

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

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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, $P_{\text{heterogeneity}} = 0.374$; and A vs G, OR = 1.30, 95% CI: 1.17, 1.45, $P_{\text{heterogeneity}} = 0.021$). 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, $P_{\text{heterogeneity}} = 0.875$; and CC vs TT, OR = 1.39, 95% CI: 1.03, 1.88, $P_{\text{heterogeneity}} = 0.979$), 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-17E, 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) cells³ 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

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polymorphisms and cancer risk were controversial. Wang et al¹¹ 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 al¹² 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–Weinberg 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

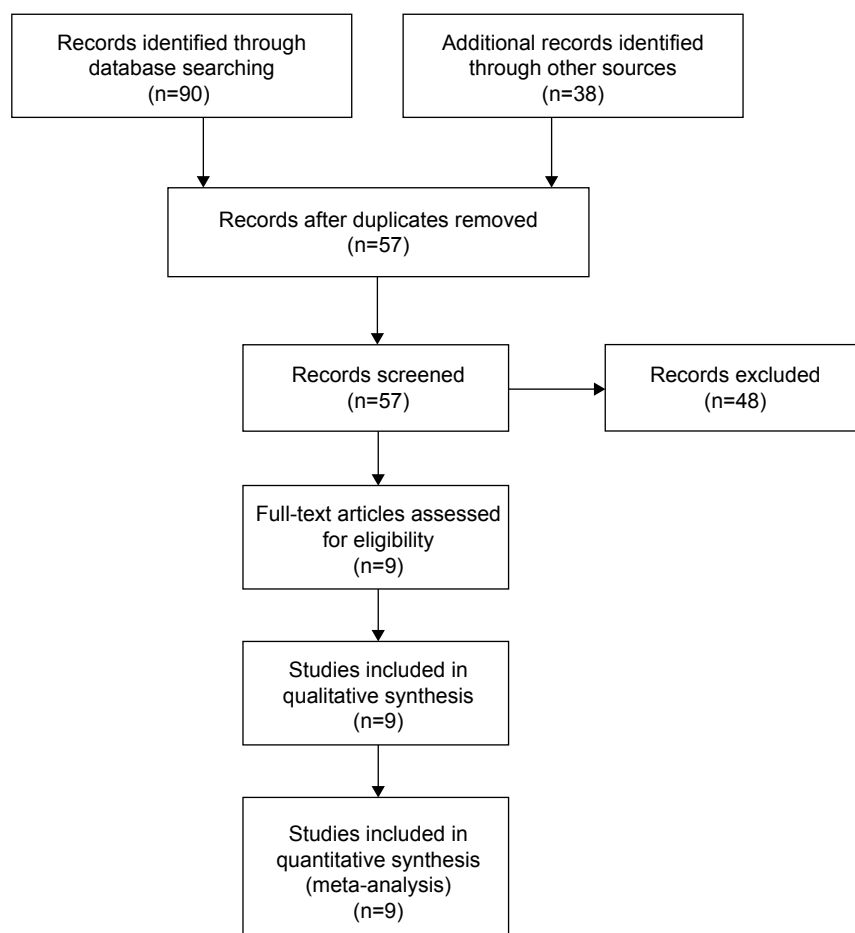


Figure 1 Flowchart of study selection.

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 ($P_{\text{Begg}}=0.466$, $P_{\text{Egger}}=0.975$; 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						HWE	
						Cases			Controls			Cases			Controls				
						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	221	55	4	419	100	4	Yes	Yes
Wu ²⁰	2010	PB	People's Republic of China	PB	Gastric cancer	210	485	250	193	371	204	540	332	55	527	214	36	No	No
Wang ¹¹	2012	PB	People's Republic of China	PB	Breast cancer	165	234	92	198	245	58	382	103	6	396	99	7	Yes	Yes
Quan ¹⁸	2012	PB	People's Republic of China	PB	Cervical cancer	93	142	76	168	215	80	222	85	4	332	126	5	Yes	Yes
Arisawa ¹⁶	2012	HB	Japan	HB	Gastric cancer	112	137	84	218	293	72	NA	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	10	69	13	2	34	2	No	No
Zhang ¹⁹	2014	PB	People's Republic of China	PB	Gastric cancer	110	102	48	258	187	67	209	30	21	429	53	30	No	No
Zhou ¹²	2013	PB	People's Republic of China	PB	Bladder cancer	79	154	68	164	204	78	240	57	4	317	124	5	Yes	Yes
Raffell ¹⁵	2013	PB	Iran	PB	Gastric cancer	56	61	44	78	72	21	NA	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–Weinberg equilibrium; NA, no data.

IL-17F 7488T/C (P_{begg} = 0.133, P_{egger} = 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, Drieser 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 arginine 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 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

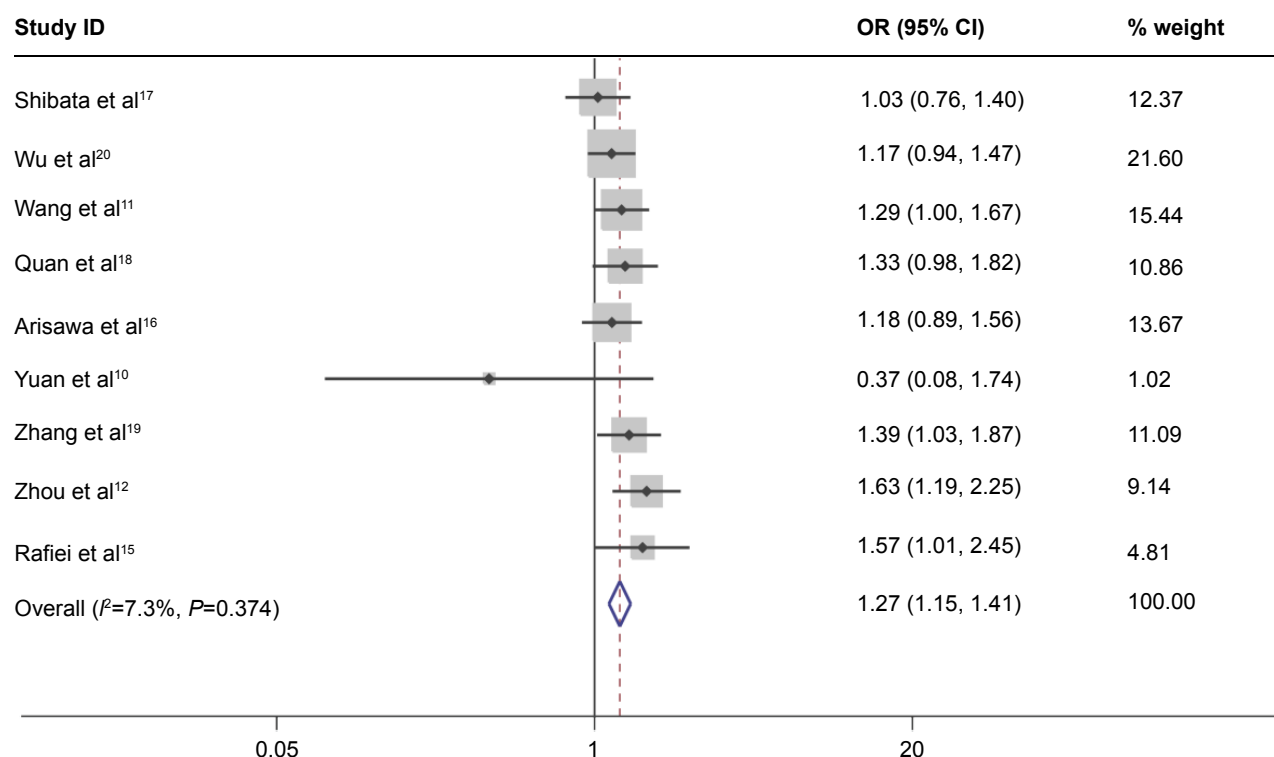


Figure 2 Forest plot of IL-17A G-197A polymorphism and cancer risk (GA/AA vs GG).

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–Weinberg equilibrium.

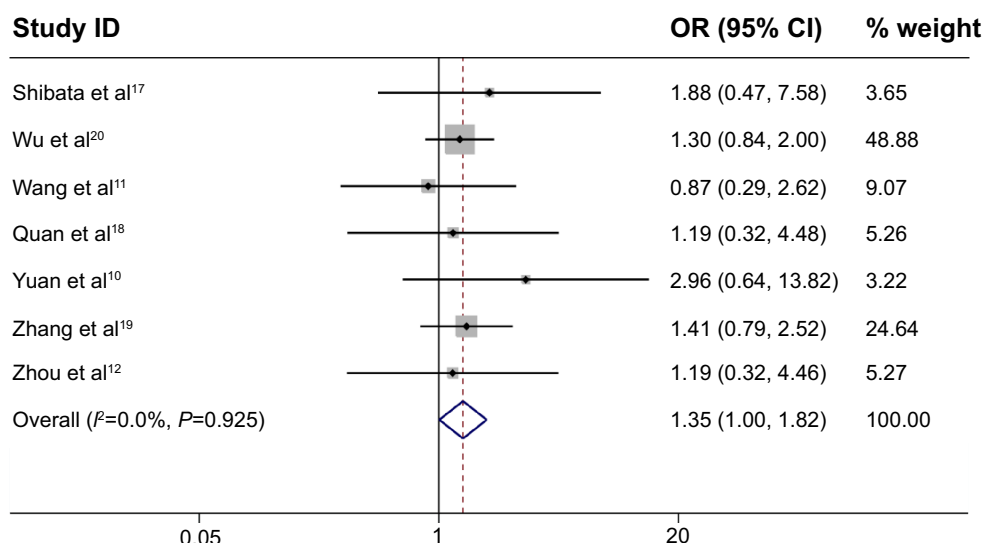


Figure 3 Forest plot of IL-17F 7488T/C polymorphism and cancer risk (CC vs TC/TT).

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–Weinberg equilibrium.

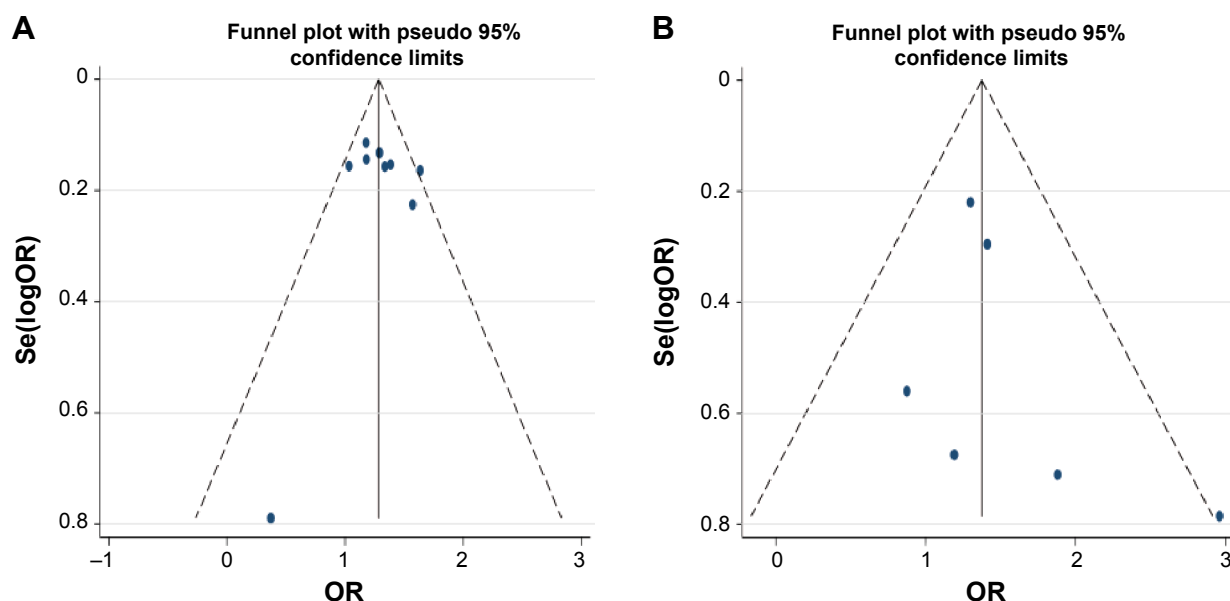


Figure 4 Funnel plots of IL-17A G-197A (**A**) and IL-17F 7488T/C (**B**) polymorphisms. **Abbreviations:** IL, interleukin; OR, odds ratio.

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

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Disclosure

The authors report no conflicts of interest in this work.

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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

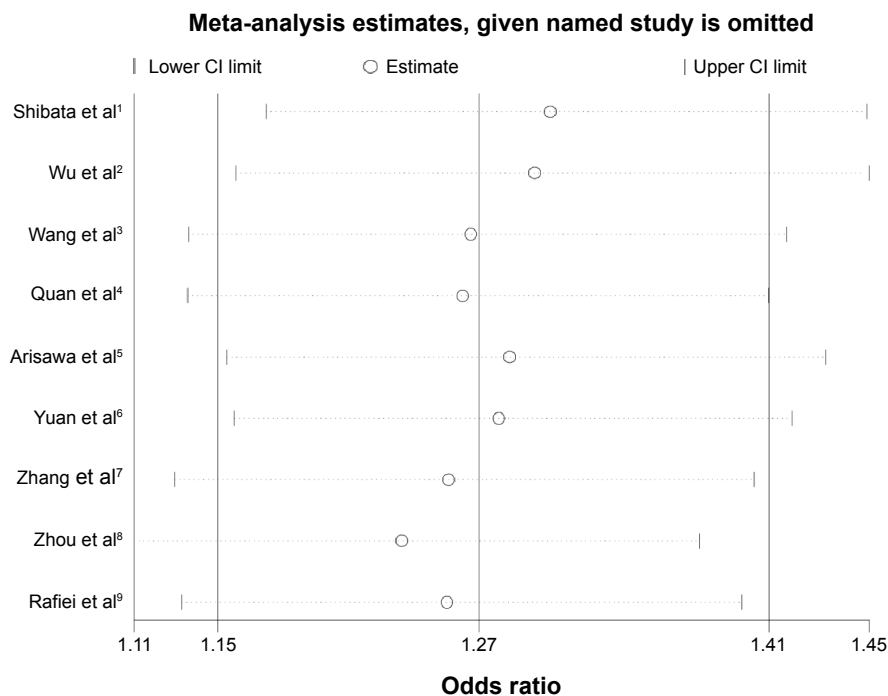


Figure S1 Sensitivity analysis of IL-17A G-197A polymorphism.
Abbreviations: IL, interleukin, CI, confidence interval.

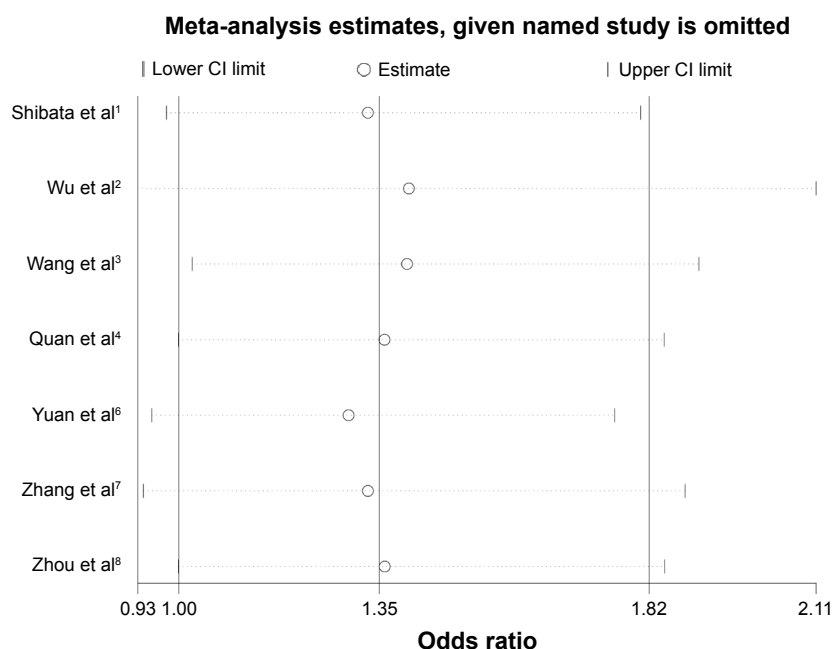


Figure S2 Sensitivity analysis of IL-17F 7488T/C polymorphism.

Abbreviations: IL, interleukin, CI, confidence interval.

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