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Lack of association between the interleukin 6 gene -174G>C polymorphism and colorectal cancer: evidence from a meta-analysis

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ABSTRACT. Interleukin 6 (*IL6*) is a pleiotropic cytokine involved in physiological processes and in a variety of human malignancies. It is thus a logical candidate for being a causative factor underlying colorectal cancer (CRC). The association between the *IL6* -174G>C polymorphism and CRC has been widely evaluated; yet, there is a lack of agreement between studies on the role of this polymorphism in CRC. We performed a meta-analysis to evaluate this association signal. Articles published before May 10, 2012 were included in the meta-analysis. A total of 11 populations incorporating 6481 cases and 7935 controls were included in our analysis. A random-effect model was applied irrespective of between-study heterogeneity. Data and study quality were assessed in duplicate. Overall, the association of the -174G>C polymorphism with CRC was not significant in an allelic comparison model [odds ratio (OR) = 0.99; 95% confidence interval

(95%CI) = 0.90-1.09; P = 0.827], a homozygote model (OR = 0.98; 95%CI = 0.83-1.15; P = 0.805), a dominant model (OR = 0.99; 95%CI = 0.87-1.13; P = 0.906), or a recessive model (OR = 0.97; 95%CI = 0.88-1.08; P = 0.610). Furthermore, the analyses of subgroups created based on common study design, genotyping methods, and ethnicity failed to find a significant association of this polymorphism with CRC. Therefore, our results collectively suggest that the *IL6* -174G>C polymorphism might not be a potential candidate for CRC risk.

Key words: Colorectal cancer; *IL6* gene; Polymorphism; Meta-analysis; Association signal

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers and one of the leading causes of cancer-related mortality in the world (Jemal et al., 2010). A strong genetic basis underlies CRC: a first-degree relative of a patient with sporadic CRC is twice as likely to develop this disease (Potter et al., 1993). However, the genetic determinants that contribute to the huge number of sporadic CRC cases remain unclear. Because of the increased risk of patients with inflammatory bowel disease of developing CRC, and the reduced risk of CRC in patients using non-steroidal anti-inflammatory drugs (NSAIDs) versus non-users (Collet et al., 1999; Smalley et al., 1999), chronic inflammation has been established as a risk factor for CRC (Rhodes and Campbell, 2002; Vagefi and Longo, 2005; Schottelius and Dinter, 2006). In light of the growing evidence for the role of inflammation in CRC, research into the role of genes known to be involved in inflammation in CRC is attracting widespread interest.

Interleukin 6 (*IL6*), a phosphorylated glycoprotein of 185 amino acids, is a pleiotropic cytokine involved in physiological processes and in a variety of human malignancies, including CRC. For example, *IL6* has been reported to promote the growth of colon cancer cells *in vitro* (Schneider et al., 2000). Through its angiogenic potency, *IL6* increases the invasiveness of colon cancer cells (Hsu and Chung, 2006), and likely promotes secondary tumor formation. Furthermore, several clinical studies have shown that the preoperative serum *IL6* level of CRC patients is higher than that of healthy controls (Kinoshita et al., 1999; Galizia et al., 2002; Chung and Chang, 2003). Higher *IL6* levels are associated with progressing tumor stages, increasing tumor size, metastasis, and decreased survival (Knupfer and Preiss, 2010). Therefore, the *IL6* gene is a logical candidate for potential causative factors of CRC. In particular, a promoter polymorphism, -174G>C in the *IL6* gene has been widely evaluated for association with CRC. Functional studies suggest that the -174G>C polymorphism influences transcription, with the GG genotype exhibiting lower *IL6* levels (Yeh et al., 2010).

Although some studies have attempted to link the *IL6* gene -174G>C polymorphism to CRC, the resulting data are often not reproducible. Therefore, to determine more precisely the role of this polymorphism in CRC, we conducted a meta-analysis to investigate the association of the *IL6* gene -174G>C polymorphism with the occurrence of CRC, while addressing between-study heterogeneity and publication bias.

MATERIAL AND METHODS

Strategy for the identification of studies

Studies were identified by searching the PubMed, EMBASE, and ISI Web of Knowledge databases for relevant articles published as of May 10, 2012. The search terms were expressed in Boolean combination, viz. (interleukin 6 OR *IL6* OR IL-6) AND (colon cancer OR rectal cancer OR colorectal cancer) AND (polymorphism OR allele OR genotype OR variant OR variation). Search results were restricted to human populations and articles written in the English language. The full texts of the retrieved articles and reviews were scrutinized to decide whether information on the topic of interest was included. The reference lists of original studies and review articles were also checked to ensure that relevant articles that were not initially identified were included in the meta-analysis. If more than one geographically or ethnically heterogeneous group was reported in any one article, each group was treated separately.

Inclusion/exclusion criteria

Studies were included if they had data on the *IL6* -174G>C genotype, estimated an odds ratio (OR) and its corresponding 95% confidence interval (95%CI), included a case-control design (retrospective or nested case-control), and involved CRC as an end point. Where there were multiple articles from the same study population, the most complete and recent results were extracted.

Extracted information

Data were collected by Z.T.W. and J.H. on *IL6* -174G>C genotype counts, case-control status, first author's last name, publication date, ethnicity of the populations studied, study design, and baseline characteristics of the study population. These data were entered into separate databases for comparison. Any encountered discrepancies were adjudicated by a discussion and a 100% consensus was reached.

Statistical analysis

We assessed the association of the *IL6* gene -174G allele with CRC relative to the -174C allele (allelic model), as well as in a homozygous contrast model (-174GG versus -174CC), a dominant model (-174GG plus -174GC versus -174CC) and a recessive model (-174GG versus -174CC plus -174GC). Unadjusted OR and 95%CI were used to compare alleles or genotypes between patients and controls. The random-effect model using the DerSimonian and Laird method was implemented to bring the individual effect-size estimates together, and the estimate of heterogeneity was taken from the Mantel-Haenszel model (Cohn and Becker, 2003).

Conformance of the -174G>C genotypes with Hardy-Weinberg equilibrium was calculated using the χ^2 test or the Fisher exact test in control groups. Possible heterogeneity between the results of individual studies or in groups defined by race or by study design or by type of CRC was assessed using the inconsistency index I^2 statistic (ranging from 0 to 100%) with higher values suggesting the existence of heterogeneity (Higgins and Thompson, 2002;

Higgins et al., 2003). In the case of between-study heterogeneity, we examined the study characteristics that could stratify the studies into subgroups with homogeneous effects.

The funnel plot and the Egger regression asymmetry test were used to examine publication bias. Probability less than 0.05 was judged significant except in the cases of the I^2 statistic and the publication Egger statistic, where a significance level of less than 0.1 was chosen. Data management and statistical analyses were performed using STATA version 11.0 for Windows (StataCorp, College Station, TX, USA).

RESULTS

Study characteristics

Based on the predefined subject terms, primary screening produced 90 potentially relevant articles, of which 11 met the inclusion criteria of attempting to evaluate the association of the *IL6* -174G>C polymorphism with CRC occurrence (Landi et al., 2003; Theodoropoulos et al., 2006; Slattery et al., 2007; Vogel et al., 2007; Kury et al., 2008; Wilkening et al., 2008; Slattery et al., 2009; Tsilidis et al., 2009; Vasku et al., 2009; Cacev et al., 2010; Abuli et al., 2011). Finally, a total of 6481 CRC patients and 7935 controls were analyzed.

Eight studies (Landi et al., 2003; Theodoropoulos et al., 2006; Vogel et al., 2007; Kury et al., 2008; Wilkening et al., 2008; Vasku et al., 2009; Cacev et al., 2010; Abuli et al., 2011) were of Caucasian populations, whereas 3 studies (Slattery et al., 2007, 2009; Tsilidis et al., 2009) were of mixed populations. A classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) genotyping assay was adopted in 3 studies (Theodoropoulos et al., 2006; Vasku et al., 2009; Cacev et al., 2010), while Taqman or other probe techniques were used in 8 studies (Landi et al., 2003; Slattery et al., 2007; Vogel et al., 2007; Kury et al., 2008; Wilkening et al., 2008; Slattery et al., 2009; Tsilidis et al., 2009; Abuli et al., 2011). Details of the selection process and the baseline characteristics of qualified studies are presented in Figure 1 and Table 1, respectively.

Quantitative analysis

As shown in Figure 2 and Table 2, overall, the *IL6* -174G>C polymorphism was not significantly associated with CRC in the allele comparison model (OR = 0.99; 95%CI = 0.90-1.09; P = 0.827), in the homozygote model (OR = 0.98; 95%CI = 0.83-1.15; P = 0.805), in the dominant model (OR = 0.99; 95%CI = 0.87-1.13; P = 0.906), or in the recessive model (OR = 0.97; 95%CI = 0.88-1.08; P = 0.610).

We also failed to find significant association in Caucasian or mixed populations stratified by ethnicity. Moreover, significantly increased risk was not found for any genetic model in the analyses performed by stratifying the study population by source of controls and genotyping methods.

Publication bias

As reflected by the funnel plots (Figure 3) and the Egger test, there was a low probability of publication bias for the *IL6* -174G>C polymorphism (P = 0.989).

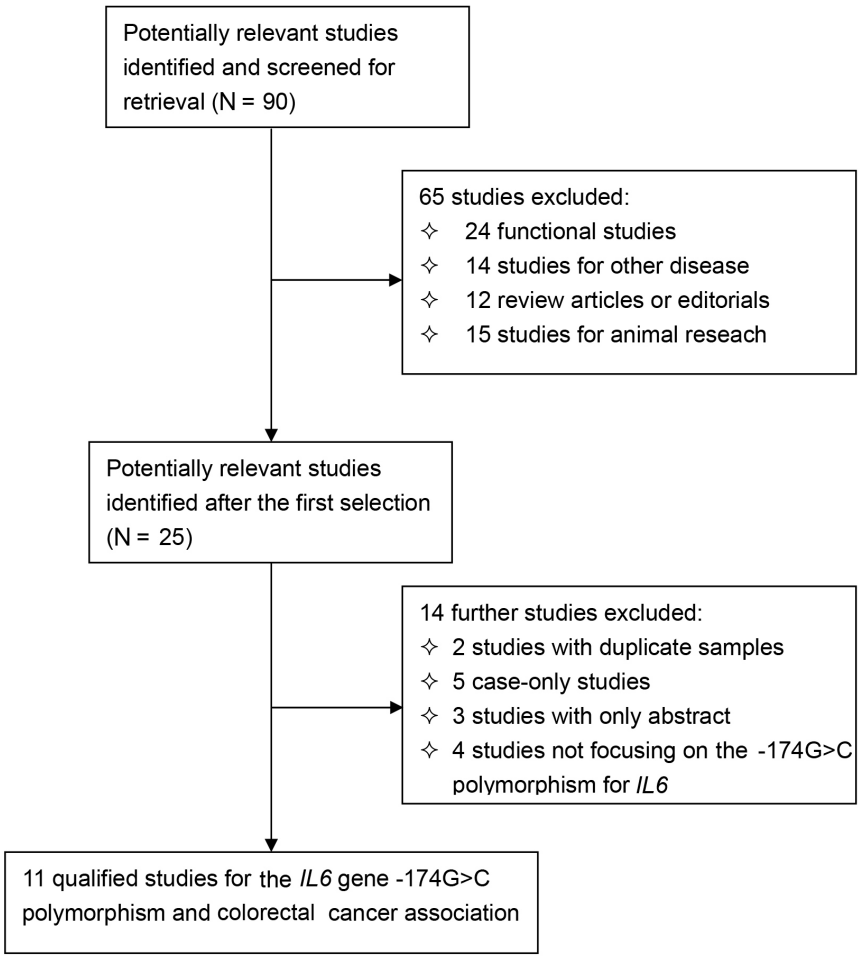

Figure 1. Flow diagram of search strategy and study selection.

Table 1. Baseline characteristics of all eligible studies.

Study	Year	Area (ethnicity)	Genotyping methods	Study design	Case			Control		
					GG	GC	CC	GG	GC	CC
Landi et al.	2003	Spain (C)	Taqman	Population	133	180	48	145	133	33
Theodoropoulos et al.	2006	Greece (C)	PCR-RFLP	Not available	111	76	35	64	86	50
Slattery et al.	2007	USA (M)	Taqman	Hospital	321	347	109	411	438	146
Vogel et al.	2007	Denmark (C)	Probe	Hospital	98	168	89	204	364	185
Wilkening et al.	2008	Sweden (C)	Taqman	Hospital	79	163	61	162	297	121
Kury et al.	2008	France (C)	Taqman	Population	363	489	171	435	504	182
Slattery et al.	2009	USA (M)	Taqman	Hospital	631	696	246	728	897	347
Tsilidis et al.	2009	USA (M)	Taqman	Hospital	68	93	39	113	170	71
Vasku et al.	2009	Czech (C)	PCR-RFLP	Not available	33	47	22	31	48	22
Cacev et al.	2010	Croatia (C)	PCR-RFLP	Hospital	64	70	26	68	75	17
Abuli et al.	2011	Spain (C)	Taqman	Hospital	586	635	184	593	623	172

C = Caucasian; M = mixed.

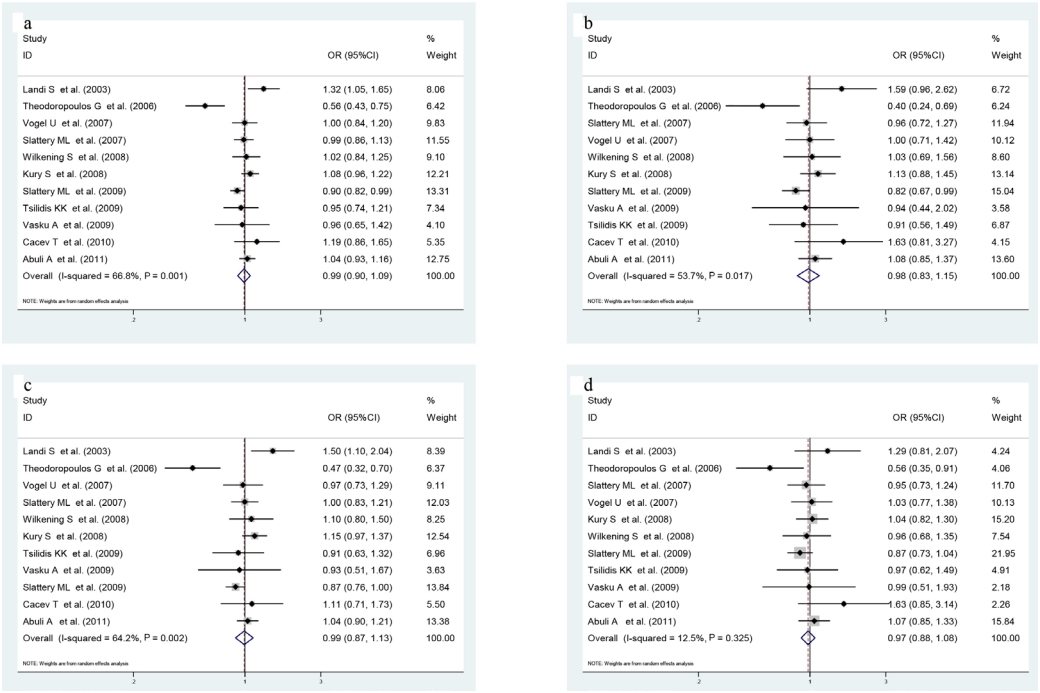

Figure 2. Overall risk estimates of the *IL6* gene -174G>C polymorphism for colorectal cancer: the combined results based on all studies showed that there was no statistically significant link between the *IL6* gene -174G>C polymorphism and colorectal cancer susceptibility in allele model (**a**), homozygote model (**b**), dominant model (**c**), as well as recessive model (**d**).

Table 2. Subgroup analysis of the *IL6* gene -174G>C polymorphism and colorectal cancer.

Variables	Allele contrast		Homozygote model		Dominant model		Recessive model	
	OR (95%CI); P	I^2 ($P_{\chi 2}$)	OR (95%CI); P	I^2 ($P_{\chi 2}$)	OR (95%CI); P	I^2 ($P_{\chi 2}$)	OR (95%CI); P	I^2 ($P_{\chi 2}$)
Total	0.99 (0.90-1.09); 0.827	66.8% (0.001)	0.98 (0.83-1.15); 0.805	53.7% (0.017)	0.99 (0.87-1.13); 0.906	64.2% (0.002)	0.97 (0.88-1.08); 0.610	12.5% (0.325)
Descent of populations								
Caucasians	1.01 (0.89-1.15); 0.873	71.0% (0.001)	1.03 (0.82-1.29); 0.797	59.0% (0.017)	1.02 (0.85-1.22); 0.839	68.8% (0.002)	1.02 (0.88-1.17); 0.794	23.3% (0.243)
Mixed	0.93 (0.86-1.00); 0.050	0.0% (0.538)	0.86 (0.74-1.01); 0.062	0.0% 0.662	0.91 (0.82-1.02); 0.097	0.0% (0.529)	0.90 (0.78-1.04); 0.141	0.0% (0.816)
Source of controls								
Hospital-based	0.98 (0.92-1.03); 0.390	0.0% (0.423)	0.95 (0.85-1.07); 0.421	0.0% (0.428)	0.97 (0.90-1.05); 0.440	0.0% (0.634)	0.97 (0.87-1.07); 0.545	0.0% (0.574)
Population-based	1.17 (0.97-1.40); 0.105	54.7% (0.137)	1.24 (0.92-1.69); 0.161	30.1% (0.232)	1.27 (0.99-1.63); 0.057	51.9% (0.149)	1.08 (0.88-1.33); 0.463	0.0% (0.408)
Not available	0.72 (0.43-1.22); 0.225	79.1% (0.029)	0.59 (0.26-1.34); 0.205	68.2% (0.076)	0.64 (0.33-1.23); 0.179	71.1% (0.063)	0.71 (0.41-1.22); 0.216	44.6% 0.179
Genotyping methods								
Taqman or probe	1.02 (0.95-1.09); 0.673	45.6% (0.075)	1.00 (0.89-1.13); 0.964	20.7% (0.265)	1.04 (0.93-1.15); 0.496	48.5% (0.059)	0.98 (0.89-1.08); 0.673	0.0% (0.776)
PCR-based	0.86 (0.53-1.38); 0.531	84.3% (0.002)	0.83 (0.35-1.97); 0.671	80.4% (0.006)	0.77 (0.44-1.36); 0.373	77.0% (0.013)	0.94 (0.50-1.78); 0.844	70.8% (0.033)

OR = odds ratio; CI = confidence interval.

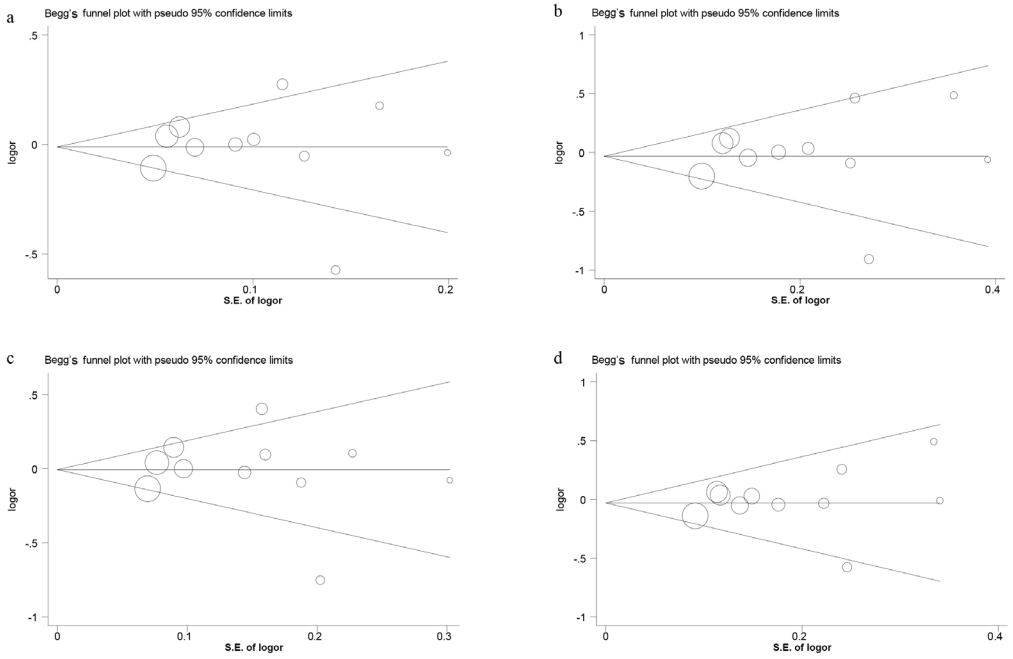

Figure 3. Begg's funnel plot of publication bias test for the *IL6* gene -174G>C polymorphism. As reflected by the funnel plots, there was no significant publication bias exiting for the *IL6* gene -174G>C polymorphism in allele model (**a**), homozygote model (**b**), dominant model (**c**), as well as recessive model (**d**).

DISCUSSION

This study consisting of 14,416 subjects from 11 populations is the first meta-analysis, to the best of our knowledge, to examine the relationship between the *IL6* -174G>C polymorphism and CRC. Although the between-study heterogeneity, albeit disturbing, could not be easily eliminated, our results suggest that the *IL6* -174G>C polymorphism might not be a potential candidate for the development of CRC. Furthermore, a low probability of publication bias makes our results more robust.

Genetic heterogeneity is an inevitable problem in any disease identification strategy (Hemminki et al., 2006). As shown in this study, we speculated that the *IL6* -174G>C polymorphism might have different roles across different ethnic populations. In our subgroup analyses for data stratified by ethnicity, *IL6* -174C in Caucasians being completely at odds with that in Mixed descendents, for comparison of allele -174G versus -174C generated a weakly and non-significant protective effect in Mixed population, but a non-significant risk effect in Caucasians, suggesting that this polymorphism might have a pleiotropic role in the pathogenesis of CRC or interact with other genetic and environmental factors. According to a recent large size study, both the *IL6* rs1800796 and rs1800795 polymorphisms were found to significantly interact with current use of aspirin/NSAIDs to alter risk of colon cancer. Individuals with a C allele at either SNP who were also current users of aspirin/NSAIDs had the lowest risk for developing colon cancer in the population studied. CRC risk was also associated with

an interaction between vitamin D receptor and *IL6* genotypes that was modified by current use of aspirin/NSAIDs (Slattery et al., 2007).

Different genetic backgrounds in different populations may cause this difference in association signal across populations or different populations may have different linkage disequilibrium (LD) patterns. A polymorphism may be in LD with another nearby causal variant in one ethnic population but not in another (Yu et al., 2010). The *IL6* -174G>C polymorphism may be in LD with different nearby causal variants in different populations. In view of the divergent genetic backgrounds, it is necessary to construct a database of polymorphisms related to CRC in each ethnic group. A recent study indicated that nearby polymorphic sites at -597, -572, and -373 might affect the activity of the *IL6* promoter and govern the impact of the polymorphism at position -174 (Terry et al., 2000), suggesting a complex regulatory network governing *IL6* gene expression. Therefore, more comprehensive haplotype-based or multiple SNP-based approaches instead of a single polymorphism-based strategy may provide precise information on the genetic contribution of *IL6* to CRC etiology.

In addition to population differences that may affect our meta-analysis, the use of different study designs across reports may also affect our results. Our results indicated that the magnitude of association was potentially reversed in population-based studies relative to hospital-based studies, although this trend was not statistically significant. In this regard, we reiterate that controlling for population stratification remains an important consideration in hospital-based studies (Salanti et al., 2005). During the course of this meta-analysis, we observed that several studies recruited subjects from a single hospital, thus narrowing the study population to a narrow socioeconomic profile. Moreover, in hospital-based studies, poor comparability between cases and controls might exert a confounding effect on association due to geographic specificities of the disease under study and differential hospitalization rates between cases and controls (Ruano-Ravina et al., 2008). In contrast, subjects drawn from a larger community or a fixed group might be more representative of the true population, leading us to believe that results from population-based studies might be more reliable. Considering the wide confidence intervals of estimates in some genetic models, more studies are required to quantify the effect size for *IL6* -174 G>C reliably.

Despite the clear strengths of our study, including relatively large sample sizes and a low probability of publication bias, it should be interpreted in light of several technical limitations. Since only published studies were retrieved in this meta-analysis and the "grey" literature (articles in languages other than English) was not included, publication bias might be possible even though our funnel plots and statistical tests did not find bias. Moreover, the single-locus-based nature of this meta-analysis precluded the possibility of studying gene-gene and gene-environment interactions, as well as haplotype-based effects, suggesting that additional studies assessing these aspects will be necessary. Furthermore, we only focused on the *IL6* -174G>C polymorphism, and did not study other genes or polymorphisms. It seems likely that the -174G>C polymorphism individually makes only a moderate contribution to CRC risk. However, the question of whether the contribution of this polymorphism may be higher when integrated with other risk factors requires additional research. Thus, conclusions on the role of *IL6* in CRC must not be drawn until large, well-performed studies can either confirm or refute our results.

In conclusion, we expand on results from previous individually underpowered studies and suggest that the *IL6* -174G>C polymorphism might not be an independent candidate for

the development of CRC. In addition, our observations leave open the question of the heterogeneous effects of the *IL6* -174C allele across different ethnic populations. Nevertheless, for practical reasons, we hope that this study will not remain just another endpoint of research, but will instead serve as a beginning to establish background data for further investigation into the association of the *IL6* gene with CRC.

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