RESEARCH ARTICLE

Lack of Association of the *MDR1* C3435T Polymorphism with Susceptibility to Gastric Cancer and Peptic Ulcer: a Systemic Review and Meta-analysis

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Abstract

Background: The multidrug resistance 1 gene (*MDR1*) C3435T polymorphism has been demonstrated to influence the P-glycoprotein (P-gp) activity level which is related to inflammation and carcinogenesis. This meta-analysis was performed to estimate the association between the *MDR1* C3435T polymorphism and the risk of gastric cancer (GC) and peptic ulcer (PU). Materials and Methods: A literature search was conducted with PubMed, Embase and the Cochrane library up to November 2013. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association. Data were analyzed using Review Manager (Version 5.2), and Stata package (version 12.0) for estimation of publication bias. Results: Six case-control studies were included, of which five were for GC and two for PU. Overall, no evidence was found for any association between the *MDR1* C3435T polymorphism and the susceptibility to GC and PU. In the stratified analysis by *H. pylori* infection status, stage and histology classification of GC, and PU type, there was still no significant association between them. Conclusions: This meta-analysis suggested that the *MDR1* C3435T polymorphism is not associated with susceptibility to GC and PU. Large and well-designed studies are warranted to validate our findings.

Keywords: Gastric cancer - peptic ulcer - gastric ulcer - duodenal ulcer - *MDR1* - polymorphism - meta-analysis

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Introduction

Peptic ulcer (PU), including gastric ulcer (GU) and duodenal ulcer (DU), remains a relatively common condition worldwide with annual incidence up to 0.19% (Sung et al., 2009), and patients with GU significantly increase the chance of developing gastric cancer (GC). GC is not only the fourth most common type of cancer in males and fifth in females globally, but also the third leading cause of death due to cancer in 2010 (Jernal et al., 2011; Lozano et al., 2012). *Helicobacter pylori* (*H. pylori*) infection, which is strongly related to GC and PU, is now recognized as a worldwide problem. Some specific genotypes of *H. pylori* have been reported to be associated with GC and PU, such as vacA d1 genotype (Basiri et al., 2014). Besides the infection with *H. pylori*, some genetic factors also play important roles in the occurrence of GC and PU. Up to now, a wide range of gastrointestinal cancer susceptibility genes have been identified, such as murine double mimute 2 (*Mdm2*) T309G, matrix metalloproteinase (*MMP*) gene, survivin gene -31G>C, epidermal growth factor (*EGF*) gene +61A>G, X-ray repair cross-complementing 1 (*XRCC1*) gene, Toll-like receptor 4 (*TLR4*) gene +896A/G, etc. (Song et al., 2013; Li et al., 2013; Liu et al., 2013; Piao et al., 2013; Wu et al., 2013; Zou et al., 2013;). The multidrug resistance 1 gene (*MDR1*), also named *ABCB1*, was suggested to be a candidate gene (located at 7q21.1) for the pathogenesis of GC and PU (Sugimoto et al., 2008).

P-glycoprotein (P-gp) encoded by *MDR1* is one of the most widely studied ATP-binding membrane transporters and expressed in normal cells of various organs such as intestine, liver, kidney, brain and placenta. Since it is involved in absorption and elimination of xenobiotics and drugs, it has a protective function in various cells and tissues/organs. Furthermore, P-gp probably plays a role in regulating cell death, differentiation and proliferation, as well as in immune response. With the decrease of P-gp activity level, inflammation and carcinogenesis may occur (Johnstone et al., 2000; Ho et al., 2003; Mizutani et al., 2008). C3435T SNP (rs1045642), one of the most popular *MDR1* polymorphisms, is located in exon 26 as a silent mutation. C3435T encodes isoleucine and affects the expression and function of P-gp both *in vitro* and *in vivo* (Breier et al., 2005).

To date, many studies that investigated the association between the *MDR1* C3435T polymorphism and risk of PU or GC have produced contradictory or inconclusive

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results in that each study had limited sample size and was not enough to demonstrate the association (Tahara et al., 2007; Sugimoto et al., 2008; Sabahi et al., 2010; Chang et al., 2010; Tahara et al., 2011; Oliveira et al., 2012). In order to estimate the risk of *MDR1* C3435T polymorphism associated with GC and PU, we carried out a meta-analysis on all eligible case-control studies.

Materials and Methods

Search strategy

All studies published in English that investigated the association between *MDR1* C3435T polymorphism and the risk to PU or GC were identified by searching from PubMed, Embase and The Cochrane Library up to November 2013. The following search criteria were used: ("multidrug resistance 1 gene" or "*MDR1*" or "*ABCB1*") AND ("gastric cancer" or "peptic ulcer" or "duodenal ulcer" or "gastric ulcer") AND ("association" or "risk" or "susceptibility"). The search was restricted to humans. Other potential eligible studies were recognized by looking through the references listed in the retrieved articles or textbooks. Disagreements were resolved through discussion between the authors.

Inclusion and exclusion criteria

Studies met the following criteria were included in our meta-analysis: (a) case-control study focused on association between *MDR1* C3435T polymorphism and risk to GC or PU, (b) contained available genotype frequency for both cases and controls, (c) all patients diagnosed with GC should be confirmed by pathological or histological examinations, (d) all patients diagnosed with PU had endoscopical and/or histological proofs, and (e) the *H. pylori* infection status was determined on the basis of histology, culture, urea breath test (UBT) or serum antibodies to *H. pylori*.

Studies were mainly excluded for the following reasons: (a) not a case-control study, (b) duplicated publications, (c) based on incomplete data, (d) not for human research, and (e) meta-analyses, letters, reviews or editorial articles.

Data extraction and quality assessment

Two of the authors extracted data independently according to the same standard. In the cases of conflicting, agreement was reached after a discussion. If conflicts still existed, an expert (Dong WG) would be invited to help make decisions. Following variables were collected from each study: the first author's name, year of publication, country of origin, ethnicity, source of controls (population or hospital based controls), genotyping method, sample sizes of genotyped cases and controls, histological classification of GC, clinical stage of GC, and *H. pylori* infection status. Subjects of different ethnicity were categorized as Caucasian and Asian.

Statistical analysis

Meta-analysis was performed by using the Cochrane Collaboration RevMan 5.2 (Copenhagen, 2013) and Stata package version 12.0 (Stata Corporation, College Station, Texas). Before estimating effect of *MDR1* C3435T polymorphism, the Hardy-Weinberg equilibrium (HWE) was calculated by employing a goodness-of-fit chi-square test for the control group of each study. HWE was accessed using Online software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) with the significance set at a p value less than 0.05. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the *MDR1* C3435T polymorphism and GC and PU risk. The pooled ORs were performed for dominant model (TT+TC *vs* CC), co-dominant models (TT *vs* CC, TC *vs* CC), and recessive model (TT *vs* TC+CC). The degree of heterogeneity between the studies was estimated using Cochran's Q-statistic with a p-value and I^2 test, ranging from 0 to 100%, which represents the proportion of inter-study variability (Higgins et al., 2002; Zintzaras et al., 2005). When a significant Q-test ($p<0.05$) or I^2 test ($I^2>50\%$) indicates heterogeneity among studies, the random effects model (DerSimonian Laird method) would be employed for meta-analysis (DerSimonian et al., 1986). On the contrary, the fixed effects model (Mantel-Haenszel method) would be used (Mantel et al., 1959) [21]. Sensitivity analysis was also performed to assess the stability of the results by omitting each single study at one time, which reflects the influence of each study data set on the summary ORs. To test the publication bias, both Funnel plots and Egger's linear regression test were used (Begg et al., 1994; Egger et al., 1997).

Results

Study characteristics

The combined search yielded 27 references. A total of six articles were ultimately included. The flow chart of study selection was summarized in Figure 1. The publication year of involved studies ranged from 2007 to 2012. Overall, there were one study about both GC and PU, four about GC, and one about PU. Four of these studies were conducted in Asian populations and two were in Caucasian populations. The total number of GC cases and controls were 496 and 724, respectively, and 554 cases and 548 controls concerned PU. In three studies, GC was classified to diffuse and intestinal type according to Lauren's classification (Lauren et al., 1965). Two studies also reported the tumor stages (Early stages include I, IIA, and IIB; Advanced stages include IIIA, IIIB, IIIC, and IV). *H. pylori* infection status was reported for cases and controls in two studies. The distribution of genotypes (includes TT, TC, CC) among the controls of the studies was in agreement with HWE for most except

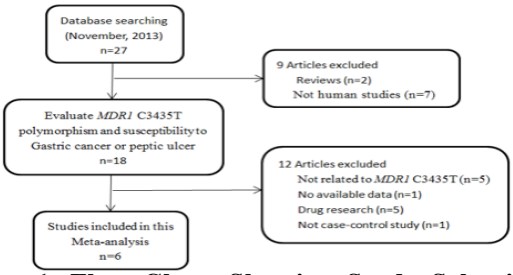

Figure 1. Flow Chart Showing Study Selection Procedure

Table 1. Charateristics of Studies Included in the Meta-analysis

Study	Year	Country	Ethnicity	Source of controls	Genotyping method	Case			Control				
						TT	TC	CC	TT	TC	CC	P_{HWE}*	T freq
GC													
Tahara	2007	Japan	Asian	HB[$]	PCR-RFLP	23	95	39	33	43	28	0.08	0.52
Sugimoto	2008	Japan	Asian	HB	PCR-RFLP	28	73	49	23	96	49	0.03	0.42
Sabahi	2010	Iran	Caucasian	HB	PCR-RFLP	21	18	9	33	75	23	0.08	0.54
Chang	2010	Korea	Asian	PB[&]	Sequencing	3	10	30	51	14	53	0	0.49
Oliveira	2012	Brazil	Caucasian	PB	PCR-RFLP	15	51	32	39	97	67	0.71	0.43
PU													
Sugimoto	2008	Japan	Asian	HB	PCR-RFLP	GU 42 DU 36	GU 117 DU 81	GU 56 DU 46	23	96	49	0.03	0.42
Tahara	2011	Japan	Asian	HB	PCR-RFLP	GU 27 DU 9	GU 52 DU 30	GU 37 DU 21	69	188	123	0.85	0.43

*HWE, Hardy-Weinberg equilibrium, PHWE was calculated by goodness-of fit chi-square test, P_{HWE}<0.05 was considered statistically significant, which means the controls of the studies wasn't in agreesment with HWE; [$]HB hospital-based controls; [&]PB population-based controls

Table 2. MDR1 C3435T Genotypes of Population in Different Clinic Factors of Gastric Cancer

Clinic factors		Studies	Case or Control	Genotypes		
				TT	TC	CC
Stage	Early/Advanced*	Tahara 2007	Case	14/10	413/53	19/20
		Sabahi 2010	Case	6/8	6/10	4/5
Histology	Intestinal/ Diffuse[#]	Tahara 2007	Case	12/11	45/45	19/20
		Sugimoto 2008	Case	22/6	51/22	38/11
		Sabahi 2010	Case	4/9	3/10	0/9
H.pylori infection	HP+/HP-[&]	Tahara 2007	Case	22/1	84/11	33/6
			Control	21/11	34/10	22/6
		Oliveira 2012	Case	15/17	23/28	5/10
			Control	41/26	49/48	21/18

*Early stage includes I, IIA, and IIB, Advanced stage includes IIIA, IIIB, IIIC, and IV; [#]Histology according to Lauren's classification; [&]HP+, *H. pylori* positive; HP-, *H. pylori* negative

Table 3. Summary of OR of the MDR1 C3435T Polymorphism and Gastric Cancer an Peptic Ulcers

Disease	Variables	Studies	Dominant model[&]		Recessive model[#]		TT *vs* CC		TC vs CC	
			OR (95% CI)	$P^{\S}$	OR (95% CI)	$P^{\S}$	OR (95% CI)	$P^{\S}$	OR (95% CI)	$P^{\S}$
GC	Total	5	0.85 (0.65, 1.10)	0.15	0.68 (0.28, 1.62)	<0.00001*	0.66 (0.32, 1.38)	0.003	1.02 (0.77, 1.35)	0.31
	Asian	3	0.73 (0.41, 1.31)	0.05	0.41 (0.11, 1.57)	<0.0001	0.44 (0.13, 1.48)	0.002	1.05 (0.74, 1.50)	0.17
	HP+	2	1.41 (0.83, 2.41)	0.6	0.67 (0.40, 1.10)	0.24	0.92 (0.48, 1.75)	0.27	1.74 (0.98, 3.07)	0.78
	HP-	2	0.91 (0.44, 1.86)	0.42	0.38 (0.03, 4.93)	0.02	0.41 (0.03, 4.94)	0.05	1.06 (0.50, 2.28)	0.96
	Early	2	0.95 (0.53, 1.73)	0.47	0.88 (0.26, 3.04)	0.06	0.72 (0.35, 1.48)	0.53	0.93 (0.33, 2.68)	0.15
	Advanced	2	1.04 (0.59, 1.84)	0.52	0.67 (0.13, 3.48)	0.007	0.60 (0.29, 1.22)	0.22	1.15 (0.43, 3.09)	0.14
	Intestinal	3	0.82 (0.55, 1.21)	0.63	1.33 (0.55, 3.21)	0.06	0.90 (0.28, 2.87)	0.04	0.84 (0.56, 1.28)	0.48
	Diffuse	3	0.99 (0.45, 2.16)	0.06	0.85 (0.39, 1.85)	0.09	0.87 (0.48, 1.60)	0.81	1.01 (0.33, 3.06)	0.008
PU	Total	2	1.04 (0.79, 1.37)	0.63	1.36 (0.98, 1.90)	0.31	1.32 (0.90, 1.92)	0.32	0.96 (0.71, 1.28)	0.82
	GU	2	1.09 (0.79, 1.50)	0.68	1.44 (0.99, 2.09)	0.77	1.43 (0.93, 2.19)	0.64	0.99 (0.71, 1.39)	0.66
	DU	2	0.98 (0.68, 1.41)	0.67	1.24 (0.56, 2.73)	0.09	1.18 (0.55, 2.52)	0.15	0.91 (0.62, 1.34)	0.92

[$]Test for heterogeneity; *Random effects model was used when the *P* for heterogeneity test was<0.05 or I^2 for heterogeneity >50%, otherwise Fixed effects model was used; [&]Dominant model, TT/TC *vs* CC; [#]Recessive model, TT *vs* TC/CC

two studies (Sugimoto et al., 2008; Chang et al., 2010). All studies conducted a PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) assay to investigate the C3435T polymorphism of *MDR1* except one (Chang et al., 2010), which used sequencing of PCR products. The detailed characteristics of the included studies were summarized in Table 1, 2.

Association between MDR 1 C3435T polymorphism and gastric cancer and peptic ulcer

Five studies reported the association between *MDR1* C3435T polymorphism and susceptibility to GC. Overall, there was no significant difference in genotype C3435T distribution between GC and control (TT+TC *vs* CC: OR=O.85, 95%CI: 0.65-1.10, *p*=0.15; TT *vs* TC+CC: OR=0.68, 95%CI: 0.28-1.62, *p*<0.00001; TT *vs* CC: OR=0.66, 95%CI: 0.32-1.38, *p*=0.003; TC *vs* CC: OR=1.02, 95%CI: 0.77-1.35, *p*=0.31). In the subgroup analysis by *H. pylori* infection status, there was no significant association in each model, and so was it in the subgroup analysis by ethnicity, stage of GC, and histological classification of GC (Table 3, Figure 2).

Only two studies reported the association between C3435T polymorphism and susceptibility to PU, all patients came from Asian population. Overall, no association was found between C3435T polymorphism and susceptibility to PU in four models (TT+TC *vs* CC: OR=1.04, 95%CI: 0.79-1.37, *p*=0.63; TT *vs* CT+CC: OR=1.36, 95%CI: 0.98-1.90, *p*=0.31; TT *vs* CC: OR=1.32, 95%CI: 0.90-1.92, *p*=0.32; TC *vs* CC: OR=0.96,

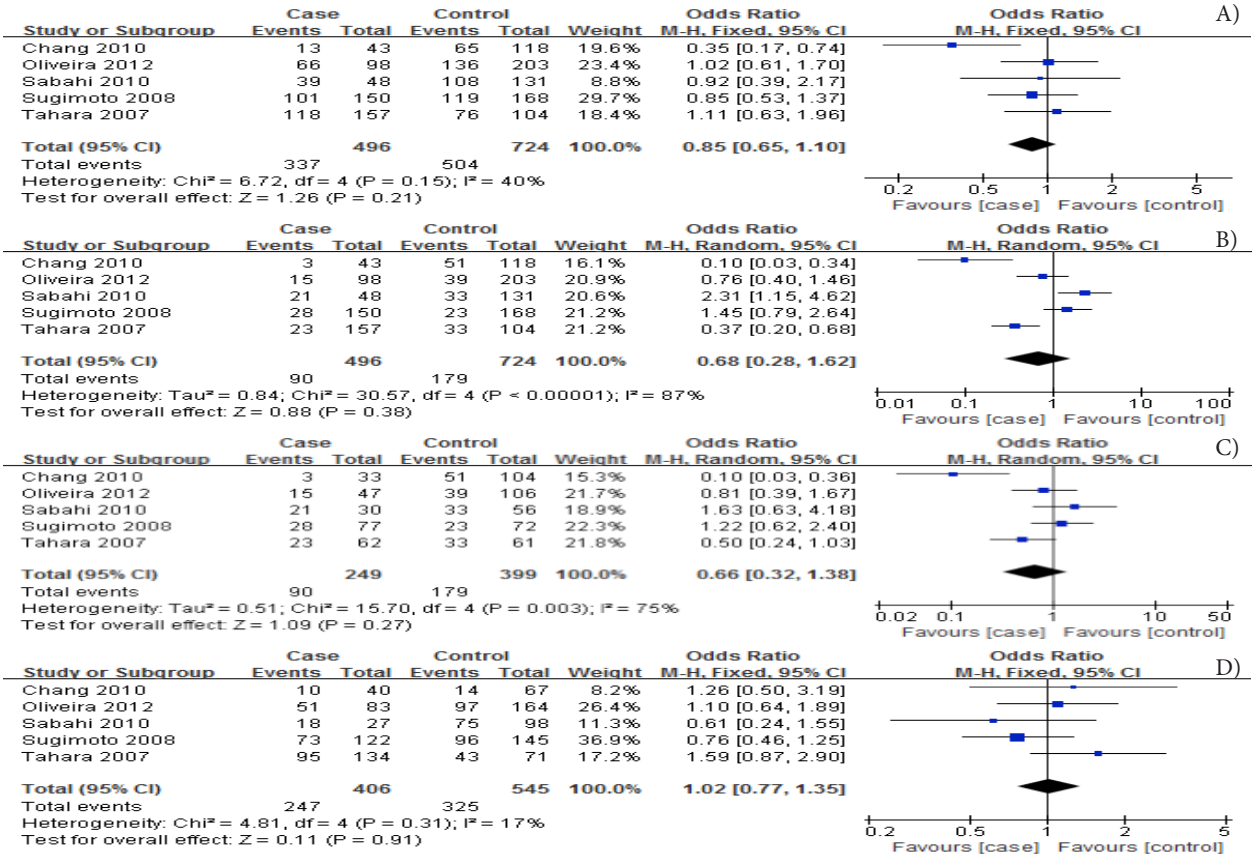

Figure 2. Meta-analysis of the Association between MDR1 C3435T Polymorphism and Susceptibility to Gastric Cancer. A) Dominant model. **B)** Recessive model. **C)** TT *vs* CC. **D)** TC *vs* CC.

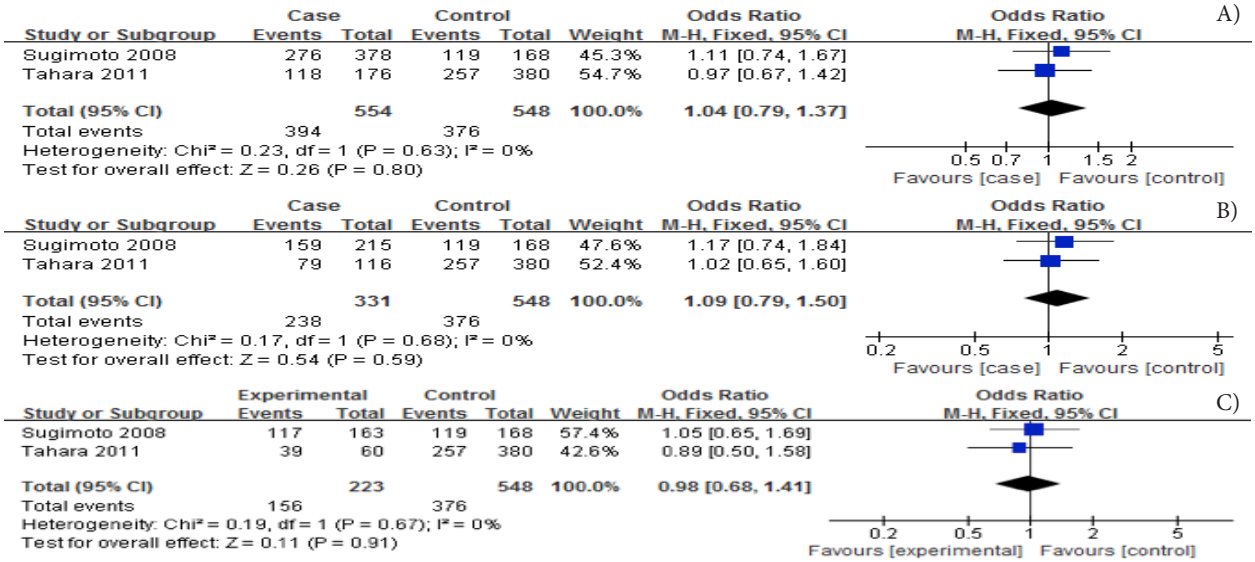

Figure 3. Meta-Analysis of the Association between C3435T Polymorphism and Susceptibility to PU in Dominant Model. A) PU. **B)** GU. **C)** DU.

95%CI:0.71-1.28, *p*=0.82). In the subgroup analysis of GU and DU, the similar results were observed (Table 3, Figure 3).

Sensitivity analysis

To assess the influence of each individual study on the pooled ORs for GC, the sensitivity analysis was performed by omitting each study from meta-analysis sequentially. The results suggested that no single study affected the pooled ORs qualitatively. When deleting the two studies deviated from HWE, no significant association was observed. It suggested that the results of this meta-analysis were stable. For the peptic ulcer, as there were only two studies included, we didn't perform the sensitivity analysis.

Publication bias

The Begg's funnel plot and Egger's test were conducted to assess publication bias among the studies selected for this meta-analysis. As for GC, the shape of

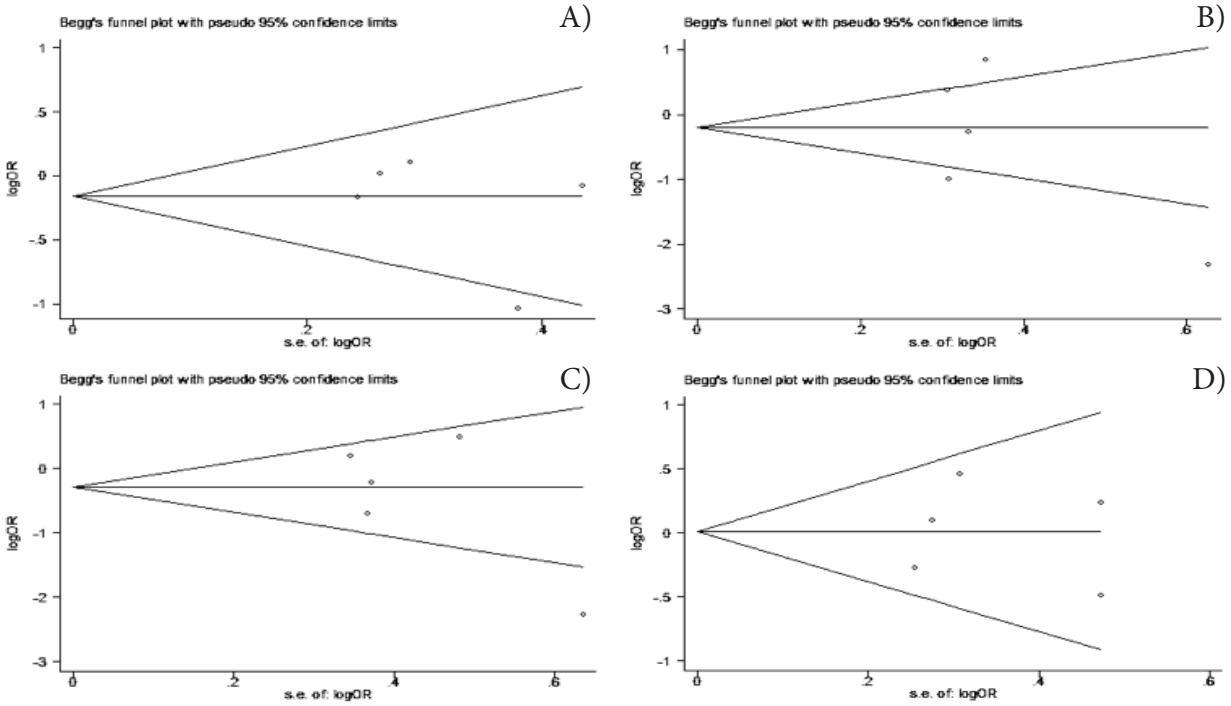

Figure 4. Begg's Funnel Plot for Publication Bias. Each point represents a separate study for the indicated association. logOR, natural logarithm of OR. Horizontal line, mean effect size. **A)** dominant model. **B)** recessive model. **C)** TT *vs* CC. **D)** TC *vs* CC.

the funnel plots revealed no asymmetry, and the Egger's test suggested no publication bias among the studies in four models ($P_{\text{dominant model}}$ =0.021, $P_{\text{recessive model}}$=0.248, $P_{\text{TT vs CC}}$=0.090, $P_{\text{TC vs CC}}$=0.775) (Figure 4). As there were only two studies for the meta-analysis on the association between *MDR1* C3435T polymorphism and risk of PU, we didn't detect the publication bias.

Discussion

The *MDR1* C3435T polymorphism has been demonstrated for its role in regulating the P-glycoprotein (P-gp) activity level which is related to the inflammation and carcinogenesis (Johnstone et al., 2000; Ho et al., 2003; Mizutani et al., 2008). P-gp functions as a transmembrane efflux pump which has an ability to protect the organism against toxic xenobiotic agents and environmental carcinogens (Breier et al., 2005; Yuan et al., 2008). In 2000, Hoffmeyer et al. (2000) first reported that healthy individuals with the *MDR1* 3435TT genotype had lower intestinal expression of P-gp and higher intestinal uptake of the oral digoxin which is a P-gp substrate. Larsen et al. (2007) found that the wild-type C allele of the synonymous polymorphism conferred a higher P-gp activity by increasing duodenal *MDR1* mRNA and P-gp levels. Markova et al. (2006) also showed C3435 allele carriers might be more effective to anti-inflammation of glucocorticoid than non-carriers. It was also supported that *MDR1* C3435T polymorphism may contribute to individual susceptibility to breast cancer, colorectal cancer, and inflammatory bowel disease, respectively (Annese et al., 2006; Wang et al., 2013; Zhang et al., 2013). As for the association between *MDR1* C3435T polymorphism and GC or PU, the results of all available studies are controversial. Tahara et al. (2011) reported that the 3435T carrier was significantly associated with a higher degree of neutrophil infiltration in *H. pylori*-positive subjects. Sabahi et al. (2010) suggested that the polymorphic homozygote (T/T) genotype showed a significant association with the incidence of gastric cancer. However, there were also some reports that found no association between *MDR1* C3435T polymorphism and risk to GC and PU (Sugimoto et al., 2008; Oliveira et al., 2012).

The present meta-analysis included 6 case-control studies, including 496 cases and 724 controls for GC analysis, and 554 cases and 548 controls for PU. As for GC analysis, there was no significant association between *MDR1* C3435T polymorphism and the risk of GC in four genetic models. Although we omitted the two studies inconsistent with HWE and deleted two studies in Caucasian population to avoid the influence of HWE or ethnicity, respectively, there was still no significant association for both. Since *H. pylori* infection status was detected in two studies, we stratified the subjects into two groups, *H. pylori* positive and *H. pylori* negative. However, stratified analysis also indicated no association between *MDR1* C3435T and the susceptibility to GC under all genetic models. In the subgroup analysis by stage and histological classification, similar results were found. For PU analysis, no matter in overall analysis or in subgroup analysis by GU and DU, no evidence showed that *MDR1* C3435T polymorphism was associated with the risk to PU, GU or DU respectively. The sensitivity analysis didn't show any significance. As for publication bias, Begg's funnel plots revealed no asymmetry, and the Egger's test suggested no publication bias among the studies of GC.

Some limitations of this meta-analysis should be addressed. Firstly, GC and PU are complex diseases with a multifactorial etiology, so the contributing pathogenetic role of lifestyle and drugs intake should also be considered. The existence of gene-environment and

gene-gene interactions may explain the discrepancy of results obtained in individual genetic association studies. Secondly, there are only two studies of peptic ulcer included in our studies, which will reduce the statistical potency. Thirdly, two studies for GC and one study for PU are not consistent with HWE, which counted for 40 percent and 50 percent, respectively. When we omitted these studies, the size of left studies was so small, so it's difficult to retrieve dependable results. Fourthly, ages, ratio of males and females, the source of controls and so on, were not matched well that may influence the results greatly. Although we tried to stratified subjectives by age or others, there were not sufficient data. Fifthly, the genotyping methods are not identical for all the investigations in selected studies. Different methods may have different results for the same sample. In spite of these, our meta-analysis also had some advantages. This may be the first meta-analysis to assess the association between *MDR1* C3435T and risk to PU. And this may be also the first analysis to take *H. pylori* infection status and GC classification into consideration. Since our sensitivity analysis indicated that there were no significant changes, the pooled ORs are likely to be reliable.

In summary, this meta-analysis supported evidence that *MDR1* C3435T polymorphism may have no association with risk of GC and PU. In the subgroup analysis by ethnicity, *H. pylori* infection status, stage and histological classification of GC, and type of PU, we obtained the similar results. Because of the above limitation, standardized unbiased genotyping methods, well-matched controls and cases, and containing more subjectives should be introduced in future studies. Also, case-control studies that investigate gene-gene and gene-environment interactions may also help to further elucidate the molecular and genetic epidemiology of cancer predisposition.

References

Annese V, Valvano MR, Palmieri O, et al (2006). Multidrug resistance 1 gene in inflammatory bowel disease: a meta-analysis. *World J Gastroenterol*, **12**, 3636-44.

Basiri Z, Safaralizadeh R, Bonyadi MJ, et al (2014). *Helicobacter pylori* vacA d1 genotype predicts risk of gastric adenocarcinoma and peptic ulcers in Northwestern Iran. *Asian Pac J Cancer Prev*, **15**, 1575-9.

Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-101.

Breier A, Barancik M, Sulova Z, et al (2005). P-glycoprotein-implications of metabolism of neoplastic cells and cancer therapy. *Curr Cancer Drug Targets*, **5**, 457-68.

Chang H, Rha SY, Jeung HC, et al (2010). Association of the *ABCB1* 3435C>T polymorphism and treatment outcomes in advanced gastric cancer patients treated with paclitaxel-based chemotherapy. *Oncol Rep*, **23**, 271-8.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.

Egger M, Davey Smith G, Schneider M, et al (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-34.

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

Ho GT, Moodie FM, Satsangi J (2003). Multidrug resistance 1 gene (*p*-glycoprotein 170): an important determinant in gastrointestinal disease? *Gut*, **52**, 759-66.

Hoffmeyer S, Burk O, von Richter O, et al (2000). Functional polymorphisms of the human multidrug resistance gene multiple sequence variations and correlation of one allele with *p*-glycoprotein expression and activity *in vivo*. *Proc Natl Acad Sci USA*, **97**, 3473-8.

Jemal A, Bray F, Center MM, et al (2011). Global Cancer Statistics. *CA Cancer J Clin*, **61**, 69-90.

Johnstone RW, Ruefli AA, Smyth MJ (2000). Multiple physiological functions for multidrug transporter P-glycoprotein? *Trends Biochem Sci*, **25**, 1-6.

Larsen UL, Hyldahl OL, Olesen L, et al (2007). Human intestinal P-glycoprotein activity estimated by the model substrate digoxin. *Scand J Clin Lab Invest*, **67**, 123-34.

Lauren P (1965). The two histological main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand*, **64**, 31-49.

Li X, Qu L, Zhong Y, et al (2013). Association between promoters polymorphisms of matrix metalloproteinases and risk of digestive cancers: a meta-analysis. *J Cancer Res Clin Oncol*, **139**, 1433-47.

Liu Y, Li L, Qi H, et al (2013). Survivin 231G.C polymorphism and gastrointestinal tract cancer risk: a meta-analysis. *PLoS One*, **8**, 54081.

Lozano R, Naghavi M, Foreman K, et al (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, **380**, 2095-128.

Mantel N, Haenszel W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, **22**, 719-48.

Markova S, Nakamura T, Sakaeda T, et al (2006). Genotype-dependent down-regulation of gene expression and function of *MDR1* in human peripheral blood mononuclear cells under acute inflammation. *Drug Metab Pharmacokinet*, **21**, 194-200.

Mizutani T, Masuda M, Nakai E, et al (2008). Genuine functions of P-glycoprotein (*ABCB1*). *Curr Drug Metab*, **9**, 167-74.

Oliveira J, Felipe AV, Chang PY, et al (2012). Association between the C3435T single-nucleotide polymorphism of multidrug resistance 1 gene and risk of gastric cancer. *Mol Med Rep*, **6**, 395-8.

Piao Y, Liu Z, Ding Z, et al (2013). EGF +61A>G polymorphism and gastrointestinal cancer risk: A HuGE review and meta-analysis. *Gene*, **519**, 26-33.

Sabahi Z, Salek R, Heravi RE, et al (2010). Association of gastric cancer incidence with *MDR1* gene polymorphism in an ethnic Iranian population. *Indian J Cancer*, **47**, 317-21.

Song B, Duan ZY, Zhong YH, et al (2013). Meta-analysis of the MDM2 T309G polymorphism and gastric cancer risk. *Asian Pac J Cancer Prev*, **14**, 6649-51.

Sugimoto M, Furuta T, Shirai N, et al (2008). *MDR1* C3435T polymorphism has no influence on developing *Helicobacter pylori* infection-related gastric cancer and peptic ulcer in Japanese. *Life Sci*, **83**, 301-4.

Sung JJ, Kuipers EJ, El-Serag HB (2009). Systematic review: the global incidence and prevalence of peptic ulcer disease. *Aliment Pharmacol Ther*, **29**, 938-46.

Tahara T, Shibata T, Yamashita H, et al (2011). Influence of *MDR1* polymorphism on *H. pylori*-related chronic gastritis. *Dig Dis Sci*, **56**, 103-8.

Tahara T, Arisawa T, Shibata T, et al (2007). Multi-drug resistance 1 polymorphism is associated with reduced risk of gastric cancer in the Japanese population. *J Gastroenterol*

Hepatol, **22**, 1678-82.
Wang ZM, Wang T, Bian JN (2013). Association between *MDR1* C3435T polymorphism and risk of breast cancer. *Gene*, **532**, 94-9.
Wu H, Xu C, Chen G, et al (2013). *XRCC1* polymorphism and prognosis of platinum-based chemotherapy in gastric and colorectal cancer: a meta-analysis. *J Gastroenterol Hepatol*. [Epub ahead of print]
Yuan H, Li X, Wu J, et al (2008). Strategies to overcome or circumvent P-glycoprotein mediated multidrug resistance. *Curr Med Chem*, **15**, 470-6.
Zhang D, Wang C, Zhou Z (2013). Meta-Analysis of *ABCB1* 3435C>T Polymorphism and Colorectal Cancer. *Pak J Med Sci*, **29**, 1269-74.
Zintzaras E, Ioannidis JP (2005). Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol*, **28**, 123-37.
Zou TH, Wang ZH, Fang JY (2013). Positive association between Toll-like receptor 4 gene +896A/G polymorphism and susceptibility to gastric carcinogenesis: a meta-analysis. *Tumour Biol*, **34**, 2441-50.