RESEARCH ARTICLE

Meta Analysis of Association of the IL-17F rs763780T>C Gene Polymorphism with Cancer Risk

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Abstract

Purpose: To investigate the association of IL-17F rs763780T>C with cancer risk. Materials and Methods: We searched the Cochrane Central Library, PubMed, MEDLINE, EMBASE, CNKI (China National Knowledge Infrastructure) and WangFang databases until May 2014 for a meta-analysis conducted using RevMan 5.2 software. Results: A total of ten papers were included into this meta analysis, involving 3, 336 cases and 4, 217 healthy people. There were no significant differences on association of IL-17F rs763780T>C polymorphism with cancer risk except in the CC *vs* TT genetic model. Although the the risk in the gastric cancer group is higher than that in control group, there were no significant differences on the association of IL-17F rs763780T>C polymorphism with other cancers. Conclusions: Our meta analysis reveal the IL-17A rs763780T>C gene polymorphism is involved in risk of gastric cancer but not other tumor types.

Keywords: IL-17F - polymorphism - cancer risk - meta-analysis

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Introduction

The WHO estimates tumor was a leading cause of death worldwide and accounted for 7.6 million deaths (13% of all deaths) in 2008 (http://www.who.int/gho/ncd/mortality _morbidity/cancer/en/index.html) Many studies indicated SNP were used to clarify the molecular in tumor (Bondy et al., 2008; Qin et al., 2014). Hereditary alterations of the critical genes are related to numerous malignancies, included tumor progress, metastasis and invasion.

Interleukin 17 (IL-17) is a pro-inflammatory cytokine, which is a larger cytokines group containing six similar members, including IL-17A to IL-17F (Kawaguchi et al., 2004). Among IL-17F lie on human chromosome 6, and the cytokine is produced by Th17 cells in respond to IL-23 (Bettelli et al., 2006). Previous reports indicated that IL-17 is involved in both innate and adaptive immunity and can act on various cell types (Kolls et al., 2004; Korn et al., 2009). Recently, more and more studies indicated that IL-17 in various tumor tissues, including gastric cancer, breast cancer, multiple myeloma, and ovarian cancer (Kato et al., 2001; Alexandrakis et al., 2006; Zhang et al., 2008; Zhu et al., 2008). Kawaguchi et al., have reported that the IL-17F 7488T/C (rs763780) variant, which causes a His-to-Arg substitution at amino acid 161 (H161R), resulting in antagonism of function of wild-type IL-17F and influences of risk of asthma (Kawaguchi et al., 2006). Moreover, the lots of studies reported that IL-17F (rs763780) gene polymorphism is involved in tumor tissues included gastric cancer, colorectal cancer, breast cancer and bladder cancer (Wu et al., 2010; Wang et al., 2012; Zhou et al., 2013; Omrane et al., 2014). However, there is a different voices, some studies reported that there were no significant differences on the association of IL-17F rs763780 gene polymorphism with the cancer risk (Shibata et al., 2009; Wang et al., 2012).

In here, we performed a meta analysis to reveal the association of IL-17F rs763780 gene polymorphism with the cancer risk in order to resolve the this dispute.

Materials and Methods

Search strategy

We searched the Cochrane Central Library, PubMed, MEDLINE, EMBASE, CNKI (China National Knowledge Infrastructure), WangFang databases until May 2014. The search terms were"Interleukin 17", "Interleukin 17", "IL-17F" or "Interleukin 17F", "tumor", "cancer", "neoplasm" or "carcinoma", "gene polymorphism" The search was limited to studies in humans. Titles and abstracts of all citations were screened independently by two reviewers. No language restrictions were applied.

Data extraction

Two reviewers independently extracted the following parameters from each study: general information, information on participants, baseline characteristics, gene types and outcomes. Discrepancies between the two reviewers were resolved by discussion and consensus.

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Table 1. The General Data of Meta Analysis

First author	Publication year	Race	Tumor style	case group				control group			
				CC	CT	TT	n	CC	CT	TT	n
Kaabachi B	2014	Tunisia	Lung cancer	1	34	204	239	0	22	236	258
Omrane I	2014	Tunisia	Colorectal cancer	1	27	72	100	1	38	98	137
Quan X	2012	Chinese	Cervical cancer	4	85	222	311	5	126	332	463
Ruan Y	2012	Chinese	Ovarian cancer	10	69	13	92	2	34	2	38
Shibata T	2009	Japanese	Gastric cancer	4	55	221	287	4	100	419	524
Wang LH	2012	Chinese	Breast cancer	6	103	382	491	7	99	396	502
Wu XQ	2010	Chinese	Gastric cancer	55	332	540	962	36	214	527	787
Zhang xk	2014	Chinese	Gastric cancer	21	30	209	260	30	53	429	512
Zhou B	2013	Chinese	Bladder cancer	4	57	240	301	5	124	317	446
Zhu Qh	2014	Chinese	Gastric cancer	17	35	241	293	29	58	463	550

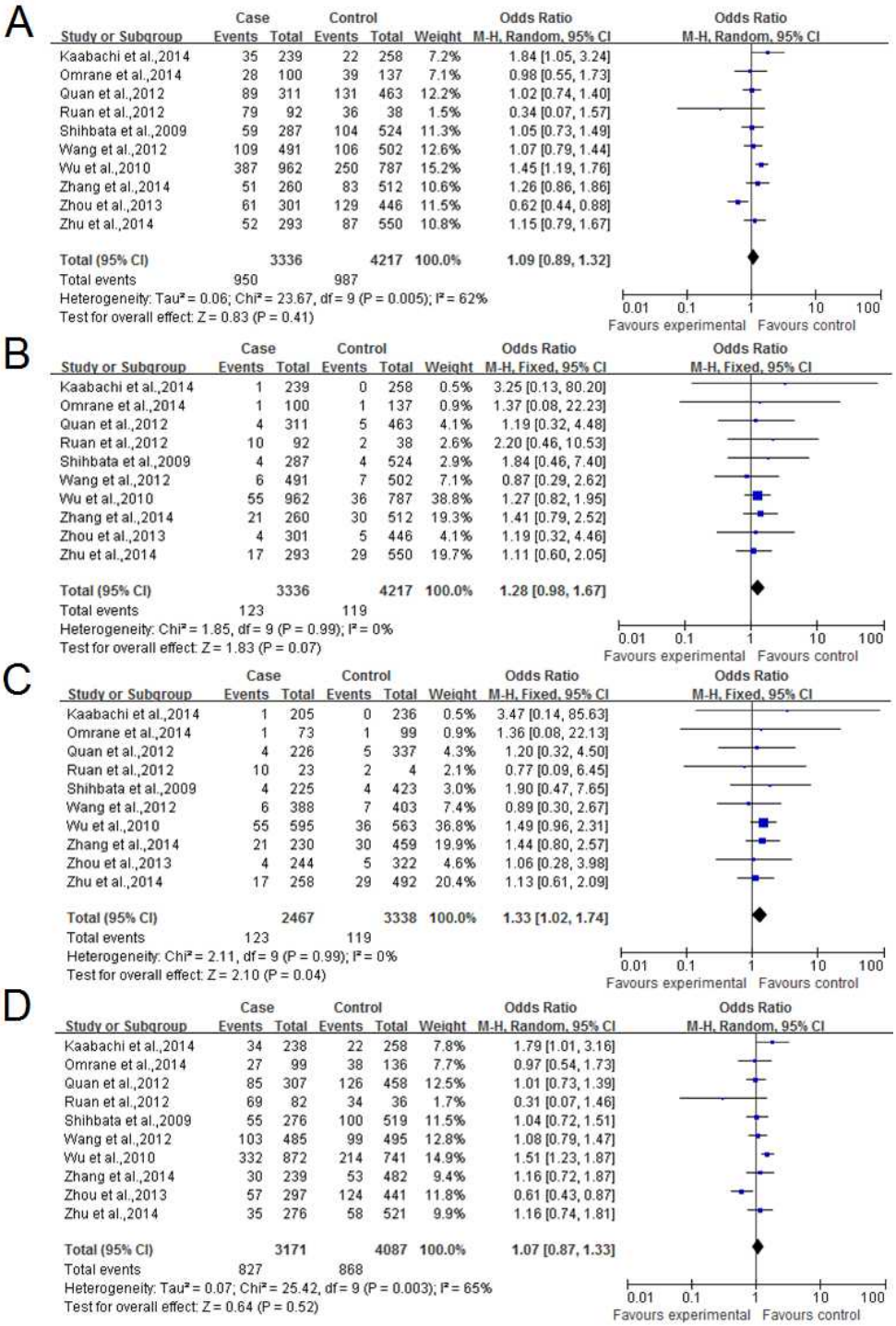

Figure 1. Meta-Analysis of the Association between IL-17F rs763780T>C Polymorphism and Susceptibility to Cancer. A) Dominant model (CC+CT *vs* TT). B) Recessive model (CT+TT *vs* CC). C) CC *vs* TT. D) CT *vs* TT.

Statistical analysis

We performed the data analysis using the meta-analysis software Review Manager, version 5.2.0. We analyzed dichotomous variables using estimation of odds risks (OR) and continuous variables using mean difference (MD), both reported with a 95% confidence interval (95%CI). The OR value represented the odds risk of an cancer risk happening the case group compared with the control group, and would be considered statistically significant at $P<0.05$ level if 95% confidence interval. Heterogeneity was evaluated by χ^2 statistic with significance set at $P<0.05$. Quantification of effect of heterogeneity was assessed by means of Isquared. We considered heterogeneity to be present if the I^2 statistic was >50%. Possible sources of heterogeneity were assessed by subgroup, sensitivity and meta-regression analyses.The $P<0.05$ was considered as significant difference.

Results

Study characteristics

After searching, total ten papers (Shibata et al., 2009; Wu et al., 2010; Quan et al., 2012; Wang et al., 2012; Yang et al., 2013; Zhou et al., 2013; Kaabachi et al., 2014; Omrane et al., 2014; Zhang et al., 2014; Zhu et al., 2014) were included into this meta analysis, involving 3, 336 cases and 4, 217 health people. All papers were involved in association of IL-17F with cancer, of which four documents (Shibata et al., 2009; Wu et al., 2010; Zhang et al., 2014; Zhu et al., 2014) were involved in association of IL-17F with gastric cancer. The publication year of involved studies ranged from 2009 to 2014 (see Table 1 for details).

Association between IL-17F rs763780T>C polymorphism and cancer risk

As shown in Fig 1A, 1B and 1D, ten studies (Shibata et al., 2009; Wu et al., 2010; Quan et al., 2012; Wang et al., 2012; Yang et al., 2013; Zhou et al., 2013; Kaabachi et al., 2014; Omrane et al., 2014; Zhang et al., 2014; Zhu et al., 2014) reported the association between IL-17F rs763780T>C polymorphism and susceptibility to cancer. The meta analysis results shown that there were no significant differences between IL-17F rs763780T>C polymorphism and cancer sensibility under three genetic models. (CC+CT *vs* TT, OR:1.09, 95%CI:0.89 to 1.32, $P=0.41$; CT+TT *vs* CC, OR:1.28, 95%CI:0.98 to 1.67, $P=0.07$; CT *vs* TT, OR:1.07, 95%CI:0.87 to 1.33, $P=0.52$) However, under CC *vs* TT genetic model, the IL-17F rs763780T>C polymorphism was higher in control group than that in case group. (OR:1.33, 95%CI:1.02 to 1.74, $P=0.04$) (Figure 1D)

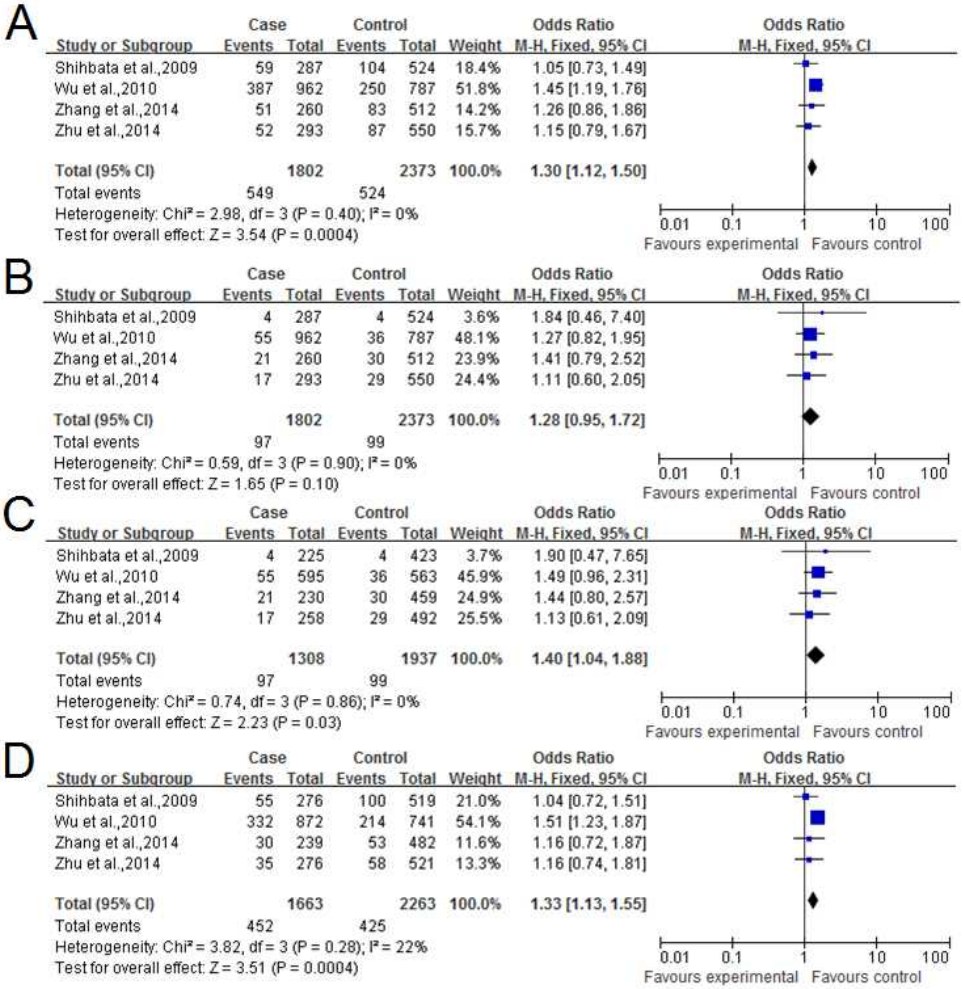

Figure 2. Meta-Analysis of the Association between IL-17F rs763780T>C Polymorphism and Susceptibility to Gastric Cancer. A) Dominant model (CC+CT *vs* TT). B) Recessive model (CT+TT *vs* CC). C) CC *vs* TT. D) CT *vs* TT

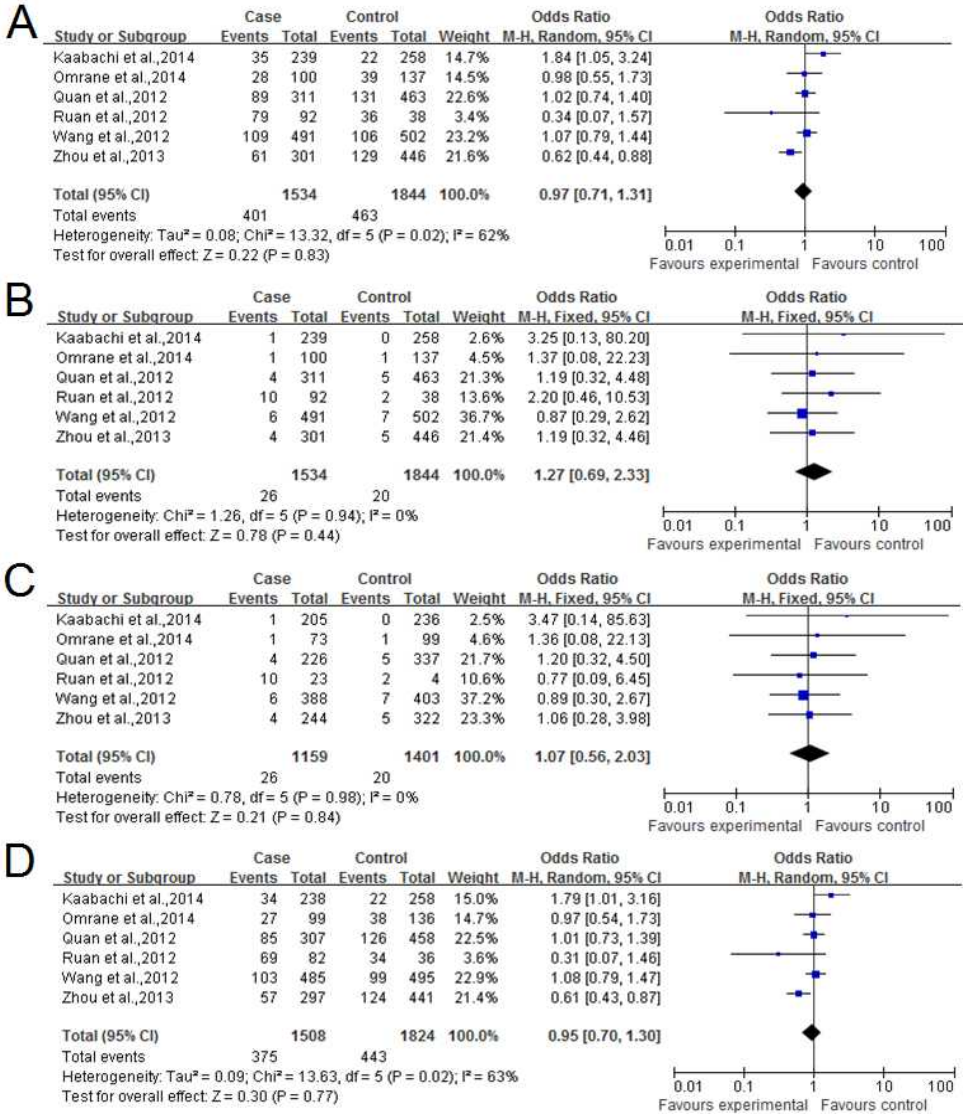

Figure 3. Meta-Analysis of the Association between IL-17F rs763780T>C Polymorphism and Susceptibility to other Cancer Types. A) Dominant model (CC+CT *vs* TT). B) Recessive model (CT+TT *vs* CC). C) CC *vs* TT. D) CT *vs* TT.

Association between IL-17F rs763780T>C polymorphism and gastric cancer risk

The meta analysis results indicated that there were no significant difference on the association of IL-17F rs763780T>C polymorphism with cancer risk between gastric cancer group and control group. (CT+TT *vs* CC, OR:1.28, 95%CI:0.95 to 1.72, *P*=0.10) (Figure 2B) However, the the risk in gastric cancer group is higher than that in control group. (CC+CT *vs* TT, OR:1.30, 95%CI:1.12 to 1.50, *P*=0.0004; CC *vs* TT, OR:1.40, 95%CI:1.04 to 1.88, *P*=0.03; CT *vs* TT, OR:1.33, 95%CI:1.13 to 1.55, *P*=0.0004) (Figure 2A, 2B and 2C)

Association between IL-17F rs763780T>C polymorphism and other cancers risk

As shown in Figure 3, the meta analysis results indicated that there were no significant difference on the association of IL-17F rs763780T>C polymorphism with other cancers risk. (CC+CT *vs* TT, OR:0.97, 95%CI:0.71 to 1.31, *P*=0.83; CT+TT *vs* CC, OR:1.27, 95%CI:0.69 to 2.33, *P*=0.44; CC *vs* TT, OR:1.07, 95%CI:0.56 to 2.03, *P*=0.84; CT *vs* TT, OR:0.95, 95%CI:0.70 to 1.30, *P*=0.77).

Discussion

In here, we first performed a meta analysis to investigate the association of IL-17F rs763780T>C polymorphism with cancer risk. The meta analysis results shown that there were no significant differences on association of IL-17F rs763780T>C polymorphism with cancer risk but the CC *vs* TT genetic model. Although the the risk in gastric cancer group is higher than that in control group, there were no significant differences on the association of IL-17F rs763780T>C polymorphism with other cancers risk.

To date, more and more studies have investigated the association between IL-17F gene polymorphism and human tumor, however, some studies reported that there were no significant differences on the association of IL-17F rs763780 gene polymorphism with the cancer risk (Shibata et al., 2009; Wang et al., 2012). IL-17F is located in 6p12, which has the ability to induce chemokines that is crucial in neutrophil recruitment as well as activation. After activating the Th17 cells, overexpression IL-17 induces multiple pro-inflammatory mediators included

cytokines, chemokines and metalloproteinases. More and more evidences reveal that IL-17 cytokine play critical role in the pathogenesis of various diseases, including tumors (Xu et al., 2010). As one of IL-17 family members, increasing data show that IL-17F gene polymorphism play important role in human diseases risk. A study reported the IL-17F rs763780T>C suppresses the expression and activity of the wild type IL-17F by causes a His-to-Arg substitution at aminoacid 161 (Kawaguchi et al., 2006). Not only more studies investigate the association between IL-17F rs763780 gene polymorphism and several disorders, including inflammatory bowel disease and asthma (Ramsey et al., 2005; Arisawa et al., 2008), but also several documents reveal the IL-17F rs763780 gene polymorphism is involved in the cancer. (Shibata et al., 2009; Wang et al., 2012) It is demonstrated that IL-17F rs763780T>C is involved in the gastric caner (Shibata et al., 2009), but not breast cancer. (Wang et al., 2012) Take together, these results suggest the IL-17F rs763780T>C gene polymorphism may play important role in the tumor pathogenesis. However, is is remain unclear whether the IL-17F rs763780T>C gene polymorphism is involved in other tumor types. In our meta analysis, we demonstrated that IL-17F rs763780T>C gene polymorphism is involved in the gastric cancer risk but other cancer types, which is consistent with the previous study (Shibata et al., 2009). For association of IL-17A rs763780T>C gene polymorphism with other cancer types included breast, more data should be needed in future.

In conclusion, our meta analysis reveal the IL-17A rs763780T>C gene polymorphism is involved in the gastric cancer risk but not other tumor types, which provides a foundation for diagnosis and treatment of gastric cancer. However, more studies should be included into this meta analysis in future.

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