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Original Article

GSTP1 exon 5 rs200139798 polymorphism and clinicopathological characteristics of gastric cancer in Chinese patients

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Abstract: This study was undertaken to detect the incidence of variations in exon 5 of *GSTP1*, a member of the glutathione-S-transferase family, in gastric cancer in relation to histological parameters. The study included 216 gastric cancers and 300 benign gastric diseases as controls. DNA was extracted from paraffin-embedded tissues and polymerase chain reaction-restriction fragment length polymorphism analysis was performed to examine the GSTP1 Ile105Val gene polymorphism in the study participants. A positive association between *GSTP1* polymorphism and gastric cancer was observed in subjects carrying at least one G allele (AG and GG); the adjusted odds ratio (OR) for GSTP1 AA versus AG+GG was 1.416 (95% confidence interval [CI] 1.007 to 1.989, after controlling for age and gender). Patients over 50 years old more frequently carried the AG+GG genotype than those aged less than 50 (P=0.011) with adjusted OR (95% CI) of 2.758 (1.227-6.201). Compared with the well-differentiated group, the incidence of the GSTP1 AA genotype was decreased in the moderately [P=0.026; OR (95% CI)=3.559 (1.072-11.813)] and poorly [P=0.003; OR (95% CI)=6.015 (1.679-21.549)] differentiated groups. The incidence of the GSTP1 AA genotype in intestinal type was higher than that in diffuse type (adjusted P=0.014; OR [95% CI]=2.210 [1.160-4.210]). All results indicated that the *GSTP1* Ile105Val variant was closely associated with an increased risk of gastric cancer, and was significantly associated with patient age, tissue differentiation degree, and Lauren classification but not with gender, gross classification, tumor size (diameter), infiltration depth, and lymph node involvement.

Keywords: Gene polymorphism, GSTP1, gastric cancer, clinicopathological characteristics

Introduction

Gastric cancer is still one of the most common cancers and the third leading cause of cancer-related deaths worldwide. Geographically, almost two-thirds of all gastric cancer cases occur in Asia, primarily concentrated in the People's Republic of China (43% of total global cases) [1]. In 2012, there were an estimated 30,949 new cases with 22,120 deaths due to gastric cancer in China. The estimated incidence of gastric cancer in China was 6.21 per 100,000. The age-standardized incidence rate was 17.85 per 100,000 by Chinese population and 23.93 per 100,000 by world population [2, 3]. Recent research has focused on the gene variants of gastric cancer patients. Gene variants in hosts can determine whether an individual has an increased risk for developing gastric cancer, especially variants in genes involved in DNA repair and detoxification. An important family in this regard is the glutathione S-transferases (GSTs), which consist of five distinct classes, namely a (GSTA1-GSTA4), ù (GSTS), ì (GSTM1–GSTM5), ð (GSTP1), è (GSTT1 and GSTT2), and æ (GSTZ1) [4, 5]. Polymorphisms of these genes affect the function of the enzymes, especially GSTP1 exon 5 variant A to G at nucleotide 1,587 (isoleucine 105 valine, rs200139798) [6]. The activity of the enzyme is affected by this substitution at position 105, which is located in the hydrophobic substrate binding site and has considerable effects depending on the type of chemical reaction. Several epidemiologic studies have explored the possible association between *GSTP1* polymorphism and the risk of cancers, such as breast cancer, prostate cancer, colon

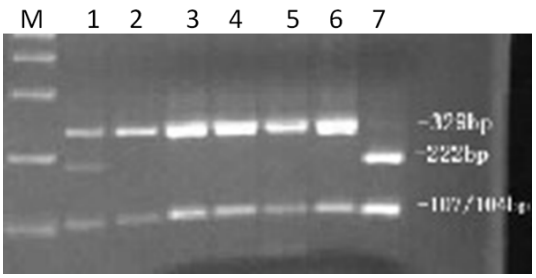

Figure 1. Representative electrophoresis gels with visualization of the exon 5 polymorphism of GSTP1. M, DNA marker (DL2000); lane 1, AG genotype; lanes 2-6, AA genotype; lane7, GG genotype.

cancer, and lung cancer [7-12]. We have previously reported that polymorphism of *GSTP1* (rs200139798) has significant effects on the risk of gastric cancer and, furthermore, has a close relationship with intestinal metaplasia of gastric tissue [13]. During the stage of intestinal metaplasia, polymorphism of *GSTP1* and *Helicobacter pylori* infection show a positive interaction [14]. However, these data were derived from blood samples and the relationship between polymorphism of *GSTP1* (rs2001-39798) in paraffin-embedded tissue samples and risk of gastric cancer and clinicopathological characteristics has not been examined.

Materials and methods

Study population

We recruited 216 patients with gastric cancer at the First Affiliated Hospital of China Medical University from March 2008 to December 2012, including 163 men and 53 women aged 28-87 years, with median age of 61.1 years. Controls were 300 cancer-free individuals recruited from the Affiliated Hospital of Shenyang Medical college (Feng Tian Hospital of Shenyang and the Fourth Hospital of Shenyang), including 227 men and 63 women aged 30-85 years, with median age of 60.8. There was no statistically significant difference in age and gender between the gastric cancer group and the controls (P>0.05). The Ethics Committee of the Shenyang Medical College and China Medical University approved the protocol and written informed consent was obtained from all subjects.

Genotyping

Genomic DNA was extracted from all samples using a standard kit-based method (GT pure™ FFPE tissue DNA Extraction KIT NO. 56404). The DNA concentration was adjusted to 50 μM using TE buffer, and all DNA preparations were stored at 4°C until use for genotyping.

Briefly, the assay for the exon 5 variant used the primer pair EX5-1 (5' GTA GTT TGC CCA AGG TCA AG 3', starting at 2,306 bp in the *GSTP1* complete code, GDB accession number X08058) and EX5-2 (5' AGC CAC CTG AGG GGT AAG 3' staring at 2,721 bp). PCR was carried out using an Eppendorf AG (Eppendorf Company, Germany) with a PCR kit (TakaRa, Dalian, China). After an initial denaturation step at 95°C for 12 minutes, 15 cycles of PCR were per-formed at 95°C for 30 seconds, 58°C for 30 seconds, 72°C for 60 seconds, followed by 25 cycles of amplification at 95°C for 30 seconds, 55°C for 30 seconds, 72°C for 60 seconds, one final elongation at 72°C for 5 minutes, and holding at 16°C.

The PCR products were digested for 3 hours at 37°C with 5 units of *AIw26I* (NEB, USA). The products were resolved by electrophoresis on 2% agarose gels, stained with ethidium bromide for 10 minutes, and photographed under UV light to infer the genotype.

Statistical analysis

Chi-squared test was used to compare the distribution of variables between cases and controls. For analyses comparing cases and controls, odds ratios (ORs) and 95% confidence intervals (CIs) for association between each genotype and the risk of gastric cancer were obtained using unconditional logistics adjusting for gender and age at diagnosis. Trend statistics for risk of gastric cancer in association with the genotypes were obtained using multivariate models. All tests were two sided, and all statistical analyses were performed using Statistical Analysis System software (SPSS 17.0).

Results

RFLP-PCR-based genotyping assay for GSTP1 exon 5 polymorphism

PCR products were digested for 2 hours at 37°C with 5 units of *AIw26I*. This generated 329 bp and 107/104 bp fragments for the homozygous wild type (AA genotype, Ile/Ile); 329 bp, 222 bp, and 107/104 bp fragments for the heterozygote type (AG genotype, Ile/Val); and 222 bp and 107/104 bp fragments for the

Table 1. Distribution of exon 5 polymorphism genotypes of *GSTP1* in gastric cancer and control groups

	Total	AA genotype n (%)	AG+GG genotype n (%)	Adjusted P	Adjusted OR (95% CI)
Control	300	248 (82.7)	52 (17.8)		1
GC group	216	163 (75.5)	53 (24.5)	0.045[1)]	1.416 (1.007~1.989)

[1)]*P*<0.05 vs. control group by Chi-squared test. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using unconditional logistics adjusting for gender and age at diagnosis.

Table 2. Interaction between *GSTP1* genotype and clinicopathological characteristics of gastric cancer

	AA genotype n (%)	AG+GG genotype n (%)	Adjusted *P*
Gender			
Male	80 (49.1)	83 (50.9)	0.769
Female	25 (47.2)	28 (52.8)	
Age			
≤50	22 (68.8)	10 (31.3)	0.011*
>50	83 (45.1)	101 (54.9)	
Diameter			
≤5 cm	59 (49.2)	62 (50.8)	0.773
>5 cm	46 (47.9)	52 (52.1)	
Differentiation			0.016*
Well	13 (76.5)	4 (23.5)	
Moderate	49 (49.0)	51 (51.0)	
Poor	43 (43.4)	56 (56.6)	
Gross			0.174
Early gastric	2 (100)	0	
B1	2 (50.0)	2 (50.0)	
B2	2 (25.0)	6 (75.0)	
B3	87 (50.9)	84 (49.1)	
B4	12 (38.7)	19 (61.3)	
Depth of invasion			0.221
SM	2 (100)	0	
MP	9 (39.1)	14 (60.9)	
SS	23 (60.5)	15 (39.5)	
SE	68 (46.9)	77 (53.1)	
SI	3 (37.5)	5 (62.5)	
N stage			0.915
No	21 (48.8)	21 (51.3)	
Yes	84 (48.6)	89 (51.4)	
Lauren			0.041*
Intestinal	45 (55.6)	36 (45.4)	
Diffuse	38 (40.4)	49 (59.6)	
Unclassified	22 (53.7)	19 (46.3)	

*P<0.05 for AG+GG vs. AA by Chi-squared test. M (mucosa), SM (submucosa), MP (muscularis), SS (subserosa), SE (serosa exposure), SI (serosa invasion), B1-4 (Borrmann I-IV). Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using unconditional logistics adjusting for gender and age at diagnosis.

homozygous mutant (GG genotype, Val/Val) (**Figure 1**).

Distribution of exon 5 polymorphism of GSTP1 in gastric cancer and control groups

A total of 300 cases in the control group were analyzed, including 248 cases with AA genotype, 45 with AG genotype, and seven with GG genotype. A total of 216 gastric cancer cases were analyzed, including 163 with AA genotype, 43 with AG genotype, and 10 with GG genotype. We compared the combined AG and GG genotypes with the AA genotype. **Table 1** shows the OR and 95% CI of *GSTP1* genotypes comparing gastric cancer cases to population control. The adjusted OR for GSTP1 AA versus AG+GG was 1.416 (95% CI 1.007 to 1.989, adjusted by age, gender).

Interaction of GSTP1 genotypes and histological parameters of gastric cancer

The distribution of *GSTP1* genotypes according to the patients' clinical characteristics is shown in **Tables 2** and **3**. The distribution of genotypes was significantly related to patient age, tumor differentiation, and Lauren type. Patients over 50 years old or morefrequently carried AG+GG genotypes compared with those less than 50 years old [P=0.011, adjusted OR (95% CI)=2.758 (1.227-6.201)]. Compared with the well-differentiated group, the frequency of the GSTP1 AA genotype was decreased in moderately [P=0.026; OR (95% CI)=3.559 (1.072-11.813)] and poorly [P=0.003; OR (95% CI)=6.015 (1.679-21.549)] differentiated groups. The frequency of GSTP1 AA genotype in intestinal type was higher than that in the diffuse type [adjusted P=0.014; OR (95% CI)=2.210 (1.160-4.210)]. No significant differences were found accord-

Table 3. Interactions between GSTP1 and tumor differentiation and Lauren type

	AA n (%)	AG+GG n (%)	P	OR (95% CI)	P	OR (95% CI)
Differentiation						
Well	13 (76.5)	4 (23.5)		1		
Moderate	49 (49.0)	51 (51.0)	0.026[1)]	3.559 (1.072~11.813)		1
Poor	43 (43.4)	56 (56.6)	0.003[1)]	6.015 (1.679~21.549)	0.275	1.375 (0.775~2.439)
Lauren						
Intestinal	45 (55.6)	36 (45.4)		1		
Diffuse	38 (40.4)	49 (59.6)	0.014[2)]	2.210 (1.160~4.210)		1
Unclassified	22 (53.7)	19 (46.3)	0.675	1.179 (0.545~2.550)	0.118	1.823 (0.855~3.886)

[1)]*P*<0.05 vs. well differentiated group by Chi-squared test.; [2)]*P*<0.05 vs. intestinal type by Chi-squared test. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using unconditional logistics adjusting for gender and age at diagnosis.

ing to male vs. female sex, tumor diameter ≤5 cm vs. >5 cm, gross type, depth of invasion, and presence of lymph node metastasis.

Discussion

Recently, scientists have paid increasing attention to the relationship between gene polymorphisms and diseases. Such studies provide a large amount of information on diseases including hereditary factors and underlying mechanisms. Many studies have investigated genetic polymorphisms in cancer and several genes have been shown to be related to gastric cancer. Some of these genes increase the risk of gastric cancer, such as cyclin D1, Fas, and vascular endothelial growth factor (VEGF), which control the proliferation and apoptosis of cells. Other genes associated with gastric cancer encode repair genes (XRCC1), oncogenes and suppressors (Ras, p53), mucins (MUC1, E-cadherin), cytokines (IL-1β, IL-10, IL-8), and metabolizing enzymes (CYP2E1, GSTT1, COX-2) [14-29].

GSTP1 is a major phase II xenobiotic-metabolizing enzyme with many functions in the human body such as detoxifying carcinogens, activating antineoplastic prodrugs, metabolizing chemotherapeutic agents, and involvement in cell cycle and apoptosis regulation [5]. We have studied the genotype distribution of polymorphisms at position 105 in GSTP1. The AG+GG genotype was found more frequently in gastric cancer than in the control group and the ORs for homozygotes of Val105Ile was 1.416. This result was in accordance with domestic serological reports [14]. The enzymatic activity of GSTP1 is influenced by polymorphisms in amino acid position 105 located in the hydrophobic substrate binding site that can affect catalytic activity, nucleophilic addition, and epoxide conjugation. The detoxification activity of the enzyme would be decreased by the GSTP1 Val 105 polymorphism; thus, the many carcinogens that enter the human body would be more likely to affect other genes, increasing the risk of gastric cancer. More recently, it has been shown that GSTP-π (encoded by *GSTP1*) acts as a regulator of mitogen-activated protein kinases [30]. In physiologic conditions, GSTP-π is an endogenous inhibitor of c-jun NH_2-terminal kinase (JNK) through interactions with the N-terminal region of the kinase. It has been hypothesized that under oxidative stress or UV radiation GSTP-π oligomerizes and disassociates from JNK, which then becomes phosphorylated. C-JUN and JNK are set from the oligomerization, which can induce cancer formation [31]. GSTP-π can also modulate the activation of p38 and extracellular-regulated kinase (ERK) [32]. The role of GSTP in the carcinogenesis of gastric cancer requires further clarification.

Furthermore, we analyzed the relationship between GSTP1 genotype and the clinicopathological parameters of gastric cancer. The variant genotype AG+GG in the gastric cancer group showed no significant difference with respect to gender, gross classification, tumor size (diameter), infiltration depth, and lymph node metastasis. However, the ratio of the AG+GG genotype was higher in subjects aged 50 years or older. Our data suggested that people older than 50 years with GSTP1 polymorphism had an increased risk of gastric cancer. The occurrence of gastric cancer is a long-term and cumulative result of the effects of carcinogenic factors. The presence of a *GSTP1* gene mutation that reduces the protective role of

GST π would increase susceptibility to gastric cancer. We also observed that the variant genotype AG+GG in the gastric cancer group was associated with the high differentiation group vs. the poor and moderate differentiation group, with 3.559- and 6.015-fold increased risk respectively. We previously reported that the expression of GST-π was higher in the well-differentiated group than in the moderate and low differentiation groups [33]. Moreover, there was hardly any expression in the poorly differentiated sample. This suggested that the mutant *GSTP1* gene might decrease detoxification in the host, leading to susceptibility to poorly differentiated gastric cancer. We also found that the variant genotype AG+GG in gastric cancer was associated with diffuse type compared with intestinal type; the risk of diffuse type gastric cancer was increased 2.210-fold. This suggested that the polymorphism of *GSTP1* was associated with the histology of gastric cancer. The mutant form of GSTP1 may induce transformation of normal cells into cancer, especially the diffuse type. Therefore, it might be possible to use *GSTP1* mutation as the breakthrough point to detect genes changes upstream and downstream of GSTP1 and determine the mechanism of gastric cancer.

In conclusion, the GSTP1 AG and GG genotype (i.e., at least one G allele) increased the risk of gastric cancer, and was associated with differentiation, diffuse type of cancer, and patient age; however, there were no significant associations with sex, gross classification, tumor size (diameter), infiltration depth, and lymph node metastasis.

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Disclosure of conflict of interest

None.

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