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IL-17A and IL-17F polymorphisms and gastric cancer risk: a meta-analysis

Z. Li, Y. Liu, D. Cao, M. Jiang and F. Luo

Lung Cancer Center, Cancer Center, State Key Laboratory of Biotherapy, West China Hospital of Sichuan University, Chengdu, China

Corresponding author: F. Luo
E-mail: luofeng_scu@yeah.net

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ABSTRACT. We conducted a meta-analysis of eligible studies to estimate the association between gastric cancer risk and rs2275913G>A IL-17A and rs763780T>C IL-17F polymorphisms. We searched the relevant studies in both Chinese and English through PubMed, the Web of Science, the Cochrane Library, and EMBASE up to January 1, 2014, including 3939 cases and 5407 controls. Seven eligible case-control studies were selected, including seven studies on rs2275913G>A IL-17A and four studies on rs763780T>C IL-17F. The rs2275913 AG [odds ratio (OR) = 1.50, 95% confidence interval (95%CI) = 1.04-2.15] and GG (OR = 1.40, 95%CI = 1.00-1.96) genotypes were significantly associated with increased risk of gastric cancer compared with the AA genotype. The rs763780 TC (OR = 1.47, 95%CI = 1.32-1.64) and TT (OR = 1.49, 95%CI = 1.11-1.99) genotypes can influence gastric cancer risk. Subgroup analysis showed that rs2275913 GG (OR = 1.35, 95%CI = 1.05-1.73) and rs763780 TC (OR= 1.44, 95%CI = 1.20-1.75) genotypes were not significantly associated with increased risk of gastric cancer in Japanese populations. Our meta-analysis is the first to indicate that the rs2275913G>A and rs763780T>C polymorphisms are risk factors for gastric cancer development.

Key words: IL-17A; IL-17F; Polymorphism; Gastric cancer

INTRODUCTION

Gastric cancer is one of the most common malignant diseases, and the fifth most common malignancy worldwide. It is estimated that 952,000 new gastric cancer cases and 723,000 deaths occurred in 2012. More than 70% of gastric cancer cases occur in developing countries, and half of these have occurred in China (IARC, 2014). The etiology of gastric cancer is not well understood. Chronic *Helicobacter pylori* infection is considered an important risk factor for gastric cancer, but *H. pylori* infection is not a sufficient risk factor (IARC, 1994), since only a few *H. pylori*-infected people develop gastric cancer during their lifetime (Lu and Li, 2014). Previous epidemical studies have shown that drinking alcohol, being overweight, and high intake of salt are the risk factors for developing gastric cancer. However, high intake of fruit and vegetables with some antioxidants, vitamins, minerals, and beta-carotene protects against gastric cancer (van den Brandt and Goldbohm, 2006).

It has been reported that chronic inflammation is a risk factor for malignant transformation, but the role inflammation plays in cancer initiation is still not completely understood (Scheller et al., 2006; Candido and Hagemann, 2013). The interleukin-17 (IL-17) family of cytokines comprises six protein members, i.e., IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. IL-17A and IL-17F are the most important members; they all located at 6q12 and comprise three exons and two introns (Iwakura et al., 2011). Previous studies have shown that over-expression of IL-17A and IL-17F contributes to the development of various cancers, such as pancreatic, gastric, and lung cancers (Cully, 2014; Dai et al., 2014; Zarogoulidis et al., 2014; Kaabachi et al., 2014).

Several previous studies have reported an association between rs2275913G>A IL-17A and rs763780T>C IL-17F and the risk of gastric cancer, but the results are inconsistent. Therefore, we conducted a meta-analysis of eligible studies to estimate the association between gastric cancer risk and rs2275913G>A and rs763780T>C polymorphisms.

MATERIAL AND METHODS

Search strategy

A comprehensive electronic search was conducted on May 1st, 2014, through the databases: PubMed, EMBASE, and the China National Knowledge Infrastructure platforms. The electronic search was performed using the following search terms: “Interluekin-17,” “IL-17,” “polymorphism”, “variant”, “gastric cancer,” and “stomach cancer.” The related articles were retrospective to identify additional potential studies. The reference lists of articles included for review and past meta-analyses were examined for any further relevant publications. No publication date or language restrictions were applied.

Study selection

The inclusion criteria for studies were as follows: the studies were of case-control design; the studies evaluated the association between gastric cancer risk and IL-17 polymorphisms; and the studies reported sufficient genotype frequencies to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

The exclusion criteria for studies were as follows: articles only having an abstract,

review articles, and comments; studies overlapping with other studies; studies having no comparison or control group; and studies having no data on genotype frequencies.

Corresponding authors were contacted in an attempt to obtain unreported genotype counts if studies were otherwise eligible.

Data extraction

Information was carefully extracted from all collected studies independently by two reviewers according to the inclusion criteria. Duplications and obviously irrelevant studies were excluded according to the exclusion criteria. We extracted the full texts of all eligible studies according to the inclusion criteria. The first author's name, publication data, sources of controls, numbers of gastric cancer cases, and controls with different genotypes were extracted for each eligible study.

Statistical analysis

All meta-analyses were conducted by the STATA 9.0 software. The Hardy-Weinberg equilibrium of the control group was assessed. ORs with 95%CIs were calculated to evaluate the strength of the association between the rs2275913G>A and rs763780T>C polymorphisms and gastric cancer risk. For the rs2275913G>A polymorphism, the pooled ORs were obtained for AG *vs* AA and GG *vs* AA. For the rs763780T>C polymorphism, the pooled ORs were obtained for CT *vs* TT and CC *vs* TT. Subgroup analysis with ethnicity was also analyzed statistically. The heterogeneity between studies was estimated by the I^2 test and heterogeneity Q statistic test. When I^2 values were in the range 0-25%, there was no heterogeneity; when I^2 values were in the range of 25-50%, there was moderate heterogeneity; and when I^2 values were in the range of 75-100%, there was a large degree of heterogeneity. A random-effect or fixed-effect model was taken to calculate the pooled ORs (95%CI) according to the degree of heterogeneity between studies. The publication bias in studies was calculated using a funnel plot.

RESULTS

Our comprehensive literature search identified a total of 33 studies for the association between rs2275913G>A and rs763780T>C and gastric cancer risk based on their titles. Eventually, seven eligible case-control studies were selected, including seven studies for rs2275913G>A and four studies for rs763780T>C. Among the 26 studies excluded, two were dissertations, three were reviews, seven did not research rs2275913G>A and rs763780T>C polymorphisms, 12 did not report the association between rs2275913G>A and rs763780T>C polymorphisms and gastric cancer risk, and two were duplicate studies.

The characteristics of the seven included studies are summarized in Table 1 (Shibata et al., 2009; Chen, 2010; Wu et al., 2010; Arisawa et al., 2012; Rafiei et al., 2013; Zhang et al., 2014; Qinghai et al., 2014) and Table 2 (Shibata et al., 2009; Wu et al., 2010; Zhang et al., 2014).

Table 1. Characteristics of case-control studies on rs2275913G>A polymorphism and gastric cancer risk included in the meta-analysis.

Study ID	Year	Country	Cases			Total cases	Controls			Total controls	P for HWE	OR (95%CI)[1]	
			AA	AG	GG		AA	AG	GG			AG *vs* AA	GG *vs* AA
Chen	2010	China	220	522	300	1042	224	541	325	1090	0.96	0.98 (0.79-1.23)	0.94 (0.73-1.20)
Shibata	2009	Japan	69	124	94	287	175	299	175	649	0.05	1.05 (0.74-1.49)	1.36 (0.94-1.98)
Wu	2010	China	250	485	210	945	193	371	193	757	0.59	1.01 (0.80-1.27)	0.84 (0.64-1.10)
Arisawa	2012	Japan	84	137	112	333	218	293	218	729	<0.001	1.21 (0.88-1.68)	1.33 (0.95-1.87)
Rafiei	2013	Iran	44	61	56	161	78	72	78	228	<0.001	1.50 (0.91-2.48)	1.27 (0.77-2.11)
Zhang	2014	China	48	102	110	260	258	187	258	703	<0.001	2.93 (1.98-4.34)	2.29 (1.57-3.35)
Qinghai	2014	China	45	122	126	293	273	216	273	762	<0.001	3.43 (2.33-5.04)	2.80 (1.92-4.09)
Pooled results			760	1553	1008	3321	1419	1979	1520	4918		1.50 (1.04-2.15)	1.40 (1.00-1.96)
P for heterogeneity												<0.001	<0.001
I^2 test												88.8%	85.4%

[1]Odds ratios (ORs) were calculated using a random-effects model. HWE = Hardy-Weinberg equilibrium; CI = confidence interval.

Table 2. Characteristics of case-control studies on rs763780T>C polymorphism and gastric cancer risk included in the meta-analysis.

Study ID	Year	Country	Cases			Total cases	Controls			Total controls	P for HWE	OR (95%CI)[1]	
			TT	TC	CC		TT	TC	CC			AG *vs* AA	GG *vs* AA
Shibata	2009	China	221	55	4	280	419	100	4	1090	0.96	1.04 (0.72-1.51)	1.90 (0.47-7.65)
Wu	2010	Japan	540	332	55	927	527	214	36	649	0.05	1.51 (1.23-1.87)	1.49 (0.96-2.31)
Zhang	2014	China	209	30	21	260	429	53	30	757	0.59	1.16 (0.72-1.87)	1.44 (0.80-2.57)
Qinghai	2014	Japan	241	35	17	293	463	58	29	729	<0.001	1.16 (0.74-1.81)	1.13 (0.61-2.09)
Pooled results			1211	452	97	1760	1838	425		4918		1.47 (1.32-1.64)	1.49 (1.11-1.99)
P for heterogeneityа												0.14	0.94
I^2 test												42.2%	0%

[1]Odds ratios (ORs) were calculated using a fixed-effects model. HWE = Hardy-Weinberg equilibrium; CI = confidence interval.

Seven studies reported the association between the rs2275913G>A polymorphism and gastric cancer risk, including 3321 gastric cancer cases and 4918 controls. Eleven studies reported the association between the rs763780T>C polymorphism and gastric cancer risk, including 3456 gastric cancer cases and 4957 controls. They were published between 2007 and 2013. Four studies were conducted in a Chinese population, two studies in a Japanese population, and one study in an Iranian population.

Four studies regarding rs2275913G>A (Arisawa et al., 2012; Rafiei et al., 2013; Zhang et al., 2014; Qinghai et al., 2014) and one study regarding rs763780T>C (Qinghai et al., 2014) did not accord with the Hardy-Weinberg equilibrium. There was a significant heterogeneity between pooled studies in terms of rs2275913G>A, and thus we used a random-effect model to assess the association between rs2275913G>A and gastric cancer risk. Our meta-analysis found that rs2275913 AG and GG genotypes were significantly associated with increased risk of gastric cancer compared with the AA genotype, and the pooled ORs (95%CI) were 1.50 (1.04-2.15) and 1.40 (1.00-1.96), respectively. Moreover, we found that rs763780 TC and TT genotypes can influence gastric cancer risk, and the ORs (95%CI) were 1.47 (1.32-1.64) and 1.49 (1.11-1.99), respectively.

Subgroup analysis showed that the rs2275913 GG genotype was not significantly associated with increased risk of gastric cancer in Japanese populations, with an OR (95%CI) of 1.35 (1.05-1.73) (Figure 1). Similarly, we found that the rs763780 TC genotype was significantly associated with increased gastric cancer risk in the Japanese population, with an OR (95%CI) of 1.44 (1.20-1.75) (Figure 2).

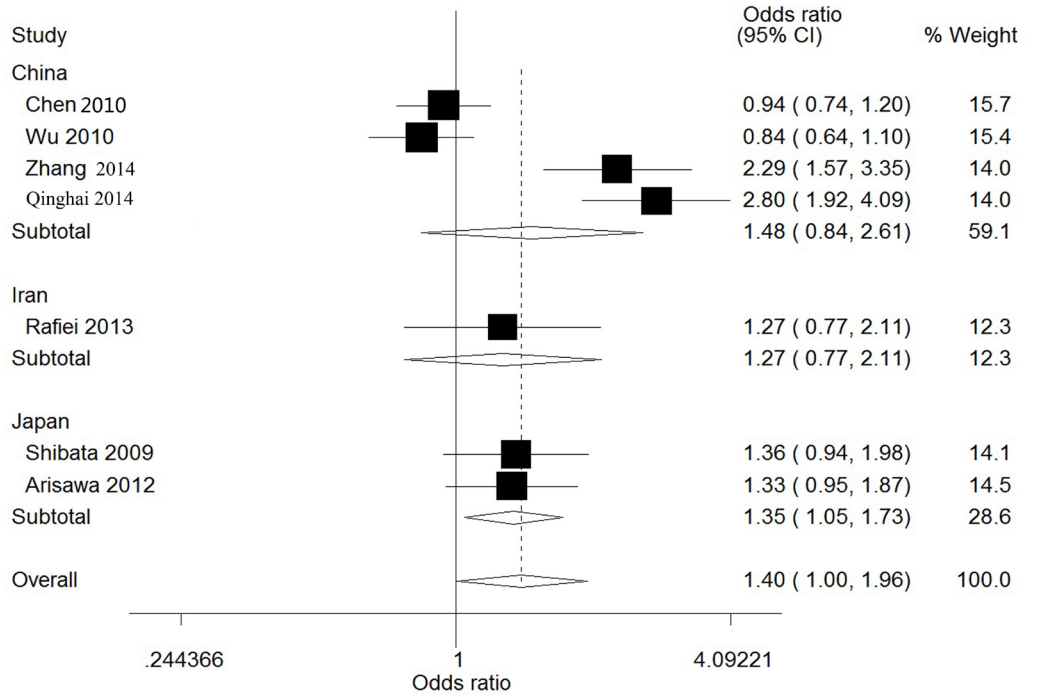

Figure 1. Subgroup analysis for association between rs2275913 GG and gastric cancer risk.

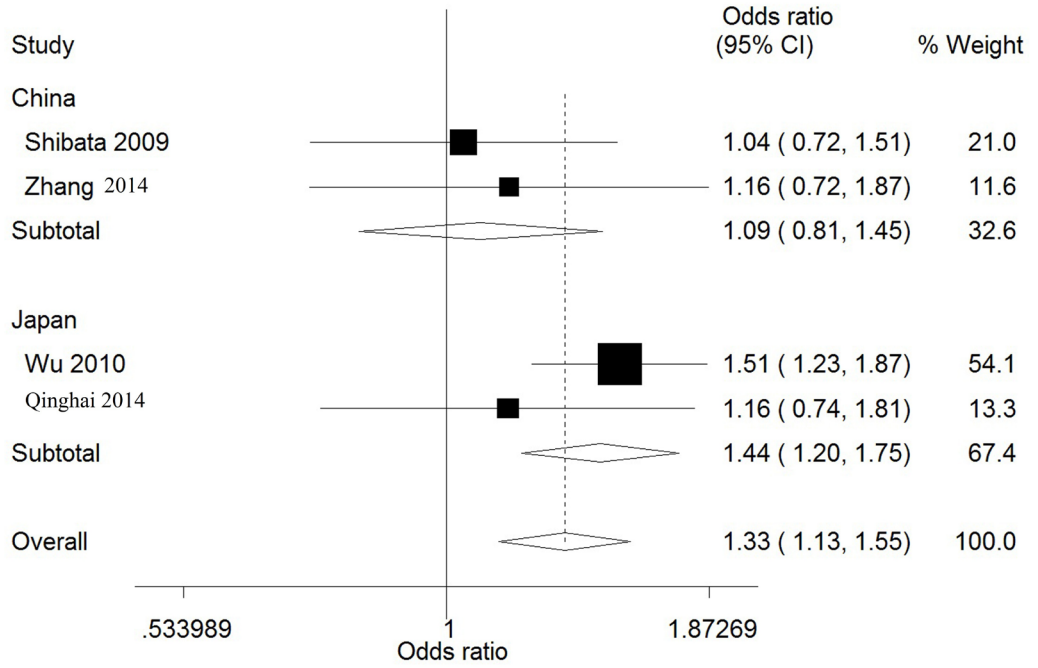

Figure 2. Subgroup analysis for association between rs763780 TC and gastric cancer risk.

The shapes of the Begg's funnel plots for rs2275913G>A and rs763780T>C were not symmetrical, which suggests publication bias in this meta-analysis (Figures 3 and 4).

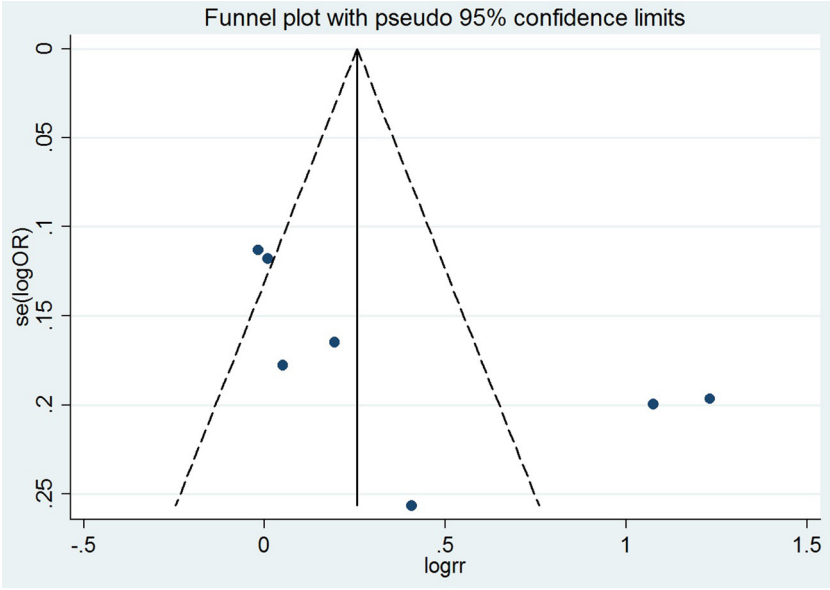

Figure 3. Funnel plots of the association between rs2275913G>A polymorphism and gastric cancer risk.

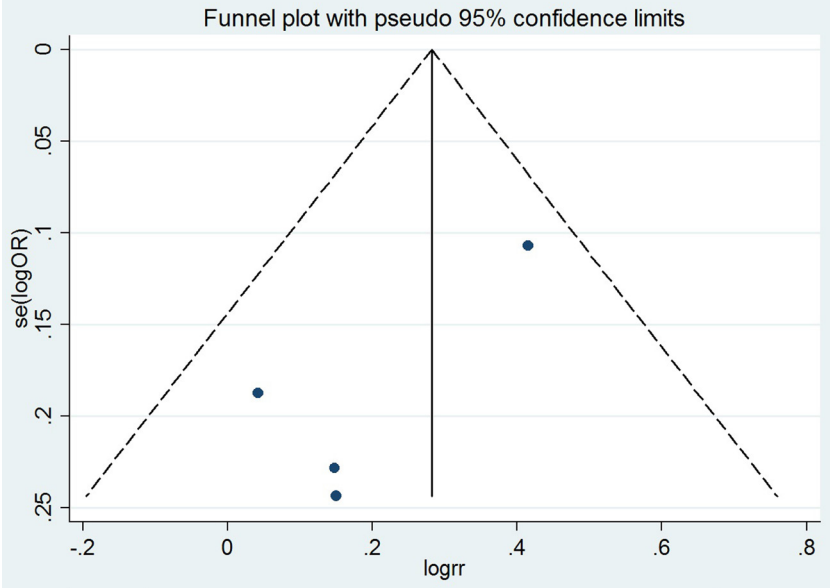

Figure 4. Funnel plots of the association between rs763780T>C polymorphism and gastric cancer risk.

DISCUSSION

Previous reports have indicated that chronic inflammation may be involved in the development of gastric cancer, since IL-17A and IL-17F are expressed by Th17 cells that mediate chronic inflammation and various diseases (Hu et al., 2013; Lee et al., 2013; Park et al., 2005). Previous studies have investigated the association between rs2275913G>A and rs763780T>C polymorphisms and the risk of gastric cancer, but the results have been inconsistent; therefore, we carried out a meta-analysis to investigate the association to obtain a reliable conclusion.

IL-17 is a relatively novel cytokine family that contains six homologous members (from IL-17A to IL-17F), which are the important inflammatory cytokines connecting innate and adaptive immunity (Kolls and Lindén, 2004). Molecular research has suggested that IL-17 is an essential proinflammatory cytokine that evokes the secretion of many cytokines and chemokines by different cell types, such as mesenchymal cells and myeloid cells, to recruit monocytes and neutrophils into the microenvironment of inflammation (Iwakura et al., 2011). Furthermore, IL-17 can promote the expression of antimicrobial peptides and facilitates host defense against infections (Kao et al., 2004; Matsuzaki and Umemura, 2007).

To date, several molecular epidemiological studies have been conducted to investigate the role of rs2275913G>A and rs763780T>C polymorphisms in the development of gastric cancer. Initially, Shibata et al. (2009) reported that the rs2275913 AA genotype was associated with a risk of gastric cancer. Chen et al. (2010) then reported that the rs2275913G>A polymorphism did not influence the risk of gastric cancer in a Chinese population. Subsequently, Arisawa et al. (2012), Rafiei et al. (2013), Qinghai et al. (2014), and Zhang et al. (2014) reported an association between rs2275913G>A and rs763780T>C polymorphisms and gastric cancer risk. Our meta-analysis showed that rs2275913G>A and rs763780T>C polymorphisms can influence the susceptibility of gastric cancer, especially in Japanese subjects.

In our meta-analysis, heterogeneity existed but could be removed with stratified analysis; meta-regression also indicated that the ethnicity and control design might contribute to heterogeneity.

Some limitations should be considered in our study. First, although we observed a significant association between the IL-17A polymorphism and the risk of gastric cancer, the small number of published papers included in this study precluded a thorough evaluation of publication bias. Second, environmental factors are also important in the development of tumor disease. The potential interactions between genetic and environmental factors may also modify the development of gastric cancer. These factors may influence the effects of IL-17 polymorphisms on susceptibility to gastric cancer, and they should be considered. Third, different genotyping methods may also have a possible effect on the frequency of the allele. Fourth, we have only reviewed published studies, but some unpublished studies, especially negative results, may affect the final conclusion.

In conclusion, our meta-analysis is the first to indicate that the rs2275913G>A and rs763780T>C polymorphisms are risk factors for gastric cancer development. Moreover, future case-control and population-based studies are needed to investigate more precisely the relationships between polymorphisms and potential gene-gene and gene-environment interactions.

Conflicts of interest

The authors declare no conflict of interest.

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