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ORIGINAL RESEARCH

Genetic association between *interluekin-4* rs2243250 polymorphism and gastric cancer susceptibility: evidence based on a meta-analysis

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Purpose: Numerous studies have suggested that the *interleukin-4* (*IL-4*) rs2243250 polymorphism is associated with gastric cancer susceptibility. However, the results were inconsistent. Hence, we carried out a meta-analysis to confirm the conclusion.

Methods: We searched PubMed, Embase, CBM, CNKI, and Wanfang Data to identify relevant studies up to August 20, 2015. Odds ratio (OR) and 95% confidence interval (CI) were used to estimate the association between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility. All the statistical analyses were performed with Stata 12.0 software.

Results: A total of eleven published case–control studies were identified, including 2,247 gastric cancer patients and 3,370 controls. Overall, no significant association between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility was observed in this meta-analysis (T vs C: OR =1.05, 95% CI =0.95–1.17; TT vs CC: OR =1.20, 95% CI =0.89–1.63; CT vs CC: OR =1.14, 95% CI =0.87–1.48; TT + CT vs CC: OR =1.13, 95% CI =0.89–1.44; TT vs CT + CC: OR =1.02, 95% CI =0.88–1.20). Similar results were found in subgroup analyses according to ethnicity and Hardy–Weinberg equilibrium in controls.

Conclusion: This meta-analysis suggests that *IL-4* rs2243250 polymorphism may not be associated with gastric cancer susceptibility. Further studies are needed to validate this conclusion.

Keywords: interleukin-4, meta-analysis, polymorphism, genetic, stomach neoplasms

Introduction

Gastric cancer is a leading cause of death by cancer worldwide and is the fifth most common cancer.[1] Gastric cancer in particular ranks as the third major malignancy in terms of mortality. Approximately 951,000 new cases of gastric cancer and 723,000 deaths were estimated worldwide in 2012.[1] Gastric cancer is classified as cardia and noncardia types in anatomy, and the latter makes up the major part of the cases. Gastric cancer is a multifactorial and complex disease that involves numerous environmental and lifestyle factors, including smoking and poor diet, and *Helicobacter pylori* infection may increase the development of gastric cancer.[2] Causes of gastric cancer are still unclear and genetic effects, especially single-nucleotide polymorphism (SNP), attract more attention to the study of gene polymorphism in relation to gastric cancer.[3,4]

Interleukin-4 (IL-4) is identified as a contributing factor to gastric carcinogenesis, and it is an indispensable element in the inflammation pathway and is considered as a basic part of the oncogenic process in gastric cancer.[5,6] IL-4 plays a vital role in tumor immunology, differentiation of hematopoietic cell, and maturation of T-helper (Th) cells to the Th2 phenotype.[7] *IL-4* gene is located on chromosome 5q31-33. The *IL-4* gene rs2243250 polymorphism, C to T base substitution at –590 of the *IL-4* promoter,

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increases the IL-4 expression.[5] Therefore, the polymorphism may modify the intensity of the inflammatory response, which contributes to gastric cancer development.[8]

Numerous studies addressed the association between *IL-4* rs2243250 polymorphism and risk of developing gastric cancer. In the past 2 years, two meta-analyses investigated the association.[9,10] Interestingly, the conclusions of the two previous meta-analyses were contradictory. In addition, more case–control studies have been published during these past 2 years. Based on all these factors, we performed this meta-analysis to try and find a more precise result on the association between *IL-4* rs2243250 polymorphism and risk of developing gastric cancer.

Materials and methods

Literature search

A comprehensive literature search was performed in PubMed, Embase, CBM, CNKI, and Wanfang Data up to August 20, 2015, to retrieve studies addressing the association between *IL-4* rs2243250 polymorphism and risk of developing gastric cancer with the following items: ([interleukin 4 OR interleukin-4 OR IL-4 OR IL4] and [gastric or stomach] and [cancer or tumor or carcinoma], and [polymorphism or mutation OR variation]). Reference lists of the included studies and recent reviews were retrieved for additional studies. No language restriction was applied in this meta-analysis.

Study selection criteria

Studies were included in this meta-analysis if they met the following criteria: 1) had a case–control design; 2) examined the association between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility; 3) included patients who were diagnosed with gastric cancer and controls who were cancer free; and 4) had sufficient data for calculating odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In addition, we excluded the following: 1) unpublished studies or abstracts; 2) studies in which the genotype distributions were not reported; and 3) studies in nonhuman subjects.

Data extraction

Two authors extracted the following information from the included studies: author name, publication year, country, ethnicity of the study subject, sample size, genotype distribution, and Hardy–Weinberg equilibrium (HWE) for controls. In addition, any disagreements were resolved by discussion.

Statistical analysis

The χ^2 test was used to examine whether the genotype frequencies in controls were consistent with HWE. The ORs and corresponding 95% CIs were calculated to assess the strength of association between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility using the following five genetic models: allelic contrast (T vs C), homozygote contrast (TT vs CC), heterozygote contrast (CT vs CC), dominant model (TT + CT vs CC), and recessive model (TT vs CT + CC).[5,11–13] Heterogeneity was detected using the Q-test and I^2 statistic.[14] The random-effects model was employed to aggregate the results of the included studies, which reduces to fixed-effects model when no between-study heterogeneity exists. Sensitivity analysis by excluding studies not in HWE in controls and subgroup analyses based on ethnicity were also performed. Publication bias was assessed by funnel plot and Egger's linear regression test to quantitatively measure the asymmetry of funnel plots.[15] The α level of significance was set at 0.05, except for the Q-test for heterogeneity (0.1).

Results

Study characteristics

Of the 95 records retrieved initially, a total of eleven published case–control studies[7,16–25] were ultimately identified involving 2,247 gastric cancer patients and 3,370 controls. Figure 1 shows the detailed flowchart of the study selection process. Table 1 lists the main characteristics of the included studies. Four studies[7,16,19,21] involved Caucasian populations, and seven studies[17,18,20,22–25] involved Asians. The genotype distributions of controls from five studies[16,17,20,23,24] were inconsistent with HWE.

Meta-analysis

The main results of this meta-analysis are listed in Table 2. Overall, no significant relationship was observed between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility in the total populations (T vs C: OR =1.05, 95% CI =0.95–1.17; TT vs CC: OR =1.20, 95% CI =0.89–1.63, Figure 2; CT vs CC: 1.14, 95% CI =0.87–1.48; TT + CT vs CC: OR =1.13, 95% CI =0.89–1.44; TT vs CT + CC: OR =1.02, 95% CI =0.88–1.20). Similarly, in the succeeding sensitivity analysis by excluding studies not in HWE in controls, no significant association was found between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility in the total populations (Table 2). Finally, even in the stratified analysis by ethnicity, we did not observe any significant association between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility (Table 2).

Publication bias

Begg's funnel plot seemed symmetric for all five genetic models. Figure 3 shows the shapes of the funnel plots of

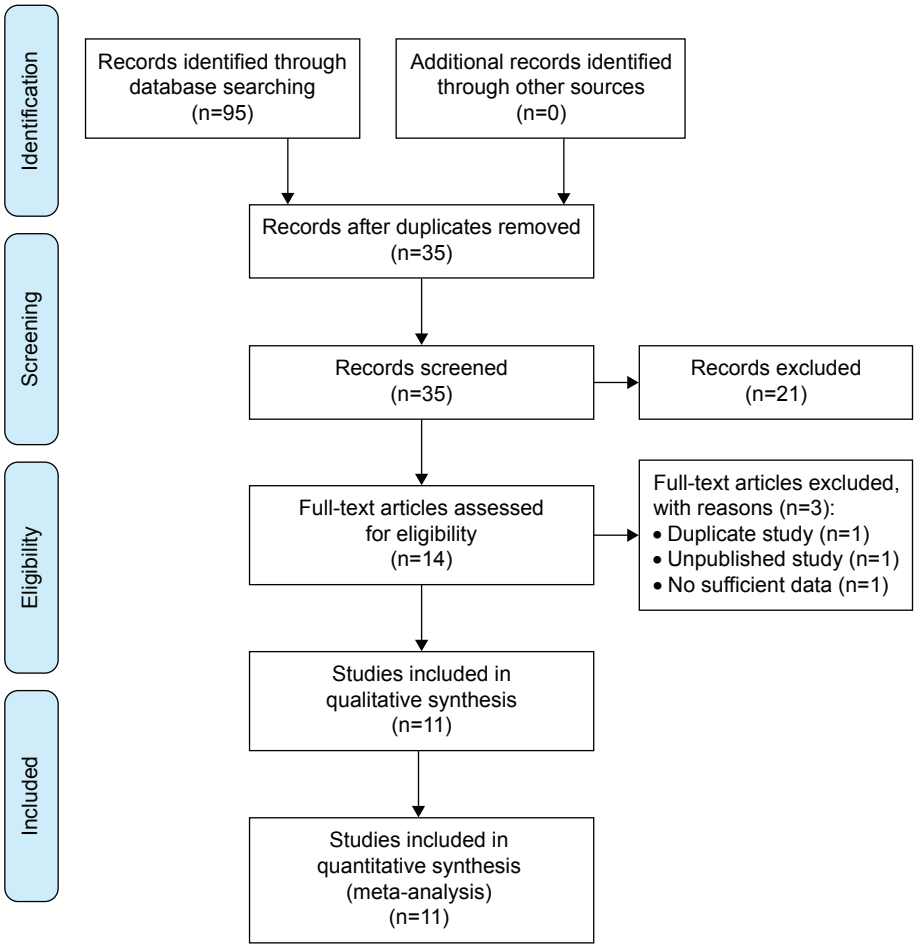

Figure 1 Flowchart of the study selection.

homozygote contrast used in the studies for examining all populations. The result was further supported by Egger's tests. No evidence of publication bias was detected in this meta-analysis (*P*=0.57 for T vs C; *P*=49 for TT vs CC; *P*=0.94 for CT vs CC; *P*=0.60 for TT + CT vs CC; *P*=0.65 for TT vs CT + CC; Table 2).

Discussion

Nowadays, genetic susceptibility in cancer development, especially SNPs, has drawn a great attention to the research of gene variation involved in carcinogenesis.[26,27] Gastric cancer is a multifactorial and complicated disease in which gene effects have been considered as a predominant component.

Table 1 Characteristics of included studies in the meta-analysis

Study	Country	Ethnicity	Sample size (case/control)	Cases			HWE in controls	Controls		
				CC	CT	TT		CC	CT	TT
El-Omar et al[16]	America	Caucasian	314/210	78	37	7	0.013	153	46	10
Wu et al[17]	People's Republic of China	Asian	220/230	5	69	146	0.016	12	55	163
Lai et al[18]	People's Republic of China	Asian	123/162	2	38	83	0.737	7	50	105
Garcia-Gonzalez et al[19]	Spain	Caucasian	404/404	283	107	14	0.971	267	123	14
Crusius et al[7]	Europe	Caucasian	242/1,154	159	76	7	0.603	824	305	25
Jia et al[20]	People's Republic of China	Asian	106/108	3	35	68	0.010	0	43	65
Zambon et al[21]	Italy	Caucasian	40/64	32	7	1	0.800	45	17	2
Ando et al[22]	Japan	Asian	330/190	26	158	146	0.248	18	92	80
Ko et al[23]	Korea	Asian	84/336	4	24	53	0.019	22	95	207
Long et al[24]	People's Republic of China	Asian	112/238	6	28	78	0.028	10	53	175
Pan et al[25]	People's Republic of China	Asian	275/274	9	85	181	0.383	8	90	176

Abbreviation: HWE, Hardy–Weinberg equilibrium.

Table 2 Meta-analysis of the association between IL-4 rs2243250 polymorphism and gastric cancer

Analysis	Number of studies	Test of association			Heterogeneity		*P*-value for Egger's test
		OR	95% CI	*P*-value	I^2	*P*-value	
T vs C							
Overall	11	1.05	0.95–1.17	0.34	0.0	0.51	0.57
HWE (yes)	6	1.05	0.92–1.21	0.44	11.0	0.35	
Caucasian	4	1.08	0.81–1.42	0.61	57.9	0.07	
Asian	7	1.03	0.90–1.18	0.63	0.0	0.93	
TT vs CC							
Overall	11	1.20	0.89–1.63	0.24	0.0	0.81	0.49
HWE (yes)	6	1.19	0.81–1.73	0.38	0.0	0.83	
Caucasian	4	1.17	0.72–1.90	0.53	0.0	0.85	
Asian	7	1.22	0.83–1.81	0.31	0.0	0.51	
CT vs CC							
Overall	11	1.14	0.87–1.48	0.34	34.2	0.13	0.94
HWE (yes)	6	1.02	0.78–1.35	0.87	30.3	0.21	
Caucasian	4	1.07	0.75–1.54	0.70	62.5	0.05	
Asian	7	1.26	0.81–1.95	0.30	10.9	0.35	
TT + CT vs CC							
Overall	11	1.13	0.89–1.44	0.33	30.0	0.16	0.60
HWE (yes)	6	1.04	0.79–1.37	0.78	33.8	0.18	
Caucasian	4	1.08	0.76–1.53	0.67	0.04	63.3	
Asian	7	1.22	0.83–1.80	0.30	0.0	0.45	
TT vs CT + CC							
Overall	11	1.02	0.88–1.20	0.76	0.0	0.98	0.65
HWE (yes)	6	1.09	0.89–1.35	0.40	0.0	0.99	
Caucasian	4	1.14	0.70–1.84	0.59	0.0	0.95	
Asian	7	1.01	0.86–1.19	0.89	0.0	0.85	

Abbreviations: CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio.

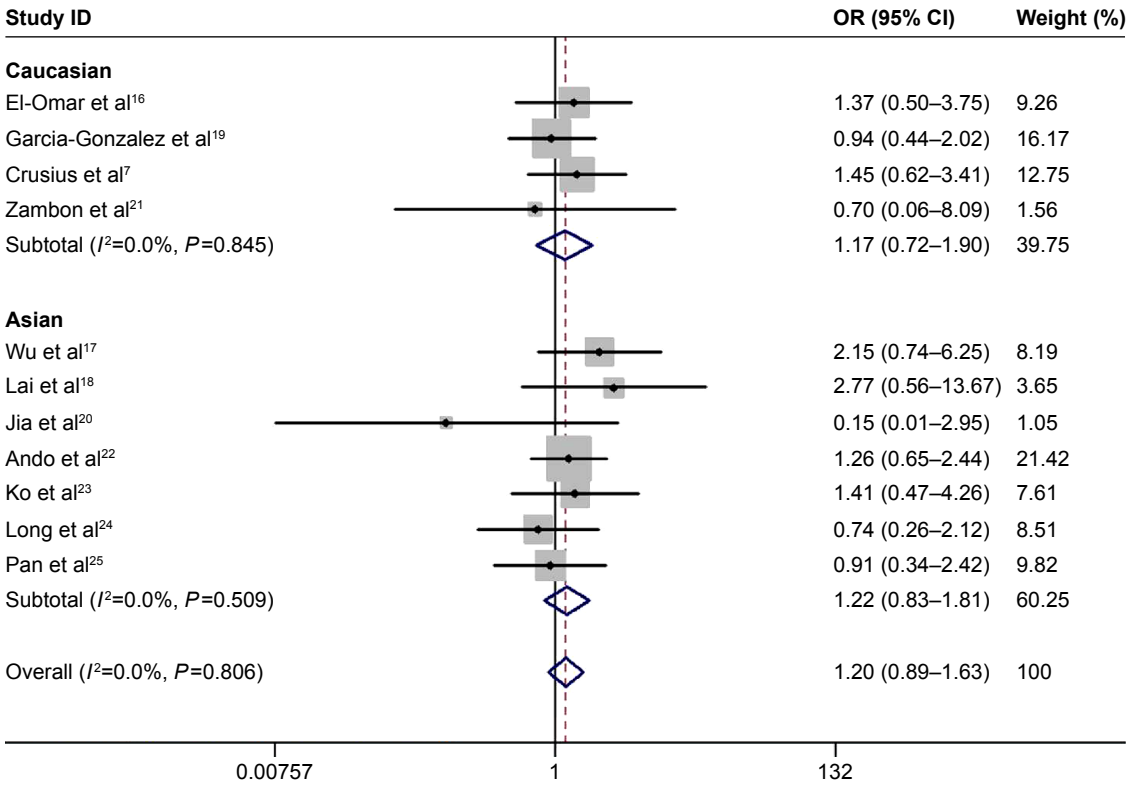

Figure 2 Forest plots of the meta-analysis for TT vs CC genetic model.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; OR, odds ratio.

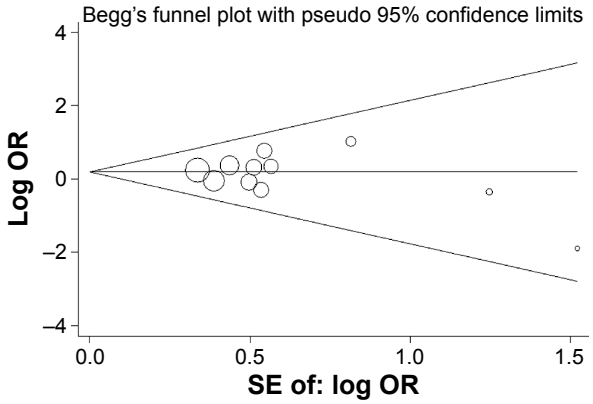

Figure 3 Begg's funnel plot of the TT vs CC genetic model.
Abbreviations: SE, standard error; OR, odds ratio.

With the development of molecular epidemiology, numerous studies addressed the effects of *IL-4* rs2243250 polymorphism on gastric cancer susceptibility. In 2003, El-Omar et al[16] investigated the proinflammatory cytokine gene polymorphism on the risk of noncardia gastric cancer and indicated that *IL-4* was not associated with any of the cancers studied. However, subsequent studies did not reveal similar results,[10,21] and the conclusion of the relationship between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility remains controversial. This meta-analysis included eleven published case–control studies and was conducted to evaluate the true association between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility; no significant difference was observed in overall analysis. Sensitivity analysis by excluding studies not in HWE in controls and subgroup analysis according to ethnicity also showed similar results.

In 2013, Zhang et al[9] performed a meta-analysis in which they investigated the *IL-4* rs2243250 polymorphism and risk of cancer and suggested that the *IL-4* rs2243250 polymorphism was not associated with increased/decreased risk of cancer. In their work, they identified eight case–control studies evaluating the association between the *IL-4* rs2243250 polymorphism and risk of gastric cancer, two of which were unpublished master thesis in the People's Republic of China.[9] As we all know, the unpublished studies were not evaluated by peer review, and more biases would be incurred if they were included in the meta-analysis. In 2014, Sun et al[10] carried out a meta-analysis to investigate the association between *IL-4* rs2243250 polymorphism and risk of gastric cancer with only seven case–control studies and suggested that *IL-4* rs2243250 polymorphism was associated with a lower gastric cancer risk under dominant model and allelic model in Caucasian. With respect to the aforementioned controversial results, we performed this meta-analysis with the most compressively literature search and excluded the unpublished studies.

Limitations

Like any meta-analysis study, this meta-analysis also has some limitations that should be taken into consideration.[28–31] First, these results are based on unadjusted estimates, which would be biased by other factors, such as other genes and environment.[32] Second, the sample size of this study is relatively small. Therefore, the statistical power to investigate the true association between *IL-4* rs2243250 polymorphism and gastric cancer susceptibility is relatively low, and the evidence in this meta-analysis might be less powerful. Third, even though we did not detect any evidence of between-study heterogeneity in the total population, we observed moderate-to-substantial between-study heterogeneity for Caucasians in allele contrast and heterozygote contrast models. This heterogeneity might be derived from the genotyping method, type of disease, and/or diverse environmental circumstances.[5,33] Furthermore, we did not perform stratification analysis according to disease type (cardia and noncardia) due to insufficient original data. In spite of these limitations, this study currently is the best available evidence with a more comprehensive literature search and no publication bias, as compared with the previous meta-analyses.

Conclusion

Despite these limitations, our meta-analysis indicated that *IL-4* rs2243250 polymorphism may not be associated with gastric cancer susceptibility. Further large-scale and well-designed studies are necessary to validate this conclusion.

Disclosure

The authors report no conflicts of interest in this work.

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