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Association between rs20417 polymorphism in cyclooxygenase-2 and gastric cancer susceptibility

Evidence from15 case-control studies

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Abstract

Objective: Previous studies have reported an association between cyclooxygenase-2 (*COX-2*) polymorphism and gastric cancer (GC) susceptibility, but their results are controversial. This meta-analysis was intended to evaluate the relationship between the *COX-2* rs20417 polymorphism and GC susceptibility in different ethnic groups.

Methods: We searched PubMed, EMBASE, Web of Knowledge, and the Chinese Biomedical Database (CBM) for relevant case-control studies published up to October 6, 2018, which reported an association between the *COX-2* rs20417 polymorphism and gastric cancer risk. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of this association.

Results: 15 papers detailing case-control studies were included in the analysis, which included a total of 2848 GC cases and 4962 healthy controls. The meta-analysis results indicated that the *COX-2* rs20417 polymorphism was associated with increased GC susceptibility under allele (G vs C: OR = 1.67, 95%CI = 1.19–2.35, $P = .003$), heterozygous (GG vs CG: OR = 1.44, 95%CI = 1.03–2.02, $P = .034$), dominant (GC+CC vs GG: OR = 1.66, 95%CI = 1.18–2.34, $P = .004$), homozygous (GG vs CC:OR = 2.20, 95%CI = 1.07–4.54, $P = .033$), and recessive models (CC vs GG+CG:OR = 2.05, 95%CI = 1.09–3.85, $P = .025$). An analysis of ethnic subgroups revealed that the *COX-2* rs20417 polymorphism was significantly associated with GC susceptibility in Asians under all 5 models (G vs C: OR = 2.22, 95%CI = 1.66–2.96, $P < .001$; GG vs CC: OR = 4.29, 95%CI = 1.94–9.50, $P < .001$; GG vs CG: OR = 1.86, 95%CI = 1.34–2.58, $P < .001$; CC vs GG+CG: OR = 3.73, 95%CI = 1.92–7.24, $P < .001$; GC+CC vs GG: OR = 2.20, 95%CI = 1.65–2.93, $P < .001$). *Helicobacter pylori* positive patients suffered a high risk of GC, compared to *H pylori* negative patients under the dominant model (OR = 3.09, 95%CI = 1.80–5.32, $P < .001$).

Conclusion: This meta-analysis of 15 case-control studies provides strong evidence that the *COX-2* rs20417 polymorphism increases the risk of GC susceptibility in general populations, especially in Asians. *Helicobacter pylori* positive patients and those with the *COX-2* rs20417 polymorphism had a higher risk of developing GC.

Abbreviations: CI = confidence interval, COX-2 = cyclooxygenase-2, GC = gastric cancer, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, OR = Odds ratio, SNP = single nucleotide polymorphism.

Keywords: cyclooxygenase-2, gastric cancer, polymorphism, rs20417

1. Introduction

With an estimated number of more than 700,000 deaths annually, gastric cancer (GC) is the 4th most common malignancy and the second leading cause of cancer-related death worldwide.[1] Fatal malignancies are mainly prevalent in Asia, especially China.[2] The exact etiology of GC is multifactorial and believed to involve host genetic variants and environmental factors, including inflammation, bacterial infection, and diet.[3–5] Although *Helicobacter pylori* infection is generally accepted as the leading risk factor for gastric cancer,[6,7] a previous study reported the occurrence of gastric cancer tumorigenesis to *H pylori* infection in only a small proportion of subjects, suggesting that individual genetic susceptibility may also play an important role in GC.[8,9]

The *COX*, (also known as prostaglandin endoperoxide synthase), is a rate-limiting enzyme for the synthesis of important prostaglandinsfrom free arachidonic acid. The *COX-2* is the inducible isoform of *COX* and is rarely expressed in normal tissues; however, it is rapidly induced by growth factors, cytokines, and tumor promoters.[10,11] The elevated expression of *COX-2* has been reported in various forms of cancer, including GC, and in precancerous tissues.[12,13] The increase in *COX-2* expression results in the inhibition of tumor growth, invasion, metastasis, apoptosis, and angiogenesis, which are widely regarded as important steps in cancer development.[10,14–17]

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Single Nucleotide Polymorphisms (SNPs) are considered to be the most common forms of genetic variation in the human genome.[18] Recently, a polymorphism in the promoter region of *COX-2* has been reported,[19] characterized by a G>C point-mutation at position –765 (rs20417). The polymorphsm has been revealed to have a functional effect on *COX-2* transcription, which may result in GC.[20,21] Although many studies have been previously performed to examine whether the *COX-2* rs20417 polymorphism increases the risk of developing GC, the results from these studies are inconsistent.[22–27] Therefore, this study aimed to perform a meta-analysis by combining the polymorphism results from all available published studies to explore the uncertain association between the *COX-2* rs20417 and risk of GC susceptibility.

2. Materials and methods

2.1. Search strategy

The meta-analysis was conducted in adherence with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[28] We retrieved potentially relevant studies on COX-2 rs20417 genetic polymorphisms and the risk of GC susceptibility from electronic databases, including Web of Knowledge, PubMed, EMBASE, and the CBM. Databases were searched for entries with dates up until October6, 2018, by using the following terms: (stomach OR gastric) and (cancer OR carcinoma OR neoplasm OR tumor OR adenocarcinoma) and (COX2 OR cyclooxygenase-2 OR PTGS2 OR cyclooxygenase II) and (variant OR polymorphism OR genotype OR SNP OR mutation OR single nucleotide polymorphism OR variation OR Alleles). In order to avoid the exclusion of any potentially relevant literature, publications listed under the references sections of retrieved articles were also reviewed carefully to find any other possibly relevant articles. The whole search process was carried out without any language restrictions. Ethical approval was not necessary since this study was based on previous publications.

2.2. Inclusion and exclusion criteria

The studies were considered eligible if the following requirements are met: First, research type design is in a case-control format with patients with GC and healthy populations as controls. Second, paper evaluates the uncertain relationship between the *COX-2*-765G/C (rs20417) polymorphism and GC susceptibility. Third, C/C, G/C, and G/G genotypes in both groups were available; and fourth, studies were performed on human beings. We further excluded studies that had no control group, review articles, letters, comments, or studies without detailed raw data regarding *COX-2*rs20417 polymorphism.

2.3. Data extraction

Two experienced authors (SM Chen, Lu Chen) independently extracted the necessary information according to a standard form. Any disagreements encountered were resolved by discussing with a third author. The following detailed information was collected carefully: First author's name, ethnicity, country of origin, publication year, number of patients with *H pylori* infection, genotyping method, the number of GC patients and controls with C/C, G/C, and G/G genotypes, and Hardy–Weinberg equilibrium (HWE) in control groups.

2.4. Methodological quality assessment

Quality assessments for eligible studies were conducted by 2 investigators independently using the Newcastle–Ottawa Scale (NOS).[29] In this methodological quality assessment scale, 9 items, each with a score value between 1 and 9, are included. A research study with a NOS score of ≥6 stars is generally considered of high-quality.

2.5. Statistical analysis

The uncertain association strength between *COX-2*rs20417 polymorphism and GC risk was assessed by calculating the Ors along with a 95%CI. $P > .05$ was regarded as consistent with HWE. The summary ORs were measured using the Z-test and combined using either the fixed- effects model (Mantel–Haenszel) or the random-effects model (DerSimonian and Laird), as previously described.[30] Heterogeneity (between-study inconsistency) was determined using the I^2 statistical tests, with $I^2 < 50\%$ revealing an absence of heterogeneity among studies. Sensitivity analysis was also conducted to explore the stability of the pooled results under all genetic models by excluding one study at a time. Furthermore, Begg's funnel plot test was utilized to explore possible publication bias, where $P < .05$ was considered to represent statistical significant. All statistical analyses were undertaken using STATA 12.0software (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of the included studies

An initial search of related electronic databases conducted according to the search strategy described above yielded 171 studies. A flow chart of the study selection process is shown in Figure 1. A total of 15 original papers that met the inclusion criteria were selected for the meta-analysis; they included an assessment of the association between *COX-2*rs20417 polymorphism and GC in 2848 cancer cases and 4962 healthy controls.[22–27,31–39] These papers reported studies of Asian (11 papers),[22–26,31,32,34–37] Caucasian (3 papers),[27,33,38] and American (1 paper)[39] (details shown in Table 1). The association between *COX-2* rs20417 polymorphism and GC susceptibility in *H pylori* positive and *H pylori* negative patients under the dominant model were available in 5 studies.[25,31,32,35,37] The frequencies of each genotype and allele, along with their HWE values are presented in Table 2. Two studies were not in agreement with the HWE method in control subjects.[23,25] The NOS score results indicated that the score ranged from 5 to 8, with an average of 6.53, showing that the methodological quality of 15 selected studies was generally reliable. Other details of the included studies are shown in Table 1.

3.2. Meta-analysis and Subgroup analysis

Overall, a total of 15 case-control studies were used to examine the association between the *COX–2* rs20417 polymorphism and GC risk, and results are shown in Table 3. The main findings of this study indicated that *COX-2* rs20417 polymorphism was

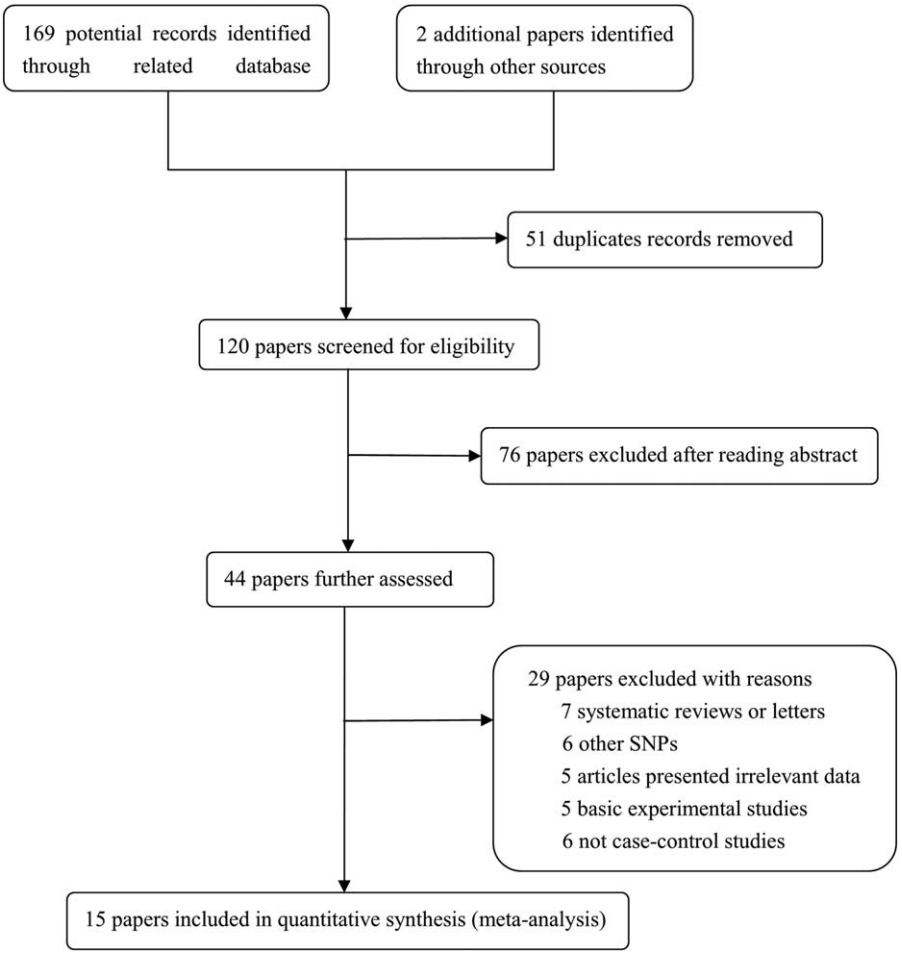

Figure 1. The detailed procedures for the literature search.

associated with increased GC susceptibility under all genetic models (G vs C: OR = 1.67, 95%CI = 1.19–2.35, $P = .003$; GG vs CG: OR = 1.44, 95%CI = 1.03–2.02, $P = .034$; GC+CC vs GG: OR = 1.66, 95%CI = 1.18–2.34, $P = .004$; GG vs CC:OR = 2.20, 95%CI = 1.07–4.54, $P = .033$; and CC vs GG+CG:OR = 2.05, 95%CI = 1.09–3.85, $P = .025$). A forest plot of pooled OR of the association between *COX-2* rs20417 polymorphism and GC risk under the dominant model is shown in Figure 2. We also

Table 1

Characteristics of the studies included in the meta-analysis.

First author	Year	Country	Ethnicity	*H pylori* (positive/negative)	Genotyping method	Number (case/control)	HWE	NOS score
Liu	2006	China	Asian	175/73	PCR-DHPLC	248/427	0.2732	6
Zhang	2006	China	Asian	NP	PCR	323/646	0.6017	7
Pereira	2006	Portugal	Caucasian	NP	PCR-RFLP	73/210	0.2792	6
Hou	2007	Poland	Caucasian	NP	TaqMan	290/409	0.8983	6
Saxena	2008	India	Asian	35/27	PCR-RFLP	62/241	0.4225	7
Sitarz	2008	Netherlands	Caucasian	NP	PCR	240/100	0.1425	5
Tang	2009	China	Asian	67/33	PCR-RFLP	100/105	0.106	5
Zhang	2011	China	Asian	NP	PCR-RFLP	357/985	0.4632	7
Zhang*	2011	China	Asian	99/55	PCR-RFLP	323/944	<0.001	8
Shin	2012	Korea	Asian	28/50	PCR-RFLP	100/100	0.5987	8
Li	2012	China	Asian	214/82	PCR-RFLP	296/319	0.6162	7
He	2014	China	Asian	67/33	PCR	100/105	0.106	8
Campanholo	2014	Brasil	American	NP	PCR-RFLP	100/150	0.0806	5
Tao	2015	China	Asian	77/59	PCR-RFLP	136/121	0.0759	6
Zou	2017	China	Asian	NP	PCR-RFLP	100/100	<0.001	7

H pylori = *Helicobacter pylori*, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–OttawaScale, NP = not provided, PCR = polymerase chain reaction, PCR-DHPLC = PCR-based denaturing high-performance liquid chromatography, PCR-RFLP = PCR-based restriction fragment length polymorphism.

Table 2

Polymorphisms genotype distribution and allele frequency in cases and controls.

First author	Genotype (N)				Allele frequency (N)							
	Case		Control		Case		Control					
rs20417 G>C	Total	GG	GC	CC	Total	GG	GC	CC	G	C	G	C
Liu 2006	248	220	27	1	427	384	43	0	467	29	811	43
Zhang 2006	323	288	35	0	646	620	26	0	611	35	1266	26
Pereira 2006	73	36	32	5	210	130	67	13	104	69	327	147
Hou 2007	290	210	70	10	409	288	110	11	490	90	686	132
Saxena 2008	62	14	29	19	241	171	62	8	57	67	404	78
Sitarz 2008	240	176	57	8	100	59	32	9	409	73	150	50
Tang 2009	100	57	34	9	105	76	24	5	148	52	176	34
Zhang 2011	357	324	33	0	985	940	45	0	681	33	1925	45
Zhang*2011	323	288	0	35	944	903	0	41	576	70	1806	82
Shin 2012	100	82	18	0	100	90	10	0	182	18	180	10
Li 2012	296	241	53	2	319	275	43	1	535	57	593	45
He 2014	100	55	11	34	105	76	24	5	121	79	176	34
Campanholo 2014	100	59	34	7	150	64	75	11	152	48	203	97
Tao 2015	136	75	46	15	121	87	28	6	196	76	202	40
Zou 2017	100	89	10	1	100	93	5	2	188	12	191	9

performed sub-group analyses to investigate the effect of ethnicity. In Asians, we found a statistically increased GC risk under all genetic models (G vs C: OR = 2.22, 95%CI = 1.66–2.96, $P < .001$; GG vs CC: OR = 4.29, 95%CI = 1.94–9.50, $P < .001$; GG vs CG: OR = 1.86, 95%CI = 1.34–2.58, $P < .001$; CC vs GG+CG: OR = 3.73, 95%CI = 1.92–7.24, $P < .001$; GC +CC vs GG: OR = 2.20, 95%CI = 1.65–2.93, $P < .001$). In Caucasians, however, such association is not seen in any comparison (Table 3). Taken together, these results indicate that *COX-2* rs20417 polymorphism was associated with an increased risk of GC in Asians. We also performed additional analysis with respect to the relationship between the *COX-2* rs20417 polymorphism and GC susceptibility in *H pylori* positive vs *H pylori* negative patients under dominant model. *Helicobacter pylori* positive patients suffered a high risk of GC compared to *H pylori* negative patients under the dominant model (OR = 3.09, 95%CI = 1.80–5.32, $P < .001$), which suggests that a *H pylori* indication is associated with the risk of gastric cancer under the dominant genetic model with respect to *COX-2* rs20417 polymorphism (Fig. 3).

3.3. Sensitivity analysis

Sequential omission of a single-study method was utilized to conduct a sensitivity analysis in all models. The summary ORs and their 95% CI showed no substantial change, confirming that the summary results of the meta-analysis are reliable and robust. Sensitivity analysis results of the association between *COX-2* rs20417 polymorphism and GC susceptibility under the dominant model are shown in Figure 4.

3.4. Publication bias

Begg's funnel plot test was used to explore a potential publication bias. No obvious publication bias was detected for the association between *COX-2* rs20417 polymorphism and GC

Table 3

Meta-analysis of the association between rs20417 polymorphism in COX-2 and gastric cancer susceptibility.

Outcome or subgroup	Study number	OR	95% CI	$P_{(Z-t)}$	I^2 (%)	$P_{(Q-t)}$
G vs C	15	1.67	1.19–2.35	.003	88.7	<.001
Asian	11	2.22	1.66–2.96	<.001	75.1	<.001
Caucasian	3	0.9	0.54–1.48	.673	81.6	.004
GG vs CC	15	2.2	1.07–4.54	.033	81.5	<.001
Asian	11	4.29	1.94–9.50	<.001	72.1	.001
Caucasian	3	0.8	0.31–2.10	.655	65.1	.057
GG vs CG	15	1.44	1.03–2.02	.034	80.2	<.001
Asian	11	1.86	1.34–2.58	<.001	65	.002
Caucasian	3	0.95	0.56–1.62	.854	73.5	.023
CC vs GG+CG	15	2.05	1.09–3.85	.025	76.3	<.001
Asian	11	3.73	1.92–7.24	<.001	61.9	.01
Caucasian	3	0.8	0.35–1.82	.597	53.6	.116
GC+CC vs GG	15	1.66	1.18–2.34	.004	84.2	<.001
Asian	11	2.2	1.65–2.93	<.001	65	.001
Caucasian	3	0.92	0.52–1.62	.776	79	.006

CI = confidence intervals, COX-2 = cyclooxygenase-2, OR = odds ratios.
P (Z–t) value for association test, *P* (Q–t) value for heterogeneity test.

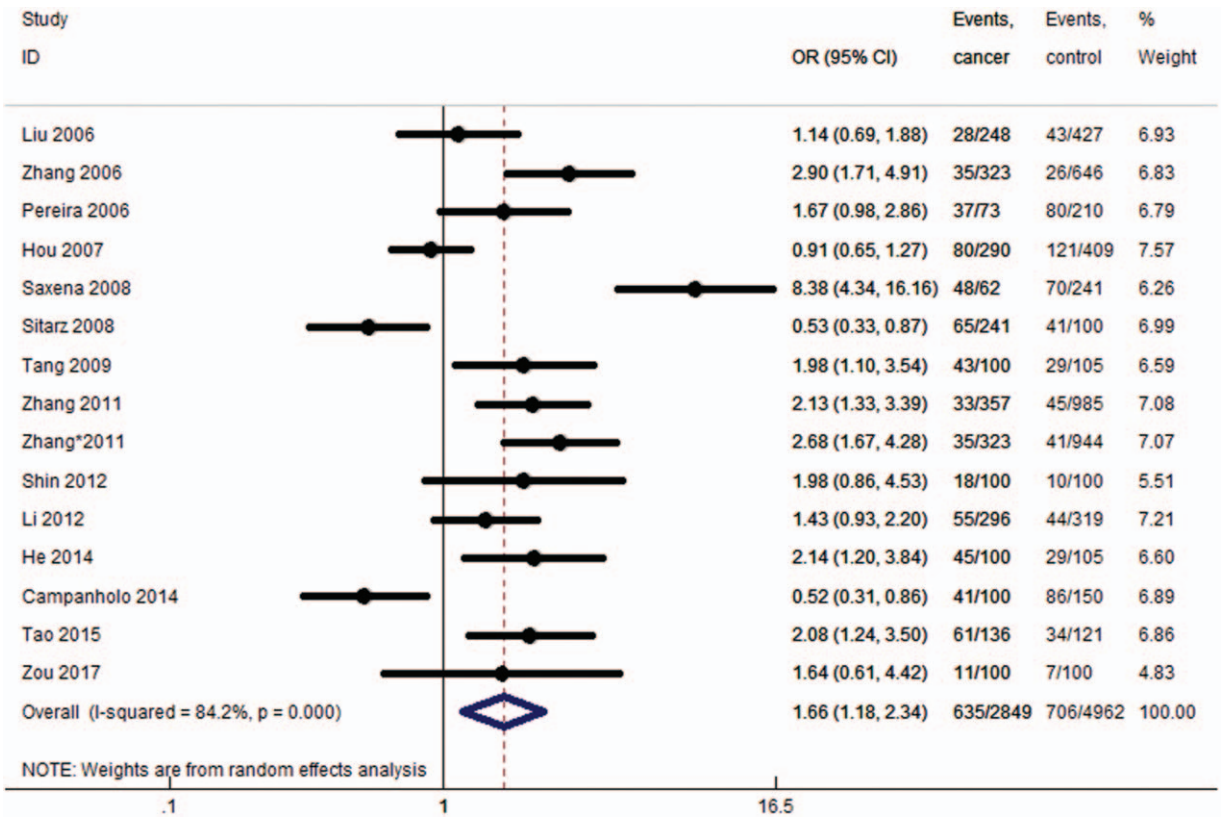

Figure 2. The forest plot of pooled odds ratios of the association of *COX-2* rs20417 polymorphism with gastric cancer susceptibility under the dominant model.

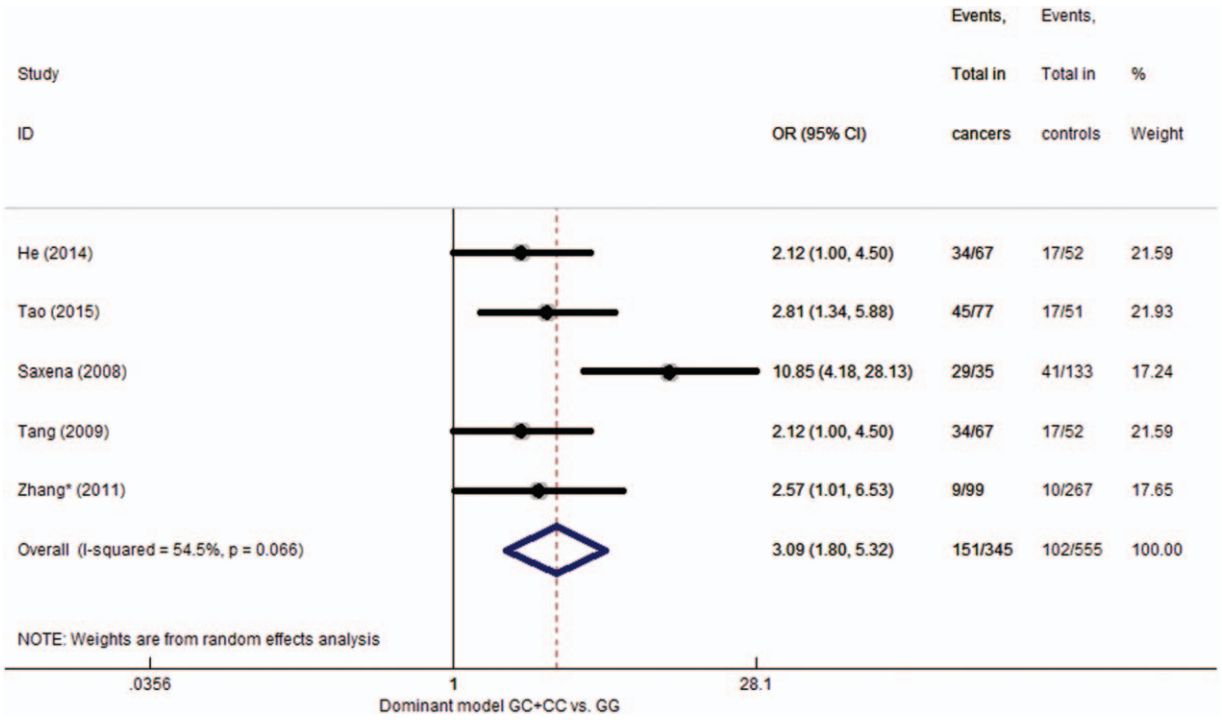

Figure 3. Meta-analysis of the relationship between the *COX-2* rs20417 polymorphism and gastric cancer susceptibility in *Helicobacter pylori* positive vs *Helicobacter pylori* negative patients under the dominant model.

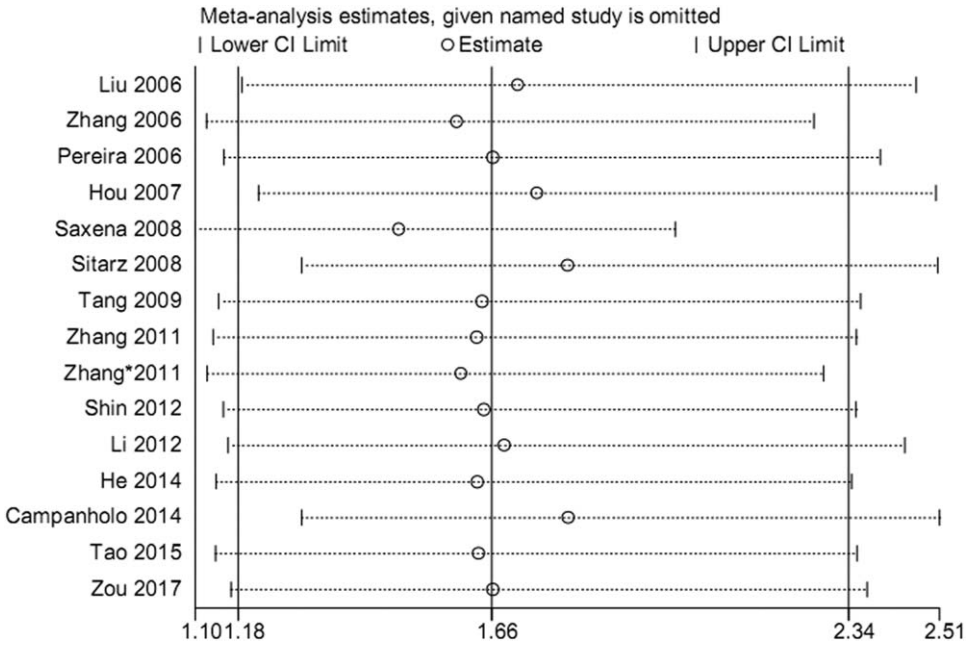

Figure 4. Sensitivity analysis of the association between *COX-2* rs20417polymorphism and the risk of gastric cancer under the dominant model.

susceptibility under the 5 models. Publication bias under the recessive model indicated that the result is statistically robust ($P = .146$, Fig. 5).

4. Discussion

In this study, we assessed the association between the *COX-2* rs20417 polymorphism and GC susceptibility by conducting an ethnic-specific meta-analysis. Fifteen independent case-control studies were included, with a total of 2848 cancer cases and 4962 healthy control subjects. The meta-analysis results presented strong evidence that the *COX-2* rs20417 polymorphism increases the risk of GC susceptibility in general populations. Subgroup analyses further indicated that, ethnicity greatly affected the link between *COX-2* rs20417 polymorphism and GC susceptibility. *COX-2* rs20417 was found to confer an elevated risk of GC susceptibility in Asians. In Caucasians, however, such an association was not observed.

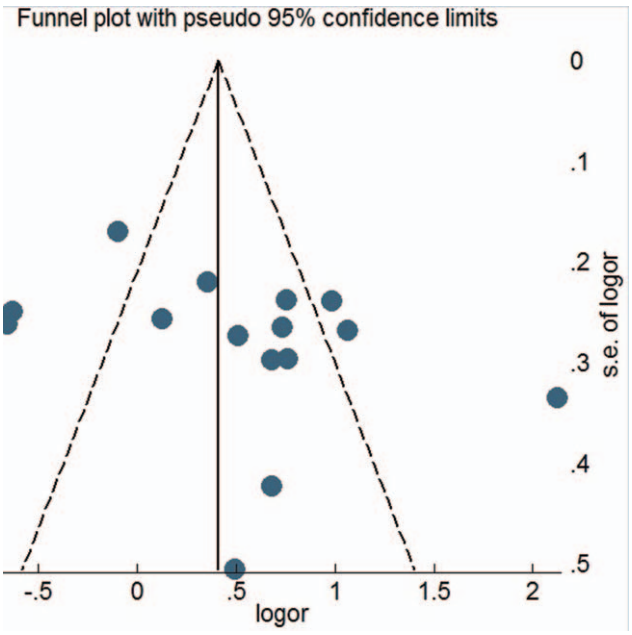

Figure 5. Publication bias detection between *COX-2* rs20417 polymorphism and gastric cancer susceptibility under dominant model.

Genetic polymorphism is regarded as an important factor for the development of cancer. Recently, significant advances in functional studies on various cancer associated SNPs have been reported.[40–42] An association between over-expression of *COX-2* gene and gastrointestinal malignancie, including gastric adenocarcinoma, has been confirmed.[12] It has been proven that the *COX-2*-765G>CSNP disrupts a SP-1 binding site, resulting in a 30% reduction of COX2 promotertranscriptional activity in vitro.[19] The frequency of *COX-2* rs20417 polymorphism seems to be different among various ethnic populations. *COX-2*-765 C carriers have been revealed to present a 3 to 8 fold increased risk of gastric cancer in some studies,[35,38] while this polymorphism was not related to gastric cancer susceptibility in other studies.[26,33] These inconclusive findings may have been caused by genotypic frequencies among various ethnic populations as well as various dietary, *H pylori* related, and environmental factors (smoking or consumption of alcohol). For example, *COX-2*-765 C allele was found in only 5% of the control groups in Korean and Chinese populations,[24,26] whereas it was reported to be present in 22% and 16% of the control groups in Portuguese and Northern Indian populations, respectively.[38,35] This may account for the differences between Asians and Caucasians in our results. Thus, more studies are needed to further explore the effect of *COX-2* rs20417 polymorphism on gastric cancer among different ethnic backgrounds.

Helicobacter pylori infection and SNPs are considered as leading pathogenic factors in GC development.[43]*Helicobacter pylori* infection induces an up-regulated transcriptional activation of inflammatory cytokines, which may contribute to further

alteration of *COX-2* expression.[44] Here, we conclude that *H pylori* positive patients suffered a high risk of GC compared to *H pylori* negative patients under the dominant model, indicating *H pylori* positive patients and patients with *COX-2* rs20417 polymorphism had a higher risk to develop GC. Our results are in line with previous studies. Tan et al also reported that the COX-2 rs20417 polymorphism may be related to an increased susceptibility of gastric cancer, especially in Asian populations.[45] However, two recent studies were not included in their study.[23,32] In another study, even though only a limited number of 11 studies were included, it was also revealed that the COX-2 rs20417 may act as a genetic biomarker of gastric cancer in Asian populations, but not in Caucasians, and *H pylori* infection may increase the susceptibility of gastric cancer in COX2 rs20417 carriers.[46]

Several limitations should be noted regarding the interpretation of our results. First, the results are based on unadjusted data. Several factors addressed across different studies, such as age, gender, environmental factors, family history, and living status, may have confounding effects and, thus, may influence the reliability of the results. Second, even in our subgroup analysis, a significant amount of heterogeneity was detected, and various potential factors accounted for this heterogeneity, including the basic characteristics of the study population and the study design. Third, 2 studies were not in agreement with HWE; even the combined ORs were not materially altered in the sensitivity analysis. Finally, owing to the limited number of studies in certain sub-groups, some conclusions from the subgroup analysis should be interpreted with caution.

In summary, the results of our meta-analysis based on 15 case-control studies indicate that the *COX-2* rs20417 polymorphism increases the risk of GC susceptibility in general populations, especially in Asian populations. *Helicobacter pylori* positive patients and patients with *COX-2* rs20417 polymorphism had a higher risk of developing GC. Further well-designed multi-ethnic epidemiological studies with large sample sizes are needed to validate these findings in the future.

Author contributions

Shimin Chen and Jiehong Wang conceived and designed the study; Lu Chen collected the data. Shimin Chen and Yuling Tan analyzed the data. Lu Chen confirmed the data. Shimin Chen and Lu Chen contributed to the writing of the manuscript and Jiehong Wang edited the manuscript.

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