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Association of the interleukin-6 gene -572G/C polymorphism with cancer risk: a meta-analysis

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ABSTRACT. The -572G/C polymorphism in interleukin-6 (*IL-6*) gene is associated with the development of cancer. However, previous studies have shown conflicting results; therefore, the association must be verified by an appropriate meta-analysis. For this purpose, we performed a literature search of the PubMed database to identify all reports on association between the *IL-6* -572G/C polymorphism and cancer risk. Summary odds ratios (OR) and 95% confidence intervals (95%CI) were calculated for the -572G/C polymorphism and cancer in a fixed- and random-effect model, as appropriate. Publication bias was evaluated using the Begg's funnel plot. The meta-analysis was performed on the STATA (v.12.0) software. Seven studies, which analyzed 3387 cases and 4529 controls, were identified. The results of the meta-analysis showed no significant association between the -572G/C polymorphism in the *IL-6* gene and cancer risk (GG *vs* CC: OR = 1.03, 95%CI = 0.76-1.40; GG *vs* CG: OR = 0.94, 95%CI = 0.82-1.09; dominant model: OR = 1.06, 95%CI = 0.92-1.21; recessive model: OR = 1.01, 95%CI = 0.86-1.18). The data were subjected to a subgroup analysis (stratified by race and cancer type), and no significant associations were

found between the -572G/C polymorphism in the *IL-6* gene and cancer risk. Therefore, the results of this meta-analysis suggested that the *IL-6* -572G/C polymorphism was not associated with an elevated risk of cancer.

Key words: Interleukin-6; Cancer risk; Polymorphism

INTRODUCTION

Cancer is one of the most common causes of death worldwide, and is a serious problem to global health (Carter et al., 2014). GLOBOCAN estimated that approximately 12.7 million new cases of cancer and 7.6 million cancer-related deaths occurred in 2008 (Jemal et al., 2011). Despite the efforts of several researchers towards elucidating the mechanism of carcinogenesis, this process remains unclear so far. A variety of risk factors contribute to cancer, including alcohol consumption, cigarette smoking, obesity, occupational exposure, a family history of cancer, and diet (Marron et al., 2010). However, a majority of the individuals exposed to these environmental factors never develop cancer, while cancer has been shown to develop in individuals who do not exhibit any of these known risk factors, suggesting genetic susceptibility to be a more significant indication of individual cancer risk.

Interleukin-6 (IL-6) is a multifunctional cytokine produced by immune, as well as some non-immune, cells; this functions both as an inflammatory mediator and a regulator of endocrine and metabolic function (Basso et al., 1996). Elevated expression of IL-6 and its major effector, signal transducer and activator of transcription-3 (STAT3), affects different stages of cancer development, including initiation, promotion, malignant conversion, invasion, and metastasis (Grivennikov et al., 2009). The *IL-6* gene is located on chromosome 7p21, and is composed of five exons, four introns, and a proximal promoter region (Bowcock et al., 1988). A number of studies have indicated that the presence of a G/C single nucleotide polymorphism (SNP) at the promoter -572 region of the *IL-6* gene (-572G/C), one of the numerous known polymorphisms in the *IL-6* gene, is related to the *IL-6* transcription rate and, as a consequence, controls the circulating IL-6 levels (Kitamura et al., 2002).

The potential association of the *IL-6* gene -572G/C polymorphism with the risk of cancer has been explored in many studies. However, the results are controversial and are not considered conclusive. These inconsistencies could partly be attributed to the insufficient power of the studies, the minimal effect of the polymorphism on cancer risk, and false-positive results. In this study, we attempted to clarify the associations between the *IL-6* gene -572G/C polymorphism and cancer risk through a meta-analysis, performed by collecting and sorting through previously published studies.

MATERIAL AND METHODS

Search strategies

A systematic literature search of the PubMed database helped identify the available related clinical studies. All search queries were updated up to December 2014 using the following key words: “IL-6”, “-572G/C”, “polymorphism”, and “cancer”. In addition, the reference lists of the included articles and relevant meta-analyses were manually searched. Studies reported by the same authors were checked for possible overlapping participant groups.

Inclusion and exclusion criteria

The studies were enrolled in the meta-analysis based on conformance to the following

inclusion criteria: 1) case-control studies; 2) studies assessing the association of the *IL-6* gene -572G/C polymorphism with cancer risk; 3) studies that provided sufficient information for estimating the odds ratio (OR) with 95% confidence interval (95%CI); 4) studies providing sufficient data to acquire the genotype frequency of the *IL-6* gene -572 G/C polymorphism. The major exclusion criteria were: 1) exclusion of a control population; 2) no available genotype frequency; and 3) duplicated studies.

Data extraction

We followed a standard protocol for the data extraction. The following data was collected from each study: first author, year of publication, area, race, source of cases and controls, number of cases and controls, samples, polymorphisms, genotype frequency, and evidence of Hardy-Weinberg equilibrium (HWE) in the controls. In cases where the original genotype frequency data was unavailable, additional data was obtained from the corresponding author of the relevant articles. For conflicting evaluations, an agreement was reached following a discussion.

Statistical analysis

The strength of associations between the *IL-6* gene -572G/C polymorphism and cancer risk was assessed by calculating the pooled OR and 95%CI, respectively, using four genetic models: homozygote comparison (GG *vs* CC), heterozygote comparison (GG *vs* CG), the dominant (CC + CG *vs* GG), and recessive (GG + CG *vs* CC) models between groups. Between-study heterogeneities were estimated using the I^2 test. I^2 represents the variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. A significant $I^2 > 50\%$ indicated heterogeneity across studies; in such cases, the random-effect model was used for meta-analysis. The fixed-effect model was used for all other cases. The sensitivity analysis was performed by removing those studies included in the meta-analysis whose genotype distributions in the control groups deviated from the HWE. Publication bias was investigated by the Begg's funnel plot; $P < 0.05$ was considered to be a statistically significant publication bias. Meta-analysis was performed using the STATA statistical software package (v.12.0; Stata Corporation, College Station, TX, USA).

RESULTS

Study characteristics

Six publications were identified based on the previously mentioned search criteria (Park et al., 2003; Slattery et al., 2007; Falleti et al., 2009; Kang et al., 2009; Tsilidis et al., 2009; Qu et al., 2014). One of these reported 2 case-control studies (Slattery et al., 2007); therefore, 7 studies were included in the final meta-analysis. The flow chart detailing the study selection criteria is presented in Figure 1; the meta-analysis included 3387 cases and 4529 controls. The included studies were published between 2003 and 2014. All articles were written in English. The conformance of the genotype distribution of all controls to the HWE was analyzed; all controls were in HWE ($P > 0.05$), except those included in the studies conducted by Slattery et al. (2007) and Tsilidis et al., 2009. Four studies were conducted in Europe (Slattery et al., 2007; Falleti et al., 2009; Tsilidis et al., 2009),

and three in Asia (Park et al., 2003; Kang et al., 2009; Qu et al., 2014). Three of these studies were concerned with colorectal cancer (CRC), two analyzed hepatocellular carcinoma (HCC), and one each was concerned with the expression of IL-6 in gastric cancer (GC) and nasopharyngeal cancer (NPC). All studies presented the numbers of the GG, CG, and CC genotypes separately. The main features of the studies included in this meta-analysis are presented in Table 1.

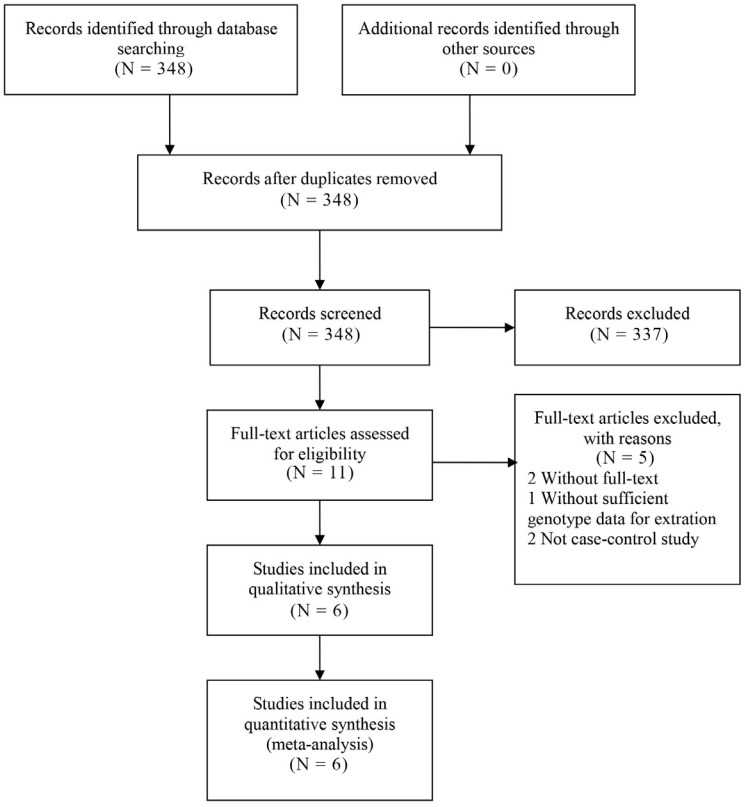

Figure 1. Flow chart of the studies included in the meta-analysis.

Table 1. Characteristics of the studies included for meta-analysis.

Study	Area	Race	Cancer type	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test
					GG	CG	CC	GG	CG	CC	
Park et al. (2003)	Korea	Asians	HCC	221/475	1	92	117	32	169	274	0.40
Slattery et al. (2007)	USA	Caucasians	CRC	1579/1977	1387	187	5	1719	247	11	0.51
Slattery et al. (2007)	USA	Caucasians	CRC	794/1005	648	124	22	863	119	23	0.00
Konstantinos et al. (2009)	USA	Caucasians	CRC	201/362	180	19	2	329	30	3	0.02
Falleti et al. (2009)	Italy	Caucasians	HCC	66/153	57	9	0	135	17	1	0.57
Kang et al. (2009)	Korea	Asians	GC	332/326	21	133	178	17	140	169	0.08
Qu et al. (2014)	China	Asians	NPC	194/231	22	79	93	20	110	101	0.19

HWE = Hardy-Weinberg equilibrium; CRC = colorectal cancer; GC = gastric cancer; HCC = hepatocellular carcinoma; NPC = nasopharyngeal cancer.

Meta-analysis results

The association between the -572G/C polymorphism in the *IL-6* gene and cancer risk, and the results of the heterogeneity test are shown in Table 2. The combined results of all studies showed that variant genotypes were not associated with increased risk of HCC in different genetic models (GG *vs* CC: OR = 1.03, 95%CI = 0.76-1.40; GG *vs* CG: OR = 0.94, 95%CI = 0.82-1.09; dominant model: OR = 1.06, 95%CI = 0.92-1.21; recessive model: OR = 1.01, 95%CI = 0.86-1.18). Furthermore, subgroup analyses were performed to explore the effect of ethnicity and cancer type on cancer risk. No significant associations were observed in Asians and Caucasians when stratified according to ethnicity (Figure 2). Furthermore, the *IL-6* gene -572G/C polymorphism was not associated with HHC and CRC risk when stratified according to the cancer type (Figure 3).

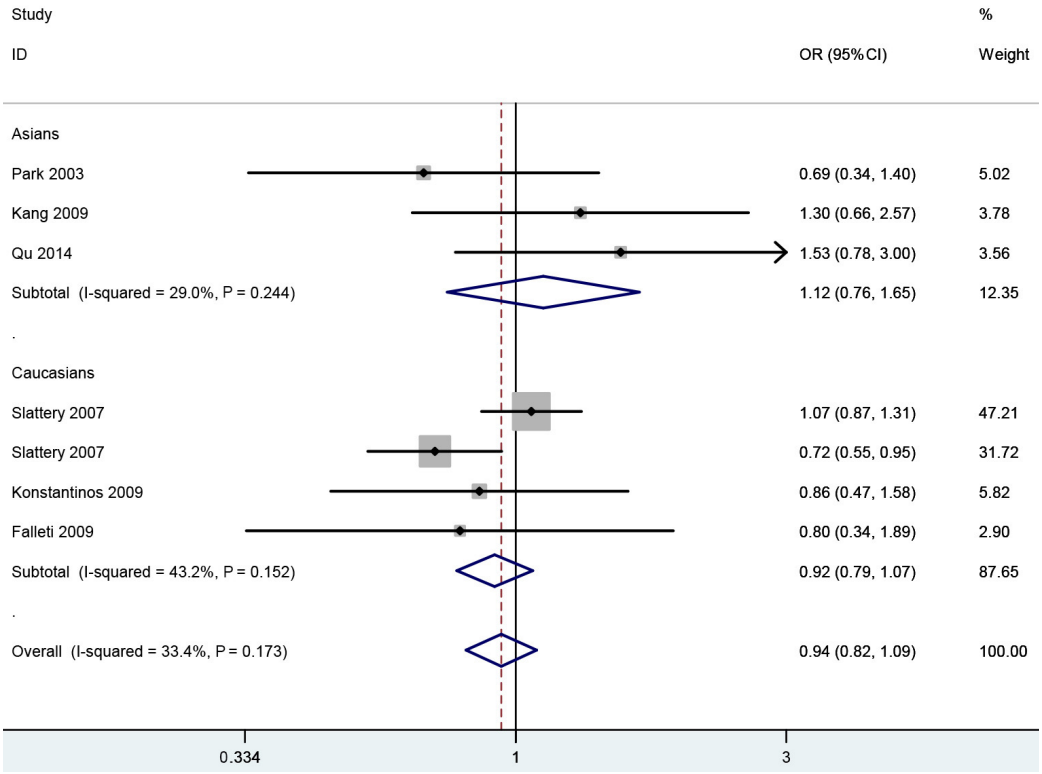

Figure 2. Forest plot of cancer cases associated with the -572G/C polymorphism in the *IL-6* gene, in the analyses stratified by race (GG *vs* CG).

Sensitivity analysis

The sensitivity of this meta-analysis was determined by omitting non-HWE studies; the results of the analysis remained unaltered, indicating that the results were statistically significant (Table 2).

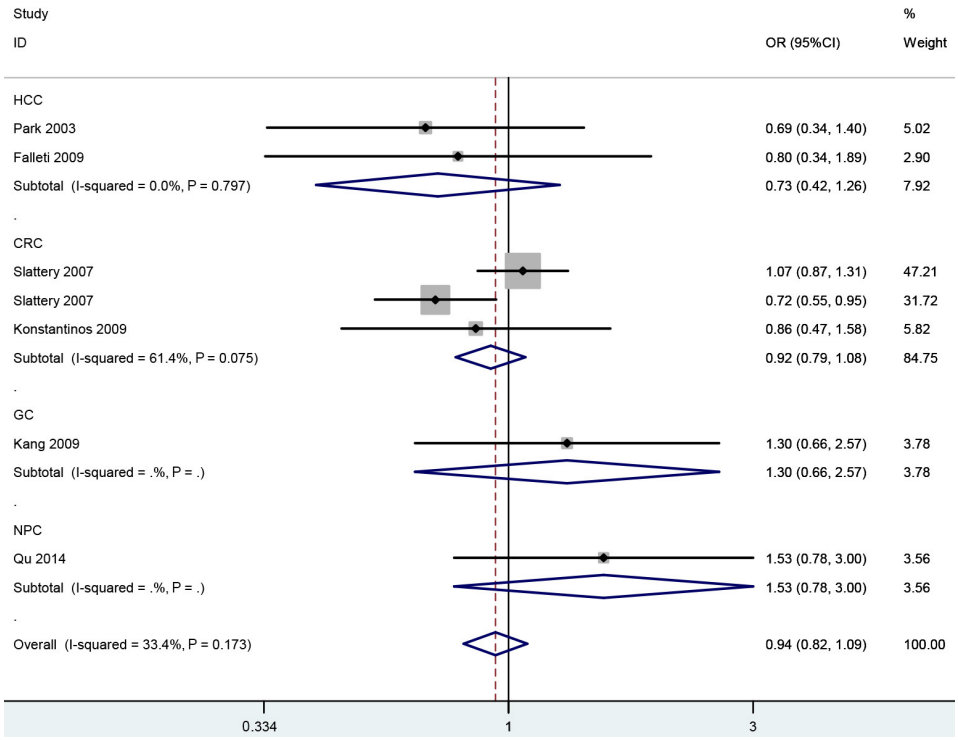

Figure 3. Forest plot of cancer cases associated with the *IL-6* gene -572G/C polymorphism, in the analyses stratified by cancer type (GG *vs* CG).

Table 2. Summary of different comparative results.

Variables	N	GG vs CC			GG vs CG			Dominant model			Recessive model		
		OR (95%CI)	I^2	P	OR (95%CI)	I^2	P	OR (95%CI)	I^2	P	OR (95%CI)	I^2	P
Total	7	1.03 (0.76-1.40)	0.0%	0.88	0.94 (0.82-1.09)	33.4%	0.17	1.06 (0.92-1.21)	25.4%	0.24	1.01 (0.86-1.18)	0.0%	0.92
Ethnicity													
Asians	3	1.08 (0.73-1.59)	0.0%	0.79	1.12 (0.76-1.65)	29.0%	0.24	0.91 (0.62-1.32)	0.0%	0.51	0.99 (0.84-1.17)	0.0%	0.58
Caucasians	4	0.96 (0.59-1.56)	0.0%	0.62	0.92 (0.79-1.07)	43.2%	0.15	1.08 (0.93-1.25)	49.2%	0.12	1.19 (0.71-1.98)	0.0%	0.92
Cancer type													
HHC	2	0.89 (0.45-1.76)	0.0%	0.83	0.73 (0.42-1.26)	0.0%	0.80	1.23 (0.72-2.10)	0.0%	0.91	1.11 (0.85-1.45)	0.0%	0.84
CRC	3	0.96 (0.58-1.56)	0.0%	0.41	0.89 (0.66-1.19)	61.4%	0.08	1.12 (0.83-1.51)	65.9%	0.05	1.18 (0.70-1.98)	0.0%	0.78
HWE													
Yes	5	1.15 (0.80-1.65)	0.0%	0.87	1.06 (0.89-1.27)	0.0%	0.50	0.93 (0.78-1.10)	0.0%	0.79	1.00 (0.85-1.18)	0.0%	0.74
No	2	0.79 (0.45-1.38)	0.0%	0.96	0.74 (0.58-0.95)	0.0%	0.59	1.33 (1.06-1.68)	0.0%	0.61	1.06 (0.59-1.93)	0.0%	0.91

N = number; I^2 = inconsistency index; CI = confidence interval; OR = odds ratio; HHC = hepatocellular carcinoma; CRC = colorectal cancer; HWE = Hardy Weinberg equilibrium.

Publication bias

The shape of the funnel plots did not reveal any evidence of the obvious asymmetry of the genetic models in the overall meta-analysis. The Begg's test did not reveal any significant evidence of publication bias for any of the genetic models (Figure 4).

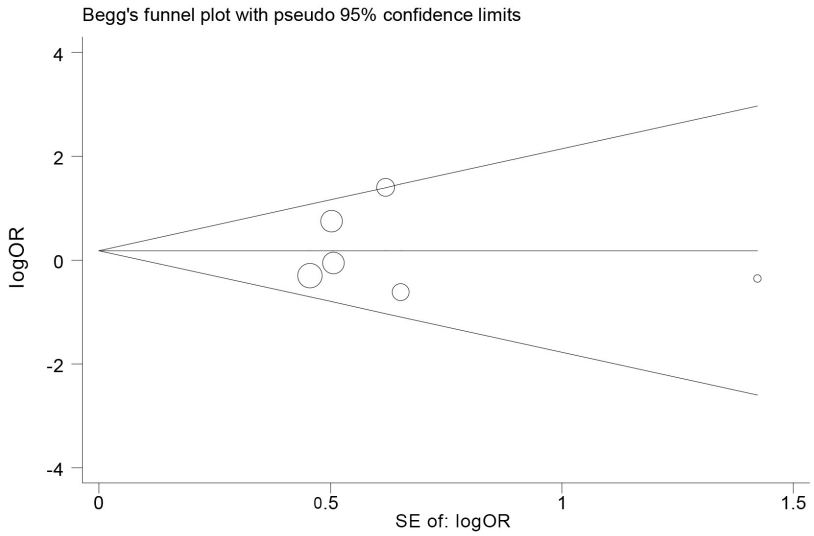

Figure 4. Begg's funnel plot test of publication bias for the association between the *IL-6* gene -572G/C polymorphism and cancer risk (GG *vs* CG).

DISCUSSION

Cancer is currently one of the leading causes of mortality worldwide. However, the mechanism of carcinogenesis has not been fully understood. Genetics and environmental factors are widely accepted as factors contributing to cancer susceptibility and outcome. IL-6 is a confirmed pleiotropic pro-inflammatory cytokine associated with cardiovascular diseases. Elevated expression of IL-6 and its major effector have been implicated in the different stages of cancer development, including initiation, promotion, malignant conversion, invasion, and metastasis (Walter et al., 2009). Several recent studies have focused on the association between the *IL-6* gene -572G/C polymorphism and cancer. However, single case-control studies with small sample sizes may have weak statistical power, thereby interfering with the precision of results (that is, false-positive or false-negative findings) (Lohmueller et al., 2003). Here, we have performed a meta-analysis of published studies to evaluate the association between the *IL-6* gene -572G/C polymorphism and risk of cancer; this is the first such analysis that has been reported to date.

This meta-analysis of 7 studies, comprising 3387 cases and 4529 controls, systematically evaluated the association between the *IL-6* gene -572G/C polymorphism and cancer risk. The results suggested the lack of a significant association between the -572G/C polymorphism and cancer risk in the overall population. The subgroup analysis by ethnicity showed no significant association between these polymorphisms in Asians and Caucasians and cancer risk. The subgroup analysis by cancer type indicated that the -572G/C polymorphism in the *IL-6* gene was not associated with increased or decreased risk of HHC and CRC. In addition, the *IL-6* -572G/C polymorphism was found to be significantly associated with increased risk of cancer in non-HWE studies. The results of this meta-analysis indicated the presence of heterogeneity between the included studies. A sensitivity analysis was conducted by limiting the studies included in the meta-analysis to those consistent with HWE; the results of this analysis revealed that this meta-analysis

was realistic and believable. However, only two studies investigated the association of the -572G/C polymorphism with the risk of GC and NPC (Kang et al., 2009; Qu et al., 2014); therefore, a greater number of original case-control studies must be performed to further evaluate the association between the *IL-6* -572G/C polymorphism and different cancer types. Publication bias was not observed in this meta-analysis.

There are some limitations to our meta-analysis. Firstly, only English language publications were extracted, thereby possibly excluding some relevant publications or unpublished studies in other languages. Secondly, a lack of original data limited further evaluations of the potential gene-gene and gene-environment interactions. Thirdly, our meta-analysis was based on unadjusted OR estimates, as not all published studies presented the adjusted ORs, or, when they did, the ORs were not adjusted by the same potential confounders, such as age, sex, and exposure.

In conclusion, the results of this meta-analysis suggested that the *IL-6* -572G/C polymorphism may not be associated with cancer risk. Large-scale case-control and population-based association studies must be performed in the future to validate the risk identified in the current meta-analysis, and investigate the effect of potential gene-gene and gene-environment interactions on cancer risk.

Conflicts of interest

The authors declare no conflict of interest.

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