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ORIGINAL ARTICLE

IL-17A G197A and IL-17F T7488C polymorphisms and cancer risk in Asian populations: a meta-analysis

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Summary

Purpose: *The association between Interleukin-17A (IL-17A) G197A and IL-17F T7488C polymorphisms and risk for specific forms of cancer is inconclusive. We conducted a meta-analysis of all published studies to estimate the association of IL-17A G197A and IL-17F T7488C polymorphisms and cancer risk.*

Methods: *A systematic computerized searching of the PubMed and Web of Science databases was performed for relevant publications. Data were extracted and statistical analysis was performed using RevMan 5.2 software.*

Results: *Eight eligible case-control studies with 3,323 cases and 3,974 controls were included into this meta-analysis. The pooled odds ratios (ORs) showed that the IL-17A G197A polymorphism increased the risk for specific forms of cancer under the following genetic models: A vs G (OR = 1.31, 95 % CI 1.13-1.52, P_h = 0.02); AA vs GG (OR = 1.81, 95 % CI 1.30-2.52, P_h = 0.007); AA/AG vs GG (OR = 1.26, 95 % CI 1.11-1.43, P_h = 0.79); AA vs AG/GG (OR = 1.72, 95 % CI 1.16-2.53, P_h <0.0001). However, the IL-17F T7488C polymorphism did not increase or decrease cancer risk under all genetic models. Stratified analysis by cancer type revealed that the IL-17A G197A polymorphism may increase the risk of gastric cancer. Further subgroup analysis by country indicated that there was a statistically increased cancer risk in China.*

Conclusions: *The present meta-analysis showed the IL-17A G197A polymorphism is associated with a significantly increased risk for specific forms of cancer, especially in gastric cancer. Subsequent studies with large sample size are warranted to validate this association.*

Key words: *cancer, IL-17A, IL-17F, meta-analysis, polymorphism*

Introduction

Cancer is a multifactorial disease associated with individual genetic backgrounds and external factors such as lifestyle and inflammation [1,2]. It has been reported that inflammation-associated molecules are associated with a majority of cancer types, and these molecules are activated by various elements related to environment and lifestyle [3].

IL-17 family of cytokines comprises 6 members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F) and displays broad influence on the pathogenesis of inflammatory disorders [4]. IL-17A is a hallmark cytokine which is released by T helper 17 (Th17) cells [5]. A substantial number of studies demonstrate that IL-17A contributes to both innate and adaptive immune responses during the pathological processes of cancer [4]. IL-17F, which is the most homologous to IL-17A in this family, shares the same receptor set IL-17RA-IL-17RC with IL-17A for downstream signaling. Similar to IL-17A, IL-17F recruited Act1 and TRAF6 for downstream signaling and activated NF-κB, MAPKs and C/EBP cascades in different cell types [6-8]. In addition, IL-17F played a protective role in tumor progression in chemically-induced colon cancer model [9].

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Several studies have investigated the association between IL-17A G197A (rs2275913) and IL-17F T7488C (rs763780) polymorphisms and cancer risk. However, the results were inconclusive. For example, some studies found that IL-17A G197A polymorphism was associated with risk of gastric cancer, cervical cancer and breast cancer [10-12]. However, other studies found no association between IL-17A G197A polymorphism and risk of gastric cancer [13]. IL-17F T7488C polymorphism was associated with risk of gastric cancer [13] but not with risk of breast and gastric cancer [10,12]. Therefore, we performed a comprehensive meta-analysis to derive a more precise estimation of the relationship between IL-17A G197A and IL-17F T7488C polymorphisms and risk for specific forms of cancer.

Methods

Literature search

To identify all articles that examined the association of IL-17A G197A and IL-17F T7488C polymorphism with cancer risk, PubMed and Web of Science databases searches were performed using the following keywords: 'IL-17', 'polymorphism' and 'cancer'. The reference lists of the identified publications were checked to identify other relevant studies.

Inclusion criteria

Eligible studies should meet the following criteria: (a) case-control studies; (b) detailed genotype data for estimating of OR and 95% CI; (c) genotype distribution in controls in accordance with Hardy–Weinberg equilibrium (HWE) ; (d) studies published in English. For studies with overlapping populations, only the most complete one was included into the meta-analysis.

Data extraction

Two investigators independently extracted and evaluated the data. The opinion of a third investigator was sought for any controversy on the baseline information. For each study, the following information was registered: first author, year of publication, country, ethnicity, source of controls, cancer type, genotyping method, HWE, the numbers of genotyped cases and controls, and gene polymorphisms.

Statistics

HWE was tested by the x^2 test and $p<0.05$ was considered as departure from HWE. Heterogeneity among studies was tested using the Q and I^2 statistics. Based on the heterogeneity test, the overall OR was calculated using fixed or random effects model with 95% CI to measure the strength of the genetic association. Subgroup analyses were also performed to test the effects of country and cancer type. A funnel plot was generated as a visual aid to detect possible publication bias. All analyses were done with RevMan software (Version 5.2., The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Results

Study characteristics

Figure 1 shows the detailed process of identifying eligible studies. A total of 6 articles, including 8 studies, met the inclusion criteria and were included in this meta-analysis. The main characteristics of eligible studies are listed in Table 1. These studies, including 3,323 cancer cases and 3,974 non-cancer controls, were performed in Asian populations. There were 5 Chinese studies, 2 Japanese and 1 Iranian. There were 4 gastric cancer studies, 2 cervical cancer studies and 2 breast cancer studies.

Meta-analysis

The evaluations of the association of IL-17A G197A and IL-17F T7488C polymorphisms with cancer risk are shown in Table 2. Three studies including 1,082 cases and 1,488 controls were eligible for the final analysis of IL-17F T7488C polymorphism. The pooled ORs for the risk for specific forms of cancer associated with IL-17F T7488C polymorphism were 1.05 (95% CI: 0.88–1.24, C vs T), 1.18 (95% CI: 0.57–2.44, CC vs CT), 1.04 (95% CI: 0.86–1.26, CT vs TT), 1.05 (95% CI: 0.87–1.27, CC/CT vs TT) and 1.17 (95% CI: 0.57–2.41, CC vs

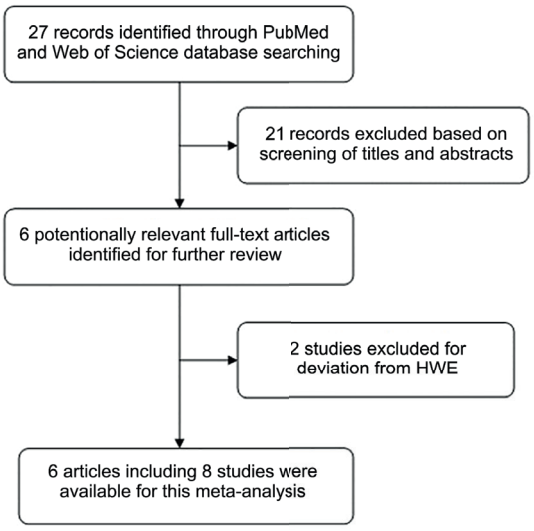

Figure 1. The detailed process of identifying eligible studies.

Table 1. Characteristics of eligible studies

First author and year of publication [Reference no.]	*Country*	*Ethnicity*	*Cancer type*	*Source of controls*	*Detection*	*IL-17 gene locus*	*Cases*	*Controls*	*p-value**
Shibata 2009 [10]	Japan	Asian	GC	HB	PCR-SSCP	rs763780	280	523	0.54
Arisawa 2012 [14]	Japan	Asian	GC	NA	PCR-SSCP	rs2275913	333	583	0.09
Wu 2010 [13]	China	Asian	GC	PB	PCR-RFLP	rs2275913	945	768	0.34
Quan 2012 [11]	China	Asian	CC	HB	TaqMan	rs2275913	311	463	0.38
Quan 2012 [11]	China	Asian	CC	HB	TaqMan	rs763780	311	463	0.10
Wang 2012 [12]	China	Asian	BC	NA	SNaPshot	rs2275913	491	501	0.16
Wang 2012 [12]	China	Asian	BC	NA	SNaPshot	rs763780	491	502	0.67
Rafiei 2013 [15]	Iran	Asian	GC	NA	PCR-RFLP	rs2275913	161	171	0.49

HWE: Hardy-Weinberg equilibrium in controls, PB: population-based, HB: hospital-based, NA: not applicable, GC: gastric cancer, CC: cervical cancer, BC: breast cancer. P*-value for HEW

Table 2. Meta-analysis results

Locus	*Comparison*	*Subgroup*	*Number*		*P_h-value**	*OR and 95%CI*
			Eligible studies	*Cases and controls*		
rs763780	C vs T	Total	3	1082/1488	0.97	1.05 (0.88-1.24)
	CC vs TT				0.70	1.18 (0.57-2.44)
	CT vs TT				0.96	1.04 (0.86-1.26)
	CC/CT vs TT				0.97	1.05 (0.87-1.27)
	CC vs CT/TT				0.69	1.17 (0.57-2.41)
rs2275913	A vs G	Total	5	2241/2486	0.02	1.31 (1.13-1.52)
		China	3	1747/1732	0.08	1.18 (1.07-1.30)
		OC	2	494/754	0.29	1.49 (1.26-1.76)
		GC	3	1439/1522	0.004	1.33 (1.01-1.76)
		OT	2	802/964	1.00	1.32 (1.15-1.51)
	AA vs GG	Total	5	2241/2486	0.007	1.81 (1.30-2.52)
		China	3	1747/1732	0.05	1.42 (1.17-1.72)
		OC	2	494/754	0.50	2.44 (1.76-3.39)
		GC	3	1439/1522	0.001	1.87 (1.03-3.41)
		OT	2	802/964	0.72	1.81 (1.37-2.40)
	AG vs GG	Total	5	2241/2486	0.68	1.12 (0.98-1.28)
		China	3	1747/1732	0.97	1.18 (1.01-1.38)
		OC	2	494/754	0.37	0.98 (0.76-1.27)
		GC	3	1439/1522	0.35	1.09 (0.92-1.30)
		OT	2	802/964	0.85	1.17 (0.94-1.44)
	AA/AG vs GG	Total	5	2241/2486	0.79	1.26 (1.11-1.43)
		China	3	1747/1732	0.77	1.25 (1.08-1.45)
		OC	2	494/754	0.28	1.28 (1.01-1.63)
		GC	3	1439/1522	0.49	1.22 (1.04-1.44)
		OT	2	802/964	0.87	1.31 (1.07-1.60)
	AA vs AG/GG	Total	5	2241/2486	<0.0001	1.72 (1.16-2.53)
		China	3	1747/1732	0.01	1.36 (0.93-1.99)
		OC	2	494/754	0.74	2.47 (1.84-3.33)
		GC	3	1439/1522	<0.0001	1.81 (0.89-3.65)
		OT	2	802/964	0.61	1.65 (1.29-2.12)

Total: overall population, OC: other country, GC: gastric cancer, OT: other tumor. *P_h-value of heterogeneity test

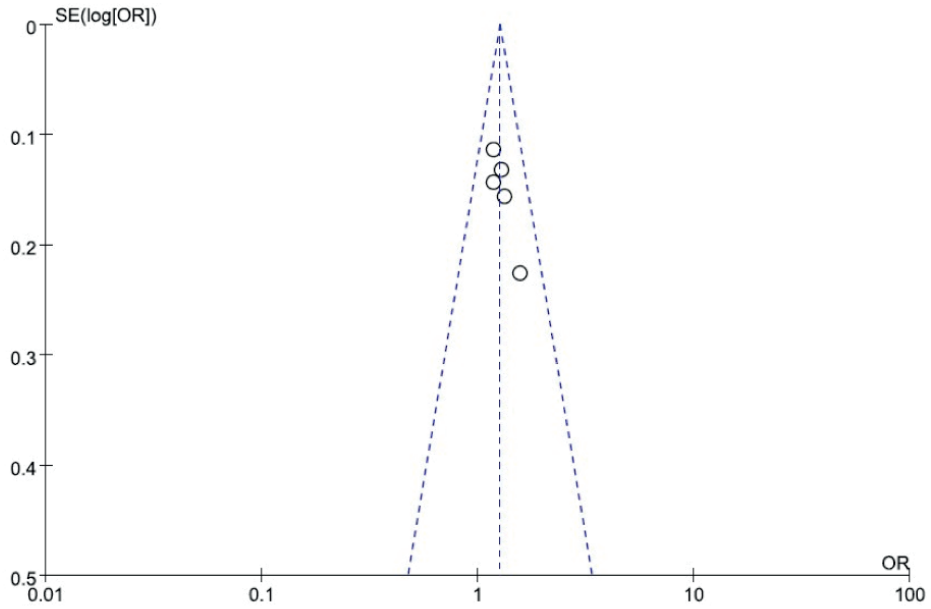

Figure 2. Funnel plots in the meta-analysis of the association between IL-17A G197A polymorphism and cancer risk (AA/AG vs GG).

CT/TT).

A total of 2,241 cases and 2,486 controls were eligible for inclusion in the analysis of IL-17A G197A polymorphism. In A vs G, AA vs GG and AA vs AG/GG model, there was evidence of heterogeneity among studies (P_h <0.05). Therefore, studies were combined using a random-effect model, and significant association was found (A vs G, OR = 1.31, 95 % CI 1.13-1.52; AA vs GG, OR = 1.81, 95 % CI 1.30-2.52; AA vs AG/GG , OR = 1.72, 95 % CI 1.16-2.53). However, in AG vs GG and AA/AG vs GG model, in which there was evidence of lack of heterogeneity among studies (P_h >0.05), the studies were performed by a fixed-effect model. The results indicated that significant association was found in AA/AG vs GG model (OR = 1.26, 95 % CI 1.11-1.43), but not in AG vs GG model (OR = 1.12, 95 % CI 0.98-1.28). Stratified analysis by country and cancer type showed the IL-17A G197A polymorphism may increase the risk of gastric cancer and increase cancer risk in China. A funnel plot was performed to assess the publication bias in IL-17A G197A polymorphism studies. Figure 2 shows that the funnel plot was symmetrical and didn't suggest a possibility of publication bias.

Discussion

Characterization and identification of genes involved in the genetic predisposition or progression of cancer are critical for both clinical practice and basic research. As proinflammatory cytokines, IL-17A and IL-17F, expressed by Th17 cells, play a role in coordinating local tissue inflammation. Numerous data have shown IL-17A and IL-17F polymorphisms were associated with cancer risk. However, the results were unclear. Therefore, we investigated the influence of the polymorphisms in these two cytokines in the risk for specific forms of cancer.

To the best of our knowledge, this is the first meta-analysis providing comprehensive insights into the association of IL-17A G197A and IL-17F T7488C polymorphisms with risk for specific forms of cancer. In the present study, we collected all available, published studies and performed a meta-analysis to examine the association. Our results indicated that IL-17F T7488C polymorphism was not statistically associated with the risk for specific forms of cancer in the Asian populations studied. However, IL-17A G197A polymorphism was associated with the risk for specific forms of cancer. In addition, in stratified analyses based on cancer type, significant association was found between gastric cancer risk and IL-17A G197A polymorphism. Subgroup analyses according to country showed significant association between IL-17A G197A polymorphism and gastric cancer risk in China.

Several limitations of this analysis should be considered. First, our results were based on unadjusted estimates, while a more precise analysis could be conducted if individual data, including age, family history, lifestyle and environmental

factors, were available. Second, publication bias is another major concern in all meta-analyses because studies reporting positive findings are more likely to be published than those reporting negative results. Third, the number of studies for subgroup analysis was small and restrained our further analysis for risk factor estimation.

In conclusion, our pooled data showed a significant association between IL-17A G197A polymorphism and the risk for specific forms of cancer in Asian populations. However, to determine the exact association between the polymorphism and cancer risk, it is essential to perform more well-designed studies with larger sample sizes in the future.

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