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

AEG 1,2 Bo Chen*  
BCDEF 1,2 Ming-xu Luo*  
ABC 1 Xin Zhou  
ABC 1 Yo Lv  
BCDEF 1,2 Guo-qiang Su

* Bo Chen and Ming-xu Luo contributed equally to this work and should be considered as co-first authors

Corresponding Author: Guo-qiang Su, e-mail: Suguoqiang66@163.com

Source of support: This research was supported (in part) by the Fujian Province Natural Science Foundation Youth Innovation Project of China (2009D003) and Natural Science Foundation for the Youth (81201892) without commercial or not-for-profit sectors

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. 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

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/895771

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]
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 is 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 focuses 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 gastroenteritis 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].
META-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 from 1.07 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.

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.

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 \( (P > 0.1, I^2 < 50\%) \), the fixed-effects model was used; otherwise, the random-effects model was used \( (P < 0.1, I^2 > 50\%) \). 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.

Figure 1. Flow chart of the literature search process.

META-ANALYSIS

Chen B. et al. Correlation between interleukin-1β-511 C/T polymorphism and gastric cancer. © Med Sci Monit, 2016; 22: 1742-1750

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Index in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

864 records identified through database

356 records after duplicates removed

356 records screened

171 full-text articles assessed for eligibility

28 studies included in meta-analysis

Excluded (n=185):
- Obviously irrelevant studies (n=131)
- Reviews or meta-analyses (n=16)
- Studies not conducted in Chinese (n=38)

Excluded (n=143):
- Not case-control studies (n=131)
- Data not available (n=3)
- Not health controls (n=19)
- Reduplicate studies (n=8)
### Table 1. Characteristics and quality of included studies.

| Studies     | Province       | Source of controls | Genotyping           | Sample (patients/controls) | genotype Patients (CC/CT/TT) | genotype Controls (CC/CT/TT) | HWE value | NOS score | Lauren type | H. pylori infection |
|-------------|----------------|--------------------|----------------------|---------------------------|-----------------------------|-----------------------------|------------|-----------|-------------|--------------------|
| He, 2002    | Liaoning       | HB                 | PCR-RFLP             | 50/50                     | 15/23/12                    | 28/19/3                     | 0.92       | 5         | No          | No                 |
| Wu, 2003    | Taiwan         | HB                 | PCR-RFLP             | 220/230                   | 69/106/45                   | 61/124/45                   | 0.21       | 7         | No          | No                 |
| Chen, 2004  | Taiwan         | HB                 | PCR-RFLP             | 142/164                   | 24/87/31                    | 34/93/37                    | 0.65       | 7         | Yes         | No                 |
| Yang, 2004  | Jiangsu        | PB                 | PCR-RFLP             | 280/258                   | 70/158/52                   | 57/136/65                   | 0.37       | 7         | No          | No                 |
| Hu, 2004    | Shanxi         | PB                 | PCR-RFLP             | 169/86                    | 34/97/38                    | 19/45/22                    | 0.66       | 7         | No          | Yes                |
| Zeng, 2005  | Shanxi         | HB                 | PCR-RFLP             | 102/102                   | 28/46/28                    | 25/52/25                    | 0.42       | 6         | Yes         | No                 |
| Zeng, 2005  | Guangdong      | HB                 | PCR-RFLP             | 104/104                   | 24/52/28                    | 32/58/14                    | 0.13       | 6         | No          | Yes                |
| Lu, 2005    | Beijing, Shan- | PB                 | DH-PYLORILC          | 250/300                   | 72/125/53                   | 67/163/70                   | 0.13       | 7         | No          | No                 |
| Zhang, 2005 | Gansu          | PB                 | PCR-RFLP             | 154/166                   | 34/78/42                    | 43/71/52                    | 0.07       | 6         | No          | No                 |
| Xing, 2006  | Shan-dong      | HB                 | Taq                  | 130/142                   | 57/33/40                    | 68/46/28                    | <0.05      | 6         | Yes         | No                 |
| Gao, 2006   | Shan-dong      | HB                 | PCR-RFLP             | 71/65                     | 25/23/23                    | 39/12/14                    | <0.05      | 5         | No          | Yes                |
| Zheng, 2007 | Shanghai       | HB                 | PCR-RFLP             | 177/298                   | 49/83/45                    | 77/140/81                   | 0.3        | 7         | No          | No                 |
| Wei, 2007   | Henan          | PB                 | PCR-SSCP             | 452/218                   | 112/290/50                  | 100/87/31                   | 0.1        | 5         | Yes         | No                 |
| Li, 2007    | Hubei          | HB                 | PCR-RFLP             | 143/264                   | 29/75/39                    | 70/137/57                   | 0.51       | 7         | No          | Yes                |
| Zhang, 2007 | Shan-dong      | PB                 | PCR-RFLP             | 214/230                   | 55/97/62                    | 56/101/73                   | 0.08       | 7         | No          | No                 |
| Sun, 2007   | Shan-dong      | HB                 | Oligochip            | 65/55                     | 39/12/14                    | 25/13/17                    | <0.05      | 6         | No          | No                 |
| Feng, 2008  | Henan          | PB                 | PCR-RFLP             | 150/154                   | 42/54/54                    | 91/33/50                    | <0.05      | 7         | No          | No                 |
| Jia, 2009   | Shanxi         | HB                 | PCR-RFLP             | 106/108                   | 13/58/35                    | 18/55/35                    | 0.64       | 7         | No          | No                 |
| Xiang, 2009 | Chong-qing     | HB                 | PCR-RFLP             | 35/70                     | 9/15/2011                   | 18/27/25                    | 0.06       | 6         | No          | Yes                |
| Chen, 2009  | Guangdong      | PB                 | PCR-RFLP             | 563/500                   | 143/309/111182/253/65       | 0.11                       | 6         | Yes         | No          | No                 |
| Yu, 2009    | Guangdong      | PB                 | PCR-RFLP             | 501/500                   | 132/269/100182/253/65       | 0.7                        | 7         | Yes         | No          | No                 |
| Jiang, 2010 | Hubei          | PB                 | PCR-RFLP             | 84/84                     | 19/44/21                    | 37/38/9                     | 0.87       | 7         | No          | Yes                |
| Li, 2010    | Sichuan        | PB                 | PCR-RFLP             | 140/165                   | 26/81/33                    | 34/94/37                    | 0.07       | 7         | No          | No                 |
| Zou, 2011   | Guangdong      | HB                 | MALDI-TOFM           | 52/52                     | 20/23/9                    | 11/28/2013                  | 0.57       | 6         | No          | No                 |
| He, 2011    | Jiangsu        | HB                 | PCR-RFLP             | 392/508                   | 72/196/124148/266/94        | 0.18                       | 7         | No          | Yes         | No                 |
| Zhang, 2012 | Jiangsu        | HB                 | PCR-RFLP             | 128/127                   | 28/61/39                    | 37/71/19                    | 0.11       | 6         | Yes         | No                 |
| Zhao, 2012  | Qinghai        | PB                 | PCR-RFLP             | 197/202                   | 31/101/65                   | 65/99/38                    | 0.98       | 7         | Yes         | No                 |
| Zhang, 2014 | 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.
Table 2. Results of meta-analysis for the IL-1β-511C/T polymorphism and GC risk.

| Subgroup | Studies | T vs. C | (OR) (95% CI) | P | I² (%) | TT vs. CC | (OR) (95% CI) | P | I² (%) | CT vs. CC | (OR) (95% CI) | P | I² (%) | (TT+CT) vs. CC | (OR) (95% CI) | P | I² (%) | TT vs. (CC+CT) | (OR) (95% CI) | P | I² (%) |
|----------|---------|---------|----------------|----|---------|-----------|----------------|----|---------|-----------|----------------|----|---------|----------------|----------------|----|---------|----------------|----------------|----|---------|
| 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     | (0.93–1.70) | 0.103 | 77.1 | 1.25     | (0.88–1.74) | 0.161 | 72.1 | 1.32 | (0.94–1.84) | 0.107 | 80.0 | 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 | 73.0 | 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 | 82.0 | 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 | 62.0 | 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 | (0.74–2.53) | 0.428 | 62.0 | 0.73 | (0.35–1.52) | 0.395 | 67.0 |

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
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.

**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 |

**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 studies.
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 for 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.
References:

1. Jemal A, Bray F, Center MM et al: Global cancer statistics. Cancer J Clin, 2011; 61(2): 69–90
2. Kiga K, Mimuro H, Suzuki M et al: Epigenetic silencing of mir-210 increases the proliferation of gastric epithelium during chronic Helicobacter pylori infection. Nat Commun, 2014; 5: 4497
3. Zhou L, Lin S, Ding S et al: Relationship of Helicobacter pylori eradication with gastric cancer and gastric mucosal histological changes: a 10-year follow-up study. Chin Med J Engl, 2014; 127(8): 1454–58
4. Lakhanpal M, Yadav DS, Devi TR et al: Association of interleukin-1B-511 C/T polymorphism with tobacco-associated cancer in northeast India: a study on oral and gastric cancer. Cancer Genet, 2014; 207(1–2): 1–11
5. Oger P, Dessaux Y, Petit A et al: Validity, sensitivity and resolution limit of the PCR-RFLP analysis of the 16S RNA gene as a tool to identify soilborne and plant-associated bacterial populations. Genet Sel Evol, 1998; 30: 1–22
6. Ragini S, Anfara K, Mohd K et al: Mucosal IgA & IL-1B in Helicobacter pylori infection. Indian J Clin Biochem, 2013; 28(1): 19–23
7. El-Omar EM, Carrington M, Chow WH et al: Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature, 2000; 404: 398–402
8. Santos JC, Ladeira MSP, Pedrazzoli J et al: Relationship of IL-1 and TNF-alpha polymorphisms with Helicobacter pylori in gastric diseases in a Brazilian population. Braz J Med Biol Res, 2012; 45(9): 811–17
9. Qiu B, Zou HY, Yang YH et al: Interleukin-1B-31 gene polymorphism in Hakka gastric cancer patients in Guangdong, China. Genet Mol Res, 2014; 13(3): 5873–79
10. Van der Ploeg AH, Kumpf O, Seelow E et al: The course of gastric cancer following surgery is associated with genetic variations of the interleukin-1 receptor antagonist and interleukin-1B. Gastric Cancer, 2015; 18(1): 77–83
11. Taguchi A, Omiya N, Shirai K et al: Interleukin-8 promoter polymorphism increases the risk of atrioesophageal gastric cancer in Japan. Cancer Epidemiol Biomarkers Prev, 2005; 14: 2487–93
12. Tatemichi M, Sawa T, Gillibert I et al: Increased risk of intestinal type of gastric adenocarcinoma in Japanese women associated with long forms of CCAAT enhancer binding protein. Cancer Lett, 2005; 217: 197–202
13. Wen YY, Pan XF, Loh M et al: Association of the IL-1B +3954 C/T polymorphism with tobacco-associated cancer in northeast India: a case-control study. Cancer Genet, 2014; 207(1–2): 1–11
14. Zhang D, Zheng H, Zhou Y et al: Association of IL-1B gene polymorphism with cachexia from locally advanced gastric cancer. BMC Cancer, 2007; 7: 45
15. Jia A, Gong J, Li YC et al: Correlation of polymorphisms of the IL-1B promoter region and tumour necrosis factor alpha gene with susceptibility of non-cardiac gastric cancer in a Han nationality of Shaanxi Chinese population. J Cancer Prev, 2014; 23(1): 35–42
16. Xue H, Lin B, NiP et al: Interleukin-1B and interleukin-1 RN polymorphisms with gastric cancer and gastric mucosal histological changes: a 10-year follow-up study. China Med J Adv Gen Surg, 2006; 9(6): 359–62
17. Zhang JR, Hu PL, Hu S et al: Association of interleukin 1B gene polymorphism and gastric cancers in high and low prevalence regions in China. Gut, 2003; 52(12): 1684–89
18. Zhang SQ, Pan YQ, Xu YQ et al: Association between IL-1 gene polymorphisms and gastric adenocarcinoma. Chin J Curr Adv Gen Surg, 2006; 9(6): 359–62
19. Zhang JX, Duan GC, Guo AY et al: Study on the relationship of IL-1B gene polymorphism with increased risk of gastric carcinoma. Chin J Cancer Prev Treat, 2007; 14(4): 258–60
20. Li C, Xia HH, Xie W et al: Association between interleukin-1 gene polymorphisms and Helicobacter pylori infection in gastric carcinogenesis in a Chinese population. J Gastrointestinal Hepatol, 2007; 22(2): 234–39
21. Zhang D, Zheng H, Zhou Y et al: Association of IL-1beta gene polymorphism with cachexia from locally advanced gastric cancer. BMC Cancer, 2007; 7: 45
22. Sun H, Wang Y, Ma X et al: A method of oligochip for single nucleotide polymorphism genotyping in the promoter region of the interleukin-1 beta gene and its clinical application. Oligonucleotides, 2007; 17(3): 336–44
23. Feng Y, Zhang I, Dai L et al: Inflammatory cytokine gene polymorphisms in gastric cancer cases’ and controls’ family members from Chinese areas at high cancer prevalence. Cancer Lett, 2008; 270(2): 250–59
24. Zhang Z, Wang S et al: Relationship between interleukin-1B-511 polymorphism and susceptibility to gastric ulcer and cancer. Chin J Biologics, 2009; 22(10): 1010–14
25. Chen B, Zeng ZR, Wu XQ et al: Association between interleukin-1B-511 polymorphism and gastric cancer in the context of the relationship between race and polymorphism on the risk of gastric cancer in the context of the relationship between race and polymorphism on the risk of gastric cancer. World J Gastroenterol, 2012; 18(47): 7093–99
26. Chen B, Zeng ZR, Wu XQ et al: Association of interleukin-1B-511 polymorphism with increased risk of certain subtypes of gastric cancer in Chinese: A case-control study. Am J Gastroenterol, 2012; 107(3): 557–64
27. Jiang DL, Chen YP, Dai Y: Association of interleukin-1beta gene polymorphism with gastric cancer and gastric mucosal histological changes: a 10-year follow-up study. Am J Gastroenterol, 2012; 107(3): 557–64
28. Chen B, Zeng ZR, Wu XQ et al: Association between interleukin-1B-511 polymorphism and susceptibility to gastric cancer. Indian J Clin Biochem, 2013; 28(1): 19–23
29. Jiang DL, Chen YP, Dai Y: Association of interleukin-1beta gene polymorphism and Helicobacter pylori infection and susceptibility to gastric cancer. Acta Med Univ Technol Huazhong, 2010; 39(5): 695–97
30. Li K, Yang J, Chen ZR: Relationships among interleukin-1beta, interleukin-1 receptor antagonist gene polymorphism and susceptibility to gastric cancer. Sichuan Da Xue Xue Bao Yi Xue Ban, 2010; 41(6): 1039–43
31. Hu QY, Chen B, Yang QT et al: Relationship between IL-1B-511 polymorphism and susceptibility to gastric cancer among ke population in Meizhou, Guangdong. Guangdong Medical Journal, 2011; 32(23): 3074–76
32. He BS, Pan YQ, Xu YF et al: Polymorphisms in interleukin-1B (IL-1B) and interleukin 1 receptor antagonist (IL-1RN) genes associate with gastric cancer risk in the Chinese population. Dig Dis Sci, 2011; 56(7): 2017–23
33. Zhang QS, Pan YQ, Xu YQ et al: Association between IL-1 gene polymorphism with Helicobacter pylori infection and gastric cancer. Chin J Lab Sci, 2012; 30(3): 207–9
34. Zhao JD, Geng PL, Li LQ et al: Associations between interleukin-1 polymorphisms and gastric cancers among three ethnicities. World J Gastroenterol, 2012; 18(47): 7093–99
35. Zhang JX, Duan GC, Guo AY et al: Study on the relationship of IL-1B gene polymorphism and Helicobacter pylori infection with gastric cancer. Medical Innovation of China, 2014; 11(27): 1–3
46. Persson C, Engstrand L, Nyrén O et al: interleukin-1 beta polymorphisms and risk of gastric cancer in Sweden. Scand J Gastroenterol, 2009; 44(3): 339–45

47. Sung JJ, Ng EK, Lin JT et al: Digestive cancer management in Asia: position statements: a report on GI Oncology Summit in 2011. J Gastroenterol Hepatol, 2012; 27(9): 1417–22

48. Yang L: Incidence and mortality of gastric cancer in China. World J Gastroenterol, 2006; 12(1): 17–20

49. Jie F: Geography (textbook) [M]. People Education Press, 2013; 5–6

50. Lauren P: 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, 1965; 64: 31–49

51. Yang J, Wu Z, Li L et al: Research progress of Lauren classification for gastric cancer. Zhong Nan Da Xue Bao Yi Xue Ban, 2015; 40(8): 934–40

52. Pharoah PD, Dunning AM, Ponder BA et al: Association studies for finding cancer-susceptibility genetic variants. Nat Rev Cancer, 2004; 4(11): 850–60

53. Cox A, Camp NJ, Nicklin MJ et al: An analysis of linkage disequilibrium in the interleukin-1 gene cluster, using a novel grouping method for multiallelic markers. Am J Hum Genet, 1998; 62(5): 1180–88