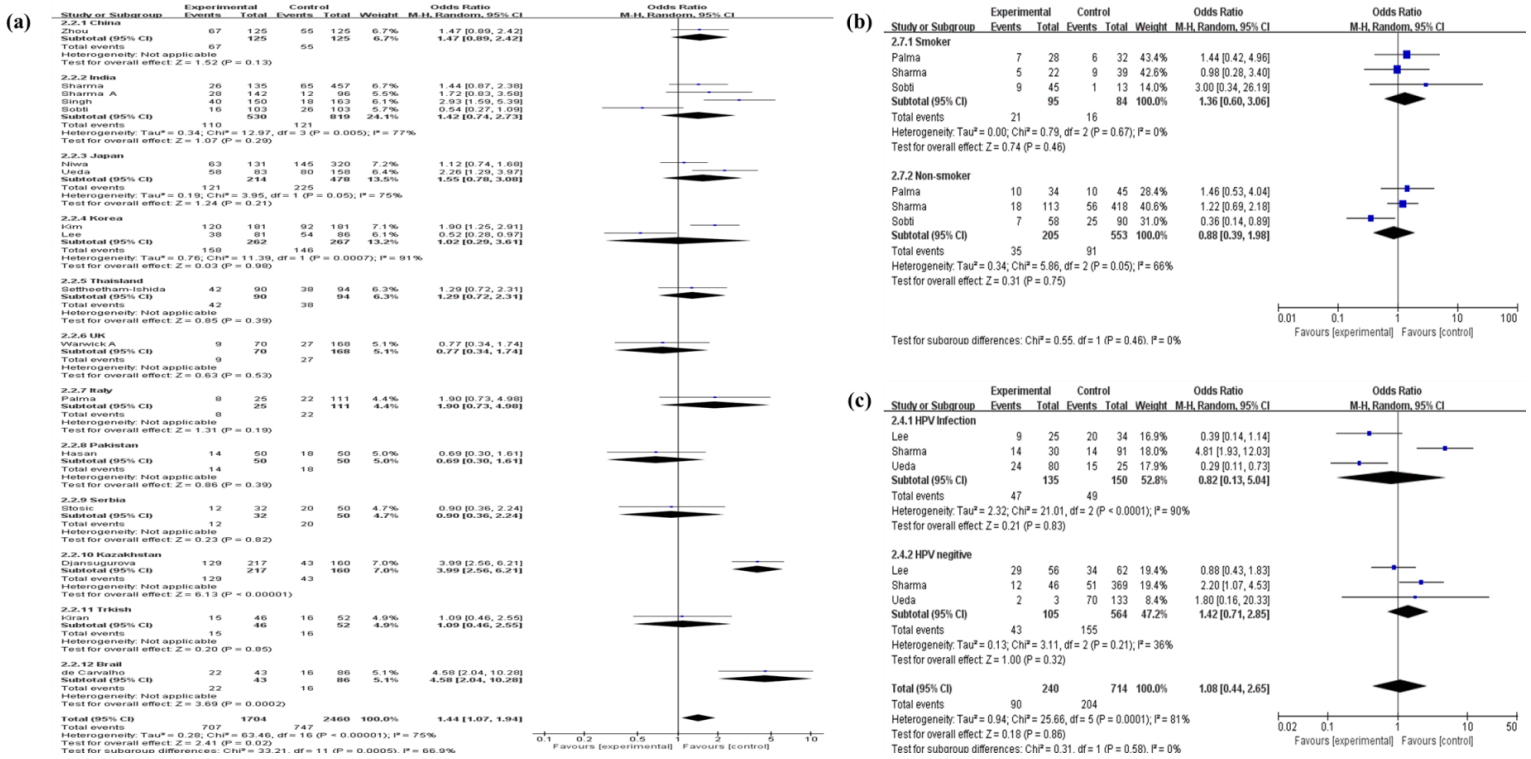

Fig. 4. Forest plots of the association between GSTM1/GSTT1 genotypes and cervical cancer. (a) Forest plot of the association between GSTM1-null genotype and CC. (b) Forest plot of the association between GSTT1-null genotype and CC. (c) Forest plot of the association between dual-null GSTM1/GSTT1 and CC.

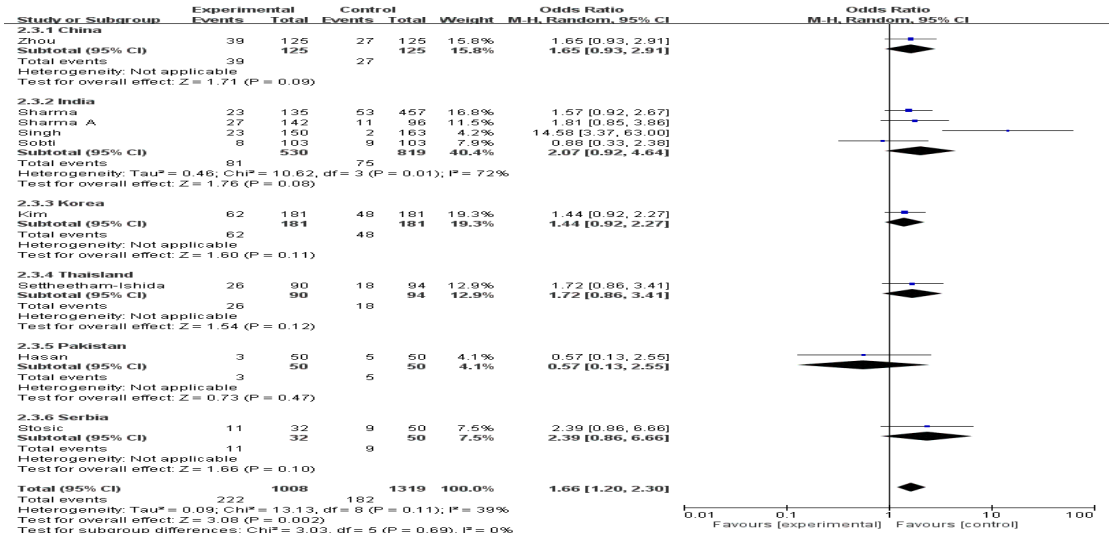

Fig. 5. Forest plot of the association between GSTM1/GSTT1 genotypes and cervical cancer.

In the subgroup analysis regarding ethnicity, the results showed that a significantly increased risk for the presence of the null genotype for GSTT1 in Kazakhstan (OR=3.99, 95% CI=2.56-6.21, p=0.00001) and Brazil (OR=4.58, 95% CI=2.04-10.28, p=0.00002) (Fig. 4a). In the subgroup analysis for smoking, there was not no significant association with CC risk in smokers (OR=1.36, 95% CI=0.60-3.06, p=0.46) or non-smokers (OR=0.88, 95% CI=0.39-1.98, p=0.75) (Fig. 4b). In the subgroup analysis for HPV infection, we found no significant association with cervical cancer in HPV-positive (OR=0.82, 95% CI=0.13-5.04, p=0.83) or -negative individuals (OR=1.42, 95% CI=0.72-2.58, p=0.32) (Fig. 4c).

The forest plot of the dual-null GSTM1/GSTT1 polymorphisms is shown in Fig. 2c. Since there was heterogeneity in the studies concerning GSTM1 (P_Q<0.001, I^2=71%), a random-effects model was used. The overall results also showed that the dual null genotype of GSTM1/GSTT1 was related to the increased risk of CC (OR=1.66, 95% CI=1.20-2.30, p=0.002). In the subgroup analysis for ethnicity, the results showed that the dual null genotype for GSTM1/GSTT1 was not associated with an increased CC risk for any countries evaluated (Fig. 5).

Publication bias. The effects of publication bias on the overall estimate were determined, and when each study was excluded one at a time, no change was found in the pooled results. Begg's funnel plot were generated to assess potential publication bias for GSTM1 and GSTT1 (Figs. 6 and 7), and the results showed no evidence of publication bias. The P values of the Egger's test for GSTM1 and GSTT1 were 0.272 and 0.033, respectively. A statistically significant publication bias was detected for GSTM1 but not for GSTT1.

Discussion

Cervical cancer has developed into a characterized by high incidence, and severely dysfunctional cosmetic defects accompanying the treatments. Moreover, major health concern problem that is genetic factors appear to play an

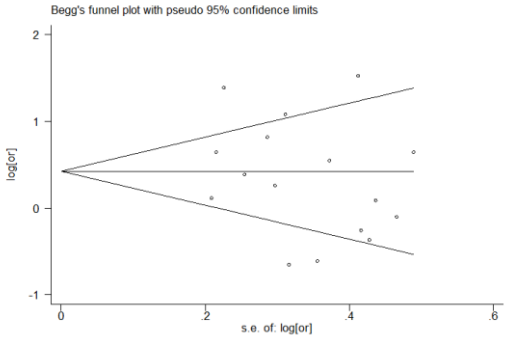

Fig. 6. A funnel plot of the association between GSTM1 and CC.

important role. Previous publications have reported an association between GSTs and cervical cancer. However, the association between these variables is controversial, and discrepancies might be due to limited sample numbers or ethnic differences. Our meta-analysis showed a possible role for GSTM1 and GSTT1 polymorphisms, which interacts with HPV infection status. The risk for cervical cancer was statistically significant in Asian populations, but not in others, indicating that these differences in cancer susceptibility varied according to ethnicity/race. Additionally, these results indicated that the allele frequency of the GSTM1-null genotype was higher in the American and Japanese than in the Chinese and Indian. The varying effects of the genotype might be attributable to differences in lifestyle, nutrition, environmental factors, and/or genetic factors.

A few studies have shown that tobacco constituents were modified by metabolizing enzymes and may promote malignant cellular growth [31]. In contrast, our study showed that the null genotypes for GSTM1 and GSTT1 did not increase risk for cervical cancer among smoking women. Authors from another publication in the same January 2010.

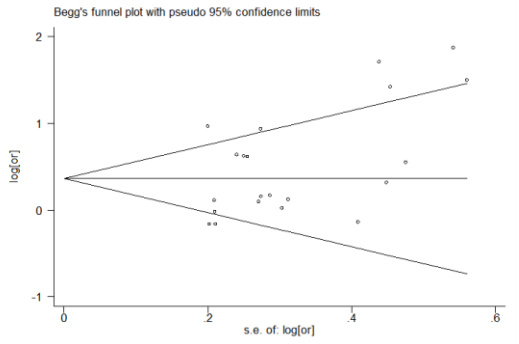

Fig. 7. A funnel plot of the association between GSTT1 and CC.

issue concluded that smoking habits, considered alone, were not found to constitute a risk factor for cervical lesions [35]. Another reason for the differences in our respective study conclusions may be false-negative results due to the lower statistical power associated with smaller sample sizes [32].

Epidemiologic studies have clearly shown that HPV infection is the cause of cervical cancer [33]. HPV was detected at a certain frequency among woman with normal cervical cytology, but not all HPV-infected individuals developed to the cervical cancer, indicating that environmental and genetic factors play important roles in cervical cancer. Evidence from other studies suggests that inherited susceptibility in the form of GST genotype may modulate the risk for HPV-related cancer since the GSTM1 homozygous-null genotype, (in addition to HPV infection), was found to increase the risk for cervical cancer [23]. Our study showed that the null GSTM1 genotype significantly increased the cervical cancer risk among HPV infected individuals, providing strong evidence for an association between GSTs and cervical cancer risk.

A limitation to the present study was that lifestyle and environmental factors were not included in the investigated list of influencing factors. For example, the pathways of carcinogen metabolism are very complex. Cervical cancer entails major environmental determinants such as age and reproductive health. Secondly, the sample size reported in the literature was still relatively small and might not provide enough statistical power to estimate the association between the null GSTM1 and GSTT1 polymorphisms and cervical cancer risk. Thirdly, some sources were population-based, while others were hospital-based; the latter are more prone to bias than the former [34].

In conclusion, the present meta-analysis provided sufficient evidence that GSTM1 and GSTT1 are associated with CC, especially in Asian groups; and that HPV-positive individuals showed a modification of the association between the GSTM1-null genotype and cervical cancer. However, no significantly increased risk for cervical cancer was uncovered in individuals with GSTM1- and GSTT1-null genotypes who were smokers. Further study of the effects of genetic-environmental interactions on cervical cancer

risk are therefore of paramount importance.

Preferences

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