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Association between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and gastric cancer risk, and their interactions with environmental factors

Z.H. Chen, J.F. Xian and L.P. Luo

The First Affiliated Hospital of Jinan University, Guangzhou, China

Corresponding author: L.P. Luo
E-mail: zuhuichen66@163.com

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ABSTRACT. Glutathione S-transferase (GST) is an important member of phase II metabolic enzymes; *GSTM1*, *GSTT1*, and *GSTP1* belong to three subfamilies of the GST enzyme. Polymorphisms in *GSTM1*, *GSTT1*, and *GSTP1* could affect detoxification processes, and increase individuals' susceptibility to cancers. We aimed to investigate the association between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and the risk of gastric cancer in a Chinese population. In addition, we also examined the effect of gene-environmental interactions, and their effect on risk of this cancer. Between July 2013 and June 2015, we recruited 242 gastric cancer patients and 396 healthy controls for our study. Polymerase chain reaction-restriction fragment length polymorphism analysis was used to characterize genetic polymorphisms in *GSTM1*, *GSTT1*, and *GSTP1*. We observed that the Val/Val genotype of *GSTP1* was associated with increased risk of gastric cancer when compared with the Ile/Ile genotype (OR = 3.19, 95%CI = 1.84-5.56). Moreover, the Val allele of *GSTP1* was associated with higher susceptibility to gastric cancer as compared with

the Ile allele (OR = 1.52, 95%CI = 1.19-1.93). However, *GSTM1* and *GSTT1* polymorphisms did not affect the development of gastric cancer. In conclusion, our study indicated that *GSTP1* Ile105Val, but not GSTM1 and GSTT1 polymorphisms, was associated with risk of gastric cancer.

Key words: Glutathione S-transferase; Polymorphism; Gastric cancer; Environmental factors

INTRODUCTION

Gastric cancer is the fourth most commonly diagnosed cancer and is the second leading cause of cancer-related deaths worldwide (Farlay et al., 2013). It has been estimated that there are approximately 952,000 new gastric cancer cases per year with 405,000 cases in China alone (Farlay et al., 2013). Incidence of this disease varies across different populations, suggesting that environmental factors play an important role in its pathogenesis. Studies have shown that many environmental factors such as *Helicobacter pylori* infection, long-term smoking, long-term drinking, family history of cancer, high intake of pickled food, low intake of fruits and vegetables, and high salted diet contribute to the development of gastric cancer (Khayatzadeh et al., 2015; den Hoed and Kuipers, 2016; Lee et al., 2016; Zhang et al., 2016). However, not all individuals with associated risk factors develop gastric cancer, suggesting that genetic factors may also contribute to its pathogenesis. An increasing number of studies reported that genetic factors such as thrombospondin-2, thrombospondin-4, miR-146a, cytochrome P450 1A1, matrix metalloproteinases, interleukin-8, prostate stem cell antigen, and interleukin-17 contribute to the development of gastric cancer (Li et al., 2015; Shi et al., 2015; Zhang et al., 2015; Hidaka et al., 2016; Lin et al., 2016; Okada et al., 2016; Qiu et al., 2016; Xia et al., 2016).

Furthermore, tar, nicotine, and carbon monoxide in cigarettes may also lead to the development of gastric cancer. These substances are first oxidized, restored, and hydrolyzed by phase I metabolic enzymes. The end-products are then metabolized by phase II metabolic enzymes and excreted out of the body. Glutathione S-transferase (GST) is an important member of phase II metabolic enzymes. *GSTM1*, *GSTT1*, and *GSTP1* are members of three subfamilies of the GST enzyme. Deletion of the *GSTM1* or *GSTT1* genes and non-synonymous *GSTP1* Ile105Val could affect the expression and activity of the enzymes, and thereby lead to impaired detoxification and cancers (Broekman et al., 2014; Rao et al., 2014; Guven et al., 2015). Previous studies have reported the association between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and gastric cancer (Tripathi et al., 2008; Nguyen et al., 2010; Yadav et al., 2010; Zhang et al., 2011; García-González et al., 2012) with inconsistent results. In addition, there are no reports about the interactions between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and smoking. In the present study, we aimed to investigate the association between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and risk of gastric cancer in a Chinese population. We also examined the effect of gene-environmental interactions on gastric cancer risk.

MATERIAL AND METHODS

Subjects

We recruited 242 gastric cancer patients and 396 healthy controls between July 2013

and June 2015. Patients were recruited from the First Affiliated Hospital of Jinan University, and the disease was confirmed in all individuals by pathologists. Those who received any form of chemotherapy prior to enrollment were excluded from this study. Patients who had prior history of other malignant tumors, metastatic tumors, recurrent tumors, malnutrition, end-stage liver, or kidney diseases were also excluded.

Controls were recruited from the hospital outpatient clinics and health examination centers. All the control subjects underwent digestive endoscopy examinations, and were confirmed to be free of gastric cancers, history of any other cancers, diseases of the digestive system, and end-stage liver or kidney diseases. Demographic information of all the participants were collected from medical records, and included gender, age, family history of cancer, smoking and drinking habits, as well as intake of pickled foods.

Written informed consents were obtained from all subjects prior to enrollment, and the study protocols were approved by the Ethics Committee of the First Affiliated Hospital of Jinan University.

Genotyping analysis

Prior to receiving any forms of treatment, blood samples were collected into EDTA tubes for total genomic DNA extraction. DNA extraction was performed using the DNA extraction kit (QIAGEN, Hilden, Germany), according to manufacturer instructions. PCR-RFLP analysis was used to characterize genetic polymorphisms in *GSTM1*, *GSTT1*, and *GSTP1*. The forward and reverse primers for *GSTM1* were 5'-GAACTCCCTGAAAAGCTAAAGC-3' and 5'-GTTGGGCTCAAATATACGGTGG-3', respectively. The forward and reverse primers for *GSTT1* were 5'-TTCCTTACTGGTCCTCCACATCTC-3' and 5'-TCACCGGATCATGGC CAGCA-3', respectively. The forward and reverse primers for *GSTP1* were 5'-GTAGTTTGC CCAAGGTCAAG-3' and 5'-AGCCACCTGAGGGGTAAG-3', respectively. The forward and reverse primers for the reference gene (β-globulin) were 5'-CAACTCATCCACGTTCACC-3' and 5'-CAACTTCATCCACGTTCACC-3', respectively. The 50-μL PCR mixture contained 5 μL 10X PCR buffer solution, 4 μL dNTP (2.5 mM), 2 μL forward and reverse primers (10 mM), 2.5 μL TaqDNA polymerase, 2 μL DNA template, and 37 μL hydrogen peroxide. The cycling conditions for *GSTT1* and *GSTM1* were as follows: 95°C for 5 min; 35 cycles of 94°C for 45 s, 58°C for 40 s, and 72°C for 50 s; final extension at 72°C for 7 min. The cycling parameters for *GSTP1* were as follows: 95°C for 5 min; 35 cycles of 94°C for 45 s, 62°C for 40 s, and 72°C for 50 s; final extension at 72°C for 7 min. Amplified *GSTT1* and *GSTM1* fragments were ran on a 8% polyacrylamide gel. The PCR products of *GSTP1* were digested by *Bsm*AI, and the DNA fragments were ran on a 12% polyacrylamide gel.

The PCR products of *GSTM1*, *GSTT1*, and *β-globulin* were 236, 480, and 268 bp, respectively. The Ile/Ile *GSTP1* fragments were 329 and 113 bp, the Ile/Val fragments were 329 and 216 bp, and the Val/Val fragments were 216 and 113 bp.

Statistical analysis

Categorical variables were reported as percentages of the total. Pearson's chi-squared and Fisher exact tests were used to determine inter-group differences. Departure from Hardy-Weinberg equilibrium (HWE) was also assessed by these tests. Multiple logistic regression analysis was carried out to evaluate the association between *GSTM1*,

GSTT1, and *GSTP1* polymorphisms and the risk of gastric cancer. Results were expressed using odds ratios (ORs) and 95% confidence intervals (CIs). The wild-type genotype was used as the reference group. Interactions between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and smoking habits were analyzed using Spearman correlation analysis. $P < 0.05$ was considered statistically significant.

RESULTS

The demographic and lifestyle characteristics of the subjects are presented in Table 1. According to chi-squared analysis, patients were more likely to be smokers ($\chi^2 = 4.82$, $P = 0.03$) and have a family history of cancers ($\chi^2 = 7.16$, $P = 0.01$) when compared to the controls. However, no significant difference was found between the two groups in age ($\chi^2 = 0.16$, $P = 0.69$), gender ($\chi^2 = 0.49$, $P = 0.48$), drinking status ($\chi^2 = 1.18$, $P = 0.28$), and intake of pickled food ($\chi^2 = 1.97$, $P = 0.16$).

Table 1. Demographic and lifestyle characteristics of the subjects.

	Patients	%	Controls	%	χ^2	P value
Age (years)						
<60	103	42.56	175	44.19		
≥60	139	57.44	221	55.81	0.16	0.69
Gender						
Male	163	67.36	256	64.65		
Female	79	32.64	140	35.35	0.49	0.48
Smoking status						
No	103	42.56	204	51.52		
Yes	139	57.44	192	48.48	4.82	0.03
Drinking status						
No	104	42.98	153	38.64		
Yes	138	57.02	243	61.36	1.18	0.28
Family history of cancer						
No	217	89.67	377	95.20		
Yes	25	10.33	19	4.80	7.16	0.01
Intake of pickled food						
No	197	81.40	339	85.61		
Yes	45	18.60	57	14.39	1.97	0.16

The genotypic distributions of *GSTM1*, *GSTT1*, and *GSTP1* are listed in Table 2. The genotypic distributions of Ile/Ile, Ile/Val, and Val/Val in the *GSTP1* gene were significantly different between the two groups ($\chi^2 = 21.04$, $P < 0.001$). However, we did not find any differences in the genotype frequencies of *GSTM1* ($\chi^2 = 1.01$, $P = 0.32$) and *GSTT1* ($\chi^2 = 0.73$, $P = 0.39$) between patients and controls. The genotypic distributions of *GSTP1* were in line with HWE in patients ($\chi^2 = 1.28$, $P = 0.26$) and controls ($\chi^2 = 3.02$, $P = 0.08$).

Logistic regression analysis was performed to assess the association between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and risk of gastric cancer (Table 3). We observed that the Val/Val genotype of *GSTP1* was associated with an increased risk of gastric cancer when compared with the Ile/Ile genotype (OR = 3.19, 95%CI = 1.84-5.56). Moreover, the Val allele of *GSTP1* showed higher association with risk of gastric cancer as compared with the Ile allele (OR = 1.52, 95%CI = 1.19-1.93). However, *GSTM1* and *GSTT1* polymorphisms did not seem to affect the gastric cancer development.

Table 2. Genotypic distributions of *GSTM1*, *GSTT1*, and *GSTP1*

Genotype	Patients	%	Controls	%	χ^2	P value	χ^2 (HWE)	P value	χ^2 (HWE)	P value
							In patients		In controls	
GSTM1										
Present	132	54.55	232	58.59						
Null	110	45.45	164	41.41	1.01	0.32				
GSTT1										
Present	101	41.74	179	45.20						
Null	141	58.26	217	54.80	0.73	0.39				
GSTP1										
Ile/Ile	83	34.30	169	42.68						
Ile/Val	110	45.45	191	48.23						
Val/Val	49	20.25	36	9.09	21.04	<0.001	1.28	0.26	3.02	0.08

Table 3. Association between *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms and gastric cancer risk.

Genotypes	Patients	%	Controls	%	OR (95%CI)[1]	P value
GSTM1						
Present	132	54.55	232	58.59	1.0 (Reference)	-
Null	110	45.45	164	41.41	1.18 (0.84-1.65)	0.32
GSTT1						
Present	101	41.74	179	45.20	1.0 (Reference)	-
Null	141	58.26	217	54.80	1.15 (0.82-1.61)	0.39
GSTP1						
Ile/Ile	81	33.47	169	42.68	1.0 (Reference)	-
Ile/Val	112	46.28	195	49.24	1.20 (0.83-1.73)	0.31
Val/Val	49	20.25	32	8.08	3.19 (1.84-5.56)	< 0.001
Allele						
Ile	276	57.02	529	66.79	1.0 (Reference)	-
Val	208	42.98	263	33.21	1.52 (1.19-1.93)	< 0.001

[1]Adjusted for gender, age, smoking status, and family history of cancer.

Spearman correlation analysis for the interaction between *GSTP1* polymorphism and environmental factors is shown in Table 4. We observed a significant interaction between smoking and *GSTP1* polymorphism (Correlation coefficient = 0.253, $P < 0.001$).

Table 4. Interaction between *GSTP1* polymorphism and environmental factors in gastric cancer risk.

	Correlation coefficient	P value
Smoking status	0.253	<0.001
Drinking status	0.068	0.31
Family history of cancer	0.094	0.17
Intake of pickled food	0.055	0.38

DISCUSSION

In the current study, we found that the *GSTP1* Val/Val genotype was associated with the development of gastric cancer, and that *GSTP1* polymorphism may interact with tobacco smoking in defining gastric cancer susceptibility.

GSTs catalyze the reaction between glutathione and electrophilic compounds, thereby increasing their water solubility to facilitate their excretion from the body. GSTs form the main detoxification system for resistance to cell damage. Polymorphisms in GSTs could alter the detoxification process, which leads to accumulation of carcinogen precursors. As a result, these can activate or convert to toxic substances, and increase susceptibility to tumors (Morsi et al., 2006; Satoh et al., 2008).

Polymorphisms in *GSTP1* could lead to reduction in enzyme activity, and are therefore associated with development of malignant tumors. Previous studies have indicated that *GSTP1* polymorphism is associated with various kinds of cancers, such as acute myeloid leukemia, lung cancer, breast cancer, colorectal cancer, brain tumor, and esophageal cancer (Cong et al., 2014; Silva et al., 2014; Song et al., 2014; Jaramillo-Rangel et al., 2015; Nasr et al., 2015; Sharma et al., 2015; Soto-Quintana et al., 2015; Zhou et al., 2015; Geng et al., 2016; Khabaz et al., 2016; Kimi et al., 2016). Several studies have also reported that *GSTP1* polymorphism is associated with risk of gastric cancer in various populations, but the results were inconsistent (Nguyen et al., 2010; Zhang et al., 2011; Bao et al., 2012; García-González et al., 2012; Jing et al., 2012; Zhang et al., 2012; Ma et al., 2013). Four studies were carried out in a Chinese population, and significant associations were found between *GSTP1* Ile105Val polymorphism and risk of gastric cancer (Bao et al., 2012; Zhang et al., 2012; Ma et al., 2013). However, several studies conducted in American, Turkish, south-European, Vietnamese, as well as Chinese populations have indicated that *GSTP1* Ile105Val polymorphism did not play a role in the development of gastric cancer (Nguyen et al., 2010; Zhang et al., 2011; García-González et al., 2012; Jing et al., 2012). In our study, we found a significant association between *GSTP1* Ile105Val polymorphism and development of gastric cancer in a Chinese population. Discrepancies between the results of our studies and that of the previous studies may be attributed to differences in ethnicities and selection of subjects, as well as disease stages and sample sizes.

Moreover, we found significant interactions between *GSTP1* Ile105Val polymorphism and tobacco smoking in risk of gastric cancer. Tobacco smoking could promote the expression of nuclear hypoxia-inducible factor-1a in humans, and the synergistic effects of tobacco smoking and *GSTP1* Ile105Val polymorphism could promote the pathogenesis of gastric cancer (Huang et al., 2012). One limitation should be considered in this study. The gastric cancer patients and control subjects were selected from only one hospital, and may not be sufficiently representative of other populations.

In conclusion, our study indicated that *GSTP1* Ile105Val polymorphism might be associated with risk of gastric cancer. In addition, *GSTP1* Ile105Val polymorphism may also interact with tobacco smoking to further increase risk of gastric cancer.

Conflicts of interest

The authors declare no conflict of interest.

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