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META-ANALYSIS

Association of *IL-17* polymorphisms with gastric cancer risk in Asian populations

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Abstract

AIM: To investigate associations between the *IL-17* rs2275913 G>A and rs763780 T>C polymorphisms and susceptibility to gastric cancer in Asian populations.

METHODS: We reviewed studies published up to 2014 on *IL-17* polymorphisms with gastric cancer susceptibility systematically. Relevant articles were identified in the MEDLINE, Science Citation Index, Cochrane Library, PubMed, EMBASE, CINAHL and Current Contents Index databases. We used version 12.0 STATA statistical software to evaluate the statistical data. Two reviewers abstracted the data independently. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated.

RESULTS: Seven independent, case-control studies were chosen for the meta-analysis, which included 3210 gastric cancer patients and 3889 healthy controls. The overall estimation showed a positive association between the *IL-17* rs2275913 G>A polymorphism and the occurrence of gastric cancer for five genetic models (all $P < 0.05$) and similar results were observed for the *IL-17* rs763780 T>C variation with four genetic models (all $P < 0.05$), but not for the dominant model ($P > 0.05$). Subgroup analysis by country revealed that the rs2275913 G>A and rs763780 T>C polymorphisms may be the main risk factor for gastric cancer in Chinese and Japanese populations.

CONCLUSION: The *IL-17* gene may be significantly correlated with gastric cancer risk in Asian populations, especially those carrying the rs2275913 G>A and rs763780 T>C polymorphisms.

Key words: *IL-17*; Genetic polymorphism; Gastric cancer; Asian populations; Meta-analysis

Core tip: There may be a relationship between the *IL-17* gene and gastric cancer risk, especially in individuals carrying the rs2275913 G>A and rs763780 T>C polymorphisms. The *IL-17* gene polymorphisms might be important in determining an individual's susceptibility to gastric cancer.

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INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide and is the second leading cause of cancer death in both sexes[1]. Gastric cancer has a major impact on public health because of its high morbidity and mortality rates[2]. There has been a steady increase in gastric cancer incidence and mortality in most countries, reaching approximately 8.52 to 9.68 people per 100000 individuals[3,4]. An estimated 988000 new cases and 736000 deaths associated with the disease have been reported annually worldwide[5]. In addition, more than 70% of cases are from developing countries and half of these cases are in China[2,6]. In China, gastric cancer is the second most common cause of cancer-related death, leading to approximately 231193 deaths in 2008[2]. Although there have been advances in the treatment strategies for gastric cancer, the prognosis of gastric cancer is still poor; the 5-year survival rate is only 20%-30% because most cases are diagnosed in an advanced stage[3]. It is universally accepted that the causes of gastric cancer are complex and include a myriad of environmental factors, inherited susceptibilities and behavioral factors, such as smoking and a high salt diet, which are especially linked to gastric cancer[7]. In recent decades, many researchers have postulated that inflammation-related gene polymorphisms, such as interleukin (*IL*)-1β, *IL-6*, *IL-16* and *IL-17A,* which induce multiple pro-inflammatory mediators, are correlated with gastric cancer[2,8].

IL-17 is a family of pro-inflammatory cytokines consisting of six similar cytokines and five receptors. IL-17A has the founding role for this new cytokine family[2]. The gene for human *IL-17* is located on chromosome 6p12 and comprises 1874 base pairs[9,10]. IL-17 is preferentially produced by T helper type 17 (Th17) cells as a homodimer; IL-17 can also be secreted by invariant natural killer T cells and IL-17-producing $CD8^+$ T cells[11,12]. Based on previous investigations, high expression of IL-17 is increasingly recognized as a potential key player in inflammation, autoimmune disease and graft-*vs*-host disease[13-15]. Furthermore, IL-17 is significantly upregulated in many tumors, such as hepatocellular carcinoma, non-small cell lung cancer, and advanced gastric cancer[16-18]. A few frequent genetic polymorphisms of the *IL-17 g*ene, such as rs2275913 G>A and rs763780 T>C, are known to play a critical role in interleukin activity by altering cytokine function and dysregulating its expression[19,20]. Once activated by single nucleotide polymorphisms (SNPs) in the *IL-17* gene, IL-17 functions as a potent inducer, similar to the role of interferon gamma, promoting Th1-related chemokine production in various tissues, resulting in neutrophil and monocyte recruitment to tumor sites. In addition, IL-17 contributes to reducing tumor growth by increasing the numbers of dendritic cells, natural killer cells, and cytotoxic T cells within the tumor microenvironment[21]. Therefore, while the question of whether *IL-17* promotes tumor growth remains controversial, we postulated that the primary functions of *IL-17* polymorphisms are originally beneficial, but that they can accelerate tumor growth because of alterations in the tumor microenvironment[22]. To date, accumulating studies provide support for this speculation[2,23], but several lines of evidence have presented contrary views[7]. The outcomes of clinical trials focusing on this issue have been inconsistent; therefore, we conducted the current meta-analysis to focus on the relationship between *IL-17* polymorphisms and susceptibility to gastric tumors.

MATERIALS AND METHODS

Search strategy

We searched the MEDLINE, Science Citation Index, Cochrane Library, PubMed, EMBASE, CINAHL and Current Contents Index databases for articles that assessed correlations between *IL-17* genetic variants and gastric cancer susceptibility, which were published up to March 31st, 2014. We utilized the search terms ("Interleukin-17" or "IL-17" or "IL 17" or "Interleukin 17" or "Interleukin-25" or "Interleukin 25" or "IL-25" or "Interleukin-17A" or "Interleukin 17A" or "IL-17A" or "CTLA-8" or "CTLA 8" or "Cytotoxic T lymphocyte-Associated Antigen 8" or "Cytotoxic T lymphocyte Associated Antigen 8") and ("stomach neoplasms" or "gastric cancer" or "stomach cancer" or "gastric neoplasms" or "gastric carcinomas" or "stomach carcinomas" or "carcinoma ventriculi" or "stomach neoplasms") in our initial search. We did not set any limitations on the language of the article. Additional potentially relevant articles were further identified by a manual search of references from retrieved articles.

Selection criteria

We evaluated studies on patients with gastric cancer and *IL-17* genetic polymorphisms as risk factors. The following inclusion criteria were applied to assess each publication for inclusion: (1) independent case-control study that evaluated the relationship between *IL-17* genetic polymorphisms and the risk of gastric cancer; (2) all patients diagnosed with gastric cancer were confirmed by histopathological examinations demonstrating the occurrence of invasion[24]; (3) the number of evaluated cancer cases was provided; (4) at least 150 cases were included in the study;

(5) the genotype number and frequency information were supplied; and (6) the controls conformed to the Hardy-Weinberg equilibrium (HWE). The exclusion criteria were the following: (1) studies on familial and hereditary gastric cancer; and (2) studies on haplotypes alone. If the same population was included in previous studies, only the most recent or largest sample size study was included.

Data extraction

To reduce bias and enhance credibility, two investigators abstracted information using a standardized protocol and data recording form independently, and any disagreements were resolved through consensus. Information was collected prospectively from each study, including the first author's surname; publication year; publication language; study type; study design; sources of controls; sample size; participant age, sex, ethnicity and country of origin; genotyping method; gene type; relevant polymorphisms; DNA sample types; genotype and mutation frequencies; and HWE evidence in controls.

Quality assessment

To determine whether the study in question was high quality, two investigators assessed the studies using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) quality score systems independently[25]. The STROBE score consists of forty assessment items associated with quality appraisal, with scores ranging from 0 to 40. According to the STROBE scores, the included studies were classified into the following three levels: low quality (0-19), moderate quality (20-29), and high quality (30-40). Any discrepancies in assigning STROBE scores to the included publications were resolved through discussion with a third reviewer.

Statistical analysis

The summary odds ratio (OR) and 95% confidence interval (CI) were calculated for the correlations between *IL-17* genetic polymorphisms and gastric cancer risk with five genetic models. 95%CIs were calculated using the *Z* test. Only crude ORs were pooled in the meta-analysis because there were adjustments for different variables in different studies. To aggregate quantitative evidence from all selected studies and minimize the variance of the summary, we conducted the current statistical meta-analyses with a random-effects model (DerSimonian and Laird method) or fixed-effects model (Mantel-Haenszel method) for individual study results when data from independent studies could be combined[26,27]. The random-effects model was applied when there was heterogeneity among studies; otherwise, we applied the fixed-effects model. The subgroup meta-analyses were also conducted by country and genotyping method to explore potential effect modification and heterogeneity across the enrolled studies, using the Cochran's *Q*-statistic ($P < 0.05$ was considered statistically significant)[27]. As a result of the low statistical power of the Cochran's *Q*-statistic, the I^2 test was also calculated to determine the possibility of heterogeneity between studies[26]. A sensitivity analysis was performed and funnel plot constructed to assess publication bias, which might affect the validity of the estimates. The symmetry of the funnel plot was further evaluated by Egger's linear regression test[28]. All tests were two-sided and a *P* value of < 0.05 was considered statistically significant. To ascertain that the results were credible and accurate, all information was entered in the STATA software, version 12.0 (Stata Corp, College Station, TX, United States).

RESULTS

Baseline characteristics of extracted articles

The original keyword search yielded 60 papers. Through screening titles, key words and abstracts, 28 of these articles were excluded (two were duplicates; five were letters, reviews or meta-analysis; eight were not human studies; and 13 were not related to the research topics). Thirty-two full-text articles were then reviewed and an additional 23 trials were excluded (three were not case-control, seven were not relevant to the *IL-17* gene, and 13 were not relevant to gastric cancer), leaving nine studies applicable for full publication review. Of these, two were excluded because of the lack of necessary data. Therefore, seven papers[2,7,20,23,29-31], representing 7099 subjects (3210 patients with gastric cancer and 3889 healthy controls), conformed to our inclusion criteria. The entire article selection process is summarized in Figure 1. The publication years ranged from 2009 to 2014. The included articles were case-control studies that evaluated the relevant correlation in a Chinese population (four studies), Japanese population (two study) or Iranian population (one study). The genotype methods included PCR-RFLP, PCR-SSCP and Sequenom MassArray. Two SNPs were addressed in the seven studies, rs2275913 G>A and rs763780 T>C polymorphisms in the *IL-17* gene. All enrolled studies showed that the genotypes in the healthy control group did not deviate from the HWE (all $P > 0.05$). All quality scores of the enrolled papers were higher than 20 (moderate-high quality). Table 1 summarizes the characteristics and methodological qualities of the enrolled studies. The number of eligible articles in the searched electronic databases from 2011 to 2014 is summarized in Figure 2.

Relationship between IL-17 genetic mutations and gastric cancer risk

Seven case-control studies referred to *IL-17* genetic variants in gastric cancer. The primary results for the correlation between *IL-17* genetic mutations

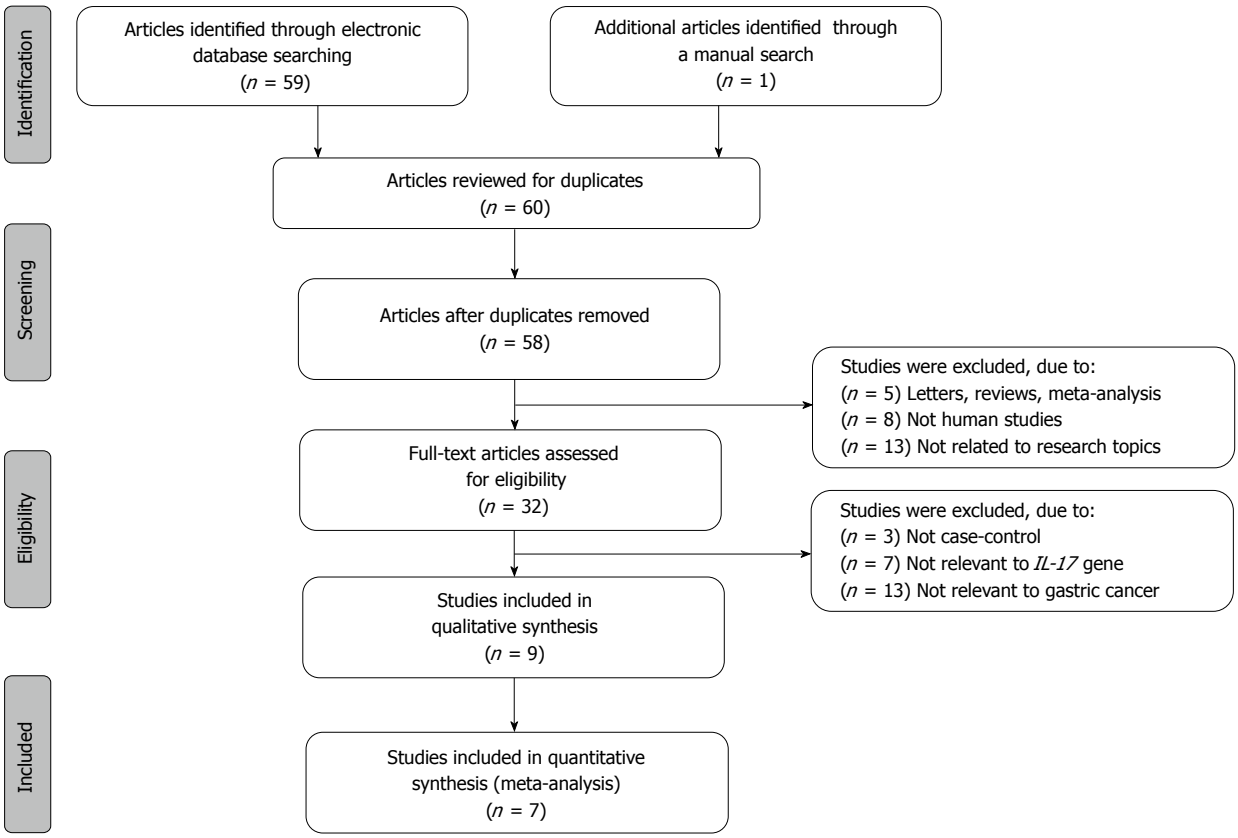


Figure 1 Flow chart of the literature search and study selection. Ultimately, seven case-control studies were included in this meta-analysis.

Table 1 Characteristics of the included studies focusing on *IL-17* genetic polymorphisms

Ref.	Year	Country	Sample size		Gender (M/F)		Age (yr)		Genotyping methods	Gene	SNP	STROBE
			Case	Control	Case	Control	Case	Control				
Wu *et al*[30]	2014	China	945	768	-	-	-	-	PCR-RFLP	*IL-17A*	rs2275913 G>A	29
Zhang *et al*[23]	2014	China	260	512	162/98	280/232	60.6 ± 10.7	51.3 ± 11.2	Sequenom MassArray	*IL-17A*	rs2275913 G>A rs763780 T>C	30
Zhu *et al*[2]	2014	China	293	550	189/104	312/238	57.5 ± 11.3	56.7 ± 12.7	Sequenom MassArray	*IL-17A* *IL-17F*	rs2275913 G>A rs763780 T>C	31
Rafiei *et al*[7]	2013	Iran	161	171	89/72	84/87	62.6 ± 12.4	60.8 ± 12.8	PCR-RFLP	*IL-17A*	rs2275913 G>A	27
Arisawa *et al*[29]	2012	China	337	587	234/103	314/273	65.3 ± 11.4	61.4 ± 13.7	PCR-SSCP	*IL-17A*	rs2275913 G>A	33
Zeng *et al*[31]	2010	China	927	777	-	-	-	-	PCR-RFLP	*IL-17F*	rs763780 T>C	29
Shibata *et al*[20]	2009	Japan	287	524	203/84	307/217	65.0 ± 11.8	55.7 ± 18.3	PCR-SSCP	*IL-17A* *IL-17F*	rs2275913 G>A rs763780 T>C	32

M: Male; F: Female; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP: Polymerase chain reaction-single-strand conformation polymorphism; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

and susceptibility to gastric cancer are summarized in Table 2 and Figure 3. The random-effects model was applied under the allele model because there was heterogeneity ($P < 0.05$). Meta-analysis results identified a positive association of the *IL-17* rs2275913 G>A mutation with the occurrence of gastric cancer with five genetic models (all $P < 0.05$). A positive relationship between the rs763780 T>C variation in the *IL-17* gene and susceptibility to gastric cancer was observed with four genetic models (all $P < 0.05$), which was not true for the dominant model ($P = 0.299$). All subgroup analysis in our current meta-analysis used random-effects because of the existing heterogeneity (all $P < 0.05$). Subgroup analysis by country indicated that the rs2275913 G>A polymorphism might be the main risk factor for gastric cancer in China and Japan for the allele model (all $P < 0.05$), but this was not the case for Iranian populations under the allele model (OR = 1.22, 95%CI: 0.90-1.65, $P = 0.207$) (Figure 4). Additionally, the *IL-17* rs763780 T>C variation, shown in Figure 4, was associated with gastric cancer susceptibility in China and Japan for the allele model (China: OR = 1.85, 95%CI: 1.32-2.59, $P < 0.001$; Japan: OR = 2.31, 95%CI: 1.71-3.12, $P < 0.001$). Additional subgroup analyses by genotyping method showed obvious positive associations between the

Table 2 Meta-analysis of the association between *IL-17* genetic polymorphisms and gastric cancer

Subgroup analysis	W allele *vs* M (Allele model)			WW + WM *vs* MM (Dominant model)			WW *vs* WM + MM (Recessive model)			WW *vs* MM (Homozygous model)			WW *vs* WM (Heterozygous model)		
	OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value
rs2275913 G>A	1.33	1.12-1.57	0.001	1.34	1.11-1.62	0.003	1.50	1.15-1.94	0.002	1.65	1.23-2.20	0.001	1.42	1.10-1.84	0.008
Country															
China	1.47	1.05-2.05	0.024	1.59	1.19-2.11	0.001	1.60	0.95-2.70	0.078	1.98	1.12-3.50	0.019	1.43	0.86-2.38	0.167
Iran	1.22	0.90-1.65	0.207	1.07	0.66-1.73	0.788	1.49	0.93-2.39	0.095	1.39	0.79-2.44	0.258	1.57	0.94-2.63	0.087
Japan	1.19	1.04-1.37	0.013	1.12	0.89-1.40	0.322	1.37	1.11-1.70	0.004	1.36	1.04-1.77	0.022	1.38	1.10-1.74	0.006
Genotyping method															
PCR-RFLP	1.11	0.98-1.26	0.088	1.24	1.02-1.52	0.034	1.15	0.79-1.69	0.468	1.23	0.97-1.57	0.088	1.13	0.67-1.93	0.644
MassArray	1.72	1.48-2.00	< 0.001	1.85	1.43-2.41	< 0.001	2.06	1.66-2.56	< 0.001	2.61	1.95-3.49	< 0.001	1.83	1.45-2.32	< 0.001
PCR-SSCP	1.19	1.04-1.37	0.013	1.12	0.89-1.40	0.322	1.37	1.11-1.70	0.004	1.36	1.04-1.77	0.022	1.38	1.10-1.74	0.006
rs763780 T>C	1.95	1.47-2.59	< 0.001	1.21	0.85-1.72	0.299	2.47	1.63-3.74	< 0.001	1.54	1.15-2.05	0.004	2.83	1.63-4.91	< 0.001
Country															
China	1.85	1.32-2.59	< 0.001	1.13	0.84-1.54	0.421	2.42	1.40-4.18	0.002	1.45	1.07-1.95	0.016	2.93	1.34-6.39	0.007
Japan	2.31	1.71-3.12	< 0.001	2.60	0.88-7.72	0.085	2.68	1.91-3.75	< 0.001	3.44	1.15-10.26	0.027	2.62	1.86-3.70	< 0.001
Genotyping method															
PCR-RFLP	1.40	1.19-1.66	< 0.001	1.40	0.91-2.14	0.122	1.51	1.24-1.84	< 0.001	1.60	1.04-2.46	0.033	1.50	1.21-1.85	< 0.001
MassArray	2.17	1.78-2.66	< 0.001	0.94	0.62-1.41	0.759	3.14	2.45-4.01	< 0.001	1.32	0.87-1.99	0.194	4.20	3.14-5.62	< 0.001
PCR-SSCP	2.31	1.71-3.12	< 0.001	2.60	0.88-7.72	0.085	2.68	1.91-3.75	< 0.001	3.44	1.15-10.26	0.027	2.62	1.86-3.70	< 0.001

W: Wild-type allele; M: Mutant allele; WW: Wild-type homozygote; WM: Heterozygote; MM: Mutant homozygote; SNP: Single nucleotide polymorphism.

rs2275913 G>A and rs763780 T>C mutations and gastric cancer risk in the PCR-RFLP, PCR-SSCP and Sequenom Mass ARRAY subgroups (all $P < 0.05$).

Sensitivity analysis and publication bias

During sensitivity analysis, the overall statistical results did not change when any single study was omitted, suggesting that the meta-analysis data are relatively stable and credible (Table 3, Figure 5). Funnel plots presented symmetrical data for the correlation between the rs2275913 G>A mutation and the risk of gastric cancer, and Egger's test suggested no publication bias ($P > 0.05$) (Figure 6). However, considering the *IL-17* rs763780 T>C variant model, the graphical funnel plots presented some asymmetrical data under the allele model, and Egger's test showed a publication bias for this association ($t = 6.54$, $P = 0.023$) (Figure 6).

DISCUSSION

The main aim of this meta-analysis was to explore the exact relationship between *IL-17* gene polymorphisms and the risk of gastric cancer. The results of our meta-analysis indicated that *IL-17* genetic polymorphisms, especially the rs2275913 G>A genetic polymorphism, were significantly correlated with an increased risk of gastric cancer under the allele and dominant models, suggesting that *IL-17* genetic variants may be crucial predictors in the development and progression of gastric cancer. Furthermore, the *IL-17* rs763780 T>C polymorphism was positively related to the susceptibility to gastric cancer for the allele model, but not for the dominant model. Generally, genetic polymorphisms contribute to inter-individual variation and can be the main genetic elements involved in the development of common and complex diseases[32]. However, the precise mechanism by which *IL-17* genetic variants increase the risk of gastric cancer is still not fully understood. IL-17 is a pro-inflammatory cytokine; it actively works with local tissue inflammation by inducing the release of pro-inflammatory and neutrophil-mobilizing cytokines[12]. Elevated IL-17 expression has been correlated with a variety of tumor tissues, including breast cancer, ovarian cancer and gastric cancer[33-35]. At present, several documents

Table 3 Univariate and multivariate meta-regression analyses of the potential source of heterogeneity

Heterogeneity factors	rs2275913 G>A						rs763780 T>C					
	Coefficient	SE	*Z*	*P* value	95%CI		Coefficient	SE	*Z*	*P* value	95%CI	
					LL	UL					LL	UL
Publication year												
Univariate	0.042	0.048	0.87	0.386	-0.053	0.137	0.034	0.065	0.52	0.601	-0.093	0.161
Multivariate	0.040	0.030	1.32	0.185	-0.019	0.098	-0.093	0.056	-1.67	0.094	-0.202	0.016
Country												
Univariate	-0.119	0.123	-0.97	0.332	-0.360	0.121	0.225	0.335	0.67	0.502	-0.432	0.882
Multivariate	0.035	0.087	0.41	0.684	-0.135	0.206	0.279	0.167	1.67	0.094	-0.048	0.606
Genotyping method												
Univariate	-0.209	0.049	-4.27	0.000	-0.305	-0.113	-0.216	0.091	-2.36	0.018	-0.395	-0.037
Multivariate	-0.218	0.051	-4.31	0.000	-0.317	0.119	-0.219	0.067	-3.27	0.001	-0.350	-0.087

UL: Upper limit; LL: Lower limit.

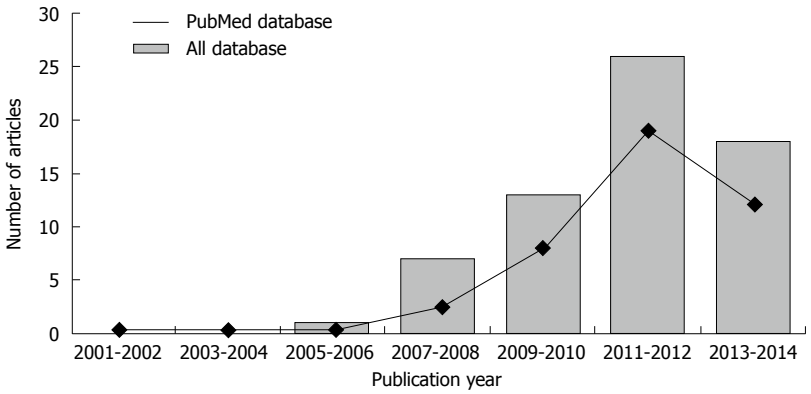


Figure 2 Distribution of the topic-related literature in electronic databases over the last decade.

and studies have revealed that two common promoter SNPs of the *IL-17A* gene (rs2275913) and *IL-17F* gene (rs763780) may be related to susceptibility to gastric carcinoma[7,36]. In addition, gene polymorphisms in the *IL-17* gene, as well as their receptors, may be involved in the development of Th1-mediated diseases, an increase in the risk of *Helicobacter pylori* (*H. pylori*) infection and the development of gastric diseases and neoplasms[37]. It is worth noting that IL-17 is secreted by T-helper cells and that it can combine with tumor necrosis factors and IL-1, which may participate in the process of inducing and mediating pro-inflammatory responses[38]. As a subset of T helper cells, Th17 cells are crucial mediators of inflammation, autoimmune disease and malignancy, especially through the production of IL-17A and IL-17F[39]. In this respect, we suspected that the *IL-17* genetic polymorphisms might affect the process of inflammation and carcinogenesis of gastric mucosa. It has been reported that the *IL-17F* rs763780 (7488T/C) is a natural IL-17F antagonist, which may result in a His-to-Arg substitution at amino acid 161 (H161R), and the genetic variant might lead to various diseases. As a result, the expression or activity of IL-17F may be suppressed in *IL-17F* (7488T/C) allele carriers[40]. More specifically, IL-17A and IL-17F have been suggested to share similar functions with respect to their ability to stimulate various chemokines, cytokines and adhesion molecules when recruiting and activating neutrophils[20]. Both cytokines, coordinately or independently, may promote the development of gastric inflammation and further induce the development of gastric malignancy. Moreover, *IL-17F* (7488T/C) is related to *H. pylori*-infection by increasing the inflammatory activity, revealing an association with the risk of intestinal-type gastric cancer[36]. A previous study by Shibata *et al*[20] also suggested that the *IL-17A* rs2275913 (G-197A) may be bound up with the degree of gastric mucosal atrophy and may elevate the risk of gastric mucosal atrophy-related disorders.

We also carefully performed stratified analyses by country to evaluate the correlation between the *IL-17* genetic variations and increased risk of gastric cancer. For the rs2275913 G>A genetic polymorphism, the country-stratified analysis results revealed that this polymorphism is closely related to an elevated risk of gastric cancer in China and Japan for the allele model. On the other hand, there was no such connection in Iran, suggesting that country differences might be a potential source of heterogeneity for this association. We speculated that country differences might be reflect differences in alleles and genotypes among different ethnic populations. However, there was a positive relationship between the *IL-17* rs763780 T>C genetic

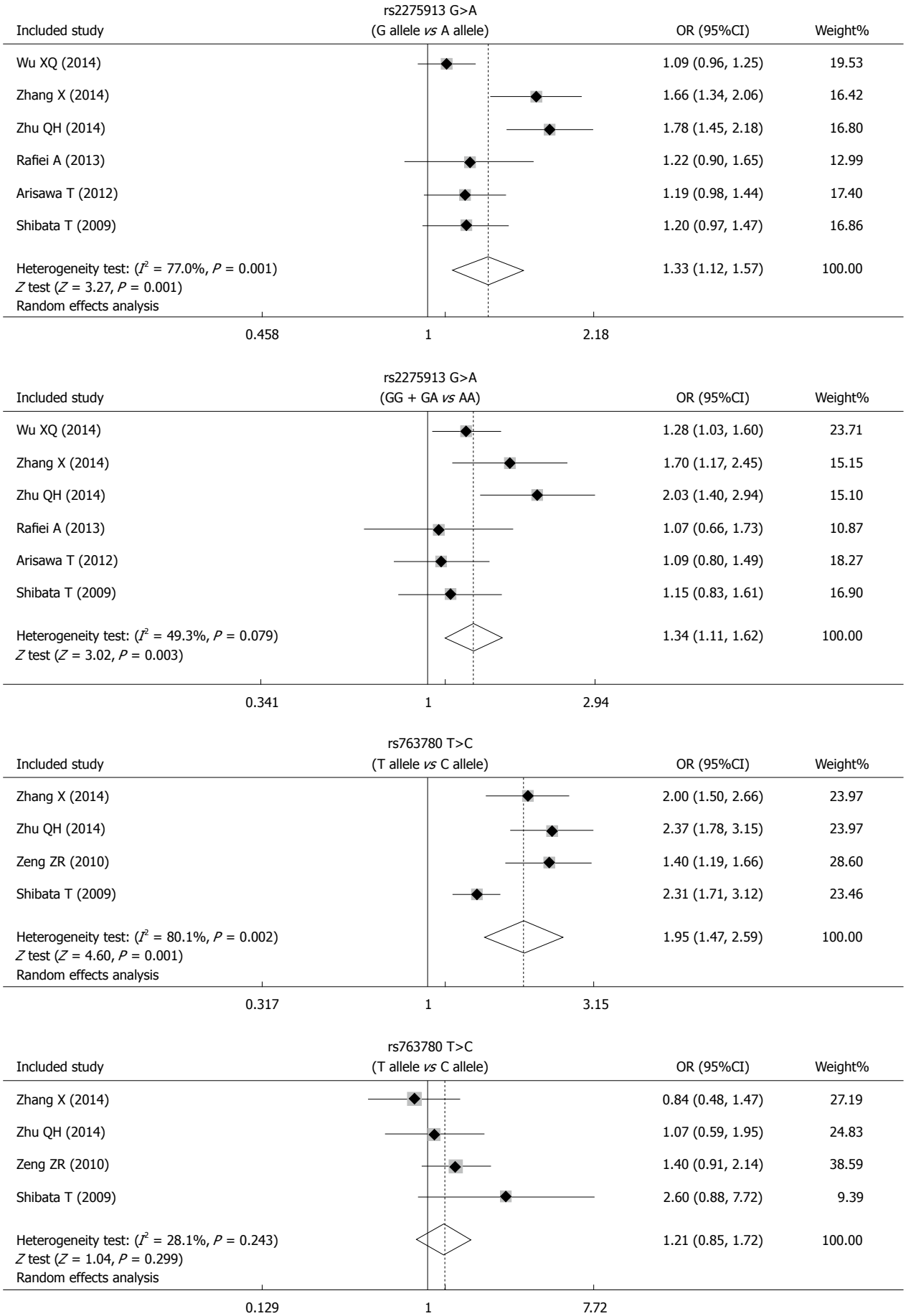
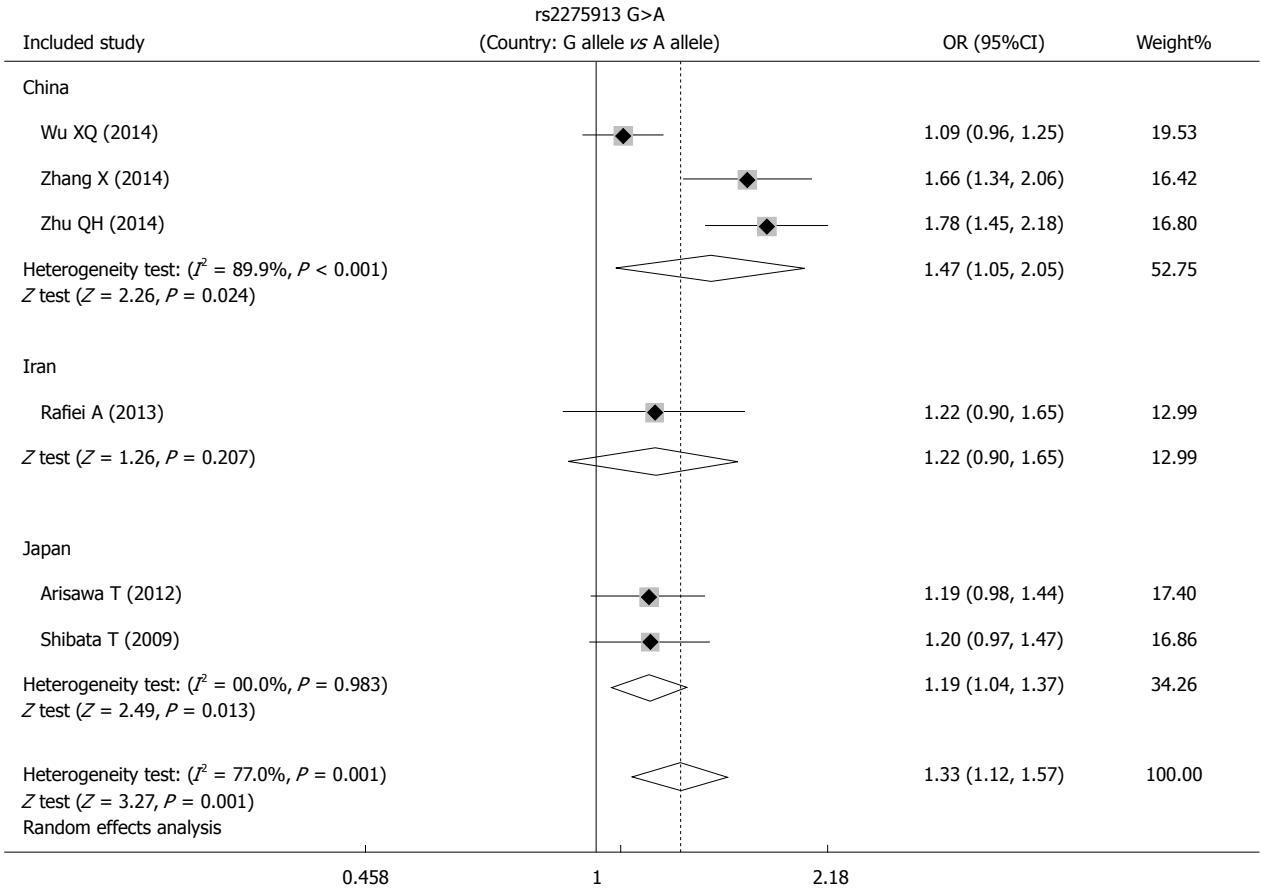
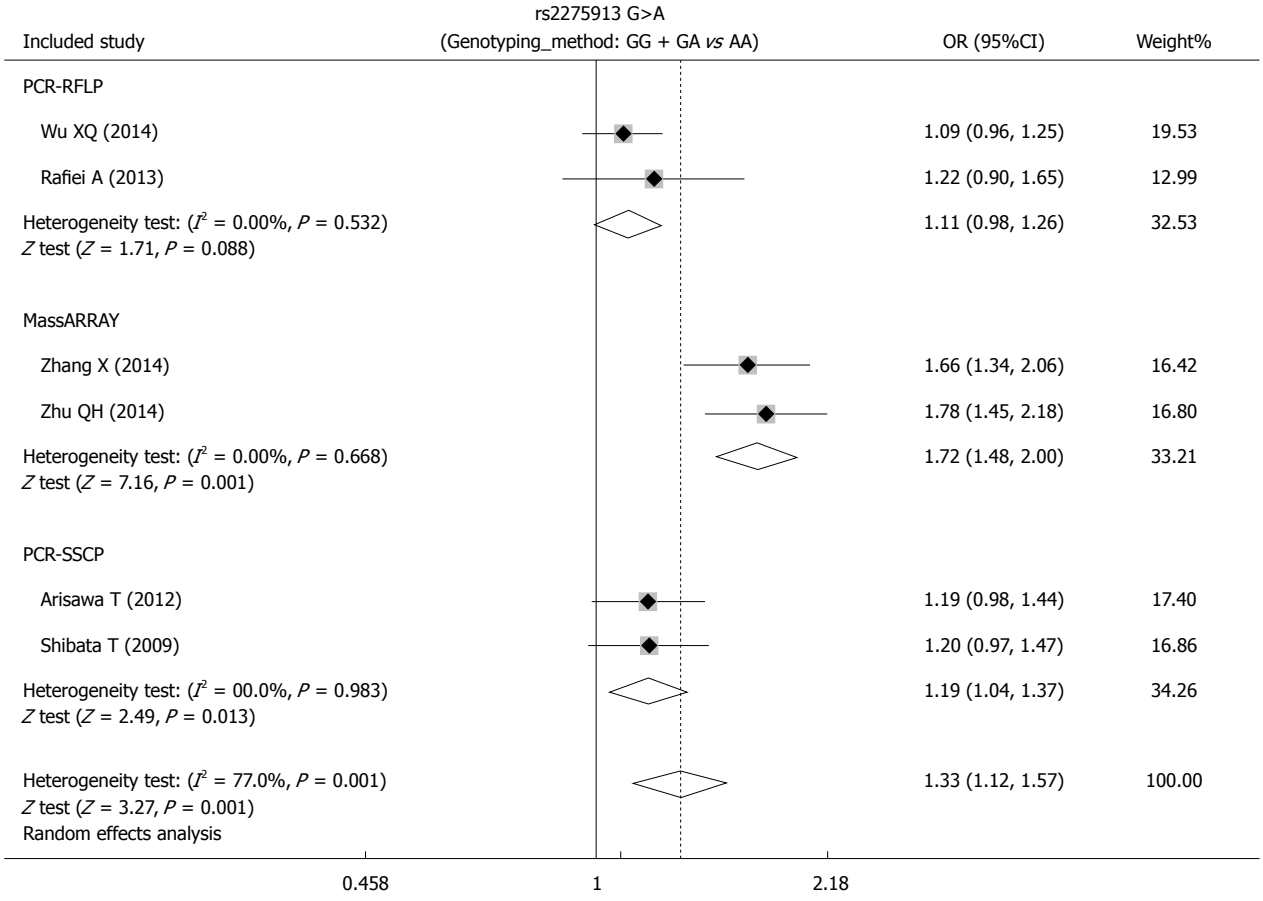


Figure 3 Forest plot of the relationships between *IL-17* polymorphisms and susceptibility to gastric cancer.


rs2275913 G>A
Included study
(Country: G allele *vs* A allele)
OR (95%CI)
Weight%
China
Wu XQ (2014)
1.09 (0.96, 1.25)
19.53
Zhang X (2014)
1.66 (1.34, 2.06)
16.42
Zhu QH (2014)
1.78 (1.45, 2.18)
16.80
Heterogeneity test: (I^2 = 89.9%, P < 0.001)
1.47 (1.05, 2.05)
52.75
Z test (Z = 2.26, P = 0.024)
Iran
Rafiei A (2013)
1.22 (0.90, 1.65)
12.99
Z test (Z = 1.26, P = 0.207)
1.22 (0.90, 1.65)
12.99
Japan
Arisawa T (2012)
1.19 (0.98, 1.44)
17.40
Shibata T (2009)
1.20 (0.97, 1.47)
16.86
Heterogeneity test: (I^2 = 00.0%, P = 0.983)
1.19 (1.04, 1.37)
34.26
Z test (Z = 2.49, P = 0.013)
Heterogeneity test: (I^2 = 77.0%, P = 0.001)
1.33 (1.12, 1.57)
100.00
Z test (Z = 3.27, P = 0.001)
Random effects analysis
0.458
1
2.18


rs2275913 G>A
Included study
(Genotyping_method: GG + GA *vs* AA)
OR (95%CI)
Weight%
PCR-RFLP
Wu XQ (2014)
1.09 (0.96, 1.25)
19.53
Rafiei A (2013)
1.22 (0.90, 1.65)
12.99
Heterogeneity test: (I^2 = 0.00%, P = 0.532)
1.11 (0.98, 1.26)
32.53
Z test (Z = 1.71, P = 0.088)
MassARRAY
Zhang X (2014)
1.66 (1.34, 2.06)
16.42
Zhu QH (2014)
1.78 (1.45, 2.18)
16.80
Heterogeneity test: (I^2 = 0.00%, P = 0.668)
1.72 (1.48, 2.00)
33.21
Z test (Z = 7.16, P = 0.001)
PCR-SSCP
Arisawa T (2012)
1.19 (0.98, 1.44)
17.40
Shibata T (2009)
1.20 (0.97, 1.47)
16.86
Heterogeneity test: (I^2 = 00.0%, P = 0.983)
1.19 (1.04, 1.37)
34.26
Z test (Z = 2.49, P = 0.013)
Heterogeneity test: (I^2 = 77.0%, P = 0.001)
1.33 (1.12, 1.57)
100.00
Z test (Z = 3.27, P = 0.001)
Random effects analysis
0.458
1
2.18

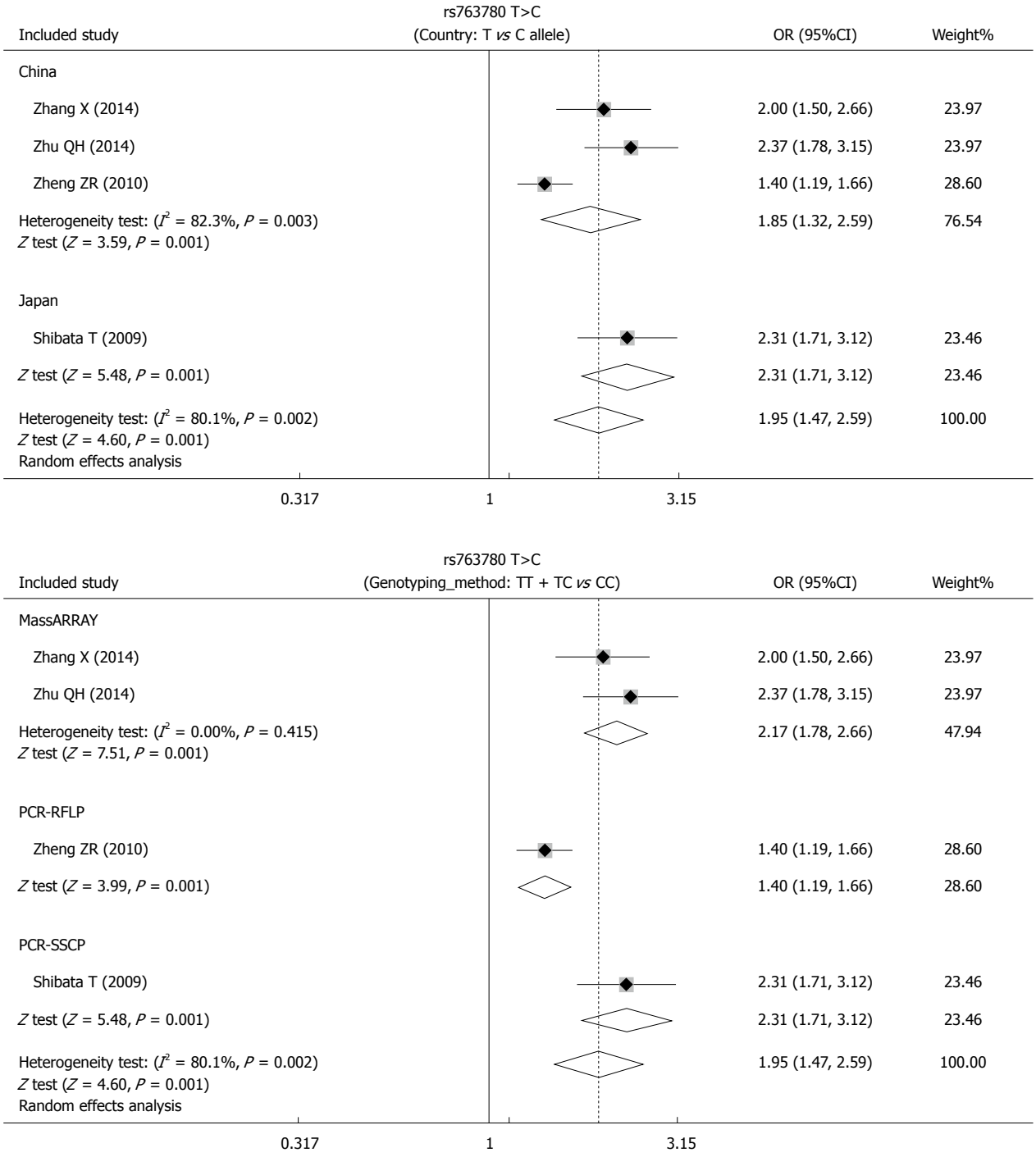


Figure 4 Subgroup analyses for the relationships between *IL-17* polymorphisms and susceptibility to gastric cancer.

polymorphism and gastric cancer in China and Japan for the allele model. Our findings were in agreement with previous reports that genetic variations in the *IL-17* gene, especially *IL-17A* (rs2275913, G-197A) and *IL-17F* (rs763780, 7488 T/C), may lead to gastric carcinoma, implying that these genetic polymorphisms could be potential markers for predicting an increased risk of gastric cancer.

Some limitations of this meta-analysis should also be considered when interpreting our results. First, this research is biased by the fact that it was conducted on a population with a single ethnicity, and the participants might not be representative of the general population. Second, publication bias may have resulted from the exclusion of unpublished data, as well as papers published in languages other than English and Chinese. A third limitation is that the controls in some of the included studies on *IL-17A* (rs2275913) and *IL-17F* (rs763780) deviated from HWE (P < 0.05). Such disequilibrium suggested that the samples were not representative of the expected genotype distribution; therefore, they may have

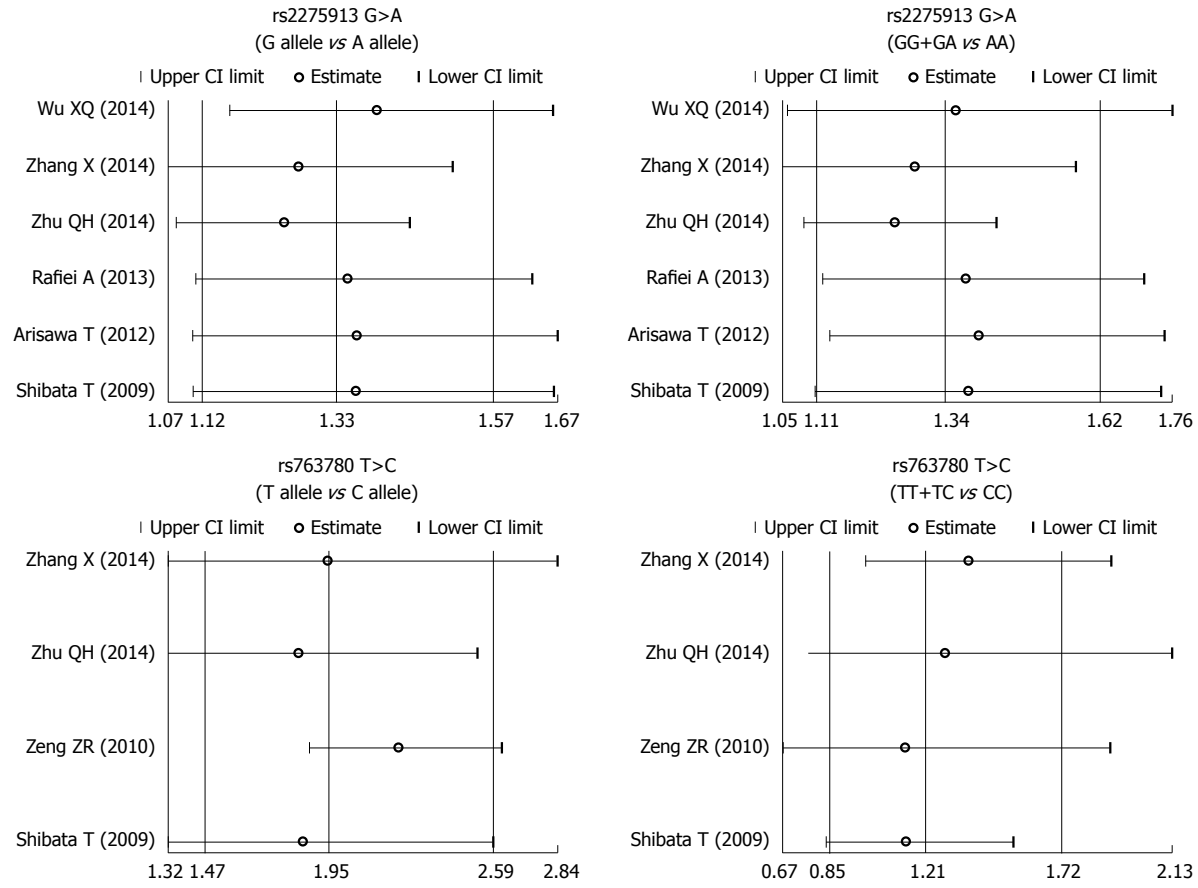


Figure 5 Sensitivity analysis of the summary odds ratio coefficients for the relationships between *IL-17* polymorphisms and susceptibility to gastric cancer.

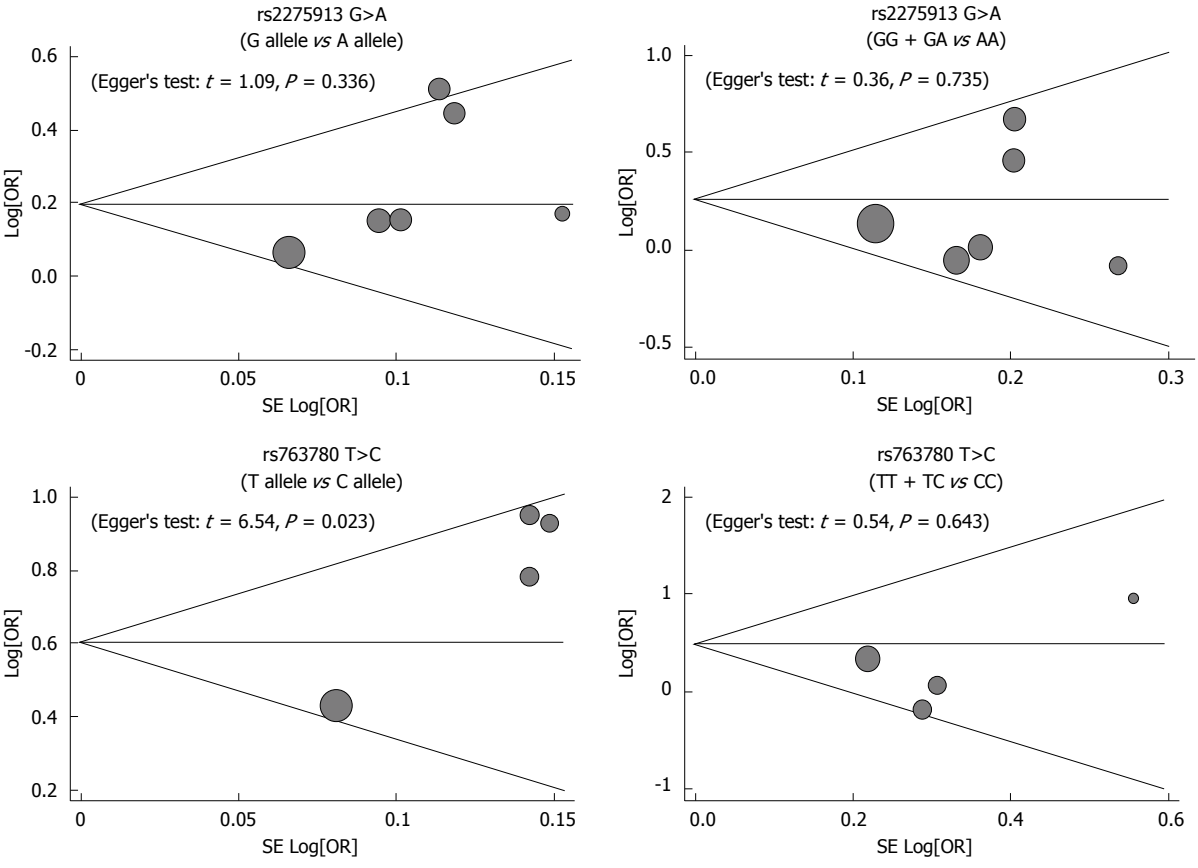


Figure 6 Funnel plot of the publication biases for the relationships between *IL-17* polymorphisms and susceptibility to gastric cancer.

distorted our findings. Fourth, the data included in this meta-analysis did not have a sufficiently large sample size for a comprehensive analysis because of the limited number of published studies and samples. Finally, we failed to uncover adequate evidence of an increased expression and function of the IL-17 axis and IL-17-driven inflammatory response associated with rs2275913A and rs763780C alleles (in the presence and absence of *H. pylori* infection), which largely restricted a comprehensive explanation of the role of IL-17 polymorphisms in the risk of gastric cancer. Future alternative experimental models for studying the development of *H. pylori* infection may be useful. In this study, the first meta-analysis on the association between the *IL-17* gene polymorphisms and gastric cancer, we used a statistical approach to rigorously quantify, combine and analyze the inconsistent results of previous studies, contributing to a more reliable understanding of the association.

In brief, this study indicated that the *IL-17* rs2275913 and rs763780 polymorphisms are associated with an increased susceptibility to gastric cancer. These results suggested that SNPs in the *IL-17* gene may have a significant relationship with the risk of gastric cancer and may be helpful in identifying individuals who are at an increased risk of developing gastric cancer. Future large, population-based and multicenter studies are warranted to determine the exact mechanism underlying the involvement of the *IL-17* gene in gastric cancer progression.

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COMMENTS

Background

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer death in both sexes worldwide. Gastric cancer has a major impact on public health because of its high morbidity and mortality rates. There has been a steady rise in gastric cancer incidence and mortality in most countries. Interleukin 17 (IL-17) is a family of pro-inflammatory cytokines composed of six similar cytokines and five receptors, with IL-17A as the founding molecule of this new cytokine family. The gene for human *IL-17* is located on chromosome 6p12 and comprises 1874 base pairs.

Research frontiers

The causes of gastric cancer are complex, and include a myriad of environmental factors and inherited susceptibilities; among its behavioral factors are smoking and a high salt diet, which have been shown to be especially linked to gastric cancer. In recent decades, many researchers have postulated that inflammation-related gene polymorphisms, such as *IL*-1β, *IL-6*, *IL-16* and *IL-17A*, which induce multiple pro-inflammatory mediators, are correlated with gastric cancer

Innovations and breakthroughs

This study indicated that the *IL-17* rs2275913 and rs763780 polymorphisms are associated with an increased susceptibility to gastric cancer. These results suggested that SNPs in the *IL-17* gene may have significant relationships with gastric cancer risk, and thus may be helpful in identifying individuals at increased risk of developing gastric cancer.

Applications

Future larger population-based and multicenter studies are warranted to confirm the exact mechanism underlying the involvement of the *IL-17* gene in gastric cancer progression.

Peer-review

The authors extracted the published data to perform a meta-analysis of the relationship between the *IL-17* gene polymorphisms and gastric cancer risk. They concluded that *IL-17* rs2275913 and rs763780 polymorphisms are associated with increased susceptibility to gastric cancer. Overall, this is a very interesting study, the experiments are well designed and conducted, the data are properly analyzed and presented, and the limitations of the study are also discussed. Thus, the result from this study may provide useful information in the field of IL-17 in gastric cancer.

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