Original Article

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

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Abstract: Background: The association between Interleukin-17(IL-17) gene polymorphisms and Helicobacter pylori (H. pylori) infection and gastric cancer susceptibility were inconsistent. We therefore performed a comprehensive meta-analysis about all three genetic polymorphisms of IL-17 to derive a more precise estimation. Methods: PubMed, Embase, CNKI and Wanfang databases were researched on the associations between IL-17A rs2275913G>A, rs3748067C>T and IL-17F rs763780 T>C polymorphisms and gastric cancer risk. Odds ratio (OR) with a 95% confidence interval (CI) was applied to assess the relationships. Publication bias, sensitivity and cumulative analysis was conducted to guarantee the strength of meta-analysis. Results: Overall, eleven related studies involving 4,478 cases and 5,612 controls were collected. Significantly increased risk between IL-17A rs2275913G>A polymorphism and gastric cancer were observed (A vs. G: OR = 1.22, 95% CI = 1.08-1.37, P<0.01, I² = 72.3%; AA vs. GG: OR = 1.55, 95% CI = 1.21-1.99, P<0.01, I² = 74.3%; GA + AA vs. GG: OR = 1.19, 95% CI = 1.05-1.39, P<0.01, I² = 48.2%; AA vs. GG + GA: OR = 1.50, 95% CI = 1.16-1.95, P<0.01, I² = 81.2%). For IL-17F rs3748067C>T and rs763780 T>C polymorphisms, only few significantly increased risk could be found in genetic models. Moreover, H. pylori infection also be proved to increase the risk of gastric cancer combined with rs3748067C>T mutation. Conclusions: Our meta-analysis suggests that the three IL-17 polymorphisms were associated with a significantly increased risk of gastric cancer, especially in Chinese.

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

Introduction

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

Chronic inflammation is a well-known risk factor for malignant transformation, but its role in cancer initiation is poorly understood [3, 4]. Interleukin-17(IL-17), a novel family of cytokines consisting of six protein members (from IL-17A to IL-17F), plays a pivotal role in many chronic inflammatory diseases and in cancer development [5]. IL-17 is produced by activated CD4+ T
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Figure 1. Flow diagram of the study selection process.

Search strategy

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

Eligibility criteria

All selected studies must complied with the following three criteria: (a) case-control study of gastric cancer and IL-17 polymorphism; (b) sufficient genotype frequency to estimate the odds...
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Table 1. Characteristics of case-control studies on IL-17A rs2275913G>A, rs3748067C>T and IL-17F rs763780 T>C polymorphisms and gastric cancer risk included in the meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Racial/ descent</th>
<th>Source of controls</th>
<th>H. pylori</th>
<th>Case</th>
<th>Control</th>
<th>Genotype distribution (G/G, G/A, A/A)</th>
<th>P for HWE*</th>
<th>G/G</th>
<th>G/A</th>
<th>A/A</th>
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<td>Shibata</td>
<td>2009</td>
<td>Japan</td>
<td>Asian</td>
<td>Hospital controls</td>
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<td>287</td>
<td>523</td>
<td>94, 124, 69</td>
<td>&lt;0.01</td>
<td>175</td>
<td>299</td>
<td>49</td>
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<td>2010</td>
<td>China</td>
<td>Asian</td>
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<td>Yes</td>
<td>24</td>
<td>230</td>
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<td>58</td>
<td>126</td>
<td>46</td>
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<tr>
<td>Chen</td>
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<td>China</td>
<td>Asian</td>
<td>Population controls</td>
<td>Yes</td>
<td>1042</td>
<td>1090</td>
<td>300, 522, 220</td>
<td>0.97</td>
<td>325</td>
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<td>Asian</td>
<td>Hospital controls</td>
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<td>333</td>
<td>583</td>
<td>112, 137, 84</td>
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<td>218</td>
<td>293</td>
<td>72</td>
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<tr>
<td>Rafiei</td>
<td>2013</td>
<td>Iran</td>
<td>Caucasian</td>
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<td>No</td>
<td>161</td>
<td>171</td>
<td>56, 61, 44</td>
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<td>78</td>
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<tr>
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<td>2014</td>
<td>China</td>
<td>Asian</td>
<td>Population controls</td>
<td>Yes</td>
<td>260</td>
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<td>110, 102, 48</td>
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<td>Hospital controls</td>
<td>Yes</td>
<td>293</td>
<td>550</td>
<td>126, 122, 45</td>
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<td>Asian</td>
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<td>239, 250, 83</td>
<td>0.17</td>
<td>260</td>
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<td>Hospital controls</td>
<td>No</td>
<td>573</td>
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<td>Population controls</td>
<td>Yes</td>
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<td>512</td>
<td>206, 30, 24</td>
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<td>Hospital controls</td>
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<td>220, 25, 48</td>
<td>&lt;0.01</td>
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<td>Wang</td>
<td>2014</td>
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<td>Asian</td>
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<td>462</td>
<td>462</td>
<td>39, 138, 285</td>
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<td>Gao</td>
<td>2015</td>
<td>China</td>
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<td>Hospital controls</td>
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<td>572</td>
<td>42, 70, 460</td>
<td>&lt;0.01</td>
<td>47</td>
<td>66</td>
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*HWE in control; MAF: Minor allele frequency in control group.

were calculated to evaluate the strength of the association of the IL-17A rs2275913G>A and rs3748067C>T and IL-17F rs763780 T>C polymorphisms with gastric cancer risk. For the IL-17A rs2275913G>A polymorphism, the pooled ORs were obtained for allele contrast (A vs. G), co-dominant model (AG vs. AA, GG vs. GA), dominant model (GA + GG vs. AA), and recessive model (GG vs. AA + GA). These genetic models were also assessed in the IL-17A rs3748067C>T and IL-17F rs763780 T>C variants. Furthermore, subgroup analysis with ethnicity and study design were analyzed statistically. Heterogeneity was assessed with the Cochran’s Q test and I² method [17, 18]. Meta-regression was conducted to examine analyses that exhibited heterogeneity. ORs were estimated with a random-effects model (DerSimonian and Laird method) when the P value was less than 0.10 or I² was greater than 50%; otherwise, a fixed-effects model (the Mantel-Haenszel method) was adopted. Cumulative...
Figure 2. OR and 95% CIs for the associated between IL-17A rs2275913G>A polymorphism with gastric cancer risk in AA vs. GG model. (A for overall populations; B for HWE subgroup; C for sperm for ethnicity subgroup; D for control sources subgroup).
Table 2. Summary ORs and 95% CI of IL-17A rs2275913G>A, rs3748067C>T and IL-17F rs763780T>C polymorphisms and gastric cancer risk

<table>
<thead>
<tr>
<th>rs2275913G&gt;A</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>P (%)</th>
<th>OR (95% CI)</th>
<th>P (%)</th>
<th>OR (95% CI)</th>
<th>P (%)</th>
<th>OR (95% CI)</th>
<th>P (%)</th>
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<th>P (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2275913G&gt;A</td>
<td>N</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
</tr>
<tr>
<td>rs3748067C&gt;T</td>
<td>N</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
</tr>
<tr>
<td>rs763780T&gt;C</td>
<td>N</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
<td>OR (95% CI)</td>
<td>P (%)</td>
</tr>
</tbody>
</table>

*Numbers of comparisons; †Test for heterogeneity; PC: Population controls; HC: Hospital controls; NA: Not available.
meta-analyses and sensitivity analyses were conducted to evaluate the stability of the results by sequentially removing each study in each polymorphism. Potential publication bias of literature was analyzed by Egger’s linear regression and Begg’s funnel plots [19]. Statistical analysis was performed using Stata version 11.0 (Stata Corporation, College Station, TX, USA) with two-sided P values; P<0.05 was considered significant.

Results

Study characteristics

In total, 88 studies were obtained through the literature search; a flow chart of the study selection process is shown in Figure 1. The title and duplicate screening step excluded 57 studies. Of the remaining 31 studies, 20 studies were excluded (five were reviews, six were not on the research polymorphism locus, and nine did not focus on the relevant gene and gastric cancer risk). Thus, data from 11 publications met the inclusion criteria [15, 20-29], of which two studies were of IL-17A rs2275913G>A [15, 24], four studies of IL-17A rs3748067C>T [22, 24, 25, 29], and four studies of IL-17F rs763780 T>C [21, 24, 25, 29]. Characteristics of the selected studies were summarized in Table 1.

Quantitative analysis

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

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

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

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

<table>
<thead>
<tr>
<th>Study omitted</th>
<th>Estimate</th>
<th>95% Conf.</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shibata (2009)</td>
<td>1.4688481</td>
<td>1.1438769</td>
<td>1.8861425</td>
</tr>
<tr>
<td>Luo (2010)</td>
<td>1.6015942</td>
<td>1.2627679</td>
<td>2.0313344</td>
</tr>
<tr>
<td>Chen (2010)</td>
<td>1.6341802</td>
<td>1.2511117</td>
<td>2.1345372</td>
</tr>
<tr>
<td>Wu (2010)</td>
<td>1.6157954</td>
<td>1.2221409</td>
<td>2.1362467</td>
</tr>
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<td>Arisawa (2012)</td>
<td>1.4849805</td>
<td>1.1446395</td>
<td>1.9265167</td>
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<td>Rafiei (2013)</td>
<td>1.4767568</td>
<td>1.1480416</td>
<td>1.899592</td>
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<td>Zhang (2014)</td>
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<td>1.5439249</td>
<td>1.1705883</td>
<td>2.03633</td>
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<td>Wang (2014)</td>
<td>1.4976768</td>
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<td>1.956412</td>
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<td>Bi (2014)</td>
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<td>Gao (2015)</td>
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<td>1.5509443</td>
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<td>1.9946474</td>
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</table>

HWE existed in all three polymorphism loci, of which two studies were of IL-17A rs2275913G>A [15, 24], four studies of IL-17A rs3748067C>T [22, 24, 25, 29], and four studies of IL-17F rs763780 T>C [21, 24, 25, 29]. Characteristics of the selected studies were summarized in Table 1.
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**IL-17A rs3748067C>T**: Five studies involving 2,160 cases and 2,422 controls were included for the determination of an association of IL-17A rs3748067C>T polymorphism with gastric cancer risk. No significant association was found in all five genetic models (for T vs. C, OR = 1.30, 95% CI = 0.84-2.03, P = 0.24, I² = 92.0%; for CT vs. CC, OR = 1.10, 95% CI = 0.81-1.51, P = 0.53, I² = 42.9%; for TT vs. CC, OR = 1.38, 95% CI = 0.70-2.70, P = 0.35, I² = 86.5% for CT + TT vs. CC, OR = 1.22, 95% CI = 0.82-1.86, P = 0.34, I² = 78.2%; for TT vs. CC + CT, OR = 1.41, 95% CI = 0.81-2.45, P = 0.22, I² = 88.4%) (Table 1). Stratified and subgroup analysis were conducted according to ethnicity and control design, which revealed few significant associations in hospital-control studies. No conspicuous change in the pooled ORs was found in the sensitivity analysis, except the study of Wang et al. Only one publication bias was revealed, indicating that our results are statistically robust (T vs. C: P = 0.23; CT vs. CC: P = 0.07; TT vs. CC: P = 0.93; CT + TT vs. CC: P = 0.04; TT vs. CC + CT: P = 0.17).

**IL-17F rs763780 T>C polymorphism**: Seven related publications with 2,917 cases and 3,776 controls reported the association of IL-17F rs763780 T>C polymorphisms with gastric cancer risk. Significant result was only observed in the TC vs. TT model (for C vs. T, OR = 1.08, 95% CI = 0.81-1.44, P = 0.60, I² = 86.3%; for TC vs. TT, OR = 1.29, 95% CI = 1.12-1.48, P<0.01, I² = 19.7%; for CC vs. TT, OR = 1.08, 95% CI = 0.67-1.75, P = 0.76, I² = 72.2%; for TC + CC vs. TT, OR = 1.07, 95% CI = 0.78-1.48, P = 0.67, I² = 79.2%; for CC vs. TT + TC, OR = 1.04, 95% CI = 0.76-1.44, P = 0.79, I² = 61.0%) (Table 2). Subsequent stratified analysis according to ethnicity and control design were conducted, which showed consistent results in the subgroup analysis of Chinese or hospital controls.

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

**IL-17 polymorphisms and H. pylori infection**: Based on the collected studies, only five eligible papers described IL-17A rs2275913G>A
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polymorphism and three papers described IL-17F rs3748067C>T polymorphisms combined with the H. pylori infection status (Table 1). Quantitative synthesis indicated H. pylori infection was an increased risk for the development of gastric cancer when combined with IL-17F rs3748067C>T mutation (for TT vs. CC, OR = 2.66, 95% CI = 1.73-4.68, P<0.01, I² = 0%; for CT + TT vs. CC, OR = 1.84, 95% CI = 1.35-2.12, P<0.01, I² = 0%; for TT vs. CC + CT, OR = 2.59, 95% CI = 1.69-3.96, P = 0.04, I² = 0%), but not with IL-17A rs2275913G>A polymorphism (Table 2).

Discussion

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

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

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

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

Figure 5. Funnel plot analysis to detect publication bias for AA vs. GG model of IL-17A rs2275913G>A polymorphism. Circles represent the weight of studies.
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cancer, but the subgroup analysis revealed a positive correlation between this polymorphism and H. pylori positive infection status. Furthermore, although risks were found in most of the genetic models of the association between gastric cancer and the IL-17F rs763780 T>C polymorphism, the pooled ORs did not change in Chinese population without any heterogeneity, demonstrating that the results of this meta-analysis are stable.

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

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

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

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

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Disclosure of conflict of interest

None.

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