Int J Clin Exp Med 2015;8(10):17623-17633
www.ijcem.com /ISSN:1940-5901/IJCEM0014661

Original Article

Association of interleukin-17 gene polymorphisms and *Helicobacter pylori* infection with gastric cancer susceptibility: a cumulative and comprehensive meta-analysis

Xue-Feng Li[1*], Ming Shen[2*], Jun-Wei Cai[1], Yu-Qin Zeng[1], Min Li[1], Gong-Li Yang[3], Xiao-Ming Xu[4], Yuan-Yuan Hu[4]

[1]Department of Endocrinology, Taihe Hospital, Hubei University of Medicine, Shiyan 442000, P. R. China; [2]Jiangsu Key Laboratory of Oral Diseases, Department of Dental Implant, Affiliated Hospital of Stomatology, Nanjing Medical University, No. 140 Hanzhong Road, Nanjing 210029, P. R. China; [3]Department of Gastroenterology, Taihe Hospital, Hubei University of Medicine, 32 South Renmin Road, Shiyan 442000, P. R. China; [4]Department of Stomatology, Taihe Hospital, Hubei University of Medicine, Center for Evidence-Based Medicine and Clinical Research, Shiyan 442000, P. R. China. [*]Equal contributors.

Received August 17, 2015; Accepted October 6, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Background: The association between Interleukin-17(IL-17) gene polymorphisms and *Helicobacter pylori* (*H. pylori)* infection and gastric cancer susceptibility were inconsistent. We therefore performed a comprehensive meta-analysis about all three genetic polymorphisms of IL-17 to derive a more precise estimation. Methods: PubMed, Embase, CNKI and Wanfang databases were researched on the associations between IL-17A rs2275913G>A, rs3748067C>T and IL-17F rs763780 T>C and gastric cancer risk. Odds ratio (OR) with a 95% confidence interval (CI) was applied to assess the relationships. Publication bias, sensitivity and cumulative analysis was conducted to guarantee the strength of meta-analysis. Results: Overall, eleven related studies involving 4,478 cases and 5,612 controls were collected. Significantly increased risk between IL-17A rs2275913G>A polymorphism and gastric cancer were observed (A vs. G: OR = 1.22, 95% CI = 1.08-1.37, P<0.01, I^2 = 72.3%; AA vs. GG: OR = 1.55, 95% CI = 1.21-1.99, P<0.01, I^2 = 74.3%; GA + AA vs. GG: OR = 1.19, 95% CI = 1.05-1.39, P<0.01, I^2 = 48.2%; AA vs. GG + GA: OR = 1.50, 95% CI = 1.16-1.95, P<0.01, I^2 = 81.2%). For IL-17F rs3748067C>T and rs763780 T>C polymorphisms, only few significantly increased risk could be found in genetic models. Moreover, *H. pylori* infection also be proved to increase the risk of gastric cancer combined with rs3748067C>T mutation. Conclusions: Our meta-analysis suggests that the three IL-17 polymorphisms were associated with a significantly increased risk of gastric cancer, especially in Chinese.

Keywords: Interleukin-17, polymorphism, stomach neoplasm, Helicobacter pylori

Introduction

Gastric cancer is one of the most common malignancies worldwide. In 2008, 989,600 cases of gastric cancer and 738,000 gastric cancer-related deaths were reported, accounting for 8% of the total cases and 10% of total deaths, respectively [1]. Incidence rates of gastric cancer are highest in Eastern Asia, Eastern Europe, and South America. Individuals infected with *Helicobacterpylori have* an increased risk of developing gastric ulcers and gastric cancer. Epidemical studies have revealed that alcohol consumption, obesity, and high sodium intake are significantly associated with gastric cancer. Moreover, a high intake of fruits and vegetables, which contain antioxidants, vitamins, minerals, and beta-carotene, reduces the risk of gastric cancer [2].

Chronic inflammation is a well-known risk factor for malignant transformation, but its role in cancer initiation is poorly understood [3, 4]. Interleukin-17(IL-17), a novel family of cytokines consisting of six protein members (from IL-17A to IL-17F), plays a pivotal role in many chronic inflammatory diseases and in cancer development [5]. IL-17 is produced by activated CD4+ T

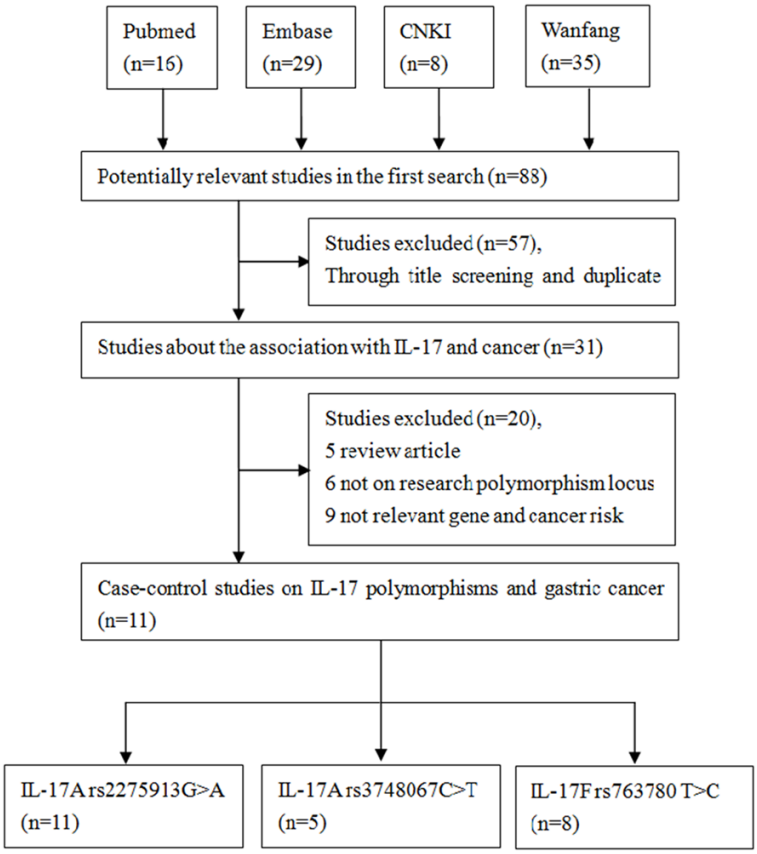

Figure 1. Flow diagram of the study selection process.

cells (Th17 cells) and other leukocytes, such as T cells, natural killer (NK) cells, lymphoid tissue inducer-like (LTi-like) cells, and neutrophils [6]. IL-17A and IL-17F are the most important members of the family, are located in chromosome 6q12, and are comprised of three exons and two introns. Several studies have revealed that IL-17A and IL-17F are over-expressed in various tumor types including breast [7], ovarian [8],and gastric cancers [9]. TNF, IL-6, IL-23, and other cytokines work in synergy to influence tumor properties in human and animal models [10, 11].

H.pylori was discovered in 1983 [12]; it is a definite carcinogen [13] and its infection induces chronic active gastritis. Cancer development in the gastric mucosa [14] is triggered by persistent *H. pylori*-driven inflammation, which transforms normal tissue to precancerous tissue.

Single nucleotide polymorphism (SNP) is an important type of gene mutation, which affects gene regulation by altering transcription and translation by inducing abnormal expression of protein and causing abnormal cell proliferation. In 2009, Shibata et al. reported the first study about the association of rs2275913 of IL-17A with gastric cancer risk in a Japanese population [15]. Since then, several studies have reported the association ofrs2275913G>A, rs374806-7C>T in IL-17A and rs763780 T>C in IL-17F with gastric cancer susceptibility, but these results were inconsistent. Considering the importance of IL-17 and *H. pylori* infection in the development of gastric cancer, we conducted a meta-analysis of all eligible studies to estimate a more precise relationship of gastric cancer with IL-17A (rs2275913G>A, rs3748067C>T) and IL-17F (rs763780 T>C) polymorphisms and *H. pylori* infection.

Materials and methods

Search strategy

Our meta-analysis according to the recommended Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. Electronic searches were conducted in two English databases (Pubmed, Embase) and two Chinese databases (China National Knowledge Infrastructure, CNKI; Wanfang) with the terms “gastric cancer,” “stomach neoplasm,” “Interleukin-17,” “IL-17,” “polymorphism,” “variant,” and their combined phrases. Genetic studies based on the association of gastric cancer withIL-17 polymorphism, published until April 1, 2015. The related articles were reviewed to identify additional potential studies.

Eligibility criteria

All selected studies must complied with the following three criteria: (a) case-control study of gastric cancer and IL-17 polymorphism; (b) sufficient genotype frequency to estimate the odds

Table 1. Characteristics of case-control studies on IL-17A rs2275913G>A, rs3748067C>T and IL-17F rs763780 T>C polymorphisms and gastric cancer risk included in the meta-analysis

First author	Year	Country	Racial/ descent	Source of controls	H. pylori	Case	Control	Genotype distribution						*P* for HWE[a]
								Case			Control			
								G/G	G/A	A/A	G/G	G/A	A/A	
Shibata	2009	Japan	Asian	Hospital controls	No	287	523	94	124	69	175	299	49	<0.01
Luo	2010	China	Asian	Hospital controls	Yes	24	230	11	12	1	58	126	46	0.13
Chen	2010	China	Asian	Population controls	Yes	1042	1090	300	522	220	325	541	224	0.97
Wu	2010	China	Asian	Population controls	No	945	768	210	485	250	193	371	204	0.35
Arisawa	2012	Japan	Asian	Hospital controls	No	333	583	112	137	84	218	293	72	0.08
Rafiei	2013	Iran	Caucasian	NA	No	161	171	56	61	44	78	72	21	0.49
Zhang	2014	China	Asian	Population controls	Yes	260	512	110	102	48	258	187	67	<0.01
Zhu	2014	China	Asian	Hospital controls	Yes	293	550	126	122	45	273	216	61	0.07
Wang	2014	China	Asian	Population controls	Yes	462	462	160	211	91	214	190	58	0.12
Bi	2014	China	Asian	Population controls	No	99	150	32	39	28	41	69	40	0.33
Gao	2015	Chin	Asian	Hospital controls	No	572	572	239	250	83	260	241	72	0.17
								C/C	C/T	T/T	C/C	C/T	T/T	
Arisawa	2012	Japan	Asian	Hospital controls	No	573	327	494	56	23	298	22	7	<0.01
Zhang	2014	China	Asian	Population controls	Yes	260	512	206	30	24	436	47	29	<0.01
Zhu	2014	China	Asian	Hospital controls	Yes	293	550	220	25	48	466	51	33	<0.01
Wang	2014	China	Asian	Population controls	Yes	462	462	39	138	285	19	118	325	0.05
Gao	2015	Chin	Asian	Hospital controls	No	572	572	42	70	460	47	66	458	<0.01
								T/T	T/C	C/C	T/T	T/C	C/C	
Shibata	2009	Japan	Asian	Hospital controls	No	280	523	221	55	4	419	100	4	0.46
Luo	2010	China	Asian	Hospital controls	Yes	24	230	14	10	0	176	51	3	0.75
Wu	2010	China	Asian	Population controls	No	927	777	540	332	55	527	214	36	0.02
Zhang	2014	China	Asian	Population controls	No	260	512	209	30	21	429	53	30	<0.01
Zhu	2014	China	Asian	Hospital controls	No	293	550	241	35	17	463	58	29	<0.01
Wang	2014	China	Asian	Population controls	No	462	462	15	98	349	10	90	362	0.13
Bi	2014	China	Asian	Population controls	No	99	150	68	22	9	108	35	7	0.07
Gao	2015	Chin	Asian	Hospital controls	No	572	572	85	67	420	42	58	472	<0.01

[a]HWE in control; MAF: Minor allele frequency in control group.

ratio (OR) and 95% confidence interval (CI); (c) published in either Chinese or English; (d) if the same or overlapping data were used, the largest or most recently published studies were selected.

Data extraction

Two reviewers (Hu and Xu) independently extracted information from all collected studies according to the inclusion criteria. A third reviewer (Yang) adjudicated all discrepancies for consistency. In all selected studies, the first author's name, publication data, country, race of the studied population (categorized as either Asian or Caucasian), sources of controls, number of cases, and controls with different genotypes were collected.

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) of the control group was assessed. ORs with 95% CIs were calculated to evaluate the strength of the association of the IL-17A rs2275913G>A andrs3748067C>T and IL-17F rs763780T>C polymorphisms with gastric cancer risk. For the IL-17A rs2275913G>A polymorphism, the pooled ORs were obtained for allele contrast (A vs. G), co-dominant model (AG vs. AA, GG vs. AA), dominant model (GA + GG vs. AA), and recessive model (GG vs. AA + GA). These genetic models were also assessed in the IL-17A rs3748067C>T and IL-17F rs763780 T>C variants. Furthermore, subgroup analysis with ethnicity and study design were analyzed statistically. Heterogeneity was assessed with the Cochran's Q test and I^2 method [17, 18]. Meta-regression was conducted to examine analyses that exhibited heterogeneity. ORs were estimated with a random-effects model (DerSimonian and Laird method) when the *P* value was less than 0.10 or I^2 was greater than 50%; otherwise, a fixed-effects model (the Mantel-Haenszel method) was adopted. Cumulative

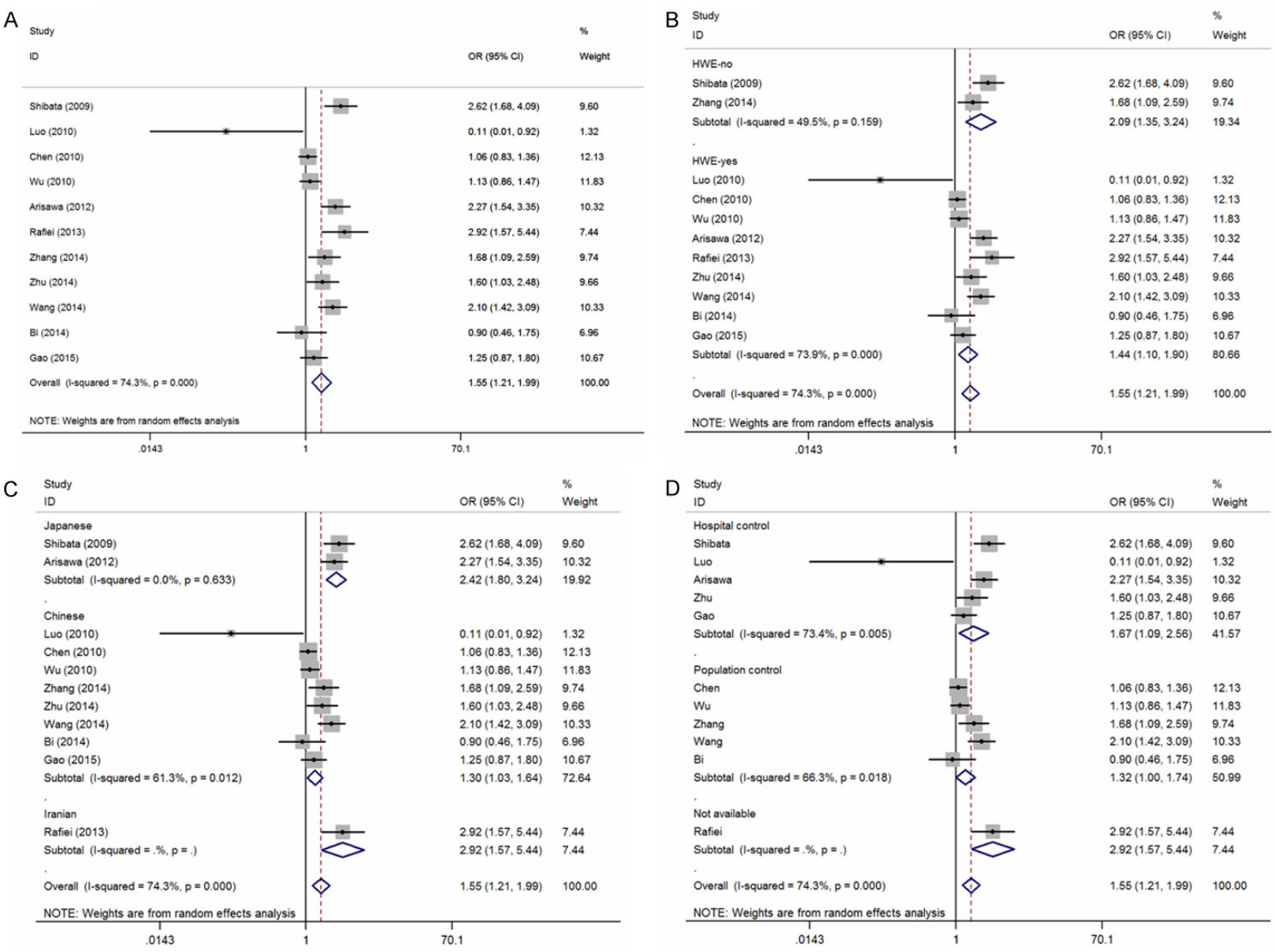

Figure 2. OR and 95% CIs for the associated between IL-17A rs2275913G>A polymorphism with gastric cancer risk in AA vs. GG model. (A for overall populations; B for HWE subgroup; C for sperm for ethnicity subgroup; D for control sources subgroup).

Table 2. Summary ORs and 95% CI of IL-17A rs2275913G>A, rs3748067C>T and IL-17F rs763780T>C polymorphisms and gastric cancer risk

	N*	A vs. G				GA vs. GG				AA vs. GG				GA + AA vs.GG				AA vs. GG + GA			
rs2275913G>A		OR	95% CI	P	I^2 (%)[a]	OR	95% CI	*P*	I^2 (%)[a]	OR	95% CI	*P*	I^2 (%)[a]	OR	95% CI	*P*	I^2 (%)[a]	OR	95% CI	*P*	I^2 (%)[a]
Total	11	1.22	1.08-1.37	<0.01	72.3	1.08	0.95-1.23	0.22	42.5	1.55	1.21-1.99	<0.01	74.3	1.19	1.05-1.39	<0.01	48.2	1.50	1.16-1.95	<0.01	81.2
HWE	9	1.18	1.03-1.36	0.02	75.4	1.12	1.01-1.23	0.03	33.2	1.44	1.10-1.90	<0.01	73.9	1.18	1.02-1.37	0.03	54.8	1.38	1.06-1.79	0.02	77.2
Ethnicity																					
Asian	10	1.19	1.06-1.33	<0.01	70.5	1.08	0.94-1.23	0.29	48.0	1.48	1.15-1.90	<0.01	73.4	1.17	1.03-1.33	0.02	49.2	1.43	1.10-1.86	0.01	81.0
China	8	1.14	1.00-1.30	0.06	70.5	1.16	1.04-1.28	<0.01	32.7	1.30	1.03-1.64	0.03	61.3	1.18	1.00-1.38	0.05	58.7	1.20	1.00-1.44	0.04	49.1
Japan	2	1.39	1.21-1.60	<0.01	0	0.84	0.67-1.05	0.13	0	2.42	1.80-3.24	<0.01	0	1.11	0.90-1.37	0.33	0	2.66	2.05-3.46	<0.01	0
Design																					
HC	5	1.21	1.00-1.45	0.05	69.0	1.00	0.86-1.15	0.96	48.2	1.67	1.09-2.56	0.02	73.4	1.11	1.14-1.30	0.06	43.9	1.69	1.05-2.71	0.03	81.4
PC	5	1.16	0.99-1.36	0.06	73.3	1.17	1.04-1.32	0.01	40.3	1.32	1.00-1.74	0.05	66.3	1.22	1.00-1.48	0.05	60.7	1.20	0.97-1.48	0.10	55.9
H. pylori																					
Positive	5	1.26	0.91-1.75	0.17	84.6	1.09	0.76-1.57	0.63	61.0	1.37	0.66-2.87	0.40	82.2	1.12	0.71-1.77	0.62	77.9	1.35	0.74-2.47	0.33	77.8
Negative	5	1.01	0.83-1.23	0.92	43.0	0.99	0.79-1.25	0.95	0	0.91	0.66-1.24	0.54	0	0.96	0.78-1.19	0.72	0	0.93	0.70-1.23	0.61	0
rs3748067C>T		T vs. C				CT vs. CC				TT vs. CC				CT + TT vs. CC				TT vs. CC + CT			
Total	5	1.30	0.84-2.03	0.24	92.0	1.10	0.81-1.51	0.53	42.9	1.38	0.70-2.70	0.35	86.5	1.22	0.82-1.86	0.34	78.2	1.41	0.81-2.45	0.22	88.4
Ethnicity																					
China	4	1.23	0.74-2.06	0.43	93.5	1.01	0.72-1.44	0.94	42.3	1.28	0.58-2.80	0.54	89.6	1.14	0.68-1.90	0.62	82.8	1.34	0.72-2.47	0.35	90.8
Design																					
HC	3	1.56	0.96-2.53	0.08	87.6	1.24	0.92-1.67	0.17	0	1.88	0.93-3.80	0.08	79.0	1.55	1.22-1.95	<0.01	33.4	1.78	0.79-3.97	0.16	87.5
PC	2	1.01	0.44-2.30	0.99	94.4	0.89	0.38-2.08	0.80	79.1	0.87	0.22-2.46	0.89	91.6	0.85	0.27-2.69	0.79	91.2	1.04	0.42-2.53	0.94	87.8
H. pylori																					
Positive	3	1.22	0.43-3.45	0.71	96.4	1.30	0.86-1.98	0.22	0	2.66	1.73-4.08	<0.01	0	1.84	1.35-2.12	<0.01	0	2.59	1.69-3.96	<0.01	0
Negative	3	1.21	0.85-1.72	0.30	48.5	0.85	0.49-1.46	0.55	0	1.56	0.41-5.89	0.51	75.6	1.13	0.74-1.71	0.51	0	1.59	0.40-6.37	0.51	77.4
rs763780T>C		C vs. T				TC vs. TT				CC vs. TT				TC + CC vs.TT				CC vs. TT + TC			
Total	8	1.08	0.81-1.44	0.60	86.3	1.29	1.12-1.48	<0.01	19.7	1.08	0.67-1.75	0.76	72.2	1.07	0.78-1.48	0.67	79.2	1.04	0.76-1.44	0.79	61.0
Ethnicity																					
China	7	1.08	0.78-1.50	0.65	88.2	1.33	1.15-1.55	<0.01	16.9	1.03	0.62-1.72	0.90	75.2	1.07	0.73-1.57	0.73	82.1	1.02	0.73-1.42	0.92	64.3
Design																					
HC	4	1.10	0.61-1.63	0.99	87.7	1.17	0.93-1.47	0.19	6.4	0.87	0.40-1.91	0.73	68.2	0.99	0.57-1.74	0.99	84.2	0.86	0.50-1.48	0.58	47.4
PC	4	1.18	0.92-1.52	1.20	68.9	1.36	1.14-1.63	<0.01	33.3	1.34	0.99-1.80	0.06	26.0	1.38	1.17-1.63	<0.01	33.7	1.07	0.86-1.34	0.54	43.2

*Numbers of comparisons; [a]Test for heterogeneity; PC: Population controls; HC: Hospital controls; NA: Not available.

Table 3. Sensitivity analyses through deleted each study to reflect the influence of the individual dataset to the pooled ORs in AA vs. GG model

Study omitted	Estimate	95% Conf.	Interval
Shibata (2009)	1.4688481	1.1438769	1.8861425
Luo (2010)	1.6015942	1.2627679	2.0313344
Chen (2010)	1.6341802	1.2511117	2.1345372
Wu (2010)	1.6157954	1.2221409	2.1362467
Arisawa (2012)	1.4849805	1.1446395	1.9265167
Rafiei (2013)	1.4767568	1.1480416	1.899592
Zhang (2014)	1.5356791	1.1649987	2.024303
Zhu (2014)	1.5439249	1.1705883	2.03633
Wang (2014)	1.4976768	1.146505	1.956412
Bi (2014)	1.6158128	1.2443976	2.098084
Gao (2015)	1.58785	1.1989176	2.102953
Combined	1.5509443	1.2059415	1.9946474

meta-analyses and sensitivity analyses were conducted to evaluate the stability of the results by sequentially removing each study in each polymorphism. Potential publication bias of literature was analyzed by Egger's linear regression and Begg's funnel plots [19]. Statistical analysis was performed using Stata version 11.0 (Stata Corporation, College Station, TX, USA) with two-sided *P* values; P<0.05 was considered significant.

Results

Study characteristics

In total, 88 studies were obtained through the literature search; a flow chart of the study selection process is shown in **Figure 1**. The title and duplicate screening step excluded 57 studies. Of the remaining 31 studies, 20 studies were excluded (five were reviews, six were not on the research polymorphism locus, and nine did not focused on the relevant gene and gastric cancer risk). Thus, data from 11 publications met the inclusion criteria [15, 20-29], of which 11 were eligible articles on IL-17A rs2275913G>A with 4,478 cases and 5,612 controls [15, 20-29], 5 were published studies on IL-17A rs3748067C>T involving 2,160 cases and 2,422 controls [22, 24, 25, 27, 29]; and 8 included researches on IL-17F rs763780 T>C consisting 2,917 cases and 3,776 controls [15, 21, 24-29]. Some studies that deviated from HWE existed in all three polymorphism loci, of which two studies were of IL-17A rs2275913G>A [15, 24], four studies of IL-17A rs3748067C>T [22, 24, 25, 29], and four studies of IL-17F rs763780 T>C [21, 24, 25, 29]. Characteristics of the selected studies were summarized in **Table 1**.

Quantitative analysis

IL-17A rs2275913G>A polymorphism: Results of the pool analyses focused on IL-17A rs2275913G>A revealed a significantly increased risk of gastric cancer associated with the genotype mutation in four genetic models (A vs. G: OR = 1.22, 95% CI = 1.08-1.37, P<0.01, I^2 = 72.3%; AA vs. GG: OR = 1.55, 95% CI = 1.21-1.99, P<0.01, I^2 = 74.3% (**Figure 2**); GA + AA vs. GG: OR = 1.19, 95% CI = 1.05-1.39, P<0.01, I^2 = 48.2%; AA vs. GG + GA: OR = 1.50, 95% CI = 1.16-1.95, P<0.01, I^2 = 81.2%) (**Table 2**). In the subsequent analysis without the two studies that deviated from HWE, a consistent association were found in all five genotype models between IL-17A rs2275913G>A polymorphism and gastric cancer risk.

Heterogeneities existed in the following four models: A vs. G, AA vs. GG, and AA vs. GG + GA. Meta-regression analyses were conducted and indicated that ethnicity (Chinese and Japanese population) could explain the τ^2 values in these genetic models(AA vs. GG: 72.5%, P = 0.02; AA vs. GG + GA: 79.6%, P<0.01). However, subgroup analysis by ethnicity and control design revealed the heterogeneities of some models, which showed increased risks.

Sensitivity analysis showed that no single study qualitatively changed the pooled ORs (**Table 3** for AA vs. GG model), indicating that the results of this meta-analysis are highly stable (**Figure 3** for AA vs. GG model). The study of Rafiei et al. [23] in 2013 showed that the results of a cumulative analysis by publication date gradually became positive with the incidence of gastric cancer (**Figure 4** for AA vs. GG model). Publication bias was determined by Begg's funnel plots, and not revealed any asymmetrical evidence (**Figure 5** for AA vs. GG model). The results were also supported further by the Egger's test analysis (A vs. G: P = 0.78; GA vs. GG: P = 0.20; AA vs. GG: P = 0.67; GA + AA vs. GG: P = 0.40; AA vs. GG + GA: P = 0.34).

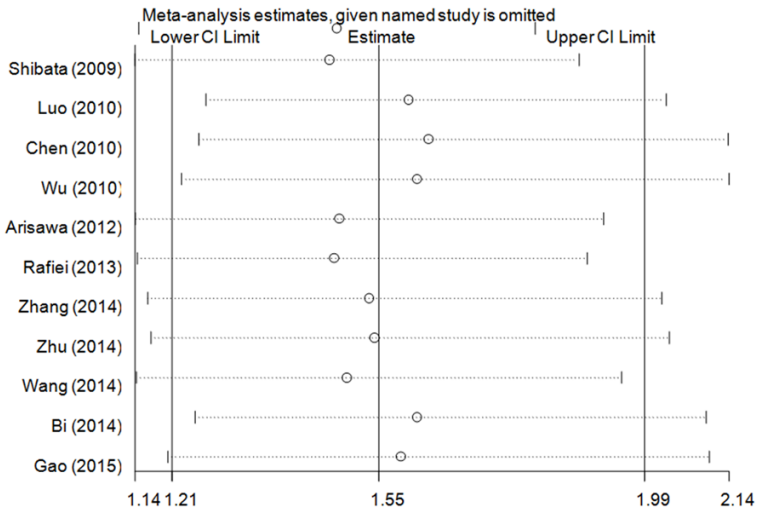

Figure 3. Sensitivity analysis through deleting each study to reflect the influence of the individual dataset to the pooled ORs in AA vs. GG model of IL-17A rs2275913G>A polymorphism.

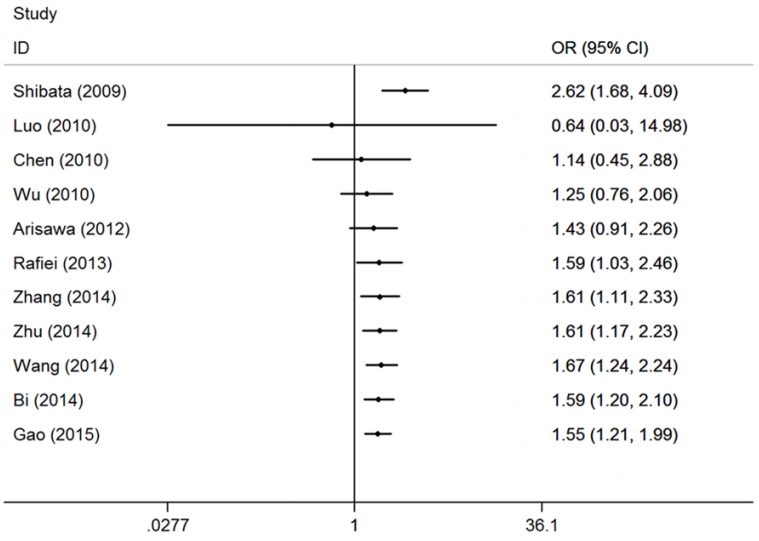

Figure 4. Cumulative meta-analyses according to publication year in AA vs. GG model of IL-17A rs2275913G>A polymorphism.

IL-17A rs3748067C>T: Five studies involving 2,160 cases and 2,422 controls were included for the determination of an association of IL-17A rs3748067C>T polymorphism with gastric cancer risk. No significant association was found in all five genetic models (for T vs. C, OR = 1.30, 95% CI = 0.84-2.03, P = 0.24, I^2 = 92.0%; for CT vs. CC, OR = 1.10, 95% CI = 0.81-1.51, P = 0.53, I^2 = 42.9%; for TT vs. CC, OR = 1.38, 95% CI = 0.70-2.70, P = 0.35, I^2 = 86.5% for CT + TT vs. CC, OR = 1.22, 95% CI = 0.82-1.86, P = 0.34, I^2 = 78.2%; for TT vs. CC + CT, OR = 1.41, 95% CI = 0.81-2.45, P = 0.22, I^2 = 88.4%) (**Table 2**). Stratified and subgroup analysis were conducted according to ethnicity and control design, which revealed few significant associations in hospital-control studies. No conspicuous change in the pooled ORs was found in the sensitivity analysis, except the study of Wang et al. Only one publication bias was revealed, indicating that our results are statistically robust (T vs. C: P = 0.23; CT vs. CC: P = 0.07; TT vs. CC: P = 0.93; CT + TT vs. CC: P = 0.04; TT vs. CC + CT: P = 0.17).

IL-17F rs763780 T>C polymorphism: Seven related publications with 2,917 cases and 3,776 controls reported the association of IL-17F rs763780 T>C polymorphisms with gastric cancer risk. Significant result was only observed in the TC vs. TT model (for C vs. T, OR = 1.08, 95% CI = 0.81-1.44, P = 0.60, I^2 = 86.3%; for TC vs. TT, OR = 1.29, 95% CI = 1.12-1.48, P<0.01, I^2 = 19.7%; for CC vs. TT, OR = 1.08, 95% CI = 0.67-1.75, P = 0.76, I^2 = 72.2%; for TC + CC vs. TT, OR = 1.07, 95% CI = 0.78-1.48, P = 0. 67, I^2 = 79.2%; for CC vs. TT + TC, OR = 1.04, 95% CI = 0.76-1.44, P = 0.79, I^2 = 61.0%) (**Table 2**). Subsequent stratified analysis according to ethnicity and control design were conducted, which showed consistent results in the subgroup analysis of Chinese or hospital controls.

Sensitivity analysis and publication bias were determined. No conspicuous change of the pooled ORs was found in the sensitivity analysis and publication bias (C vs. T: P = 0.83; TC vs. TT: P = 0.26; CC vs. TT: P = 0.35; TC + CC vs.TT: P = 0.43; CC vs. TT + TC: P = 0.08), except the study of Wu et al.

IL-17 polymorphisms and H. pylori infection: Based on the collected studies, only five eligible papers described IL-17A rs2275913G>A

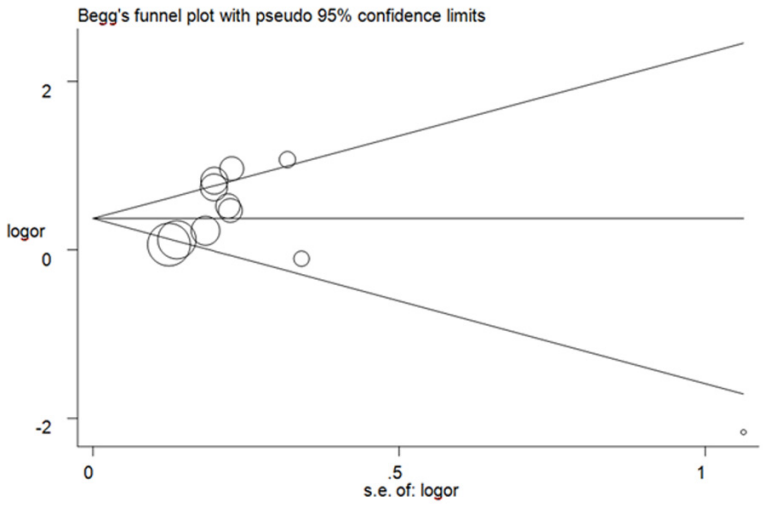

Figure 5. Funnel plot analysis to detect publication bias for AA vs. GG model of IL-17A rs2275913G>A polymorphism. Circles represent the weight of studies.

polymorphism and three papers described IL-17F rs3748067C>T polymorphisms combined with the H. pylori infection status (**Table 1**). Quantitative synthesis indicated H. pylori infection was an increased risk for the development of gastric cancer when combined with IL-17F rs3748067C>T mutation (for TT vs. CC, OR = 2.66, 95% CI = 1.73-4.68, P<0.01, I^2 = 0%; for CT + TT vs. CC, OR = 1.84, 95% CI = 1.35-2.12, P<0.01, I^2 = 0%; for TT vs. CC + CT, OR = 2.59, 95% CI = 1.69-3.96, P = 0.04, I^2 = 0%), but not with IL-17A rs2275913G>A polymorphism (**Table 2**).

Discussion

Genetic susceptibility to cancers has attracted growing attention to the study of gene polymorphisms involved in tumorigenesis. Inflammation and related cytokines play an important role during the epithelial transformation from an ulcer to gastric cancer. The inflammatory state is necessary to maintain and promote cancer progression, involving tumor tissue rebuilding, angiogenesis, metastasis, and suppression of the innate anticancer immune response [30]. Genetic and epigenetic mutations trigger cell transformation and maintain the autonomous proliferation of the transformed cells.

IL-17, a novel cytokine family consisting of six homologous members (from IL-17A to IL-17F), plays an important role in connecting innate and adaptive immunity [31]. Molecular research had suggested that IL-17 is an essential proinflammatory cytokine that evokes cytokine and chemokine secretion by different cell types, such as mesenchymal cells and myeloid cells, to recruit monocytes and neutrophils into the inflammatory microenvironment [32]. Furthermore, IL-17 promotes the expression of antimicrobial peptides and facilitates host defense mechanism against infections [33, 34].

Several molecular epidemiological studies have been conducted to evaluate the risk of IL-17 polymorphismsingastric cancer susceptibility. However, the results always conflicted with published articles. In 2006, Shibata et al. [15] reported that the A allele (OR = 1.42, 95% CI = 1.09-1.85, P = 0.01) and A/A homozygote (OR = 3.53, 95% CI = 2.34-5.34, P<0.0001) of the IL-17A rs2275913G>A polymorphism have significantly increased risks for the development of gastric cancer in a Japanese population. However, in 2007, Chen et al. [20] found no significant association in a Chinese population. In the subsequent published articles by Arisawa et al. [22], Rafiei A et al. [23], Zhu et al. [25], and Zhang et al. [24], significantly elevated risks of gastric cancer were observed because of the IL-17A rs2275913G>A mutation. Our meta-analysis revealed a significantly increased risk for gastric cancer in most of the genetic models of the IL-17A rs2275913G>A polymorphism. Similar results were found when the data were stratified by ethnicity and design. According to our analysis, heterogeneity could be revealed with stratified analysis; moreover, meta-regression indicated that the ethnicity might contribute to the heterogeneity.

For the IL-17A rs3748067C>T and IL-17F rs763780 T>C polymorphisms, there are five and eight research articles from 2009, including 2,160 cases with 2,422 controls, and 2,917 cases with 3,776 controls, respectively. Results of the overall population studies demonstrated a negative association of the IL-17A rs3748067C>T polymorphism with gastric can-

cer, but the subgroup analysis revealed a positive correlation between this polymorphism and H. pylori positive infection status. Furthermore, although risks were found in most of the genetic models of the association between gastric cancer and the IL-17F rs763780 T>C polymorphism, the pooled ORs did not change in Chinese population without any heterogeneity, demonstrating that the results of this meta-analysis are stable.

The association between H. pylori infection and gastric cancer has been reported previously. Our meta-analysis also found that the H. pylori infection combined with IL-17A rs3748067C>T was associated with gastric cancer susceptibility. However, because of the small sample size and limited studies, it is currently unclear whether the polymorphism is merely a marker of H. pylori-induced gastric cancer in patients. Further research is needed to investigate this relationship.

Our meta-analysis, including 4,478 cases and 5,612 controls from 11 published studies explored the association of IL-17 polymorphism with gastric cancer risk. The included cases and controls in this meta-analysis were more extensive than in the prior four meta-analyses in terms of the number of contained studies [35-37]. Furthermore, this study conducted a more comprehensive and detailed evaluation than the prior meta-analyses. Overall, we found that IL-17A rs2275913G>A polymorphism was significantly associated with gastric cancer risk based on both the total population and subgroup analyses, which was consistent with prior results. Moreover, for the first time, our results suggested that IL-17A rs3748067C>T might increase the risk of gastric cancer when combined with H. pylori infection.

Despite our efforts, there are some of the limitations in performing a cumulative and comprehensive meta-analysis. First, all results are based on unadjusted estimates that lacked original data from the selected studies. The assessment of the relation of the gene-environment interactions with gastric cancer development could not be observed. Second, because of the small sample size and limited research, the evaluation of the effect of gene-gene interactions and the haplotype analyses could not be conducted and illustrated clearly. Third, only studies published in Chinese and English were included. Fourth, heterogeneity was exhibited in some models in our meta-analysis, but meta-regression and subgroup analyses were conducted to reduce and avoid the occurrence of heterogeneity, which may leaded to a decrease in the reliability of these results.

In conclusion, our results were significant as they indicated that the three polymorphisms of *IL-17* gene play an important role during gastric cancer development, especially when combined with H. pylori infection. Moreover, further case-control studies are needed to more precisely investigate the relationships between polymorphisms and potential gene-gene and gene-environment interactions.

Acknowledgements

Supported by grant No. D20142102 from Ministry of Education of Hubei Province.

Disclosure of conflict of interest

None.

Address correspondence to: Yuan-Yuan Hu, Department of Stomatology, Taihe Hospital, Hubei University of Medicine, Center for Evidence-Based Medicine and Clinical Research, 32 South Renmin Road, Shiyan 442000, P. R. China. Tel: +86 719 8801427; Fax: +86-719-8801218; E-mail: hyy-19820922@yeah.net

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] van den Brandt PA, Goldbohm RA. Nutrition in the prevention of gastrointestinal cancer. Best Pract Res Clin Gastroenterol 2006; 20: 589-603.

[3] Scheller J, Ohnesorge N, Rose-John S. Interleukin-6 trans-signalling in chronic inflammation and cancer. Scand J Immunol 2006; 63: 321-9.

[4] Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol 2013; 33 Suppl 1: S79-84.

[5] Wu D, Wu P, Huang Q, Liu Y, Ye J, Huang J. Interleukin-17: a promoter in colorectal cancer progression. Clin Dev Immunol 2013; 2013: 436307.

[6] Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. Nat Rev Immunol 2010; 10: 479-89.

[7] Yang L, Qi Y, Hu J, Tang L, Zhao S, Shan B. Expression of Th17 cells in breast cancer tissue and its association with clinical parameters. Cell Biochem Biophys 2012; 62: 153-9.
[8] Lan C, Huang X, Lin S, Huang H, Cai Q, Lu J, Liu J. High density of IL-17-producing cells is associated with improved prognosis for advanced epithelial ovarian cancer. Cell Tissue Res 2013; 352: 351-9.
[9] Meng XY, Zhou CH, Ma J, Jiang C, Ji P. Expression of interleukin-17 and its clinical significance in gastric cancer patients. Med Oncol 2012; 29: 3024-8.
[10] Becker C, Fantini MC, Schramm C, Lehr HA, Wirtz S, Nikolaev A, Burg J, Strand S, Kiesslich R, Huber S, Ito H, Nishimoto N, Yoshizaki K, Kishimoto T, Galle PR, Blessing M, Rose-John S, Neurath MF. TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. Immunity 2004; 21: 491-501.
[11] Qian X, Gu L, Ning H, Zhang Y, Hsueh EC, Fu M, Hu X, Wei L, Hoft DF, Liu J. Increased Th17 cells in the tumor microenvironment is mediated by IL-23 via tumor-secreted prostaglandin E2. J Immunol 2013; 190: 5894-902.
[12] Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983; 1: 1273-5.
[13] Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001; 345: 784-9.
[14] Posselt G, Backert S, Wessler S. The functional interplay of Helicobacter pylori factors with gastric epithelial cells induces a multi-step process in pathogenesis. Cell Commun Signal 2013; 11: 77.
[15] Shibata T, Tahara T, Hirata I, Arisawa T. Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis. Hum Immunol 2009; 70: 547-51.
[16] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-41.
[17] Attia J, Thakkinstian A, D'Este C. Meta-analyses of molecular association studies: methodologic lessons for genetic epidemiology. J Clin Epidemiol 2003; 56: 297-303.
[18] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.
[19] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.
[20] Jian CJ. Association study of polymorphisms in il23r and il17a genes with the susceptibility of gastric cancer. [Master's thesis]. Nanjing: Nanjing Medical University; 2010.
[21] Wu X, Zeng Z, Chen B, Yu J, Xue L, Hao Y, Chen M, Sung JJ, Hu P. Association between polymorphisms in interleukin-17A and interleukin-17F genes and risks of gastric cancer. Int J Cancer 2010; 127: 86-92.
[22] Arisawa T, Tahara T, Shiroeda H, Matsue Y, Minato T, Nomura T, Yamada H, Hayashi R, Saito T, Matsunaga K, Fukuyama T, Hayashi N, Otsuka T, Fukumura A, Nakamura M, Shibata T. Genetic polymorphisms of IL17A and pri-microRNA-938, targeting IL17A 3'-UTR, influence susceptibility to gastric cancer. Hum Immunol 2012; 73: 747-52.
[23] Rafiei A, Hosseini V, Janbabai G, Ghorbani A, Ajami A, Farzmandfar T, Azizi MD, Gilbreath JJ, Merrell DS. Polymorphism in the interleukin-17A promoter contributes to gastric cancer. World J Gastroenterol 2013; 19: 5693-9.
[24] Zhang X, Zheng L, Sun Y. Analysis of the association of interleukin-17 gene polymorphisms with gastric cancer risk and interaction with Helicobacter pylori infection in a Chinese population. Tumour Biol 2014; 35: 1575-80.
[25] Qinghai Z, Yanying W, Yunfang C, Xukui Z, Xiaoqiao Z. Effect of interleukin-17A and interleukin-17F gene polymorphisms on the risk of gastric cancer in a Chinese population. Gene 2014; 537: 328-32.
[26] Yuan L. Association Analysis of Interleukin-17 Genes' Single Nucleotide Polymorphisms (SNPs) with H. Pylori Infection Associated Gastric Disease in Chinese Population [Master's thesis]. Chongqing: Third Military Medical University; 2010.
[27] Wang N, Yang J, Lu J, Qiao Q, Bao G, Wu T, He X. IL-17 gene polymorphism is associated with susceptibility to gastric cancer. Tumour Biol 2014: 35: 10025-30.
[28] Bi L. The association between IL-17A and IL-17F gene polymorphisms and the gastric cancer risk in Suzhou population [Master's thesis]. Suzhou: Soochow University 2014.
[29] Gao YW, Xu M, Xu Y, Li D, Zhou S. Effect of three common IL-17 single nucleotide polymorphisms on the risk of developing gastric cancer. Oncol Lett 2015; 9: 1398-402.
[30] Chechlinska M, Kowalewska M, Nowak R. Systemic inflammation as a confounding factor in cancer biomarker discovery and validation. Nat Rev Cancer 2010; 10: 2-3.
[31] Kolls JK, Linden A. Interleukin-17 family members and inflammation. Immunity 2004; 21: 467-76.
[32] Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity 2011; 34: 149-62.
[33] Matsuzaki G, Umemura M. Interleukin-17 as an effector molecule of innate and acquired immunity against infections. Microbiol Immunol 2007; 51: 1139-47.

[34] Kao CY, Chen Y, Thai P, Wachi S, Huang F, Kim C, Harper RW, Wu R. IL-17 markedly up-regulates beta-defensin-2 expression in human airway epithelium via JAK and NF-kappaB signaling pathways. J Immunol 2004; 173: 3482-91.
[35] Dai W, Zhou Q, Tan X, Sun C. IL-17A (-197G/A) and IL-17F (7488T/C) gene polymorphisms and cancer risk in Asian population: A meta-analysis. Onco Targets Ther 2014; 7: 703-11.
[36] Feng B, Fan Y, Wang W, Yao G, Zhai J. IL-17A G197A and C1249T polymorphisms in gastric carcinogenesis. Tumour Biol 2014; 35: 9977-85.
[37] Niu YM, Yuan H, Zhou Y. Interleukin-17 gene polymorphisms contribute to cancer risk. Mediators Inflamm 2014; 2014: 128490.