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
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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 I² statistics (P < 0.05). Additionally, the I²-value was applied to quantitatively evaluate the heterogeneity (I² < 25%, low heterogeneity; 25% ≤ I² ≤ 75%, moderate heterogeneity; I² > 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...
| Study          | Year | Location | Methodology | Population | n | AA  | AD  | AA  | AD  | AA  | AD  | MAFs | HWE  | NA  |
|---------------|------|----------|-------------|------------|----|-----|-----|-----|-----|-----|-----|------|------|-----|
| Deans 2007    | 32   | UK       | TaqMan      | Caucasian  | 197/224 | 71  | 83  | 43  | 225 | 169 | 79  | 101  | 44   | 259  | 189  | 0.421 | 0.257 |
| Gatti 2007    | 33   | Brazil   | PCR-RFLP    | Mixed      | 56/112 | 42  | 13  | 1   | 97  | 15  | 48  | 53   | 11   | 73   | 39   | 0.334 | 0.509 |
| Crusius 2008  | 34   | France   | PCR-RFLP    | Caucasian  | 243/1138 | 78  | 122 | 43  | 278 | 208 | 415 | 517  | 206  | 1347 | 929  | 0.408 | 0.044 |
| Zhao 2010     | 35   | China    | PCR-RFLP    | Mixed      | 142/200 | 105 | 37  | 0   | 247 | 37  | 198 | 2    | 0    | 398  | 2    | 0.005 | 0.943 |
| Pohjanen 2013 | 36   | Finland  | PCR-RFLP    | Caucasian  | 56/179 | 14  | 34  | 8   | 62  | 50  | 37  | 86   | 56   | 160  | 198  | 0.553 | 0.706 |
| Cao 2014      | 37   | China    | PCR-RFLP    | Mixed      | 162/162 | 72  | 62  | 28  | 206 | 188 | 87  | 59   | 16   | 233  | 91   | 0.280 | 0.210 |
| Sampaio 2015  | 38   | Portugal | SSP-PCR     | Caucasian  | 50/50  | 17  | 25  | 8   | 59  | 41  | 19  | 25   | 6    | 63   | 37   | 0.370 | 0.608 |
| Attar 2017    | 39   | Iran     | SSP-PCR     | Mixed      | 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), heterozygote (CG vs. GG: OR = 1.007, 95% CI 0.902–1.263, p = 0.447), dominant (CC+CG vs. GG: OR = 1.021, 95% CI 0.903–1.155, p = 0.737, Figure 2A), and recessive (CC vs. GG+CG: 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: OR = 1.068, 95% CI 0.902–1.263, p = 0.447), heterozygote (CG vs. GG: OR = 1.007, 95% CI 0.902–1.263, p = 0.447), dominant (CC+CG vs. GG: OR = 1.021, 95% CI 0.903–1.155, p = 0.737, Figure 2A), and recessive (CC vs. GG+CG: 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 GC. However, subgroup analysis by source of controls showed a significant association between IL-6 −174 G>C polymorphism and risk of GC 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.
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 |
|------------|---------------|---------------|---------------|------------|-----------------|
|            |               |               | P² (%) | P-value | OR | 95% CI | Z-stat | P-value | P_Begg | P_Egger |
| 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   |
There was a significant heterogeneity under all five genetic models for both CRC and GC. As shown in tables 2 and 3, the I² 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

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**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 I² 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

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**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 ($P_{Egger} = 0.113$ and $P_{Egger} = 0.044$). 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 −174 G>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 performed subgroup analysis by genotyping methods and source of controls. In the same year, Liu et al., have performed a meta-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-
IL-6 −174 G>C, Colorectal and Gastric Cancer

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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