Lack of association between IL-6 -174G>C polymorphism and lung cancer: a meta-analysis

Y. Liu, X.L. Song, G.L. Zhang, A.M. Peng, P.F. Fu, P. Li, M. Tan, X. Li, M. Li and C.H. Wang

Department of Respiratory Medicine,
Shanghai Tenth People's Hospital of Tongi University, Zhabei, Shanghai, China

Corresponding author: C.H. Wang
E-mail: liuyang8631@163.com

ABSTRACT. The results of previous case-control studies examining the relationship between the interleukin (IL)-6 gene -174G>C polymorphism and lung cancer are controversial. In this study, we evaluated the relationship between the IL-6 gene -174G>C polymorphism and lung cancer. We selected 5 case-control studies related to the IL-6 gene -174G>C polymorphism and lung cancer by searching the PubMed, EMBase, Chinese Biomedical Literature Database, and Wanfang database. We utilized the Q-test and I^2 test to determine heterogeneity between each study. To merge the odds ratios (OR) and 95% confidence intervals (CI), we utilized the fixed effects model and random effect model for analyses. The present study included 2801 patients with lung cancer and 3234 cancer-free control subjects. The meta-analysis revealed no association between the IL-6 gene -174G>C polymorphism and lung cancer in either genotype or allele distribution [CC+GC *vs* GG: OR = 1.04, 95%CI (0.86-1.26), P = 0.70; GG+GC *vs* CC: OR = 0.93, 95%CI (0.82-1.05), P = 0. 23; CC *vs* GG: OR = 1.08, 95%CI (0.95-1.23), P = 0.23; C allele *vs* D allele: OR

= 1.03, 95%CI (0.96-1.11), P = 0.44]. We concluded that the IL-6 gene -174G>C polymorphism was not associated with lung cancer.

Key words: Gene polymorphism; Interleukin-6; Lung cancer; Meta-analysis

INTRODUCTION

Lung cancer is the most frequently occurring cancer worldwide, and 1.3 million new patients are diagnosed with lung cancer each year (Herbst et al., 2008). Recently, lung cancer has been recognized as a complex multifactorial disease resulting from the interactions between various genetic and environmental factors (Yokota et al., 2010). Inflammation is involved in the development of carcinogenesis (Seitz and Stickel, 2006), and studies have suggested that key cytokines in inflammation pathways may play a role in carcinogenesis (Chen et al., 2005). Interleukin-6 (IL-6) is a cytokine that exerts both proinflammatory and anti-inflammatory effects (Blanco et al., 2007; Sansone et al., 2012) and plays a key role in the inflammatory signaling pathway. Previous studies have reported that the -174G>C polymorphism in the promoter region of IL-6 is associated with the transcription activity of IL-6, and some studies investigated the association between the IL-6 gene -174G>C polymorphism and lung cancer, but the results are controversial. This may be because of inadequate sample sizes, patient selection, and ethnicity of the populations studied. Additionally, a single study may be insufficient for detecting the potential small effect of the polymorphism on lung cancer. Meta-analysis is useful for investigating associations between diseases and risk factors as it involves a quantitative approach that combines the results of different studies on the same topic, and thus may provide more reliable conclusions (Duval and Tweedie, 2000; Higgins et al., 2003). Given the important role of IL-6 in the pathogenesis of lung cancer, a meta-analysis was performed that included all eligible case-control studies to estimate the association between this polymorphism and lung cancer risk.

MATERIAL AND METHODS

Literature collection and screening

To identify all articles that explored the association between IL-6 polymorphisms and lung cancer risk, we conducted a literature search of the PubMed, EMBase, Chinese Biomedical Literature Database, and Wanfang database using the terms "lung cancer (Mesh)" or "lung neoplasm" and "Interleukin-6" or "IL-6", "polymorphism, or SNP, or genotype, or -174G>C", without any restriction on language or publication year. Using online retrieval and literature review, references obtained using these databases were reviewed to ensure that no relevant studies were missed.

The inclusion criteria for the present study were as follows: 1) independently published case-control or cohort studies on the relationship between the IL-6 polymorphism and lung cancer; 2) similar themes and methods; 3) sufficient information was provided to calculate the odds ratio (OR) and 95% confidence interval (CI), and 4) the distribution of genotypes in the control groups was consistent with Hardy-Weinberg equilibrium (HWE). Accordingly, the following exclusion criteria were used: 1) abstracts and reviews, 2) studies in which geno-

type frequencies were not reported, and 3) repeated or overlapped publications. For studies involving the same case series by the same authors, the most recently published studies or studies that included the largest numbers of subjects were included.

Quality assessment and data extraction

Two reviewers (Yang Liu, Xiao-Lian Song) independently evaluated the studies and extracted the data using a standard approach based on the above-mentioned inclusion criteria. Discrepancies were resolved through discussion. We utilized the Cochrane Handbook 5.2 quality evaluation criteria to assess the methodological quality of included studies.

For each study, we recorded the first author's last name, year of publication, ethnicity of participants, numbers of cases and controls, and frequency of insertion or deletion genotypes. Hardy-Weinberg equilibrium was assessed using the χ^2 test.

Statistical analysis

For each case-control study, the HWE of genotypes in the control group was assessed by using Person's Chi-square test. OR and 95%CI were used to assess the strength of the association between the -174G>C polymorphism and lung cancer risk. We performed the meta-analysis using the RevMan 5.2 software, which was provided by the Cochrane Collaboration. We utilized the Q-test and I^2 test to examine the heterogeneity between each study. In the present study, we selected the fixed effects model to merge the OR values. Analysis of sensitivity included the difference of point estimation and confidence intervals of the combined effects value of different models to identify changes in the results. To test publication bias, we utilized the RevMan 5.2 statistical software to construct the funnel plot. $P < 0.05$ was considered to be statistically significant.

RESULTS

Study identification

A total of 354 studies were preliminarily detected; 341 studies were excluded because the IL-6 gene polymorphism was not examined, the studies only included gene expression analysis, or they were not relevant to lung cancer. Eight studies were further excluded because they were reviews, the IL-6 -174G>C genotype was not examined, or they were duplicated publications. A total of 5 studies (Campa et al., 2004, 2005; Seifart et al., 2005; Colakogullari et al., 2008; Vogel et al., 2008), including 2801 patients with lung cancer and 3234 cancer-free control subjects.

Quantitative synthesis

The result of meta-analysis for the association between lung cancer and IL-6 gene polymorphism in 5 case-control studies is shown in Figures 1-4. No significant association between the IL-6 -174G>C polymorphism and susceptibility to lung cancer was identified in any of the genetic models [CC+GC *vs* GG: OR = 1.04, 95%CI (0.86-1.26), P = 0. 70; GG+GC *vs* CC: OR = 0.93, 95%CI (0.82-1.05), P = 0. 23; CC *vs* GG: OR = 1.08, 95%CI (0.95-1.23), P = 0. 23; C allele *vs* D allele: OR = 1.03, 95%CI (0.96-1.11), P = 0.44].

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95%CI	Year	Odds Ratio M-H, Random, 95%CI
Campa et al., 2004	179	243	152	207	14.8%	1.01 [0.66, 1.54]	2004	
Campa et al., 2005	1366	1995	1367	1982	42.2%	0.98 [0.85, 1.12]	2005	
Seifart et al., 2005	298	403	540	744	25.3%	1.07 [0.81, 1.41]	2005	
Colakogullari et al., 2008	34	44	31	58	4.4%	2.96 [1.24, 7.09]	2008	
Vogel et al., 2008	69	116	153	243	13.3%	0.86 [0.55, 1.36]	2008	
Total (95% CI)		2801		3234	100.0%	1.04 [0.86, 1.26]		
Total events	1946		2243					

Heterogeneity: Tau² = 0.02; Chi² = 6.69, df = 4 (P = 0.15); I² = 40%
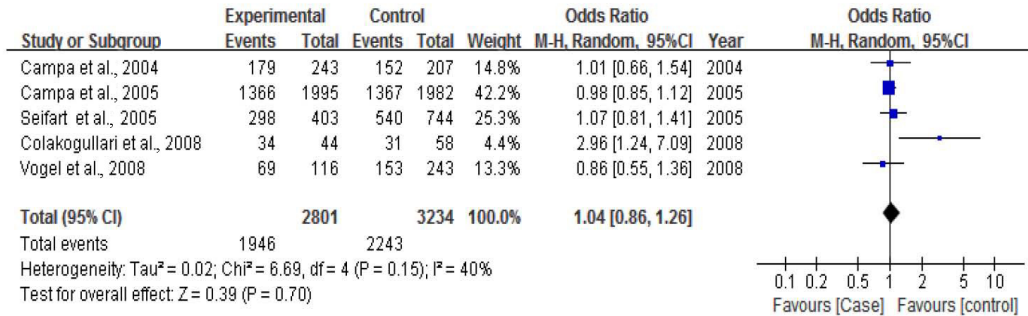Test for overall effect: Z = 0.39 (P = 0.70)

Figure 1. Forest plot of lung cancer risk associated with IL-6 -174G>C polymorphism. (CC+GC *vs* GG). The squares and horizontal lines correspond to the study-specific OR and 95%CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI. In this analysis, the random-effects model was used.
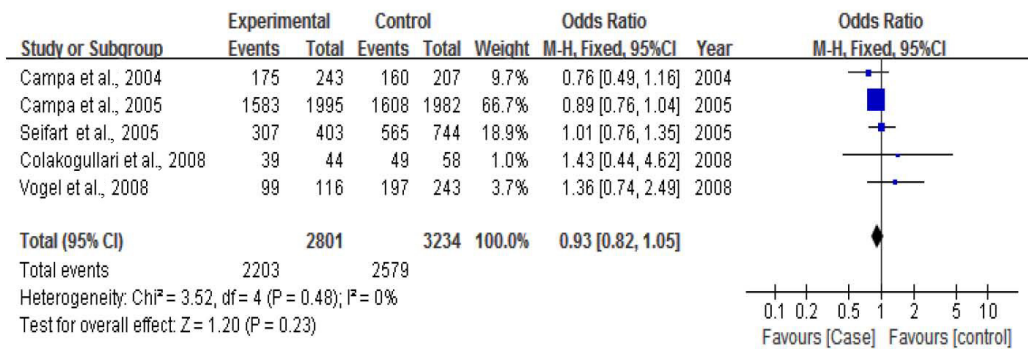
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95%CI	Year	Odds Ratio M-H, Fixed, 95%CI
Campa et al., 2004	175	243	160	207	9.7%	0.76 [0.49, 1.16]	2004	
Campa et al., 2005	1583	1995	1608	1982	66.7%	0.89 [0.76, 1.04]	2005	
Seifart et al., 2005	307	403	565	744	18.9%	1.01 [0.76, 1.35]	2005	
Colakogullari et al., 2008	39	44	49	58	1.0%	1.43 [0.44, 4.62]	2008	
Vogel et al., 2008	99	116	197	243	3.7%	1.36 [0.74, 2.49]	2008	
Total (95% CI)		2801		3234	100.0%	0.93 [0.82, 1.05]		
Total events	2203		2579					

Heterogeneity: Chi² = 3.52, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)

Figure 2. Forest plot of association between lung cancer risk and IL-6 -174G>C polymorphism. (GG+GC *vs* CC). The squares and horizontal lines correspond to the study-specific OR and 95%CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI. In this analysis, the fixed-effects model was used.
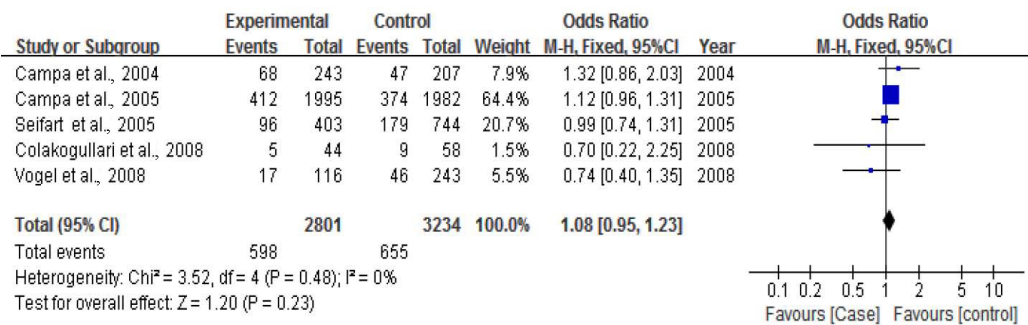
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95%CI	Year	Odds Ratio M-H, Fixed, 95%CI
Campa et al., 2004	68	243	47	207	7.9%	1.32 [0.86, 2.03]	2004	
Campa et al., 2005	412	1995	374	1982	64.4%	1.12 [0.96, 1.31]	2005	
Seifart et al., 2005	96	403	179	744	20.7%	0.99 [0.74, 1.31]	2005	
Colakogullari et al., 2008	5	44	9	58	1.5%	0.70 [0.22, 2.25]	2008	
Vogel et al., 2008	17	116	46	243	5.5%	0.74 [0.40, 1.35]	2008	
Total (95% CI)		2801		3234	100.0%	1.08 [0.95, 1.23]		
Total events	598		655					

Heterogeneity: Chi² = 3.52, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)

Figure 3. Forest plot of lung cancer risk associated with IL-6 -174G>C polymorphism. (CC *vs* GG). The squares and horizontal lines correspond to the study-specific OR and 95%CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI. In this analysis, the fixed-effects model was used.
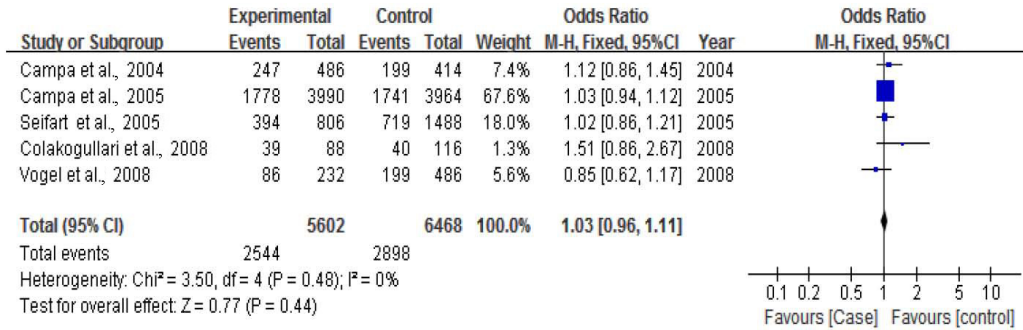
Figure 4. Forest plot of lung cancer risk associated with IL-6 -174G>C polymorphism. (C *vs* G). The squares and horizontal lines correspond to the study-specific OR and 95%CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI. In this analysis, the fixed-effects model was used.

Publication bias analysis

We utilized the RevMan 5.2 software to analyze publication bias; the funnel plot (Figure 5) showed that the points were evenly distributed and symmetrical, and most points were within the 95%CI. The shape of funnel plots showed no obvious asymmetry and the result of the Egger's test showed no statistical evidence of bias. This indicates that there was no publication bias and that the results of the study were credible.
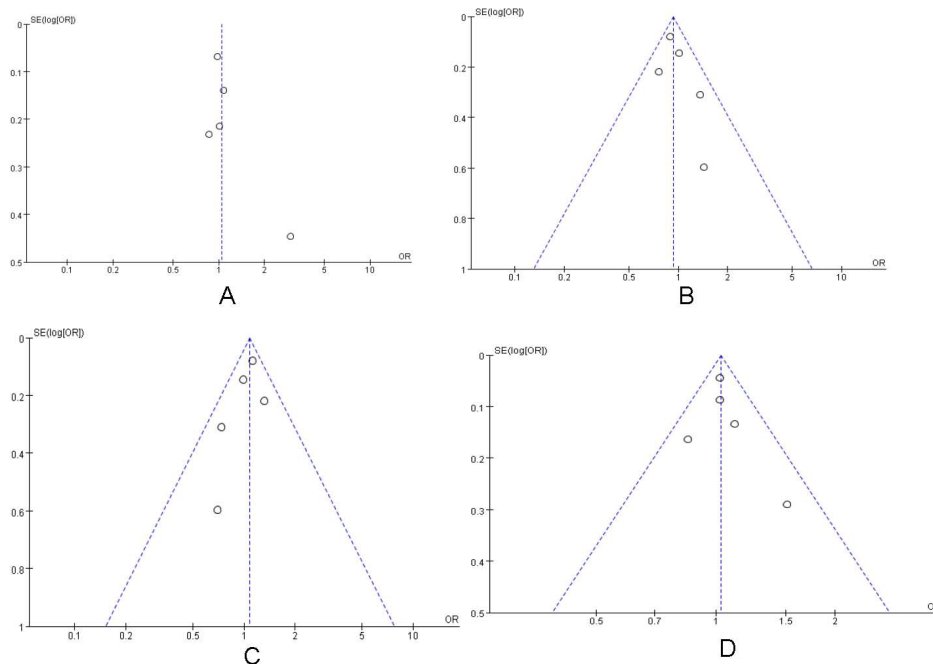

Figure 5. Begg's funnel plot to test for publication bias. Each circle denotes an independent study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line indicates mean effect size. **A.** (CC+GC *vs* GG). **B.** (GG+GC *vs* CC). **C.** (CC *vs* GG). **D.** (C *vs* G).

DISCUSSION

In the present study, we performed a meta-analysis to evaluate the association of IL-6 gene -174G>C polymorphism with lung cancer. We did not find any association between IL-6 gene polymorphism and lung cancer.

Several case-control studies have been conducted to determine the association between IL-6 polymorphisms and lung cancer risk (Bai et al., 2013; Kiyohara et al., 2014); however, the results were still inconclusive. In this meta-analysis, we found that IL6 -174G>C was not associated with lung cancer. Notably, the IL-6 -174G>C polymorphism was only detected in the Caucasian population. Campa et al. (2004, 2005) reported an increased risk of squamous cell lung cancer; however, because of the limited amount of data available, we could not further analyze the association in squamous cell cancer and further studies are necessary.

In this meta-analysis, we found that the -174C allele was not a risk factor for lung cancer, which can be explained based on the following: first, the etiology of lung cancer is complex and the single-nucleotide polymorphisms in the IL-6 promoter region may interact with other risk factors, such as smoking. Second, polymorphisms in the promoter region of IL-6 may have a complex interactive effect that increases both IL-6 transcriptional activity and lung cancer risk. Finally, different cytokines may function as a complex network, and altered expression of a single cytokine may not significantly affect the network.

The present study examined 5 independent case-control studies and found that the IL-6 gene -174G>C polymorphism was not associated with the susceptibility to lung cancer. However, further studies and screening of etiological relations between the functional polymorphism loci of the IL-6 gene and the susceptibility to lung cancer are still required.

In conclusion, we observed no association between the IL-6 gene -174G>C polymorphism and lung cancer.

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