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META-ANALYSIS

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Correlation Between Interleukin-1β-511 C/T Polymorphism and Gastric Cancer in Chinese Populations: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Several studies have indicated that interleukin (IL)-1β-511 C/T polymorphism may contribute to individual susceptibility to gastric cancer, but the results vary among regions and races. No relevant meta-analysis has been conducted in a Chinese population. Therefore, we performed the current meta-analysis to investigate the possible correlation between IL-1β-511 C/T polymorphism and gastric cancer susceptibility in Chinese subjects.

Material/Methods: PubMed, EmBase, Cochrane Library, Chinese Biology Medicine (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases were searched for case-control studies published before 21 January 2015 and investigating a correlation between IL-1β-511 C/T polymorphism and gastric cancer susceptibility. Two investigators independently screened the studies, extracted data, and evaluated the quality of included studies with the Newcastle-Ottawa scale. Meta-analysis was conducted with STATA 12.0.

Results: A total of 27 articles from 28 case-control studies were collected. Meta-analysis showed that IL-1β-511C/T polymorphism was related to increased susceptibility to gastric cancer in Chinese subjects [T *vs.* C: *OR*=1.21, *95%CI* (1.07–1.37), *P*<0.01; TT *vs.* CC: *OR*=1.41, *95%CI* (1.11–1.80), *P*<0.01; CT *vs.* CC: *OR*=1.26, *95% CI* (1.05–1.50), *P*<0.01; TT+CT *vs.* CC: *OR*=1.31, *95%CI* (1.08–1.58), *P*<0.01; and TT *vs.* CT+CC: *OR*=1.24, *95%*CI (1.05–1.47), *P*<0.01]. Subgroup analysis showed a significant correlation between IL-1β-511C/T polymorphism and susceptibility to gastric cancer in residents of southern China and in patients with intestinal-type gastric cancer, but not in residents of northern China or in patients with diffuse gastric cancer. Moreover, *H. pylori*-infected subjects carrying T (CT+TT) exhibited a relatively higher risk of GC [*OR*=2.4, *95% CI* (1.2–5.1), *P*=0.02].

Conclusions: IL-1β-511C/T polymorphism is significantly associated with increased susceptibility to gastric cancer in residents of southern China and in intestinal-type gastric cancer. We also found a synergistic interaction between IL-1β-511C/T polymorphism and *H. pylori* infection in the development of GC.

MeSH Keywords: China • Interleukin-1beta • Meta-Analysis • Polymorphism, Single-Stranded Conformational • Stomach Neoplasms

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Background

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer-related death worldwide [1]. An estimated total of 989 600 new GC cases and 738 000 deaths occurred in 2008, of which more than 70% occurred in developing countries, with the majority from China [1]. GC is a gastrointestinal malignancy caused by environmental and hereditary factors. *Helicobacter pylori* infection and inflammation are important risk factors of GC [2,3]. IL-1β is an important pro-inflammatory cytokine, mainly produced by inflammatory cells (such as monocytes and macrophages) during the uptake of antigen-antibody complex and antigen presentation, and may expand the inflammatory and immune response [3]. In sustained inflammation due to gastric injury, IL-1β may promote COX-2 and iNOS production to inhibit apoptosis and induce cell injury [4]. Thus, the IL-1β-related cascade has been proposed as an important mechanism underlying the pathogenesis of GC. Moreover, IL-1β is effective in inhibiting the secretion of gastric acid, with potency 6000 times that of H2 receptor antagonists and 100 times that of proton pump inhibitors [5]. The IL-1β-induced inhibition of gastric acid secretion provides a favorable condition for the survival of *H. pylori* in the gastric mucosa and may further cause atrophy of the gastric mucosa [3], which creates favorable conditions for malignant transformation of gastric epithelial cells [6].

It has been demonstrated that GC susceptibility genes, combined with environmental factors, may play an important role in the development of cancer. In 2000, El-Omar [7] first reported that IL-1β gene polymorphism increased the risk of GC onset, a finding subsequently confirmed by later studies [8–10]. The IL-1β gene is mapped to chromosome 2q14 and has 3 single-nucleotide polymorphisms (SNPs): 31 T/C, 511 C/T, and 3954 C/T. These 3 SNPs are located in the promoter region of chromosome 2q14 and are thought to cause the overexpression of IL-1β. The correlation between SNP 31T/C and GC has been widely accepted [11,12], but few studies have investigated SNP 3954 C/T [13,14]. Thus, this study focusses on the relationship between GC and 511 C/T polymorphism. Xue et al. [15] and Park et al. [16] have examined the correlation between IL-1β gene polymorphism and GC by meta-analysis, but the population of the studies was worldwide and the language was limited to English. China has the largest population worldwide, but weather this polymorphism increases GC susceptibility in Chinese populations remains controversial and no relevant meta-analyses have been performed. Therefore, we conducted a meta-analysis to examine the correlation between IL-1β-511C/T polymorphism and GC susceptibility in Chinese populations.

Material and Methods

This study was conducted according to the PRISMA statement [17].

Inclusion and exclusion criteria

According to the PICOS principles, the inclusion criteria were: 1) case-control studies in which gene frequency or odds ratio and 95% confidence interval (CI) were included; 2) Chinese patients with pathologically proven GC were recruited; 3) IL-1β-511C/T polymorphism was investigated as an exposure factor; 4) the outcome was onset risk for GC, irrespective of death; and 5) controls were recruited from communities or hospitals and were healthy subjects or volunteers without GC symptoms. Exclusion criteria were: 1) studies in which subjects did not meet the inclusion criteria; 2) subjects whose controls were recruited from gastritis or gastric ulcer patients; 3) subjects whose medical information was incomplete or could not be obtained; and 4) subjects whose language was not Chinese or English.

Literature searching

PubMed, EmBase, Cochrane Library, Chinese Biology Medicine, Chinese National Knowledge Infrastructure, and Wanfang databases were searched for studies, published before January 201, on the relationship between IL-1β-511 C/T polymorphism and GC susceptibility in Chinese populations. The search terms were: gastric cancer, gastric carcinoma, polymorphism, variant, mutation, IL-1β, and interleukin-1β. For example, in PubMed the search strategy was: #1 gastric cancer, #2 gastric carcinoma, #3 interleukin-1β, #4 IL-1β, #5 polymorphism, #6 variant, #7 mutation, #8 (#1 OR #2) AND (#3 OR #4) AND (#5 OR #6 OR #7).

Data extraction

Two investigators independently screened studies and evaluated the study quality. The following information was collected from the studies: first author, publication year, province where the study was conducted, sample size, source of controls, methods for genotyping, *Helicobacter pylori* infection status, genotype frequency including genotype frequency in different types (Lauren's classification) of GC, and *P* value of Hardy-Weinberg equilibrium (HWE). If the *P* value of HWE was not provided, it was calculated with chi square test according to α=0.05. The collected data were double-checked and any discrepancy was resolved by discussion or by contacting the study authors.

Quality evaluation

The quality of case-control studies was evaluated according to the Newcastle-Ottawa scale (NOS). A total of 8 items are included in the NOS and the maximum score is 9 "stars" [18].

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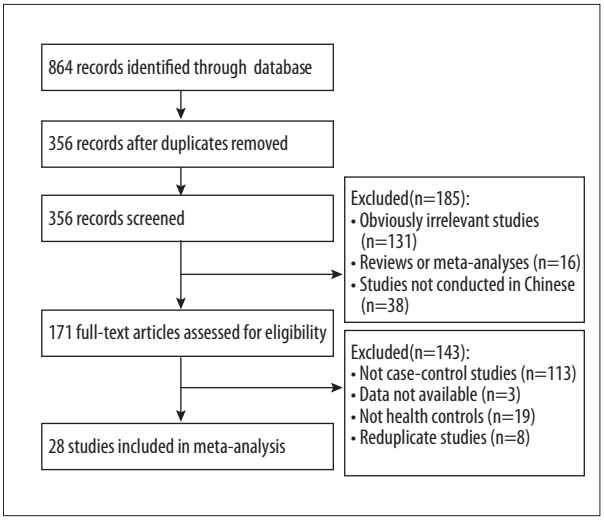

Figure 1. Flow chart of the literature search process.

Statistical analysis

Statistical analysis was performed with STATA 12.0. The overall correlation was evaluated with OR and 95% CI of allele model (T *vs.* C), codominant gene model (TT *vs.* CC; CT *vs.* CC), dominant gene model (TT+CT *vs.* CC), and recessive gene model (TT *vs.* CT+CC).

The I^2 test was used for test of heterogeneity. If there was mild heterogeneity among studies ($P \geq 0.1$, $I^2 < 50\%$), the fixed-effects model was used; otherwise, the random-effects model was used ($P < 0.1$, $I^2 \geq 50\%$). In addition, subgroup analysis was used to identify the source of heterogeneity on the basis of regions, sources of controls, methods of genotyping, and shift in HWE. In studies in which Lauren's classification of GC was given, subgroup analysis was done according to the intestinal-type and diffuse-type of GC. To avoid the influence of large bias on the overall effectors, stepwise exclusion was employed for the analysis of sensitivity. Funnel plot and Egger's test were used to test for publication bias.

Results

Literature searching

The literature search process is shown in Figure 1. The initial literature search identified 864 articles. After removal of duplicate articles, 356 articles remained. After the title and abstract of these articles were screened, we excluded the 131 studies unrelated to IL-1β-511C/T polymorphism, 16 reviews or meta-analyses, and 38 studies that were not from Chinese populations. The full text of each of the remaining articles was reviewed, then we excluded studies without data, studies that were not case-control studies, and studies whose control groups included unhealthy subjects. Finally, 28 case-control studies from 27 articles [19–45] were included for further analysis.

Characteristics and methodological quality of included studies

The 28 articles were studies conducted with Chinese subjects (including those from Hong Kong, Macao, and Taiwan). Of the 28 studies, 12 were published in English and 16 in Chinese (Table 1). A total of 5136 GC patients and 5332 healthy controls were included in the 28 studies. China was divided into northern and southern China according to the Qinling-Huaihe line. Patients were recruited from northern China in the 28 studies and from southern China in 14 studies. Population-based (PB) controls were recruited in 13 studies and hospital-based (HB) controls in 15. Lauren's classification was noted in 4 studies. The NOS score of included studies is shown in Table 1.

Meta-analysis

Five gene models had obvious heterogeneity; therefore, the random-effects model was used. As shown in Table 2, the onset risk for GC in mutant T allele carriers was 1.21 times that in non-carriers [TT *vs.* CC: *OR*=1.41, *95%CI* (1.11–1.80); CT *vs.* CC: *OR*=1.26, *95% CI* (1.05–1.50); TT+CT *vs.* CC: *OR*=1.31, *95%CI* (1.08–1.58); TT *vs.* CT+CC: *OR*=1.24, *95%CI* (1.05–1.47)]. Each study was omitted in the allele model for sensitivity analysis and the results showed that the effect value ranged from1.07 to 1.37, and 95% CI was 1.04–1.40, suggesting this meta-analysis is statistically robust and reliable.

Subgroup analysis

Patients were divided into the southern China group and northern China group. Four gene models proved that IL-1β-511C/T polymorphism increased the susceptibility of GC in patients in southern China. However, no significant correlation between this polymorphism and GC susceptibility was found in patients in northern China in any gene model (Table 2).

Lauren's classification was mentioned in 4 studies [30,37,38,44]. The test for heterogeneity showed little heterogeneity among studies (I^2=0, *P*=0.837), and the fixed-effects model was used. Meta-analysis showed that, in the intestinal-type of GC, the onset risk for GC in mutant T allele carriers was 1.58 times that in non-carriers (*OR*=1.58, *95%CI*: 1.40~1.79, *P*<0.01) and consistent results were found in the dominant gene model, codominant gene model, and recessive gene model, but in diffuse-type GC, no correlation was observed in any allele model (Table 2). A forest plot of subgroup meta-analysis according to Lauren's classification in T *vs.* C gene model is shown in Figure 2.

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Table 1. Characteristics and quality of included studies.

Studies	Province	Source of controls	Genotyping	Sample (patients/ controls)	Genotype		HWE value	NOS score	Lauren type	*H. pylori* infection
					Patients (CC/CT/TT)	Controls (CC/CT/TT)				
He, 2002 [19]	Liaoning	HB	PCR-RFLP	50/50	15/23/12	28/19/3	0.92	5	No	No
Wu, 2003 [20]	Taiwan	HB	PCR-RFLP	220/230	69/106/45	61/124/45	0.21	7	No	No
Chen, 2004 [21]	Taiwan	HB	PCR-RFLP	142/164	24/87/31	34/93/37	0.65	7	No	Yes
Yang, 2004 [22]	Jiangsu	PB	PCR-RFLP	280/258	70/158/52	57/136/65	0.37	7	No	No
Hu, 2004 [23]	Shanxi	PB	PCR-RFLP	169/86	34/97/38	19/45/22	0.66	7	No	No
Zeng, 2005 [24]	Shanxi	HB	PCR-RFLP	102/102	28/46/28	25/52/25	0.42	6	No	Yes
Zeng, 2005 [24]	Guangdong	HB	PCR-RFLP	104/104	24/52/28	32/58/14	0.13	6	No	Yes
Lu, 2005 [25]	Beijing, Shandong	PB	DH. PYLORILC	250/300	72/125/53	67/163/70	0.13	7	No	No
Zhang, 2005 [26]	Gansu	PB	PCR-RFLP	154/166	34/78/42	43/71/52	0.07	6	No	No
Xing, 2006 [27]	Shandong	HB	Taq	130/142	57/33/40	68/46/28	<0.05	6	No	Yes
Gao, 2006 [28]	Shandong	HB	PCR-RFLP	71/65	25/23/23	39/12/14	<0.05	5	No	No
Zheng, 2007 [29]	Shanghai	HB	PCR-RFLP	177/298	49/83/45	77/140/81	0.3	7	No	No
Wei, 2007 [30]	Henan	PB	PCR-SSCP	452/218	112/290/50	100/87/31	0.1	5	yes	No
Li, 2007 [31]	Hubei	HB	PCR-RFLP	143/264	29/75/39	70/137/57	0.51	6	No	Yes
Zhang, 2007 [32]	Shandong	PB	PCR-RFLP	214/230	55/97/62	56/101/73	0.08	7	No	No
Sun, 2007 [33]	Shandong	HB	Oligochip	65/55	39/12/14	25/13/17	<0.05	6	No	No
Feng, 2008 [34]	Henan	PB	PCR-RFLP	150/154	42/54/54	91/33/30	<0.05	7	No	No
Jia, 2009 [35]	Shanxi	HB	PCR-RFLP	106/108	13/58/35	18/55/35	0.65	7	No	No
Xiang, 2009 [36]	Chongqing	HB	PCR-RFLP	35/70	9/15/2011	18/27/25	0.06	6	No	No
Chen, 2009 [37]	Guangdong	PB	PCR-RFLP	563/500	143/309/111	182/253/65	0.11	6	Yes	No
Yu, 2009 [38]	Guangdong	PB	PCR-RFLP	501/500	132/269/100	182/253/65	0.7	7	Yes	No
Jiang, 2010 [39]	Hubei	PB	PCR-RFLP	84/84	19/44/21	37/38/9	0.87	7	No	Yes
Li, 2010 [40]	Sichuan	PB	PCR-RFLP	140/165	26/81/33	34/94/37	0.07	7	No	No
Zou, 2011 [41]	Guangdong	HB	MALDI-TOFM	52/52	20/23/9	11/28/2013	0.57	6	No	No
He, 2011 [42]	Jiangsu	HB	PCR-RFLP	392/508	72/196/124	148/266/94	0.18	7	No	Yes
Zhang, 2012 [43]	Jiangsu	HB	PCR-RFLP	128/127	28/61/39	37/71/19	0.11	6	No	Yes
Zhao, 2012 [44]	Qinghai	PB	PCR-RFLP	197/202	31/101/65	65/99/38	0.98	7	Yes	No
Zhang, 2014 [45]	Henan	PB	PCR-RFLP	65/130	12/34/19	10/76/44	<0.05	7	No	No

HB – hospital-based; PB – population-based; PCR-RFLP – restriction fragment length polymorphism polymerase chain reaction; DHPLC – denaturing high performance liquid chromatography; Taq – Taq polymerase chain reaction; MALDI-TOFMS – matrix-assisted laser desorption ionization time of flight mass spectrometry.

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Table 2. Results of meta-analysis for the IL-1β-511C/T polymorphism and GC risk.

Subgroup	Studies	T *vs.* C			TT *vs.* CC			CT *vs.* CC			(TT+CT) *vs.* CC			TT *vs.* (CC+CT)		
		OR (95% CI)	*P*	I^2 (%)	OR (95% CI)	*P*	I^2 (%)	OR (95% CI)	*P*	I^2 (%)	OR (95% CI)	*P*	I^2 (%)	OR (95% CI)	*P*	I^2 (%)
Total	28	1.21 (1.07–1.37)	0.003	78.7	1.41 (1.11–1.80)	0.005	75.1	1.26 (1.05–1.50)	0.013	68.8	1.31 (1.08–1.58)	0.005	75.3	1.24 (1.05–1.47)	0.013	65.6
Region	28															
North	13	1.27 (0.99–1.55)	0.060	82.7	1.42 (0.93–.170)	0.103	77.1	1.25 (0.88–1.74)	0.161	72.1	1.32 (0.94–1.84)	0.107	80	1.22 (0.83–2.20)	0.118	58.1
South	15	1.58 (1.11–2.24)	0.015	74.5	1.45 (1.07–2.00)	0.016	73	1.28 (1.03–1.59)	0.029	66.0	1.32 (1.05–1.65)	0.016	71.4	1.26 (0.99–1.60)	0.062	69.4
Source of controls	28															
Population based	13	1.31 (1.07–1.60)	0.008	84.7	1.57 (1.06–2.32)	0.023	82	1.48 (1.12–1.97)	0.006	77.9	1.52 (1.13–2.05)	0.005	82.3	1.24 (0.99–1.55)	0.108	73.7
Hospital based	15	1.13 (0.96–1.32)	0.132	69.2	1.38 (1.02–1.86)	0.084	67.6	1.09 (0.94–1.26)	0.245	32.4	1.14 (0.92–1.41)	0.234	59.9	1.28 (1.03–1.60)	0.054	57.1
Genotyping	28															
PCR-RFLP	24	1.24 (1.08–1.42)	0.002	78.6	1.56 (1.20–2.02)	0.002	75.4	1.32 (1.19–1.46)	0	54.6	1.35 (1.12–1.63)	0.002	70.5	1.29 (1.08–1.55)	0.006	65.6
Other	4	1.04 (0.72–1.51)	0.819	81.8	1.00 (0.57–1.75)	0.992	68.8	1.30 (1.04–1.64)	0.024	91.6	1.03 (0.49–2.19)	0.934	90.4	0.97 (0.63–1.47)	0.871	56.6
HWE	28															
Yes	23	1.19 (1.05–1.34)	0.005	74.6	1.41 (1.10–1.81)	0.006	73.3	1.26 (1.06–1.50)	0.009	62.8	1.30 (1.08–1.58)	0.004	74.3	1.22 (1.07–1.46)	0.037	66.6
No	5	1.30 (0.74–2.27)	0.366	89.1	1.33 (0.58–3.08)	0.502	84.1	1.185 (0.50–2.81)	0.700	85.3	1.25 (0.55–2.82)	0.594	34.1	1.35 (0.83–2.20)	0.226	64.8
Lauen type	4															
Intestinal	4	1.58 (1.40–1.79)	0.00	0	2.71 (2.08–3.52)	0	0	1.81 (1.29–2.53)	0.001	62	1.96 (1.51–2.54)	0	42	1.83 (1.39–2.41)	0	21.1
Diffuse	4	1.09 (0.9–1.32)	0.374	27.9	0.95 (0.44–2.02)	0.883	61.1	1.02 (0.86–1.54)	0.231	56.2	1.43 (0.74–1.60)	0.428	62	0.73 (0.35–1.52)	0.395	67

Subgroup analysis was also performed according to the source of controls, methods of genotyping, and shift in HWE, and results are shown in Table 2

Interactions with *H. pylori* infection, IL-1β-31 polymorphism for GC

Interaction between *H. pylori* infection and IL-1β-511 polymorphism for GC was investigated in 7 studies [21,24,27,31,39,42,43]. As in shown in Table 3, *H. pylori* infection was associated with a trend towards an increased risk of GC, with a pooled OR of 1.9 (*95% CI*: 1.1–3.5, *P*=0.03) in non-carriers of T allele. In subjects not infected with *H. pylori*, the carriage of T (CT+TT) was not associated with an increased susceptibility to GC, with a pooled OR of 1.3 (*95% CI*: 1.0–1.70, *P*=0.75). However, *H. pylori*-infected subjects with carriage of T (CT+TT) exhibited a relatively higher risk of GC, with an OR of 2.4 (*95% CI:* 1.2-5.1, *P*=0.02). These data demonstrate a

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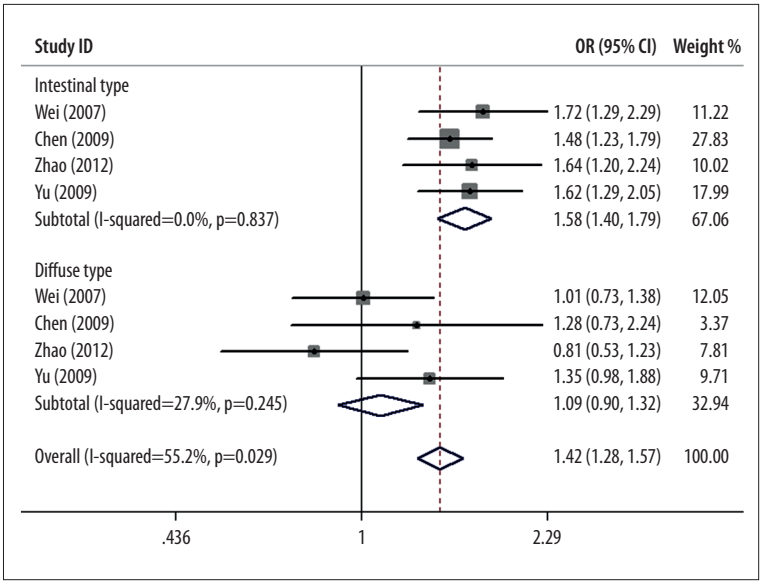

Figure 2. Forest plot of subgroup meta-analysis according to Lauren's classification in T *vs.* C gene model.

Table 3. Combined risks of IL-1β-511 polymorphism and *H. pylori* infection for GC.

IL-1β-511 polymorphism	*H. pylori* infection	OR (95% CI)	P value
C homozygote	(–)	1	–
T carrier	(–)	1.3 (1.0–1.7)	0.75
C homozygote	(+)	1.9 (1.1–3.5)	0.03
T carrier	(+)	2.4 (1.2–5.1)	0.02

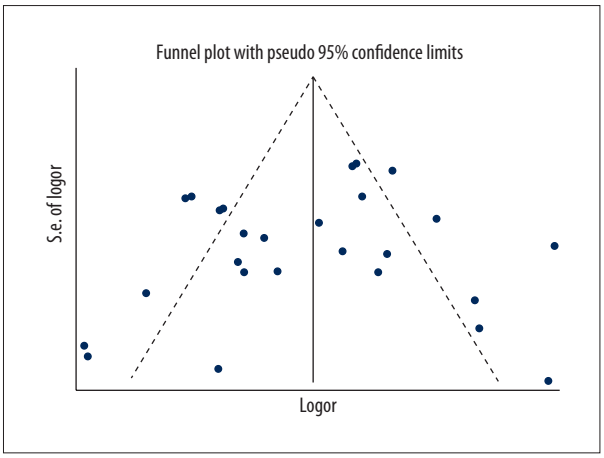

Figure 3. Funnel plot of publication bias on the basis of T *vs.* C gene model.

synergistic interaction between IL-1β-511 and *H. pylori* infection in the occurrence or development of GC.

Within the included studies, the possible interaction between IL-1β-511 and IL-1β-31 polymorphisms in the development of GC was examined only in Zeng's research [24], but no linkage disequilibrium was found.

Publication bias

The Begg's funnel plots of 5 gene models were symmetrical (Figure 3). Egger's test also showed no publication bias (Egger value was 0.694, 0.509, 0.426, 0.381, and 0.310 for T *vs.* C, TT *vs.* CC, CT *vs.* CC, TT+CT *vs.* CC, and TT *vs.* CT+CC, respectively) in our research.

Discussion

Since El-Omar first reported that the IL-1β-511 gene allele T carriers was associated with a trend towards an increased onset risk of GC in whites [7], several subsequent studies have reported that this association varies among different regions, races, and cultural habits [31,44,46]. The relationship between IL-1β 511C/T polymorphisms and GC susceptibility in Chinese populations had been investigated in numerous case-control studies, but conflicting results were reported [36].We conducted a meta-analysis to investigate this possible correlation in Chinese populations by using 5 gene models. A total of 28 case-control studies were recruited from 27 relevant studies, and this meta-analysis showed that IL-1β 511C/T polymorphism significantly increased GC susceptibility in Chinese subjects, a finding which is consistent with those

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of Yu [38] and Zhao [44]. Subgroup analysis showed that IL-1β 511C/T polymorphism increased the onset risk for GC in Chinese subjects in southern China, but not in northern China. According to Lauren's classification, IL-1β 511C/T polymorphism increased the onset risk for intestinal-type GC, but not for diffuse-type GC.

The incidence of GC was influenced by regional differences. East Asians have relatively higher morbidity of GC, especially in China, Japan, and Korea, accounting for 60% of GC cases worldwide [47]. The number of GC cases in China accounted for 40% in these 3 countries, although the incidence is lower than in Japan and Korea. Epidemiological statistics also showed the incidence of GC was not entirely consistent in different regions [48]. The Qinling-Huaihe line is the geographical boundary between northern and southern China, with differences in hereditary background, climate, and diet and other lifestyle factors [49]. In this study, we investigated the association between IL-1β-511C/T polymorphism and onset risk for GC in Chinese subjects in southern and northern China. Our results showed that IL-1β-511C/T polymorphism significantly increased GC susceptibility of Chinese in southern China, but not in northern China. This finding implies that the hereditary background is different between GC patients in these 2 regions.

In 1965, Lauren classified GC into the intestinal type and diffuse type according to the pathological features [50]. This analysis showed that IL-1β-511C/T polymorphism significantly increased the onset risk for intestinal-type GC, but had no influence on the onset risk of diffuse-type GC. Intestinal-type GC was generally accompanied by high or moderate differentiation and has a relatively good prognosis, but diffuse-type GC was the opposite [51]. The IL-1β-511C/T gene was correlated with occurrence of intestinal-type GC, but determining whether detection of its mutation would help to assess the prognosis of GC needs epidemiological studies.

The potential mechanisms of tumorigenesis are inexplicable as a result of the involvement of multiple risk factors, including the complicated gene-environment and gene-gene interactions [52]. *H. pylori* infection is regarded as the major cause of GC among environmental factors [2]. In this meta-analysis, we found the susceptibility to GC was significantly increased for T carriers of IL-1β-511C/T polymorphism with *H. pylori* infection, suggesting that a synergistic interaction between IL-1β-511 and *H. pylori* infection exists in the development of GC, which is consistent with results reported by Li [31].

Gastric epithelial cells were damaged by inflammation and immune response induced by vacuole toxin and ammonia generated by *H. pylori*. As a pro-inflammatory factor produced in response to various stimuli, IL-1β plays an important role in the promotion of inflammatory response and expansion of immune responses. Moreover, the overexpression of IL-1β can inhibit gastric acid secretion, thus providing a more favorable environment for the survival and growth of *H. pylori*, which could further cause atrophy and damage of the gastric mucosa [6]. There 2 mechanisms may explain the conclusion that IL-1β-511C/T polymorphism and its expression contribute to host susceptibility to GC in subjects with *H. pylori* infection.

Cox first reported the linkage disequilibrium in the interleukin-1 gene cluster and synergistic effects between IL-1β-511 and IL-1β-31polymorphism in 212 white subjects [53]. However, in Zeng's study [24] no evidence of linkage disequilibrium was found between the 2 SNPs in both high prevalence and low prevalence regions, suggesting that the 2 SNPs were independent risk factors for GC in both areas.

We acknowledge that our study has limitations. 1) The sample size of studies included was not large. 2) Some models have considerable heterogeneity. 3) There were differences in patients and controls among studies, and the sources of controls were inconsistent among studies; in several studies, some controls were recruited from hospitals but others from the general population, thus introducing the possibility of selection bias. 4) Only 4 studies stratified patients according to Lauren's classification, and subgroup analysis for pathological types other than intestinal-type GC and diffuse-type GC could not be conducted. Because of these factors, the universality of our conclusions is limited. Multicenter, randomized, controlled studies with larger sample sizes are needed to confirm the relationship between IL-1β-511C/T polymorphism and GC susceptibility. Confirmation of this relationship may provide new ideas and clues for the prevention and therapy of GC and accelerate realization of its clinical value.

Conclusions

This meta-analysis indicated that IL-1β-511C/T polymorphism was significantly associated with increased susceptibility to GC in Chinese populations, mainly in residents of southern China and in intestinal-type GC. We found a synergistic interaction between IL-1β-511C/T polymorphism and *H. pylori* infection in the development of GC. However, further studies are needed to clarify the specific mechanism of the IL-1β-511C/T polymorphisms in the etiology of gastric cancer.

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