Research Article

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IL-17 gene rs3748067 C>T polymorphism and gastric cancer risk: A meta-analysis

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Abstract: Objective: The purpose of this study was to investigate the correlation between Interleukin 17 (IL-17) gene rs3748067 C>T polymorphism and gastric cancer risk through pooling the open published data. Method: Case-control or cohort studies relevant to IL-17 gene rs3748067 C>T polymorphism and gastric cancer susceptibility were systematic searched for in the databases of CNKI, Pubmed, Medline, Embase and Web of science. The association between IL-17 gene rs3748067 C>T polymorphism and gastric cancer risk were expressed with an odds ratio(OR) and 95% confidence interval (95% CI). Statistical heterogeneity across the studies was evaluated by I2 test. Publication bias was evaluated by Begg's funnel plot and Egger's line regression test. Results: Finally, seven case-control studies were included in our present study. Because of the statistical heterogeneity among the included studies for the aspects of dominant (TT+CT vs CC), recessive (TT vs CT+CC) and homozygous genetic model (TT vs CC), the data was pooled by random effect model. The pooled ORs were OR=0.99 (95% CI: 0.65-1.52), OR =1.23 (95% CI: 0.73-2.06) and OR=1.14 (95% CI: 0.58-2.27) for dominant, recessive and homozygous genetic model respectively. The pooled data indicated no correlation between IL-17 gene rs3748067 C>T polymorphism and gastric cancer risk. Significant publication bias was found in the dominant genetic model ($p<0.05$), but not in recessive and homozygous genetic model ($p>0.05$). Conclusion: Based on the present evidence, there was no correlation between IL-17 gene rs3748067 C>T polymorphism and gastric cancer susceptibility in all genetic model. However, for the small sample size, significant heterogeneity and publication bias, the conclusion should be further evaluated through well designed case-control or cohort studies.

Keywords: Gastric cancer; IL-17; susceptibility; Polymorphism; meta-analysis

1 Introduction

Interleukin 17 (IL-17 or IL-17A), a pro-inflammatory cytokine produced by a group of T-helper cells is known as Th17 cells in response to their stimulation with IL-23. Previously studies have identified that IL-17 plays an important role in the development of chronic inflammation and tumors. Faghih et al. [1] evaluate the function of IL-17 in tumor draining lymph nodes of breast cancer patients and found its positive association with tumor progression. Other publications also found IL-17A was elevated in malignant tissues compared to normal tissues in gastric cancer [2] and lung cancer [3]. The results of the previously published studies indicated that IL-17 expression may in associated with the cancer susceptibility. Single nucleotide polymorphism (SNP) is a variation in a single nucleotide that occurs at a specific position in the genome. As known SNP is an important mechanism for gene expression regulation, which may affect a variety diseases susceptibility such as sickle-cell anemia [4], β-thalassemia and cystic fibrosis [5].

IL-17 gene rs3748067 C>T was an important SNP site which was widely discussed in association with cancer. And the correlation between IL-17 gene rs3748067 C>T polymorphism and gastric cancer risk has been evaluated according to the previously published studies. However, the results were quite different for the different patients selection criteria small sample size and different SNP detection assay.

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2 Methods

2.1 Studies searching methods

Case-control or cohort studies related to related to IL-17 gene rs3748067 C>T Polymorphism and gastric cancer were systematic searched for in the CNKI, Pubmed, Medline, Embase, Cochrane, CBM, OVID and Web of science databases by two reviewers (Wang Ying and Yu Yingcong) independently. The searching words were: Polymorphism, genetic variants, gastric cancer, gastric carcinoma, gastric tumor, IL-17, interleukin-17. The references of the included studies were also reviewed to find other potential suitable publications. The publication searching procedure is shown in Figure 1.

2.2 Inclusion and exclusion criteria

Studies included in this meta-analysis should meet the following criteria: (1) The study type should be a case-control or cohort study; (2) The diagnosis of gastrointestinal cancer should be confirmed by pathology or cytology; (3) Patients should be East Asia ethnicity; (4) The genotyping method should be correct; (5) Sufficient data should be provided for calculate the odds ratio. The exclusion criteria were: (1) The review or case report study type; (2) Duplicate published articles; (3) People of other ethnicities; (4) Not enough data could be drawn from the original studies.

2.3 Data extraction

Two reviewers independently reviewed the full text paper and extracted the data. The first and corresponding authors, year of the paper publication, genotyping methods and CC, CT and TT genotype distribution were extracted from the original included studies. The data was crossed checked by two reviewers (Wang Ying and Yu Yingcong). If there were conflicts about the data, a third reviewer joined the discussion and made the final decision.

2.4 Statistical analysis

The data analysis was made by Stata 11.0 statistical software. The correlation between IL-17 gene rs3748067 C>T polymorphism and gastric cancer risk was demonstrated by odds ratio (OR) and 95% confidence interval (95% CI). Z test was used to evaluated the significance of OR. Statistical heterogeneity across the 7 publications were assessed by I^2 test with a P-value<0.05 as statistically significant.

The Begg's funnel plot and Egger's line regression test were used for evaluating the publication bias.

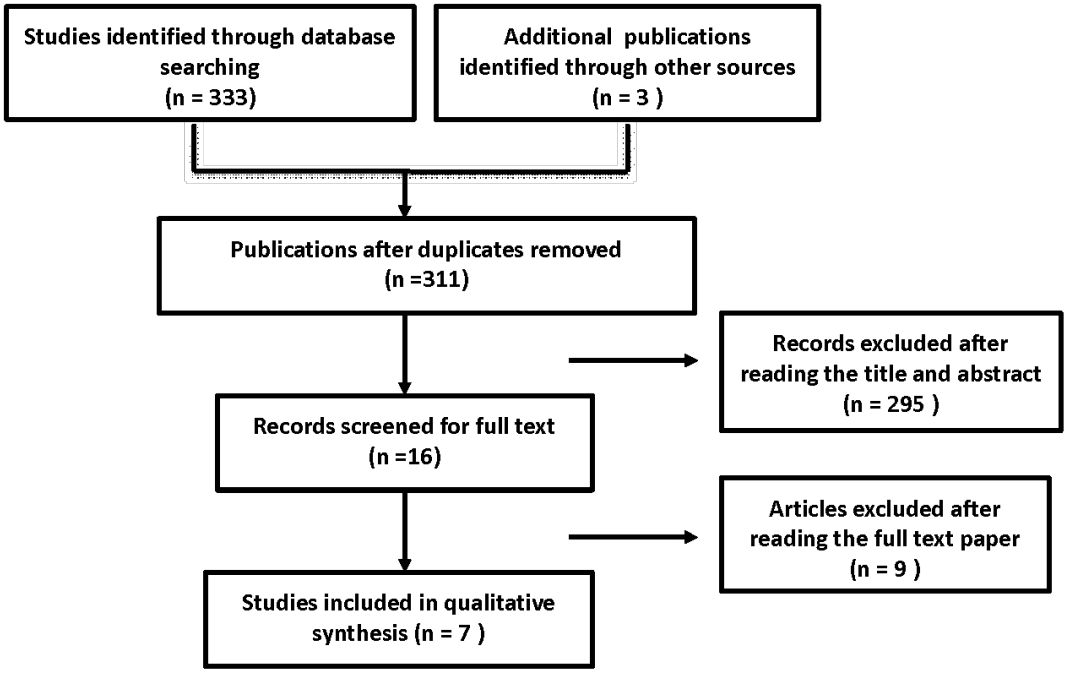

Figure 1. The publication searching flow chart

3 Results

3.1 General information for the included 7 studies

Finally, seven case-control studies [6-12] were included in our present meta-analysis. Among the included 7 publications, 6 used hospital based subjects as the control and 1 used population based people as control. For the genotyping methods, 3 studies used PCR_RFLP assay to test the TT, CC and CT genotype distribution and other 4 used MassARRAY assay as the detection method. The main character and general information of the include 7 case-control studies were demonstrated in Table 1.

3.2 For dominant genetic model (TT+CT vs CC)

We first evaluated the statistical heterogeneity across the studies. And significant statistical heterogeneity was found in the dominant genetic model (I^2=81.6%, p=0.00). The data was pooled using random effect model. The pooled OR=0.99 (95% CI:0.65-1.52) which indicating no correlation between IL-17 rs3748067 C>T polymorphism and gastric cancer risk, Figure 2.

Table 1. The general information and character of the included 7 studies

Author	Year	Control type	Methods	Number		genotyping distribution(case/control)		
				case	Control	TT	CC	CT
Wang N[6]	2014	Hospital based	PCR_RFLP	462	462	285/425	39/19	138/118
Zhu QH[7]	2014	Hospital based	MassARRAY	293	550	48/33	220/466	25/51
Zhang XK[8]	2014	Population based	MassARRAY	260	512	24/29	206/436	30/47
Gao YW[9]	2015	Hospital based	PCR_RFLP	572	572	460/458	42/47	70/66
Gao W[10]	2015	Hospital based	PCR_RFLP	386	374	26/6	308/323	52/45
Qi WT[11]	2015	Hospital based	MassARRAY	252	252	211/221	16/9	25/22
Hou CG[12]	2015	Hospital based	MassARRAY	362	362	274/286	18/10	34/30

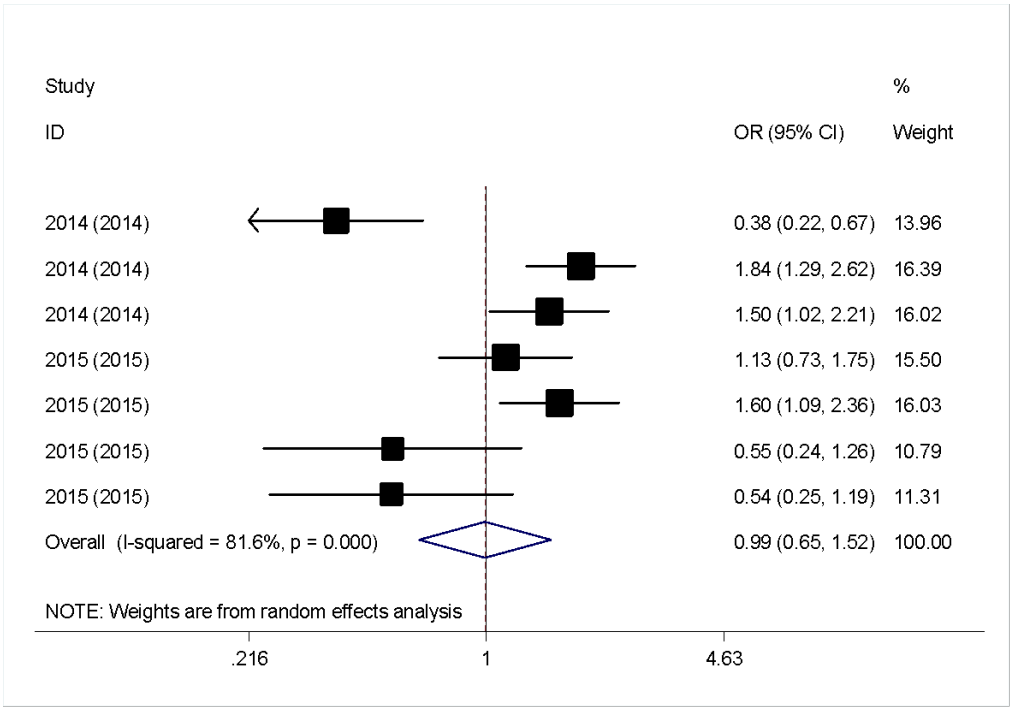

Figure 2. The forest plot of rs3748067 C>T plymorphism and gastric cancer risk for the dominant genetic model.

3.3 For recessive genetic model (TT vs CT+CC)

Significant statistical heterogeneity across the studies were found in recessive genetic model (I^2=90.2%, p=0.00). The OR =0.23 (95% CI:0.73-2.06) was pooled by random effect model. The data indicated no correlation between IL-17 gene rs3748067 C>T polymorphism and gastric cancer susceptibility, Figure 3.

3.4 For homozygous genetic model (TT vs CC)

Because of significant statistical heterogeneity, the data was pooled through random effect model. The pooled OR was 1.14 with its 95% corresponding confidence interval of 0.58-2.27. The pooled results indicated no correlation between IL-17 gene rs3748067 C>T polymorphism and gastric cancer susceptibility in homozygous genetic model, Figure 4.

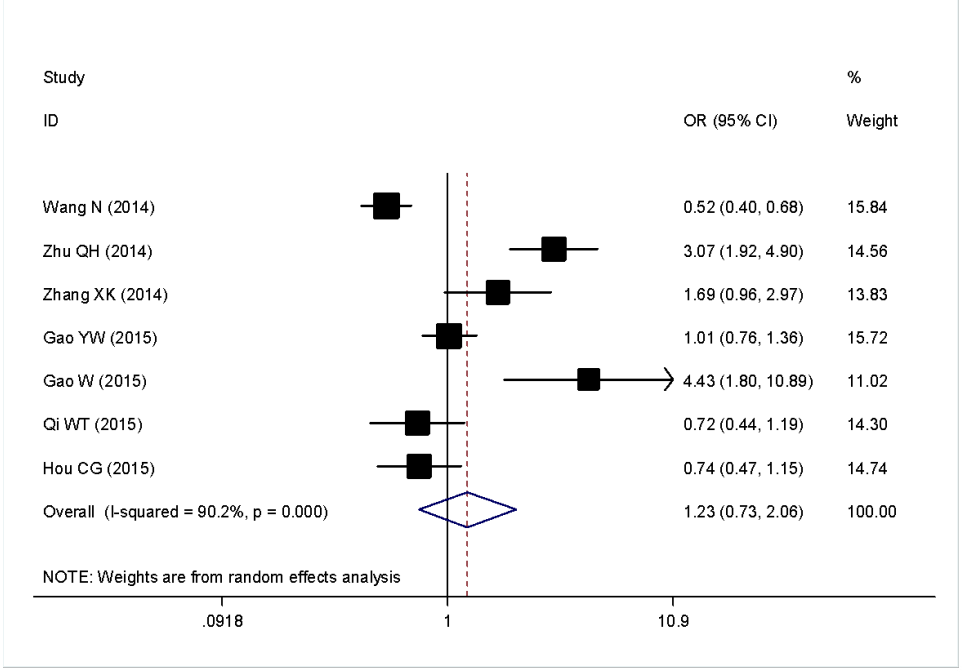

Figure 3. The forest plot of rs3748067 C>T polymorphism and gastric cancer risk for the recessive genetic model.

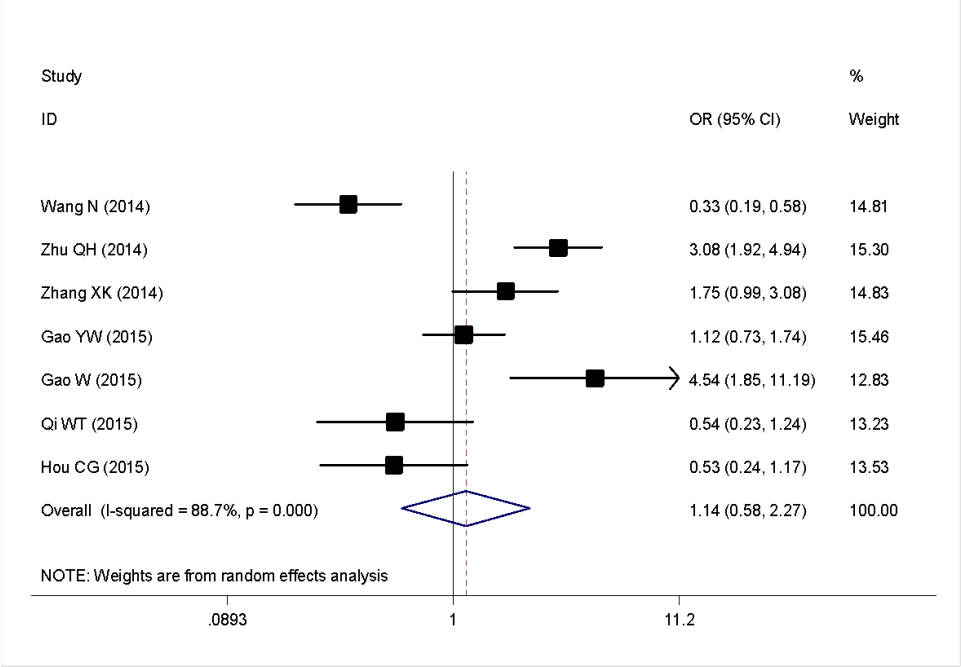

Figure 4. The forest plot of rs3748067 C>T polymorphism and gastric cancer risk for the homozygous genetic model

3.5 Publication bias

For dominant genetic model (TT+CT vs CC), the Begg's funnel plot (Figure 5) and Egger's line regression test indicated significant publication bias (t=-3.35, p=0.02). For recessive genetic model, the Begg's funnel plot was symmetric at the bottom (Figure 6), but the Egger's line regression test demonstrated no publication bias (t=2.05, p=0.09). In the aspect of homozygous genetic model, both Begg's funnel plot (Figure 7) and Egger's line regression test (t=0.50, p=0.64) showed no publication bias.

4 Discussion

Gastric cancer, the most diagnosed malignant carcinoma of digestive system is the 4th leading cause of cancer related death. Especially in China, more new cases of gastric cancer are diagnosed each year than any other country. Moreover, the gastric cancer patients were generally at advanced stage when diagnosed, which is different from Europe developed countries and Japan. 21320 new cases and 10540 death of gastric cancer were reported in the year 2012 in U.S [13]. Known risk factors for gastric cancer includes *Helicobacter pylori* infection, high intake of salted, pickled or smoked foods, as well as dried fish, heavy alcohol consumption and other dietary factors [14]. Studies also found the increased gastric risk in subjects with a family history of non-hereditary gastric cancer [15, 16].

IL-17 produced by a group of T-helper cells is known as Th17 cells in response to their stimulation with IL-23. Published evidence demonstrated IL-17 plays an important role in the development of many disease including cancers. And several studies have indicated the association between the IL-17 expression and gastric cancer. Meng et al [2] evaluate the expression of interleukin-17 and its clinical significance in gastric cancer patients. They found IL-17 expression was significant elevated in patients with gastric cancer. They speculate IL-17 may be involved in the progression of gastric cancer and played an important role in its development. SNP is a variation in a single nucleotide that occurs at a specific position in the genome. As known SNP is an important mechanism for gene expression regulation. IL-17 has server SNP locus such as rs2275913, rs3748067, rs10484879, rs763780 and et al. Association between IL-17 SNP and cancer risk was most discussed in the locus of rs3748067. Several published studies have evaluate IL-17 gene rs3748067 C>T polymorphism and gastric cancer risk. But the results of published studies were quite different because of different patients selection criteria small sample size and different SNP detection assay. Qi and his colleagues [11] investigate the role of three IL-17 gene single nucleotide

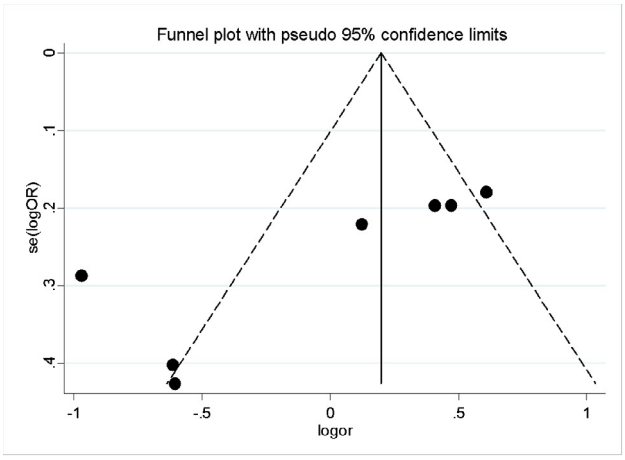

Figure 5. The Begg's funnel plot for evaluation publication bias in dominant genetic model (TT+CT vs CC).

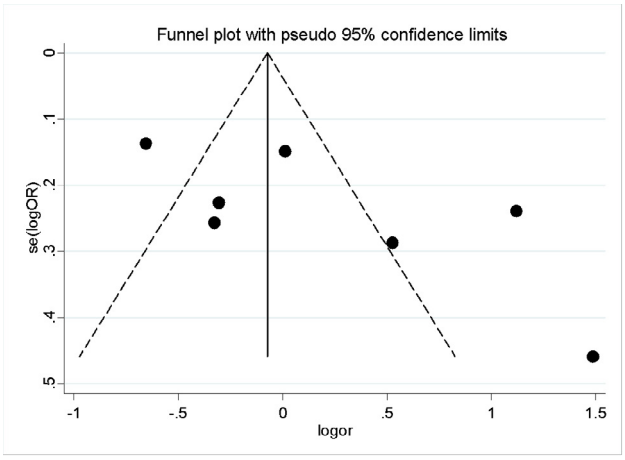

Figure 6. The Begg's funnel plot for evaluation publication bias in recessive genetic model (TT vs CT+CC).

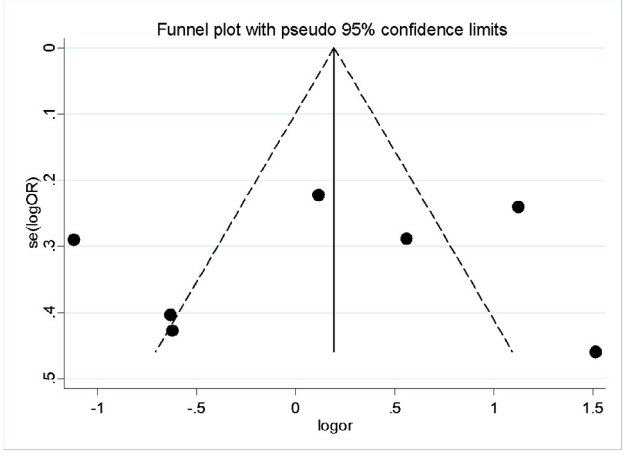

Figure 7. The Begg's funnel plot for evaluation publication bias in homozygous genetic model (TT vs CC)

polymorphisms (SNP) in the development of gastric cancer. They found IL-17 rs3748067 C>T polymorphisms play an important role in the risk of gastric cancer in the Chinese population. Gao et al. [9] discussed IL-17 gene rs3748067 C>T single nucleotide polymorphisms and gastric cancer susceptibility. However, they found no association between rs3748067 polymorphisms and the risk of developing gastric cancer. To further investigate the conflict results of the published studies, we performed this meta-analysis by pooling all the open published data in order to clarify facts. In our present study, we pooled the data from 7 published case-control studies and did not find any association between IL-17 gene rs3748067 C>T single nucleotide polymorphisms and gastric cancer susceptibility in dominant(TT+CT vs CC), recessive (TT vs CT+CC) and homozygous genetic model. So, based on the present evidence, there was no correlation between IL-17 gene rs3748067 C>T Polymorphism and gastric cancer risk in all genetic model. However, there are several limitations for the present meta-analysis which may decrease the credibility of the conclusion. The limitations include: (1) For all genetic models, there are significant heterogeneity across the included 8 publications. The statistical heterogeneity can decrease the statistical power. (2) Significant publication bias existed in the dominant genetic model. (3) There are two methods for the SNP detection; and this maybe a potential source of clinical heterogeneity; (4) Only English and Chinese literatures were included in this study, this may lead to publication selection bias.

In conclusion, because of the above limitations and small sample size of each include study, the conclusion should be further investigated through well designed case-control or cohort studies.

Conflict of interest: Authors state no conflict of interest

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