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Meta-analysis of association between GSTM1 gene polymorphism and cervical cancer

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ABSTRACT

Objective: To investigate association between glutathione S-transferases (GSTs) and cervical cancer. **Methods:** Published literature from PubMed, EMBASE, and other databases were retrieved. All studies evaluating the association between GSTM1/GSTT1 polymorphisms and cervical were included. Pooled odds ratio (*OR*) and 95% confidence interval (*CI*) were calculated using fixed- or random-effects model. **Results:** A total of 15 case-control studies were included in the meta-analysis of GSTM1 genotypes (1 825 cases and 2 104 controls). The overall result showed that the association between GSTM1 null genotype and risk for cervical cancer was statistically significant (*OR*=1.53, 95%*CI*=1.18-2.00). Great heterogeneity was found between studies. Subgroup analysises were performed based on smoking and ethnicity. Our results showed that smokers with null GSTM1 genotype had higher risk of cervical cancer (*OR*=1.56, 95%*CI*=1.01-2.41). For the ethnicity stratification, significant increased risk of null GSTM1 genotype was found in Chinese and Indian population, but no increased risk in other population. **Conclusions:** This meta-analysis provides strong evidence that the GSTM1 null genotype is associated with the development of cervical cancer, and especially in Chinese and Indian population, and smoking shows a modification on the association between GSTM1 null genotype and cervical cancer.

1. Introduction

Cervical cancer is the third commonest cancer in women, and the seventh overall, with an estimated 530 000 new cases in 2008. More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancers. High-risk regions are Eastern and Western Africa (ASR greater then 30 per 100 000), Southern Africa (26.8 per 100 000), South-Central Asia (24.6 per 100 000), South America and Middle Africa (ASRs 23.9 and 23.0 per 100 000, respectively). Rates are lowest in Western Asia, Northern America and Australia/New Zealand (ASRs less than 6 per 100 00)[1]. The different incidence in different areas indicates the genetic factors and environmental factors play a role in the development of cervical cancer.

It is well established that human papilloma virus (HPV) infection is a necessary but insufficient event for the development of cervical cancer[2-5], because not all HPV-infected patients do develop cervical cancer. Therefore, there are other cofactors for cervical cancer development. Previous studies showed the glutathione S-transferases (GSTs) genetic variants is related to the risk of several cancers, including breast, lung, prostate, bladder and nasopharyngeal cancer risk[6-8]. There is large number of epidemiological studies concerning the association between GSTM1 and risk of cervical cancer in different populations, however, the results is inconsistent[9-12]. Although there is meta-analysis regarding on the two gene polymorphism and cervical cancer, no gene-environment interaction was explored, especially for Asian population. Therefore, we conducted a meta-analysis regarding the effect of GSTM1

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gene polymorphism on cervical cancer risk, and also explore the gene-environment interaction on cervical cancer risk.

2. Materials and methods

2.1. Selection criteria and search strategy

Identification of relevant studies was carried out through a search of Medline and EMbase up to May 2011 using the following terms without any restriction on language: 1)cervical$. ab, ti; 2) (carcino$ or cancer$ or neoplasm$ or tumour$ or tumor$). ab, ti; 3) adenocarcinoma$. ab, ti; 4) or/2-3; 5) 1 and 4; 6) (glutathione S-transferase or GST or GSTM or GSTM1). ab, ti; 7)5 and 6.

The literature search was performed up to December 2011. The inclusion criteria were as following: case-control studies that investigated the association between GSTM1 polymorphism and risk of cervical cancer; Studies presented original data and the number of null genotype of GSTM1 in cases and controls. For each study, the following information were excluded: name of the first author, publication year, ethnicity(county), number of cases and controls; number of null genotype for GSTM1 in cases and controls. Two authors independently assessed the articles for inclusion/exclusion, resolved disagreements, and reached consistency.

2.2. Statistical analysis

The association between GSTM1 polymorphism and cervical cancer was estimated by calculating pooled *OR*s and 95% *CI*s. The significant of the pooled *OR* was estimated by *Z* test ($P<0.05$ was considered statistically significant). The I^2-based *Q* statistic test was performed to evaluate variations due to heterogeneity rather than chance. A random-effects or fixed effects methods[13,14] model was used to calculate pooled effect estimates in the presence ($P \leqq 0.1$) or absence ($P>0.1$) of heterogeneity. Begg´s funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detecting bias or systematic heterogeneity[15]. As asymmetric funnel plot indicated a relationship between effect and study size, which suggested the possibility of either publication bias or a systematic difference between smaller and larger studies (small study effects). Furthermore, publication bias was assessed by Egger´s test[16]. Studies were categorized into subgroups based on ethnicity and smoking status. The data analysis was performed (STATA, version 10, StataCorp LP, College Station, TX).

3. Results

The literature search identified 132 potentially relevant studies. Of the 132 literatures, 104 literuatures were irrelevant, and 5 studies were excluded because of various reasons (2 study was conducted on overlapping population, and 3 studies did not include controls in analysis). Finally, 15 literatures met the inclusion criteria and were included. 15 case-control studies were included in the meta-analysis of GSTM1 genotypes (1 825 cases and 2 104 controls). For the meta-analysis of GSTM1, 2 studies on China, 4 studies on India, 3 studies on Japan, 2 studies on Korea, 2 studies on Italy, one study in America and Thailand. There were 994 cases of null genotype and 934 controls of null genotype, with adjusted *OR* as 1.14(0.95-1.32). Study characteristics included in the meta-analysis are presented in Table 1, and *P* for heterogeneity was <0.05.

The forest plot of the meta-analysis of GSTM1 is shown

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

ID	Ethnicity	Study design	Mean age of cases	Mean age of controls	Cases	Controls	Null genotype		Adjusted *OR*
							Cases	Controls	
Song 2006[9]	China	Hospital-based	49.05	47.22	130	130	77	57	NA
Zhou 2006[17]	China	Hospital-based	40.66	50.50	125	125	73	54	1.85(1.12-3.05)
Singh 2008[10]	India	Population-based	45.20	50.30	150	168	64	40	1.52(1.10-2.00)
Sobti 2006[18]	India	Hospital-based	48.60	48.00	103	103	42	38	NA
Niwa 2005[19]	Japan	Hospital-based	47.20	56.20	131	320	70	184	0.85(0.56-1.20)
Lee 2004[20]	Korea	Hospital-based	NA	NA	81	86	42	42	1.20(0.60-2.10)
Kim 2000[21]	Korea	Population-based	46.50	46.50	181	181	95	96	2.40(1.53-3.78)
Sharma 2004[22]	India	Hospital-based	NA	NA	142	96	81	33	2.50(1.40-4.50)
Chen 1999[23]	America	Hospital-based	NA	NA	190	206	101	118	0.80(0.60-1.30)
Joseph 2006[24]	India	Population-based	46.00	47.00	147	165	79	54	2.40(1.53- .78)
Palma 2010[11]	Italy	Population-based	NA	NA	81	111	49	58	1.93(0.96-3.88)
Nishino 2008[25]	Japan	Population-based	41.60	40.60	124	125	77	59	1.92(1.04-3.54)
Ueda 2008[26]	Japan	Population-based	NA	NA	144	54	75	28	NA
Settheetham-Ishida 2009[27]	Thailand	Population-based	NA	NA	69	72	54	56	0.62(0.30-2.03)
Agodi 2010[12]	Italy	Hospital-based	NA	NA	27	162	15	17	NA

in Figure 1. Because of the heterogeneity among studies (P_Q<0.001, I^2=74.5%), a random-effects model was used. The overall result showed that the association between GSTM1 null genotype and risk for cervical cancer was statistically significant (*OR*=1.54, 95%*CI*=1.18-2.00). The adjusted pooled *OR*(95%*CI*) of GSTM1 null genotype for cervical cancer were 1.14(0.95-1.32). No significant increased risk of cancer was observed, and also great heterogeneity was found between studies.

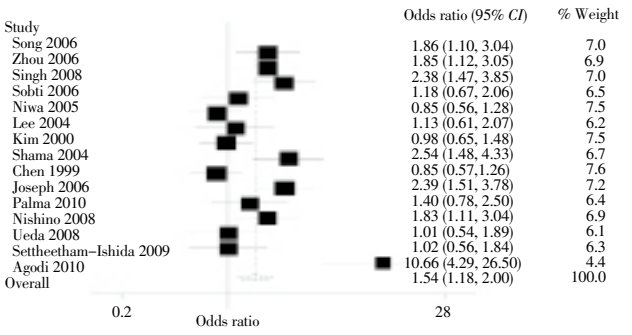

Figure 1. Forest plot for the overall association between GSTM1 gene polymorphism and cervical cancer risk.

Subgroup analysis was performed based on smoking and ethnicity (Figure 2 and 3). The result showed that smokers with null GSTM1 genotype had higher risk of cervical cancer (*OR*=1.56, 95%*CI*=1.01-2.41), while no significant increased risk was found in non-smokers. After stratification, the heterogeneity was significantly decreased (*P*=0.09 for non smokers and *P*=0.12 for smokers). For the ethnicity stratification, significant increased risk of null GSTM1 genotype was found in Chinese (*OR*=1.85, 95%*CI*=1.30-2.63) and Indian population (*OR*=2.07, 95%*CI*=1.49-2.88), but no increased risk in other population. However, no significant decreased risk was found in American population.

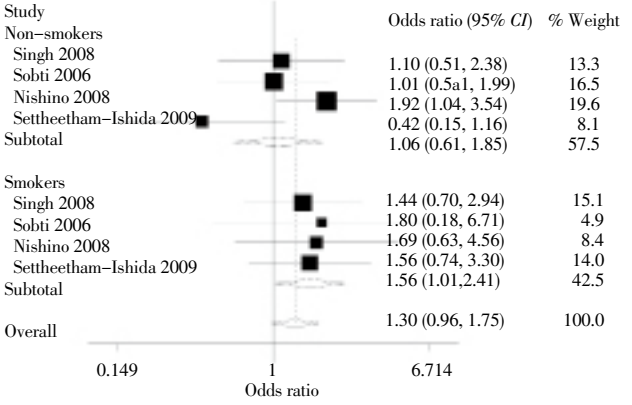

Figure 2. Relationship between GSTM1 gene polymorphism and cervical cancer risk by smoking status.

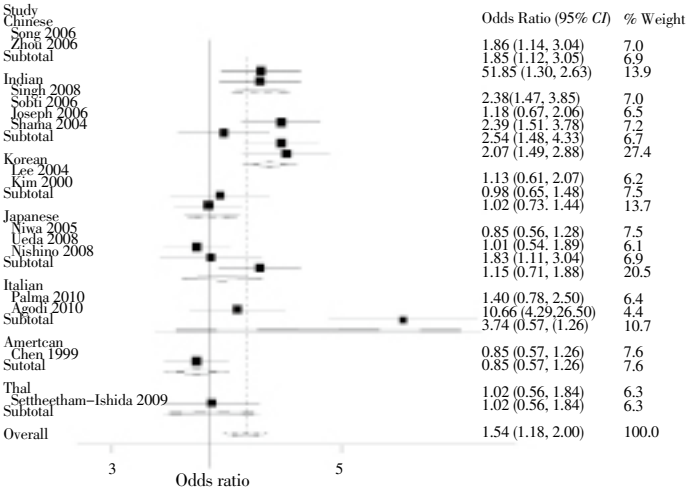

Figure 3. Relationship between GSTM1 gene polymorphism and cervical cancer risk by ethnicity.

Begg´s funnel plot were generated to assess potential publication bias for GSTM1 (Figure 4), and the symmetry of the studies in the funnel plot showed no publication bias in this meta-analysis. The Egger´s test showed no publication bias for GSTM1 (*P* value was 0.11). Moreover, the sensitivity analysis showed the robust of our meta-analysis after excluding an large sample size study[19].

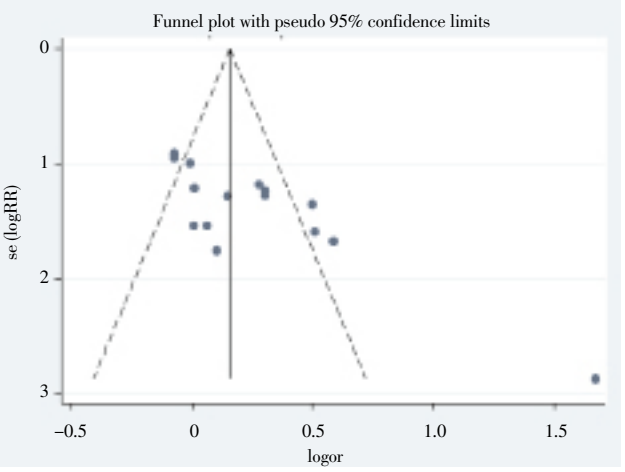

Figure 4. Funnel plot for GSTM1 gene polymorphism and cervical cancer risk.

4. Discussion

Previously, genetic factors are considered as important factors in the development of cervical cancer. Previously, many studies investigated the association between GSTM1 polymorphism and cervical cancer. However, the association between them is controversial. Some studies reported that the null genotypes are positively correlated, inversely correlated, or not correlated with with the risk for cervical cancer in different ethnic populations. These discrepancies

could have been due to limited sample numbers and ethnic differences. Therefore, we conducted a meta-analysis of 15 published case-control studies to investigate the role of GSTM1 polymorphism in cervical cancer. The meta-analysis result showed that the association between GSTM1 null genotype and the risk for cervical cancer is statistically significant in smokers, and Chinese and Indian population but not in other populations.

Many studies have reported the effect of ethnic differences on genetic predisposition to human diseases. For example, the incidence of cervical cancer is high in southern Africa, and is almost five-folds higher than in the Northern America and Australia[1]. It showed there were differences in ethnicities or in environment. In addition, the data showed that the allele frequency of GSTM1 null genotype was higher in American and Japanese than in Chinese and India populations. In the present study, we found that the association between GSTM1 null genotype and the risk of cervical cancer was statistically significant in Chinese and Indian but not in other populations. The reasons of the variation in the effect of the genotype might be the different of lifestyle, nutrition, environmental factors, and genetic factors in different ethnicities.

The association between cervical cancer and cigarette smoking has been discussed since the late 1970s, and numerous studies represented by Winkelstein[28] and the IARC Multi-centre Cervical Cancer Study Group[29] have reported that the risk of developing cervical cancer was elevated two- to three-folds by smoking after adjusting for HPV infection status. Our study showed the cigarette could play an interaction role with null GSTM1 genotype, those smokers carrying the null genotype possessed increased susceptibility to cervical carcinogenesis.

There are some limitations to this meta-analysis. Firstly, the sample size reported in the literature is still relatively small and might not provide sufficient power to estimate the association between the null GSTM1 polymorphism and cervical cancer risk. Secondly, it is widely recognized that environmental risk factors, such as exposure to HPV infection, cervical lesion type and genital health are major contributors to cervical cancer development. Understanding the interaction between environmental exposure and null GSTM1 polymorphism is an important priority; however, the lack of available data precludes examination of gene-environment interactions in this meta-analysis. Our sensitivity analysis showed that the combined *OR*s did not change after the exclusion of studies with large sample size, suggesting that our results are methodologically robust. Begg´s test also showed no evidence of potential publication bias, indicating that the preferential publication of positive results does not occur.

In conclusion, this meta-analysis provide strong evidence that the GSTM1 null genotype is associated with the development of cervical cancer, and especially in Chinese and Indian population, and smokers showed a modification on the association between GSTM1 null genotype and cervical cancer. Well-designed and large sample studies should be performed to confirm this finding. Also, further studies investigating the effect of gene-environment interactions on cervical cancer risk are required.

Conflict of interest statement

We declare that we have no conflict of interest.

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