RESEARCH ARTICLE

The 765G>C Polymorphism in the Cyclooxygenase-2 Gene and Gastric Cancer Risk: an Update by Meta-analysis

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Abstract

Background: The 765G>C polymorphism in cyclooxygenase-2 (COX-2) gene has been extensively investigated for association with gastric cancer (GC). However, the results of different studies have been inconsistent. The aim of this study is to comprehensively evaluate the genetic risk of -765G>C polymorphism in the COX-2 gene for GC. Materials and Methods: We searched Pubmed, Embase, Medline, CNKI database, Wanfang database, Weipu database, and Chinese Biomedical database, covering all publications (last search been performed on Jan 10, 2014). Statistical analyses were performed using Revman 5.2 and STATA 10.0 software. Results: A total of 1,874 cases and 3,005 controls in 10 case-control studies were included in this meta-analysis. The results indicated that the variant C allele carriers (GC+CC) had a 69% increased risk of GC when compared with the homozygote GG (odds ratio (OR)=1.69, 95% confidence interval (CI), 1.10-2.61 for GC+CC *vs* GG). In the subgroup analysis by ethnicity, significant elevated risks were associated with C allele carriers in Asians (OR=1.75, 95%CI=1.40-2.18, and *p*<0.00001) and in Indians (OR=8.38, 95%CI=4.34-16.16, and *p*<0.00001) but not in Caucasians (OR=1.07, 95%CI=0.81-1.42, and *p*=0.62) or in Dutch (OR=0.53, 95%CI= 0.33-0.87, and *p*= 0.01).In the subgroup analysis by *Helicobacter pylori* (*H. pylori*) status, a significantly increased risk was identified among *H. pylori* (+) (OR=3.58, 95%CI=2.33-3.50, and *p*<0.00001) and *H. pylori* (-) (OR=2.32, 95%CI=1.46-3.69, and *p*=0.0004). Conclusions: This meta-analysis suggested that the -765G>C polymorphism in the COX-2 gene could be a risk factor for GC in Asians and Indians.

Keywords: Cyclooxygenase-2 (COX-2) - gastric cancer - polymorphism - meta-analysis

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Introduction

Gastric cancer (GC) is rampant in many countries around the world. By some estimates, it is the fourth most common cancer and the second leading cause of cancer-related death worldwide (Kamangar et al., 2006; Ajani et al., 2013). In 2013, around 21600 people were diagnosed with GC and approximately 10990 people died of the disease in the United States (Crew et al., 2006). The development of GC is a complex and multi-factorial disease involving genetic variations, environmental exposures, and gene-environment interactions (Wang et al., 2007; Cook et al., 2010; Sethi et al., 2012; Siegel et al., 2013). *Helicobacter pylori* (*H. pylori*) infection, drinking, environmental tobacco smokes and nitrites represent the most important exogenous risk factors. Although these factors have been documented to influence the risk of GC, not all individuals develop the disease, even though they are exposed in the same environment. This indicates that genetic differences, such as variants, may contribute to GC pathogenesis. Therefore, numerous published studies have focused on the association of genetic variants with GC susceptibility (Zhou et al., 2007; Zhou et al., 2008), and among them, cyclooxygenase-2 (COX-2) gene has been extensively studied.

COX-2, an inducible isoform of COX to inflammatory cytokines, only expressed by various stimulus such as growth factors, cytokines, mitogens, is often undetectable in normal tissue, whereas in tumor tissue specimens its expression is observably higher (Bakhle et al., 2001; Cao et al., 2002). In particular, increased COX-2 expression is linked to progression of gastric cancer and precancerous tissues by activating angiogenesis, inhibiting apoptosis, and accelerating invasion and metastasis (Murata et al., 1999; Uefuji et al., 2000; Ohno et al., 2001; Tatsuguchi et al., 2004). Genetic variants, such as single nucleotide polymorphisms (SNPs) in the promoter region of the COX-2 encoding gene, which features guanine (G) converting to cytosine (C) at position -765 bp of the promoter region, affecting transcription activity of -765G>C (rs20417) polymorphism of COX-2 and its functional activity (Szczeklik et al., 2004; Sitarz et al., 2008).

There have been a large number of studies investigating this -765G>C polymorphism with GC risk; however, the results were inconsistent and inconclusive (Liu et al., 2006;

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Shin et al., 2012). Considering a single study may lack the power to provide reliable conclusion, we performed a meta-analysis to investigate these associations. This is, to our knowledge, the most comprehensive meta-analysis of genetics studies on the association between GC susceptibility and the -765G>C polymorphism in COX-2 gene.

Materials and Methods

Literature search

A systematic literature search in Pubmed, Medline (Ovid), Embase, Chinese biomedical database (CBM), China national knowledge infrastructure (CNKI), Weipu, and Wanfang database was carried out to identify studies involving association between the -765G>C polymorphism of COX-2 gene and GC risk (last search was updated on Jan 10, 2014). The search terms were used as follows: "stomach neoplasm or GC" and "COX-2 or PTGS2 or cyclooxygenase-2" in combination with "polymorphism or variant or mutation". The search results were limited to English and Chinese languages. Studies included in our meta-analysis met the following inclusion criteria: (1) evaluation of the -765G>C polymorphism of COX-2 gene and GC risk, (2) the design had to be a case-control study, (3) sufficient data (genotype distributions for cases and controls) to estimate an odds ratio (OR) with its 95% confidence interval (CI), and (4) genotype distributions in control group should be consistent with Hardy-Weinberg equilibrium (HWE). Studies were excluded if one of the following existed: (1) no controls, (2) genotype frequencies or number not reported, and (3) abstracts, reviews, and repeat studies. If more than one article were published by the same authors using the same case series, studies with the largest size of samples or recently published were included.

Data extraction

Two independent reviewers (FZ and HZ) collected the data and reached a consensus on all items. In case of disagreement, a third author would assess these articles. The following items were extracted from each study: first author's name, year of publication, original country, ethnicity, average age, sample size, genotype number in cases and controls, and genotyping method.

Statistical analysis

The strength of association between COX-2-765G>C polymorphism and GC risk was assessed by OR with 95%CI. We first estimated with the risk of dominant model (CC+GC *vs* GG), and then estimated the risks of (C *vs* G). The pooled OR was calculated by a fixed-effects model or a random-effects model according to the heterogeneity. Heterogeneity was checked by a X^2-based Q statistic and $p<0.10$ was considered statistically significant. If the result was $p>0.10$, OR was pooled according to the fixed-effect model; otherwise, the random effect model was used. The statistical significance of OR was analyzed by Z test, and $p<0.05$ was considered as statistically significant. To evaluate the ethnic-specific effects, subgroup analyses was performed by ethnicity. For the subgroup analysis by ethnicity, the study populations were stratified into four groups: Asians, Caucasians, Indians, and Dutch. Sensitivity analysis was also performed by sequence excluding individual study to check the robustness of the result (Zhang et al., 2010). The possible publication bias was examined visually in a Begg's funnel plot and the degree of asymmetry was tested by Egger's test (Begg et al., 1994; Egger et al., 1997; Liu et al., 2010).

HWE was tested by using an internet-based program (Zhang et al., 2010). Statistical analysis was performed using Revman 5.2 and STATA 10.0 softwares (Zhang et al., 2011).

Results

Study inclusion and characteristics

As shown in Figure 1, a total of 57 results were identified after an initial search from the selected electronic databases. After reading the titles and abstracts, 25 potential articles were included for full-text view. After reading full texts, 13 studies were excluded for being irrelevant to GC risk and COX-2-765G>C gene. Then, an additional 2 articles were excluded for repeat or overlapping studies (Zhang et al., 2006; 2011). Finally, a total of 10 case-control studies in 10 articles which met our inclusion criteria were identified, including 1874 cases and 3005 controls. The characteristics of each case-control study are listed in Table 1. Genotype and allele distributions for each case-control study are shown in Table 2. There were 6 case-controls of Asians (Liu et al., 2006; Tang et al., 2009; Zhang et al., 2011; 2012; Li et al., 2012; Shin et al., 2012), 2 of Caucasians (Pereira et al., 2006; Hou et al., 2007), 1 Indians (Saxena et al., 2008) and 1 Dutch (Sitarz et al., 2008). All the included 8 eligible reports were written in English and 2 were written in Chinese language.

Quantitative data synthesis

All studies: As shown in Figure 2, the heterogeneity of (CC+ GC *vs* GG) for all 10 studies was assessed and

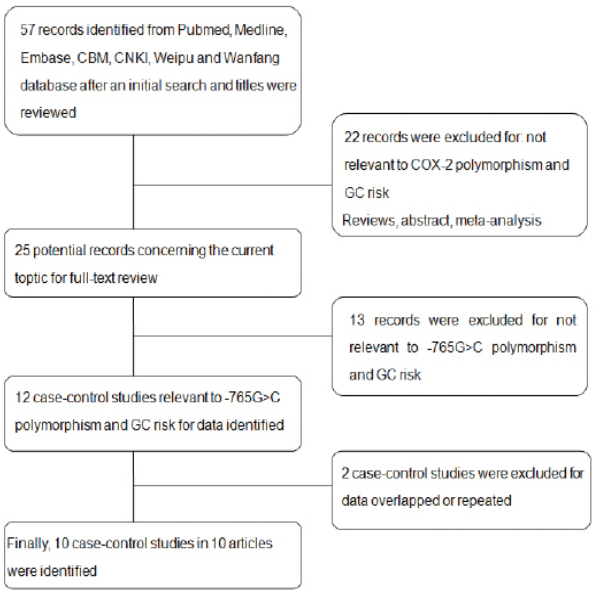

Figure 1. Flow Diagram of Included/ Excluded Studies. GC=Gastric Cancer

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

First author	Year	Country	Ethnicity	Case age age(year)	Cases/ Controls	HP stutas HP(+)	HP(-)	Mixed	Sex M	F	Genotyping method	Quality scores
Pereira et al	2006	Portugal	Caucasians	54.2±11.3	73/ 210	NM	NM	NM	36	37	PCR-RFLP	33
Liu et al	2006	China	Asians	59.0±12.3	247/427	175	73	0	181	67	DHPLC	33
Hou et al	2007	Poland	Caucasians	NM	290/409	NM	NM	NM	NM	NM	TaqMan	33
Saxena et al	2008	India	Indians	56.60±15.42	62/241	35	27	0	47	15	PCR-RFLP	34
Sitarz et al	2008	Netherlands	Dutch	45(21-85)	241/100	NM	NM	NM	NM	NM	PCR-sequence	31
Zhang	2009	China	Asians	NM	142/150	99	43	0	89	53	PCR	27
Tang et al	2009	China	Asians	58.5±11.2	100/105	67	33	0	68	32	PCR-RFLP	29
Zhang et al	2011	China	Asians	NM	323/944	99	55	169	217	106	PCR-RFLP	30
Li et al	2012	China	Asians	44.0±16.6	296/319	214	82	0	127	169	PCR-RFLP	34
Shin et al	2012	Korea	Asians	64.8(26-87)	100/100	28	50	22	83	17	PCR-RFLP	30

*PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; DHPLC, PCR-based denaturing high-performance liquid chromatography; NM, not mentioned; HP(+), H. pylori infection(positive); HP(-), H. pylori infection (negtive)

Table 2. Distribution of COX-2-765G>C Genotype and Allele among Gastric Cancers and Controls

Study	Cases (n)			Controls (n)			Cases (n)		Controls (n)		HWE[1] for control
	CC	GC	GG	CC	GC	GG	C	G	C	G	*p*
Tang et al	9	34	57	5	24	76	52	148	34	176	0.11
Pereira et al	5	32	36	13	67	130	42	104	93	327	0.28
Saxena et al	19	29	14	8	62	171	67	57	78	402	0.42
Liu et al	0	27	220	0	43	384	27	467	43	811	0.27
Hou et al	10	70	210	11	110	288	90	490	132	686	0.9
Sitarz et al	8	57	176	9	32	59	73	409	50	150	0.14
Zhang et al	35	0	288	41	0	903	70	576	82	1806	0.46
Li et al	2	53	241	1	43	275	57	535	45	593	0.62
Shin et al	0	18	82	0	10	90	18	182	10	190	0.6
Zhang	5	24	113	4	11	135	34	250	19	281	0.21

*[1]HWE, Hardy-Weinberg equilibrium

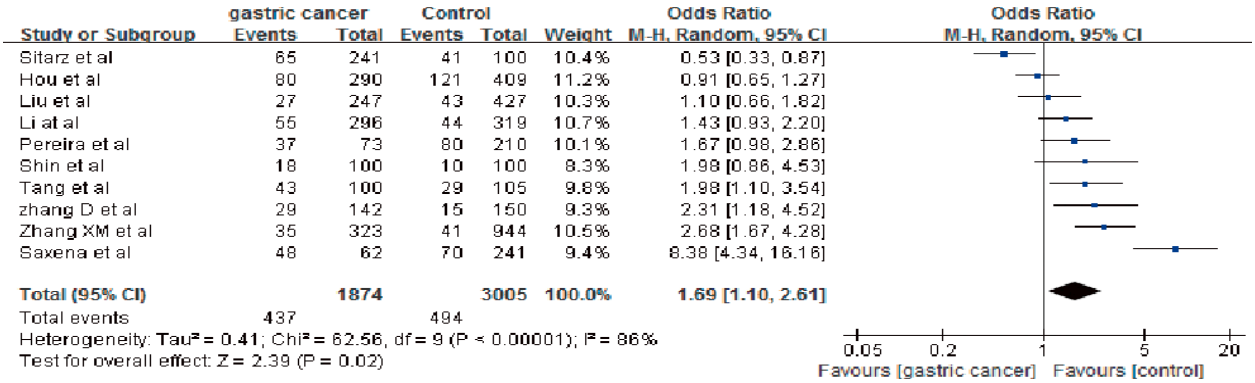

Figure 2. Meta-analysis with a Random-Effects Model for the Association between Gastric Cancer Risk and the COX-2-765G>C Polymorphism (CC+GC *vs* GG). CI=confidence interval; OR, odds ratio

the value of χ^2 was 62.56 with 9 degrees of freedom and $p<0.00001$ in a random-effects model. Additionally, the I-square, which is another index of the test of heterogeneity, was 86%, suggesting a moderate heterogeneity. Thus, we chose the random-effects model to synthesize the data. Overall, OR was 1.69 (95%CI=1.10-2.61), and the test for overall effect Z value was 2.39 (p=0.002) for (CC+GC *vs* GG) model. The results suggested a significant association between the -765G>C polymorphism of COX-2 gene and GC risk.

Subgroup analyses: Subgroup analyses by ethnicity and *H. pylori* status were performed. For ethnicity (GC+CC *vs* GG, Figure 3A), the analysis was stratified into four subgroups: Asians, Caucasians, Indians and Dutch. Significantly increased risks were found among Asians (OR=1.75, 95%CI=1.40-2.18, and p=0.002) and Indians (OR=8.38, 95%CI=4.34-16.16, and $p<0.00001$) but not in Caucasians (OR=1.07, 95%CI=0.81-1.42, and p=0.62) or Dutch (OR=0.53, 95%CI=0.33-0.87, and p=0.01). Similarly, in the subgroup analysis by *H. pylori* status (GC+CC *vs* GG, Figure 3B), the analysis was stratified into two subgroups: *H. pylori* (+), *H. pylori* (-), a significantly increased risk was identified among *H. pylori* (+) (OR=3.58, 95%CI=2.33-3.50, and $p<0.00001$) and *H. pylori* (-) (OR=2.32, 95%CI=1.46-3.69, and p=0.0004). Summary results of other comparisons are listed in Table3.

H. pylori status (+) patients

A total of four case-control studies performed among *H. pylori* status (+) patients were identified in this meta-analysis. Three studies were performed among Asians, and one among Indians. Subgroup analyses was also performed according to ethnicity (GC+CC *vs* GG, figure not shown), significant increased risks of *H. pylori*

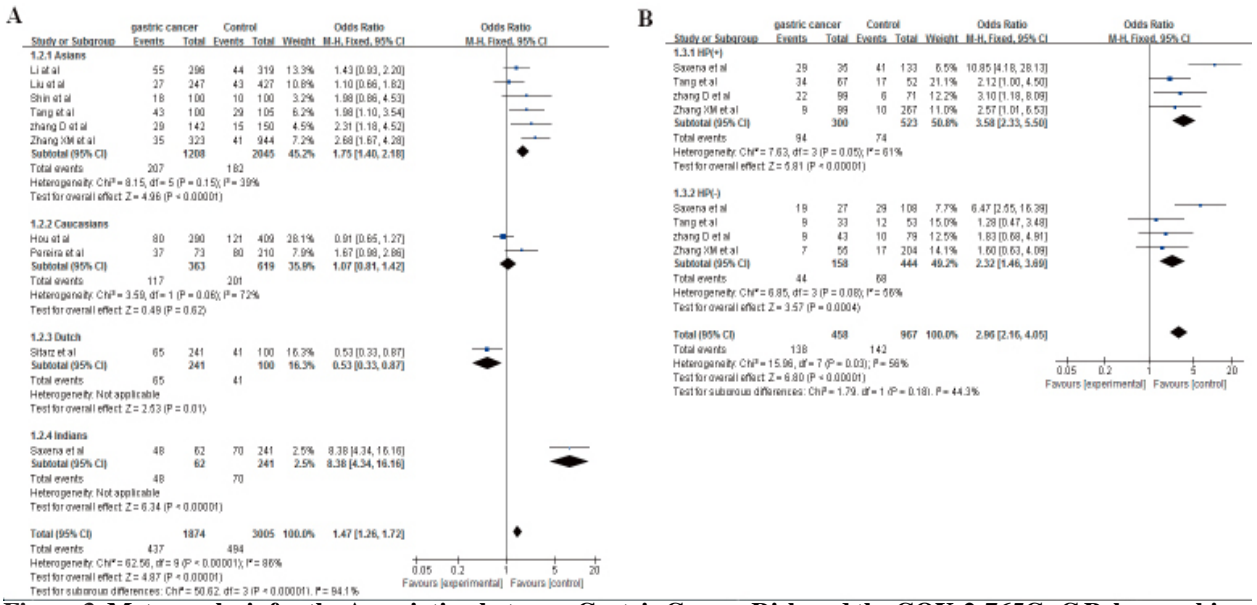

Figure 3. Meta-analysis for the Association between Gastric Cancer Risk and the COX-2-765G>C Polymorphism (CC+GC *vs* GG): A, Subgroup Analysis by Ethnicity; B, Subgroup Analysis by *H. pylori* Status. CI=confidence interval; OR, odds ratio

Table 3. The Meta-analysis for the Associations Between COX-2-765G>C Polymorphism and Risk of GC

Total	10	1874/3005	1.69 (1.10, 2.61)	0.02	1.61 (1.05, 2.48)	0.03
Subgroup by ethnicity						
Asians	6	1208/2045	1.75 (1.40, 2.18)	<0.00001	1.80 (1.49, 2.18)	<0.00001
Caucasians	2	363/619	1.07 (0.81, 1.42)	0.62	1.08 (0.85, 1.37)	0.53
Indians	1	62/241	8.38 (4.34, 16.16)	<0.00001	6.06 (3.95, 9.30)	<0.00001
Dutch	1	241/100	0.53 (0.33, 0.87)	0.01	0.54 (0.36, 0.80)	0.003
Subgroup by HP status						
HP+	4	300/523	3.58 (2.33, 5.50)	<0.00001	NA	NA
Asians	3	265/390	2.50 (1.52, 4.12)	0.0003	NA	NA
Indians	1	35/133	10.85 (4.18, 28.13)	<0.00001	NA	NA
HP-	4	158/444	2.32 (1.46, 3.69)	0.0004	NA	NA

*aP value for Z test; NA not appliable; GC gasric cancer

status (+) patients were found among Asians (OR=2.50, 95%CI=1.52-4.12, p=0.0003) and Indians (OR=10.08, 95%CI=4.18-28.13, p<0.00001). Summary results of comparisons are listed in Table 3.

Heterogeneity, sensitivity analysis

Heterogeneity was determined using the χ^2-based Q-test, and heterogeneity was found in two pooling models (p< 0.00001 in both models), so the random model was utilized to generate a larger pool of studies with 95%CIs. After sequentially excluding each case-control study, statistically similar results were obtained for (GC+CC *vs* GG) (all P values were ≤ 0.05), suggesting the stability of this meta-analysis (Data not shown).

Publication bias

The publication bias was assessed by Begg's funnel plot and Egger's test. The graphical funnel plot of 10 studies of the -765G>C polymorphism of COX-2 gene appeared to be asymmetrical in the (CC+GC *vs* GG) (Figure 4). Publication bias might occur if smaller studies showed no significant results remain unpublished, leading to an asymmetrical appearance of the funnel plot with a gap at the bottom of the graph.

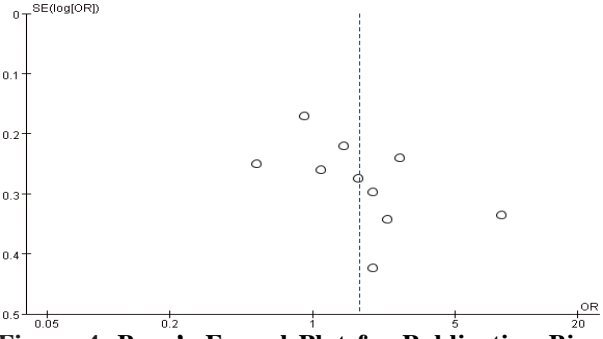

Figure 4. Begg's Funnel Plot for Publication Bias in Selection of Studies on the COX-2-765G>C Polymorphism and Gastric Cancer Risk (CC+GC *vs* GG). OR=odds ratio

Discussion

It is well known that GC is a sophisticated and mutifactorial disease, and both environmental and genetic factors contribute to the pathogenesis of the disease (Berlau et al., 2004; Yaghoobi et al., 2004). There is individual susceptibility to GC even with the same environmental exposure. Genetic factors, including variants in genes involved in the pathogenesis of GC

may contribute to these differences (Goto et al., 2005; Shibata et al., 2010; Sethi et al., 2012; Liu et al., 2013; Chen et al., 2014; Li et al., 2014). Therefore, during the past 10 years, genetic susceptibility evoked researchers' interest, and studies concerning polymorphisms of genes involved in the pathogenesis of GC are expanding each year. The -765G>C polymorphism of the COX-2 gene in the etiology of GC is one of the most widely studied. A large number of studies suggested that this polymorphism is associated with risk of GC. To date, conclusions of the association of COX-2-765G>C polymorphism with GC is still uncertain; thus, we performed a meta-analysis to specifically assess the association. Considering the genetic background may affect the results of meta-analysis, subgroup analyses was performed by ethnicity and *H. pylori* status.

Consistent with the previous meta-analysis (Jiang et al., 2007; Liu et al., 2010; Wen et al., 2013; Wang et al., 2013), we found significant increased risk -765G>C polymorphism with GC, strongly suggesting that this polymorphism may contribute to GC pathogenesis and help to explain individual differences of host susceptibility. After subgroup analyses according to ethnicity, we found that the variant C allele carriers (CC+GC) had a 79% increased risk of GC in Asians, but not in Caucasians. It is possible that different genetic backgrounds may account for these differences. In addition, GC is a sophisticated disease which is also related to environmental factors. Thus, further studies are demanded to assess the effect of gene-environment interactions in different ethnicities and to validate these findings.

When stratified separately according to *H. pylori* status, we found a significant association between this polymorphism with GC risk both in *H. pylori* (+) populations and in *H. pylori* (-) populations. Subgroup analysis was also performed among *H. pylori* (+) populations, significant increased risk of GC was found among Asians and Indians, suggesting a possible role of ethnic differences in genetic backgrounds and etiology. These results indicated no possibility of *H. pylori* status differences in GC pathogenesis. However, there are only four studies for this polymorphism. It is likely that the results may be attributed to chance because a small number of studies may have insufficient statistical power to detect a slight association. Therefore, additional studies are warranted to further validate *H. pylori* status differences in the effect of this polymorphism on GC risk.

Heterogeneity is one of the important issues when performing meta-analysis. We found that heterogeneity between studies existed in overall comparisons. After subgroup analysis by ethnicity, the heterogeneity was effectively decreased or removed in Asians and Indians, suggesting that differences of genetic background existed among different ethnicity, which might account for the heterogeneity of this meta-analysis. The stability of this meta-analysis was analyzed by sequentially excluding individual studies, our results indicated stability of results (Data not shown). To date, there are four independent reports related to meta-analyses of the -765G>C polymorphism with GC risk, all of them showed significant associations. In consistent with previous studies, our results also indicate that this polymorphism may play a major role in GC susceptibility.

Compared with previous meta-analyses, our study has some advantages. First of all, it updates the recent data for this polymorphism and GC risk. Then, this is the first time to study the *H. pylori* status effect on COX-2-765G>C polymorphism. Finally, the methodological issues for meta-analysis, such as heterogeneity, publication bias, and stability of results were all well investigation. The limitations of the present study should be addressed. Firstly, in this study, all eligible studies were published reports written in English and Chinese indexed by the selected databases. It is possible that some potential published studies in other languages or unpublished studies could be missed. Secondly, some studies were excluded due to lack of original data by email from the correspondences; we could not evaluate the potential interactions of gene-gene and gene-environment, which may lead to a selection bias. Thirdly, this meta-analysis included data from Asians, Caucasians ,Indians, and Dutch population, no studies were from Africans; thus, our study may be applicable to only these ethnic groups. And the last, data were not stratified by other factors such as age, gender, lifestyle, drinking and smoking status because insufficient information could be extracted from the primary publication. It is worth mentioning a study published by Gu et al (Gu et al., 2012), the results indicated that COX-2 was also proved to play an important role in inducing the expression of P-glycoprotein in human gastric adenocarcinoma cell line via the NF-kappa B pathway with pacliaxel, which may providing a totally different vision for personalized therapy for GC patients and clinical research.

To determine a precise association between the COX-2-765G>C and GC genetic susceptibility, it is essential to design and perform scientific and rigorous studies with large sample sizes in the future.

In conclusion, to our knowledge, this is the most comprehensive meta-analysis to date to assess relationship between the -765G>C polymorphism in COX-2 gene and GC risk. Our results indicated the COX-2-765G>C polymorphism was significantly associated with increased risk of GC whether or not by *H. pylori* infection, especially for Asians and Indians. Regarding some limitations for this study, therefore the results should be explained with great caution, and more studies should also investigate gene-gene and gene-environment interactions to better display the association between the -765G>C polymorphisms in COX-2 gene and GC risk.

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