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Glutathione S-transferase M1 and T1 polymorphisms and cervical cancer risk: A meta-analysis

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There were some studies on the associations between Glutathione S-transferase M1 (*GSTM1*) and Glutathione S-transferase T1 (*GSTT1*) polymorphisms and cervical cancer (CC) risk, but the results were inconsistent. Thus, a meta-analysis was performed.

The electronic databases PubMed, Science Direct, CBM, and CNKI were searched for possible studies. Finally, 16 studies (1,627 cases and 2,161 controls) were included. For the *GSTM1* and *GSTT1* polymorphisms, the unadjusted odds ratios (OR) and 95% confidence intervals (95% CI) from each study were used to estimate summary OR. Subgroup analyses by ethnicity and histological type of CC were also performed.

For the *GSTM1* polymorphism, the null genotype of *GSTM1* was associated with an increased CC risk in total population (OR=1.32, 95% CI=1.06-1.66). Similar association was found in Asians (OR=1.47, 95% CI=1.11-1.94), but not in Caucasians (OR=0.96, 95% CI=0.73-1.27). For the *GSTT1* polymorphism, the null genotype of *GSTT1* was not statistically significantly associated with CC risk in total population (OR=1.36, 95% CI=0.97-1.90). This result was also found in Asians (OR=1.27, 95% CI=0.87-1.85) and Caucasians (OR=1.09, 95% CI= 0.66-1.79), but not in Latinos (OR=4.58, 95% CI= 2.04-10.28). For the *GSTM1/GSTT1* interaction analysis, the dual null genotypes of *GSTM1/GSTT1* were significantly associated with increased CC risk in total population (OR=1.77, 95% CI= 1.14-2.75), and all the six studies were from Asia. For subgroup analyses by histological type of CC, the three aspects of the analyses above were all not significantly associated with CC risk in squamous cell carcinoma and adenocarcinoma, respectively.

The null genotype of *GSTM1* and the dual null genotypes of *GSTM1*/*GSTT1* were risk factors in CC, and the null genotype of *GSTT1* was not associated with CC risk.

Key words: Cervical cancer, genetic polymorphism; glutathione S-transferase M1, glutathione S-transferase T1, meta-analysis

Cervical cancer (CC) is the seventh in frequency overall, but the second most common cancer among women worldwide, with an estimated 493,000 new cases and 274,000 deaths in the year 2002 [1]. In general terms, it is much more common in developing countries, where 83% of cases occur and where cervical cancer accounts for 15% of female cancers, with a risk before age 65 of 1.5%. In developed countries, cervical cancer accounts for only 3.6% of new cancers, with a cumulative risk (0 to 64) of 0.8%[1]. It is widely known that human papilloma virus (HPV) is the dominating etiological agent [2]. Epidemiological studies have established that sexual history (such as multiple sexual partners, sexual activity in adolescent girls), sexually transmitted diseases (STDs), weak immune system such as from HIV infection, cigarette smoking which increases the risk of precancerous changes [2], low socioeconomic background [3], have been confirmed to be risk factors for CC. There is likely to be a complex interaction between environmental and genetic factors in the development of CC.

Glutathione S-transferases (*GSTs*) are a family of phase II enzymes involved in the detoxification of various exogenous as well as endogenous reactive species [4], catalyzing the conjugation of glutathione with electrophilic compounds including carcinogens and cytotoxic drugs. *GSTM1* is one of the genes encoding the *Mu* class of *GSTs*, which is lo-

cated on chromosome 1p13.3 and contains 10 exons. The Theta class of *GSTs* is encoded by the *GSTT1* gene, which is mapped to chromosome 22q11.23 and contains six exons. The most common genotypes of *GSTM1* and *GSTT1* genes is homozygous deletion (null genotype), which has been suggested to be associated with the loss of enzyme activity, increased vulnerability to cytogenetic damage and resulted in the increased susceptibility to cancer [5-6]. There were some studies on the associations between *GSTM1* and *GSTT1* genes and CC risk, but the results were inconsistent. Hence, a meta-analysis was performed.

Materials and methods

Search strategy. The electronic databases PubMed, Science Direct, CBM (Chinese Biomedicine Database), and CNKI (China National Knowledge Infrastructure) were searched for possible studies, using the search strategy: ("glutathione S-transferase" or "Glutathione Transferase" or "*GST*" or "*GSTM*" or "*GSTM1*" or "*GSTT*" or "*GSTT1*") and ("cervix" or "cervical" or "cervical cancer" or "Cervix Uteri" or "Uterine Cervical Neoplasms") and ("Polymorphism" or "Polymorphisms" or "Genetic polymorphism" or "genotype"). An upper date of the retrieval was December 16, 2010. The search was done without restriction on language, and all eligible articles' references were checked for other relevant articles.

Selection and exclusion criteria. Selection criteria: (1) case-control studies which evaluated associations between *GSTM1* and *GSTT1* polymorphisms and CC risk; (2) case population must not include precancerous lesions patients; (3) control population must not include malignant tumor patients. Exclusion criteria: (1) if the overlapping population were in different studies, only the most complete or largest articles were included, the others were excluded; (2) precancerous lesions included in the cases; (3) insufficient data.

Data extraction. To ensure the accuracy of the extracted information, two authors extracted information independently and difference was settled by reaching an agreement in all authors. The following information was extracted from included studies: first author, year of publication, published language, ethnicity, area of studies, sample size of cases and controls, source of controls, genotypes frequency of cases and controls, histological type of CC.

Statistical analysis. Statistical analyses were performed using software Review Manager (version 5.0.23) and STATA (version 11.0). Heterogeneity among studies was determined using a χ^2-based Q-statistic and I^2-statistic. For the possible genotypes of *GSTM1* and *GSTT1* status, the unadjusted odds ratios (OR) and 95% confidence intervals (95% CI) from each study were used to estimate summary OR. When there was some evidence of heterogeneity in the analysis ($P_{Q\text{-statistic}}<0.10$ or I^2-statistic>50%), summary odds ratios were determined using a random-effects model in which the contribution of each study was weighted by the inverse of the sum of the inter- and intra-study variance, otherwise using fixed-effects model. Subgroup analyses by ethnicity and histological type of CC were also performed. Publication bias was assessed by funnel plot and Egger's regression test. All the P values were two-sided. To ensure the reliability and the accuracy of the results, two authors inputted the data in the statistic software programs independently and got the same results.

Results

Identification of relevant studies. With our search criterion, 123 individual records were found, but only 31 full-text articles [7-37] were preliminarily identified for further detailed evaluation. According to the exclusion criteria, 15 articles were excluded including 5 articles containing overlapping population [7-11], 8 precancerous lesions included in the cases [12-19], 2 without sufficient data [20-21]. At last, data were available from 16 individual case–control studies[22-37], Table 1 presented characteristics of these 16 case–control studies (a total of 1,627 CC cases and 2,161 controls). 14 studies on *GSTM1* polymorphism (a total of 1,514 CC cases and 1,907 controls), 12 studies on *GSTT1* polymorphism (a total of 1,187 CC cases and 1,590 controls), and 6 studies on *GSTM1–GSTT1* interaction analysis (a total of 791 CC cases and 767controls) were included in the meta-analysis.

Meta-analysis. Table 2 listed the main results of this meta-analysis. For the *GSTM1* polymorphism, the between-study heterogeneity was significant when all 14 studies were pooled into meta-analysis (I^2 = 58.8%, P_H = 0.003), thus; the random-effects model was used to pool the results. The results of pooling all studies showed that the null genotype of *GSTM1* was associated with an increased CC risk in total population ($OR_{random\text{-}effects}$ = 1.32, 95% CI=1.06-1.66) (Fig. 1A). In the subgroup analyses by ethnicity, the results showed that the null genotype of *GSTM1* was also associated with an increased CC risk in Asians ($OR_{random\text{-}effects}$ = 1.47, 95% CI=1.11-1.94), but not in Caucasians ($OR_{fixed\text{-}effects}$ = 0.96, 95% CI=0.73-1.27). For individual subgroups of Asian population, the null genotype of *GSTM1* was also associated with an increased CC risk in Chinese ($OR_{fixed\text{-}effects}$ = 2.01, 95% CI=1.46-2.79) and Indians ($OR_{fixed\text{-}effects}$ =1.84, 95% CI=1.37-2.48), but not in Koreans ($OR_{fixed\text{-}effects}$ = 1.02, 95% CI=0.73-1.44), Japanese ($OR_{fixed\text{-}effects}$ =0.85, 95% CI=0.56-1.28) and Thais ($OR_{fixed\text{-}effects}$ =1.02, 95% CI=0.56-1.84). Subgroup analyses by histological type of CC showed that the null genotype of *GSTM1* was not significantly associated with CC risk in squamous cell carcinoma ($OR_{random\text{-}effects}$ =1.23, 95% CI=0.90-1.69) and adenocarcinoma ($OR_{fixed\text{-}effects}$ =1.26, 95% CI=0.64-2.48).

For the *GSTT1* polymorphism, the between-study heterogeneity was also significant when all 12 eligible studies were pooled into meta-analysis (I^2 = 70.8%, P_H<0.0001), thus; the random effects model was used to pool the results. The combined results showed that the null genotype of *GSTT1* was not statistically significantly associated with CC risk in total population ($OR_{random\text{-}effects}$ = 1.36, 95% CI=0.97-1.90) (Fig. 1B). In the subgroup analyses by ethnicity, the results showed that

Table 1. Characteristics of studies included in this meta-analysis

Reference	Language	Ethnicity	Area	Source of controls	Sample size (cases/controls)	Polymorphisms	histological type of CC
Ma CL2009[22]	Chinese	Asian	China	hospital	43/45	M1	NM#
Song GY2008[23]	Chinese	Asian	China	population	130/130	M1	Ad†, SCC§
Zhou Q2006[24]	Chinese	Asian	China	hospital	125/125	M1, T1, I*	NM
Kiran B2010[25]	English	Caucasian	Turkey	hospital	46/52	M1, T1	NM
Palma S2010[26]	English	Caucasian	Italy	population	25/111	M1, T1	NM
Settheetham-Ishida W2009[27]	English	Asian	Thailand	population	90/94	M1, T1, I	SCC
de Carvalho CR2008[28]	English	Latino	Brazil	population	43/86	T1	Ad
Singh H2008[29]	English	Asian	India	population	150/168	M1, T1, I	NM
Sobti RC2006[30]	English	Asian	India	population	103/103	M1, T1, I	Ad, SCC
Niwa Y2005[31]	English	Asian	Japan	population	131/320	M1, T1	Mixed¶
Lee SA2004[32]	English	Asian	Korea	hospital	215/98	M1, T1	NM
Sharma A2004[33]	English	Asian	India	population	142/96	M1, T1, I	SCC
Kim JW2000[34]	English	Asian	Korea	population	181/181	M1, T1, I	Mixed
Chen C1999[35]	English	Caucasian	USA	population	190/206	M1	SCC
Warwick AP 1994[36]	English	Caucasian	UK	population	77/190	M1	SCC
Warwick A1994[37]	English	Caucasian	UK	hospital	70/168	T1	SCC

*(*I, GSTM1-GSTT1 interaction analysis; #NM, not mentioned; †Ad, adenocarcinoma; §SCC, Squamous cell carcinoma; ¶ Mixed, the original study mentioned having adenocarcinoma and Squamous cell carcinoma in CC, but the data were not presented respectively.)*

the null genotype of *GSTT1* was associated with an increased CC risk in Latinos ($OR_{fixed\text{-}effects}$ =4.58, 95% CI= 2.04-10.28), but not in Asians ($OR_{random\text{-}effects}$ =1.27, 95% CI=0.87-1.85) and Caucasians ($OR_{fixed\text{-}effects}$ =1.09, 95% CI= 0.66-1.79). For individual subgroups of Asian population, the null genotype of *GSTT1* was also not significantly associated with CC risk in Chinese ($OR_{fixed\text{-}effects}$ = 1.47, 95% CI=0.89-2.42), Indians ($OR_{random\text{-}effects}$ =1.43, 95% CI=0.52-3.93), Koreans ($OR_{random\text{-}effects}$ = 1.02, 95% CI=0.29-3.61), Japanese ($OR_{fixed\text{-}effects}$ =1.12, 95% CI=0.74-1.68) and Thais ($OR_{fixed\text{-}effects}$ =1.29, 95% CI=0.72-2.31). Subgroup analyses by histological type of CC showed that the null genotype of *GSTT1* was not significantly associated with CC risk in squamous cell carcinoma ($OR_{random\text{-}effects}$ =1.00, 95% CI=0.60-1.65) and adenocarcinoma ($OR_{random\text{-}effects}$ =1.97, 95% CI=0.30-13.11).

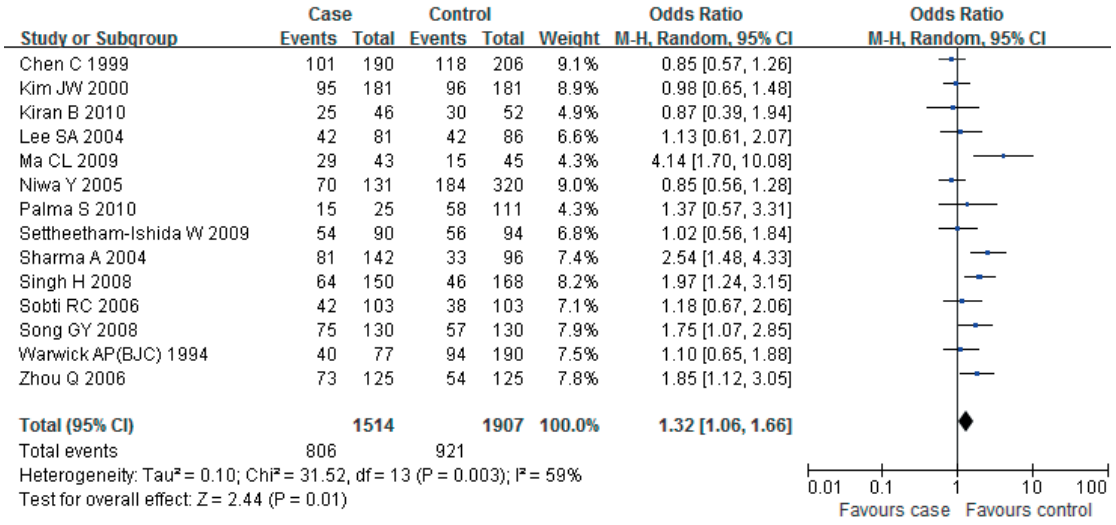
For the *GSTM1–GSTT1* interaction analysis, the between-study heterogeneity was still significant when all 6 eligible studies were pooled into meta-analysis (I^2 = 54.6%, P_H = 0.051), thus; the random-effects model was used to pool the results. The combined result showed that the dual null genotypes of *GSTM1/GSTT1* were significantly associated with increased CC risk in total population ($OR_{random\text{-}effects}$ = 1.77, 95% CI= 1.14-2.75) (Fig. 1C), and all the 6 studies were from Asia. For individual subgroups of Asian population, the dual null genotypes of *GSTM1/GSTT1* were all not significantly associated with CC risk in Chinese ($OR_{fixed\text{-}effects}$ = 1.65, 95% CI= 0.93-2.91), Indians ($OR_{random\text{-}effects}$ = 2.58, 95% CI= 0.65-10.25), Koreans ($OR_{fixed\text{-}effects}$ = 1.44, 95% CI= 0.92-2.27) and Thais ($OR_{fixed\text{-}effects}$ = 1.72, 95% CI= 0.86-3.41). Subgroup analyses by histological type of CC showed that the dual null genotypes of *GSTM1/GSTT1* were not significantly associated with CC risk in squamous cell carcinoma ($OR_{fixed\text{-}effects}$ =1.53, 95% CI=0.98-2.41) and adenocarcinoma ($OR_{fixed\text{-}effects}$ =1.04, 95% CI=0.12-9.12).

Publication bias. Funnel plots and Egger's regression test were performed to assess the publication bias of the literatures. Only one $P_{Egger's\ test}$=0.034 was less than 0.05, which was in the meta-analysis of the association between genotypes of *GSTM1* and CC risk in small subgroup analysis of Chinese population. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all the other comparisons (e.g. Fig. 2). Furthermore, Egger's regression test was used to provide statistical evidence for publication bias, and all the other $P_{Egger's\ test}$>0.05 (Table 2). The above results did not suggest obvious publication bias in all the other comparisons.

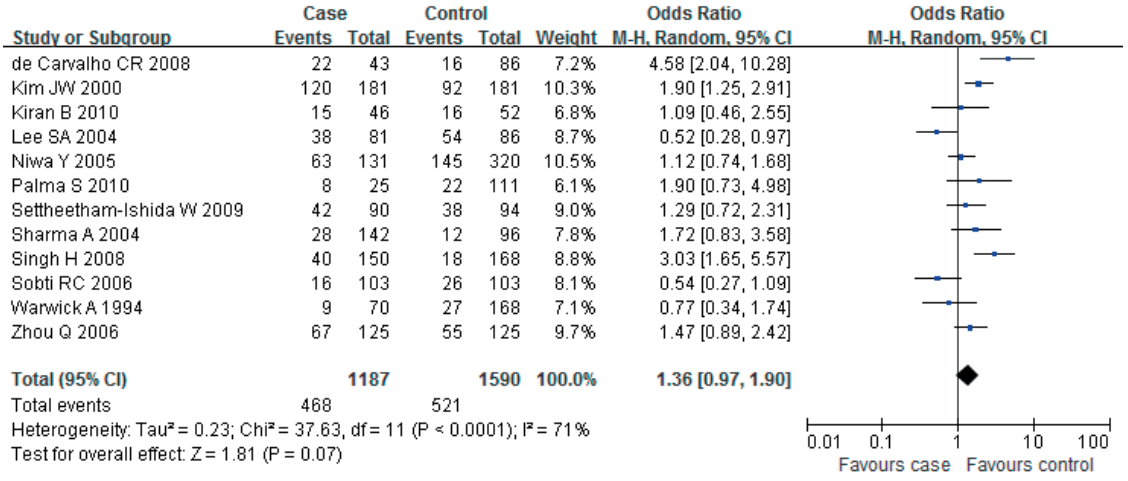
Discussion

Both our meta-analysis and a meta-analysis [38] by Economopoulos et al. published in December 2010 on the same issue concluded that *GSTM1* polymorphism was associated with an increasing risk of CC risk in total population, but the *GSTT1* polymorphism was not. Compared with Economopoulos et al.'s meta-analysis, our meta-analysis had some differences. Firstly, our meta-analysis included three new eligible studies published in Chinese [22-24] and two new case-control studies [25-26] in English in 2010, and excluded four studies [13, 16, 18, 19] that had precancerous lesions patients in cases. Secondly, Asians (including Chinese, Indians, Koreans, Japanese and Thais), Caucasians and Latinos were stratified by ethnicity in our meta-analysis, while Chinese (including Koreans, Japanese and Thais) and non-Chinese were stratified

(A)



(B)



(C)

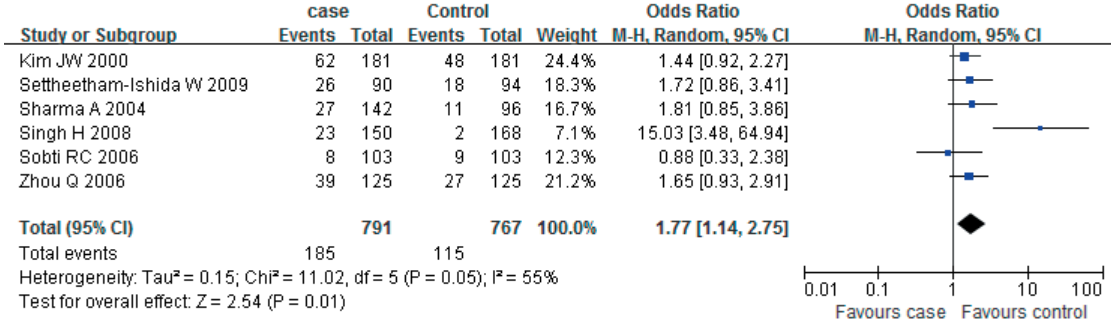


Figure 1. Forest plots of pooled OR with 95% CI for associations between GSTs polymorphisms and CC risk. (The squares and horizontal lines corresponded to the study-specific OR and 95% CI; the box size was proportional to the meta-analysis study weight; the diamond represented the pooled OR and 95% CI). (A) *GSTM1* polymorphisms and CC risk in total population (random effects). (B) *GSTT1* polymorphisms and CC risk in total population (random effects). (C) *GSTM1–GSTT1* interaction analysis on CC risk in total population (all were Asians) (random effects).

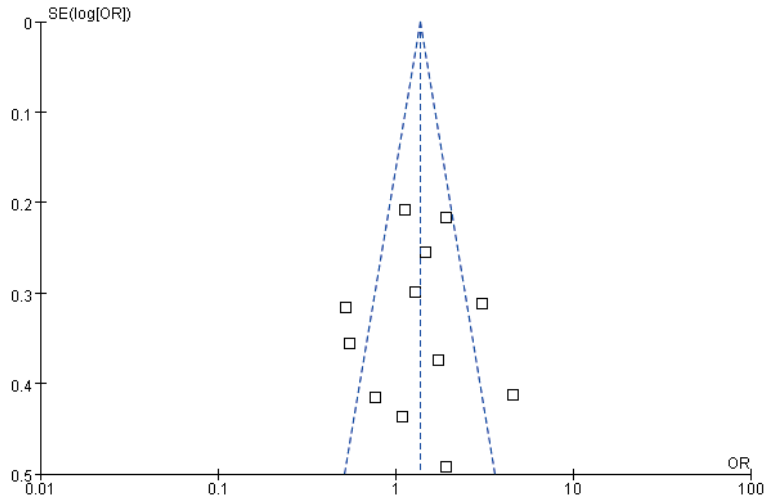


Figure 2. Funnel plot for publication bias test in the meta-analysis of the association between genotypes of *GSTT1* and CC risk in total population ($P_{Egger's\ test}$=0.985>0.05)

in Economopoulos et al.'s meta-analysis. To *GSTM1* polymorphism, in our meta-analysis, the null genotype of *GSTM1* was significantly associated with an increased CC risk in Asians, but not in Caucasians. For individual subgroups of Asian population, the null genotype of *GSTM1* was also associated with an increased CC risk in Chinese and Indians, but not in Koreans, Japanese and Thais. While in Economopoulos et al.'s meta-analysis, the null genotype of *GSTM1* was significantly associated with an increased CC risk in non-Chinese, but not in Chinese. To *GSTT1* polymorphism, in our meta-analysis, the null genotype of *GSTT1* was associated with an increased CC risk in Latinos, but not in Asians (including each individual subgroups analyses of Asian population) and Caucasians. While in Economopoulos et al.'s meta-analysis, neither Chinese nor non-Chinese had significantly association between the null genotype of *GSTT1* and CC risk. Finally, the *GSTM1–GSTT1* interaction analysis and subgroup analyses by histological type of CC were analyzed in our meta-analysis, while they were not mentioned in Economopoulos et al.'s meta-analysis.

When stratified for ethnicity in our meta-analysis, the inconsistent effects among different ethnicities may indicate different effects of *GSTM1* and *GSTT1* polymorphisms on CC risk in different ethnic groups and a possible role of ethnic differences in genetic backgrounds. For subgroup analyses by histological type of CC, all the polymorphisms were not significantly associated with CC risk in squamous cell carcinoma and adenocarcinoma, respectively. The discrepancies between the total meta-analyses and subgroup analyses by histological type of CC in *GSTM1* polymorphism and the *GSTM1–GSTT1* interaction analysis indicated that subgroup analyses by histological type might be false negative results because of a lower statistical power owing to the smaller sample sizes.

For the *GSTM1–GSTT1* interaction analysis, the dual null genotypes of *GSTM1/GSTT1* were significantly associated with increased CC risk in total population, and all the 6 studies were from Asia. But for each individual subgroups analyses of Asian population, there were not significantly associations respectively. The reason of these differences might be that small genetic association studies having insufficient power could inevitably increase the risk that chance could be responsible for their conclusions, while combining data from all eligible studies by meta-analysis has the advantage of reducing random error and obtaining precise estimates for some potential genetic associations. Thus, the result of total Asian population was still reliable.

The *GSTM1* subfamily mainly metabolizes polyaromatic hydrocarbons and the benzo-α-pyrene class of carcinogens, whereas *GSTT1* is known to metabolize carcinogens like monohaloethanes and ethylene oxide [29]. In our meta-analysis, in Asians, the null genotype of *GSTM1* was found to be associated with an increased CC risk, but the null genotype of *GSTT1* was not. These results indicated that *GSTM1* polymorphism might be more susceptive in Asians on CC risk. Our meta-analysis also found that the dual null genotypes of *GSTM1/ GSTT1* resulted in increased CC risk (OR = 1.77, 95% CI= 1.14-2.75) compared with *GSTM1* polymorphism alone (OR=1.47, 95% CI=1.11-1.94) in Asians. These results indicate that the combination of *GSTM1* and *GSTT1* genetic polymorphisms is an important genetic risk factor for CC in Asians. The reason may be that although some substrates are metabolized by specific *GST* isozymes, they have overlapping substrate specificities and therefore, combinations of the null genotypes of *GSTM1/ GSTT1* could confer an even higher risk [39]. This has also been observed in several tumors, such as colorectal cancer [40], bladder cancer [41] and hepatocellular carcinoma [42], et al.

GST genetic polymorphisms have been extensively studied and several meta-analyses combining data from multiple stud-

Table 2. Summary of pooled odds ratios (OR) with confidence intervals (CI) in the meta-analysis.

Polymorphism	Null vs. Present*	Studies(No. of cases/ No. of controls)	Odds ratio		M#	Heterogeneity		$P_{Egger's\ test}$ §
			OR [95% CI]	P_{OR}		I^2 (%)	P_H †	
GSTM1	Total studies	14(1,514/1,907)	1.32[1.06,1.66]	**0.01**	R	58.8	0.003	0.174
	Subgroup analyses by ethnicity							
	Asians	10(1,176/1,348)	1.47[1.11,1.94]	**0.007**	R	64.1	0.003	0.105
	Asians -Chinese	3(298/300)	2.01[1.46,2.79]	**<0.001**	F	32.6	0.227	**0.034**
	Asians -Indians	3(395/367)	1.84[1.37,2.48]	**<0.001**	F	48.5	0.143	0.728
	Asians -Koreans	2(262/267)	1.02[0.73,1.44]	0.895	F	0.0	0.703	-
	Asians -Japanese	1(131/320)	0.85[0.56,1.28]	0.430	F	-	-	-
	Asians -Thais	1(90/94)	1.02[0.56,1.84]	0.953	F	-	-	-
	Caucasians	4(338/559)	0.96[0.73,1.27]	0.781	F	0.0	0.721	0.378
	Subgroup analyses by histological type of CC							
	Squamous cell carcinoma	6(692/819)	1.23[0.90,1.69]	0.196	R	54.9	0.050	0.348
	adenocarcinoma	2(40/233)	1.26[0.64,2.48]	0.508	F	0.0	0.817	-
GSTT1	Total studies	12(1,187/1,590)	1.36[0.97,1.90]	0.07	R	70.8	<0.0001	0.985
	Subgroup analyses by ethnicity							
	Asians	8(1,003/1,173)	1.27[0.87,1.85]	0.215	R	73.3	0.0005	0.581
	Asians -Chinese	1(125/125)	1.47[0.89,2.42]	0.130	F	-	-	-
	Asians -Indians	3(395/367)	1.43[0.52,3.93]	0.491	R	85.1	0.001	0.596
	Asians -Koreans	2(262/267)	1.02[0.29,3.61]	0.977	R	91.2	0.001	-
	Asians -Japanese	1(131/320)	1.12[0.74,1.68]	0.591	F	-	-	-
	Asians -Thais	1(90/94)	1.29[0.72,2.31]	0.394	F	-	-	-
	Caucasians	3(141/331)	1.09[0.66,1.79]	0.730	F	0.0	0.369	0.083
	Latinos	1(43/86)	4.58 [2.04,10.28]	**0.0002**	F	-	-	-
	Subgroup analyses by histological type of CC							
	Squamous cell carcinoma	4(394/461)	1.00[0.60,1.65]	0.984	R	51.3	0.104	0.605
	adenocarcinoma	2(54/189)	1.97[0.30,13.11]	0.483	R	78.1	0.033	-
GSTM1-GSTT1 interaction analysis	Total studies(all were Asians)	6(791/767)	1.77[1.14,2.75]	**0.011**	R	54.6	0.051	0.239
	Subgroup analyses by ethnicity							
	Asians -Chinese	1(125/125)	1.65[0.93,2.91]	0.086	F	-	-	-
	Asians -Indians	3(395/367)	2.58[0.65,10.25]	0.178	R	81.2	0.005	0.523
	Asians -Koreans	1(181/181)	1.44[0.92,2.27]	0.110	F	-	-	-
	Asians -Thais	1(90/94)	1.72[0.86,3.41]	0.124	F	-	-	-
	Subgroup analyses by histological type of CC							
	Squamous cell carcinoma	3(324/293)	1.53[0.98,2.41]	0.063	F	0.0	0.472	0.209
	adenocarcinoma	1(11/103)	1.04[0.12,9.12]	0.969	F	-	-	-

(the genetic comparison model for GSTM1-GSTT1 interaction analysis was Dual null genotype vs. Non-null genotype ; # M, model of meta-analysis; R,random-effects model; F, Fixed-effects model; †P_H, the P value of heterogeneity test; § $P_{Egger's\ test}$, the P value for Egger's test; -, data can not be calculated out; P_{OR}s and $P_{Egger's\ test}$ were reported in bold if less than 0.05.)*

ies have been published to investigate the associations between *GST* polymorphisms and various cancers [42-46]. Wang et al. suggested the null genotypes of *GSTM1* and *GSTT1* were both associated with increased hepatocellular carcinoma risk [42]. Yang et al. found that the null genotypes of *GSTM1* and *GSTT1* were both not significantly associated with esophageal cancer risk [43]. Dahabreh et al. [44] found that the *GSTT1* deletion was significantly associated with myelodysplastic syndrome, while the null *GSTM1* genotype was not. In our meta-analysis, we found that *GSTM1* polymorphism was associated with an increasing risk of CC risk, but the *GSTT1* polymorphism was not. Thus, the *GSTM1* and *GSTT1* polymorphisms may exert different effects in different kinds of cancers and those various gene-variant associations may result from the different mechanisms of carcinogenesis among different cancers. Zhou et al. [45] found that the *GSTM1* polymorphism was associated with an increasing risk of nasopharyngeal cancer, but the *GSTT1* polymorphism was not, which was the same with Mo et al' [46] results on prostate cancer risk and our results on CC risk. These results further confirmed the probability of our conclusions.

However, there were some limitations in our meta-analysis. Firstly, the eligibility criteria for inclusion of controls were different from each other. Some sources of controls were population-based, while the others were hospital-based (Table1). The hospital-based studies are more prone to bias

than population-based studies [47]. Secondly, we didn't perform subgroup analysis on smoking status and HPV infection status et al, because of the lack of sufficient data. In spite of these, our present meta-analysis also had some advantages. Firstly, substantial number of cases and controls were pooled from different studies, which greatly increased statistical power of the analysis. Secondly, no publication biases were detected, only except one smallest comparison, indicating that almost the whole pooled results may be unbiased.

In conclusions, the null genotype of *GSTM1* and the dual null genotypes of *GSTM1*/*GSTT1* were risk factors in CC, and the null genotype of *GSTT1* was not associated with CC risk.

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