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Research Article

Association of Genetic Polymorphisms in Tumour Necrosis Factor-Alpha (TNF-α-308G/A) and Interleukin-6 (IL-6-174G/C and IL-6-634C/G) with Lung Cancer Risk: A Meta-Analysis

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ABSTRACT

The aim of this study was to examine the association of Tumour Necrosis Factor-Alpha (TNF-α) and Interleukin-6 (IL-6) gene polymorphisms with the risk of developing lung cancer. We searched several electronic databases, including PubMed and Excerpt Medica Database (EMBASE), for a total of 17 studies involving 4,094 cases and 4,988 controls, which were included in a meta-analysis. The effects of three polymorphisms, TNF-α-308G/A, IL-6-174G/C and IL-6-634C/G, were evaluated. The pooled Odds Ratio (OR) with 95% Confidence Interval (95% CI) was calculated by RevMan software. Heterogeneity was also assessed. Based on our results, we found an association between the TNF-α-308G/A polymorphism and lung cancer risk under the dominant model (GG+GA *vs.* AA, OR=0.60, 95% CI: 0.40 to 0.89). For the IL-6-174G/C polymorphisms, the pooled ORs (95% CI) of GG/GC *vs.* CC, GG *vs.* GC/CC, GC *vs.* CC, and GG *vs.* CC were 1.22 (1.02 to 1.46), 1.22 (1.01 to 1.48), 1.22 (1.01 to 1.48), and 1.12 (0.87 to 1.44), respectively. For the IL-6-634C/G polymorphisms, the pooled ORs (95% CI) of CC/CG *vs.* GG, CC *vs.* CG/GG, and C *vs.* G were 1.04 (0.68 to 1.58), 0.69 (0.57 to 0.85), and 0.79 (0.67 to 0.93), respectively. The results of our analysis of these IL-6 polymorphisms revealed an association between IL-6 and lung cancer risk. This association, however, was not as strong as the association between TNF-α-308G/A polymorphisms and lung cancer risk. Because the current study was limited in sample size, further studies are needed to reveal more precise associations.

Keywords: Meta-analysis; Gene polymorphisms; Tumor necrosis factor alpha; Interleukin-6; Lung cancer

INTRODUCTION

Lung cancer is currently the most common worldwide cause of major cancer-related morbidity and mortality [1]. It is also one of the most fatal malignancies [2]. According to several recent studies, chronic low-grade inflammation is closely related to the incidence of lung cancer. High levels of pro-inflammatory cytokines, such as Tumour Necrosis Factor Alpha (TNF-α) and Interleukin-6 (IL-6), have been reported to be directly correlated with several inflammatory diseases, as well as lung cancer [3]. Tumour necrosis factor-alpha is a major inflammatory growth factor that plays a vital role in the regulation of immune and inflammatory responses. Genetic variants of the TNF-α gene may affect the host immune system and correlate with lung cancer risk. As the 308(G/A) polymorphism in the TNF-α promoter region is associated with altered protein levels and transcription rates [4], we explored the relationship between this polymorphism and lung cancer risk. IL-6 is a key pro-inflammatory cytokine that may also play a critical role in carcinogenesis and regulate the expression of several genes involved in inflammation; it is expressed in tumor-infiltrating cells [5]. Hence, we also analyzed two polymorphisms in the IL-6 promoter region, 174(G/C) and 634(C/G). Genetic variants, especially functional polymorphisms located in the promoter regions of candidate genes, are known to quantitatively alter gene expression. Although several studies have reported on these IL-6 and TNF-α gene polymorphisms, the results have been inconsistent and even controversial. We have also not been able to draw conclusions that agree with the existing literature. These discrepancies may arise from a variety of factors, including differences in study populations or the use of small sample sizes. A meta-analysis would thus aid in revealing a more precise association between these gene polymorphisms and lung cancer risk. A stable and reliable conclusion is necessary to unify these inconsistences

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and provide more conclusive results.

MATERIALS AND METHODS

Search strategy

We conducted a systematic literature search of the PubMed database and Excerpta Medica Database (EMBASE) from the earliest available date through October 2015 using the terms "Tumor necrosis factor alpha-308 or TNF-alpha-308 or Interleukin-6 or IL-6" and "Single Nucleotide Gene Polymorphism or SNPs or Nucleotide Gene Polymorphism, Single" and "Lung Cancer or Pulmonary Cancer or Lung Neoplasm" without any language restrictions. In addition, we included a manual search step to add more studies to our reference list. All distinctly irrelevant studies, case reports, editorial comments, and review articles were excluded [6,7,8].

Inclusion criteria and exclusion criteria

Eligible studies from our literature search had to fulfill the following inclusion criteria:

- Published studies based on case-control designs assessing the association between these gene (TNF-α-308G/A or IL-6-174G/C or IL-6-634C/G) polymorphisms and lung cancer risk,
- Case–control studies based on unrelated individuals, and
- Studies reporting sufficient sample sizes, distributions of alleles, genotype frequency data, and other information.

Studies were excluded for the following reasons:

- The study did not pertain to gene polymorphisms,
- The study had insufficient information for data extraction and
- The study was not conducted in humans. If a study reported results from different ethnicities, we treated those ethnicities independently.

Quality assessment

Two authors independently assessed the quality of every imported article according to a trial quality tool, which was adapted from existing quality tools, was used to divide the trials into four quality categories: A. low risk of bias in the randomization process; B. moderate risk of bias; C. high risk of bias; D. insufficient information to score allocation concealment. Quality assessments were conducted and evaluated by 5 reviewers.

Data extraction

Data were extracted independently by two reviewers based on the inclusion criteria listed above. Any inconsistencies were discussed, and consensus was reached. The following data were obtained: name of first author, year of publication, site of original research, ethnicity of the population, number of patient cases, number of controls, type of controls, method of genotyping, and whether the gene distribution of the controls was in compliance with Hardy-Weinberg Equilibrium (HWE). This information is reported in Tables 1 and 2.

Statistical analyses

RevMan software (Review Manager, Version 5.3 for Windows, The Cochrane Collaboration, Oxford, UK, 2014) was used for the statistical analyses. Pooled Odds Ratios (ORs) and 95% Confidence Intervals (CI) were calculated for the five gene comparisons (homozygote comparison, heterozygote comparison, dominant model, and recessive model and allele model) and used to assess the associations between TNF-α-308G/A, IL-6-174G/C or IL-6-634C/G polymorphisms and lung cancer risk. Moreover, heterogeneity was measured by the Chi-square Q statistic. If the result of the Q test was PQ<0.05 or $I^2 \geq 50\%$ (indicating the presence of heterogeneity), a random-effects model was used to estimate the OR. Otherwise, a fixed-effects model was used. Subgroup analyses were conducted according to race distribution to explore the reasons for heterogeneity. Moreover, to explore the

Table 1: Basic information for the articles included.

First author	Year	Country	Ethnicity	Polymorphisms	Sample size		Method	HWE
					cases	controls		
					202	205	PCR-RELP	Yes
Stankovic	2009	Serbia	European	TNF-α-308G/A	70	102	PCR-RELP	Yes
Flego	2009	Croatia	European	TNF-α-308G/A	230	230	PCR-RELP	Yes
Reyes-Gibby	2009	America	Caucasians	TNF-α-308G/A	103	566	TaqMan	Yes
Flego	2013	Croatia	European	TNF-α-308G/A	305	230	PCR-RELP	Yes
Shukla	2012	India	Asian	TNF-α-308G>A	208	204	PCR-RELP	Yes
Küçükaycan	2002	Netherlands	Caucasian	TNF-α-308G/A	163	335	PCR	Yes
Safa Kaabachi	2013	Tunisia	African	TNF-α-308G/A	133	174	PCR-RELP	Yes
			Caucasian	TNF-α-308G/A				
Reyes-Gibby	2007	America	African-Americans	IL-6-174G/C	482	121	TaqMan	Yes
			European	TNF-α308G/A				
Carola Seifart	2005	Germany	European	IL-6-174G/C	117	243	PCR-RELP	Yes
Ulla Vogel	2007	Denmark	European	IL-6-174G/C	403	744	PCR	Yes
Chikako Kiyohara	2013	Japan	Asian	IL-6-174G/C	462	379	TaqMan	Yes
Lu Bai	2013	China	Asian	IL-6-634C/G	193	211	TaqMan	Yes
Adeline Seow [7]	2005	Singapore	Asian	IL-6-634C/G	126	162	PCR	Yes
Wei-Yen Lim[1][8]	2011	Singapore	Asian	IL-6-634C/G	298	718	PCR	Yes

TNF: Tumour Necrosis Factor; IL: Interleukin; PCR: Polymerase Chain Reaction; PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; HWE: Hardy-Weinberg Equilibrium

Table 2: Distribution of genotypes and alleles for TNF-α-308G/A and IL-6-174G/C and IL-6-634C/G.

Locus	Research	Year	Number of cases			Number of controls			Number of cases		Number of controls	
			GG	GA	AA	GG	GA	AA	G	A	G	A
TNF-α -308G/A	Shih	2006	110	75	15	169	34	2	295	105	372	38
	Stankovic	2009	57	13	0	71	28	3	127	13	170	34
	Flego	2009	169	52	9	171	53	6	390	70	395	65
	Reyes-Gibby	2009	64	34	5	398	155	13	162	44	951	181
	Flego	2013	219	72	14	171	53	6	510	100	395	65
	Shukla	2012	159	41	0	178	30	0	359	49	386	30
	Küçükaycan	2002	113	39	1	237	91	7	265	41	565	105
	Safa Kaabachi	2013	73	50	10	142	29	3	196	70	313	35
	Reyes-Gibby	2007	341	128	13	83	33	5	810	154	199	43
	Carola Seifart	2005	80	36	1	171	67	4	196	38	409	75
			GG	GC	CC	GG	GC	CC	G	C	G	C
IL-6-174G/C	Ulla Vogel	2007	105	202	96	204	361	179	412	394	769	719
	Carola Seifart	2005	47	52	17	90	107	46	146	86	287	199
	Chikako Kiyohara	2013	28	175	259	13	116	250	231	693	142	616
	Reyes-Gibby	2007	231	189	61	62	44	14	651	311	168	72
			CC	CG	GG	CC	CG	GG	C	G	C	G
IL-6-634C/G	Lu Bai	2013	86	89	18	125	69	16	261	125	319	101
	Adeline Seow	2005	70	46	8	97	55	10	186	62	249	75
	Wei-Yen Lim	2011	163	123	12	449	231	38	449	147	1129	307

TNF: Tumour Necrosis Factor; IL: Interleukin

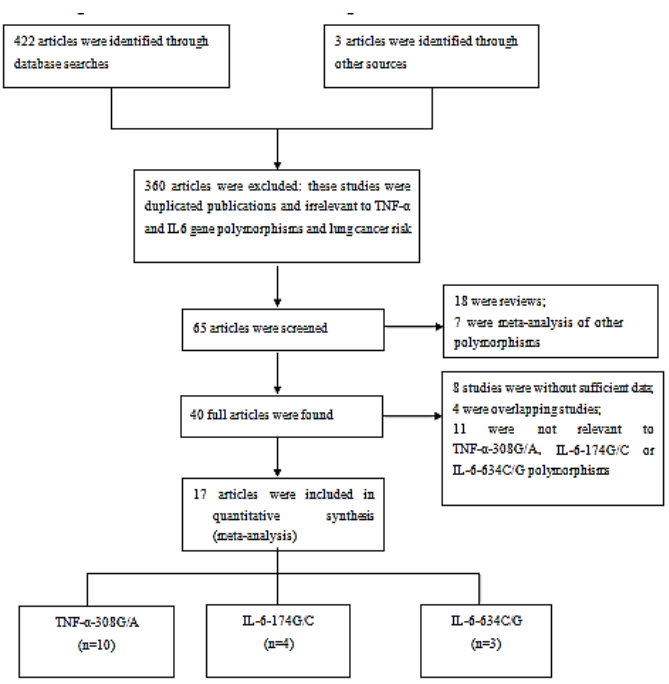

Figure 1: Flow chart for literature screening.

impact of single article on the overall estimate, sensitivity analysis was performed by sequential omission of individual studies (Tables 1 and 2) (Figure 1).

RESULTS

Characteristics of the included studies

The process of screening articles is shown in Figure 1. A total of 425 studies were identified after an initial search followed by a manual search. There were 360 duplicated publications. Obvious irrelevant studies were excluded. Eighteen reviews and 7 meta-analyses of other polymorphisms were excluded after review of the titles and abstracts of all articles. After reading the full text of the 40 remaining studies (based on the previously described inclusion and exclusion criteria), 8 articles were excluded for lacking sufficient data, 4 were found to be overlapping studies, and 11 were irrelevant to the TNF-alpha-308 G/A or IL-6-174 G/C or IL-6-634 C/G polymorphisms. Ultimately, 17 relevant articles were included

in the meta-analysis. Ten articles pertained to TNF-α-308G/A, 4 pertained to IL-6-174G/C, and 3 pertained to IL-6-634C/G. The genotype distributions of all of the included articles were consistent with HWE ($p < 0.05$).

Association between the TNF-α-308G/A polymorphism and lung cancer risk

As shown in Table 3, ten studies including a total of 2013 patient cases and 2410 controls were selected to evaluate the association between TNF-α-308G/A and lung cancer risk. The results revealed that the TNF-α-308G/A polymorphism is associated with an increased risk of lung cancer under five comparison models: dominant model (GG+GA *vs.* AA, OR=0.60, 95% CI: 0.40 to 0.89, P=0.01), recessive model (GG *vs.* GA+AA, OR=0.75, 95% CI: 0.52 to 1.06, P=0.10), heterozygous genotype comparison (GA *vs.* AA, OR=0.77, 95% CI: 0.50 to 1.18, P=0.23), homozygous genotype comparison (GG *vs.* AA,OR=0.61, 95% CI: 0.30 to 1.28, P=0.19) and allele comparison (G *vs.* A, OR=0.76, 95% CI: 0.54 to 1.05, P=0.10). The forest plot for the dominant model of TNF-α-308G/A is shown in Figure 2 (Table 3).

Association between the IL-6-174G/C polymorphism and lung cancer risk

We identified four studies that investigated the association between the IL-6-174G/C polymorphism and lung cancer risk, which included 1464 patient cases and 1487 controls, using five different comparisons: dominant model (GG+GC *vs.* CC, OR=1.22, 95% CI: 1.02 to 1.46, P=0.03), recessive model (GG *vs.* GC+CC, OR=1.01, 95% CI: 0.83 to 1.23, P=0.91), heterozygous genotype comparison (GC *vs.* CC, OR=1.22, 95% CI: 1.01 to 1.48, P=0.04), homozygous genotype comparison (GG *vs.* CC, OR=1.12, 95% CI: 0.87 to 1.44, P=0.38) and allele comparison (G *vs.* C, OR=1.11, 95% CI: 0.89 to 1.37, P=0.36). The results are shown in Table 3. The forest plot for the dominant model of IL-6-174G/C is shown in Figure 3.

Association between the IL-6-634C/G polymorphism and lung cancer risk

We identified a single article that included three studies with a total of 617 patient cases and 1,091 controls that investigated the association between the IL-6-634C/G polymorphism and lung cancer risk. All of the studies were carried out in Europe. Our analysis is shown in Table 3, and the results of the five comparisons are as follows: dominant model (CC + CG *vs.* GG, OR=1.04, 95% CI: 0.68 to 1.58, P=0.87), recessive model (CC *vs.* CG+GG, OR=0.69, 95% CI: 0.57 to 0.85, P=0.0004), heterozygous genotype comparison (CG *vs.* GG, OR=1.34, 95% CI: 0.86 to 2.10, P=0.20), homozygous genotype comparison (CC *vs.* GG, OR=0.87, 95% CI: 0.56 to 1.35, P=0.54) and allele comparison (C *vs.* G, OR=0.79, 95% CI: 0.67 to 0.93, P=0.005). The forest plot for the recessive model of IL-6-634C/G is shown in Figure 4(Table 4).

Subgroup analysis

We conducted further subgroup analyses based on ethnicity. All of the subgroup results are shown in Table 4. Two studies on the TNF-α-308G/A polymorphism [9,10] were conducted in Asian cohorts, five [11-15] were conducted in European cohorts, three were were conducted in [13,16,17]Caucasian cohorts, and two [13,18] were conducted in African cohorts. Our meta-analysis revealed a statistically significant association between the TNF-α-308G/A polymorphism and lung cancer risk in Asians. Among the IL-6-174G/C studies, one [13] was conducted in Caucasian and African cohorts; one [19] in Asian cohorts; and the remaining [13,14,20] in European cohorts. Similarly, we found a significant relationship between IL-6-174G/C and increased lung cancer risk specifically in Asians. We were not able to perform an analysis for other Single Nucleotide Polymorphisms (SNPs) as we lacked sufficient information from individual subgroups.

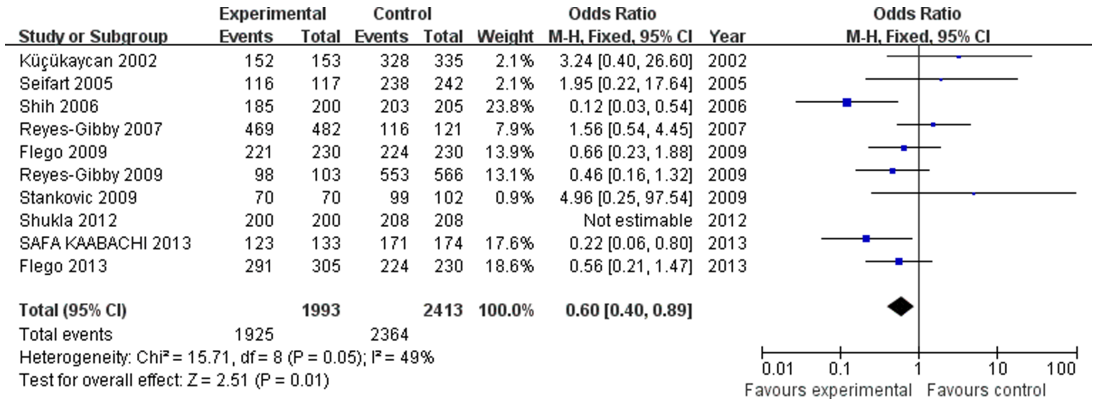

Figure 2: Forest plots of the association between the TNF-α-308G/A gene polymorphisms and risk of lung cancer under dominant model (contrast GG + GA *vs.* AA). OR: odds ratio; TNF-α: tumor necrosis factor-alpha.

Table 3: Main results of the meta-analysis.

Locus	Number of studies	Comparison	Test of association				PQ value	I^2 (%)	Model
			OR	95% CI	PA value	Z			
TNF⇩ 308G/A	10	GG + GA *vs.* AA	0.6	0.40-0.89	0.01	2.51	0.05	49	F
	10	GG *vs.* GA + AA	0.75	0.52-1.06	0.1	1.62	0.0001	83	R
	10	GA *vs.* AA	0.77	0.50-1.18	0.23	1.21	0.52	0	F

	10	GG *vs.* AA	0.61	0.30-1.28	0.19	1.31	0.01	60	R
	10	G *vs.* A	0.76	0.54-1.05	0.1	1.65	0.0001	85	R
IL-6-174G/C	4	GG+GC *vs.* CC	1.22	1.02-1.46	0.03	2.16	0.17	40	F
	4	GG *vs.* GC+CC	1.01	0.83-1.23	0.91	0.11	0.24	28	F
	4	GC *vs.* CC	1.22	1.01-1.48	0.04	2.07	0.41	0	F
	4	GG *vs.* CC	1.12	0.87-1.44	0.38	0.89	0.16	41	F
	4	G *vs.* C	1.11	0.89-1.37	0.36	0.92	0.03	66	R
IL-6-634C/G	3	CC + CG *vs.* GG	1.04	0.68-1.58	0.87	0.16	0.58	0	F
	3	CC *vs.* CG + GG	0.69	0.57-0.85	0.0004	3.52	0.31	15	F
	3	CG *vs.* GG	1.34	0.86-2.10	0.2	1.29	0.66	0	F
	3	CC *vs.* GG	0.87	0.56-1.35	0.54	0.62	0.46	0	F
	3	C *vs.* G	0.79	0.67-0.93	0.005	2.81	0.38	0	F

OR: Odds Ratio; CI: Confidence Interval; F: Fixed-effects model; R: Random-effects model.P_A: P value for test of the association; P_Q: P value for between study heterogeneity

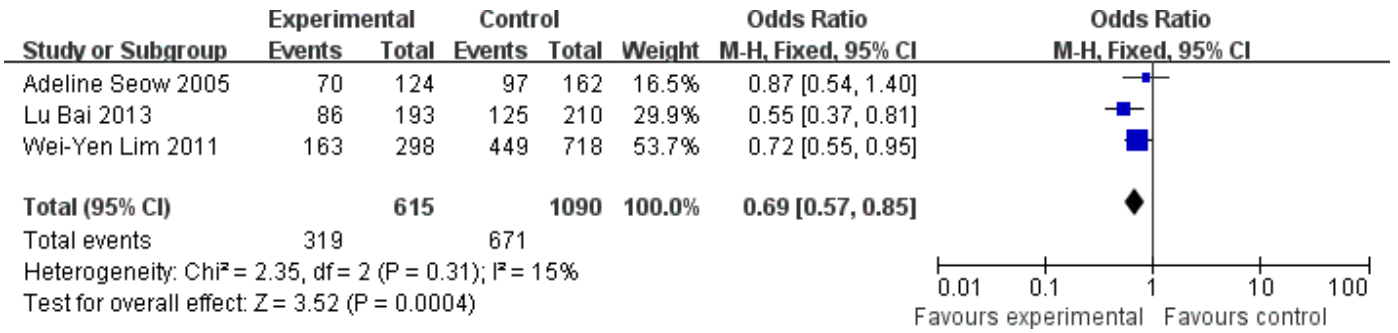

Figure 3: Forest plots of the association between the IL-6-174G/C gene polymorphisms and risk of lung cancer under dominant model (contrast GG+GC *vs.* CC). OR: Odds Ratio; IL: Interleukin.

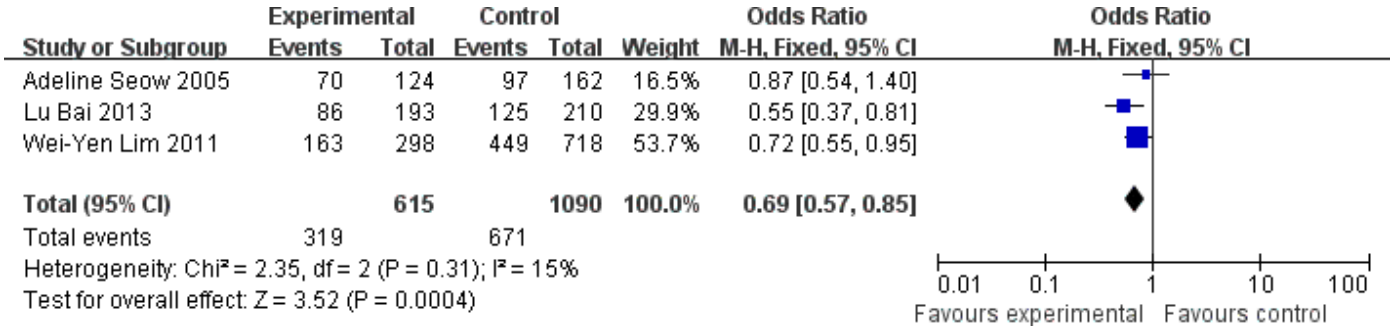

Figure 4: Forest plots of the association between the IL-6-634C/G gene polymorphisms and risk of lung cancer under recessive model (contrast CC *vs.* CG + GG). OR: Odds Ratio; IL: Interleukin.

Table 4: The results of the subgroup analyses.

Gene polymorphism	Comparison	OR (95% CI)			
		Asian	European	Caucasians	African
TNF-α-308G/A	GG + GA *vs.* AA	0.12 [0.03, 0.54]	0.79 [0.42, 1.48]	1.01 [0.47, 2.19]	0.39 [0.14, 1.08]
	GG *vs.* GA + AA	0.39 [0.28, 0.54]	0.97 [0.77, 1.22]	0.97 [0.74, 1.26]	0.44 [0.29, 0.68]
	GA *vs.* AA	0.29 [0.06, 1.36]	0.79 [0.41, 1.53]	1.05 [0.48, 2.32]	0.63 [0.21, 1.92]
	GG *vs.* AA	0.09 [0.02, 0.39]	0.79 [0.43, 1.48]	1.00 [0.46, 2.18]	0.33 [0.12, 0.91]
	G *vs.* A	0.38 [0.28, 0.51]	0.96 [0.78, 1.17]	0.98 [0.77, 1.23]	0.47 [0.33, 0.69]
IL-6-174G/C	GG+GC *vs.* CC	1.52 [1.15, 2.01]	1.07 [0.83, 1.38]	1.17 [0.61, 2.22]	NA
	GG *vs.* GC+CC	1.82 [0.93, 3.56]	0.99 [0.78, 1.25]	1.25 [0.74, 2.12]	0.92 [0.33, 2.63]
	GC *vs.* CC	1.46 [1.09, 1.95]	1.09 [0.83, 1.43]	1.06 [0.54, 2.11]	NA
	GG *vs.* CC	2.08 [1.05, 4.11]	1.04 [0.77, 1.41]	1.31 [0.64, 2.70]	NA
	G *vs.* C	1.45 [1.14, 1.83]	1.02 [0.88, 1.18]	1.17 [0.82, 1.66]	0.93 [0.34, 2.52]

Sensitivity analysis

Sensitivity analysis was done for each result, reflecting the influence of the individual data set to the pooled ORs. After removing the maximum-weight study, the pooled OR remained unchanged, which indicate that high reliability in our conclusions (data not shown).

DISSCUSSION

Over the past several decades, the link between TNF-α and IL-6 variations and disease have garnered increasing attention. However, the field is lacking in consistent and reliable conclusions regarding potential links between TNF-α and IL-6 gene polymorphisms and lung cancer risk. Meta-analyses, however, may provide more definitive conclusions. With a large sample size and comprehensive statistical analyses, the present meta-analysis demonstrated that TNF-α-308G/A is associated with a decreased risk of lung cancer under a dominant genetic model (GG+GA VS AA). However, our findings were not statistically significant. IL-6-174G/C polymorphisms have a slight association with an increased risk of lung cancer under the dominant genetic model. Moreover, we also detected an association between IL-6-634C/G and lung cancer risk under the recessive genetic model. Our subgroup analysis of TNF-α-308G/A and IL-6-174G/C revealed a stronger association between these polymorphisms and lung cancer risk in Asian populations than in other races. Based on these results, the IL-6 gene may play an important role in the pathogenesis of lung cancer. However, sufficient evidence is lacking to show a more detailed relationship between these gene polymorphisms and lung cancer risk. Therefore, more original and higher quality studies regarding the association between TNF-α-308G/A, IL-6-174G/C, and IL-6-634C/G gene polymorphisms and lung cancer are essential for more accurate results. Shih et al. [9] provided the first report of an association between TNF-α-308G/A gene polymorphisms and the risk of non-small-cell lung cancer (NSCLC) in a Chinese population. Their methods and sample size, however, varied significantly from those of our study. Nonetheless, we drew similar conclusions to those reported by Shih et al. specifically; we showed a weak association between TNF-α-308G/A gene polymorphisms and lung cancer risk. TNF-α is a pro-inflammatory cytokine and a central mediator of the immune response involved in a wide range of inflammatory pathways and infectious diseases [21]. As TNF-α is closely relied upon as a defense mechanism against disease, its regulation and expression after gene conversion can become increasingly uncontrollable. Therefore, we cannot confirm that our results are entirely thorough. Further studies are needed to assess multiple conditions of TNF-α expression to validate our findings.

An autocrine or paracrine factor, IL-6 may have direct effects on tumour cells to modulate their growth. IL-6 may also indirectly promote tumour cell growth by inducing the acute phase reaction, inhibiting apoptosis and angiogenesis [22]. The 5 kb IL-6 gene is located on chromosome 7p21-14 and contains 4 introns and 5 exons. The promoter region contains many different regulatory elements, including transcription factor binding sites for NF-IL6, NF-κB, Fos/Jun, CRBP, glucocorticoid receptor, and others [23]. Transcription factors play a critical role in the expression of IL-6. Hence, polymorphisms in the promoter region of the IL-6 gene may cause variations in transcription, causing the gene locus to strongly impact its expression and susceptibility to diseases. Specifically, in the current meta-analysis, we found that polymorphisms of IL-6-174G/C and IL-6-634C/G were associated with the occurrence and development of lung cancer, but these connections were negligible. Thus, although our results were very different from those of previous studies, we illustrate that some connections exist between IL-6 and lung cancer. This association may become more pronounced upon further investigation.

The association of cytokine gene polymorphisms in TNF-α and IL-6 with lung cancer risk has been reported in recent years. The results of our study may not be in accordance with other published findings, which may be attributed to certain limitations in the present meta-analysis. For instance, several SNPs in the TNF-α and IL-6 genes have been identified. However, because TNF-α-308 G/A, IL-6-174 G/C and IL-6-634C/G gene polymorphisms are the most widely researched, our study was limited to these three polymorphisms. Further investigation into the link between lung cancer and other TNF-α and IL-6 gene polymorphisms should be conducted in future studies. Additionally, the sample sizes used in our subgroup analyses were limited, making it impossible to stratify according to different tumour types. Therefore, we performed only a subgroup analysis stratifying for ethnicity. Furthermore, we could not precisely demonstrate the interactions between gene/gene and gene/environmental factors due to a lack of specific data published in each study.

In conclusion, we illustrate that TNF-α gene polymorphisms at position 308G/A and IL-6 gene polymorphisms at positions 174G/C and 634C/G have weak associations with lung cancer. However, the mechanism(s) underlying these correlations have yet to be determined [8]. We can be almost certain, however, that such occurrences in gene exchange may lead to differences in gene expression that can have an impact on lung cancer risk. To reach a more definitive conclusion, further studies are needed to assess multiple polymorphisms in the TNF-α and IL-6 genes. Larger sample sizes in case-control studies conducted with different pathological types to investigate the interactions between TNF-α and IL-6 with other individual genes and environmental factors may further contribute to our knowledge of lung cancer pathogenesis.

CONCLUSION

The association of cytokine gene polymorphisms in TNF-α and IL-6 with lung cancer risk has been reported in recent years. The results of our study may not be in accordance with other published findings, which may be attributed to certain limitations in the present meta-analysis. For instance, several SNPs in the TNF-α and IL-6 genes have been identified. However, because TNF-α-308 G/A, IL-6-174 G/C and IL-6-634C/G gene polymorphisms are the most widely researched, our study was limited to these three polymorphisms. Further investigation into the link between lung cancer and other TNF-α and IL-6 gene polymorphisms should be conducted in future studies. Additionally, the sample sizes used in our subgroup analyses were limited, making it impossible to stratify according to different tumour types. Therefore, we performed only a subgroup analysis stratifying for ethnicity. Furthermore, we could not precisely demonstrate the interactions between gene/gene and gene/environmental factors due to a lack of specific data published in each study.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

INFORMED CONSENT

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

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