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Original Article

Association between four SNPs in IL-4 and the risk of gastric cancer in a Chinese population

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Abstract: Gastric cancer (GC) is the 5th most prevalent cancer. The etiology of GC is still poorly understood. We performed a case-control study in a Chinese population to investigate the association of rs2243248 (-1098 G/T), rs2227284 (-33 C/T), rs2243250 (-589 T/C) and rs2070874 (-107 T/C) polymorphisms and haplotypes with the development of gastric cancer in a Chinese population. A total of 362 patients with gastric cancer and 384 controls were recruited between December 2013 and December 2015. Genotyping of rs2243248 (-1098 G/T), rs2227284 (-33 C/T), rs2243250 (-589 T/C) and rs2070874 (-107 T/C) was performed in a 384-well plate format on the sequenom MassARRAY platform, and analyzed by MALDI-TOF MS. The TC and CC genotypes of rs2243250 (-589 T/C) were associated with an increased risk of gastric cancer when compared with the TT genotype, with adjusted ORs (95% CI) of 1.52 (1.07-2.15) and 2.13 (1.30-3.51), respectively. The TTTT haplotype revealed a reduced risk of gastric cancer (OR=0.65, 95% CI=0.45-0.94). No linkage disequilibrium was found among IL-4 rs2243248, rs2227284, rs2243250 and rs2070874. In summary, our findings support a significant association of IL-4 rs2243250 polymorphism with the risk of gastric cancer in the Chinese population, and IL-4 haplotype contributes to the development of this disease.

Keywords: IL-4, polymorphism, haplotype, gastric cancer

Introduction

Gastric cancer (GC) is the 5th most prevalent cancer and the 3nd deadliest cancer worldwide [1]. To date, GC is still prevalent in Asian countries, such as China and Japan [1]. The etiology of GC is still poorly understood. Studies provide evidences that alcohol consumption, Helicobacter pylori (H. pylori) infection, obesity, and a high salt diet may contribute to the progress of GC [2]. Currently, Helicobacter pylori (H. pylori) infection has been considered as a crucial event in the development of atrophic gastritis, and it also contributes to the pathogenesis of gastric carcinoma [3-5]. Previous studies have found that almost half of the population in the world is infected with H. pylori [6]. However, most infected individuals infected H. pylori actually develop gastric cancer eventually, suggesting that other factors, such as genetic and environmental factors, play an important role in the risk of gastric cancer [7].

The inflammatory microenvironment is involved in the gastric cancer risk, since the gastric cancer is a pathogen-induced carcinoma. The interleukins (IL) play an important role in the mechanism of inflammation. IL-4 is a typical cytokine of Th2 cells, and it plays an important role in inhibiting the inflammation reaction and transplantation rejection due to the cytokine network to the Th1 [8]. IL-4 also contributes to the activating macrophages and suppressing the secretion of proinflammatory cytokines to promote tumor cells proliferation [9]. The gene encoding IL-4 is located on chromosome 5 (5q31.1), and has approximated 10 Kb of base pairs and 4 exons [10]. Some studies have revealed an association between IL-4 genetic polymorphisms and gastric cancer risk, but their results

Table 1. Demographic and clinical characteristics of included subjects

Variable	Patients N=362	%	Controls N=384	%	χ^2	*P* value
Sex						
Female	116	32.04	183	47.66		
Male	246	67.96	201	52.34	18.91	<0.001
Irregular dietary habit						
No	242	66.85	303	78.91		
Yes	120	33.15	81	21.09	13.76	<0.001
Age, years						
Mean age	54.53±8.78		54.85±9.76			
≤50	97	26.80	128	33.33		
>50	265	73.20	256	66.67	3.78	0.06
Family history of cancer						
No	332	91.71	367	95.57		
Yes	30	8.29	17	4.43	4.70	0.03
Smoking habit						
Never	189	52.21	234	60.94		
Few-moderate	121	33.43	119	30.99		
Heavy	52	14.36	31	8.07	9.48	0.01
Drinking habit						
Never	139	38.40	207	53.91		
Few-moderate	131	36.19	143	37.24		
Heavy	92	25.41	34	8.85	39.97	<0.001
H. pylori						
No	100	27.62	199	51.82		
Yes	262	72.38	185	48.18	45.43	<0.001

are conflicting [11-15]. Four common variation SNPs are reported and have multiple functions in many cancers, including rs2243248 (-1098 G/T), rs2227284 (-33 C/T), rs2243250 (-589 T/C) and rs2070874 (-107 T/C) [16-22]. So far, no study investigates the association between rs2227284, rs2070874 and rs180127 and risk of gastric cancer. Therefore, we carried out a case-control study to investigate the association of rs2243248 (-1098 G/T), rs2227284 (-33 C/T), rs2243250 (-589 T/C) and rs2070874 (-107 T/C) polymorphisms and haplotypes with the development of gastric cancer in a Chinese population.

Materials and methods

Subjects

A hospital-based case-control study was performed in this study. A total of 362 gastric cancer patients were collected from the Affiliated Hospital, Logistics University of People's Armed Policed Force and Navy General Hospital of Chinese PLA between December 2013 and December 2015. All patients with gastric cancer were confirmed by pathological examination with pathologists. The inclusion criteria for gastric cancer patients included patients with no history of metastasis or recurrent tumor, not receiving any chemotherapy and anti-cancer treatment, and without end-stage liver or kidney diseases.

A total of 384 controls were healthy individuals that received digestive endoscopy examinations were enrolled from the outpatient clinics and physical examination centers of the affiliated hospital of Logistics University of People's Armed Policed Force and Navy General Hospital of Chinese PLA. These control subjects were confirmed to have no history of any malignant tumors and digestive diseases. All participants were informed the general purpose of our study prior to enrollment. Signed consent forms were obtained from all participants. The study obtained approval from the ethics committee of the affiliated hospital of Logistics University of People's Armed Policed Force and Navy General Hospital of Chinese PLA.

The demographic and clinical variables of patients with gastric cancer and control subjects were recruited from their medical records. The demographic variables included sex, age, family history of cancer, irregular dietary habit, smoking habit and drinking habit. The clinical variables included H. pylori.

The H. pylori infection was confirmed by ELISA (Diagnostic Automation, CA, United States) and/or a rapid urea breath test. Positive results

Table 2. Relationship between IL-4 rs2243248 (-1098 G/T), rs2227284 (-33 C/T) and rs2070874 (-107 T/C) and risk of gastric cancer

Variable	Patients N=362	%	Controls N=384	%	χ^2 value	*P* value	Patients		Controls	
							χ^2 for HWE	*P* value	χ^2 for HWE	*P* value
rs2243248 (-1098 G/T)										
GG	171	47.24	191	49.74						
GT	141	38.95	149	38.80						
TT	50	13.81	44	11.46	1.06	0.59	3.64	0.06	3.16	0.08
rs2227284 (-33 C/T)										
CC	155	42.82	170	44.27						
CT	163	45.03	162	42.19						
TT	44	12.15	52	13.54	0.71	0.70	0.01	0.91	1.79	0.18
rs2243250 (-589 T/C)										
TT	144	39.78	187	48.70						
TC	156	43.09	154	40.10						
CC	62	17.13	43	11.20	8.40	0.02	3.03	0.08	1.71	0.19
rs2070874 (-107 T/C)										
TT	327	90.33	354	92.19						
TC	25	6.91	25	6.51						
CC	10	2.76	5	1.30	2.09	0.35	60.15	<0.001	24.31	<0.001

by either of the two examinations were considered as H. pylori infection.

DNA extraction and genotyping

Three mL peripheral venous blood samples, collected from each participant after enrollment, were kept in tubes with 0.5 M ethylenediaminetetraacetic acid. Genomic DNA was extracted using a TIANamp Blood DNA Kit (Tiangen, Beijing, China) according to the manufacturer's instructions, and kept at -80°C for later use. Genotyping of rs2243248 (-1098 G/T), rs2227284 (-33 C/T), rs2243250 (-589 T/C) and rs2070874 (-107 T/C) was performed in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). Primers of the four SNPs for polymerase chain reaction amplification and single base extension assays were designed by Sequenom Assay Design 3.1 software. The PCR reaction for genotyping IL-4 rs2243248 (-1098 G/T), rs2227284 (-33 C/T), rs2243250 (-589 T/C) and rs2070874 (-107 T/C) was carried out in a 5 μL reaction mixture, following by the SAP and iPLEX reaction. The PCR products of IL-4 rs2243248 (-1098 G/T), rs2227284 (-33 C/T), rs2243250 (-589 T/C) and rs2070874 (-107 T/C) are then desalted, dispensed to a SpectroCHIP and analyzed with MALDI-TOF MS.

Statistical analysis

The differences in the demographic and clinical variables of patients with gastric cancer and controls were analyzed by Chi-square test or Fisher's exact test. The Hardy-Weinberg equilibrium (HWE) of genotype distributions of IL-4 rs2243248 (-1098 G/T), rs2227284 (-33 C/T), rs2243250 (-589 T/C) and rs2070874 (-107 T/C) was assessed by Chi-square (χ^2) test with one degree of freedom. Binary logistic regression analysis was used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs). The linkage disequilibrium and haplotype analyses for IL-4 rs2243248, rs2227284, rs2243250 and rs2070874 were evaluated by SHEsis software (http://analysis.bio-x.cn/myAnalysis.php) [23]. Statistical analysis was also performed using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp). Statistical significance was indicated by a value of *p*-value <0.05.

Results

We observed that significant differences were found between sex (χ^2=18.91, P<0.001), regular diet (χ^2=13.76, P<0.001), family history of cancer (χ^2=4.70, P=0.03), smoking habit (χ^2=9.48, P=0.01), drinking habit (χ^2=39.97,

Table 3. Association of environmental factors with the risk of gastric cancer

Variable		*B*	*S.E*	*Wald*	*P* value	*OR (95% CI)*
Age		-0.001	0.009	0.01	0.92	0.99 (0.98-1.02)
Sex	Female					1.0 (Ref.)
	Male	0.79	0.17	21.71	<0.001	2.20 (1.58-3.07)
Irregular dietary habit	No					1.0 (Ref.)
	Yes	0.67	0.19	12.87	<0.001	1.96 (1.36-2.83)
Family history of cancer	No					1.0 (Ref.)
	Yes	1.03	0.35	8.70	0.003	2.80 (1.41-5.53)
Smoking habit	Never					1.0 (Ref.)
	Few-moderate	0.22	0.18	1.44	0.23	1.24 (0.87-1.77)
	Heavy	0.67	0.27	6.12	0.01	1.96 (1.15-3.35)
Drinking habit	Never					1.0 (Ref.)
	Few-moderate	0.29	0.18	2.71	0.10	1.34 (0.95-1.90)
	Heavy	1.48	0.25	35.42	<0.001	4.41 (2.70-7.18)
H. pylori	No					1.0 (Ref.)
	Yes	1.13	0.17	43.88	<0.001	3.11 (2.22-4.35)
rs2243248 (-1098 G/T)	GG			0.99	0.61	1.0 (Ref.)
	GT	0.05	0.18	0.07	0.80	1.06 (0.74-1.48)
	TT	0.26	0.26	0.99	0.32	1.29 (0.78-2.14)
rs2227284 (-33 C/T)	CC			0.08	0.03	1.0 (Ref.)
	CT	-0.01	0.18	0.00	0.95	0.99 (0.70-1.40)
	TT	-0.08	0.26	0.08	0.77	0.93 (0.55-1.55)
rs2243250 (-589 T/C)	TT			10.89	0.01	1.0 (Ref.)
	TC	0.42	0.18	5.51	0.02	1.52 (1.07-2.15)
	CC	0.76	0.25	8.92	0.00	2.13 (1.30-3.51)
rs2070874 (-107 T/C)	TT			2.94	0.23	1.0 (Ref.)
	TC	0.19	0.33	0.33	0.56	1.21 (0.64-2.28)
	CC	0.98	0.60	2.68	0.10	2.68 (0.82-8.70)

P<0.001) and H. pylori infection (χ^2=45.43, P<0.001) (**Table 1**).

A significant difference was found in the genotype frequencies of IL-4 rs2243250 (-589 T/C) between gastric cancer patients and controls (χ2=8.40, P=0.02). We observed that the rs2070874 (-107 T/C) genotype frequencies deviated from the HWE in both gastric cancer patients (χ^2 for HWE: 60.15; P<0.001) and controls (χ^2 for HWE: 24.31; P<0.001). However, the rs2243248 (-1098 G/T), rs2227284 (-33 C/T) and rs2243250 (-589 T/C) were in line with HWE in both patients with gastric cancer and controls (**Table 2**).

By binary logistic regression analysis, we observed that patients with gastric cancer were more likely to be male (OR=2.20, 95% CI=1.58-3.07), have a habit of irregular dietary (OR=1.96, 95% CI=1.36-2.83) and heavy smoking (OR=1.96, 95% CI=1.15-3.35) and drinking habit (OR=4.41, 95% CI=2.70-7.18), have infection of H. pylori (OR=3.11, 95% CI=2.22-4.35), and have a family history of cancer (OR=2.80, 95% CI=1.41-5.53) (**Table 3**). Moreover, we indicated that the TC and CC genotypes of rs2243250 (-589 T/C) were associated with an increased risk of gastric cancer when compared with the TT genotype, with adjusted ORs (95% CI) of 1.52 (1.07-2.15) and 2.13 (1.30-3.51), respectively (**Table 3**). However, no significant differences were found between rs2243248 (-1098 G/T), rs2227284 (-33 C/T) and rs2070874 (-107 T/C) polymorphisms and gastric cancer risk.

No linkage disequilibrium was found among IL-4 rs2243248, rs2227284, rs2243250 and rs2070874 (**Figures 1** and **2**). Eight common haplotypes (frequency >0.03) were selected,

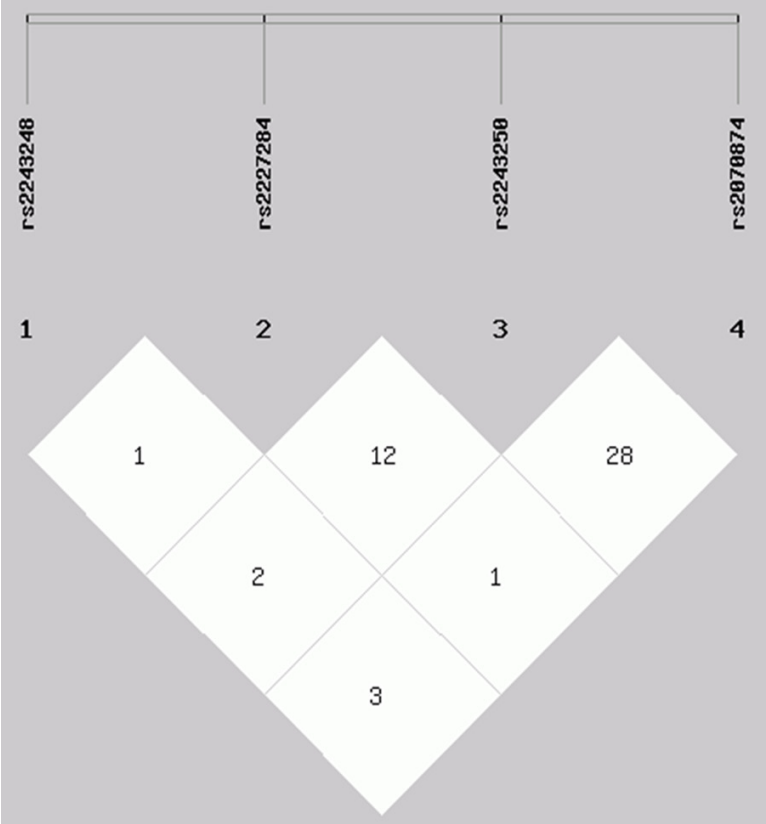

Figure 1. D' of linkage disequilibrium test for IL-4 rs2243248, rs2227284, rs2243250 and rs2070874.

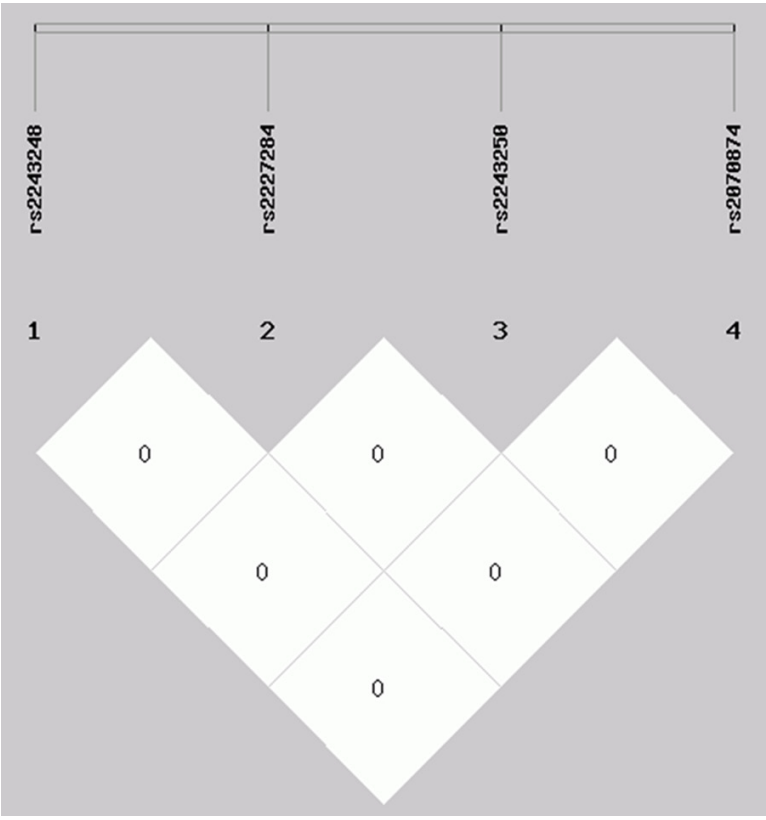

Figure 2. r^2 of linkage disequilibrium test for rs2243248, rs2227284, rs2243250 and rs2070874.

and the TTTT haplotype revealed a reduced risk of gastric cancer (OR=0.65, 95% CI=0.45-0.94) (**Table 4**). The other seven haplotypes were not correlated with the development of gastric cancer.

Discussion

This present study explored the potential association of IL-4 polymorphisms and haplotypes with the susceptibility to gastric cancer. We observed that the TC and CC genotypes of IL-4 rs2243250 (-589 T/C) were associated with an elevated risk of gastric cancer, and the TTTT haplotype was correlated with a reduced risk of gastric cancer.

H. pylori is an established risk factor for the risk of gastric cancer, and it is reported that about 75% of gastric cancer could be attributed to the long-term infection of *H. pylori* [24]. The long-term infection of *H. pylori* could cause inflammation in the microenvironmentals, such as cytokines, chemokines and oxidative free radicals. Inflammation caused by *H. pylori* shows a Th2-mediated response. IL-4 is an important cytokine of Th2 cells, which contributes to the development of Th2 in the response process of *H. pylori* inflammatory. Previous study has reported that IL-4 is produced by the dendritic cells medicated through *H. pylori* infected gastric epithelial cells [25]. Experimental study has revealed that the T cells produced by IL-4 in the peripheral blood are correlated with prognosis and recur-

Table 4. Haplotype analysis of rs2243248-rs2227284-rs2243250-rs2070874 and gastric cancer risk

Haplotype	Patients	%	Controls	%	OR (95% CI)	*P* value
GCCT	67	8.72	75	10.36	0.96 (0.68-1.36)	0.82
GCTC	22	2.86	15	2.07	1.67 (0.86-3.26)	0.13
GCTT	220	28.65	270	37.29	0.83 (0.66-1.03)	0.09
GTCT	25	3.26	36	4.97	0.73 (0.43-1.23)	0.24
GTTT	141	18.36	125	17.27	1.28 (0.98-1.67)	0.07
TCCT	37	4.82	33	4.56	1.23 (0.76-2.00)	0.39
TCTT	119	15.49	102	14.09	1.31 (0.98-1.75)	0.06
TTTT	52	6.77	82	11.33	0.65 (0.45-0.94)	0.02

Global χ^2=16.71, *P* value =0.02.

rence of gastric cancer [26]. Another study has reported that IL-4 mRNA expression could be used as a molecular marker for the stage and differentiation of gastric cancer [27]. Single nucleotide polymorphisms in IL-4 change the levels of gene expression, and consequently influence the susceptibility to diseases.

The association of IL-4 polymorphisms with the development of gastric cancer was reported by many previous studies, but the results of these studies are inconsistent [11-15, 28]. Wu et al. carried out a study of 1045 patients with gastric cancer and 1100 healthy controls in a Chinese population, and found that the TC/CC genotype of rs2070874 showed a protective effect on the risk of gastric cancer compared with the rs2070874 TT genotype [14]. Talebkhan Y et al. performed a study of 31 patients with gastric cancer and 46 controls, and found that IL-4 rs2243250 T allele carriers augmented the risk of gastric cancer to 9.70 fold when compared with those with the C allele [11]. In addition, and the IL-4 rs2243250 T allele showed a drastically amplified risk of gastric cancer for subjects with positive H. pylori [11]. Nevertheless, some studies reported contrary conclusions. Pan et al. recruited a study of 308 pairs of gastric cancer patients and controls, and indicated that IL-4 rs2243250 (-589 T/C) was not correlated with overall gastric cancer risk [12]. Lai et al. done a study of 123 patients with gastric cancer, but failed to find any significant correlation between IL-4 polymorphism and gastric cancer risk [29]. One meta-analysis with seven studies showed that IL-4 rs2243250 polymorphism was associated with a reduced risk of gastric cancer risk in Caucasians, but significant association was absent in Asians [15]. A recent meta-analysis with 11 published case-control studies revealed that IL-4 rs2243250 could not influence the gastric cancer susceptibility [30]. In our study, we found that the TC and CC genotypes of IL-4 rs2243250 were associated with an increased risk of gastric cancer. In addition, we firstly revealed the IL-4 TTTT haplotype was correlated with the gastric cancer risk. The different findings of these studies may be attributed to different genotyping methods and random errors.

The main limitation of this study was that the patients with gastric cancer and controls were recruited from only one hospital, which could not represent other ethnicities. The selection bias is unavoidable. In addition, more interleukin related genes were not considered in this study. Therefore, further studies among other ethnicities are necessary to validate the specific role of IL-4 polymorphism in gastric cancer risk.

In summary, our findings support a significant association of IL-4 rs2243250 polymorphism with the risk of gastric cancer in the Chinese population, and IL-4 TTTT haplotype contributes to the susceptibility to this disease. Further studies are needed to establish the value of IL-4 as a risk biomarker for gastric cancer.

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Disclosure of conflict of interest

None.

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