RESEARCH ARTICLE

Association Between the GSTP1 Codon 105 Polymorphism and Gastric Cancer Risk: an Updated Meta-analysis

Li-Dao Bao[1], Jian-Xiang Niu[2], Hui Song[3], Yi Wang[1], Rui-Lian Ma[1], Xian-Hua Ren[1], Xin-Lin Wu[2]*

Abstract

Objective: The current meta-analysis was performed to address a more accurate estimation of the association between glutathione S-transferase P1 (GSTP1) codon 105 polymorphism and risk of gastric cancer (GC), which has been widely reported with conflicting results. Methods: A comprehensive literature search was conducted to identify all the relevant studies. Fixed or random effect models were selected based on the heterogeneity test. Publication bias was estimated using Begg's funnel plots and Egger's regression test. Results: A total of 20 studies containing 2,821 GC cases and 6,240 controls were finally included in the analyses. Overall, no significant association between GSTP1 polymorphism and GC risk was observed in worldwide populations. However, subgroup analysis stratified by ethnicity showed that GSTP1 polymorphism was significantly associated with increased risk of GC in Asians (G vs. A, OR = 1.273, 95%CI=1.011-1.605; GG vs. AA, OR=2.103, 95%CI=1.197-3.387; GG vs. AA+AG, OR =2.103, 95%CI=1.186-3.414). In contrast, no significant association was found in Caucasians in any genetic models, except for with AG vs. AA (OR=0.791, 95%CI=0.669-0.936). Furthermore, the GSTP1 polymorphism was found to be significantly associated with GC in patients with *H. pylori* infection and in those with a cardiac GC. Subgroup analysis stratified by Lauren's classification and smoking status showed no significant association with any genetic model. No studies were found to significantly influence the pooled effects in each genetic mode, and no potential publication bias was detected. Conclusions: This meta-analysis suggested that the GSTP1 polymorphism might be associated with increased risk of GC in Asians, while GSTP1 heterozygote genotype seemed to be associated with reduced risk of GC. Since potential confounders could not be ruled out completely, further studies are needed to confirm these results.

Keywords: GSTP1 - gastric cancer - gene polymorphism - *Helicobacter pylori*

Asian Pacific J Cancer Prev, **13**, 3687-3693

Introduction

Gastric cancer (GC) is the fourth most common malignancies in the world and the second leading cause of cancer death (Catalano and Graziano, 2011). Despite the decline in the number of cases, GC remains one of the leading causes of death in Korea and other East-Asian countries such as Japan and China (Hong et al., 2006). Like other malignant tumors, the conventional therapeutic methods including surgical, chemotherapy and radiotherapy gives little hope for restoration of health because of poor diagnosis and serious side effects. In this perspective, early screening of the risk factors may be an effective mans of primary prevention for GC.

At present, GC has been well-known as a multistep and multifactorial process involving different components. Environmental factors including dietary habits, smoking, drinking, and helicobacter pylori infection have been found to be associated with the development of GC (Fuchs and Mayer, 1995; Neugut et al., 1996). Among these factors, *H.pylori* has been established as a definite carcinogen for the development of GC by the World Health Organization (WHO) (Humans, 1994). However, only about 1% of infected individuals develop GC, and the GC incidence is lower in some countries with high prevalence of H.pylori infections such as India, Bangladesh, Pakistan, and Thailand (Graham et al., 1991; Parsonnet et al., 1997; Singh and Ghoshal, 2006). These discrepancies may be attributed to the diverse host's genetic makeup.

Glutathione S-transferases (GSTs) are dimeric proteins encoded by a family of distinct genes and responsible for the metabolism of many electrophlic compounds. GSTs are important phase II enzymes, which could catalyze the conjugation of mutagenic electrophilic compounds with reduced glutathione forming less toxic and more water-soluble compounds (Ketterer, 1988). GSTP1 is a member of the GST superfamily, which plays an important role in the inactivation of toxic and carcinogenic electrophiles. An A/G single nucleotide polymorphism (SNP) located within the substrate-binding domain of GSTP1 results

*[1]Department of Pharmacy, [2]Department of General Surgery Affiliated Hospital of Inner Mongolia Medical University, Hohhot City, Inner Mongolia, [3]Department of Medicine of Jinan Central Hospital, and Medical School of Shandong University, Jinan City, Shandong Province, China *For correspondence: 349881704@qq.com*

in an amino acid substitution of isoleucine by valine (Ile105Val), which could influence the enzyme activity (Ali-Osman et al., 1997). The Val105 form of GSTP1 enzyme may be 2-3 times less stable than the canonical Ile105 form and may be associated with a higher level of DNA adducts (Rebbeck, 1997; Johansson et al., 1998).

In the past decades, there has been increasing interest in the study of the association between GSTP1 polymorphism and the risk of GC. However, these studies provided conflicting results. Some studies indicated that the GSTP1 val allele was associated with increased risk of GC (Zhang et al., 2007; Zendehdel et al., 2009; Deng et al., 2011; Jiang et al., 2011), while other studies showed no association (Wideroff et al., 2007; Kang et al., 2008; Nguyen et al., 2010; Yadav et al., 2010), and even associated with reduced risk of GC (Martinez et al., 2006). To make a more accurate estimate of the association between GSTP1 and risk of GC, we performed a meta-analysis from all eligible studies.

Materials and Methods

Literature and search strategy

A computerized literature search was conducted to identify the relevant available studies published in English or Chinese from 5 databases including PubMed, ISI Web of Science, China National Knowledge Infrastructure (CNKI), Database of Chinese Scientific and Technical Periodicals (VIP), and China Biology Medical literature database (CBM). The search strategy to identify all possible studies involved use of combinations of the following key words: ("glutathione S-transferase P1" or "GST P1") and ("gastric" or "stomach") and ("cancer" or "tumor" or "carcinoma") and "polymorphism". The reference lists of review articles, clinical trials, and meta-analyses were also hand-searched for the collection of other relevant studies. If more than one article were published using the same case series, only the study with largest sample size was selected. The literature search was updated on May 1, 2012.

Inclusion criteria

The studies included must meet the following criteria: (1) evaluating the association between GSTP1 polymorphisms and the risk of GC; (2) case-control or cohort design; (3) providing sufficient data for calculation of odds ratio (OR) with the corresponding 95% confidence interval (95%CI). When genotype frequencies and OR with 95%CI were all not available, authors were contacted to request the relevant information. All identified studies were carefully reviewed independently by two investigators to determine whether an individual study was eligible for inclusion in this meta-analysis.

Data extraction

Data were extracted independently by two investigators who reached a consensus on all of the items. The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity of the study population; (5) source of control subjects; (6) numbers of cases and controls; (7) gender and age of enrolled subjects; and (8) numbers of genotypes in cases and controls.

Statistical analysis

We use χ^2 analysis with exact probability to test departure from Hardy-Weinberg equilibrium (HWE) for the genotype distribution. The association between GSTP1 polymorphisms and GC was estimated by calculating pooled ORs and 95%CI. The significance of the pooled effect size was determined by Z test. Heterogeneity among studies was assessed using Q test as well as the I^2 statistic (Higgins and Thompson, 2002). The DerSimonian and Laird random effect model (REM) was used as the pooling method when $I^2 > 50\%$, otherwise, the Mantel-Haenszel fixed effect model (FEM) was considered to be the appropriate choice (Higgins and Thompson, 2002). Subgroup analyses were stratified by ethnicity, H.pylori infection status, smoking habit, and the location and Lauren's classification of GC. Cumulative meta-analysis was performed to assess whether the combined estimate changed in the same direction over time (Lau et al., 1992). Influential analysis was undertaken by removing an individual study each time to check whether any of single study could bias the overall estimate (Tobias, 1999). Begg's funnel plots and Egger's regression test were undertaken to assess the potential publication bias (Harbord et al., 2006). Probability less than 0.05 was judged significant except for the I^2 statistic. Data analysis was performed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of studies

82 relevant studies concerning GSTP1 polymorphisms and GC were identified. Of these, 59 studies were excluded by reading titles and abstracts. Of the remaining 23 studies, one study was meta-analysis (Zhou et al., 2009), while two studies were excluded due to duplication or reporting other GSTP1 polymorphism (Alves et al., 2000; Tripathi et al., 2011). Thus, 20 studies met the inclusion criteria. All the included studies used blood samples for DNA extraction. Genotyping was performed by using PCR-RFLP, real-time PCR, or Taqman SNP genotyping assay. These studies were performed in a wide range of geographical settings leading to a diversity of racial groups. Among them, 11 studies were performed in Asian countries including China (Setiawan et al., 2001; Roth et al., 2004; Mu et al., 2005; Zhang et al., 2007; Deng et al., 2011; Jiang et al., 2011; Zhang et al., 2011), Japan (Katoh et al., 1999), Vietnam (Nguyen et al., 2010), and Korea (Hong et al., 2006; Kang et al., 2008), while 9 studies were conducted in Caucasians including Sweden (Zendehdel et al., 2009), Indian (Tripathi et al., 2008; Malik et al., 2009; Yadav et al., 2010), Spain (Martinez et al., 2006), Turkey (Tamer et al., 2005), Poland (Lan et al., 2001), and USA (Wideroff et al., 2007). Genotype distribution in control groups were in HWE except for 4 studies (Katoh et al., 1999; Tamer et al., 2005; Jiang et al., 2011; Zhang et al., 2011).The detailed characteristics of the included studies were shown in the Table 1.

Table 1. Characteristics of Individual Studies Included in the Meta-analysis

Authors	Year	Country	Ethnicity	Genotyping method	No. of case/control (M/F)	Genotypes distribution						PHWE[a]
						Case			Control			
						AA	AG	GG	AA	AG	GG	
Jiang	2011	China	Asian	PCR-RFLP	(76/22)/(98/51)	79	7	12	108	33	8	0.018
Deng	2011	China	Asian	PCR-RFLP	160/130	80	48	32	104	23	3	0.221
Zhang	2011	China	Asian	CTPP	(122/72)/(243/169)	107	52	35	235	115	62	0.000
Yadav	2010	Inidan	Caucasian	PCR-RFLP	68/270	75	58[b]		173	97[b]		NA[c]
Nguyen	2010	Vietman	Asian	Taqman	(47/12)/(75/34)	30	28[b]		65	43[b]		NA[c]
Zendehdel	2009	Sweden	Caucasian	Pyrosequencing	(110/16)/(389/82)	47	56	19	208	207	38	0.175
Malik	2009	Indian	Caucasian	PCR-RFLP	(90/18)/(139/56)	62	36	10	111	75	9	0.410
Tripathi	2008	Indian	Caucasian	PCR-RFLP	(64/24)/(66/23)	46	26	4	52	36	12	0.153
Kang	2008	Korea	Asian	PCR-RFLP	(261/139)/(499/304)	271	110	16	547	235	19	0.287
Zhang	2007	China	Asian	PCR-RFLP	(145/55)/(596/227)	119	46	35	513	283	27	0.108
Wideroff	2007	USA	Caucasian	Taqman	114/206	52	46	16	91	94	21	0.649
Ruzzo	2007	Italy	Caucasian	PCR-RFLP	90/122	49	30	11	53	61	8	0.082
Hong	2006	Korea	Asian	PCR-RFLP	(66/42)/(119/119)	66	38	4	158	74	6	0.439
Martinez	2006	Spain	Caucasian	Taqman	86/220	61	23	2	107	90	23	0.532
Tamer	2005	Turkey	Caucasian	PCR	(47/23)/(115/89)	38	23	9	90	74	40	0.001
Mu	2005	China	Asian	PCR-RFLP	(138/68)/(287/128)	125	62	9	265	116	12	0.872
Roth	2004	China	Asian	Taqman	(37/53)/(252/202)	56	27	7	283	142	29	0.057
Lan	2001	Poland	Caucasian	PCR-RFLP	(200/104)/(275/152)	142	133	25	177	202	42	0.153
Setiawan	2001	China	Asian	PCR-RFLP	81/419	61	19	1	296	115	8	0.407
Katoh	1996	Japan	Asian	PCR-RFLP	(98/42)/(72/50)	99	36	5	93	24	5	0.047

[a]p for Hardy–Weinberg equilibrium test in controls; [b]these data represents the total number of AA and AG; [c]the HWE test could not be performed; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism

Table 2. Summary of ORs for Various Genetic Contrasts on the Association Between GSTP1 Polymorphism and Risk of GC

Contrasts	Comparisons	No. of studies	Test of association			Test of heterogeneity	
			OR	95%CI	Statistical model	I^2 (%)	p value[a]
G vs. A	Overall	18	1.066	(0.892-1.275)	REM	79	0.000
	Asians	10	1.273	(1.011-1.605)*	REM	77.8	0.000
	Population-based	6	1.182	(1.041-1.340)*	FEM	45.2	0.104
	Hospital-based	4	1.532	(0.833-2.815)	REM	89.8	0.000
	Caucasians	8	0.857	(0.676-1.088)	REM	71.3	0.000
	Population-based	7	0.883	(0.681-1.144)	REM	73.4	0.001
	Hospital-based	1	0.683	(0.451-1.035)	----	----	---
GG vs. AA	Overall	18	1.395	(0.938-2.075)	REM	74.7	0.000
	Asians	10	2.013	(1.197-3.387)**	REM	71.8	0.000
	Population-based	6	1.757	(0.886-3.487)	REM	71.2	0.004
	Hospital-based	4	2.543	(0.939-6.889)	REM	78.4	0.003
	Caucasians	8	0.921	(0.544-1.561)	REM	67.8	0.003
	Population-based	7	0.999	(0.562-1.776)	REM	68.6	0.004
	Hospital-based	1	0.533	(0.236-1.206)	---	---	---
AG vs. AA	Overall	18	0.899	(0.758-1.066)	REM	57.5	0.001
	Asians	10	1.009	(0.788-1.292)	REM	65.6	0.002
	Population-based	6	0.937	(0.798-1.101)	FEM	9.3	0.356
	Hospital-based	4	1.050	(0.528-2.089)	REM	84.1	0.000
	Caucasians	8	0.791	(0.669-0.936)**	FEM	27.3	0.211
	Population-based	7	0.796	(0.669-0.948)*	FEM	37.3	0.144
	Hospital-based	1	0.736	(0.403-1.344)	---	---	---
GG vs. AA+AG	Overall	18	1.465	(1.001-2.145)	REM	74.0	0.000
	Asians	10	2.103	(1.186-3.414)**	REM	73.6	0.000
	Population-based	6	1.750	(0.833-3.679)	REM	76.1	0.001
	Hospital-based	4	2.439	(0.986-6.035)	REM	74.6	0.008
	Caucasians	8	1.033	(0.640-1.669)	REM	64.1	0.007
	Population-based	7	1.121	(0.666-1.885)	REM	64.5	0.010
	Hospital-based	1	0.605	(0.277-1.320)	---	---	---
GG + AG vs. AA	Overall	20	1.105	(0.855-1.206)	REM	67.1	0.000
	Asians	11	1.180	(0.945-1.473)	REM	65.6	0.001
	Population-based	6	1.060	(0.912-1.233)	FEM	0	0.783
	Hospital-based	5	1.375	(0.796-2.375)	REM	83.1	0.000
	Caucasians	9	0.842	(0.656-1.080)	REM	61.8	0.007
	Population-based	8	0.862	(0.658-1.130)	REM	64.9	0.006
	Hospital-based	1	0.665	(0.385-1.147)	---	---	---

[a]p value for heterogeneity based on Q test; FEM, fixed effect model; REM, random effect model; *P<0.05, **P<0.01

Table 3. Subgroup Analysis of the Association Between GSTP1 Polymorphism and Risk of GC

Contrasts	Comparisons	No. of studies	Test of association			Test of heterogeneity	
			OR	95%CI	Statistical model	I^2 (%)	p value[a]
G vs. A	Overall	18	1.066	(0.892-1.275)	REM	79	0.000
	Asians	10	1.273	(1.011-1.605)*	REM	77.8	0.000
	Population-based	6	1.182	(1.041-1.340)*	FEM	45.2	0.104
	Hospital-based	4	1.532	(0.833-2.815)	REM	89.8	0.000
	Caucasians	8	0.857	(0.676-1.088)	REM	71.3	0.000
	Population-based	7	0.883	(0.681-1.144)	REM	73.4	0.001
	Hospital-based	1	0.683	(0.451-1.035)	----	----	---
GG vs. AA	Overall	18	1.395	(0.938-2.075)	REM	74.7	0.000
	Asians	10	2.013	(1.197-3.387)**	REM	71.8	0.000
	Population-based	6	1.757	(0.886-3.487)	REM	71.2	0.004
	Hospital-based	4	2.543	(0.939-6.889)	REM	78.4	0.003
	Caucasians	8	0.921	(0.544-1.561)	REM	67.8	0.003
	Population-based	7	0.999	(0.562-1.776)	REM	68.6	0.004
	Hospital-based	1	0.533	(0.236-1.206)	---	---	---
AG vs. AA	Overall	18	0.899	(0.758-1.066)	REM	57.5	0.001
	Asians	10	1.009	(0.788-1.292)	REM	65.6	0.002
	Population-based	6	0.937	(0.798-1.101)	FEM	9.3	0.356
	Hospital-based	4	1.050	(0.528-2.089)	REM	84.1	0.000
	Caucasians	8	0.791	(0.669-0.936)**	FEM	27.3	0.211
	Population-based	7	0.796	(0.669-0.948)*	FEM	37.3	0.144
	Hospital-based	1	0.736	(0.403-1.344)	---	---	---
GG vs. AA+AG	Overall	18	1.465	(1.001-2.145)	REM	74.0	0.000
	Asians	10	2.103	(1.186-3.414)**	REM	73.6	0.000
	Population-based	6	1.750	(0.833-3.679)	REM	76.1	0.001
	Hospital-based	4	2.439	(0.986-6.035)	REM	74.6	0.008
	Caucasians	8	1.033	(0.640-1.669)	REM	64.1	0.007
	Population-based	7	1.121	(0.666-1.885)	REM	64.5	0.010
	Hospital-based	1	0.605	(0.277-1.320)	---	---	---
GG + AG vs. AA	Overall	20	1.105	(0.855-1.206)	REM	67.1	0.000
	Asians	11	1.180	(0.945-1.473)	REM	65.6	0.001
	Population-based	6	1.060	(0.912-1.233)	FEM	0	0.783
	Hospital-based	5	1.375	(0.796-2.375)	REM	83.1	0.000
	Caucasians	9	0.842	(0.656-1.080)	REM	61.8	0.007
	Population-based	8	0.862	(0.658-1.130)	REM	64.9	0.006
	Hospital-based	1	0.665	(0.385-1.147)	---	---	---

[a]p value for heterogeneity based on Q test; FEM, fixed effect model; REM, random effect model; *P<0.05, **P<0.01

Quantitative data synthesis

Results of pooled analysis on the associations between GSTP1 polymorphism and the risk of GC were shown in Table 2. Overall, the combined results showed no significant association between GSTP1 polymorphism and GC in worldwide populations. However, when stratifying by ethnicity, the pooled results showed that GSTP1 val allele was significantly associated with increased risk of GC in Asians (G vs. A, OR = 1.273, 95%CI=1.011-1.605). Significant association was also found in genotype contrasts (GG vs. AA, OR=2.103, 95%CI=1.197-3.387; GG vs. AA+AG, OR =2.103, 95%CI=1.186-3.414) (Figure 1). The results were not significantly altered after excluding the study deviated from HWE or by excluding studies in which the 95%CI did not overlap the lines of the pooling results. In contrast, no significant association was found in Caucasians in any genetic models, except for the AG vs. AA (OR=0.791, 95%CI=0.669-0.936). However, when we excluded the study by Martinez et al.(Martinez et al., 2006), the unique study in which the GSTP1 val/val genotype was found to be related with reduced GC, the significant association was disappeared (OR=0.841, 95%CI=0.705-1.003).

As H. pylori infection, smoking, location and classification of GC might be potential confounders, we further investigated the association between GSTP1 polymorphism and GC in subgroup analysis stratified by the above parameters. As shown in Table 3, GSTP1 polymorphism was found to be significantly associated with GC in patient with H. pylori infection (G vs. A, OR=1.238, 95%CI=1.009-1.520; GG vs. AA, OR=2.837, 95%CI=1.631-4.963; GG vs. AA+AG, OR=3.049, 95%CI=1.766-5.261), which was not observed in patient without H. pylori infection (G vs. A, OR=0.920, 95%CI=0.578-1.465; GG vs. AA, OR=1.742, 95%CI=0.601-5.050; GG vs AA+AG, OR=2.101, 95%CI=0.780-5.660). Significant association was also found in cardia GC (G vs. A, OR=1.306, 95%CI=1.025-1.663; GG vs. AA, OR=1.921, 95%CI = 1.138-3.242; GG vs. AA+AG, OR=1.779, 95%CI=1.092-2.899), but not in non-carida GC. Subgroup analysis stratified by Lauren's classification showed no significant association between GSTP1 polymorphism and GC, which might be associated with the limited studies included. As the studies reporting the smoking status only provided the numbers of genotype AA and the sum of AG and GG, thus we only performed the analysis in dominant genetic model (AG/GG vs. AA), but did not found significant association.

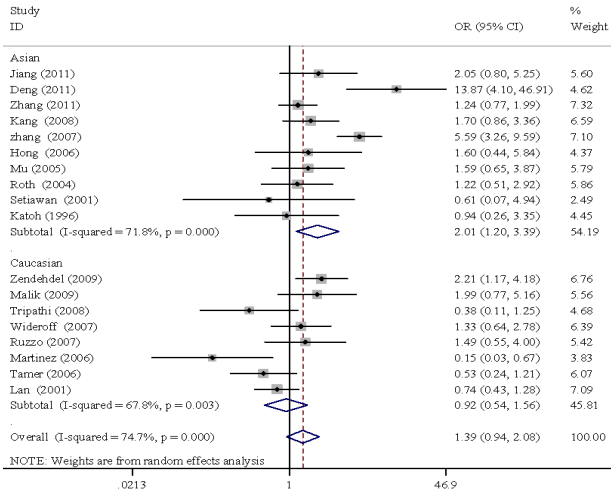

Figure 1. Meta-analysis for GSTP1 Polymorphism and the Risk of GC (GG vs. AA). Each study was shown by a point estimate of the effect size (OR) (size inversely proportional to its variance) and its 95% confidence interval (95%CI) (horizontal lines). The white diamond denotes the pooled OR

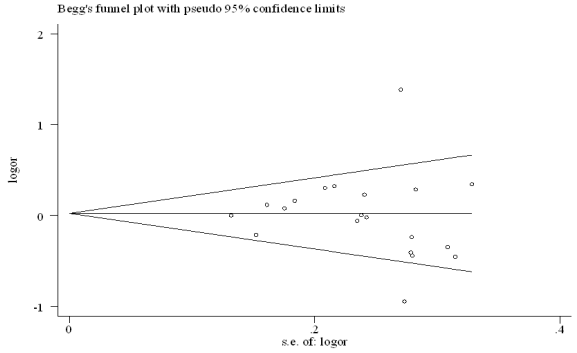

Figure 2. Begg's Funnel Plot with the Egger's Test for Publication Bias of GSTP1 Polymorphisms and the Risk of GC (GG vs. AA). The horizontal line in the funnel plot indicates the fixed-effects summary estimate, whereas the diagonal lines pseudo-95% CI limits about the effect estimate. In the absence of publication bias, studies will be distributed symmetrically above and below the horizontal line

Influence analysis and cumulative analysis

After excluding studies that deviated from HWE in controls, and those in which 95%CI did not overlap the lines of the pooling results, no other studies were found to significantly influence the pooled effects in each genetic model. In the cumulative meta-analysis, no particular time trend was found in the summary estimate.

Publication bias

Funnel plots were generated to assess publication bias. The Egger's test was performed to statistically evaluate funnel plot symmetry. The results suggested no publication bias for the association of the GSTP1 polymorphisms and the risk of GC ($P_{Egger\ test}$ = 0.776 for GG vs. AA) (Figure 2).

Discussion

The incidence and mortality of GC have fallen dramatically over the past several decades, but GC remains a major public health issue as the fourth most common cancer and the second leading cause of cancer death worldwide (Crew and Neugut, 2006).The wide geographic variation of GC in terms of incidence and mortality indicates the role of genetic and environmental factors in the pathogenesis of this cancer. Human cytosolic GSTs are important phage II metabolizing enzymes that detoxify free radicals and other carcinogens. GST polymorphisms have been shown to be related with colorectal cancer, breast cancer, as well as GC. Although increasing studies about the association between GSTP1 polymorphism and the risk of GC were performed in the recent several decades, however, conflicting results were obtained ranging from strong links to no association. The divergent results may be attributed to the differences in racial origin of the population, the *H. pylori* infection, smoking, alcohol drinking, location and classification of GC, etc (Brenner et al., 2009). Because of the above-mentioned conflicting results from relatively small studies underpowered to detect the effects, a meta-analysis should be an appropriate approach to obtain a more definitive conclusion.

In this study, a total of 20 studies containing 2821 gastric cancer cases and 6240 controls were finally included in the analyses for the association between the GSTP1 polymorphisms and the risk of GC. The data showed that GSTP1 polymorphism was significantly associated with increased risk of GC in Asians (G vs. A, OR = 1.273, 95%CI=1.011-1.605; GG vs. AA, OR=2.103, 95%CI=1.197-3.387; GG vs. AA+AG, OR =2.103, 95%CI=1.186-3.414), although no significant association was found in worldwide population and in Caucasians. The results were not significantly altered after excluding the study deviated from HWE or by excluding studies in which the 95%CI did not overlap the lines of the pooling results, indicating the robustness of the results. In the subgroup analysis, GSTP1 polymorphism was found to be significantly associated with GC in patient with H. pylori infection (G vs. A, OR=1.238, 95%CI=1.009-1.520; GG vs. AA, OR=2.837, 95%CI=1.631-4.963; GG vs. AA+AG, OR=3.049, 95%CI=1.766-5.261) and in patient with cardiac GC(G vs. A, OR=1.306, 95%CI=1.025-1.663; GG vs. AA, OR=1.921, 95%CI = 1.138-3.242; GG vs. AA+AG, OR=1.779, 95%CI=1.092-2.899), but was not observed in patient without H. pylori infection and in patient with non-cardia GC. Subgroup analysis stratified by Lauren's classification and smoking status showed no significant association in each genetic model, which might be related with the limited studies included.

To the best of our knowledge, this is the second meta-analysis addressing the associations between the GSTP1 polymorphisms and the risk of GC. The first meta-analysis performed by Zhou et al. included 10 studies (Katoh et al., 1999; Setiawan et al., 2001; Mu et al., 2005; Tamer et al., 2005; Hong et al., 2006; Martinez et al., 2006; Ruzzo et al., 2007; Wideroff et al., 2007; Zhang et al., 2007; Tripathi et al., 2008), which were all included in our meta-analysis. The current meta-analysis also included an additional 10 studies primarily published between 2008 and 2012. The meta-analysis by Zhou et al. (2009) did not found significant association between GSTP1 polymorphism and risk of GC in worldwide populations, which was similar to the results of the current study. However, the current study revealed that GSTP1 val allele might be associated

with increased risk of GC in Asians by analyzing 11 studies, while the previous meta-analysis did not found significant association in Asians from 5 studies. The previous meta-analysis found that patients with GC had a significantly higher frequency of AA (OR = 1.53, 95% CI = 1.14, 2.06) and lower frequency of AG (OR = 0.70, 95% CI = 0.55, 0.89) than non-cancer patients among Caucasians. A similar result was found in this study (AG vs. AA, OR=0.791, 95%CI=0.669-0.936). These data indicated that GSTP1 val/val genotype might be associated with increased risk of GC in Asians, while GSTP1 val/ile genotype might be associated with reduced risk of GC in Caucasians. In fact, the prevalence of different GSTP1 genotypes varies between different populations and ethnic groups. For example, in Western studies, 7-11% of the study populations have been reported to have the GSTP1 G/G genotypes (Wideroff et al., 2007). However, in Asia these genotypes have been reported to be present in 1.9-3% (Setiawan et al., 2001). This discrepancy in GSTP1 genotypes may be related with the observed different influence on the risk of GC.

Despite the clear strengths of our study such as the larger sample size comparing with the previous individual ones, it dose have some limitations. First, the present meta-analysis was based primarily on unadjusted effect estimates and CIs (since most studies did not provide the adjusted OR and 95%CI controlling for potential confounding factors), thus the effect estimates were relatively imprecise. Second, the gene-gene and gene-environment interactions were not addressed in this meta-analysis, and thus the potential roles of the above gene polymorphism may be masked or magnified by other gene-gene/gene-environment interactions. Thirdly, it has been well-known that the GST enzymes have overlapping substrate specificities, and it has been suggested that individual deficiencies in some isoforms can be compensated by others if they are not functionally hampered by genetic polymorphisms. Thus, its possible that deficiencies of certain GST isoenzymes (such as GSTP1) may be compensated by others isoforms such as GSTM (Setiawan et al., 2001). Lastly, although the funnel plot and Egger's test showed no publication bias, selection bias may also exist because only published studies in English or Chinese were retrieved.

In summary, this updated meta-analysis systematically analyzed the association between GSTP1 polymorphisms and the risk of GC. The data clearly showed that the GSTP1 valval genotype significantly increased the risk of GC in Asians. In contrast, GSTP1 heterozygote genotype seemed to be associated with reduced risk of GC. Due to the limited studies and the potential confounders, further studies were needed to confirm these results.

Acknowledgements

The author(s) declare that they have no competing interests.

References

Ali-Osman F, Akande O, Antoun G, Mao JX, Buolamwini J (1997). Molecular cloning, characterization, and expression in Escherichia coli of full-length cDNAs of three human glutathione S-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. *J Biol Chem*, **272**, 10004-12.

Alves C, Silva F, Gusmao L, et al (2000). Extended structural variation of a pentanucleotide repeat in the GSTP1 gene: characterisation in a normal population and in thyroid and gastric tumours. *Eur J Hum Genet,* **8**, 540-4.

Brenner H, Rothenbacher D, Arndt V (2009). Epidemiology of stomach cancer. *Meth Mol Biol*, **2**, 467-78.

Catalano V, Graziano F (2011). Management of Advanced Gastric Cancer. *Chemotherapy*, **?**, 28-43.

Crew KD, Neugut AI (2006). Epidemiology of gastric cancer. *World J Gastroenterol*, **12**, 354-62.

Deng SL, Yuan T, Chen M, et al (2011). Relationship between the polymorphism of GSTP1 and susceptibility to gastric cancer in southwest Chinese. *China J Mod Med*, **21**, 73-4.

Fuchs CS, Mayer RJ (1995). Gastric carcinoma. *N Engl J Med*, **333**, 32-41.

Graham DY, Adam E, Reddy GT, et al (1991). Seroepidemiology ofHelicobacter pylori infection in India. *Digestive Dis Sci,* **36**, 1084-8.

Harbord RM, Egger M, Sterne JA (2006). A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*, **25**, 3443-57.

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

Hong SH, Kim JW, Kim HG., et al (2006). Glutathione S-transferases (GSTM1, GSTT1 and GSTP1) and N-acetyltransferase 2 polymorphisms and the risk of gastric cancer. *J Prev Med Public Health*, **39**, 135-40.

Humans IWGotEoCRt (1994). Schistosomes, Liver Flukes and Helicobacter pylori. Lyon, France.

Jiang YL, Zhu XQ, Xu L (2011). Relationship between gastric cancer and glutathione S-transferase P1 gene polymorphism in the elderly. *Chin J Geriatr*, **30**, 651-3.

Johansson AS, Stenberg G, Widersten M, Mannervik B (1998). Structure-activity relationships and thermal stability of human glutathione transferase P1-1 governed by the H-site residue 1051. *J Mol Biol*, **278**, 687-98.

Kang JM, Kim N, Cho SI, et al (2008). Effects of Genetic Polymorphisms of Glutathione S-transferase P1 on Helicobacter pylori-associated Gastric Cancer. *Gut Liver,* **2**, 23-9.

Katoh T, Kaneko S, Takasawa S, et al (1999). Human glutathione S-transferase P1 polymorphism and susceptibility to smoking related epithelial cancer; oral, lung, gastric, colorectal and urothelial cancer. *Pharmacogenetics*, **9**, 165-9.

Ketterer B (1988). Protective role of glutathione and glutathione transferases in mutagenesis and carcinogenesis. *Mutat Res,* **202**, 343-61.

Lan Q, Chow WH, Lissowska J, et al (2001). Glutathione S-transferase genotypes and stomach cancer in a population-based case-control study in Warsaw, Poland. *Pharmacogenetics*, **11**, 655-61.

Lau J, Antman EM, Jimenez-Silva J, et al (1992). Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med,* **327**, 248-54.

Malik MA, Upadhyay R, Mittal RD, et al (2009). Role of xenobiotic-metabolizing enzyme gene polymorphisms and interactions with environmental factors in susceptibility to gastric cancer in Kashmir Valley. *J Gastrointest Cancer*, **40**, 26-32.

Martinez C, Martin F, Fernandez JM, et al (2006). Glutathione S-transferases mu 1, theta 1, pi 1, alpha 1 and mu 3 genetic polymorphisms and the risk of colorectal and gastric cancers

in humans. *Pharmacogenomics*, **7**, 711-8.
Mu LN, Lu QY, Yu SZ, et al (2005). Green tea drinking and multigenetic index on the risk of stomach cancer in a Chinese population. *Int J Cancer*, **116**, 972-83.
Neugut AI, Hayek M, Howe G (1996). Epidemiology of gastric cancer. *Semin Oncol*, **23**, 281-91.
Nguyen TV, Janssen MJ, van Oijen MG, et al (2010). Genetic polymorphisms in GSTA1, GSTP1, GSTT1, and GSTM1 and gastric cancer risk in a Vietnamese population. *Oncol Res*, **18**, 349-55.
Parsonnet J, Friedman G, Orentreich N, Vogelman H (1997). Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. *Gut*, **40**, 297-301.
Rebbeck TR (1997). Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. *Cancer Epidemiol Biomarkers Prev*, **6**, 733-43.
Roth MJ, Abnet CC, Johnson LL, et al (2004). Polymorphic variation of Cyp1A1 is associated with the risk of gastric cardia cancer: a prospective case–cohort study of cytochrome P-450 1A1 and GST enzymes. *Cancer Causes Control,* **15**, 1077-83.
Ruzzo A, Canestrari E, Maltese P, et al (2007). Polymorphisms in genes involved in DNA repair and metabolism of xenobiotics in individual susceptibility to sporadic diffuse gastric cancer. *Clin Chem Lab Med*, **45**, 822-8.
Setiawan VW, Zhang ZF, Yu GP, et al (2001).GSTP1 polymorphisms and gastric cancer in a high-risk Chinese population. *Cancer Causes Control,* **12**, 673-81.
Singh K, Ghoshal UC (2006).Causal role of Helicobacter pylori infection in gastric cancer: an Asian enigma. *World J Gastroenterol*, **12**, 1346-51.
Tamer L, Ates NA, Ates C, et al (2005).Glutathione S-transferase M1, T1 and P1 genetic polymorphisms, cigarette smoking and gastric cancer risk. *Cell Biochem Funct*, **23**, 267-72.
Tobias A (1999). Assessing the influence of a single study in the meta-analysis estimate. *Stata Tech Bull*, **7**, 15-7.
Tripathi S, Ghoshal U, Ghoshal UC, et al (2008). Gastric carcinogenesis: Possible role of polymorphisms of GSTM1, GSTT1, and GSTP1 genes. *Scand J Gastroenterol*, **43**, 431-9.
Tripathi S, Ghoshal U, Mittal B, et al (2011). Association between gastric mucosal glutathione-S-transferase activity, glutathione-S-transferase gene polymorphisms and Helicobacter pylori infection in gastric cancer. *Indian J Gastroenterol*, **30**, 257-63.
Wideroff L, Vaughan TL, Farin FM, et al (2007). GST, NAT1, CYP1A1 polymorphisms and risk of esophageal and gastric adenocarcinomas. *Cancer Detect Prev*, **31**, 233-6.
Yadav DS, Devi TR, Ihsan R, et al (2010). Polymorphisms of glutathione-S -transferase genes and the risk of aerodigestive tract cancers in the Northeast Indian population. *Genet Test Mol Biomarkers,* **14**, 715-23.
Zendehdel K, Bahmanyar S, McCarthy S, et al (2009). Genetic polymorphisms of glutathione S-transferase genes GSTP1, GSTM1, and GSTT1 and risk of esophageal and gastric cardia cancers. *Cancer Causes Control*, **20**, 2031-8.
Zhang A, Liu B, Wang L, et al (2011). Glutathione S-transferase Gene Polymorphisms and Risk of Gastric Cancer in a Chinese Population. *Asian Pac J Cancer Prev*, **12**, 3421-5.
Zhang Y, Sun LP, Chen W, et al (2007). A molecular epidemiological study on the relationship between the polymorphism of GSTP1 and susceptibility to gastric cancer in northern Chinese. *Yi Chuan,* **29**, 293-300.
Zhou Y, Li N, Zhuang W, et al (2009). Glutathione S-transferase P1 gene polymorphism associated with gastric cancer among Caucasians. *Eur J Cancer*, **45**, 1438-42.