The Association between GSTM1, GSTT1 Genetic Variants and Gastric Carcinoma Susceptibility in Chinese: A Systematic Review Article

Dingyun YOU 1, Nanjia LU 2, Donghui DUAN 2, *Hui LI 3, *Wenhua XING 2

1. Dept. of Science and Technology, Kunming Medical University, Kunming, China
2. Zhejiang Provincial Key Laboratory of Pathophysiology, School of Medicine, Ningbo University, Ningbo, China
3. Institute of Non-Communicable Disease Control and Prevention, Ningbo Municipal Center for Disease Control and Prevention, Ningbo, China

*Corresponding Author: Email: 315928139@qq.com

(Received 04 Feb 2015; Accepted 19 Jul 2016)

Abstract

Background: Glutathione S-transferases (GSTs) have been investigated as potential carcinoma susceptible genes. However, the relationship between GSTs (GSTM1, GSTT1) variants and gastric carcinoma (GC) risk has been controversial in Chinese population.

Methods: A comprehensive literature search strategy (PubMed, Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Wan fang Database, etc.) was launched. Crude odds ratios (ORs) and confidence intervals (95% CI) were applied to estimate the strength of the association.

Results: Significant associations between GSTs genetic polymorphisms and GC were evidenced under random-effects model (OR\textsubscript{GSTM1}=1.56, 95% CI: 1.39 to 1.76, I\textsuperscript{2} = 50.7%, P<0.0001; OR\textsubscript{GSTT1}=1.24, 95% CI: 1.10 to 1.39, I\textsuperscript{2} = 43.6%, P=0.014; OR\textsubscript{GSTM1-GSTT1}=1.51, 95% CI: 1.26 to 1.81, I\textsuperscript{2} = 59.7%, P=0.004). The pooled ORs were not qualitatively changed when any single study was omitted by sensitivity analysis.

Conclusion: Our results indicated an increased GC risk in Chinese population with GSTM1 and GSTT1 null genotype and GSTM1-GSTT1 dual null genotype. Further multi-center studies are needed to investigate the gene-gene and gene-environment interactions on the susceptibility of GC.

Introduction

Gastric carcinoma (GC) is one of the most common malignant tumors and is the second leading cause of cancer-related death across the worldwide (1). GC is a major health issue in China (2); its incidence is high, accounts for over 40% of all new GC cases (3).

Studies involved in twins, familial clustering, and different ethnicities have identified that genetic factors contributed to GC susceptibility (4). Glutathione S-transferases (GSTs) family, known as phase II isoenzymes, has proved to be involved in detoxifying several carcinogens and plays a critical role in the deactivation of toxic and carcinogenic electrophile (5-7). The GST family included four gene subfamilies (GSTA, GSTM, GSTT, and GSTP), GSTM1 and GSTT1 are located in 1p13.3 and 22q11.23 in the human chromosome, and has been studied widely (8-11). Polymorphisms within GSTM1 and GSTT1 genes either decrease or abolish their enzyme activities (12). The most common variant of GSTM1 and GSTT1 genes is homozygous deletion (null geno-
type), which can detoxify several xenobiotics and lower the defense against oxidative stress (8, 13-14).

A meta-analysis involved in 46 studies observed evidence for GSTT1 null polymorphism and GC risk in East Asians and Indians, but not in Caucasian, and Middle Eastern and African populations (15). Another meta-analysis with 8,203 GC cases and 13,866 controls showed that GSTT1 null allele was associated with increased risk of GC in Europeans and Asians (16). Whereas, no statistical significance was observed for the GSTT1, GSTM1 genotypes and GC risk in Taiwanese (17). The above indicate that these associations vary in different populations.

Substantial studies have investigated the associations between GSTM1 and GSTT1 genetic polymorphisms and GC risk in Chinese population. However, the results have been controversial. Therefore, we performed a meta-analysis to explore the above association with increased sample size and statistical power.

Methods

Literature review

Two reviewers independently conducted a comprehensive literature search in PubMed, EMBASE, Web of science, Chinese Biomedical Database, Chinese National Knowledge Infrastructure and Wan fang Data, up to Apr 2016 without language restriction. Besides, we also searched two websites (http://www.baidu.com and http://scholar.google.com). The reference lists of available articles were also retrieved simultaneously. The following search strategies were used: ("glutathione s-transferase" or "GST" or "GSTM1" or "GSTT1") AND ("gastric" or "stomach") AND ("cancer" or "carcinoma" or "tumor") AND ("China" or "Chinese" or "Taiwan"). When there was more than one article published, only the latest and /or the most comprehensive one would be adopted.

Inclusion and exclusion criteria

All inclusive studies should comply with the following criteria: 1) case–control or cohort studies; 2) the articles provided raw data or sufficient information to calculate odds ratios (ORs) with 95% confidence intervals (CIs); 3) if studies contained overlapping data, only the one with the largest sample size was included.

Exclusion criteria were: 1) not related case–control or cohort studies; 2) abstract, case report, review article, and other meta-analysis; and 3) studies that contained overlapping data.

Data extraction and synthesis

According to the inclusion criteria, relevant data were extracted from the included studies by two independent reviewers. Discrepancy was resolved by discussion among all reviewers. The following data were extracted: first author, years of publication, geographical location, study time, criteria of pathologic diagnosis, source of control, characteristic of cases and controls, genotype frequencies of null GSTM1, null GSTT1 and dual null GSTM1-GSTT1 in cases and controls (Table 1). Meanwhile, sub-group analyses based on geographical location, number of cases, source of control and test material were also performed.

Statistical analysis

1) ORs and 95% CIs were applied to evaluate the strength of associations between the GSTs and gastric carcinoma risk; 2) statistical heterogeneity was calculated by Q and I² statistics (18). The Q test and I² were used to evaluate the proportion of the total variation from heterogeneity (19), When P value of heterogeneity tests was (P≤0.1), a random-effect model was performed. Otherwise, a fixed-effect model was used (20). Heterogeneity was divided into high heterogeneity (I²≥50%) and low heterogeneity (I²<50%); 3) in order to explore the potential heterogeneity, subgroup analysis were also performed by geographical location (Northeast China, North China, East China, Central China, South China, Southwest China, Northwest China, and Taiwan), number of cases (<100 vs. ≥100), and sources of control (population-based, hospital-based, mixed); 4) Sensitivity analysis was used to determine the stability of the results after removing one study at a time. Galbraith plot was also performed to identify the potential heterogeneity; 5)
The potential publication bias was assessed using Begg's funnel plot (21) and Egger's linear regression test (22), and $P<0.05$ was regarded as representative of statistically significant; and 6) all analyses were performed by STATA version 12.0 (Stata Corporation, College station, TX, USA), and all $P$ values were two-sided.

**Results**

**The selection and characteristics of studies**

After a comprehensive search of the above databases, a total of 142 articles were identified, 46 irrelevant articles were excluded by reviewing their abstracts, 16 articles were excluded for overlapping data, 36 articles were excluded for meta-analysis, review, only cases and other populations, and other 7 articles were excluded due to unavailable information. Finally, the remaining 37 full-text publications (18-54) were used to evaluate the associations of $GSTM1$ and $GSTT1$ genetic polymorphisms with gastric carcinoma susceptibility (Fig. 1).

The characteristics of the included studies were shown in Table 1. There were 34 studies concerning about $GSTM1$ and GC susceptibility (4841 cases and 7608 controls) (23-35,37,39-57,59), 23 articles about $GSTT1$ (3865 cases and 5915 controls) (23,26,28-29,32-39,41,45,50-58), and 12 articles about both $GSTM1$ and $GSTT1$ (1577 cases and 2982 controls) (23,28,33,35,37,39,51,53-57).

![Fig. 1: Flow chart of study selection](http://ijph.tums.ac.ir)
In order to explore the potential heterogeneity, sub-group analyses concerning geographical location (Northeast China (24,25,27), North China (49), East China (23,26,28-33,35,38,39,41-43,45,46,48,50,52,53), Central China (36,37,39,40,54), South China (47,51,55,59), Southwest China (56), Northwest China (57,58), and Taiwan (34,44), case number (≥100 (29,31-34,37,41-48,50,52-56,58,59) and <100 (23-28,30,35,36,38,39,40,49,51,57).), and sources of control (population-based (23,25,26,28-33,35,35-38,40,43,46-49,51,53-59) and hospital-based (24,27,34,39,41,42,44,45,50,52)) were performed.

Results of Overall Meta-analysis

- **GSTM1 null genotype with GC risk:** A total of 34 studies showed a significant association between the GSTM1 null genotype and GC risk in Chinese population under random-effect model (OR=1.56, 95% CI: 1.39-1.76, I²=50.7%, P<0.000) (Fig. 2a).

- **GSTT1 null genotype with GC risk:** A total of 23 studies controls demonstrated that GSTT1 null genotype was significantly related with GC risk in Chinese population under random-effect model (OR=1.24, 95% CI: 1.10 to 1.39, I²=43.6%, P=0.014) (Fig. 2b).

- **2.3. Dual-null genotype of GSTM1-GSTT1 with GC risk:** Dual-null genotype of GSTM1-GSTT1 had a significant association with GC in Chinese population under random-effect model (OR=1.51, 95% CI: 1.26 to 1.81, I²=59.7%, P=0.004) (Fig. 2c).

Results of Sub-group analysis

We did not detect significant increased risk for GC in either North or Taiwan in GSTM1 meta-analysis or in the East or Taiwan in GSTT1 meta-analysis. Cases number <100 had a higher risk than cases number ≥100 in both GSTM1 and GSTT1 meta-analysis. In addition, population-based studies had a higher risk than hospital-based studies in GSTM1 meta-analysis. The heterogeneity test demonstrated that studies from Taiwan were major sources of heterogeneity for GSTM1 meta-analysis (I²=71.2%). In the analysis of the relationship between GSTM1-GSTT1 genetic polymorphisms and GC risk, significant associations were found in South China, Northwest of China and hospital-based studies, however, we observed high heterogeneities in South China (I²=71.4%).

Galbraith plot and sensitivity analysis

In this meta-analysis, Galbraith plot was used to identify the possible sources of heterogeneity. Three articles, two articles and two articles were identified as outliers by Galbraith plot in GSTM1, GSTT1 and GSTM1-GSTT1 meta-analysis, respectively. (Data not shown). After omitting those studies, the heterogeneity was reduced (OR_{GSTM1}=1.57, 95% CI: 1.41-1.76, P<0.001, I²=39.4%; OR_{GSTT1}=1.29, 95% CI: 1.15 -1.43, P<0.001, I²=30.6%; OR_{GSTM1-GSTT1}=1.46, 95% CI: 1.29-1.64, P<0.001, I²=37.4%). Meanwhile, sensitivity analysis did not change the results of each meta-analysis (Fig. 3).

Potential publication bias

Begg’s funnel plots and Egger’s tests were applied to assess the potential publication bias for GSTM1 meta-analysis (Fig. 4a and Fig. 4b), GSTT1 meta-analysis (Fig. 4c and Fig. 4d), and dual-null genotype of GSTM1-GSTT1 meta-analysis (Fig. 4e and Fig. 4f). The fail-safe number was taken to evaluate further the publication bias.
Fig. 2: (a) Forest plot for GSTM1 meta-analysis; (b) Forest plot for GSTT1 meta-analysis; (c) Forest plot for GSTM1-GSTT1 meta-analysis
You et al.: The Association between GSTM1, GSTT1 Genetic Variants and Gastric …

Fig. 3: (a) Sensitivity analysis for GSTM1 meta-analysis; (b) Sensitivity analysis for GSTT1 meta-analysis; (c) Sensitivity analysis for GSTM1-GSTT1 meta-analysis
Fig. 4: Begg’s funnel plot was used to detect potential publication bias qualitatively, and Egger’s linear regression test was used to quantify the potential presence of publication bias. (a)(b) Publication bias for GSTM1 meta-analysis. (c)(d) Publication bias for GSTT1 meta-analysis. (e)(f) Publication bias for GSTM1-GSTT1 meta-analysis.

Publication bias was evidenced (GSTM1: $P_B<0.001$, $P_E<0.001$; GSTT1: $P_B=0.007$, $P_E=0.015$; GSTM1-GSTT1: $P_B=0.024$, $P_E=0.019$). However, after we omitted the outliers’ articles according to the Galbraith plot, no publication bias was observed by Egger’s test in GSTM1-GSTT1 meta-analysis.

The fail-safe number ($N_{0.05}$) was 1000 and 248 in GSTM1 and GSTT1 meta-analysis respectively, which indicated that if we want to turn the results, at least 1000 and 248 non-statistically significant studies should be further included in relevant meta-analysis. Therefore, our results were robust and reliable.
Discussion

The pooled and sub-group analysis identified a positive association between GSTM1, GSTT1 and GSTM1-GSTT1 genetic polymorphisms and GC susceptibility in Chinese population. This is consistent with previous studies. A meta-analysis showed homozygous deletion in GSTM1 increased risk of GC in different ethnics (including Japanese, Chinese, Indians, Caucasians and Africans) (60).

However, significant heterogeneity was noticed. Studies from East China and Taiwan were the main heterogeneity for GSTM1 meta-analysis. The eastern region is rich in seafood, which is typically high in salt for longer storage. Fujian, an eastern coastal region, is a representative high-risk area for GC. Inhabitants’ diet includes dried shrimp sauce and pickled fish (48, 61). As well known, a high salt diet is a significant risk factor for the development of GC. The high osmotic pressure caused by dietary salt can damage the gastric mucosa, which will lead to extensive diffuse hyperemia, necrosis, hemorrhage etc. (62) and then accelerate the potential carcinogenicity of carcinogenic compounds. Meanwhile, studies in Chinese have confirmed that pickled food is rich in amine, which can synthesize a hard carcinogenic substance (N-nitroso compound) in the stomach. Thus, traditional Asian pickled vegetables have been classified as possible human carcinogen by the International Agency for Research on Cancer (IARC) (63, 64).

Furthermore, the population from East China, such as Fujian, Shanghai, and Southern Jiangsu, favors of sweet food. Available nutrition epidemiological studies have considered sugar as a vital risk factor for GC. Increasing daily sugar intake was responsible for the susceptibility of stomach cancer in both male and female in island residents (65). Diet with high sugar can damage the gastric mucosa, thus accelerate the absorption of carcinogenic substances (66).

To further explore the potential heterogeneity, we performed Galbraith plot analysis. In the GSTM1 meta-analysis, three studies were identified as potential heterogeneous sources (27, 34, 49). These three studies with small sample size might contribute to potential bias. While in the GSTT1 meta-analysis, two studies were spotted as outliers (29, 43), no statistical significant heterogeneity was observed after omitted those two studies ($I^2=30.6\%$).

Due to the heterogeneity and publication bias, the following limitations should be claimed: 1) studies included in our meta-analysis were mainly hospital-based studies, which were not as representative as population-based studies; 2) our meta-analysis included few studies with relatively small sample size, which might contribute to potential publication bias; 3) the sample size included in our meta-analysis is not very large, which may not have sufficient statistical power to evaluate the relevant associations; 4) we did not assess the gene-gene and gene-environment interactions due to unavailable data; 5) we spotted publication bias, but the fail-safe number illustrated the impact of publication bias was negligible, and the conclusion was reliable.

Conclusion

The findings indicate that GSTs genetic polymorphisms are associated with the increased GC risk in Chinese. However, larger sample size and multi-center studies are needed to confirm our findings, and gene-gene and gene-environment interactions should be explored further in the future.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgments

This study was supported by Ningbo Leading Team of Science and Technology Innovation
program (2012B82018-24), 2014 Ningbo Medical Science and Technology Project (2014A17) and Ningbo University Scientific Research Fund (XK15D243). The authors declare that there is no conflict of interests.

References

1. Jemal A, Center MM, DeSantis C, Ward EM (2010). Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev*, 19(8): 1893-907.

2. Zhang XM, Wang Z, Liang JW, Zhou ZX (2014). Analysis of laparoscopy-assisted gastric cancer operations performed by inexperienced junior surgeons. *Asian Pac J Cancer Prev*, 15(12): 5077-81.

3. Ferlay J, Soerjomataram I, Dikshit R, Mathers C, Rebelo M, et al. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, 136(5): E359-86.

4. Malaty HM, Engstrand L, Pedersen NL, Graham DY (1994). Helicobacter pylori infection: genetic and environmental influences. A study of twins. *Ann Intern Med*, 120(12): 982-6.

5. Oakley A (2011). Glutathione transferases: a structural perspective. *Drug Metab Rev*, 43(2): 138-51.

6. Strange RC, Spiteri MA, Ramachandran S, Fryer AA (2001). Glutathione-S-transferase family of enzymes. *Mutat Res*, 482(1-2): 21-6.

7. Bhardwaj R, Sharma PK, Jadon SP, Varshney R (2012). A combination of 2-deoxy-D-glucose and 6-aminonicotinamide induces cell cycle arrest and apoptosis selectively in irradiated human malignant cells. *Tumour Biol*, 33(4): 1021-30.

8. Strange RC, Fryer AA (1999). The glutathione S-transferases: influence of polymorphism on cancer susceptibility. *LARC Sci Publ*, (148):231-49.

9. Thakur H, Gupta L, Sobti RC, Janmeia AK, Seth A, Singh SK (2011). Association of GSTM1T1 genes with COPD and prostate cancer in north Indian population. *Mol Biol Rep*, 38(3): 1739-93.

10. Ye Z, Song H, Higgins JP, Pharoah P, Danesh J (2006). Five glutathione s-transferase gene variants in 23,452 cases of lung cancer and 30,397 controls: meta-analysis of 130 studies. *PLoS Med*, 3(4): e91.

11. Yu KD, Di GH, Fan L, Wu J, Hu Z, Shen ZZ (2009). A functional polymorphism in the promoter region of GSTM1 implies a complex role for GSTM1 in breast cancer. *Eur J Cancer*, 23(7): 2274-87.

12. Hayes JE, AmlaNordström RC (2000). Glutathione S-transferase polymorphisms and their biological consequences. *Pharmacology*, 61(3): 154-60.

13. Dong LM, Potter JD, White E, Ulrich CM, Cardon LR, Peters U (2008). Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. *JAMA*, 299(20): 2423-36.

14. Soy M, Vinod T, Reddy KS, Gopalakrishnan S, Adithan C (2007). Genetic polymorphisms of glutathione transferase genes (GSTM1, GSTT1 and GSTP1) and upper aerodigestive tract cancer risk among smokers, tobacco chewers and alcoholics in an Indian population. *Eur J Cancer*, 43(18): 2698-706.

15. Wang Q, Chen Y, Zhang Y, Wu X, He H, Li X, et al (2014). Quantitative assessment of the influence of glutathione S-transferase T1 null variant on gastric cancer risk. *Tumour Biol*, 35(1): 849-58.

16. Sun W, Yao L, Jiang B (2014). Meta-analysis: glutathione S-transferase T1 null allele is associated with gastric cancer risk. *Tumour Biol*, 35(1): 239-45.

17. Wu MS, Chen CJ, Lin MT, Wang HP, Shun CT, Sheu JC, et al. (2002). Genetic polymorphisms of cytochrome p450 2E1, glutathione S-transferase M1 and T1, and susceptibility to gastric carcinoma in Taiwan. *Int J Colorectal Dis*, 17(5): 338-43.

18. Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, 21(11): 1539-58.

19. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J (2006). Assessing heterogeneity in meta-analysis: Q statistic or I² index. *Psychoh Methods*, 11(2): 193-206.

20. Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a
simple, graphical test. BMJ, 315(7109): 629-34.
23. Cai L, Yu SZ (1999). The Effects of the Risk Factors for Stomach Cancer Were Analyzed Employing the General Relative Risk Model. Chin J Prevent Control Chronic Dis, 7(2).
24. Jiang YH, Ju ZY, Ren CS, Lv QJ, Wei W (2000). Study On the Relationship between the Glutathione S-transferase Gene Deletion, Environmental Factors and Susceptibility to Gastric Carcinoma. Chin Public Health, 16(10): 877-879.
25. Liu Y, Xu RT, Sun GF, Shang XL, Wang Q (2000). The Relationship of GSTM1 Gene Homozygous Deletion Polymorphism and occurrence of Gastric Cancer. J Chin Med Univ, 29(4): 287-289.
26. Setiawan VW, Zhang ZF, Yu GP, Li YL, Lu ML, Tsai CJ, et al (2000). GSTT1 and GSTM1 Null Genotypes and the Risk of Gastric Cancer: A Case-Control Study in a Chinese Population. Cancer Epidemiol Biomarkers Prev, 9(1): 73-80.
27. Ju ZY, Jang YH, Xiao F (2001). A Molecular Epidemiology study on the relationship between Glutathione S-transferase genetic polymorphisms, environment factors and susceptibility to Gastric Cancer. Chin J Epidemiol, 22(6): 469-470.
28. Qian Y, Xu YC, Shen HB, Tan Y, Zhou L, Yu RB (2001). A Molecular Epidemiology study on the relationship between Glutathione S-transferase M1, T1 genetic polymorphisms and susceptibility to Gastric Cancer. Chin Public Health, 17(1): 101-103.
29. Gao CM, Takezaki T, Wu JZ, Li ZY, Liu YT, Li SP (2002). Glutathione-S-transferases M1 (GSTM1) and GSTT1 genotype, smoking, consumption of alcohol and tea and risk of esophageal and stomach cancers: a case-control study of a high-incidence area in Jiangsu Province, China. Cancer Lett, 188(1): 95-102.
30. Gong I, Sun HL, Xu YQ (2002). The study of correlation between the deletion of GSTM1 gene and gastric cancer. Med J Wannan Univ, 21(3): 181-182.
31. Li HQ, Zhou T, Wen PE, Yang QS, Jing SK (2002). A study of CYP1A1 and GSTM1 Genotypes Associated with Susceptibility to Gastric Cancer, Chronic Atrophic Gastritis and Gastric Ulcer Disease. J Oncol, 11(1): 25-28.
32. Mu LN. Risk factors, protective factors and molecular epidemiological study on three upper GI cancers in Taixing area [PhD thesis]. School of Public Health, Fudan University, China; 2002.
33. Shen J, Wang RT, Xing HX, Wang LW, Wang CX, Wang BY, et al (2002). Case-control study of the polymorphisms of phase I and phase II metabolic genes and stomach cancer susceptibility. Tumor J, 22(1): 9-13.
34. Wu MS, Chen CJ, Lin MT, Wang HP, et al. (2002). Genetic polymorphisms of cytochrome P450 2E1, glutathione S-transferase M1 and T1, and susceptibility to gastric carcinoma in Taiwan. Int J Colorectal Dis, 17(5): 338-43.
35. Zheng TR, Zheng QH, Gong FS, Xie YQ, Wang XR (2002). Gene deletion polymorphisms of GSTM1 and GSTT1 and susceptibility to stomach neoplasm. J Practical Oncol, 17(3): 155-157.
36. Ye M, Liu JY, Deng CS (2003). Relationship between xenobiotic-metabolizing enzyme gene polymorphisms and genetic susceptibility of gastric cancer. World Chin J Digesitol, 11(9): 1314-1317.
37. Liu J, Zhang WY, Wei Y, Gao P, Zhang YC, Deng CS, et al. (2003). The correlation of Glutathione S-transferase M1,T1 polymorphisms and Helicobacter pylori infection and gastric adenocarcinoma. J Mathemat Med, 16(1): 26-28.
38. Qian Y, Xu YC, Shen HB, Zhou L, Yu RB, Niu JY, et al. (2003). Relationship Between CYP2E1, GSTT1 Genetic Polymorphisms and susceptibility to Gastric Cancer. Chin J PrevControlChronic Non-commun Dis, 11(3): 107-109.
39. Shen Xb, Zhang J, Zhu LJ, Pu YP (2004). Relationship Between Glutathione S-Transferase M1,T1 Genetic Polymorphism, Smoking and Alcohol Consumption and Susceptibility to Stomach Cancer. J Environ Health, 21(4): 210-214.
40. Zhang YC, Deng CS, Zhu YQ (2004). Relationship between Glutathione S-transferase M1 Genetic Polymorphisms and Cigarette Smoking and Susceptibility of Cardial Carci-
nomma. Cancer Research on Prevention and Treatment, 31(7): 441-3.
41. Zhang J. Study on Genetic Polymorphisms of Metabolic Enzymes and Environmental Exposure Associated with Gastric Cancer [Master's thesis]. School of Public Health, Southeast Univ, China; 2004.
42. Li H, Chen XL, Li HQ (2005). Polymorphism of CYPIA1 and GSTM1 genes associated with susceptibility of gastric cancer in Shandong Province of China. World J Gastroenterol, 11(37): 5757-62.
43. Shen J, Wang RT, Xu YC, Wang LW, Wang XR (2005). Interaction models of CYPIA1, GSTM1 polymorphisms and tobacco smoking in intestinal gastric cancer. World J Gastroenterol, 11(38): 6056-60.
44. Lai KC, Chen WC, Tsai FJ, Li SY, Chou MC, Jeng LB (2005). Glutathione S-transferase M1 Gene Null Genotype and Gastric Cancer Risk in Taiwan. Hepatogastroenterology, 52(66): 1916-9.
45. Yang YF. Study on The Interaction of Environment and Genetic Risk Factors in Gastric Cancer [Master's thesis]. School of Public Health, Southeast Univ, China; 2006.
46. Zhou T, Fan W, Han W, Gao YJ, Yuan MB, Li JM, et al. (2006). The study of the association of GSTM1 gene polymorphism with susceptibility to gastric cancer. Chin J Care Adv Gen Surg, 9(6): 355-358.
47. Huang X. A case-control study on the association between genetic polymorphisms of CYP1A1, GSTM1 and gastric cancer susceptibility in GuangXi Province [PhD thesis]. Med J Guangxi Univ, China; 2007.
48. Yu SZ, Mu LN, Cai L (2007). Using case-control study and molecular epidemiological methods to detect risk and protective factors on upper GI cancers in two districts, Southern China. Chin J Clinicians (Electronic Version), 1(2): 86-90.
49. Li ZT, Xu LD, Liu XD (2008). The relationship between GSTM1 genetic Polymorphisms and susceptibility of Gastric cancer. Chin J Misdiagn, 8(6): 1312-13.
50. Shen XB. Analysis and Risk Assessment of Environmental and Genetic Risk Factors on Primary Gastric Cancer [PhD thesis]. Southeast Univ, China; 2008.
51. Xie SQ, Huang X, Lu YF (2008). Relationship Between Glutathione S-Transferase M1,T1 gene null genotype, Smoking and Alcohol Consumption and Susceptibility to Stomach Cancer in the Guangxi Zhuang Chinese population. Clinical Focus, 23(19): 1393-95.
52. Feng JY, Yan YY, Shen XB (2009). Multi-gene Risk Analysis of Susceptibility Genes On Primary Gastric Cancer. Proceedings of the 8th National Postgraduate Symposium on Environmental and Occupational Medicine. 78-80.
53. Moy KA, Yuan JM, Chung FL, Wang XL, Berg DVD, Wang RW, et al. (2009). Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms and gastric cancer risk: a prospective study of men in Shanghai, China. Int J Cancer, 125(11): 2652-9.
54. Lao YP. Genetic Polymorphisms of metabolic enzymes and gastric carcinoma susceptibility [Master's thesis]. Central South Univ, China; 2009.
55. Zhang AP, Liu BH, Wang I, Gao Y, Li F, Sun SX (2011). Glutathione S-transferase Gene Polymorphisms and Risk of Gastric Cancer in a Chinese Population. Asian Pac J Cancer Prev, 12(12): 3421-5.
56. Jing C, Huang ZJ, Duan YQ, Wang PH, Zhang R, Lao KS, et al. (2012). Glutathione-S-transferases Gene Polymorphism in Prediction of Gastric Cancer Risk by Smoking and Helicobacter Pylori Infection Status. Asian Pac J Cancer Prev, 13(7): 3325-8.
57. Zhang D. The relationship between CYPIA1, GSTT1, GSTM1 and GSTP1 genetic Polymorphisms and susceptibility of Ningxia Hui People cardia cancer [Master's thesis]. School of Clinical Medicine, Med J Ningxia Univ, China; 2012.
58. Liu L, Zhang D, Fan H, Gao P (2013). Relationship between GSTT1, GSTP1 Gene Polymorphism and Cardia Cancer Genetic Susceptibility in Ningxia Hui Ethnicity. Med J Ningxia Univ, 35(2): 168-171.
59. Wang WW, Yang WM, Zhang YX (2013). Correlation between GSTM1 gene polymorphism and the susceptibility to gastric in the middle-aged and elderly in Hainan province. Hainan Med J, 24(4): 474-475.
60. Lao X, Peng Q, Lu Y, Li S, Qin X, Chen Z, et al (2014). Glutathione S-transferase gene GSTM1, gene-gene interaction, and gastric
cancer susceptibility: evidence from an updated meta-analysis. Cancer Cell Int, 14(1): 127.
61. Lin C (2002). The molecular epidemiology research of Gastric carcinoma in Fujian province. Higher Education Press, Beijing.
62. Shikata K, Kiyohara Y, Kubo M, Yonemoto K, Ninomiya T, Shirot A, et al. (2006). A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. Int J Cancer, 119(1): 196-201.
63. Zhao DL, Chen WQ, Yu TT, He YT, Chen ZF, Wen DG, et al (2011). A population-based matched case-control study on the risk factors of gastric cardia cancer. Chinese Journal of Oncology, 33(10): 775-8.
64. Zhang XW, Pan SD, Feng YL, Liu JB, Dong J, Zhang YX, et al. (2011). Relationship between genetic polymorphism in microRNAs precursor and genetic predisposition of hepatocellular carcinoma. Chinese Journal of Preventive Medicine, 45(3): 239-43.
65. Qiu JL, Chen K, Wang JY, Zhang LJ, Shui LM (2003). Relationship between nutrient intake and gastric cancer in island residents. J Nutr, 25(1): 23-8.
66. Lilienfeld DE, Garagliano CF (1979). Gastric cancer etiology: a biochemical hypothesis. Mod Hypotheses, 5(1): 145-51.
| No. | Study (ref.) | Area | Study time | Pathologic diagnosis | Source of controls | Case group | Control group | Null GSTM1/Group number | Null GSTT1/Group number | Dual Null/Group number |
|-----|--------------|------|------------|----------------------|-------------------|------------|--------------|------------------------|------------------------|-----------------------|
| a1  | (59)         | Hainan | 2005-2010  | ALL                  | Population        | 130 cases  | 138 controls | 39/130                 | 26/138                 |                       |
| a2  | (58)         | Ningxia (Hui) | 2009.1-2012.3 | ALL                  | Population        | 110 cases(GCA,87 men,23 women,mean age 56.27±7.39 yr) | 220 controls(154 men,66 women, mean age 58.80±7.43 yr) | 49/110 | 73/220 |                       |
| b3  | (56)         | Chengdu | 2007.4-2011.4 | ALL                  | Population        | 410 cases   | 410 population controls matched by gender and age | 240/410 | 207/410 | 236/410 | 202/410 | 131/410 | 98/410 |
| a4  | (57)         | Ningxia (Hui) | 2006.1-2010.10 | ALL                  | Population        | 40 cases(GCA,27 men,13 women,mean age 57.24±6.43 yr) | 80 controls(46 men,34 women, mean age 56.77±7.21 yr) | 30/40 | 45/80 | 19/40 | 23/80 | 14/80 | 12/80 |
| b5  | (55)         | Southern (China) | 2007.1-2011.1 | ALL                  | Population        | 194 cases(age 40-75 yr) | 412 controls(age 35-77 yr) | 105/194 | 194/412 | 114/194 | 198/412 | 67/194 | 90/412 |
| a6  | (53)         | Shanghai | 1986.1-2002.9 | PARTIAL              | Population        | 312 cases   | 936 controls matched by date of birth (within 2 yr), date of biospecimen collection (within 1 month) and neighborhood of residence at recruitment. Individual matching by 1:3. | 98/170 | 415/735 | 97/170 | 415/735 | 55/170 | 231/735 |
| a7  | (52)         | Nanjing (Han) | NA              | ALL                  | Hospital          | 374 cases(273 men,101 women, Mean age 61.15±12.61 yr, rang 18-90 yr) | 374 controls matched by residence, sex, age (with in 5 yr) | OR=1.251,(95%CI:0.976-1.604) | OR=1.033,(95%CI:0.805-1.326) |                       |
| a8  | (54)         | NA      | 2006.7-2007.8 | NA                  | Population        | 123 cases(72 men, 51 women, mean age 55.2±10.6 yr) | 129 controls(80 men,49 women, mean age 53.7±12.3 yr) | 93/123 | 71/129 | 77/123 | 63/129 | 41/123 | 23/129 |
| a9  | (49)         | Tangshan | 2006.1-2007.10 | NA                  | Population        | 42 cases (31 men, 11 women, age 58.9 yr, rang 42-71.) | 42 controls matched by sex and age | 18/42 | 26/42 |                       |
| a10 | (51)         | Guangxi (Zhuang) | 2006.8-2007.5 | ALL                  | Population        | 70 cases(AC,55 men,15 women, mean age 56.6±14.4 yr, rang 27-84.) | 100 controls (72 men, 28 women, mean age 53.3±12.4 yr, rang 23-84.) | 39/70 | 39/100 | 48/70 | 50/100 | 28/70 | 14/100 |
| a11 | (50)         | Nanjing (Jiangsu, Han) | NA              | ALL                  | Hospital          | 503 cases (366 men, 137 women, mean age:61.6±12.25 yr, rang 21-90) | 503 controls matched by residence, sex, age (within 5 yr) | 245/503 | 217/503 | 219/503 | 215/503 |                       |
| a12 | (47)         | Guangxi (Han, Zhuang) | 2005.7-2006.11 | ALL                  | Population        | 121 cases(AC,92 men,29 women, mean age:52.66±13.35 yr, rang 34-75, 67 Zhuang people, 138 controls(106 men,32 women, mean age 49.6±14.31 yr, rang 28-72, 76 Zhuang people, 62 Han people) | 66/121 | 54/138 |                       |

Table 1: Characteristics of the studies evaluating the effects of GSTM1 and GSTT1 polymorphisms on the risk of GC

Available at: [http://ijph.tums.ac.ir](http://ijph.tums.ac.ir)
You et al.: The Association between GSTM1, GSTTI Genetic Variants and Gastric ...

| Study No. | Sample Size | Location | Date       | Setting | Number of Cases | Number of Controls | Matched Variables | OR (95% CI) |
|-----------|-------------|----------|------------|---------|----------------|-------------------|-------------------|-------------|
| a13       | 101 cases   | Changle  | 1996-1998  | ALL     | 101            | 101               | residence, sex, age | 3.27 (1.14-9.39) |
| a14       | 100 cases   | Nanjing  | NA         | ALL     | 244            | 62                | residence, sex, age | 117/244 80%  |
| a15       | 123 cases   | Taiwan   | 2000.1-2002.12 | ALL    | 121            | 121               | residence, sex, age | 73/123 60%  |
| b16       | 102 cases   | Shangdong | 1998.1-2000.1 | ALL   | 62             | 62                | normal gastrointestinal mucous membrane | 67/100 60%  |
| b17       | 114 cases   | Yanzhong | 1997.1-1998.12 | ALL    | 693            | 693               | 310 case's siblings | 71/111 60%  |
| a19       | 72 cases    | Hubei    | NA         | ALL     | 114            | 114               | residence, sex, age | 44.997/7 2% |
| b20       | 60 cases    | Nanjing  | 2002-2003 | ALL     | 60             | 60                | age55-70 year | 31/60 60%  |
| b21       | 121 cases   | Nanjing  | 2002.5-2003.12 | ALL   | 121            | 121               | ethnicity, residence, age | 54/121 60%  |
| b22       | 90 cases    | Jintan, Huai'an | NA     | ALL     | 90             | 90                | ethnicity, residence, age | 54/90 60%  |

Available at: [http://ijph.tums.ac.ir](http://ijph.tums.ac.ir)
| No. | Study Area | Region (China) | Study Details | Population Characteristics | Controls Matched by | Odds Ratio (95% CI) |
|-----|------------|----------------|---------------|----------------------------|---------------------|---------------------|
| 23  | Hubei      | NA             | ALL           | 127 cases (AC, 39 early stage, 88 advanced stage, 76 intestinal type, 51 diffuse type) | 114 controls | 78/127, 53/114, 76/127, 55/114, 48/127, 23/114 |
| 24  | Hubei (Han) | NA             | ALL           | 56 cases (AC, 42 men, 14 women, mean age 57.6, range 22-79) | 56 controls matched by sex (39 men, 17 women), age (mean age 58.0, range 26-86) | 33.992/56, 25.984/56 |
| 25  | Taiwan     | 1996-1999      | ALL           | Hospital | 356 cases (AC, 218 men, 138 women, mean age 62.0±13.3, range 25-87) | 278 unaffected controls (156 men, 122 women), age (mean age 61.6±13.1, range 22-86) | 173/356, 136/278, 181/356, 130/278 |
| 26  | Huaian (Jiangsu) | 1987-2000.12 | ALL           | Population | 153 cases (ones were from hospital aged 40-81 yr, the others were from the regional cancer registry) | 223 controls matched by sex, ethnicity, and age | 90/153, 133/223, 71/153, 119/223 |
| 27  | Shangdong   | 1998.1-2000.1  | ALL           | Population | 102 cases | 62 controls | OR=2.72 (95% CI: 1.3-5.6) |
| 28  | Yangzhou   | 1997.1-1998.12 | ALL           | Population | 112 cases | 675 controls | 71/112, 361/675, 43/110, 309/675, 30/107, 161/662 |
| 29  | Anhui (Han) | NA             | ALL           | Population | 32 cases (19 men, 13 women, age 36-74 yr) | 88 controls (46 men, 42 women, age 32-79 yr) | 25/32, 50/88 |
| 30  | Fuzhou (Fujian) | NA PARTIAL   | Population | 92 cases | 92 controls matched by ethnicity, residence, age (within 5 yr) | 64/92, 48/92, 49/92, 38/92, 30/92, 15/92 |
| 31  | Taixing (Jiangsu) | NA NA   | NA            | 197 cases | 393 controls | 128/197, 235/393, 94/197, 192/393 |
| 32  | Shenyang    | 1999.9-2000.12 | ALL           | Hospital | 50 cases | 50 controls matched by age (±5 yr), sex, ethnicity | 33/50, 17.05/50 |
| 33  | Jintan (Jiangsu) | 1998.4-1999.7 | PARTIAL      | Population | 89 cases | 94 controls matched by age (±3 yr), sex | 55/89, 44/94, 51/89, 46/94, 34/94, 30/94 |
| 34  | Yangzhou (Jiangsu) | 1995.1-1995.6.30 | ALL          | Population | 91 cases | 429 controls | 42/87, 212/419, 44/81, 190/418 |
| 35  | NA         | NA             | ALL           | Population | 99 cases | 364 controls | 63/99, 186/364 |
| 36  | Benxi       | 1999.9-1999.12 | ALL           | Hospital | 41 cases | 41 controls matched by ethnicity, sex, age (within 2 yr) | 24/41, 14/41 |
| 37  | Changle (Fujian) | NA ALL       | Population | 95 cases | 94 controls matched by ethnicity, residence, sex, age (within 3 yr) | 60/95, 43/94, 41/95, 47/94, 27/95, 26/94 |

*a* Articles published in Chinese; *b* Articles published in English; *c* Pathologic diagnosis: **ALL**: Gastric cases were confirmed by pathologic diagnosis; **PARTIAL**: part of Gastric cases were confirmed by pathologic diagnosis; **NA**: relative data were not available in original studies.