REVIEW

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Association of Promoter Region Polymorphisms of *IL-10* Gene with Susceptibility to Lung Cancer: Systematic Review and Meta-Analysis

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Abstract

Objective: Epidemiological studies have suggested that the promoter region polymorphisms of *interleukin-10 (IL-10)* gene may be associated with an increased risk of lung cancer. However, those studies results are controversial. Thus, a comprehensive meta-analysis was performed to evaluate the association of promoter region polymorphisms of *IL-10* gene with susceptibility to lung cancer. **Methods:** a comprehensive search of PubMed, EMBASE, and CNKI databases was performed to find all eligible studies up to September 15, 2018. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of such association. **Results:** A total number of 19 case-control studies with 4084 cases and 6,131 controls were selected. The overall meta-analysis results showed that the *-592A>C* polymorphism was significantly associated with lung cancer risk under four genetic models, i.e., allele (CT vs. TT: OR= 1.17, 95% CI 1.01-1.35, p=0.02), homozygote (CC vs. AA: OR= 1.64, 95% CI 1.29-2.02, p≤0.001), heterozygote (CA vs. AA: OR= 1.26, 95% CI 1.06-1.50, p≤0.001), and dominant (CC+CA vs. AA: OR= 1.31, 95% CI 1.11-1.54, p=0.001). However, there was no significant association between *-819T>C* and *-1082A>G* polymorphisms of *IL-10* and lung cancer risk. Similarly, subgroup analyses by ethnicity detected significant association between *IL-10 -592A>C* and lung cancer among Asians and Caucasians. **Conclusions:** Our meta-analysis suggests that the *IL-10 -592A>C* polymorphism might be risk factor for lung cancer, especially among Asian and Caucasians. In contrast, the *IL-10 -819T>C* and *-1082A>G* polymorphisms are not significantly associated with increased risk of lung cancer.

Keywords: Lung cancer- *interleukin 10*- polymorphism- meta-analysis

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Introduction

Lung cancer is one of the most commonly diagnosed cancer (12.7% of the total cancer diagnoses) as well as the leading cause of cancer death (18.2% of the total cancer deaths) among all cancer patients worldwide (Mehrabi et al., 2017; Zhong et al., 2012). Lung cancer critically can be divided into two groups include Non-Small Cell Lung Carcinoma (NSCLC) and Small cell lung carcinoma (SCLC), which the first one accounts for about 80% of all lung cancers. Although, the mean onset age for lung cancer has been estimated ranged 60 to 70 years, less than 10% of all cases occurred at an early age (Rosenberger et al., 2008). Although tobacco smoke is probably the predominant etiological risk factor for lung cancer, the pathoetiology of lung cancer is not fully understood. Interestingly, lung cancer develops only in a small proportion of chain smokers (less than 11%), which indicating that genetic factors might play a critical role in its carcinogenic mechanisms (Cavic et al., 2014).

Genetic factors involved in lung cancers have been extensively studied and to date several genetic polymorphisms have been identified as candidates by meta-analyses. Epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog (KRAS) deleterious mutations occur mutually among 5-15% of lung cancer cases (Choughule et al., 2014). The promoter region polymorphisms of *IL-10* gene has been associated with susceptibility to several cancers including lung cancer (Namazi et al., 2018; Sheikhpour et al., 2017). However, published data on the possible association of *IL-10* polymorphism with lung cancer have generated

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inconclusive results. For example, Zhang et al found a significant association between the *-819T>C* and *-592A>C* polymorphisms of IL-10 and lung cancer in a Chinese population (Zhang et al., 2015), while Hsia et al., (2014) have reported that the genotypes of *IL-10 -819TC* polymorphism may have a protective effect on lung cancer risk in a Taiwanese population. Therefore, to estimate the effect of promoter region polymorphisms of *IL-10* gene and lung cancer risk, as well as to quantify the potential between-study heterogeneity, we performed this meta-analysis based on published case-control studies.

Materials and Methods

Search strategies

We systematically searched several online databases including PubMed, EMBASE, Web of Science, Google Scholar, China Biological Medicine Database, and China National Knowledge Infrastructure comprehensively for all studies on the association of promoter region polymorphisms of *IL-10* gene with lung cancer up to September 15, 2018. The combinations of following keywords and terms were used: (''*lung carcinomas*'' or ''*lung adenocarcinoma*'' or ''*lung cancer*'' or ''*small cell lung cancer*'' or ''*Non-Small Cell Lung Cancer*'') and (''*-1082 G>A*'' or ''*rs1800896*'' or ''*-819 T>C*'' or ''*rs1800871*'' or ''*-592A>C*'' or ''*rs1800872*'') and (''*polymorphism*'' or ''*single nucleotide polymorphism*'' or ''*variation*'' or ''*mutation*''). Moreover, the reference lists of retrieved studies were hand-searched to find out the missing studies. All analyses of this meta-analysis were based on previous published studies, and this meta-analysis did not have original data. Thus, no ethical approval and patient consent are required.

Inclusion and exclusion criteria

Inclusion criteria were: 1) studies with case-control or cohort design; 2) evaluation of association of promoter region polymorphisms of IL-10 gene with lung cancer risk; 3) provided sufficient data to calculate the odds ratios (ORs), 95% confidence intervals (CIs). Accordingly, exclusion criteria were: 1) linkage studies or family based studies; 2) studies did not provided genotype frequencies; 3) duplicates or overlapping data; and 4) abstracts, reviews, meta-analyses, case reports, editorials, and animal studies.

Data extraction

The identified studies were reviewed separately by two authors independently and carefully to extraction necessary data and then recorded in a standardized form. We have resolved any disagreement by a discussion with the senior investigator. We sought the following data from each study: first author's name, year of publication, ethnicity of each study population, country, source of controls, genotyping method, number of cases and controls, as well as numbers of cases and controls for *IL-10* polymorphisms, minor allele frequency (MAF) in healthy subjects, and evidence of Hardy-Weinberg equilibrium (HWE).

Statistical analysis

All of the calculations were performed using Comprehensive Meta-Analysis (CMA) version 2.0 (Biostat, USA). Two-sided P-values<0.05 were considered statistically significant. The strength of association of promoter region polymorphisms of IL-10 gene with lung cancer risk was assessed using ORs and 95%CIs. The Z-test was employed to determine the significance of the pooled ORs.

Pooled ORs were calculated under four genetic models, i.e., allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB+BA vs. AA), and recessive (BB vs. BA+AA), which a ''A'' denotes a major allele; ''B'' denotes a minor allele. Between studies heterogeneity was tested by the Cochran Q-test, in which p-value less than 0.05 showed presence of heterogeneity. In addition, we used the I^2 to detect the degree of heterogeneity between the included studies (I^2=0-25%, no heterogeneity; I2=25-50%, moderate heterogeneity; I^2>50%, large heterogeneity). The study-specific ORs were pooled using a fixed-effect or random-effect model depending on the heterogeneity. When a Q test indicated P<0.05 or I^2>50%, a random-effect model was used; otherwise, a fixed-effect model was applied. The departure from Hardy-Weinberg equilibrium (HWE) in the controls was assessed using Pearson's χ^2 test. Subgroup analyses based on ethnicity, source of controls (SOC), and genotyping methods were also performed. The stability of pooled results or influence of individual studies on the pooled ORs was tested through sensitivity analysis by omitting each study sequentially. Publication bias was estimated using the egg's funnel plot and Egger linear regression test. If the publication bias observed, the Duval and Tweedie ''*trim and fill*'' method was used to adjust the bias.

Results

After a comprehensive literatures search we have identified 81 articles, then we reviewed all retrieved articles in accordance with the defined criteria. Of those articles, 62 articles were excluded due to be reviews, previous meta-analyses, case reports, letters, no detailed genotyping data, and duplicate publication. Finally, a total of 19 case-control studies in ten publications (Colakogullari et al., 2008; Hao et al., 2009; Hart et al., 2011; Hsia et al., 2014; Liang et al., 2011; Peddireddy et al., 2016; Seifart et al., 2005; Shih et al., 2005; Vogel et al., 2008; Zhang et al., 2015) were included in the meta-analysis. The details of each study were shown in Table 1. Of those studies, seven case-control studies with 1839 cases and 2,613 controls were on *-592A>C*, five studies with 963 cases and 1558 controls on *-819T>C*, and seven case-control studies with 1,282 cases and 1,960 controls on *-1082A>G*. Among the included studies, eleven were preformed among the Asians and eight among the Caucasians. The sample size in cases ranged between 44 and 436. Three genotyping methods were utilized in the selected studies, including PCR-RFLP, PCR-SSP, and TaqMan.

Table 1. Characteristics of the Studies Included in Meta-Analysis

First Author	Ethnicity (Country)	SOC	Genotyping Methods	Case/Control	Cases					Control					MAFs	HWE
					Genotypes			Alleles		Genotypes			Alleles			
-592A>C					AA	AC	CC	A	C	AA	AC	CC	A	C		
Shih 2005	Taiwan(Asian)	HB	PCR-RFLP	154/205	66	70	18	202	106	116	76	13	308	102	0.24	0.9
Colakogullari 2008	Turkey(Caucasian)	HB	PCR-SSP	44/59	2	23	19	27	61	7	25	27	39	79	0.66	0.74
Vogel 2008	Denmark(Caucasian)	HB	PCR	403/744	13	149	241	175	631	42	250	452	334	1154	0.77	0.34
Liang 2011	China(Asian)	HB	PCR-RFLP	116/120	69	36	11	174	58	69	44	7	182	58	0.24	0.99
Hart 2011	Norway(Caucasian)	HB	TaqMan	434/433	15	175	243	205	661	26	144	264	196	672	0.77	0.28
Hsia 2014	Taiwan(Asian)	HB	PCR-RFLP	358/716	173	145	40	491	225	368	277	71	1013	419	0.29	0.07
Zhang 2015	China(Asian)	HB	PCR-RFLP	330/336	64	156	110	284	376	85	176	75	346	326	0.48	0.37
-819T>C					TT	TC	CC	T	C	TT	TC	CC	T	C		
Seifart 2005	Germany(Caucasian)	HB	PCR-RFLP	77/242	2	14	24	18	62	14	88	140	116	368	0.76	0.97
Shih 2005	Taiwan(Asian)	HB	PCR-RFLP	154/205	66	58	30	190	128	104	86	15	294	116	0.28	0.62
Colakogullari 2008	Turkey(Caucasian)	HB	PCR-SSP	44/59	2	23	19	27	61	7	26	26	40	78	0.66	0.89
Hsia 2014	Taiwan(Asian)	HB	PCR-RFLP	358/716	212	128	18	552	164	372	265	79	1009	423	0.29	0
Zhang 2015	China(Asian)	HB	PCR-RFLP	330/336	108	135	87	351	309	145	144	47	434	238	0.35	0.24
-1082A>G					AA	AG	GG	A	G	AA	AG	GG	A	G		
Seifart 2005	Germany(Caucasian)	HB	PCR-RFLP	39/243	6	21	12	33	45	86	115	42	287	199	0.4	0.73
Shih 2005	Taiwan(Asian)	HB	PCR-RFLP	115/205	115	39	0	269	39	194	11	0	399	11	0.02	0.69
Colakogullari 2005	Turkey(Caucasian)	HB	PCR-SSP	44/59	11	30	3	52	36	33	21	5	87	31	0.26	0.53
Hao 2009	China(Asian)	PB	TaqMan	44/52	36	7 (AG+GG)		-	-	46	6 (AG+GG)		-	-	-	
Hart 2011	Norway(Caucasian)	HB	TaqMan	436/435	120	207	109	447	425	104	226	105	434	436	0.5	0.41
Hsia 2014	Taiwan(Asian)	HB	PCR-RFLP	358/716	273	69	16	615	101	561	130	25	1252	180	0.12	0
Peddireddy 2016	India(Asian)	HN	PCR-RFLP	246/250	156	69	21	381	111	130	84	36	344	156	0.31	0

Table 2. Summary Risk Estimates for Association between IL-10 Polymorphism and Risk of Lung Cancer.

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio (OR)				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{OR}	P_{OR}	P_{Beggs}	P_{Eggers}
-592A>C	C vs. A	Fixed	49.9	0.06	1.14	1.03-1.25	2.68	0.007	1	0.75
	CC vs. AA	Fixed	0	0.68	1.64	1.29-2.02	4.16	≤0.001	0.54	0.35
	CA vs. AA	Fixed	37.21	0.14	1.26	1.06-1.50	2.68	≤0.001	0.22	0.14
	CC+CA vs. AA	Fixed	15.63	0.31	1.31	1.11-1.54	3.27	0.001	0.36	0.18
	CC vs. CA+AA	Random	62.3	0.01	1.16	0.89-1.52	1.12	0.26	0.54	0.28
Asians	C vs. A	Fixed	43.73	0.14	1.26	1.11-1.43	3.61	≤0.001	0.73	0.86
	CC vs. AA	Fixed	17.91	0.3	1.61	1.22-2.21	3.43	0.001	0.73	0.63
	CA vs. AA	Fixed	20.93	0.28	1.16	0.96-1.40	1.58	0.11	1	0.95
	CC+CA vs. AA	Fixed	35.76	0.19	1.25	1.04-1.49	2.49	0.01	1	0.81
	CC vs. CA+AA	Fixed	0	0.4	1.52	1.19-1.93	3.41	0.001	0.73	0.78
Caucasians	C vs. A	Fixed	0	0.67	0.99	0.85-1.15	-0.09	0.92	1	0.76
	CC vs. AA	Fixed	0	0.89	1.7	1.09-2.65	2.36	0.01	1	0.24
	CA vs. AA	Fixed	0	0.85	2.08	1.32-3.27	3.18	0.001	0.29	0.19
	CC+CA vs. AA	Fixed	0	0.81	1.76	1.13-2.71	2.54	0.01	1	0.26
	CC vs. CA+AA	Fixed	0	0.4	1.52	1.19-1.93	3.41	0.001	0.73	0.78
-819T>C	T vs. C	Random	95.76	≤0.001	0.98	0.86-1.11	-0.25	0.8	0.8	0.74
	TT vs. CC	Random	87.95	≤0.001	1.53	0.57-4.06	0.85	0.39	0.8	0.96
	TC vs. CC	Fixed	19.96	0.28	1.01	0.84-1.22	0.16	0.87	0.8	0.3
	TT+TC vs. CC	Random	94.81	≤0.001	0.71	0.30-1.71	-0.74	0.45	0.8	0.68
	TT vs. TC+CC	Random	92.33	≤0.001	0.98	0.33-2.41	-0.04	0.96	0.8	0.71
-1082A>G	G vs. A	Random	90.8	≤0.001	1.51	0.95-2.38	1.76	0.07	0.13	0.06
	GG vs. AA	Random	71.79	≤0.001	1.15	0.63-2.08	0.46	0.64	0.46	0.33
	GA vs. AA	Random	88.58	≤0.001	1.67	0.92-3.04	1.7	0.08	0.45	0.04
	GG+GA vs. AA	Random	89.81	≤0.001	1.76	0.97-3.20	1.86	0.06	0.76	0.07
	GG vs. GA+AA	Fixed	53.87	0.07	1.02	0.81-1.30	0.23	0.81	0.8	0.9
Asians	G vs. A	Random	95.29	≤0.001	1.64	0.63-4.22	1.03	0.3	1	0.35
	GG vs. AA	Random	80.06	0.02	0.79	0.29-2.10	-0.46	0.64	NA	NA
	GA vs. AA	Random	92.73	≤0.001	1.56	0.60-4.03	0.91	0.36	1	0.39
	GG+GA vs. AA	Random	92.97	≤0.001	1.68	0.65-4.32	1.07	0.28	0.73	0.44
	GG vs. GA+AA	Random	73.27	0.05	0.83	0.36-1.91	-0.42	0.67	NA	NA
Caucasians	G vs. A	Random	82.69	0.003	1.46	0.82-2.59	1.31	0.18	1	0.11
	GG vs. AA	Random	73.42	0.02	1.72	0.59-5.00	1	0.31	1	0.39
	GA vs. AA	Random	87.66	≤0.001	1.95	0.61-6.24	1.13	0.25	1	0.15
	GG+GA vs. AA	Random	87.64	≤0.001	1.99	0.65-6.08	1.21	0.22	1	0.09
	GG vs. GA+AA	Fixed	36.07	0.2	1.14	0.86-1.51	0.93	0.35	1	0.77

Quantitative Synthesis

IL-10 -592A>C Polymorphism

The summary of the meta-analysis of the association between *IL-10 -592A>C* polymorphism and lung cancer risk were listed in Table 2. There was a significant association between the *-592A>C* polymorphism and lung cancer risk under four genetic models, i.e., allele (CT vs. TT: OR= 1.14, 95% CI 1.03-1.25, p=0.007), homozygote (CC vs. AA: OR= 1.64, 95% CI 1.29-2.02, p≤0.001, Figure 1A), heterozygote (CA vs. AA: OR= 1.26, 95% CI 1.06-1.50, p≤0.001), and dominant (CC+CA vs. AA: OR= 1.31, 95% CI 1.11-1.54, p=0.001, Figure 1B). Stratified analysis by ethnicity revealed that there was a significant association between *IL-10 -592A>C* polymorphism and lung cancer among Asians under four genetic models, i.e., allele (C vs. A: OR= 1.26, 95% CI 1.11-1.43, p≤0.001), homozygote (CC vs. AA: OR= 1.64, 95% CI 1.22-2.21, p=0.001), dominant (CC+CA vs. AA: OR= 1.25, 95% CI 1.04-1.49, p≤0.001), and recessive (CC vs. CA+AA: OR= 1.52, 95% CI 1.19-1.93, p=0.001), and Caucasians under four genetic models, i.e., homozygote (CC vs. AA: OR= 1.70, 95% CI 1.09-2.65, p=0.01), heterozygote (CA vs. AA: OR= 2.08, 95% CI 1.32-3.27, p=0.001), dominant (CC+CA vs. AA: OR= 1.76, 95% CI 1.13-2.71, p=0.01), and recessive (CC vs. CA+AA: OR= 1.52, 95% CI 1.19-1.93, p=0.001).

IL-10 -1082A>G and -819T>C Polymorphisms

The summary of the meta-analysis of the association between *-1082A>G* and *-819T>C* polymorphisms of *IL-10* gene and lung cancer risk were listed in Table 2. The pooled results showed that there was no

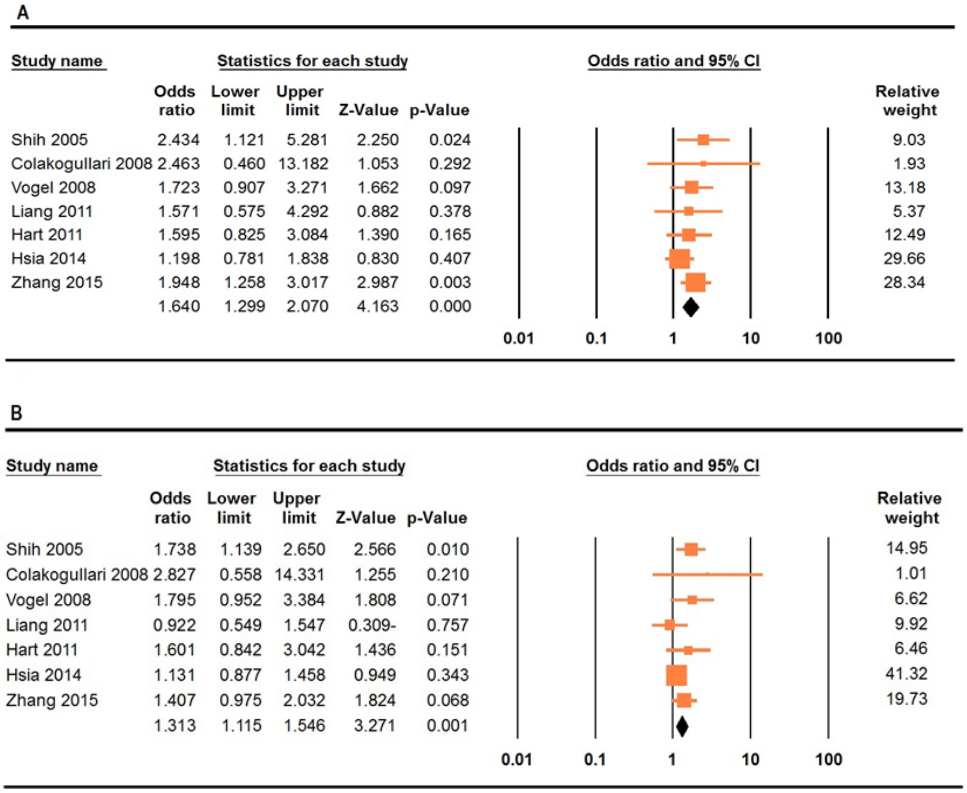

Figure 1. Forest Plots Showed Significant Association between IL-10 -592A>C Polymorphism and Lung Cancer. A, homozygote model (AA vs. CC); B, dominant model (CC+CA vs. AA).

significant association between *-1082A>G* and *-819T>C* polymorphisms of IL-10 gene and lung cancer in overall population under all five genetic models. Moreover, stratified analysis by ethnicity also revealed that there was not a significant association between *-1082A>G* and *-819T>C* polymorphisms of *IL-10* gene and lung cancer among Asians and Caucasians (Table 2).

Heterogeneity test and Sensitivity analysis

There was a significant in almost genetic models for *IL-10 -592A>C* and *-819T>C* polymorphisms. We have performed sensitivity analysis to detect the influence of each study on the pooled OR by deleting the single study and by deleting those studies did not accordance with HWE. However, sensitivity analysis suggested that a single study did not significantly change the pooled ORs, which indicated our meta-analysis results were robust and stable.

Publication bias

To determine the possible publication bias of the literature, we used the Begg's funnel plot and Egger test. The shapes of Begg's funnel plot did not show evidence of obviously asymmetrical for *IL-10 -592A>C* and *-819T>C* polymorphisms under all five genetic models and further confirmed by Egger test (Table 2).

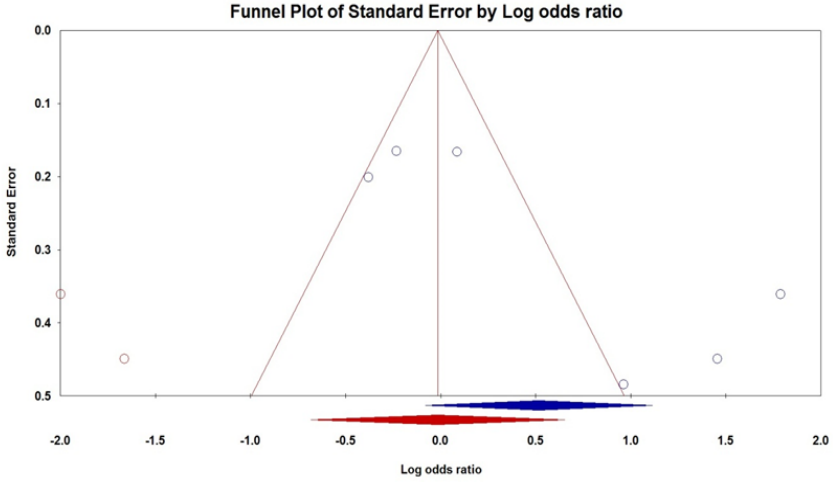

Figure 2. Begg's Funnel Plots of IL-10 -1082A>G Polymorphism and Lung Cancer Risk for Publication Bias Test under Heterozygote Model (GA vs. AA).

Although, Egger's test revealed a significant publication bias under the heterozygote genetic model (GA vs. AA: PBeggs = 0.45 and PEggers = 0.04, Figure 2) for *IL-10 -1082A>G* polymorphism. Therefore, the Duval and Tweedie non-parametric ''trim and fill'' method was applied to the publication bias result *IL-10 -1082A>G* polymorphism. However, the outcomes showed that the current meta-analysis with and without ''*trim and fill*'' did not draw different results, indicating that our results were statistically reliable.

Discussion

To date, several case-control studies that have been performed to evaluate the association of *IL-10* polymorphisms with the risk of lung cancer. However, the results are controversial due to the relatively small sample size of individual study, the different distributions of cases or healthy subjects, different lung cancer types, and the different genotyping methods. Meta-analysis as a powerful tool can provide more reliable results than a single study especially in explaining controversial conclusions. Thus, we performed this meta-analysis with larger sample size and subgroup to achieve a better understanding of the association of promoter region polymorphisms of *IL-10* gene with lung cancer risk. To the best of our knowledge, our meta-analysis, on the basis of 19 case-controls 4,084 cases and 6,131 controls is the largest and most comprehensive assessment to evaluate association of *IL-10* with lung cancer and the final results showed that *-592A>C* polymorphism was associated with an increased lung cancer risk.

In 2012, Wang et al., (2012) in a meta-analysis based on three studies have evaluated the association of *IL-10 - 819C>T* polymorphism and lung cancer. Their results showed that *IL-10 - 819C>T* polymorphism was significantly associated with increased risk of lung cancer. However, Yu et al., (2013) in a meta-analysis of four case-controls studies found that the *IL-10 -819 C>T* polymorphism was not significantly associated with lung cancer. In other meta-analysis, Peng et al., have reported that the *IL-10 1082G>A*, *819C>T* and *592C>A* polymorphisms were significantly associated with risk of lung cancer (Peng et al., 2012). Although the previous meta-analyses have reported positive association between *IL-10* gene polymorphisms and lung cancer, the number of studies that they have included considerably smaller than that needed to receive the reliable results. Thus, those meta-analyses results should be interpreted with caution. Because, the number of studies included considerably smaller than that needed to receive the reliable results. However, our meta-analysis could offer adequate power to detect the association between *IL-10* gene polymorphisms and lung cancer. In addition, in this meta-analysis we have performed subgroup analysis by ethnicity and the significant associations were only found for *IL-10 -592A>C* polymorphism among Asians and Caucasians. Therefore, *IL-10 -592A>C* polymorphism may be important factor contributed to lung cancer development.

Between studies heterogeneity is one of the challenging issues in a meta-analysis (Aslebahar et al., 2019; Yazdi et al., 2017). In a meta-analysis, heterogeneity could explain by sample study design, size, genotyping methods, source of controls, cancer types, life style, and so on (Jafari Nedooshan et al., 2017; Mehdinejad et al., 2017; Sobhan et al., 2017a; Sobhan et al., 2017b). In the current meta-analysis there was significant heterogeneity for *-819T>C* and *-1082A>G* polymorphisms under almost genetic models. Thus, we conducted subgroup analyses based on ethnicity and the types of control groups. However, the results showed that the heterogeneity may have resulted due to something more than ethnicity and the types of control groups. Moreover, publication bias is another key factor that might affect the quality and reliability of a meta-analysis (Sadeghiyeh et al., 2017). There was publication bias for *IL-10 -1082A>G* polymorphism under heterozygote genetic model might be due insufficient size of sample. Moreover, the ''*trim and fill*'' method results did not draw different results, indicating that the results were statistically reliable.

Although we conducted the most comprehensive meta-analysis based on all eligible studies, some limitations of this meta-analysis should be acknowledged. First, the number of eligible case-control studies included in this meta-analysis was small which limited statistical power to detect a potential association for those polymorphisms. Second, the sample size of some subgroups in the stratified analyses was limited, which may have reduced the statistical power to explore the association of the polymorphism with lung cancer susceptibility. Third, we have only included published studies in English in the meta-analysis. It is possible that some related unpublished studies and in other languages were missed; therefore, publication bias may have been present, even though statistical analysis indicated this not to be the case. Finally, lung cancer as most malignancies is a multifactorial disease that results from complex interactions between genetic and environmental factors. Our results were based on unadjusted estimates and a more precise analysis could be conducted if other covariates such as age, gender, smoking status, type of lung cancer, environmental factors, and lifestyle are available. Further evaluation of lung cancer risk should pay more attention to the potential interactions between gene-gene, gene-environment, and even between *IL-10 -592A>C*, *-819T>C* and *-1082A>G* polymorphisms.

In summary, our findings suggest that *IL-10 -592A>C* polymorphism might be risk factor for lung cancer, especially among Asians and Caucasians. However, *IL-10 -819T>C* and *-1082A>G* polymorphisms did not significantly associated with increased risk of lung cancer. Moreover, further studies with large sample sizes and well-designed multicenter analyses are required to clarify the association of *IL-10* polymorphisms with susceptibility of lung cancer.

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