Association of IL-6 –174 G>C Polymorphism with Susceptibility to Colorectal Cancer and Gastric Cancer: a Systematic Review and Meta-Analysis

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ABSTRACT

Background: The –174G>C (rs1800795) polymorphism at interleukin 6 (IL-6) gene has been reported to be related with the occurrence of colorectal (CRC) and gastric (GC) cancers. However, the results had been conflicting and controversial. In order to give a comprehensive and precise result, we summarized available data to analyze the association of this polymorphism with CRC and GC risk.

Methods: A comprehensive literature search on PubMed, Elsevier Science Direct, and CNKI database was performed to identify all eligible studies up to May 15, 2019. The strength of association was assessed by odds ratios (ORs) with 95% confidence intervals (CI).

Results: A total of 29 case-control studies including 16 studies with 7,560 cases and 9,574 controls on CRC and 13 studies with 1,445 cases and 2,918 controls on GC were selected. Overall, pooled data showed that the IL-6 –174G>C polymorphism was not significantly associated with increased risk of CRC and GC in overall. When stratified by ethnicity, we found a statistically significant association between the IL-6 –174 G>C polymorphism and CRC risk in Asians (CC vs. GG: OR = 1.860, 95% CI 1.061–3.258, p = 0.030; and CC vs. CG+GG: OR = 1.941, 95% CI 1.131–3.331, p = 0.016).

Conclusion: The meta-analysis suggests that IL-6 –174G>C polymorphism was not significantly associated with the increased risk of CRC and GC in overall population. However, the results showed that IL-6 –174G>C polymorphism may be associated with risk of GC in Asians. Further studies including a larger sample size will be necessary to clarify these results.

KEYWORDS

colorectal cancer; gastric cancer; interleukin 6; association; meta-analysis

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Received: 2 July 2019
Accepted: 4 September 2019
Published online: 10 February 2020

Acta Medica (Hradec Králové) 2019; 62(4): 137–146
https://doi.org/10.14712/18059694.2020.2

INTRODUCTION

Digestive system cancers especially colorectal cancer (CRC) and Gastric cancer (GC) are the most common causes of cancer-related death worldwide (1–3). CRC and GC were the fourth and second most common causes of cancer-related mortality worldwide in 2016, respectively (4, 5). The exact mechanism of CRC and GC is still not fully understood. However, CRC and GC are multifactorial and multistep diseases caused by complex interactions between environmental triggers and genetic factors (6, 7). To date, a wide range of gastrointestinal cancer susceptibility gene variations have been evaluated. Interleukin 6 (IL-6) gene promoter region polymorphisms have already been correlated to increased risks of developing CRC and GC (8, 9).

IL-6 is a pleiotropic cytokine with a wide range of biological activities in immune regulation, hematopoiesis, inflammation and oncogenesis. IL-6 is implicated in a wide variety of inflammation-associated disease states, such as diabetes mellitus, systemic juvenile rheumatoid arthritis and malignant diseases. The human IL-6 gene is mapped to chromosome 7p21-24, with an upstream promoter containing 303 bp, contains five exons and spans approximately 6.2 kb (10). Accumulating evidence indicates pathological roles for IL-6 in different malignancies, such as breast, vulvar, ovarian, hepatocellular, lung, gastric and colorectal cancer (11).

To date, several polymorphisms in the promoter region of the IL-6 gene including -598A>G, −597G>A, −572 C>G, and −174 G>C have been identified and are implicated in the increased level of IL-6. Of these polymorphisms, −174 G>C (rs1800795) is the most studied functional polymorphism in different malignancies. IL-6 −174 G>C is demonstrated to impact the adherence of the glucocorticoid receptor and then results in repressive transcriptional activation. Lots of studies have reported the role of IL-6 −174 polymorphism in the predisposition to CRC and GC. However, these studies results are inconclusive and also inconsistent. This may be because of inadequate sample sizes, patient selection, genotyping methods, and ethnicity of the populations studied. Moreover, an individual study may be insufficient to evaluate the potential small effect of the IL-6 −174 G>C polymorphism on risk of CRC and GC. Therefore, we performed a meta-analysis of all available eligible case-control studies to verify the precise association of the IL-6 −174 G>C (rs1800795) polymorphism with CRC and GC risk.

MATERIAL AND METHODS

LITERATURE COLLECTION AND SCREENING

A flow-diagram outlining the identification, screening, eligibility, and final datasets was constructed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 guidelines. To identify all articles that evaluated the association of IL-6 −174 G>C polymorphism with CRC and GC risk, we performed a comprehensive literature search of the PubMed, EMBASE, Elsevier Science Direct, Google scholar, Chinese Biomedical Literature database, China National Knowledge Infrastructure database (CNKI), and Wanfang database up to May 15, 2019. The following keywords and terms were used: ("colorectal cancer" Or "CRC" OR "bowel cancer" OR "colon cancer") AND ("gastric cancer" OR "GC" OR "stomach cancer") AND (Interleukin 6 OR IL-6 OR "−174G>C" OR "rs1800795") AND ("gene" OR "polymorphism" OR "mutation" OR "variation"). In addition, reference list of obtained literatures was reviewed to ensure that no relevant studies were missed.

INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria for the present study were as follows: 1) published case-control or cohort studies; 2) studies evaluated the association of IL-6 −174 G>C polymorphism with CRC and GC; 3) studies with sufficient data to calculate the odds ratio (OR) and 95% confidence interval (CI). Accordingly, the following exclusion criteria were used: 1) abstracts, posters, case reports, reviews, and letter to editors; 2) case only studies, sibling or linkage studies; 3) the study reported duplicated data or containing overlapping data.

DATA EXTRACTION

The data from the published studies were extracted independently by two of the authors, and the disagreement was resolved by a discussion involving a senior author. For each study, the following data were collected: first author's name, year of publication, country, ethnicity (Caucasian, Asian, African and others), sources of healthy controls, number of cases and controls, genotyping methods, allele numbers and genotype distributions in cases and controls, minor allele frequencies (MAFs) in control subjects, and the results of Hardy-Weinberg equilibrium (HWE) test.

STATISTICAL ANALYSIS

An ethical approval was not necessary as this study was a meta-analysis based on previous studies. The association of IL-6 −174 G>C polymorphism with CRC and GC risk was measured by ORs and its corresponding 95% CIs. The estimates of pooled ORs were obtained by calculating a weighted average of OR from each study and the significance of pooled ORs was determined by the Z-test. In this meta-analysis, the pooled ORs for IL-6 −174 G>C polymorphism was calculated under five genetic models, i.e., allele (C vs. G), homozygote (CC vs. GG), heterozygote (CG vs. GG), dominant (CC+CG vs. GG) and recessive (CC vs. CG+GG). Between-studies heterogeneity was assessed by a Chi-squared Q-test and I^2 statistics ($P < 0.05$). Additionally, the I^2-value was applied to quantitatively evaluate the heterogeneity ($I^2 < 25\%$, low heterogeneity; $25\% \leq I^2 \leq 75\%$, moderate heterogeneity; $I^2 > 75\%$, high heterogeneity). The fixed-effects model (the Mantel-Haenszel method) and the random-effects model (the DerSimonian-Laird method) were utilized to pool ORs. Sensitivity analysis was used by omitting individual studies each time to assess the stability of the pooled results. The Hardy-Weinberg equi-

librium (HWE) test for each study was performed using chi-square test), and $P < 0.05$ was considered to indicate significant disequilibrium. We carried out subgroup analysis by cancer type, ethnicity, genotyping methods, source of controls and HWE (fall in HWE). Begg's funnel plot and Egger's test were used to evaluate the publication bias in the meta-analysis, in which $P < 0.05$ indicated that the result was statistically significant. All statistical analyses were performed using the comprehensive meta-analysis (CMA) software (version 2.0, Biostat, USA). Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

LITERATURE SELECTION AND STUDY CHARACTERISTICS

A total of 118 articles were identified through the initial search in the database and by hand searching. As shown in Figure 1, after carefully screening the title and abstracts of the initial publications, 20 studies were promptly excluded. Consequently, 29 case-control studies were included in this meta-analysis. The characteristics of each study are summarized in Table 1. Of those studies, 16 studies with

Tab. 1 Main characteristics of studies included in this meta-analysis.

First Author	Country (Ethnicity)	Genotyping Method	SOC	Case/ Control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
Colorectal Cancer					GG	GC	CC	G	C	GG	GC	CC	G	C		
Landi 2003 (12)	Spain (Caucasian)	TaqMan	PB	361/311	133	180	48	446	276	145	133	33	423	199	0.319	0.761
Theodoropoulos 2006 (13)	Greece (Caucasian)	PCR-RFLP	NS	222/200	111	76	35	298	146	64	86	50	214	186	0.465	0.054
Gunter 2006 (14)	USA (Caucasian)	TaqMan	HB	204/190	79	90	35	248	160	83	81	26	247	133	0.350	0.384
Gaustadnes 2006 (15)	Denmark (Caucasian)	CE	PB	230/540	64	115	51	243	217	184	263	93	631	449	0.415	0.952
Slattery 2007 (16)	USA (Caucasian)	TaqMan	HB	777/995	321	347	109	989	565	411	438	146	1260	730	0.366	0.098
Vogel 2007 (17)	Denmark (Caucasian)	Probe	HB	355/753	98	168	89	364	346	204	364	185	772	734	0.487	0.371
Wilkening 2008 (18)	Sweden (Caucasian)	TaqMan	HB	303/580	79	163	61	321	285	162	297	121	621	539	0.464	0.480
Kury 2008 (19)	France (Caucasian)	TaqMan	PB	1023/1121	363	489	171	1215	831	435	504	182	1374	868	0.387	0.078
Slattery 2009 (20)	USA (Caucasian)	TaqMan	HB	1573/1972	631	696	246	1958	1188	728	897	347	2353	1591	0.403	0.014
Tsilidis 2009 (21)	USA (Caucasian)	TaqMan	HB	200/354	68	93	39	229	171	113	170	71	396	312	0.440	0.626
Vasku 2009 (22)	Czech (Caucasian)	PCR-RFLP	HB	100/100	32	46	22	110	90	31	47	22	109	91	0.455	0.600
Ognjanovic 2010 (23)	USA (Caucasian)	TaqMan	PB	117/221	71	46	0	188	46	103	118	0	324	118	0.267	≤0.001
Cacev 2010 (24)	Croatia (Caucasian)	PCR-RFLP	HB	160/160	64	70	26	198	122	68	75	17	211	109	0.340	0.581
Abuli 2010 (25)	Spain (Caucasian)	TaqMan	HB	1405/1388	586	635	184	1807	1003	593	623	172	1809	967	0.348	0.672
Basavaraju 2015 (26)	Scotland (Caucasian)	TaqMan	HB	388/495	140	184	64	464	312	172	245	78	589	401	0.405	0.549
Banday 2017 (27)	Kashmiri (Asian)	PCR-RFLP	PHB	142/194	85	43	14	213	71	145	46	3	316	52	0.134	0.764
Gastric Cancer																
El-Omar 2003 (28)	USA (Caucasian)	TaqMan	PB	213/209	88	91	43	267	177	83	98	28	264	154	0.368	0.912
Hwang 2003 (29)	USA (Caucasian)	PCR-RFLP	HB	30/30	19	9	2	37	13	22	8	0	52	8	0.133	0.399
Hwang 2003	USA (Asian)	PCR-RFLP	HB	30/30	30	0	0	60	0	30	0	0	60	0	0.000	NA
Kamangar 2006 (30)	Finland (Caucasian)	TaqMan	PB	102/152	21	54	27	96	108	51	58	43	160	144	0.473	0.003
Xing 2006 (31)	China (Asian)	PCR-RFLP	PB	65/71	62	3	0	127	3	67	4	0	138	4	0.028	0.807

Deans 2007 (32)	UK (Caucasian)	TaqMan	HB	197/224	71	83	43	225	169	79	101	44	259	189	0.421	0.257
Gatti 2007 (33)	Brazil (Mixed)	PCR-RFLP	HB	56/112	42	13	1	97	15	48	53	11	73	39	0.334	0.509
Crusius 2008 (34)	France (Caucasian)	PCR-RFLP	PB	243/1138	78	122	43	278	208	415	517	206	1347	929	0.408	0.044
Zhao 2010 (35)	China (Asian)	PCR-RFLP	NS	142/200	105	37	0	247	37	198	2	0	398	2	0.005	0.943
Pohjanen 2013 (36)	Finland (Caucasian)	PCR-RFLP	PB	56/179	14	34	8	62	50	37	86	56	160	198	0.553	0.706
Cao 2014 (37)	China (Asian)	NS	NS	162/162	72	62	28	206	188	87	59	16	233	91	0.280	0.210
Sampaio 2015 (38)	Portugal (Caucasian)	SSP-PCR	NS	50/50	17	25	8	59	41	19	25	6	63	37	0.370	0.608
Attar 2017 (39)	Iran (Asian)	SSP-PCR	HB	100/361	60	30	7	150	47	161	187	13	509	213	0.295	≤0.001

PCR: Polymerase Chain Reaction Restriction; PCR–RFLP: Polymerase Chain Reaction Restriction Fragment Length Polymorphism; CE: Primer extension and capillary electrophoresis; HB: Hospital Based; PB: Population Based; NS: Not stated; MAFs: Minor Allele Frequencies; HWE: Hardy-Weinberg Equilibrium; NA: Not Applicable.

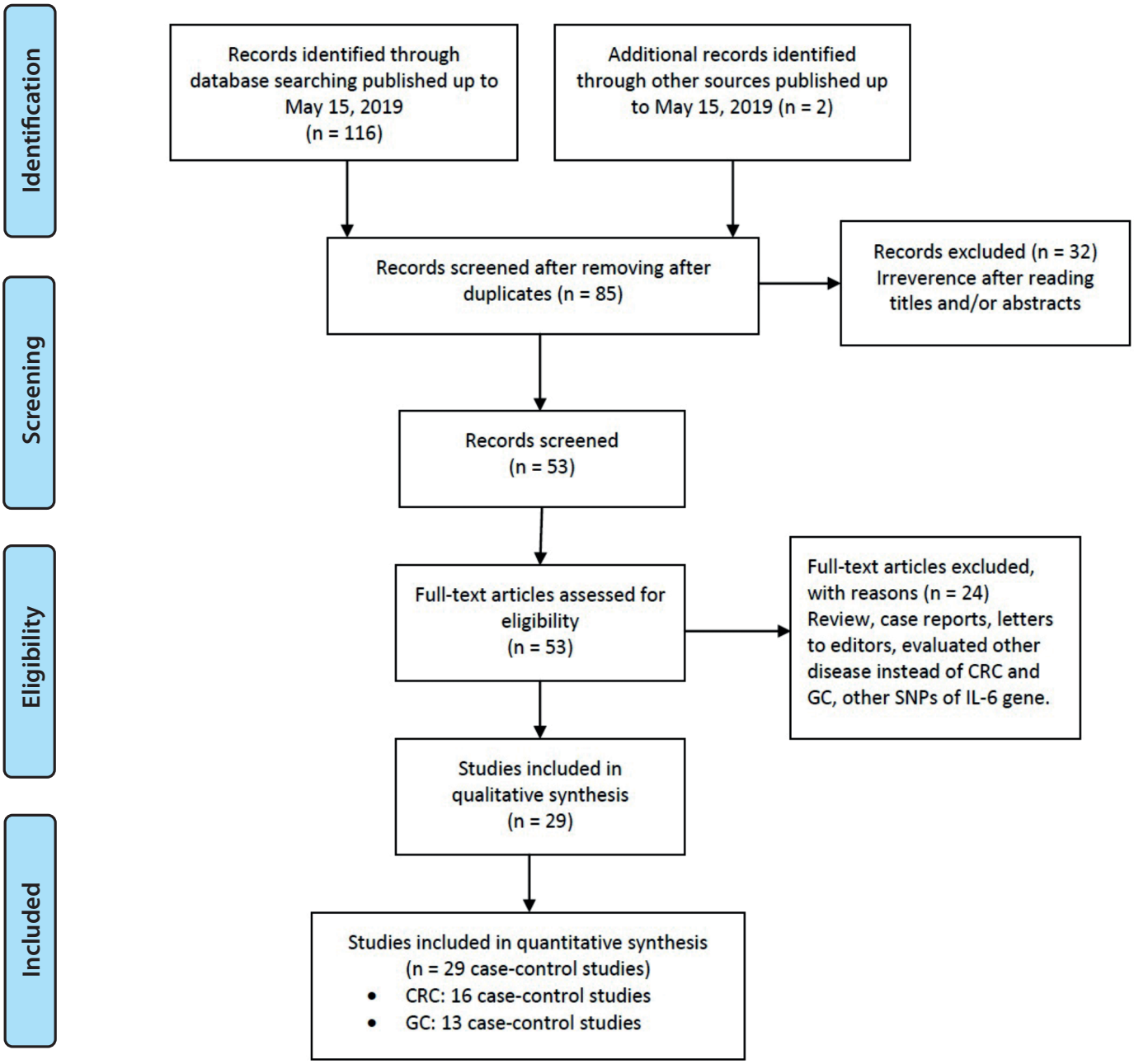

Fig. 1 The study selection and inclusion process.

7,560 cases and 9,574 controls were on CRC (12–27), and 13 studies with 1,445 cases and 2,918 controls were on GC (28–39). These included studies were published between 2003 and 2017. Twenty-two studies populations come from Caucasians, six studies were Asians, and only one from mixed populations. The genotype and allele distributions of the IL-6 –174 G>C polymorphism were shown in Table 1. Genotype distributions in the controls of all studies were in HWE except for five studies (Table 1).

QUANTITATIVE SYNTHESIS

IL-6 -174G>C Polymorphism and CRC

Table 2 shows the results of the association between IL-6 –174 G>C polymorphism and CRC risk. Overall, the pooled data showed that the IL-6 –174 G>C polymorphism was not significantly associated with an increased risk of CRC under all five genetic models, i.e., allele (C vs. G: OR = 1.028, 95% CI 0.936–1.128, p = 0.566), homozygote (CC vs. GG: OR = 1.068, 95% CI 0.902–1.263, p = 0.447), heterozygote (CG vs. GG: OR = 1.007, 95% CI 0.902–1.124, p = 0.904), dominant (CC+CG vs. GG: OR = 1.021, 95% CI 0.903–1.155, p = 0.737, Figure 2A), and recessive (CC vs. CG+GG: OR = 1.037, 95% CI 0.917–1.171, p = 0.564). When further analyzed by genotyping methods, we have not found a significant association between IL-6 –174 G>C polymorphism and CRC. However, subgroup analysis by source of controls showed a significant association between IL-6 –174 G>C polymorphism and risk of CRC under the homozygote model (CC vs. GG: OR = 1.273, 95% CI 1.042–1.556, p = 0.018) in population-based (PB) group studies.

IL-6 -174G>C Polymorphism and GC

Table 3 shows the results of the association between IL-6 –174 G>C polymorphism and GC risk. Overall, the pooled data showed that there was no significant association between IL-6 –174 G>C polymorphism and increased risk of GC under all five genetic models, i.e., allele (C vs. G:

Tab. 2 Meta-analysis results of association of IL-6 -174 G>C polymorphism with CRC risk.

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	C vs. G	Random	72.34	≤0.001	1.028	0.936–1.128	0.574	0.566	0.558	0.491
	CC vs. GG	Random	62.56	0.001	1.068	0.902–1.263	0.760	0.447	0.198	0.110
	CG vs. GG	Random	53.39	0.006	1.007	0.902–1.124	0.121	0.904	1.000	0.916
	CC+CG vs. GG	Random	67.49	≤0.001	1.021	0.903–1.155	0.336	0.737	0.964	0.781
	CC vs. CG+GG	Random	42.66	0.041	1.037	0.917–1.171	0.576	0.564	0.113	0.044
Genotyping Method										
TaqMan	C vs. G	Random	51.33	0.030	1.012	0.937–1.093	0.299	0.765	1.000	0.696
	CC vs. GG	Fixed	21.34	0.253	1.002	0.904–1.110	0.031	0.975	0.251	0.095
	CG vs. GG	Random	49.53	0.037	1.017	0.908–1.139	0.295	0.768	1.000	0.969
	CC+CG vs. GG	Random	56.96	0.013	1.018	0.907–1.143	v0.303	0.762	0.858	0.840
	CC vs. CG+GG	Fixed	0.00	0.746	0.988	0.900–1.086	–0.243	0.808	0.175	0.055
PCR-RFLP	C vs. G	Random	90.52	≤0.001	1.081	0.619–1.886	0.273	0.785	0.308	0.196
	CC vs. GG	Random	86.82	≤0.001	1.345	0.472–3.829	0.555	0.579	0.308	0.072
	CG vs. GG	Random	74.52	0.008	0.919	0.558–1.512	–0.333	0.739	0.734	0.603
	CC+CG vs. GG	Random	86.40	≤0.001	0.991	0.525–1.871	–0.028	0.978	0.734	0.565
	CC vs. CG+GG	Random	81.96	0.001	1.374	0.602–3.137	0.754	0.451	0.308	0.055
Source of Controls										
HB	C vs. G	Fixed	0.00	0.548	0.983	0.934–1.036	–0.636	0.525	0.474	0.102
	CC vs. GG	Fixed	0.00	0.572	0.971	0.872–1.080	–0.548	0.584	0.210	0.053
	CG vs. GG	Fixed	0.00	0.934	0.975	0.902–1.055	–0.621	0.534	0.591	0.503
	CC+CG vs. GG	Fixed	0.00	0.774	0.975	0.906–1.050	–0.668	0.504	0.720	0.241
	CC vs. CG+GG	Fixed	0.00	0.738	0.984	0.893–1.085	–0.320	0.749	0.107	0.032
PB	C vs. G	Random	70.12	0.018	1.097	0.899–1.338	0.911	0.362	1.000	0.721
	CC vs. GG	Fixed	21.43	0.280	1.273	1.042–1.556	2.364	0.018	1.000	0.096
	CG vs. GG	Random	74.65	0.008	1.089	0.796–1.490	0.532	0.595	0.734	0.602
	CC+CG vs. GG	Random	76.71	0.005	1.111	0.812–1.519	0.657	0.511	0.734	0.666
	CC vs. CG+GG	Fixed	0.00	0.400	1.139	0.950–1.365	1.407	0.159	1.000	0.267

CRC: colorectal cancer; PCR–RFLP: Polymerase Chain Reaction Restriction Fragment Length Polymorphism; HB: Hospital Based; PB: Population Based.

OR = 1.282, 95% CI 0.927–1.774, p = 0.134), homozygote (CC vs. GG: OR = 1.209, 95% CI 0.967–1.512, p = 0.096), heterozygote (CG vs. GG: OR = 1.097, 95% CI 0.736–1.634, p = 0.649), dominant (CC+CG vs. GG: OR = 1.117, 95% CI 0.759–1.644, p = 0.573), and recessive (CC vs. CG+GG: OR = 1.115, 95% CI 0.803–1.548, p = 0.517, Figure 2B). When further analyzed by ethnicity, we found a statistically significant association between IL-6 –174 G>C polymorphism and CRC risk under two genetic models i.e., homozygote (CC vs. GG: OR = 1.860, 95% CI 1.061–3.258, p = 0.030) and recessive (CC vs. CG+GG: OR = 1.941, 95% CI 1.131–3.331, p = 0.016) in Asians, but not in Caucasians.

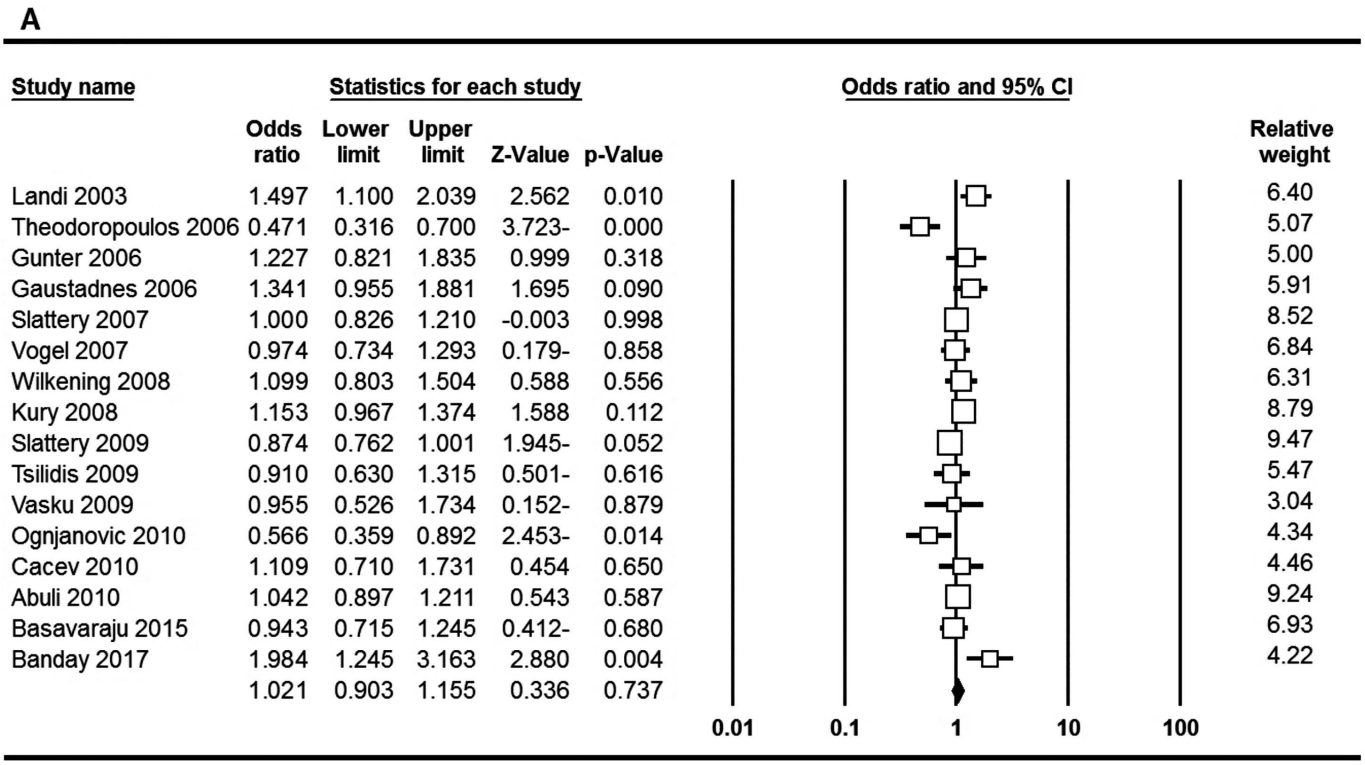

Fig. 2 Forest plot for association of IL-6 –174 G>C polymorphism with CRC and GC risk in random-effects model. A: CRC (dominant model: CC+CG vs. GG); B: GC (recessive model: CC vs. CG+GG).

Tab. 3 Meta-analysis results of association of IL-6 –174 G>C polymorphism with GC risk.

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	C vs. G	Random	86.50	≤0.001	1.282	0.927–1.774	1.499	0.134	0.731	0.561
	CC vs. GG	Random	43.05	0.071	1.209	0.967–1.512	1.666	0.096	0.858	0.646
	CG vs. GG	Random	80.63	≤0.001	1.097	0.736–1.634	0.456	0.649	0.631	0.527
	CC+CG vs. GG	Random	81.53	≤0.001	1.117	0.759–1.644	0.563	0.573	1.000	0.653
	CC vs. CG+GG	Random	52.05	0.027	1.115	0.803–1.548	0.649	0.517	1.000	0.956
Ethnicity										
Caucasian	C vs. G	Fixed	25.45	0.235	1.084	0.961–1.222	1.319	0.187	0.548	0.862
	CC vs. GG	Fixed	21.99	0.262	1.152	0.901–1.472	1.131	0.258	0.548	0.816
	CG vs. GG	Fixed	20.91	0.270	1.137	0.941–1.373	1.328	0.184	0.548	0.688
	CC+CG vs. GG	Fixed	0.00	0.466	1.182	0.988–1.413	1.832	0.067	1.000	0.833
	CC vs. CG+GG	Fixed	45.88	0.086	1.040	0.837–1.291	0.352	0.881	0.763	0.859
Asian	C vs. G	Random	94.58	≤0.001	2.618	0.739–9.277	1.491	0.136	0.734	0.797
	CC vs. GG	Fixed	0.00	0.529	1.860	1.061–3.258	2.168	0.030	NA	NA
	CG vs. GG	Random	91.58	≤0.001	1.752	0.471–6.517	0.837	0.403	1.000	0.421
	CC+CG vs. GG	Random	91.78	≤0.001	1.845	0.522–6.525	0.951	0.342	1.000	0.468
	CC vs. CG+GG	Fixed	0.00	0.925	1.941	1.131–3.331	2.407	0.016	NA	NA
Genotyping Method										
TaqMan	C vs. G	Fixed	0.00	0.604	1.148	0.968–1.362	1.584	0.113	1.000	0.616

	CC vs. GG	Fixed	0.00	0.677	1.304	0.931–1.828	1.542	0.123	0.296	0.475
	CG vs. GG	Random	70.75	0.033	1.159	0.692–1.940	0.559	0.576	0.296	0.032
	CC+CG vs. GG	Fixed	47.78	0.147	1.169	0.908–1.505	1.213	0.225	1.000	0.194
	CC vs. CG+GG	Fixed	13.27	0.316	1.207	0.896–1.624	1.239	0.215	1.000	0.821
PCR-RFLP	C vs. G	Random	82.35	≤0.001	1.327	0.728–2.420	0.925	0.355	0.452	0.517
	CC vs. GG	Random	68.86	0.022	0.616	0.206–1.844	−0.866	0.386	0.734	0.572
	CG vs. GG	Random	86.24	≤0.001	1.374	0.566–3.337	0.701	0.483	1.000	0.766
	CC+CG vs. GG	Random	87.81	≤0.001	1.321	0.531–3.289	0.598	0.550	1.000	0.817
	CC vs. CG+GG	Random	63.96	0.040	0.618	0.250–1.531	−1.039	0.299	1.000	0.657
Source of Controls										
HB	C vs. G	Fixed	32.59	0.217	0.919	0.750–1.125	−0.820	0.412	0.734	0.837
	CC vs. GG	Fixed	52.39	0.098	1.075	0.687–1.682	0.315	0.753	0.734	0.825
	CG vs. GG	Random	73.58	0.010	0.585	0.317–1.080	−1.714	0.086	0.734	0.925
	CC+CG vs. GG	Random	80.19	0.002	0.620	0.318–1.208	−1.405	0.160	0.734	0.898
	CC vs. CG+GG	Fixed	46.16	0.134	1.211	0.804–1.826	0.916	0.360	1.000	0.956
PB	C vs. G	Fixed	41.99	0.142	1.079	0.940–1.239	1.079	0.281	0.462	0.548
	CC vs. GG	Fixed	53.38	0.092	1.140	0.857–1.517	0.901	0.368	0.734	0.515
	CG vs. GG	Fixed	39.23	0.160	1.189	0.955–1.479	1.550	0.121	0.806	0.966
	CC+CG vs. GG	Fixed	10.90	0.344	1.255	0.995–1.508	1.917	0.055	0.806	0.697
	CC vs. CG+GG	Random	68.17	0.024	0.919	0.571–1.481	−0.346	0.730	0.308	0.496

GC: gastric cancer; PCR–RFLP: Polymerase Chain Reaction Restriction Fragment Length Polymorphism; HB: Hospital Based; PB: Population Based; NA: Not Applicable.

HETEROGENEITY ANALYSIS AND SENSITIVITY ANALYSIS

There was a significant heterogeneity under all five genetic models for both CRC and GC. As shown in tables 2 and 3, the I^2 decreased obviously and p-value exceeded 0.05 after excluding by source of controls for CRC and by ethnicity and source of controls for GC, indicating that ethnicity and source of controls are the major source of heterogeneity in this meta-analysis. Sensitivity analysis was performed by sequentially removing each study to examine the influence of the removed data to the overall ORs. No individual study significantly altered the pooled ORs. Moreover, by limiting the meta-analysis to those studies in accordance with HWE, the sensitivity analysis was performed in another way. However, the corresponding ORs were not substantially altered in comparisons, indicating that our results were relatively robust.

PUBLICATION BIAS

Begg's test and Egger's test were calculated to assess the publication bias of literatures. The shapes of the funnel

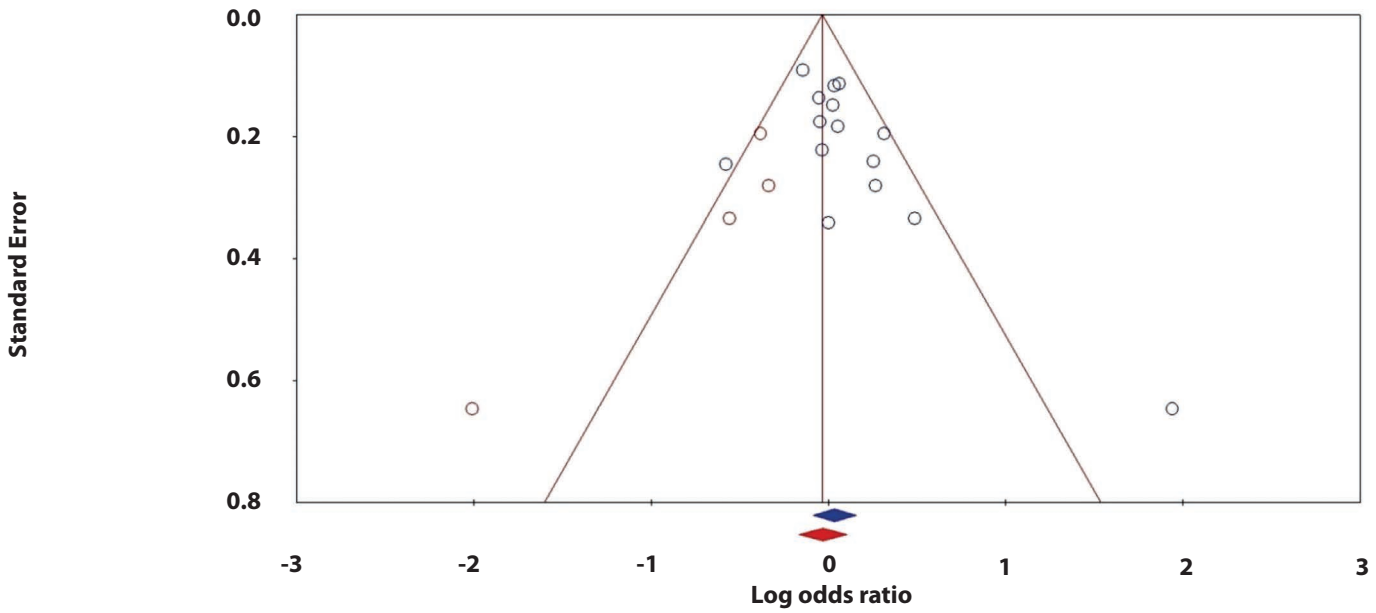

Fig. 3 Funnel plot for publication bias in the meta-analysis of IL-6 -174 G>C polymorphism with CRC under recessive model (CC vs. CG+GG). Blue line without and red line with trim and fill test.

plot did not reveal any publication bias for IL-6 polymorphism and GC risk under all five genetic models. In addition, No statistically significant difference was found in the Egger's test. However, there was a possible publication bias between IL-6 polymorphism and CRC risk under recessive model (P_{Beggs} = 0.113 and P_{Eggers} = 0.044). Therefore, we have used The Duval and Tweedie non-parametric "trim and fill" method to adjust publication bias. As shown in figure 3, meta-analysis with and without "trim and fill" did not draw different conclusion, suggesting that the results of synthetic analysis were robust.

DISCUSSION

To date, several case-control studies and meta-analyses have explored the association of IL-6 –174 G>C polymorphism on the susceptibility to CRC and GC. However, the small size, different genotyping methods and ethnicity, and the minor statistical power of the single epidemiological studies caused to the lack in consistency of those studies results. Thus, we did this meta-analysis to study the association of IL-6 –174 G>C polymorphism with susceptibility to CRC and GC. Our results suggested that the IL-6 –174G>C polymorphism was not significantly associated with increased risk of CRC and GC in overall population. In this meta-analysis, we found that similar mechanisms adapted by GC and CRC to development.

In the current meta-analysis based on 16 case-control available studies with 7,560 cases and 9,574 controls up to December 2018, our results indicated that there was no significant association between IL-6 –174G>C polymorphism and CRC risk. In 2013, Hu et al. performed a meta-analysis of eleven individual studies with 6,481 cases and 7,935 controls to evaluate the association of IL-6 –174G>C polymorphism with risk of CRC. Similarly, they have not found a significant association between IL-6 –174G>C polymorphism and CRC (9). In 2016, Wang et al., conducted a meta-analysis to explore the association of polymorphisms at IL-6/JAK/STAT3 pathway genes with CRC risk. Their results indicated that IL-6 –174G>C polymorphism (allele model: OR = 1.05, 95% CI = 1.00, 1.09) and JAK2 (recessive model: OR = 1.40, 95% CI = 1.15, 1.65) were significantly associated with increased risk of CRC. However, their results showed that the IL-6 –174G>C polymorphism was significantly associated with increased risk of CRC in Caucasians (40). Inconsistent with their results, our pooled data showed that the IL-6 –174G>C polymorphism did not significantly associated with increased risk of CRC in Caucasians.

Previously, the relationship between IL-6 –174 G>C polymorphism and GC risk has been systematically evaluated, but their results had been conflicting and controversial. In the current meta-analysis we found that the IL-6 –174G>C polymorphism was not significantly associated with increased risk of GC in overall. Recently, Wang et al., performed a meta-analysis to evaluate the association of IL-6 –174 G>C, -572 G>C and -597 G>A with GC risk (8). Their results showed that IL-6 polymorphisms were not associated with increased risk of GC. However, their results should be interpreted with caution due to the limited number of selected studies. Compared with their meta-analysis, we only focused on the association of IL-6 –174G>C polymorphism with GC, while they analyzed different polymorphisms at other interleukin genes, including IL-6 rs1800796, IL-8 rs4073, IL-10 rs1800871, IL-10 rs1800872 and IL-10 rs1800896 polymorphisms with GC risk up to May 2018. Moreover, we perfumed subgroup analysis by genotyping methods and source of controls. In the same year, Liu et al., have performed a met-analysis of 13 studies (1,446 cases and 2,918 controls) to explore the roles of polymorphisms at IL-2, IL-4, IL-6 and IL-8 genes with GC risk (41). Their results revealed that IL-6 –572C>G polymorphism was significantly associated with the risk of GC, but not IL-6 –174G>C polymorphism. Inconsistent with their results, we found a statistically significant association between IL-6 –174G>C polymorphism and GC risk in Asians under two genetic models i.e., homozygote (CC vs. GG: OR = 1.860, 95% CI 1.061–3.258, p = 0.030) and recessive (CC vs. CG+GG: OR = 1.941, 95% CI 1.131–3.331, p = 0.016).

Between-studies heterogeneity was demonstrated under all five genetic models for both CRC and GC, and we then conducted a subgroup analysis to explore the potential sources of heterogeneity, including ethnicity, source of controls, and genotyping methods. The results manifested that the heterogeneity could be mainly attributed by source of controls for CRC and by ethnicity and source of controls for GC. However, CRC and GC have a complex etiology and pathophysiology generated by the interaction of several genes and environmental factors (7, 42). Thus, besides the indeterminate number of characteristics that vary among studies, other confounding factors such as age, gender, lifestyle further contribute to between-study heterogeneity (43, 44). In addition, there was a publication bias across the selected studies in this meta-analysis. We suggested that the detected publication bias in a few studies could be attributed to relative small sample sizes in certain studies.

Though we included the latest data, several potential limitations must also be noticed in our meta-analysis. First, most of the selected studies were performed among Caucasians and Asians. Moreover, subgroup analysis based on ethnicity could not be assessed on CRC. Therefore, there was a lack of statistical power to better evaluate the association of IL-6 –174 G>C polymorphism with CRC and GC risk, especially in subgroup analysis. In addition, this bias may exist because the individuals may not be a full representative of the whole population. Thus, future studies with large sample sizes in different ethnicities are needed to determine the potential effects of ethnic variation on CRC and GC susceptibility. Second, our search results were restricted to publications in Chinese and English, other relevant published and unpublished studies, which are likely to have null results, were not included. Third, there was a significant publication bias in this meta-analysis under recessive model for CRC, which may be due to the small number of studies in the meta-analysis. Fourth, our meta- analysis was largely performed by unadjusted estimates, because of the limitations in selected studies that presented adjusted estimates. Finally, gene-gene and gene-environment interactions were not analyzed due to the lack of original data. It is possible that specific envi-

ronmental and lifestyle factors may alter the association of IL-6 –174 G>C polymorphism with CRC and GC risk.

In conclusion, our meta-analysis suggested that the IL-6 –174 G>C polymorphism was not significantly associated with increased risk of CRC and GC in overall population. However, subgroup analysis by ethnicity showed that IL-6 –174 G>C polymorphism might be associated with an increased risk of GC in Asians. Due to the limitations, studies with larger sample size and in different ethnicities are needed to confirm our results.

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