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Potential effects of IL-17A rs2275913 and IL-17F rs763780 polymorphisms on susceptibility to gastric cancer in Chinese population: a meta-analysis

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Abstract. – OBJECTIVE: This meta-analysis aims to clarify the effect of IL-17 polymorphisms on the susceptibility to GCa in the Chinese population.

MATERIALS AND METHODS: Relevant pieces of literature were searched in PubMed, Web of School, VIP, and CNKI using the key words as "IL-17, gastric/stomach cancer" or "IL-17 polymorphisms, gastric/stomach cancer susceptibility". The odds ratio (OR) and 95% confidence interval (CI) in the selected studies were calculated using RevMan5.3 and STATA12.0.

RESULTS: A total of 12 investigations reporting mutations in IL-17A rs2275913 and IL-17F rs763780 were enrolled. There were 11 studies reporting rs2275913 G>A, involving 3299 cases of GCa patients and 3339 cases of healthy controls. The random-effects model was performed since the heterogeneity test results of the recessive genetic model (GG&GA *vs*. AA) and the allelic model (G *vs*. A) of IL-17A rs2275913 G>A were I2>66%/*p*=0.001. Meanwhile, the dominant genetic model (GG *vs*. GA&AA) and the super-dominant genetic model (GA *vs*. GG&AA) of IL-17A rs2275913 G>A were I2< 50%/*p*>0.05, and the fixed-effects model was used. The meta-analysis showed that IL-17A rs2275913 G>A was positively correlated with GCa susceptibility under four genetic models (*p*<0.05). Five studies reporting IL-17F rs763780 T>C were enrolled, including 2535 cases of GCa patients and 2402 cases of healthy controls. The heterogeneity test showed that, except for the super-dominant genetic model, the *p*-value was <0.00001 in the dominant, recessive, and allelic models, and their I2 values were 87%, 88%, and 93%, respectively. Hence, a random-effects model was selected. IL-17F rs763780 T>C was positively correlated with GCa susceptibility under the super-dominant genetic model (*p*=0.003), rather than the other three models (*p*>0.05).

CONCLUSIONS: IL-17A rs2275913 G>A polymorphism contributes to susceptibility to GCa in the dominant, recessive, allelic, and super-dominant models. Meanwhile, IL-17F rs763780 T>C polymorphism is positively correlated with GCa susceptibility in the super-dominant model.

Key Words:
IL-17A rs2275913, IL-17F rs763780, Gastric cancer, Meta-analysis.

Introduction

Gastric cancer (GCa) is the fifth most prevalent cancer in the world. In 2012, about 952,000 new cases of GCa (accounting for 7% of total) and 723,000 GCa-related deaths were reported[1]. The incidence of GCa varies a lot across continents. The males in Northeast Asia (Japan, Korea, and China) are the most affected populations, with an incidence of 36/100,000 per year. In North America, Africa, South Asia, and Oceania (including Australia and New Zealand), the incidence of GCa remains the lowest with 4-10/100,000[2]. In 2015, there were 679,100 new

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cases and 498,000 death cases of GCa in the Chinese population, which ranks second and third in cancer morbidity and mortality, respectively[3]. The etiology of GCa involves multiple risk factors, such as genetic susceptibility, environmental factors, and microbial infections. Although *Helicobacter pylori* (*H. pylori*) infection is confirmed to exert an important role in the pathogenesis of GCa[4,5], only a small part of infected people develops into GCa, suggesting that the genetic susceptibility may be crucial in the tumorigenesis of GCa.

Interleukin-17A (IL-17A) locates on chromosome 6p12 and encodes a 155 amino acid glycoprotein[6]. IL-17 family includes six members (IL-17A to IL-17F), which are involved in chronic inflammatory diseases and cancers[7-9]. Activated T cells induce the production of IL-17, such as Th17 cells, natural killer cells, mast cells, and neutrophils[10]. Currently, IL-17A rs2275913 (G-197A) and IL-17F rs763780 (C7488T) have been extensively studied. The A/G polymorphism of IL-17A rs2275913 is located at the codon from position -197. The rs763780C/T polymorphism is located in the IL-17F, resulting in a His-to-Arg substitution at amino acid 161. Recent studies have shown that these two functional SNPs could affect the susceptibilities to asthma[11], arthritis[12], and even cancer[8]. Potential effects of IL-17A rs2275913 and IL-17F rs763780 polymorphisms on the susceptibility to GCa are well-concerned nowadays[13-21]. However, relevant studies reported a controversial conclusion. This study focused on their correlation in the Chinese population.

Materials and methods

Searching Strategy

Relevant studies published before January 30, 2019 were searched in PubMed, Web of School, VIP, and CNKI using the key words as "IL-17, gastric/stomach cancer" or "IL-17 polymorphisms, gastric/stomach cancer susceptibility". No limitations were set on languages. The references in relevant reports were manually reviewed.

Inclusion and Exclusion Criteria

Inclusion criteria were applied: (1) case-control studies on assessing the effect of IL-17 gene polymorphism on GCa susceptibility; (2) GCa patients were pathologically diagnosed; (3) case numbers of GCa patients and controls were provided; (4) sample size was over 150; (5) raw data were provided to calculate OR and 95% CI; (6) controls in the study was in accordance to HWE; (7) subjects were Chinese population.

Exclusion criteria were applied: (1) familial and hereditary GCa cases; (2) haplotype cases; (3) data did not conform with the researches. Studies with the latest or the largest sample size were selected if data were overlapping.

Data Acquisition

Data acquisition was independently conducted by two investigators, and any disagreements were determined by the third investigator. For each literature, the basic data included the first author, year of publication, race of subjects, case number, genotyping method for IL-17A or IL-17F polymorphisms, and HWE in controls were recorded.

Statistical Analysis

OR and 95% CI were calculated to evaluate the effect of IL-17 polymorphisms on susceptibility to GCa. The fixed-effect model was used when $p<0.05$; otherwise, the random-effects model was used. Sensitivity analysis reflected the stability and reliability of the results by removing one individual study each time and recalculating their ORs. For each study, χ^2 was used to test HWE in the gene distribution of the control group, and $p<0.05$ was considered to be unbalanced. Begg's funnel plot and Egger regression test were utilized for evaluating the publication bias. Statistical analysis was performed using RevMan5.3 and STATA12.0 (London, UK).

Results

Characteristics of the Studies

314 pieces of literature reporting IL-17 and GCa were searched from PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and VIP databases. After the initial screening, 143 repetitive and 112 unrelated studies were excluded. For the remaining 31 studies, 6 non-Chinese population, 10 reviews, and 3 conducted in other cities were excluded. Finally, 12 eligible studies were included in this study (Figure 1).

The basic characteristics of the selected studies were depicted in Table I. The 12 case-control studies in the Chinese populations from different provinces were published in English-language journals from 2010 to 2016. The number of cases

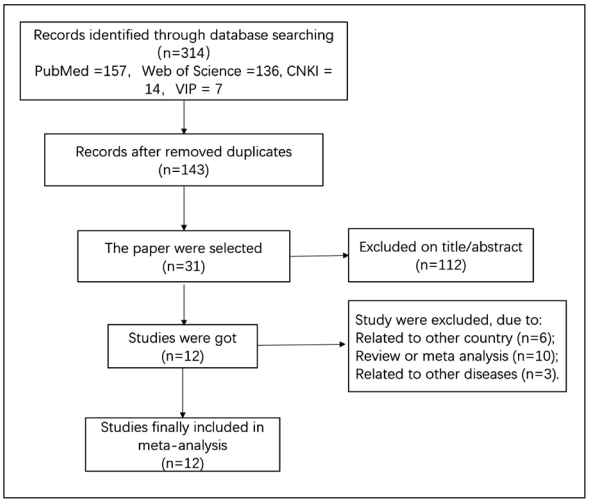

Figure 1. Flow diagram of the publication selection process.

ranged from 153 to 1121, and that of the normal controls ranged from 207 to 1216. The genotypic methods included PCR-RFLP, RT-PCR, and Sequenom Mass Array. The control groups in all eligible studies followed HWE (p>0.001).

Correlation Between IL-17A rs2275913 (G197A), IL-17F Rs763780 (C7488T) Polymorphism and Susceptibility to GCa

There were 11 studies reporting rs2275913 G>A, involving 3299 cases of GCa patients and 3339 cases of healthy controls. The preliminary results of the effect of IL-17 rs2275913 G>A on GCa susceptibility were shown in Figure 2. The heterogeneity test results of the recessive genetic model (GG&GA *vs.* AA) and the allelic model (G *vs.* A) of IL-17A rs2275913 G>A were I^2>66%/p=0.001, so the random-effects model was selected. Meanwhile, the dominant genetic model (GG *vs.* GA&AA) and the super-dominant genetic model (GA *vs.* GG&AA) of IL-17A rs2275913 G>A were I^2<50%/p>0.05, which were subjected to the fixed-effects model. Our data demonstrated the positive effect of IL-17 rs2275913 G>A on GCa susceptibility in the four genetic models (p<0.05).

Five studies reporting IL-17F rs763780 T>C were enrolled, including 2535 cases of GCa patients and 2402 cases of healthy controls. The heterogeneity test showed that, except for the super-dominant genetic model, the p-value was <0.00001 in the dominant, recessive, and allelic models, and their I^2 values were 87%, 88%, and 93%, respectively. Hence, a random-effects model was selected. IL-17F rs763780 T>C was positively correlated with GCa susceptibility under the super-dominant genetic model (p=0.003), rather than the other three models (p>0.05) (Figure 3).

Subgroup analysis on the location of GCa showed a significant difference in the allele A frequencies of rs2275913 between the non-cardia cancer group and the control group, which was higher in the former one (OR=1.29, 95% CI = 1.03-1.60, p=0.02). Meanwhile, A allele of rs2275913 indeed increased the susceptibility to GCa in GCa patients infected with *H. pylori* (OR=1.61, 95% CI=1.38-1.87, p<0.00001) (Figure 4). However, we did not observe such a significant difference in GCa patients without *H. pylori* infection (data not shown).

Sensitivity Analysis and Publication Bias

Removing any single study did not change the overall results, indicating that our results were stable and reliable. The symmetrically distributed funnel plots were identified on uncovering the correlation between rs2275913 G>A with GCa susceptibility in the super-dominant genetic model. Besides, the Egger test did not reveal any shift (p=0.345) (Figure 5). The dominant genetic model of the correlation between rs2275913 G>A and GCa susceptibility presented the publication bias (t=4.62, p=0.001). Publication bias was also identified in the dominant genetic model of the correlation between rs763780 T>C and GCa susceptibility (t=-3.36, p=0.044) (Figure 5).

Discussion

This meta-analysis aims to investigate the relationship between IL-17 rs2275913 G>A and rs763780 T>C polymorphisms and GCa susceptibility in the Chinese population. It is concluded that the rs2275913 G>A polymorphism contributed to GCa susceptibility in the four heritage models of dominant, recessive, super-dominant, and allelic one. In addition, the rs763780 T>C polymorphism led to GCa susceptibility in the super-dominant model, rather than the other three genetic models. Generally speaking, individual variation could result from genetic polymorphisms[22].

IL-17 is a novel cytokine that is important in the innate and adaptive immunity[23]. As an essential pro-inflammatory cytokine, it protects the inflammatory infiltration by releasing pro-inflammatory and neutrophils[24]. IL-17 also

Table I. Basic characteristics of the selected studies.

Author	Year	Country	Journal name/ publication origin	Genotyping methods	SNP loci (PHWE)	Sample size	Control	Sample
Xu BL	2015	China	GMR	PCR	rs2275913 (PHWE=0.86)	202 (125 males and 77 females)	237 (104 males and 113 females)	Blood
Zhang	2014	China	Tumor Biol	PCR	rs2275913 (PHWE=0.057)	260 (98 females and 162 males)	512 (232 female and 280 male)	Blood
Zhou Fei	2016	China	Oncotarget	Real time-PCR	rs2275913 (PHWE=0.160)	1121	1216	Blood
Yang LJ	2016	China	Eur Rev Med Pharmacol Sci	RFLP-PCR	rs763780 (PHWE=0.003)	386 (221 males and 165 females)	375 (219 males and 155 females)	Blood
W.T. Qi	2015	China	GMR	Real time-PCR	rs2275913 (PHWE=0.47)	252 (97 females and 155 males)	252 (97 females and 155 males)	Blood
Wangnan	2014	China	Tumor Biol	PCR-RFLP	rs2275913 (PHWE=0.12)/ rs763780 (PHWE=0.13)	462 (165 females and 297 males)	462 (165 females and 297 males)	Blood
Zhu Qinghai	2014	China	Gene	PCR-MALDITOF	Rs2275913 (PHWE=0.07)	293 (104 females and 189 males)	550 (238 females and 312 males)	Blood
Chenggong Hou	2015	China	Int J Clin Exp Pathol	Sequenom MassArray	Rs2275913 (PHWE=0.97)	326 (116 females and 201 males)	326 (116 females and 201 males)	Blood
W.M. Zhao	2016	China	GMR	PCR-RFLP	rs2275913 (PHWE=0.44)/ rs763780 (PHWE=0.11)	153 (46 females and 107 males)	207 (87 females and 120 males)	Blood
Yawen Gao	2015	China	Oncol Lett	PCR-RFLP	rs2275913 (PHWE=0.17)/ rs763780 (PHWE=0.09)	572 (220 females and 52 males)	572 (220females and 352 males)	Blood
Xiaoqin Wu	2010	China	Int J of Cancer	PCR-RFLP	rs2275913 (PHWE=0.49)/ rs763780 (PHWE=0. 82)	962 (308 females and 654 males)	787 (275 females and 512 males)	Blood
Zhengbing Ren	2014	China	Biomarkers	PCR	Rs2275913 (PHWE=0.256)	243 (84 females and 159 males)	476 (188 females and 288 males)	Blood

SNP = Single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium; PHWE = P value of Hardy-Weinberg Equilibrium test in controls for each locus; PCR = polymerase chain reaction.

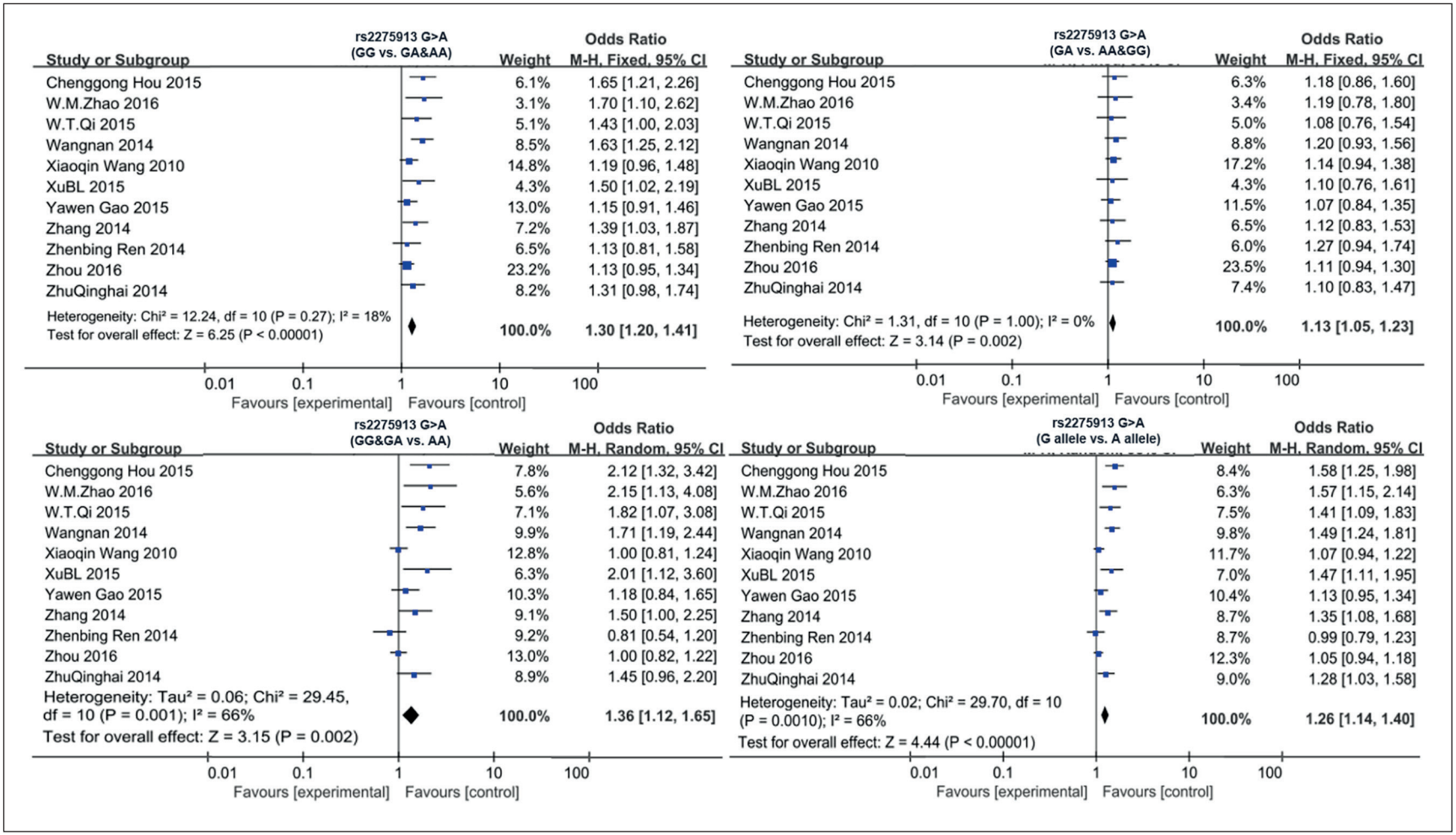

Figure 2. Forest plots of the correlation between rs2275913 polymorphism and GCa susceptibility.

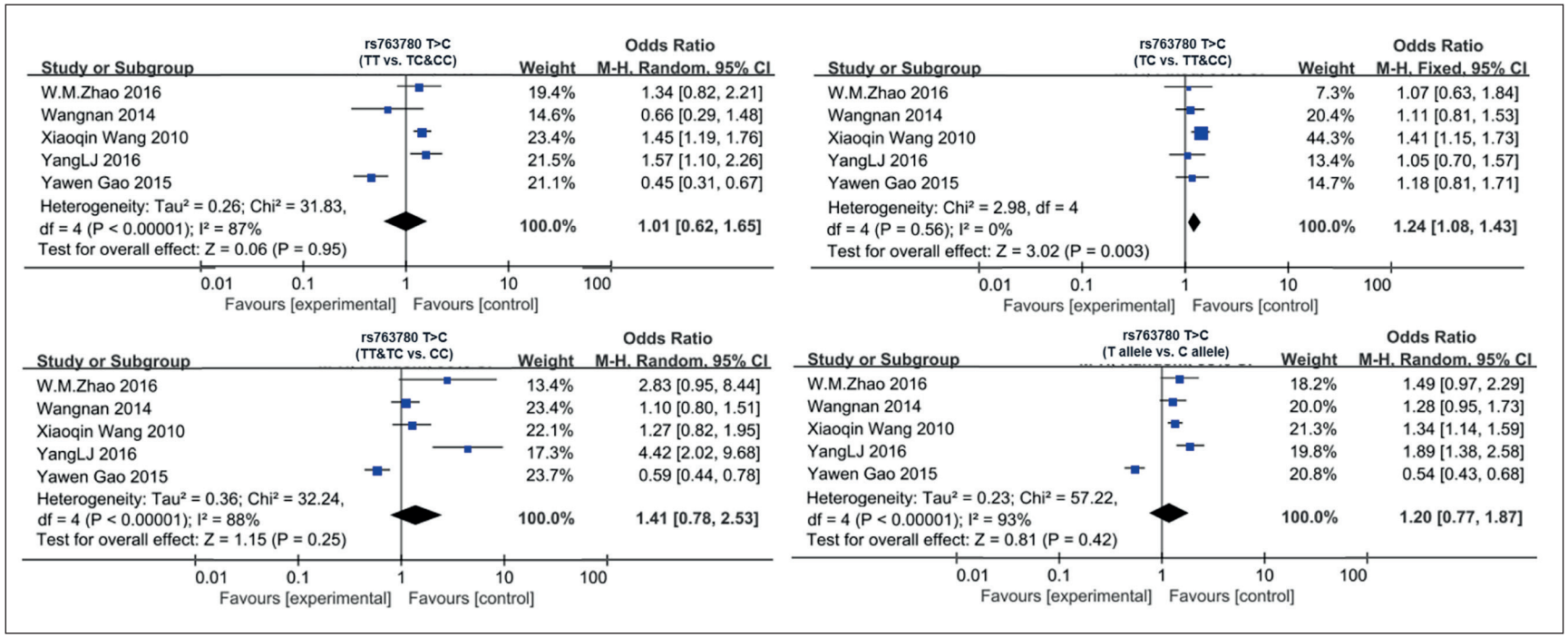

Figure 3. Forest plots of the correlation between rs763780 polymorphism and GCa susceptibility.

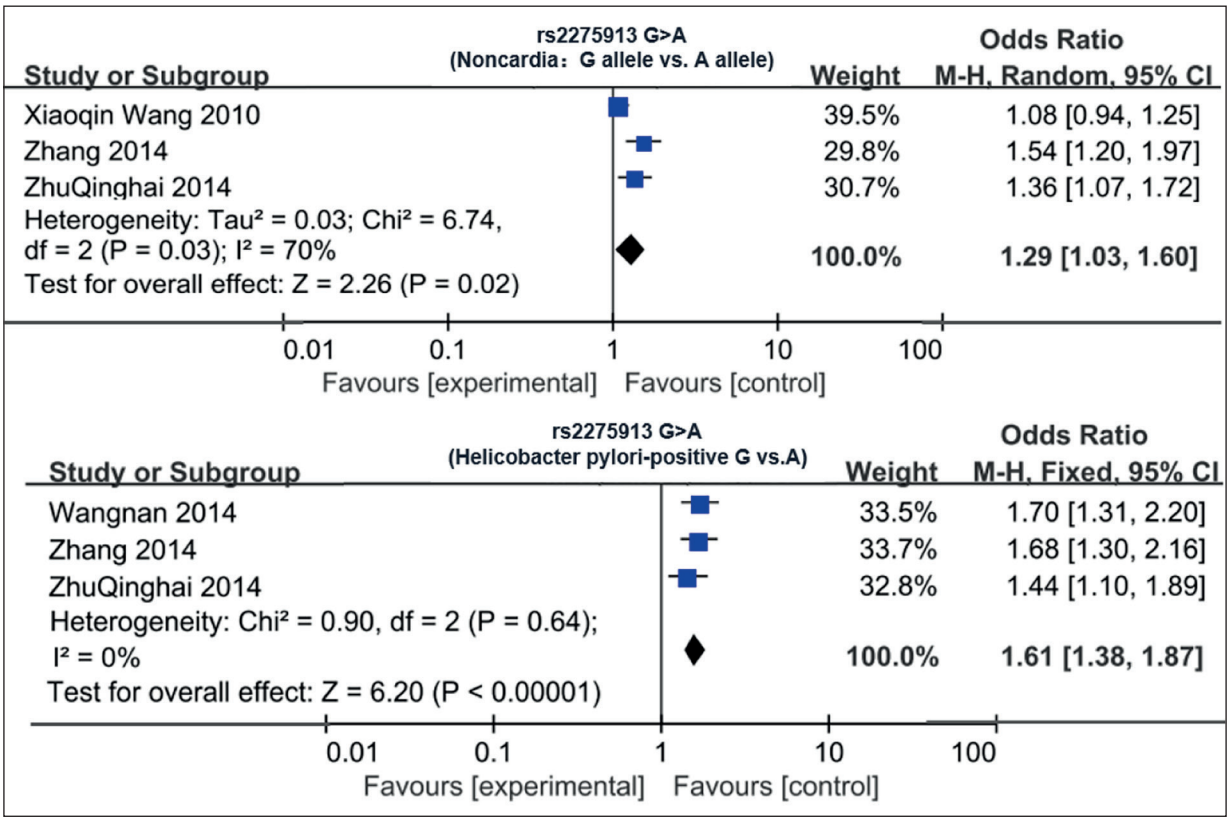

Figure 4. Subgroup analysis on the correlation between IL-17 polymorphisms and GCa susceptibility.

upregulates the expressions of the antimicrobial peptides to promote the host defense[25,26]. Th17 cells are a branch of T helper cells, which are important mediators in the inflammatory responses, autoimmune diseases, and malignancies. The polymorphism of IL-17a rs2275913 is located in the 5'UTR, allowing its capacity of transcriptional regulation[27]. The rs763780 polymorphism locates on the coding region and can affect the structure and function of the proteins[18,28]. Recently, many epidemiological studies uncovered the role of IL-17 gene polymorphism in the susceptibility to GCa, but their conclusions are controversial[19,21,29-33]. Shibata et al[29] reported the influence of AA genotype of IL-17A rs2275913G> A on the increased risk of GCa, especially the intestinal subtype. Nevertheless, Wu et al[30] reported that although the rs763780 polymorphism is associated with GCa, the rs2275913 polymorphism is irrelevant. A

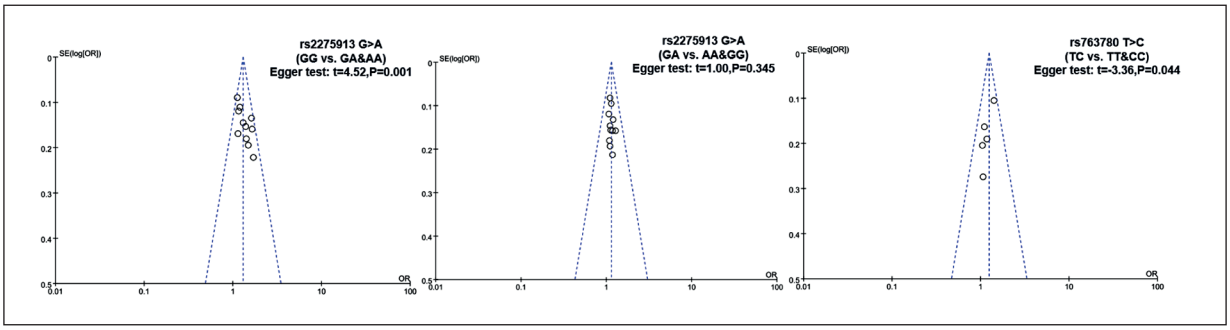

Figure 5. Begg's funnel plot of publication bias test.

great number of studies reported the positive effect of IL-17A rs2275913G>A polymorphism on GCa susceptibilities in different populations with different sample sizes[18,19,31,32,34]. Nevertheless, Gao et al[21] reported that it is the rs763780 polymorphism to be associated with susceptibility to GCa, especially in alcohol-drinking patients, rather than the IL-17A rs2275913G> A gene polymorphism. These inconsistent results may be explained by different sample sizes, populations, races, and inclusive criteria.

Our study found that *H. pylori* infection and the location of GCa were influencing factors for the effect of IL-17A rs2275913 G> A polymorphism on the susceptibility to GCa in the Chinese population. IL-17 is a vital regulator in infectious diseases and immune-mediated gastrointestinal diseases. IL-17 secretion is stimulated by *H. pylori* infection in human gastric mucosa[6]. However, due to the small sample size and limited researches, it is unclear whether IL-17 gene polymorphism is a marker of *H. pylori*-induced GCa.

Some limitations in this meta-analysis should be noteworthy. Firstly, all results were based on unadjusted estimates that lacked raw data from the enrolled studies. We were unable to assess the relationship between genetic-environment interactions and GCa progression. Secondly, the sample size was relatively small. Thirdly, this study only included studies conducted in the Chinese population and published in Chinese or English language. Fourthly, heterogeneity was existed in some models, indicating that the included population here could not completely represent the general population.

Conclusions

We found that IL-17A rs2275913 G>A gene polymorphism led to GCa susceptibility in the Chinese population in the four genetic models, especially in those with *H. pylori* infection. IL-17F rs763780 T>C polymorphism had a certain impact on GCa susceptibility in the Chinese population under the super-dominant genetic model. Further researches with a larger sample size are still required to strengthen our conclusion.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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