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

Chunmei Liu¹, Yan Zeng², Xizhen Ma³, Yuewen Qi¹, Shuai Zhang¹, Rui Lv¹, Hong Yu¹

¹Department of Pathogen Biology, Qingdao University, Qingdao 266001, Shandong, China
²WestChina School of Preclinical and Forensic Medicine, Sichuan University, No. 3 Section 17, South Renmin Road, Chengdu 610041, Sichuan Province, China
³Department of Physiology, Qingdao University, Qingdao 266001, Shandong, China

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
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.

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-statistic ≤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) [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 genotypes (Cases/Controls) | Genotyping methods |
|--------------|------|---------|-----------------|--------------|------------------------------------------|-------------------|
| **GSTM1:**   |      |         |                 |              |                                          |                   |
| Warwick AP   | 1994 | UK      | 48.5            | HCC          | 9/27                                     | PCR               |
| Sharam A     | 2004 | India   | 49.2±8.8       | HCC          | 81/33                                    | mPCR              |
| Sharma       | 2015 | India   | 42.1±11.7      | PCC          | 79/160                                   | PCR               |
| Kiran        | 2010 | Turkish | 53.7±10.35     | PCC          | 25/30                                    | mPCR              |
| Chen         | 1999 | USA     | NM              | HCC          | 101/118                                  | PCR               |
| Singh        | 2008 | India   | 45.2±8.8       | HCC          | 64/46                                    | mPCR              |
| Stosic       | 2014 | Serbia  | 44.54±12.19    | PCC          | 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±13           | HCC          | 29/15                                    | PCR               |
| Ueda         | 2010 | Japan   | 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 | Korea   | NM              | HCC          | 42/42                                    | PCR               |
| Hasan        | 2015 | Pakistan | NM           | PCC          | 37/17                                    | mPCR              |
| Natphopsuk   | 2015 | Thailand | NM            | HCC          | 130/125                                  | PCR               |

| **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 | 53.7±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              |
| Study            | Year | Country    | Mean ± SD | Type   | Cases/Frequency |
|------------------|------|------------|-----------|--------|-----------------|
| Stosic           | 2014 | Serbia     | 44.54 ± 12.19 | HCC    | 38/20           |
| Kim              | 2000 | Korean     | 46.5 ± 10.1  | PCC    | 120/92          |
| Djansugurova     | 2013 | Kazakhstan | NM        | PCR    | 129/43          |
| Palma            | 2010 | Italy      | 41.7 ± 12.3  | PCC    | 8/22            |
| Sobti            | 2006 | India      | 48.6 ± 9.9   | PCC    | 16/26           |
| Lee              | 2004 | Korea      | NM         | HCC    | 38/54           |
| Hasan            | 2015 | Pakistan   | NM         | PCC    | 14/18           |
| Settheetham-Ishida | 2009 | Thailand   | NM         | HCC    | 42/38           |
| Niwa             | 2005 | Japan      | 47.2 ± 12.2  | HCC    | 63/145          |
| Zhou             | 2006 | China      | 50.66      | HCC    | 67/55           |
| Sharam A         | 2004 | India      | 49.2 ± 8.8†  | PCC    | 27/11           |
| Sharma           | 2015 | India      | 42.1 ± 11.7† | HCC    | 23/53           |
| Singh            | 2008 | India      | 45.2 ± 8.8†  | PCC    | 23/2            |
| Stosic           | 2014 | Serbia     | 44.54 ± 12.19 | HCC    | 38/20           |
| Kim              | 2000 | Korea      | 46.5 ± 10.1  | PCC    | 62/48           |
| Sobti            | 2006 | India      | 48.6 ± 9.9†  | PCC    | 8/9             |
| Hasan            | 2015 | Pakistan   | NM         | PCC    | 3/5             |
| Settheetham-Ishida | 2009 | Thailand   | NM         | HCC    | 26/18           |
| Zhou             | 2006 | China      | 50.66      | HCC    | 39/27           |

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.
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.

http://www.ijSciences.com

Volume 6 – January 2017 (01)
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.
An Updated Meta-Analysis: Cervical Cancer Risk Conferred by GSTM1 and GSTT1 Polymorphisms

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.
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<0.001, I²=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
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.

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.

**References**

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulient J and Jemal A: Global cancer statistics. CA Cancer J Clin 65: 87-108, 2015.
2. Cancer IA ARo. Cervical Cancer incidence and mortality worldwide in 2008[J]. Extraído de, acesso em [11 de abril de 2013] 2012.
3. Schiffman M, Castle PE,Jeronomo J, Rodriguez AC and Wacholder S: Human papillomavirus and cervical cancer. Lancet. 370: 890-907, 2007.
4. Wang SS, Bratti MC, Rodriguez AC, Herrero R, Burk RD, Porras C, et al: Common variants in immune and DNA repair genes and risk for human papillomavirus persistence and progression to cervical cancer. J Infect Dis 199: 20-30, 2009.
5. Miller III MC, Mohrenweiser HW and Bell DA: Genetic variability in susceptibility and response to toxicants. Toxicol Lett 120: 259-268, 2001.
6. Singh H, Sachan R, Devi S, Pandey SN and Mittal B: Association of GSTM1, GSTT1, and GSTM3 gene polymorphisms and susceptibility to cervical cancer in a North Indian population. Am J Obstet Gynecol 198: 303 e1-6, 2008.
7. Agodi A, Barchitta M, Cipresso R, Marzagalli R, La Rosa N, Caruso M, et al: Distribution of p53, GST, and MTHFR polymorphisms and risk of cervical intraepithelial lesions in sicy. Int J Gynecol Cancer 20: 141-146, 2010.
8. Song G, Song Z, Xu J and Shao S: Association of single nucleotide polymorphism in glutathione S-transferase-M1 with susceptibility to cervical cancer in Shaxi Province. Chin J Cancer Prev Treat 15: 1054-1056, 2008.
9. Higgins J and Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Me 21: 1539-1558, 2002.
10. Warwick A, Redman C, Jones P, Fryer A, Gilford J, Alldersea J, et al: Progression of cervical intraepithelial neoplasia to cervical cancer: interactions of cytochrome P450 CYP2D6 EM and glutathione s-transferase GSTM1 null genotypes and cigarette smoking. Brit J Cancer 70: 704, 1994.
11. Sharma A, Gupta S, Sodhani P, Singh V, Sehgal A, Sardana S, et al: Glutathione S-transferase M1 and T1 Polymorphisms, Cigarette Smoking and HPV Infection in Precancerous and Cancerous Lesions of the Uterine Cervix. Asian Pac Cancer Prev 16:6429, 2015.
12. Sharma A, Sharma J, Murthy N, and Mitra A: Polymorphisms at GSTM1 and GSTT1 gene loci and susceptibility to cervical cancer in Indian population. Neoplasma 51: 12-16, 2003.
13. Kian B, Karkucak M, Ozan H, Yakut T, Ozerrkan K, Sag S, et al: GST (GSTM1, GSTT1, and GSTP1) polymorphisms in the genetic susceptibility of Turkish patients to cervical cancer. J Gynecol Oncol 21: 169-173, 2001.
14. Chen C, Madeleine MM, Weiss NS and Daling JR: Glutathione S-transferase M1 genotypes and the risk of squamous carcinoma of the cervix: a population-based case-control study. Am J Epidemiol 150: 568-572, 1999.
15. Stosic I, Grujicic D, Arsenijevic S, Brkic M and Milosevic-Djordjevic O: Glutathione S-transferase T1 and M1 polymorphisms and risk of uterine cervical lesions in women from central Serbia. Asian Pac J Cancer Prev 15: 3201-3205, 2013.
16. Kim JW, Lee CG, Park YG, Kim KS, Kim IK, Sohn YW, et al: Combined analysis of germline polymorphisms of p53, GSTM1, GSTT1, CYP1A1, and CYP2E1. Cancer 88: 2082-2091, 2000.
17. Djansugurova LB, Perfiljeva AV, Zhunusova GS, Djantaeva KB, Iksoon OA and Khussainova EM: The determination of genetic markers of age-related cancer pathologies in populations from Kazakhstan. Frontiers in Genetics 4: 70 , 2013.
18. Yao L, Wenjing M and Qing L: Association between genetic polymorphism of GSTM1, CYP2E1 and susceptibility to cervical cancer and its prencancerous lesions in Uighur women in Xinjiang. Prog Obstet Gynecol 11: 012, 2009.
19. Ma C, Liu Y, Lu X and Ma H: The relationship between GSTM1 and incidence of cervical cancer in Uighur women in xinjiang. Chin J Obstet Gynecol 44: 629-631, 2009.
20. Ueda M, Toji E, Nunobiki O, Sato N, Izuma S, Torii K, et al: Germline polymorphisms of glutathione-S-transferase GSTM1, GSTT1 and p53 codon 72 in cervical carcinogenesis. Human cell. 23: 119-125, 2010.
21. Palma S, Novelli F, Padua L, Venuti A, Prignano G, Mariani L, et al: Interaction between glutathione-S-transferase polymorphisms, smoking habit, and HPV infection in cervical cancer risk. J Cancer Res Clin Oncol 136: 1101-1109, 2010.
22. Sobti R, Kaur S, Kaur P, Singh J, Gupta I, Jain V, et al: Interaction of passive smoking with GST (GSTM1, GSTT1, and GSTP1) genotypes in the risk of cervical cancer in India.
An Updated Meta-Analysis: Cervical Cancer Risk Conferred by GSTM1 and GSTT1 Polymorphisms

Cancer Genet Cytogen 166: 117-123, 2006.

23. Lee S-A, Kim JW, Roh JW, Choi JY, Lee K-M, Yoo K-Y, et al: Genetic polymorphisms of GSTM1, p21, p53 and HPV infection with cervical cancer in Korean women. Gynecol Oncol 93: 14-18, 2004.

24. Hasan S, Hameed A, Saleem S, Shahid S, Haider G and Azhar A: The association of GSTM1 and GSTT1 polymorphisms with squamous cell carcinoma of cervix in Pakistan. Tumor Biol 36: 5195-5199, 2015.

25. Natphopsuk S, Settheetham-Ishida W, Settheetham D and Ishida T: Lack of Participation of the GSTM1 Polymorphism in Cervical Cancer Development in Northeast Thailand. Asian Pac J Cancer Prev 16: 1935-1937, 2014.

26. Settheetham-Ishida W, Yuenyao P, Kularbkaew C, Settheetham D and Ishida T: Glutathione S-transferase (GSTM1 and GSTT1) polymorphisms in cervical cancer in Northeastern Thailand. Asian Pac J Cancer Prev 10: 365-368, 2009.

27. Niwa Y, Hirose K, Nakanishi T, Nawa A, Kuzuya K, Tajima K, et al: Association of the NAD(P)H: quinone oxidoreductase C609T polymorphism and the risk of cervical cancer in Japanese subjects. Gynecol Oncol 96: 423-429, 2005.

28. Zhou Q, Wang J, Shao S, Ma XC Ding L: The study of the relationship between glutathione S-transferase M1, T1 genotypes and the risk of cervical cancer. Modern Prev Med 33: 269-271, 2006.

29. Warwick A, Sarhanis P, Redman C, Pemble S, Taylor JB, Ketterer B, et al: Theta class glutathione S-transferase GSTT1 genotypes and susceptibility to cervical neoplasia: interactions with GSTM1, CYP2D6 and smoking. Carcinogenesis 15: 2841-2845, 1994.

30. De Carvalho C, da Silva I, Pereira J, de Souza N, Focchi G and Ribalta J: Polymorphisms of p53, GSTM1 and GSTT1, and HPV in uterine cervix adenocarcinoma. Eur J Gynaecol Oncol 29: 590-593, 2007.

31. Prokopczyk B, Cox JE and Hoffmann D: Identification of tobacco-specific carcinogen in the cervical mucus of smokers and nonsmokers. J Natl Cancer Inst 89: 868-873, 1997.

32. Wang D, Wang B, Zhu J, Liu D and Sun G: Glutathione S-transferase M1 and T1 polymorphisms and cervical cancer risk: A meta-analysis. Neoplasma 58: 352, 2011.

33. Zeller JL, Lynn C and Glass RM: Carcinoma of the Cervix. J Am Med Assoc 298: 2336-2336, 2007.

34. Wacholder S, Silverman DT, McLaughlin JK and Mandel JS: Selection of controls in case-control studies: II. Types of controls. Am J Epidemiol 135(9):1029-41, 1992.

Acknowledgements
We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.