Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

The IL-17A G-197A and IL-17F 7488T/C polymorphisms are associated with increased risk of cancer in Asians: a meta-analysis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
24 September 2015
Number of times this article has been viewed

Huifen Wang[1,*]
Yanli Zhang[1,*]
Zhaolan Liu[2]
Yin Zhang[3]
Hongchuan Zhao[1]
Shiyu Du[1]

[1]Department of Gastroenterology, China-Japan Friendship Hospital, [2]Center for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, [3]Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, People's Republic of China

*These authors contributed equally to this work

Background: Interleukin-17 (IL-17) is a family of emerged pro-inflammatory cytokines. The IL-17A and IL-17F are two important members of IL-17 family. Previous studies have shown that the functional IL-17A G-197A and IL-17F 7488T/C polymorphisms may contribute to susceptibility to cancer but the results were inconclusive. This meta-analysis was performed to determine the exact association between IL-17 polymorphisms and cancer risk.

Methods: Online databases were searched to identify eligible case–control studies. Pooled odds ratios (ORs) and confidence intervals (CIs) were calculated by fixed-effect models or random-effect models. Publication bias was detected by Egger's test and Begg's test.

Results: Nine eligible case–control studies of IL-17A G-197A and seven studies of IL-17F 7488T/C, including 3,181 cases and 4,005 controls, were identified. Pooled analysis suggested the variant IL-17A-197A allele was associated with increased risk cancer (GA/AA vs GG, OR =1.27, 95% CI: 1.15, 1.41, $P_{heterogeneity}$ =0.374; and A vs G, OR =1.30, 95% CI: 1.17, 1.45, $P_{heterogeneity}$ =0.021). For IL-17F 7488T/C, the homozygote 7488CC genotype significantly increased risk of cancer (CC vs TC/TT, OR =1.36, 95% CI: 0.97, 1.91, $P_{heterogeneity}$ =0.875; and CC vs TT, OR =1.39, 95% CI: 1.03, 1.88, $P_{heterogeneity}$ =0.979), especially for gastric cancer.

Conclusion: The variant IL-17A-197A allele and IL-17F 7488CC genotype were associated with increased risk of cancer, especially for gastric cancer.

Keywords: interleukin-17, gene polymorphism, gastric cancer, risk, meta-analysis

Introduction

Interleukin 17 (IL-17) family is a subset of newly identified pro-inflammatory cytokines. The IL-17 family consists of six members, namely IL-17A, IL-17B, IL-17C, IL-17D, IL-17D, and IL-17F, according to structure similarity and order of discovery.[1,2] The IL-17 receptor family includes five members: IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE.[1] IL-17A and IL-17F are produced by T helper 17 (Th17) cells[3] and are located just adjacent to each other on chromosome 6. Compared with other family members, IL-17A and IL-17F are most homologous in amino acid sequence.[4] IL-17A is the fundamental member of IL-17 family. Evidence demonstrated that IL-17A could induce the expression of various pro-inflammatory genes like metalloproteinase,[5] by activating pro-inflammatory signaling pathways. The IL-17A exerts its modulator function in both innate and adaptive immune systems, and plays an important role in the host defense against extracellular bacteria, protozoa, and fungi.[6,7]

Two common single nucleotide polymorphisms in the region of IL-17A (rs2275913, G-197A) and IL-17F (rs763780, 7488T/C) have been identified and recent studies suggest that the two functional single nucleotide polymorphisms influence the susceptibility to asthma,[8] arthritis,[9] and even cancer.[10–12] But, the reports about IL-17A/F

Correspondence: Shiyu Du
Department of Gastroenterology, China-Japan Friendship Hospital, 2 Yinghua Dongjie, Chaoyang, Beijing 100029, People's Republic of China
Tel +86 10 8420 5504
Fax +86 10 8420 5504
Email dushiyu1975@126.com

polymorphisms and cancer risk were controversial. Wang et al[11] found IL-17A G-197A, but not IL-17F 7488T/C, polymorphism was not associated with the risk of breast cancer. On the other hand, Zhou et al[12] reported both IL-17A G-197A and IL-17F 7488T/C polymorphisms were associated with the development and tumor stage of bladder cancer. It remains inconclusive whether the IL-17A G-197A and IL-17F 7488T/C polymorphisms are correlated with cancer risk or not. Therefore, we performed this meta-analysis to determine the strength of association between IL-17A G-197A and IL-17F 7488T/C polymorphisms and cancer risk by identifying and pooling eligible studies and evaluate the effect of cancer types.

Materials and methods

Selection of eligible studies

To identify eligible studies, we searched PubMed, EMBASE, and Web of Science. Combination of the following key words were used: "IL17A" OR "IL17F", "rs275913" OR "rs763780" to "IL-17" OR "interleukin 17", "polymorphism" OR "single nucleotide polymorphism" OR "SNP", and "neoplasms" OR "cancer" OR "tumor" for Asians. No limitation was performed. The latest research was performed on April 13, 2015. Searching strategy is presented in the supplementary materials (Table S1).

Inclusion and exclusion criteria

Eligible studies were selected according to the following inclusion criteria: 1) case–control studies; 2) investigating the association between IL-17 polymorphisms (IL-17A G-197A and IL-17F 7488T/C) and risk of cancer; 3) cancer diagnosed by histopathology; and 4) available genotype frequencies. Studies that did not provide a detailed genotype frequency were excluded. Titles and abstracts of records were first screened and full text papers were further evaluated to confirm eligibility. Two reviewers (HW and HZ) extracted eligible studies independently according to the inclusion criteria. Disagreement between the two reviewers was discussed until consensus was achieved.

Data extraction

The following data were collected by two reviewers (HW and HZ) independently with a predesigned data-collection form: name of first author, year of publication, country where the study was performed, cancer types, study design, number of cases and controls, genotype frequency in cases and controls. According to the source of control, study design was defined as hospital-based or population-based. Though we defined the hospital-based and hospital-based study, the inclusion criteria and results were same. Sample size was judged with a threshold of 500 participants (large >500 or small <500). Chi-square test for goodness was used for the test of fit Hardy–Winberg equilibrium (HWE) in the controls and $P<0.05$ was considered as disequilibrium of HWE. Two reviewers reached consensus on each item.

Statistical analysis

Pooled odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated to estimate the association strength between IL-17A G-197A and IL-17F 7488T/C polymorphisms and cancer risk. Chi-square based on Q test was used to check the statistical heterogeneity between studies, and the heterogeneity was considered significant when $P<0.10$. The fixed-effects model (based on the Mantel–Haenszel method) and random-effects model (based on the DerSimonian–Laird method) were used to pool the data from different studies. The fixed-effects model was used when there was no significant heterogeneity; otherwise, the random-effects model was applied.[13] The pooled ORs were achieved by calculating a weighted average of OR from each study. A 95% CI was used for statistical significance test and a 95% CI without 1 for OR indicating a significantly increased or reduced cancer risk. The pooled ORs were calculated for five comparison models: allele comparison (A vs a), homozygote comparison (AA vs aa), heterozygote comparison (Aa vs aa), dominant comparison (AA/Aa vs aa), and recessive comparison (AA vs Aa/aa) (A: the mutant allele, a: the wild allele; the -197A and 7488C alleles were considered as mutant alleles).

Subgroup analyses were conducted according to cancer types, study design, HWE, and sample size. Subgroup analysis was not performed for those subgroups with less than two studies. Meta-regression was performed to detect the source of heterogeneity. Publication bias was detected by Begg's test and the Egger' linear regression test, and a $P<0.05$ was considered significant.[14] Sensitivity analyses were performed to identify individual study's effect on pooled results and test the reliability of results; all *P*-values were two-sided. All statistical analyses were calculated with STATA software (version 12.0; StataCorp, College Station, TX, USA).

Results

The process of study selection is shown in Figure 1. In summary, nine studies[10–12,15–20] about IL-17A G-197A and seven studies of IL-17F 7488T/C were identified. The baseline

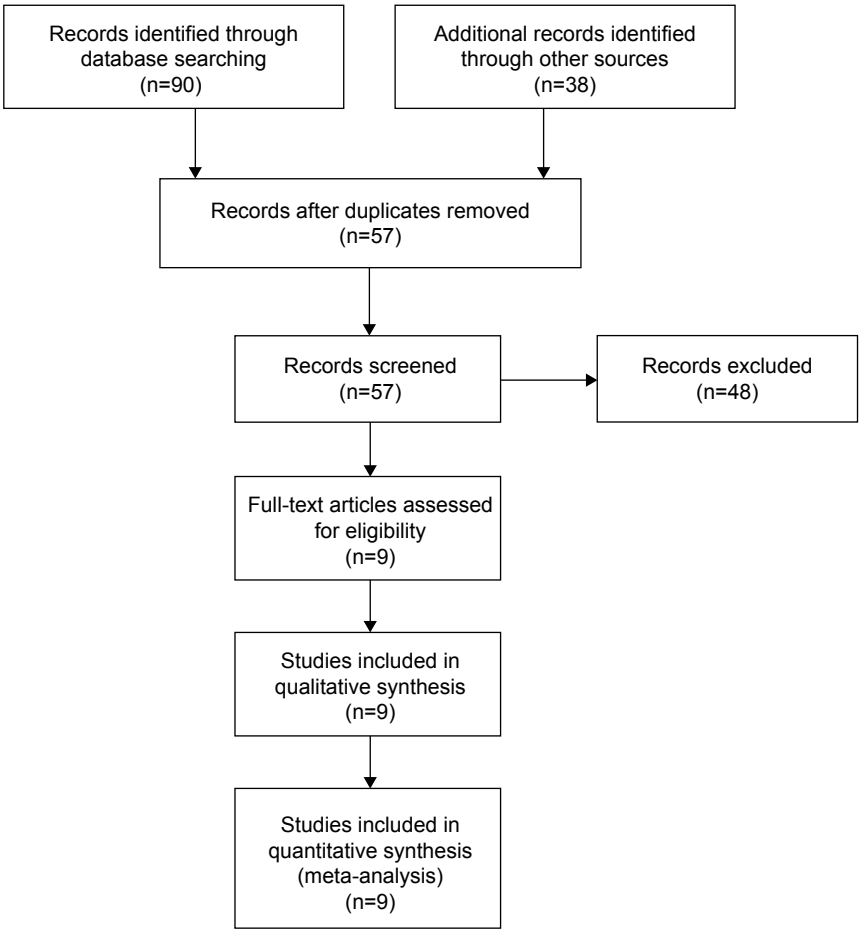

Figure 1 Flowchart of study selection.

characteristics of eligible studies are shown in Table 1. Of note, all eligible studies were conducted in Asia.

Meta-analysis results

A total of nine studies, involving 3,181 cases and 4,005 controls, were available for the analysis of IL-17A G-197A. By pooling eligible studies, we found carriers of the variant -197A allele were associated with a significantly increased risk of cancer (GA/AA vs GG, OR =1.27, 95% CI: 1.15, 1.41; $P_{\text{heterogeneity}}$ =0.374, Figure 2). Subgroup analyses were further conducted to evaluate the influence of predefined factors. The pooled results did not differ between different cancer types, but significant associations were most found in subgroups of population-based, large-sized studies and studies in agreement with HWE. Meta-analysis for IL-17A G-197A is shown in Table 2.

A total of seven studies, including 2,262 cases and 3,261 controls, contributed to the analysis of IL-17F 7488T/C. Results showed that the homozygote of 7488CC genotype significantly increased susceptibility to cancer (CC vs TC/TT, OR =1.36, 95% CI: 0.97, 1.91, $P_{\text{heterogeneity}}$ =0.875; Figure 3). Subgroup analysis indicated the IL-17F 7488T/C was only associated with risk of gastric cancer but not other cancer types. HWE results affected the pooled results, but study design did not. Meta-analysis for IL-17F 7488T/C is shown in Table 3.

Meta-regression analysis

As shown in Tables 2 and 3, significant heterogeneity was observed in several comparison models, and meta-regression analysis was performed. According to meta-regression results, sample size, cancer types, and HWE were the source of heterogeneity for both IL-17A G-197A and IL-17F 7488T/C.

Publication bias and sensitivity analysis

Egger's test and Begg's test were performed to detect potential publication bias. The results suggested that no publication bias existed for the analysis IL-17A G-197A (Pbegg =0.466, Pegger =0.975; Figure 4A) nor the analysis of

Table 1 Baseline characteristics of eligible studies

Reference	Year	Control	Country	Study design	Cancer types	IL-17A G-197A						IL-17F 7488T/C						
						Cases			Controls			HWE	Cases			Controls			HWE
						GG	GA	AA	GG	GA	AA		TT	TC	CC	TT	TC	CC	
Shibata[17]	2009	HB	Japan	HB	Gastric cancer	94	124	69	175	299	49	Not	221	55	4	419	100	4	Yes
Wu[20]	2010	PB	People's Republic of China	PB	Gastric cancer	210	485	250	193	371	204	Yes	540	332	55	527	214	36	No
Wang[11]	2012	PB	People's Republic of China	PB	Breast cancer	165	234	92	198	245	58	Yes	382	103	6	396	99	7	Yes
Quan[18]	2012	PB	People's Republic of China	PB	Cervical cancer	93	142	76	168	215	80	Yes	222	85	4	332	126	5	Yes
Arisawa[16]	2012	HB	Japan	HB	Gastric cancer	112	137	84	218	293	72	Yes	NA	NA	NA	NA	NA	NA	NA
Yuan[10]	2012	HB	People's Republic of China	HB	Ovarian cancer	12	60	20	2	24	12	Not	10	69	13	2	34	2	No
Zhang[19]	2014	PB	People's Republic of China	PB	Gastric cancer	110	102	48	258	187	67	Not	209	30	21	429	53	30	No
Zhou[12]	2013	PB	People's Republic of China	PB	Bladder cancer	79	154	68	164	204	78	Yes	240	57	4	317	124	5	Yes
Rafiei[15]	2013	PB	Iran	PB	Gastric cancer	56	61	44	78	72	21	Yes	NA	NA	NA	NA	NA	NA	NA

Notes: Yes means analyzed with the statistical software HWE. No means not analyzed with the statistical software HWE.
Abbreviations: HB, hospital-based studies; PB, population-based studies; IL, interleukin; HWE, Hardy–Winberg equilibrium; NA, no data.

IL-17F 7488T/C (Pbegg =0.133, Pegger =0.428; Figure 4B). Individual studies' influence was determined by sensitivity analysis, which showed that the pooled results were stable and not affected by individual studies (Figures S1 and S2).

Discussion

Accumulating evidence indicates that IL-17 functions as modulator in the process of tumorigenesis and metastasis. It was found that IL-17 could induce and activate the STAT signaling pathway and promote invasion of lung cancer.[21] On the other hand, IL-17 also promotes tumor invasion by modulating tumor microenvironment.[22,23] Additionally, Droeser et al found that IL-17 was associated with sensitivity to platinum-chemotherapy in ovarian carcinoma.[24] As a result, the expression level of IL-17 is unregulated in multiple cancers, and the level of IL-17 is correlated with progression and survival in glioblastoma and ovarian carcinoma,[25,26] indicating the prognostic value of IL-17. The IL-17F 7488T/C polymorphism causes an amino acid substitution from histamine to argentine at codon 161 (H161R), which leads to a natural antagonist of wide-type IL-17. It was demonstrated by Kawaguchi et al that this functional polymorphism could influence the susceptibility to asthma.[8] As for the IL-17A G-197A polymorphism, which is located in the promoter region of IL-17, it has been reported that, upon stimulation peripheral blood mononuclear cells with variant genotypes (-197AG or -197AA) secreted significantly more IL-17 than the wild type (-197GG) cells.[27] This study showed that the IL-17A G-197A polymorphism could alter the promoter activity of IL-17A and cause differential production of IL-17. Taken together, these lines of evidence indicate the two polymorphisms can alter the function and production of IL-17 and it is biologically plausible that these two polymorphisms may influence susceptibility to cancer.

In the current meta-analysis, we found that both IL-17A G-197A and IL-17 7488T/C polymorphisms are associated with increased of risk of cancer. For, the IL-17A G-197A polymorphism, a significantly increased risk of cancer was found in all comparisons. While for the IL-17F 7488T/C, only carriers of the homozygote IL-17F 7488CC genotype were associated significantly increased risk of cancer and individuals with only one 7488C allele (the 7488CT genotype) showed no change cancer risk in overall analysis. One of the possible explanations is that the 7488C is a recessive allele, and in the presence of 7488T allele, the antagonizing effect of the mutated IL-17 will be compensated by the wild-type IL-17.

Subgroup analyses were performed to evaluate the effect of cancer type, study design, sample size, and HWE. In the

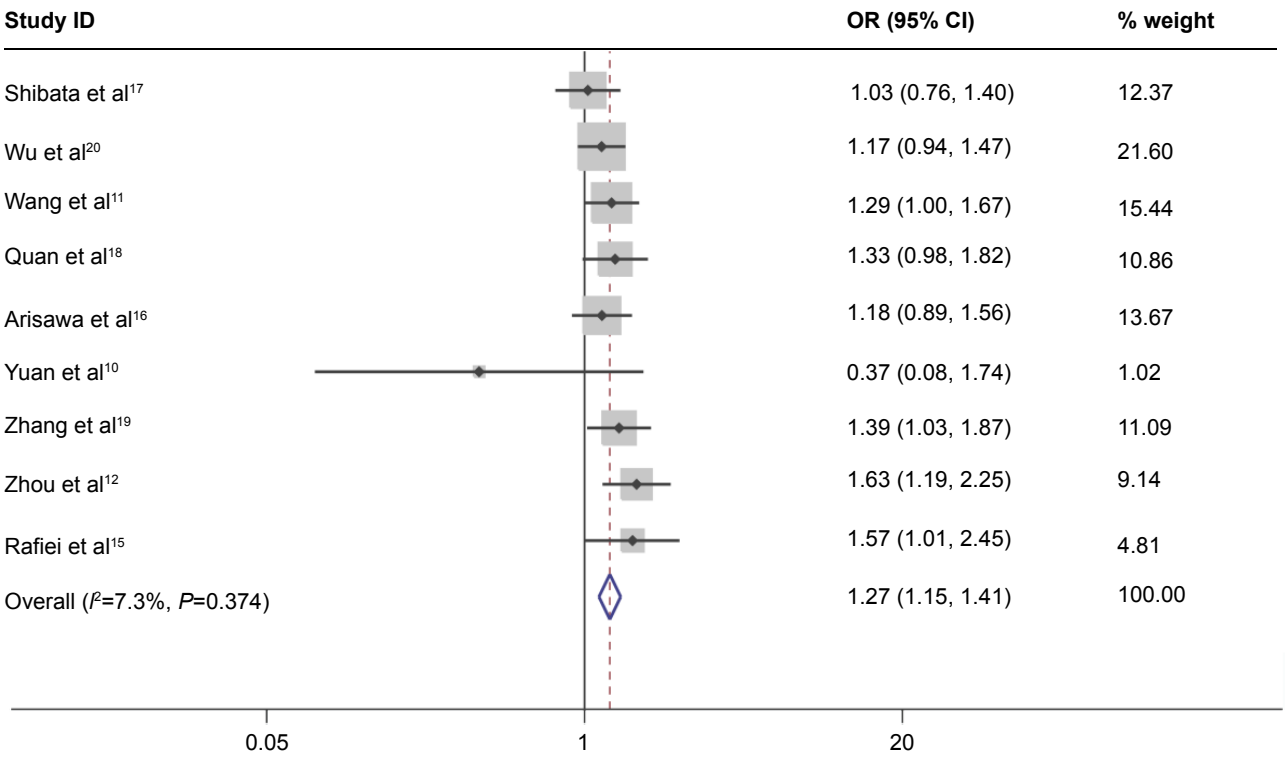

Figure 2 Forest plot of IL-17A G-197A polymorphism and cancer risk (GA/AA vs GG).
Abbreviations: IL, interleukin; OR, odds ratio; CI, confidence interval.

Table 2 Meta-analysis results for IL-17A G-197A polymorphism

	Studies	AA vs GG		GA vs GG		GA/AA vs GG		AA vs GG/GA		A vs G	
		OR (95% CI)	Het	OR (95% CI)	Het	OR (95% CI)	Het	OR (95% CI)	Het	OR (95% CI)	Het
Total	9	1.80 (1.40, 2.31)*	0.004	1.12 (1.01, 1.25)*	0.105	1.27 (1.15, 1.41)*	0.374	1.64 (1.22, 2.20)*	<0.001	1.30 (1.17, 1.45)*	0.021
Source of controls											
PB	6	1.69 (1.32, 2.16)*	0.045	1.24 (1.10, 1.41)*	0.802	1.34 (1.19, 1.51)*	0.635	1.50 (1.15, 1.94)*	0.006	1.30 (1.15, 1.48)*	0.039
HB	3	1.90 (1.01, 3.57)*	0.037	0.83 (0.66, 1.03)	0.527	1.08 (0.88, 1.33)	0.319	1.85 (0.94, 3.62)	0.003	1.24 (0.95, 1.62)	0.055
Cancer types											
GC	5	1.94 (1.32, 2.85)*	0.001	1.06 (0.92, 1.21)	0.131	1.21 (1.07, 1.38)*	0.517	1.93 (1.18, 3.15)*	<0.001	1.33 (1.13, 1.56)*	0.013
Others	4	1.69 (1.23, 2.33)*	0.175	1.24 (1.04, 1.48)*	0.257	1.36 (1.15, 1.61)*	0.247	1.42 (1.07, 1.89)*	0.139	1.27 (1.09, 1.49)*	0.15
HWE											
Yes	6	1.80 (1.37, 2.36)*	0.02	1.18 (1.03, 1.34)*	0.057	1.303 (1.16, 1.47)*	0.557	1.64 (1.20, 2.26)*	<0.001	1.32 (1.16, 1.49)*	0.027
No	3	1.60 (0.80, 3.24)	0.01	0.93 (0.58, 1.49)	0.356	1.17 (0.94, 1.44)	0.137	1.52 (0.70, 3.28)	0.001	1.22 (0.93, 1.59)	0.068
Sample size											
Large	7	1.78 (1.41, 2.25)*	0.019	1.13 (0.96, 1.32)	0.071	1.26 (1.14, 1.40)*	0.508	1.68 (1.24, 2.28)*	<0.001	1.29 (1.18, 1.41)*	0.132
Small	2	1.03 (0.10, 10.27)	0.009	0.93 (0.39, 2.20)	0.213	1.36 (0.90, 2.06)	0.077	1.32 (0.30, 5.69)	0.004	1.13 (0.46, 2.74)	0.005

Note: *Statistically significant association.
Abbreviations: Het, *P*-value of heterogeneity; HB, hospital-based studies; PB, population-based studies; GC, gastric cancer; OR, odds ratio; CI, confidence interval; HWE, Hardy–Winberg equilibrium.

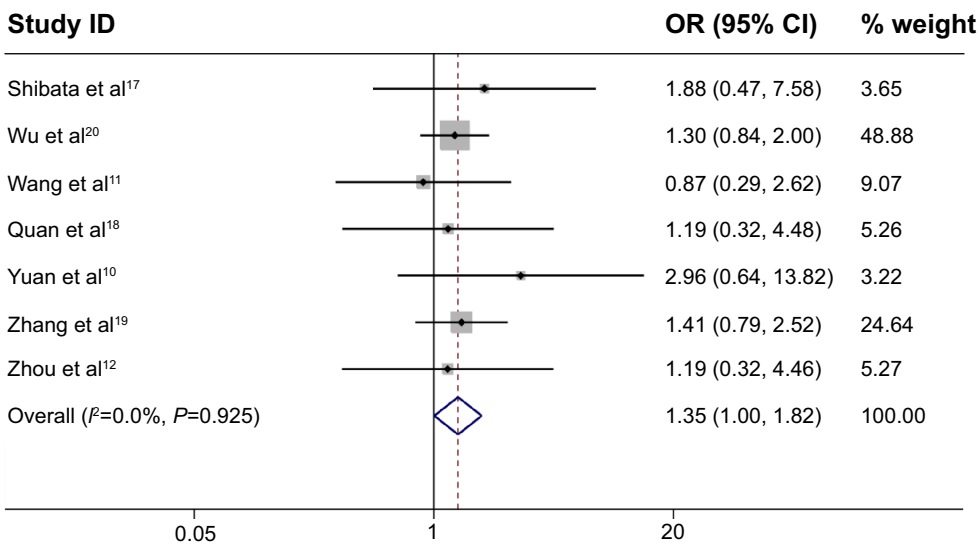

Figure 3 Forest plot of IL-17F 7488T/C polymorphism and cancer risk (CC vs TC/TT).
Abbreviations: IL, interleukin; OR, odds ratio, CI, confidence interval.

sub-group analysis of cancer types, we found the IL-17F polymorphism increased risk of gastric cancer but no significant association was found for other cancers, indicating IL-17F may have a cancer-type-specific function. Additionally, it was also proposed that IL-17 production was associated with helicobacter pylori infection (IL-8 and IL-ref24) and IL-17 polymorphism could affect gastric cancer susceptibility by overproduction of IL-17 and subsequently overstimulation of immune system.

Heterogeneity was observed in some comparison models. We then performed a meta-regression analysis to identify the source of the heterogeneity and found that cancer types, study design, sample size, and HWE contributed to heterogeneity. But Begg's test and Egger's test showed that the pooled results were not biased. Sensitivity analysis also indicated that the results were stable and robust.

Actually, no previous meta-analysis about IL-17A and IL-17F has been performed. Our study made some significant contributions to new knowledge for the IL17 single nucleotide polymorphisms researches.[15,17,18,20] Our study first reported that the variant IL-17A -197A allele and IL-17F 7488CC genotype were associated with increased risk of cancer, especially for gastric cancer. As genome-wide association studies is a powerful tool to determine the association between gene polymorphisms and cancer risk; we have searched the databases and no genome-wide association studies reported significant association between IL-17A or IL-17F polymorphism and cancer risk. Limitations of this

Table 3 Meta-analysis results for IL-17F 7488T/C polymorphism

	Number of Studies	CC vs TT		TC vs TT		TC/CC vs TT		CC vs TT/TC		C vs T	
		OR (95% CI)	Het	OR (95% CI)	Het	OR (95% CI)	Het	OR (95% CI)	Het	OR (95% CI)	Het
Total	7	1.39 (1.03, 1.88)*	0.979	1.02 (0.78, 1.33)	0.001	1.05 (0.82, 1.35)	0.001	1.35 (1.00, 1.82)*	0.925	1.08 (0.90, 1.30)	0.009
Cancer types											
GC	3	1.49 (1.06, 2.10)*	0.937	1.29 (1.00, 1.65)*	0.18	1.33 (1.09, 1.64)*	0.24	1.36 (0.97, 1.91)	0.875	1.32 (1.15, 1.51)*	0.466
Others	4	1.04 (0.53, 2.05)	0.983	0.85 (0.61, 1.19)	0.059	0.87 (0.64, 1.18)	0.081	1.32 (0.70, 2.46)	0.65	0.93 (0.75, 1.15)	0.174
HWE											
Yes	4	1.15 (0.61, 2.17)	0.868	0.92 (0.71, 1.19)	0.071	0.93 (0.73, 1.19)	0.08	1.18 (0.62, 2.21)	0.87	0.95 (0.77, 1.17)	0.133
No	3	1.47 (1.04, 2.07)*	0.989	1.29 (0.89, 1.88)	0.176	1.38 (1.06, 1.79)*	0.254	1.41 (1.00, 1.97)*	0.598	1.34 (1.17, 1.55)*	0.635
Source of controls											
PB	5	1.37 (1.00, 1.87)*	0.917	1.04 (0.76, 1.43)	0.001	1.06 (0.79, 1.44)	<0.001	1.27 (0.93, 1.74)	0.963	1.09 (0.83, 1.45)	0.923
HB	2	1.69 (0.52, 5.42)	0.771	0.90 (0.46, 1.77)	0.251	1.00 (0.61, 1.61)	0.295	2.39 (0.86, 6.64)	0.664	1.07 (0.84, 1.37)	0.002

Note: *Significant association.
Abbreviations: OR, odds ratio; CI, confidence interval; Het, *P*-value of heterogeneity; HB, hospital-based studies; PB, population-based studies; GC, gastric cancer; HWE, Hardy–Winberg equilibrium.

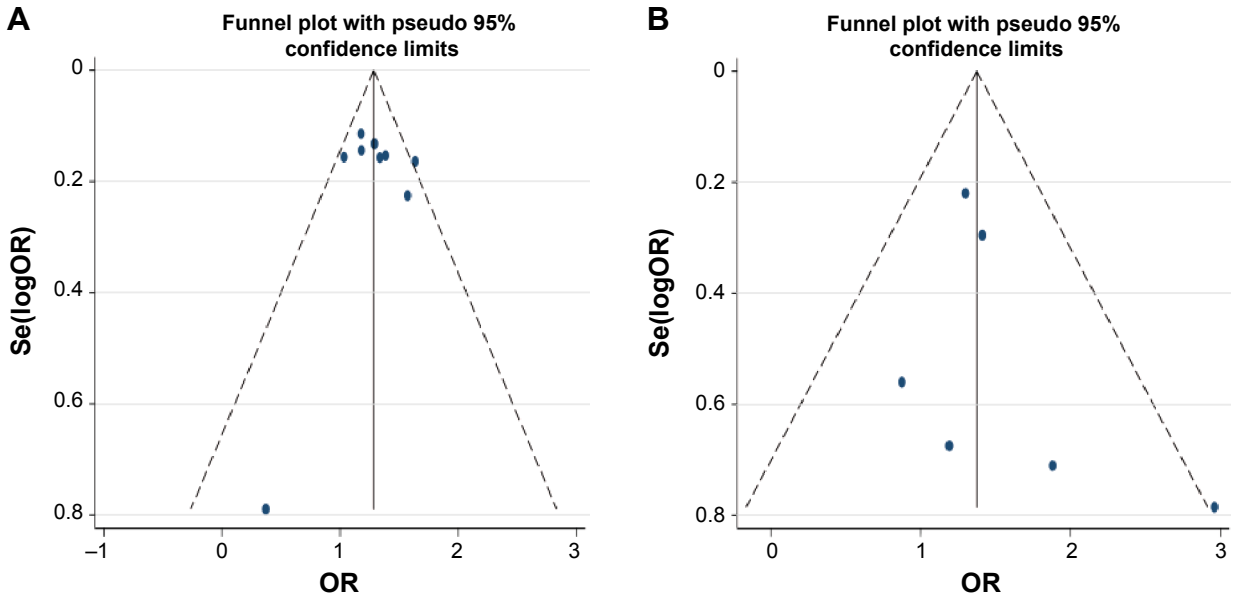

Figure 4 Funnel plots of IL-17A G-197A (**A**) and IL-17F 7488T/C (**B**) polymorphisms.
Abbreviations: IL, interleukin; OR, odds ratio.

meta-analysis should be noted. First, number of eligible studies was relatively small. Given limited number of studies, subgroup analyses for common cancer types was unavailable. In this meta-analysis, only subgroup analysis for gastric cancer was performed. Second, due to lack of individual data, we could not analyze the effect of other confounding factors, like smoking status, living habits, and so on.

Conclusion

In this meta-analysis, we pooled 3,181 cases and 4,005 controls and found that carriers of the variant IL-17A-197A allele and IL-17F 7488CC genotype were associated with increased risk of cancer, especially for gastric cancer.

Acknowledgments

This study was granted by China-Japan Friendship Hospital Youth Science and Technology Excellence Project (No. 2015-QNYC-B-02) and the Research Fund of the China-Japan Friendship Hospital (No. 2014-2-MS-9).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol*. 2009;9:556–567.
2. Akhavanpoor M, Gleissner CA, Gorbatsch S, et al. CCL19 and CCL21 modulate the inflammatory milieu in atherosclerotic lesions. *Drug Des Devel Ther*. 2014;8:2359–2371.
3. McGeachy MJ, Cua DJ. Th17 cell differentiation: the long and winding road. *Immunity*. 2008;28:445–453.
4. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. *Immunity*. 2011;34:149–162.
5. Zhu S, Qian Y. IL-17/IL-17 receptor system in autoimmune disease: mechanisms and therapeutic potential. *Clin Sci*. 2012;122:487–511.
6. LeibundGut-Landmann S, Gross O, Robinson MJ, Osorio F, Slack EC. Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17. *Nat Immunol*. 2007;8: 630–638.
7. Acosta-Rodriguez EV, Rivino L, Geginat J, et al. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol*. 2007;8:639–646.
8. Kawaguchi M, Takahashi D, Hizawa N, et al. IL-17F sequence variant (His161Arg) is associated with protection against asthma and antagonizes wild-type IL-17F activity. *J Allergy Clin Immunol*. 2006;117: 795–801.
9. Nordang GB, Viken MK, Hollis-Moffatt JE, et al. Association analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. *Rheumatology*. 2009;48:367–370.
10. Yuan Y, Hu Y, Tao K, RZ. Association analysis of IL-17A and IL-17F gene polymorphism with epithelial ovarian cancer. *J Hunan Normal Univ*. 2012;9:21–24.
11. Wang L, Jiang Y, Zhang Y, et al. Association analysis of IL-17A and IL-17F polymorphisms in Chinese Han women with breast cancer. *PLoS One*. 2012;7:e34400.
12. Zhou B, Zhang P, Wang Y, et al. Interleukin-17 gene polymorphisms are associated with bladder cancer in a Chinese Han population. *Mol Carcinog*. 2013;52:871–878.
13. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127:820–826.
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
15. Rafiei A, Hosseini V, Janbabai G, et al. Polymorphism in the interleukin-17A promoter contributes to gastric cancer. *World J Gastroenterol*. 2013; 19:5693–5699.
16. Arisawa T, Tahara T, Shiroeda H, et al. Genetic polymorphisms of IL17A and pri-microRNA-938, targeting IL17A 3′-UTR, influence susceptibility to gastric cancer. *Hum Immunol*. 2012;73:747–752.
17. Shibata T, Tahara T, Hirata I, Arisawa T. Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis. *Hum Immunol*. 2009;70:547–551.

18. Quan Y, Zhou B, Wang Y, et al. Association between IL17 polymorphisms and risk of cervical cancer in Chinese women. *Clin Dev Immunol*. 2012;2012:258293.
19. 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;35:1575–1580.
20. Wu X, Zeng Z, Chen B, et al. Association between polymorphisms in interleukin-17A and interleukin-17F genes and risks of gastric cancer. *Int J Cancer*. 2010;127:86–92.
21. Li Q, Han Y, Fei G, Guo Z, Ren T, Liu Z. IL-17 promoted metastasis of non-small-cell lung cancer cells. *Immunol Lett*. 2012;148:144–150.
22. Olsson Akefeldt S, Maisse C, Belot A, et al. Chemoresistance of human monocyte-derived dendritic cells is regulated by IL-17A. *PLoS One*. 2013;8:e56865.
23. Hayata K, Iwahashi M, Ojima T, et al. Inhibition of IL-17A in tumor microenvironment augments cytotoxicity of tumor-infiltrating lymphocytes in tumor-bearing mice. *PLoS One*. 2013;8:e53131.
24. Droeser RA, Guth U, Eppenberger-Castori S, et al. High IL-17-positive tumor immune cell infiltration is indicative for chemosensitivity of ovarian carcinoma. *J Cancer Res Clin Oncol*. 2013;139:1295–1302.
25. Lan C, Huang X, Lin S, et al. High density of IL-17-producing cells is associated with improved prognosis for advanced epithelial ovarian cancer. *Cell Tissue Res*. 2013;352:351–359.
26. Cui X, Xu Z, Zhao Z, et al. Analysis of CD137L and IL-17 expression in tumor tissue as prognostic indicators for gliblastoma. *Int J Biol Sci*. 2013;9:134–141.
27. Chabaud M, Fossiez F, Taupin JL, Miossec P. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. *J Immunol*. 1998;161:409–414.

Supplementary materials

Table S1 Searching strategy

Searching strategy for PubMed: ((interleukin-17) OR IL17) AND (((single nucleotide polymorphism) OR polymorphism) OR SNP) AND (((neoplasms) OR cancer) OR tumor); records identified: 32
Searching strategy for PubMed: ((interleukin-17) OR IL17) AND (((single nucleotide polymorphism) OR polymorphism) OR SNP) AND (((neoplasms) OR cancer) OR tumor); records identified: 10
Searching strategy for Web of Science: (interleukin-17) AND (polymorphism) AND (cancer); records identified from Web of Science: 21
Searching strategy for China National Knowledge Infrastructure: ((interleukin-17) OR IL17) AND (polymorphism) OR mutation) AND (tumor) OR cancer) records identified: 27

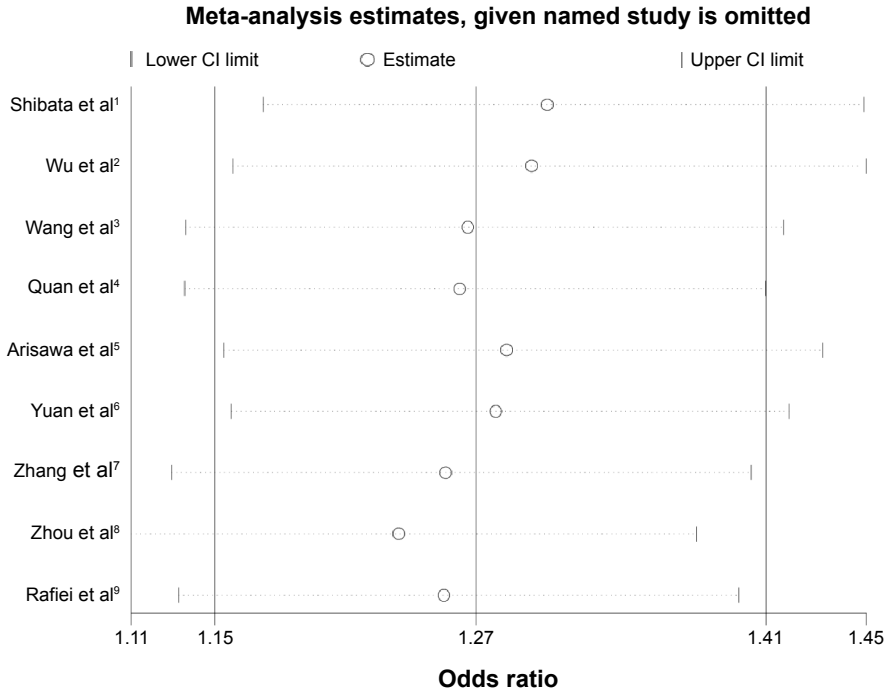

Figure S1 Sensitivity analysis of IL-17A G-197A polymorphism.
Abbreviations: IL, interleukin, CI, confidence interval.

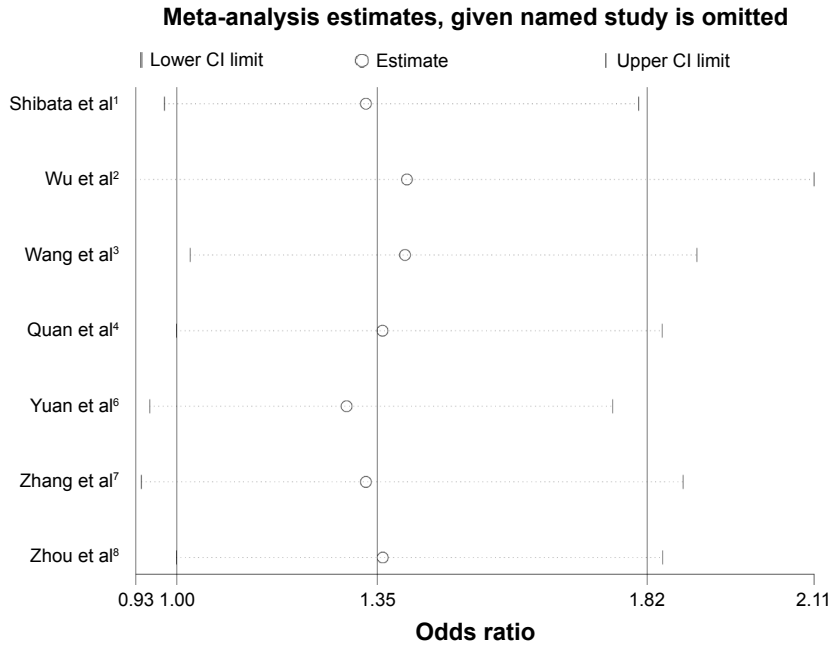

Figure S2 Sensitivity analysis of IL-17F 7488T/C polymorphism.
Abbreviations: IL, interleukin, CI, confidence interval.

References

1. Shibata T, Tahara T, Hirata I, Arisawa T. Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis. *Hum Immunol*. 2009;70:547–551.
2. Wu X, Zeng Z, Chen B, et al. Association between polymorphisms in interleukin-17A and interleukin-17F genes and risks of gastric cancer. *Int J Cancer*. 2010;127:86–92.
3. Wang L, Jiang Y, Zhang Y, et al. Association analysis of IL-17A and IL-17F polymorphisms in Chinese Han women with breast cancer. *PLoS One*. 2012;7:e34400.
4. Quan Y, Zhou B, Wang Y, et al. Association between IL17 polymorphisms and risk of cervical cancer in Chinese women. *Clin Dev Immunol*. 2012; 2012:258293.
5. Arisawa T, Tahara T, Shiroeda H, et al. Genetic polymorphisms of IL17A and pri-microRNA-938, targeting IL17A 3′-UTR, influence susceptibility to gastric cancer. *Hum Immunol*. 2012;73:747–752.
6. Yuan Y, Hu Y, Tao K, RZ. Association analysis of IL-17A and IL-17F gene polymorphism with epithelial ovarian cancer. *J Hunan Normal Univ*. 2012;9:21–24.
7. 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: 1575–1580.
8. Zhou B, Zhang P, Wang Y, et al. Interleukin-17 gene polymorphisms are associated with bladder cancer in a Chinese Han population. *Mol Carcinog*. 2013;52:871–878.
9. Rafiei A, Hosseini V, Janbabai G, et al. Polymorphism in the interleukin-17A promoter contributes to gastric cancer. *World J Gastroenterol*. 2013;19:5693–5699.