Investigation on the association between *IL-10* C819T gene polymorphisms and susceptibility to gastric cancer

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ABSTRACT. We conducted a case-control study to investigate the association between the interleukin-10 (*IL-10*) C819T polymorphism and susceptibility to gastric cancer in a Chinese population. A total of 157 patients with gastric cancer and 249 controls were consecutively enrolled from the Guizhou Provincial People's Hospital between October 2012 and February 2015. The polymerase chain reaction-restriction fragment length polymorphism technique was used to genotype for *IL-10* C819T. As determined by χ^2-test, there was a significant difference in genotype distributions of *IL-10* C819T between gastric cancer patients and controls (χ^2 = 7.09; P = 0.03). Based on unconditional logistic regression analysis, the TT genotype of *IL-10* C819T was significantly associated with increased risk of gastric cancer when compared with that of the CC genotype [odds ratio (OR) = 2.24;

95% confidence interval (CI) = 1.17-4.26; P = 0.008]. In a dominant model, we found that the CT + TT genotype of *IL-10* C819T was associated with susceptibility to gastric cancer compared to that of the CC genotype (OR = 1.63; 95%CI = 1.02-2.64). In a recessive model, the TT genotype of *IL-10* C819T was correlated with a higher risk of gastric cancer when compared with that of the CC + CT genotype (OR = 1.75; 95%CI = 1.01-3.02). In conclusion, our study suggests that the *IL-10* C819T polymorphism is associated with an increased risk of gastric cancer in co-dominant, dominant, and recessive models.

Key words: *IL-10* C819T; Polymorphism; Gastric cancer

INTRODUCTION

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death worldwide (International Agency for Research on Cancer, 2012). It is indicated that *Helicobacter pylori* infections are associated with susceptibility to gastric cancer (Figueiredo et al., 2015; Venerito et al., 2015). However, the precise etiology of this cancer remains unclear. Many previous studies have reported that polymorphisms in inflammation-related genes, such as tumor necrosis factor-alpha, toll-like receptors, and interleukins (IL), may be involved in the development of gastric cancer (Assis et al., 2014; Castaño-Rodríguez et al., 2014; Li et al., 2014; Qadri et al., 2014).

IL-10 is a pleiotropic cytokine, and a wealth of evidence supports its regulatory role in carcinogenesis and tumor growth (Tanikawa et al., 2012; Holan et al., 2014; Qi et al., 2014; Yu et al., 2014). There are several polymorphisms in the *IL-10* gene, and *IL-10* C819T (rs1800871) is a common single nucleotide polymorphism (SNP) in the promoter region. Many studies have reported the association between the *IL-10* C819T gene polymorphism and development of gastric cancer, but the results are inconclusive (Kamangar et al., 2006; Sugimoto et al., 2007; Xiao et al., 2009; Sun et al., 2010; Liu et al., 2011; Xue et al., 2012; Zeng et al., 2012). Therefore, we carried out a hospital-based case-control study to evaluate the correlation between the *IL-10* C819T polymorphism and susceptibility to gastric cancer in a Chinese population.

MATERIAL AND METHODS

Patients

Samples from a total of 157 patients with gastric cancer were consecutively collected from the Gastrointestinal Department of Internal Medicine, Guizhou Provincial People's Hospital between October 2012 and February 2015. These patients received gastrointestinal endoscopy and were diagnosed independently by two pathologists.

Control samples were consecutively were collected from individuals who obtained regular health examinations. All control subjects received the gastrointestinal endoscopy and were confirmed to be free of gastric cancer by pathologists. All control subjects were free of cancers, digestive diseases, and serious kidney and liver diseases. Finally, a total of 249 subjects were recruited as controls.

The demographic, lifestyle, and clinical information were collected from medical records, including gender, age, family history of cancer, body mass index (BMI), tobacco smoking, alcohol consumption, tumor-node-metastasis (TNM) stage, Lauren classification, and presence of *H. pylori* infection. The *H. pylori* infection was determined by a rapid urea breath test.

Signed informed consent was obtained from each participant prior to joining this study, and the protocol was approved by the Ethics Committee of Guizhou Provincial People's Hospital.

DNA extraction and genotyping

Collected blood samples were stored in a tube with ethylene diamine tetra-acetic acid and kept at -20°C until use. TIANamp Blood DNA Kit (Tiangen, Beijing, China) was used to perform DNA extraction. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was used to genotype for the *IL-10* C819T polymorphism. The forward and reverse primers of *IL-10* C819T for PCR were 5'-TCATTCTATGTGCTGGAGATGG-3' and 5'-TGGGGGAAGTGGGTAAGAGT-3', respectively. The restriction enzyme for *IL-10* C819T was *Mse*I. The digested fragments for the C allele of *IL-10* C819T were 93 and 116 bp, and the fragment for the T allele was 209 bp. The PCR consisted of: denaturation at 95°C for 5 min; 30 cycles of denaturation at 95°C for 30 s, annealing at 59°C for 60 s, and extension at 72°C for 60 s; and a final extension step at 72°C for 10 min.

Statistical analysis

The demographic, lifestyle, and clinical data as well as genotype distributions between gastric cancer patients and control subjects were analyzed by chi-square test. The goodness-of-fit χ^2-test was used to analyze whether the genotype distribution of *IL-10* C819T deviated from the Hardy-Weinberg equilibrium (HWE). The association between demographic, lifestyle, and clinical characteristics and the development of gastric cancer was estimated by univariate logistic regression analysis. Unconditional regression analysis was used to analyze the association between the *IL-10* C819T polymorphism and risk of gastric cancer. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to describe the results. The statistical analysis was conducted by the SPSS 17.0 statistical software (SPSS, Chicago, IL, USA).

RESULTS

The demographic and clinical characteristics of gastric cancer patients and control subjects are described in Table 1. Compared with the controls, patients with gastric cancer were more likely to be male (OR = 1.53; 95%CI = 1.00-2.36), be older (OR = 1.57; 95%CI = 1.03-2.40), have a higher BMI (OR = 1.96; 95%CI = 1.15-3.34), have a habit of alcohol consumption (OR = 1.69; 95%CI = 1.11-2.58), and suffer from *H. pylori* infection (OR = 1.97; 95%CI = 1.29-3.01). However, no significant difference was identified between gastric cancer patients and control subjects in terms of tobacco smoking and family history of cancer. Of 157 patients with gastric cancer, 73 (46.50%) of them were at TNM stage I-II, 84 (53.50%) were at TNM stage III-IV, 82 (52.23%) were intestinal type, and 75 (47.77%) were diffuse type.

Table 1. Characteristics of patients with gastric cancer and control subjects.

Variables	Patients	%	Controls	%	χ^2 test	OR (95%CI)	P value
Age, years							
<55	65	41.40	131	52.61		1.00 (Ref.)	-
≥55	92	58.60	118	47.39	4.85	1.57 (1.03-2.40)	0.03
Gender							
Female	57	36.31	116	46.59		1.00 (Ref.)	-
Male	100	63.69	133	53.41	4.16	1.53 (1.00-2.36)	0.04
BMI							
<55	117	74.52	212	85.14		1.00 (Ref.)	-
≥55	40	25.48	37	14.86	7.06	1.96 (1.15-3.34)	0.008
Tobacco smokers							
No	88	56.05	159	63.86		1.00 (Ref.)	-
Yes	69	43.95	90	36.14	2.46	1.39 (0.90-2.12)	0.12
Alcohol consumption							
No	71	45.22	145	58.23		1.00 (Ref.)	-
Yes	86	54.78	104	41.77	6.55	1.69 (1.11-2.58)	0.01
Family history of cancer							
No	143	91.08	238	95.58		1.00 (Ref.)	-
Yes	14	8.92	11	4.42	3.37	2.12 (0.87-5.30)	0.07
H. pylori infection							
No	67	42.68	148	59.44		1.00 (Ref.)	-
Yes	90	57.32	101	40.56	10.86	1.97 (1.29-3.01)	0.001
TNM stage							
I-II	73	46.50					
III-IV	84	53.50					
Lauren classification							
Intestinal	82	52.23					
Diffuse	75	47.77					

The number of CC, CT, and TT genotypes of *IL-10* C819T were 38 (24.20%), 83 (52.87%), and 36 (22.93%) in gastric cancer patients, respectively. The number of CC, CT, and TT genotypes of IL-10 C819T were 85 (34.14%), 127 (51.00%), and 36 (14.46%) in control subjects, respectively (Table 2). By the χ^2-test, there was a significant difference between genotype distributions of *IL-10* C819T in gastric cancer patients and controls (χ^2 = 7.09; P = 0.03). By chi-square test, the genotype distributions of *IL-10* C819T did not deviate from the HWE in gastric cancer patients and control subjects, and the P values were 0.47 and 0.30, respectively.

Table 2. Distribution of *IL-10* C819T between gastric cancer patients and controls.

IL-10 C819T	Patients	%	Controls	%	χ^2 test	P value	P for HWE	
							In cases	In controls
CC	38	24.20	85	34.14				
CT	83	52.87	127	51.00				
TT	36	22.93	36	14.46	7.09	0.03	0.47	0.30

By unconditional logistic regression analysis, the TT genotype of *IL-10* C819T was significantly associated with increased risk of gastric cancer when compared with the CC genotype (OR = 2.24; 95%CI = 1.17-4.26; P = 0.008) (Table 3). In a dominant model, we found that the CT + TT genotype of *IL-10* C819T was associated with susceptibility to gastric cancer compared to the CC genotype (OR = 1.63; 95%CI = 1.02-2.64; P = 0.03). In a recessive model, the TT genotype of *IL-10* C819T was correlated with a higher risk of gastric cancer when compared with the CC + CT genotype (OR = 1.75; 95%CI = 1.01-3.02; P = 0.03).

Table 3. Association between *IL-10* C819T gene polymorphisms and development of gastric cancer.

IL-10 C819T	Patients	%	Controls	%	OR (95%CI)[1]	P value
Co-dominant						
CC	38	24.20	85	34.14	1.0 (Ref.)	-
CT	83	52.87	127	51.00	1.46 (0.89-2.42)	0.11
TT	36	22.93	36	14.46	2.24 (1.17-4.26)	0.008
Dominant						
CC	38	24.20	85	34.14	1.0 (Ref.)	-
CT+TT	119	75.80	163	65.46	1.63 (1.02-2.64)	0.03
Recessive						
CC+CT	121	77.07	212	85.14	1.0 (Ref.)	-
TT	36	22.93	36	14.46	1.75 (1.01-3.02)	0.03

[1]Adjusted for age, gender, BMI, alcohol consumption, and *Helicobacter pylori* infection.

DISCUSSION

We conducted a case-control study to investigate the association between the *IL-10* C819T polymorphism and development of gastric cancer, and we found that the TT genotype of *IL-10* C819T was associated with susceptibility to gastric cancer.

The *IL-10* gene has a key role in regulating the complex network of reactions in the process of carcinogenesis. The level of *IL-10* gene production is associated with autoimmunity, transplantation tolerance, and carcinogenesis. Functional polymorphisms of *IL-10* could alter the anti-inflammatory process. Previous studies have investigated the association between the *IL-10* C819T polymorphism and development of several kinds of cancers, such as breast cancer, prostate cancer, acute myeloid leukemia, lung cancer, and esophageal cancer (Kong et al., 2010; Liu et al., 2010; Yao et al., 2013; Yang and Fa, 2015; Zhang et al., 2015). Kong et al. (2010) conducted a study in a Chinese population and suggested that there was no association between the *IL-10* C819T polymorphism and risk of breast cancer. Liu et al. (2010) identified the role of three SNPs in the promoter of *IL-10* in the risk of prostate cancer, and they reported that *IL-10* C819T was not a risk factor for prostate cancer. Yao et al. (2013) reported that the *IL-10* C819T site was associated with acute myeloid leukemia in a Chinese population. Zhang et al. (2015) performed a case-control study with 330 lung cancer patients and 336 cancer free controls and reported that the *IL-10* C819T polymorphism is a molecular marker for lung cancer susceptibility. Yang and Fa (2015) did not suggest a significant association between the *IL-10* C819T polymorphism and susceptibility to esophageal cancer.

Previous studies have reported the association between the *IL-10* C819T polymorphism and development of gastric cancer, but the results are inconclusive (Kamangar et al., 2006; Sugimoto et al., 2007; Xiao et al., 2009; Sun et al., 2010; Liu et al., 2011; Xue et al., 2012; Zeng et al., 2012). Several studies suggested that the *IL-10* C819T polymorphism was associated with an increased risk of gastric cancer in Japanese and Chinese populations (Sugimoto et al., 2007; Sun et al., 2010; Xue et al., 2012; Zeng et al., 2012). However, some studies did not find a significant role for the *IL-10* C819T polymorphism in susceptibility to gastric cancer (Kamangar et al., 2006; Xiao et al., 2009; Liu et al., 2011). In our study, we found that *IL-10* C819T was correlated with the development of gastric cancer, and the results of our study are in line with the results of previous studies.

In conclusion, our study suggests that the *IL-10* C819T polymorphism is associated with an increased risk of gastric cancer in co-dominant, dominant, and recessive models. Further studies with larger sample sizes are greatly needed to confirm our findings.

Conflicts of interest

The authors declare no conflict of interest.

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