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Original Article

Roles of IL-4 genetic polymorphisms and haplotypes in the risk of gastric cancer and their interaction with environmental factors

Yuting Yun[1], Weiguo Dong[1], Chunhua Chen[2], Huimin Zhang[3], Niu Shi[3], Miao He[4], Xiufeng Chen[4]

[1]Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, China; [2]Department of Gastroenterology, The Affiliated Hospital of Inner Mongolia Medical College, Hohhot, China; [3]Department of Gastroenterology, The People's Hospital of Inner Mongolia Autonomous Region, Hohhot, China; [4]Department of Gastrointestinal Surgery, Chongqing Cancer Institute, Chongqing, China

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Abstract: Gastric cancer (GC) is the fifth most common cancer and imposes a global cancer burden. IL-4 is a typical cytokine of Th2 cells. IL-4 genetic polymorphisms have multiple functions in many cancers. We performed a case-control study in the Chinese population, and evaluated the association between rs2243250 (590 C/T), rs2227284 (107 T/C), rs2070874 (166 T/C) and rs1801275 (576 Q/R) and gastric cancer risk. A total of 340 gastric cancer patients and 364 controls were enrolled into our study. SNP genotyping of IL-4 rs2243250, rs2227284, rs2070874 and rs1801275 was done in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). We observed the CC genotype of IL-4 rs2243250 was associated with risk of gastric cancer when compared with the TT genotype (OR=2.36, 95% CI=1.49-3.75). Moreover, individuals harboring the CT+CC genotype exposed a higher risk of gastric cancer in comparison with the TT genotype (OR=1.66, 95% CI=1.17-2.35). However, there was no significant association between IL-4 rs2227284, rs2070874 and rs1801275 and gastric cancer risk. The TT+CT genotype of IL-4 rs2243250 showed a significant increased risk of gastric cancer in males (OR=2.48, 95% CI=1.67-3.68) and those without a family history of cancer (OR=1.97, 95% CI=1.44-2.70). In ever drinkers (OR=2.04, 95% CI=1.24-3.37) and H. pylori infected patients (OR=2.31, 95% CI=1.38-3.86), the TT+CT genotype of IL-4 rs2243250 had a higher risk of gastric cancer than non-drinkers (OR=1.77, 95% CI=1.20-2.61) and non-H. pylori infected ones (OR=1.76, 95% CI=1.19-2.62). The CTCA (OR=1.54, 95% CI=1.06-2.24), CTCG (OR=1.83, 95% CI=1.16-2.86) and CTTG (OR=1.89, 95% CI=1.16-3.07) haplotypes showed an increased risk in gastric cancer, while the TCTG (OR=0.22, 95% CI=0.09-0.52), TTCG (OR=0.47, 95% CI=0.32-0.69) and TTTA (OR=0.58, 95% CI=0.42-30.79) haplotypes were associated with an reduction risk of gastric cancer. In conclusion, our study indicated that the IL-4 rs2243250 CC genotype and CT+CC genotype were associated with gastric cancer risk in the Chinese population, and IL-4 haplotypes plays an important role in the development of gastric cancer.

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

Introduction

Gastric cancer (GC) is the fifth most common cancer and imposes a global cancer burden [1]. Although the mortality rate of gastric cancer has declined in recent years [2], many patients are diagnosed at an advanced stage with lymphatic or distant metastasis in the absence of specific symptoms, especially those with early-stage GC. Therefore, it is of great important to early detection for gastric cancer. *Helicobacter pylori* (*H. pylori*) infection is now accepted as a crucial event in the development of atrophic gastritis, and is implicated in the development of gastric carcinoma [1-3]. Gastric cancer develops incrementally beginning with chronic inflammation, and progressing through atrophic inflammation, intestinal metaplasia and dysplasia and finally frank malignancy [4]. Whereas most infected individuals are asymptomatic, chronic *H. pylori* infection in susceptible individuals is associated with variable degrees of mucosal damage. As a result, only a small percentage of infected individuals actually develop gastric cancer. The development of gastric cancer seems to be determined by the bacterial

virulence factors, other environmental factors and genetic factors. Recently, many studies have indicated that many genetic factors play an important role in the development of gastric cancer [5].

The inflammatory microenvironment plays a role in the development of gastric cancer, because the gastric cancer is a pathogen-induced carcinoma. The interleukins (IL) mediate various effects in inflammation. IL-4 plays an important role in regulating the differentiation and activation of T and B lymphocytes and promoting the immune response to Th2 cells [6]. IL-4 has a critical role in alternatively activating macrophages (AAMs) and inhibiting the secretion of proinflammatory cytokines to promote tumor cells, such as IL-1, IL-6 and tumor necrosis factor-α [7]. Previous experimental study have indicated that the IL-4 was unregulated in gastric cancer patients [8]. The gene encoding IL-4 is located on chromosome 5 (5q31.1), and it is in conjunction with other genes for Th2 cytokines. The IL-4 gene has approximated 10Kb of base pairs, and included 4 exons [9]. The polymorphisms of rs2243250, rs2227284, rs2070874 and rs1801275 are the commonly variation of this gene, and the four SNPs have multiple functions in many cancers [10-16]. Currently, several studies reported the association between IL-4 rs2243250 and risk of gastric cancer, but the results are inconsistent. However, no study investigated the rs2227284, rs2070874 and rs180127 and risk of gastric cancer in the current study, we performed a case-control study in a Chinese population, and evaluated the association between rs2243250 (590 C/T), rs2227284 (107 T/C), rs2070874 (166 T/C) and rs1801275 (576 Q/R) and gastric cancer risk.

Materials and methods

Subjects

A hospital-based case-control study was performed in this study. A total of 340 gastric cancer patients were collected from the department of gastroenterology, the People's Hospital of Inner Mongolia Autonomous Region between 2013 and 2015. All gastric cancer patients underwent upper gastrointestinal endoscopy, and then they were confirmed by pathological examination with pathologists. None of patients had received preoperative chemotherapy and anti-cancer treatment prior to enrollment. Gastric cancer patients who had a prior history of metastasis or recurrent tumors, malnutrition, and end-stage liver or kidney diseases were excluded from this study.

During the same time period, a total of 364 controls were recruited from the outpatient clinics of the People's Hospital of Inner Mongolia Autonomous Region and health examination centers between 2013 and 2015. All the control subjects received digestive endoscopy examinations, and they had no history of malignant tumors and digestive diseases.

The demographic and clinical characteristics of gastric cancer patients and controls were collected from the medical records or a self-designed questionnaire. The questionnaire involved sex, age, family history of cancer, smoking habit, drinking habit, TNM stage at diagnosis, tumor size, and Lauren classification.

H. pylori specific IgG was taken to determine whether the involved subjects had *H. pylori* infection by ELISA (Diagnostic Automation, CA, United States) and/or a rapid urea breathe test. Positive by either of the two examinations was considered as *H. pylori* infection.

A face-to-face investigation was conducted in our study. The investigation was completed by trained investigators who received uniform training. All participants were informed the general purpose of our study, but not the research hypothesis, before agreeing to participate. The performance of our study was approved by the ethics committee of the People's Hospital of Inner Mongolia Autonomous Region. All included subjects voluntary participated in our study and signed informed consents prior to enrollment.

The average age of gastric cancer patients was 54.68±8.80 years (ranged 29 to 84 years), and there were 107 (31.47%) females and 233 (68.53%) males. The average age of controls was 54.76±9.81 years (ranged 27 to 91 years), and there were 170 (46.70%) males and 194 (53.30%) females.

DNA extraction and genotyping

Each patient was asked to provide a 3-mL peripheral venous blood sample before receiv-

Table 1. Demographic and clinical characteristics of included subjects

	Variable	Patients N=340	%	Controls N=364	%	χ^2	*P* value
Sex	Female	107	31.47	170	46.70		
	Male	233	68.53	194	53.30	17.09	<0.001
Age, years	Mean age	54.68±8.80		54.76±9.81		-0.12	0.91
	≤50	92	27.06	122	33.52		
	>50	248	72.94	242	66.48	3.47	0.06
Family history of cancer	No	311	91.47	348	95.60		
	Yes	29	8.53	16	4.40	5.02	0.03
Smoking habit	Never	186	54.71	217	59.62		
	Ever	154	45.29	147	40.38	1.73	0.19
Drinking habit	Never	188	55.29	245	67.31		
	Ever	152	44.71	119	32.69	10.72	0.001
H. pylori infection	No	97	28.53	189	51.92		
	Yes	243	71.47	175	48.08	39.89	<0.001
TNM stage	I-II	140	41.18				
	III-IV	200	58.82				
Tumor size, cm	<5	151	44.41				
	≥5	189	55.59				
Lauren classification	Intestinal	131	38.53				
	Diffuse	209	61.47				

Table 2. Genotype distributions of IL-4 rs2243250 (590 C/T), rs2227284 (107 T/C), rs2070874 (168 T/C) and rs1801275 (576 Q/R) between gastric cancer patients and controls

Variable	Patients N=340	%	Controls N=364	%	χ^2 value	*P* value	χ^2 for HWE in Controls	*P* value
rs2243250								
TT	116	34.12	182	50.00				
CT	151	44.41	133	36.54				
CC	73	21.47	49	13.46	19.68	<0.001	3.22	0.07
rs2227284								
TT	227	66.76	246	67.58				
TC	75	22.06	79	21.70				
CC	38	11.18	39	10.71	0.06	0.97	47.77	<0.001
rs2070874								
TT	99	29.12	113	31.04				
TC	146	42.94	159	43.68				
CC	95	27.94	92	25.27	0.71	0.71	2.75	0.09
rs1801275								
AA	122	35.88	145	39.84				
AG	161	47.35	155	42.58				
GG	57	16.76	64	17.58	1.68	0.43	0.10	0.75

ing any anti-cancer treatment. These samples were kept in tubes containing 0.5 M ethylene diaminetetraacetic acid. Genomic DNA was isolated from whole blood using a TIANamp Blood DNA Kit (Tiangen, Beijing, China) according to the manufacturer's instructions, and the DNA samples were stored in -20°C until using. SNP genotyping of was done in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). Primers 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 rs2243250 (590 C/T), rs2227284 (107 T/C), rs2070874 (168 T/C) and rs1801275 (576 Q/R) was performed in 5 μL, following by the SAP and iPLEX reaction. The samples are then analyzed with MALDI-TOF MS.

Table 3. Association of environmental factors and IL-4 rs2243250 (590 C/T), rs2227284 (107 T/C), rs2070874 (168 T/C) and rs1801275 (576 Q/R) with risk of gastric cancer

Variables	B	S.E.	Wals	*P* value	Adjusted OR[1]	95% C.I.
Sex						
Female					1.0	Reference
Male	0.74	0.17	19.01	0.00	2.09	1.50-2.91
Age	0.01	0.01	0.30	0.59	1.01	0.99-1.02
Family history of cancer						
No					1.0	Reference
Yes	0.91	0.35	6.73	0.01	2.49	1.25-4.95
Drinking habit						
Never					1.0	Reference
Ever	0.46	0.17	7.55	0.01	1.59	1.14-2.21
Smoking habit						
Never					1.0	Reference
Ever	0.25	0.17	2.26	0.13	1.28	0.93-1.77
H. pylori infection						
No					1.0	Reference
Yes	1.10	0.17	41.70	0.00	2.99	2.15-4.17
rs2243250						
TT			15.70	0.00	1.0	Reference
CT	0.50	0.18	7.95	0.01	1.66	1.17-2.35
CC	0.86	0.24	13.27	0.00	2.36	1.49-3.75
CT+CC	0.61	0.16	13.70	0.00	1.84	1.33-2.54
rs2227284						
TT			0.50	0.78	1.0	Reference
TC	0.13	0.20	0.41	0.52	1.14	0.77-1.69
CC	0.11	0.26	0.17	0.68	1.11	0.66-1.87
TC+CC	0.11	0.17	0.37	0.54	1.11	0.79-1.56
rs2070874						
TT			0.51	0.77	1.0	Reference
TC	0.04	0.19	0.04	0.85	1.04	0.71-1.52
CC	0.15	0.22	0.48	0.49	1.16	0.76-1.78
TC+CC	0.08	0.18	0.22	0.64	1.09	0.77-1.54
rs1801275						
AA			3.00	0.22	1.0	Reference
AG	0.26	0.18	2.02	0.16	1.29	0.91-1.85
GG	-0.08	0.24	0.10	0.75	0.93	0.58-1.47
AG+GG	0.17	0.17	1.01	0.31	1.18	0.85-1.65

[1]Adjusted for age, sex, family history of cancer, smoking habit, drinking habit and *H. pylori*.

Statistical analysis

Categorical variables are displayed as percentages and frequencies (%). The differences between gastric cancer patients and controls in terms of demographic characteristics were analyzed by Chi-square test. Whether the IL-4 rs2243250 (590 C/T), rs2227284 (107 T/C), rs2070874 (168 T/C) and rs1801275 (576 Q/R) were deviation from the Hardy-Weinberg equilibrium were analyzed by Chi-square (χ^2) test with one degree of freedom. Relationship between IL-4 rs2243250 (590 C/T), rs2227284 (107 T/C), rs2070874 (168 T/C) and rs1801275 (576 Q/R) and risk of gastric cancer were analyzed by multivariate logistic regression analysis, and the results were expressed by odds ratios (ORs) and 95% confidence intervals (CIs). The results were adjusted for potential risk factors of gastric cancer. The linkage disequilibrium and haplotype analysis were evaluated by SHEsis software [17]. The statistical analysis was performed by IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp). *P*-value <0.05 was regarded as significant difference.

Results

Comparison with controls, gastric cancer patients were more likely to be males (χ^2= 17.09, P<0.001), have a family history of cancer (χ^2=5.02, P=0.03), a habit of drinking habit (χ^2=10.72, P=0.001) and infection of *H. pylori* (χ^2=39.89, P<0.001) (**Table 1**).

We observed that the genotype distributions of IL-4 rs2243250 (P=0.07), rs2070874 (P=0.09) and rs1801275 (P= 0.75) were not deviated from the Hardy-Weinberg equilibrium in the controls, while rs2227284 was (P<0.001) (**Table 2**; Supplementary Data).

By multivariate logistic regression analysis, we found that males (OR=2.09, 95% CI=1.50-2.91), those with a family history of cancer

Table 4. Interaction between environmental factors and IL-4 rs2243250 (590 C/T) in the risk of gastric cancer

Variables	Patients		Controls		OR	95% CI	*P* value
	CC	TT+CT	CC	TT+CT	TT+CT vs CC		
Sex							
Female	45	62	81	89	1.25	0.77-2.04	0.36
Male	71	162	101	93	2.48	1.67-3.68	<0.001
Family history of cancer							
No	107	204	177	171	1.97	1.44-2.70	<0.001
Yes	9	20	5	11	1.01	0.27-3.77	0.99
Drinking habit							
Never	71	117	127	118	1.77	1.20-2.61	0.004
Ever	45	107	55	64	2.04	1.24-3.37	0.005
H. pylori infection							
No	30	67	96	93	1.76	1.19-2.62	0.005
Yes	86	157	86	89	2.31	1.38-3.86	0.002

Table 5. Association between clinical characteristics and IL-4 rs2243250 (590 C/T) in gastric cancer patients

Variables	Patients		OR	95% CI	*P* value
	CC	TT+CT	TT+CT vs CC		
TNM stage					
I-II	56	84			
III-IV	60	140	1.56	0.99-2.45	0.06
Tumor size, cm					
<5	54	97			
≥5	62	127	1.14	0.73-1.79	0.57
Lauren classification					
Intestinal	47	84			
Diffuse	69	140	1.14	0.72-1.80	0.59

(OR=2.49, 95% CI=1.25-4.95), ever drinkers (OR=1.59, 95% CI=1.14-2.21) and H. pylori infected subjects (OR=2.99, 95% CI=2.15-4.17) were associated with risk of developing gastric cancer (**Table 3**).

We observed the CC genotype of IL-4 rs2243250 was associated with risk of gastric cancer when compared with the TT genotype (OR=2.36, 95% CI=1.49-3.75). Moreover, individuals harboring the CT+CC genotype exposed a higher risk of gastric cancer in comparison with the TT genotype (OR=1.66, 95% CI=1.17-2.35) (**Table 3**). However, there was no significant association between IL-4 rs2227284, rs2070874 and rs1801275 and gastric cancer risk.

The interaction analyses showed that the TT+CT genotype of IL-4 rs2243250 showed a significant increased risk of gastric cancer in males (OR=2.48, 95% CI=1.67-3.68) and those without a family history of cancer (OR=1.97, 95% CI=1.44-2.70). Moreover, in ever drinkers (OR=2.04, 95% CI=1.24-3.37) and H. pylori infected patients (OR=2.31, 95% CI=1.38-3.86), the TT+CT genotype of IL-4 rs2243250 had a higher risk of gastric cancer than non-drinkers (OR=1.77, 95% CI=1.20-2.61) and non-H. pylori infected ones (OR=1.76, 95% CI=1.19-2.62) (**Table 4**). However, we did not find any interaction between clinical characteristics and IL-4 rs2243250 polymorphism in gastric cancer patients (**Table 5**).

The haplotype analysis did not show linkage disequilibrium (**Figure 1**). Twelve common haplotypes (frequency >0.03 in either the patients or controls has been selected) accounted for the main haplotypes in gastric cancer patients and controls (**Table 6**). The CTCA (OR=1.54, 95% CI=1.06-2.24), CTCG (OR=1.83, 95% CI=1.16-2.86) and CTTG (OR=1.89, 95% CI=1.16-3.07) haplotypes showed an increased risk in gastric cancer, while the TCTG (OR=0.22, 95% CI=0.09-0.52), TTCG (OR=0.47, 95% CI=0.32-0.69) and TTTA (OR=0.58, 95% CI=0.42-30.79) haplotypes were associated with an reduction risk of gastric cancer. The other six haplotypes were not associated with gastric cancer risk.

Discussion

In this study, we observed that the IL-4 rs2243250 was associated with gastric cancer risk. The CCTG, CTCG, CTTA, TTCA, TTCG and TTTG haplotypes were related to the risk of gastric cancer.

H. pylori is an important reason for the development of gastric cancer, and long-term *H. pylori* accounts for about 75% of gastric cancer [18]. During the inflammation caused by *H. pylori* infection, many cytokines, chemokines, oxidative free radicals, and growth factors are produced in the microenvironments. These cyto-

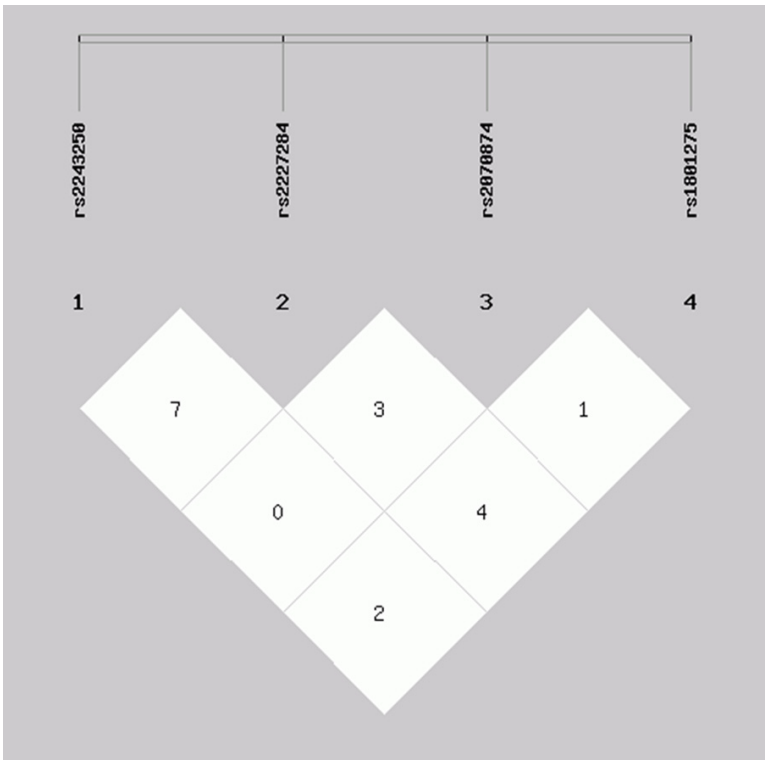

Figure 1. The linkage disequilibrium of IL-4 rs2243250, rs2227284, rs2070874 and rs1801275.

Table 6. Haplotype analysis of the association between IL-4 rs2243250-rs2227284-rs2070874-rs1801275 and gastric cancer risk

Haplotype	Patients	%	Controls	%	OR (95% CI)[1]	*P* value
CTCA	70	10.30	52	7.10	1.54 (1.06-2.24)	0.02
CTCG	53	7.80	33	4.50	1.83 (1.16-2.86)	0.01
CTTA	70	10.20	70	9.70	1.09 (0.77-1.55)	0.63
CTTG	46	6.80	28	3.80	1.89 (1.16-3.07)	0.01
TCCA	27	4.00	32	4.40	0.91 (0.54-1.54)	0.73
TCCG	24	3.60	15	2.00	1.82 (0.94-3.50)	0.07
TCTA	35	5.20	32	4.40	1.22 (0.75-2.00)	0.43
TCTG	6	0.90	30	4.10	0.22 (0.09-0.52)	<0.001
TTCA	96	14.20	103	14.20	1.02 (0.76-1.38)	0.89
TTCG	41	6.00	89	12.20	0.47 (0.32-0.69)	<0.001
TTTA	72	10.60	126	17.30	0.58 (0.42-0.79)	<0.001
TTTG	81	12.00	70	9.60	1.32 (0.94-1.85)	0.11

Overall P<0.001.

kines can lead to DNA damage and epigenetic modifications of DNA, which result in tumorigenesis and progression [19-21]. HP inflammation presents a Th2-mediated response. IL-4 is regarded as a typical cytokine of Th2 cells, and it plays an important role in promoting the occurrence and development of Th2 during the process of the inflammatory response. It is reported that IL-4 is produced by dendritic cells conditioned through the medium of *H. pylori* infected gastric epithelial cells [22]. Previous study have indicated that more IL-4 producing T cells in the peripheral blood are associated with the prognosis of gastric cancer patients [8]. Genetic polymorphisms in IL-4 may influence the individualized expression of protein, and thus influence the susceptibility to gastric cancer.

Several previous studies have reported the association between IL-4 genetic polymorphisms and gastric cancer risk, but the results are inconsistent [23-27]. Wu et al. performed a case-control study of 1045 gastric cancer patients and 1100 controls in a Chinese population, and this study indicated that individuals carrying TC/CC genotype of IL-4 rs2070874 had a 0.73 fold risk of gastric cancer when compared with the TT genotype [26]. Sugimoto et al. performed a study in a Japanese population, and they reported that rs2243250 T allele and rs2070874 C allele was significantly related to a reduced risk of non-cardia gastric cancer [25]. A recent study performed a study with 58 gastric cancer patients and 46 controls,andindicatedthatIL-4rs2243250 T carriers increased the risk of gastritis when compared with the C allele carriers, and the IL-4 rs2243250 polymorphism had an interaction with H. pylori neutrophil activating protein antibodies [23]. However, Pan et al. performed a case-control study with 308 pairs of gastric cancer patients and controls, and they reported that IL-4 rs2243250 had no

association with the gastric cancer risk [24]. Sun et al. performed a meta-analysis with seven studies, and reported that IL-4 polymorphism was related to a lower gastric cancer risk in Caucasians [27]. In our case-control study, we observed that IL-4 rs2243250 CC genotype and CT+CC genotype were related to an increased risk of gastric cancer, and we firstly reported that the IL-4 haplotypes were associated with gastric cancer risk. Therefore, the role of IL-4 in the development of gastric cancer requires more studies to further confirmation.

Our study found an interaction between IL-4 rs2243250 polymorphism and males, drinking habit and *H. pylori* infection. A previous study reported that IL-4 gene polymorphisms concur in selecting the H. pylori infecting strain and influencing the IL-4 signaling pathway [28]. Moreover, a recent study indicated that IL-4 rs2243250 polymorphism augmented the risk of gastric cancer in *H. pylori* positive subjects, which is in line with our results [23]. A previous study found that IL-4 diplotype had an interaction with drinking status to the risk of early stage of oral and pharyngeal carcinomas [29]. We firstly reported an interaction between IL-4 rs2243250 and drinking and males in the risk of gastric cancer, further studies are greatly warranted to confirm our results.

Two limitations should be considered in this study. First, the gastric cancer patients and controls were collected from only one hospital in China, which may not well represent the whole Chinese population, and the selection bias is unavoidable. Second, only 340 gastric cancer patients and 364 controls were enrolled into this study, and the results could be undervalued due to the limitation of sample size.

In conclusion, our study indicated that the IL-4 rs2243250 CC genotype and CT+CC genotype were associated with gastric cancer risk in a Chinese population, and IL-4 haplotypes plays an important role in the development of gastric cancer. IL-4 could be used as a potential biomarker for early detection of gastric cancer.

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Disclosure of conflict of interest

None.

Address correspondence to: Weiguo Dong, Department of Gastroenterology, Renmin Hospital of Wuhan University, No. 99 of Ziyang Road, Wuhan, China. Tel: +86-13986167388; E-mail: dwg@whu.edu.cn; dongwg_wg@163.com

References

[1] Blaser MJ and Parsonnet J. Parasitism by the "slow" bacterium helicobacter pylori leads to altered gastric homeostasis and neoplasia. J Clin Invest 1994; 94: 4-8.

[2] Huang JQ, Sridhar S, Chen Y and Hunt RH. Meta-analysis of the relationship between CagA seropositivity and gastric cancer. Gastroenterology 1998; 126: 1169-1179.

[3] Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N and Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001; 345: 784-789.

[4] Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--first American cancer society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992; 52: 6735-6740.

[5] Choi YJ and Kim N. Gastric cancer and family history. Korean J Intern Med 2016; 31: 1042-1053.

[6] Stott B, Lavender P, Lehmann S, Pennino D, Durham S and Schmidt-Weber CB. Human IL-31 is induced by IL-4 and promotes TH2-driven inflammation. J Allergy Clin Immunol 2013; 132: 446-454, e445.

[7] Van Dyken SJ and Locksley RM. Interleukin-4- and interleukin-13-mediated alternatively activated macrophages: roles in homeostasis and disease. Annu Rev Immunol 2013; 31: 317-343.

[8] Ubukata H, Motohashi G, Tabuchi T, Nagata H, Konishi S and Tabuchi T. Evaluations of interferon-γ/interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients. J Surg Oncol 2010; 102: 742-747.

[9] Sutherland GR, Baker E, Callen DF, Hyland VJ, Wong G, Clark S, Jones SS, Eglinton LK, Shannon MF and Lopez AF. Interleukin 4 is at 5q31 and interleukin 6 is at 7p15. Hum Genet 1988; 79: 335-337.

[10] Chang WS, Wang SC, Chuang CL, Ji HX, Hsiao CL, Hsu CM, Tsai CW, Liu SP, Hsu PC, Lo YL and

Bau DT. Contribution of Interleukin-4 genotypes to lung cancer risk in Taiwan. Anticancer Res 2015; 35: 6297-6301.
[11] Luo Y, Ye Z, Li K, Chen R, Li S and Pang J. Associations between polymorphisms in the IL-4 and IL-4 receptor genes and urinary carcinomas: a meta-analysis. Int J Clin Exp Med 2015; 8: 1227-1233.
[12] Duan Y, Pan C, Shi J, Chen H and Zhang S. Association between interleukin-4 gene intron 3 VNTR polymorphism and cancer risk. Cancer Cell Int 2014; 14: 131.
[13] Sun Z, Pei J, Cui F, Jing Y and Hu C. Lack of association between IL-4 -588C>T polymorphism and NHL susceptibility. Tumour Biol 2014; 35: 4897-4900.
[14] Wu H, Hu J, Liu B, Tao Y, Zhou X and Yuan X. Lack of association between interleukin-4 -524C>T polymorphism and colorectal cancer susceptibility. Tumour Biol 2014; 35: 3657-3662.
[15] Guo J, Shi L, Li M, Xu J, Yan S, Zhang C and Sun G. Association of the interleukin-4Rα rs18-01275 and rs1805015 polymorphisms with glioma risk. Tumour Biol 2014; 35: 573-579.
[16] Zhang J, Xie D, Zhou H, Fan R, Zhang L, Li C, Jin S, Meng Q and Lu J. The -590C/T polymorphism in the IL-4 gene and the risk of cancer: a meta-analysis. Tumour Biol 2013; 34: 2261-2268.
[17] Shi YY and He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005; 15: 97-98.
[18] Peleteiro B, Bastos A, Ferro A and Lunet N. Prevalence of Helicobacter pylori infection worldwide: a systematic review of studies with national coverage. Dig Dis Sci 2014; 59: 1698-1709.
[19] Yasmin R, Siraj S, Hassan A, Khan AR, Abbasi R and Ahmad N. Epigenetic regulation of inflammatory cytokines and associated genes in human malignancies. Mediators Inflamm 2015; 2015: 201703.
[20] Ernst P. Review article: the role of inflammation in the pathogenesis of gastric cancer. Aliment Pharmacol Ther 1999; 13 Suppl 1: 13-18.
[21] Fernandes JV, Cobucci RN, Jatoba CA, Fernandes TA, de Azevedo JW and de Araujo JM. The role of the mediators of inflammation in cancer development. Pathol Oncol Res 2015; 21: 527-534.
[22] Kido M, Tanaka J, Aoki N, Iwamoto S, Nishiura H, Chiba T and Watanabe N. Helicobacter pylori promotes the production of thymic stromal lymphopoietin by gastric epithelial cells and induces dendritic cell-mediated inflammatory Th2 responses. Infect Immun 2010; 78: 108-114.
[23] Talebkhan Y, Doozbakhshan M, Saberi S, Esmaeili M, Karami N, Mohajerani N, Abdirad A, Eshagh Hosseini M, Nahvijou A, Mohagheghi MA and Mohammadi M. Serum antibodies against helicobacter pylori neutrophil activating protein in carriers of IL-4 C-590T genetic polymorphism amplify the risk of gastritis and gastric cancer. Iran Biomed J 2016; [Epub ahead of print].
[24] Pan XF, Wen Y, Loh M, Wen YY, Yang SJ, Zhao ZM, Tian Z, Huang H, Lan H, Chen F, Soong R and Yang CX. Interleukin-4 and -8 gene polymorphisms and risk of gastric cancer in a population in southwestern China. Asian Pac J Cancer Prev 2014; 15: 2951-2957.
[25] Sugimoto M, Yamaoka Y and Furuta T. Influence of interleukin polymorphisms on development of gastric cancer and peptic ulcer. World J Gastroenterol 2010; 16: 1188-1200.
[26] Wu J, Lu Y, Ding YB, Ke Q, Hu ZB, Yan ZG, Xue Y, Zhou Y, Hua ZL, Shu YQ, Liu P, Shen J, Xu YC and Shen HB. Promoter polymorphisms of IL2, IL4, and risk of gastric cancer in a high-risk Chinese population. Mol Carcinog 2009; 48: 626-632.
[27] Sun Z, Cui Y, Jin X and Pei J. Association between IL-4 -590C>T polymorphism and gastric cancer risk. Tumour Biol 2014; 35: 1517-1521.
[28] Zambon CF, Basso D, Marchet A, Fasolo M, Stranges A, Schiavon S, Navaglia F, Greco E, Fogar P, Falda A, D'Odorico A, Rugge M, Nitti D and Plebani M. IL-4 -588C>T polymorphism and IL-4 receptor alpha [Ex5+14A>G; Ex11+828A>G] haplotype concur in selecting H. pylori cagA subtype infections. Clin Chim Acta 2008; 389: 139-145.
[29] Yang CM, Chen HC, Hou YY, Lee MC, Liou HH, Huang SJ, Yen LM, Eng DM, Hsieh YD and Ger LP. A high IL-4 production diplotype is associated with an increased risk but better prognosis of oral and pharyngeal carcinomas. Arch Oral Biol 2014; 59: 35-46.