Chapter 10
Association Between IL6 Gene Polymorphisms and Gastric Cancer Risk: A Meta-Analysis of Case-Control Studies

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Abstract Interleukin-6 (IL-6) is a multifunctional cytokine, which plays a vital role in inflammation as well as tumorigenesis. Several studies have demonstrated that the association of IL6 -174 G/C (rs1800795) and -572 G/C (rs1800796) promoter polymorphisms influences transcription and has been found to trigger the risk of gastric tumor advancement with inconsistent and controversial result. The present study aims at collecting eligible articles through extensive search in PubMed, MEDLINE, and Embase databases. Additionally, the analysis also included 15 case–control investigations. MetaGenyo web tool was used to perform the meta-analysis. No substantial association was observed between IL6 polymorphisms and GC. In conclusion, our study signifies that polymorphisms of IL6, -174 G/C, and -572 G/C are not linked with GC risk.

Keywords Gastric cancer · IL-6 gene · -174 G/C · -572 G/C · Meta-analysis

Abbreviations

GC	Gastric cancer
IL-6	Interleukin 6
H. pylori	*Helicobacter pylori*
NLM	National Library of Medicine
SNPs	Single nucleotide polymorphisms
CBLD	Chinese Biomedical Literature Database

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HWE	Hardy–Weinberg equilibrium
P value	Probability value
OR	Odds ratio

10.1 Introduction

Inflammation is an essential innate immune response induced by microbial infection and tissue damage. Numerous studies have provided a wide range of clinical evidence that chronic inflammation is linked with elevated risk of Gastric cancer (GC) (Greten and Grivennikov 2019; Multhoff et al. 2011; Bockerstett and DiPaolo 2017). Cytokines are a wide range of small proteins secreted by immune cells, including nucleated cells and work as an intracellular messenger in the immune system (Lowry 1993). Cytokine is a key mediator of diagnosis and treatment during inflammation in many diseases (Verma et al. 2016). The potential association between multifunctional cytokines and GC has been examined by several investigators. Among those, Interleukin 6 (IL-6) is known to function as both a pro-inflammatory cytokine as well as an anti-inflammatory myokine regulator (Tanaka et al. 2014). IL-6 belongs to a family of pleiotropic cytokine and modulates cell proliferation and differentiation. Previous data has demonstrated that IL-6 level was increased in mucosa, which leads to the inflammatory microenvironment in *Helicobacter pylori* (*H. pylori*) related gastritis (Yamaoka et al. 1996). Further, overexpression of IL6 is strongly associated with an increased risk of GC development and progression (Madej-Michniewicz et al. 2015). Therefore, based on the earlier reports, IL-6 is closely linked to occurrence and development of cancer.

The gene coding for IL6 is located on chromosome 7p21 and comprises 184 amino acids, which fold as a 4 alpha-helix bundle structure (Choy and Rose-John 2017). Understanding the genetic diversity with population genetic structure of IL6 will aid in predicting tumor risk as well as in reducing mortality. To date, several single nucleotide polymorphisms (SNPs) have been identified in the promoter region of IL6 (Terry et al. 2000). Among them, IL6 -174 G/C (rs1800795) and -572 G/C (rs1800796) are the most widely studied polymorphisms in several cancers including GC. However, previous investigations have yielded varying results regarding the relationship between IL6 promoter polymorphisms and gastric cancer (Chakraborty et al. 2017; Markkula et al. 2014). It could be because of the insignificant sample size, variations in genotyping methods, and ethnicity of the populations. In order to assess the precise role of IL6 promoter polymorphism on GC susceptibility, we have conducted this meta-analysis of all existing case–control studies.

10.2 Methods

10.2.1 Study Selection Strategy

To evaluate the relation between IL6 promoter polymorphisms and the risk of GC, all potentially pertinent articles were searched and identified according to the PRISMA guidelines (Liberati et al. 2009). Pubmed, Web of Science, and EMBASE Database were searched using the following keywords: Interleukin-6 and gastric cancer, IL6, IL6 -174 G/C, rs1800795, -572 G/C, and rs1800796. The last search was executed on 26 April 2020.

10.2.2 Literature Inclusion and Exclusion Criteria

Two investigators selected eligible studies independently. Studies that met the following criteria were included in this meta-analysis: (1) case–control study on GC and IL6 promoter polymorphisms; (2) genotypes available for calculating odds ratio (OR) and 95% confidence interval (CI). The exclusion criteria for this meta-analysis were as follows: (1) studies with no specific control group; (2) non-availability of genotype data. The quality evaluation of all eligible studies and data extraction of information was made with consensus and the discrepancy between investigators was resolved by cross-checking the data. From each paper, name of the first author, publication year, country and ethnicity of the participants, genotypes in cases and control subjects were collected and documented in Table 10.1.

10.2.3 Statistical Analysis

The strength of association between IL6 polymorphism (-174 G/C and -572 G/C) and GC was assessed for all studies. The crude ORs and their corresponding 95% confidence interval (CI) limits were calculated. The presence of heterogeneity was evaluated with the Cochran's Q test and inconsistency I2 statistics. Based on the extent of heterogeneity, fixed effects model (FEM) or random effects model (REM) were adopted for pooled analysis. The association between IL6 polymorphisms and GC was analyzed in dominant, recessive, and allelic genetic models. To assess the robustness of the study, sensitivity analysis was performed by overlooking each study one time and estimating the Odd Ratio (OR) for the remaining studies. Publication bias was measured by the use of a funnel plot and Egger's test. MetaGenyo web tool was used to perform the meta-analysis (Martorell-Marugan et al. 2017).

Table 10.1 The characteristics of included studies in present meta-analysis

First author (year)	Country/ ethnicity	Case/ control	Cases			Control			HW *P* value
			CC	GC	GG	CC	GC	GG	
IL6 -174 G/C (rs1800795)									
Dos Santos et al. (2019)	Brazil/ Caucasian	52/87	6	17	29	10	35	42	0.517
Attar et al. (2017)	Iran/ Caucasian	100/ 361	7	30	63	13	187	161	<0.001
Ramis et al. (2017)	Brazil/ Caucasian	0.09/38	0	2	7	2	13	23	0.927
Sampaio et al. (2015)	Portugal/ Caucasian	50/50	8	25	17	6	25	19	0.608
Pohjanen et al. (2013)	Finland/ Caucasian	56/179	8	34	14	56	86	37	0.706
Yong et al. (2010)	China/Asian	142/ 200	0	37	105	0	2	198	0.943
Crusius et al. (2008)	France/ Caucasian	243/ 1138	43	122	78	206	517	415	0.044
Deans et al. (2007)	UK/ Caucasian	197/ 224	43	83	71	44	101	79	0.258
Gatti et al. (2007)	Brazil/ Caucasian	56/112	1	13	42	11	53	48	0.509
Kamangar et al. (2006)	Finland/ Caucasian	102/ 152	27	54	21	43	58	51	0.004
Xing et al. (2006)	China/Asian	65/71	0	3	62	0	4	67	0.807
El-Omar et al. (2003)	USA/ Caucasian	209/ 213	28	98	83	34	91	88	0.205
Hwang et al. (2003)	USA/ Caucasian	30/30	2	9	19	0	8	22	0.399
IL6 -572 G/C (rs1800796)									
Mrtinez-Campos et al. (2019)	Mexico/ Caucasian	122/ 122	18	55	49	15	58	49	0.733
Dos Santos et al. (2019)	Brazil/ Caucasian	52/87	2	10	40	1	22	64	0.555
Kang et al. (2009)	Korea/Asian	332/ 326	21	133	178	17	140	169	0.078
Xing et al. (2006)	China/Asian	65/71	2	4	59	4	11	56	0.005
Hwang et al. (2003)	USA/Asian	30/30	16	13	1	16	13	1	0.394
Hwang et al. (2003)	USA/ Caucasian	30/30	3	16	11	5	7	18	0.020

10.3 Results

10.3.1 Characteristics of Published Studies

Our systematic literature search identified 436 articles. Based on the inclusion and exclusion criteria, unrelated or duplicate studies were excluded by reading titles and abstracts. Ninety-six relevant articles were selected for further assessment and 71 studies were consequently excluded after reading the full text to avoid discrepancy. Finally, 15 case–control studies fulfilled our study criteria (Fig. 10.1). Out of which, IL6 -174 G/C genotypes were extracted from thirteen papers (Dos Santos et al. 2019; Attar et al. 2017; Ramis et al. 2017; Sampaio et al. 2015; Pohjanen et al. 2013; Yong et al. 2010; Crusius et al. 2008; Deans et al. 2007; Gatti et al. 2007; Kamangar et al. 2006; Xing et al. 2006; El-Omar et al. 2003; Hwang et al. 2003). The IL6 -572 G/C genotypes were extracted from six papers (Dos Santos et al. 2019; Xing et al. 2006; Hwang et al. 2003; Martínez-Campos et al. 2019; Kang et al. 2009). Hwang et al. paper has analyzed samples from two ethnicities, hence it is considered as two studies (Hwang et al. 2003). The genotype distributions and main characteristics of studies are presented in Table 10.1. For IL6 -174 G/C, the heterogeneity test indicated significant heterogeneity between studies (CG+CC vs. GG: $P_{\text{heterogeneity}} < 0.001$, $I^2 = 72\%$), but no heterogeneity was observed between studies of IL6 -572 G/C (CG+CC vs. GG: $P_{\text{heterogeneity}} = 0.232$, $I^2 = 27\%$) (Table 10.2).

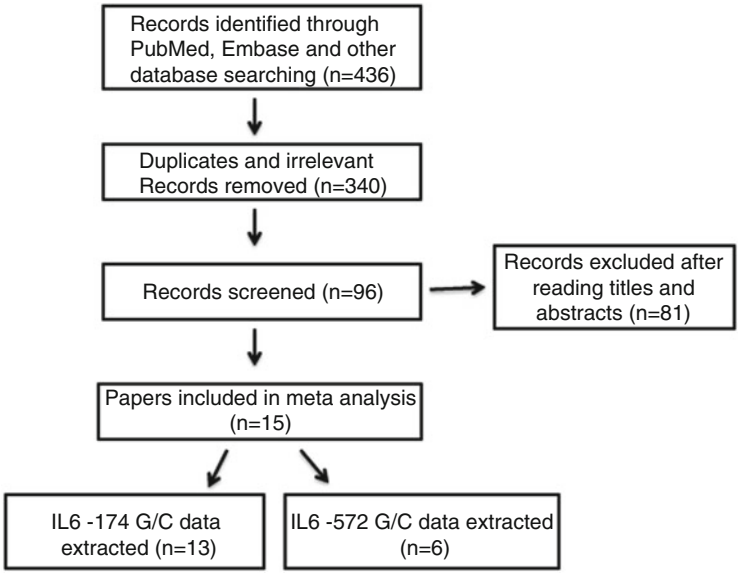

Fig. 10.1 Flowchart of study selection for the current study

Table 10.2 Associations of interleukin 6 gene polymorphisms with the risk of gastric cancer

IL6 -174 G/C (rs1800795)		Allele model (C vs. G)	Recessive model (CC vs. GC+GG)	Dominant model (CG +CC vs. GG)
Number of studies		13	11	13
Test of association	OR	0.96	0.95	1.01
	95% CI	[0.74–1.24]	[0.77–1.16]	[0.69–1.48]
	p value	0.738	0.584	0.960
	Model	REM	FEM	REM
Test of heterogeneity	*p* value	<0.001	0.222	<0.001
	I^2%	76%	23%	79%
Publication bias	Egger's test *p* value	0.903	0.980	0.791
IL6 -572 G/C (rs1800796)		Allele model (C vs. G)	Recessive model (CC vs. GC+GG)	Dominant model (CG +CC vs. GG)
Number of studies		6	6	6
Test of association	OR	0.99	1.11	0.94
	95% CI	[0.82–1.18]	[0.74–1.66]	[0.74; 1.19]
	p value	0.872	0.627	0.611
	Model	FEM	FEM	FEM
Test of heterogeneity	p value	0.440	0.773	0.232
	I^2%	0%	0%	27%
Egger's test *p* value		0.680	0.642	0.968

FEM fixed effect model, *REM* random effect model, *OR* Odds ratio, *95% CI* 95% confidence interval

10.4 Quantitative Data Synthesis

To explore the correlation between IL6 promoter polymorphisms and the risk of GC, 15 studies of IL6 -174 G/C polymorphism (1311 cases/ 2855 control), and six studies of IL6 -572 G/C polymorphism (631 cases /666 controls) were used. Meta-analysis of IL6 -174 G/C polymorphism and GC is documented in Fig. 10.2a, which did not reveal significant association between IL6 -174 G/C polymorphism and gastric cancer in the allelic model (C vs. G; OR = 0.96, 95% CI: 0.74–1.24, P = 0.738), recessive model (CC vs. GC+GG; OR = 0.95, 95% CI: 0.77–1.16, P = 0.584), and dominant models (CG+CC vs. GG; OR = 1.01, 95% CI: 0.69–1.48, P = 0.960). The pooled effect estimates presented in Fig. 10.2b shows that IL6 -572 G/C is not associated with GC in allelic model (C vs. G; OR = 0.99, 95% CI: 0.82–1.18, P = 0.872), recessive model (CC vs. GC+GG; OR = 1.11, 95% CI: 0.74–1.66, P = 0.627), and dominant models (CG+CC vs. GG; OR = 0.94, 95% CI: 0.74–1.19, P = 0.611).

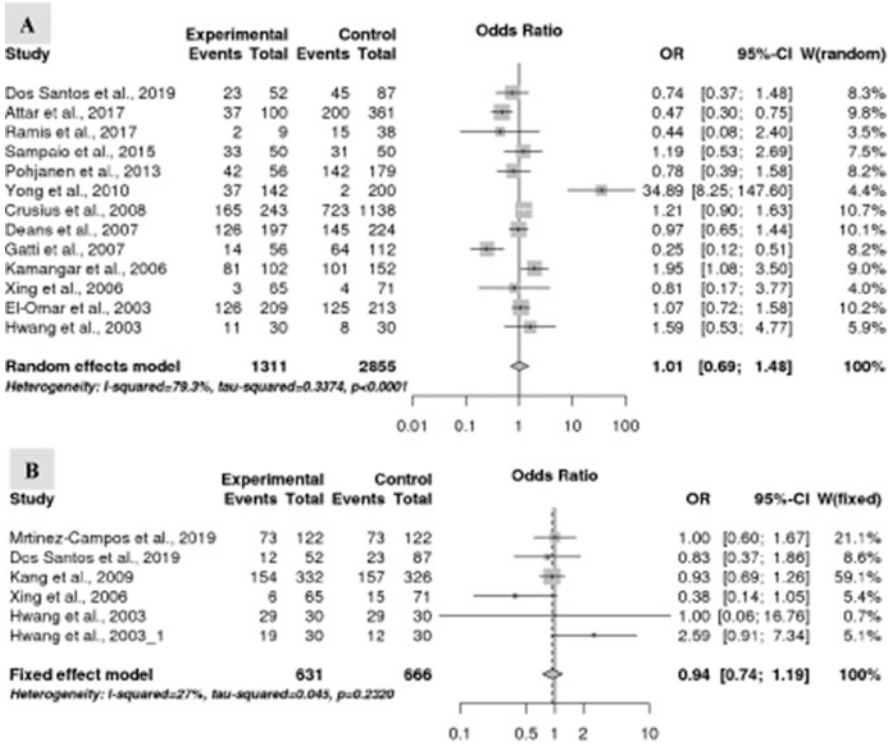

Fig. 10.2 Forest Plot of meta-analysis of the IL-6 polymorphism and gastric cancer risk. (**a**) IL6 -174 G/C; (**b**) IL6 -572 G/C

10.4.1 Sensitivity Analysis and Publication Biases

Sensitivity analysis was carried out with pooled effect estimates by omitting each study one time to evaluate the stability of the outcomes. The outcomes of sensitivity analysis presented in Fig. 10.3 suggest that no single study could influence the pooled ORs of IL6 -174 G/C and IL6 -572 G/C polymorphisms. Visual inspection of Begg's funnel plots did not show asymmetry for both IL6 -174 G/C and IL6 -572 G/C polymorphisms (Fig. 10.4a, b) indicating that there is no publication bias. The same was confirmed by Egger's test p values ($P > 0.05$).

10.5 Discussion

Despite recent progress in clinical practice, GC remains the third most common cancer-related death worldwide. According to current data, in 2017, more than 1.22 million new cases of GC occurred and nearly 8,65,000 patients have died due to GC

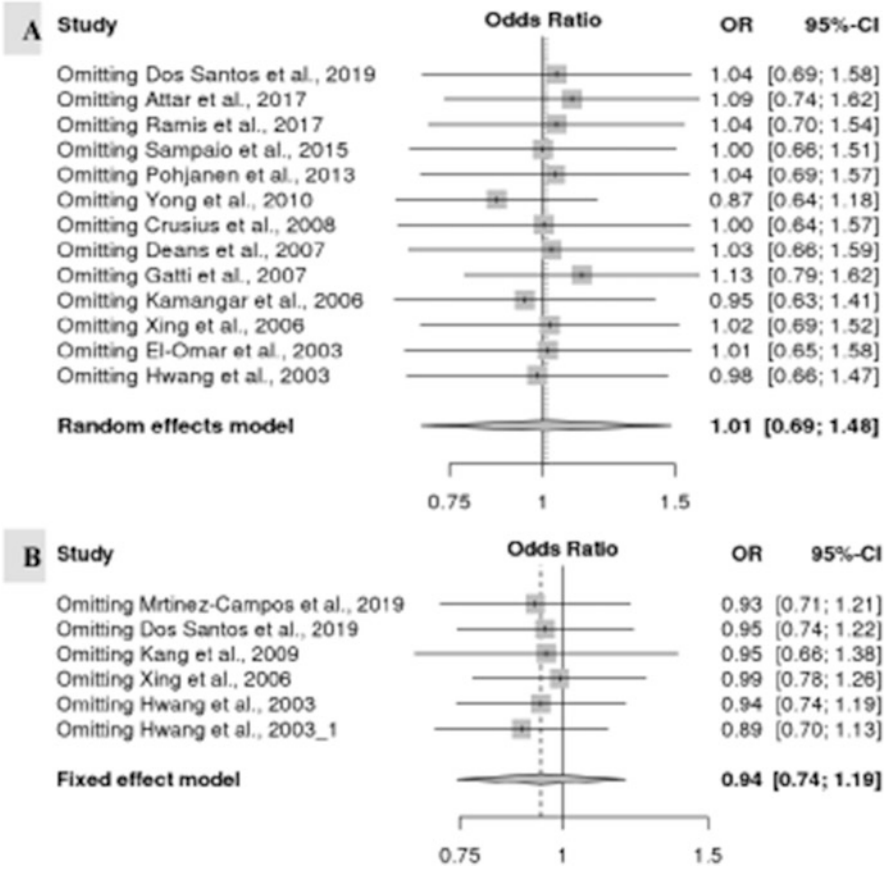

Fig. 10.3 Sensitivity analysis for the association between IL-6 polymorphisms and gastric cancer risk. (**a**) IL6 -174 G/C; (**b**) IL6 -572 G/C

(Russi et al. 2019; Etemadi et al. 2020). To date, the exact causes of GC still remain unknown. Nevertheless, it has been proven that cytokines play a role in inflammation, and can also induce cell transformation in the development of cancer and chemoresistance (Conlon et al. 2019; Verma et al. 2020). Interleukins are low-molecular-weight cytokine expressed by leukocytes and are involved in normal functioning of the immune system. Further, disruptions of interleukins level may lead to immune deficiencies and tumorigenesis (Larsen et al. 2018). Subsequently, it has been reported that some mutations in interleukin genes lead to increased risk of GC development (Wang et al. 2014).

To date, several case–control studies have explored the association between IL6 -174 G/C and IL6 -572 G/C polymorphism on the susceptibility to GC. However, small sample sizes, different genotyping methods, and variation in minor allele frequencies across ethnicities leads to the lack of consistency in results. Therefore, we have performed the present meta-analysis to precisely study the association of

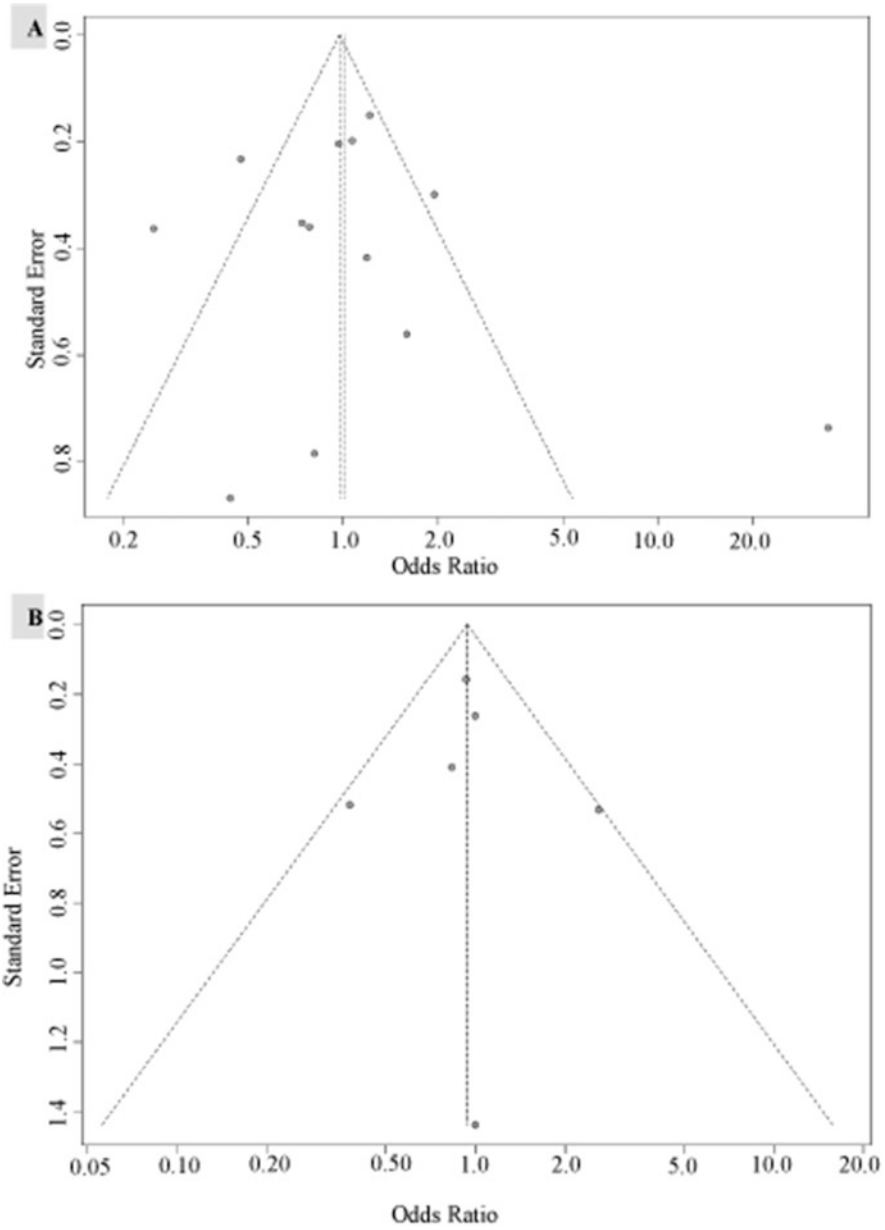

Fig. 10.4 Funnel plot to publication bias in meta-analysis about IL-6 polymorphisms and gastric cancer risk. (**a**) IL6 -174 G/C; (**b**) IL6 -572 G/C

IL6 polymorphism with GC risk. In this comprehensive meta-analysis we have observed that the IL6 -174 G/C and IL6 -572 G/C polymorphisms are not significantly associated with the risk of GC. The results of this meta-analysis are consistent with the results of previous meta-analysis in which no association between GC risk and IL6 -174 G/C (Jafari-Nedooshan et al. 2019; Yunxia Liu et al. 2018; Wang et al. 2018, 2012) or IL6 -572 G/C (Wang et al. 2018, 2012; Peng et al. 2018; Du et al. 2015) was documented. However, some meta-analyses have demonstrated increased GC risk for IL6 -174 G/C (Wang et al. 2018; Tian et al. 2015) or IL6 -572 G/C (Liu et al. 2018) in Asian populations.

In conclusion, our study indicates that the IL6 -174 G/C and IL6 -572 G/C polymorphisms are not correlated with GC risk. Soon, a large population based case–control studies would be potentially needed for validation of Interleukin 6 gene association with GC risk.

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