Int J Clin Exp Med 2015;8(9):15317-15328
www.ijcem.com /ISSN:1940-5901/IJCEM0012910

Original Article

Interleukin-10 promoter polymorphism and susceptibility to lung cancer: a systematic review and meta-analysis

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Received July 15, 2015; Accepted July 30, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: Background: Interleukin-10 (IL-10) is a multifunctional cytokine with both immunosuppressive and anti-angiogenic properties and it plays an important role in the pathogenesis of cancer. A number of studies have examined the association between its promoter -1082/-819/-592 polymorphism and risk of lung cancer. However, the results are inconsistent and inconclusive. The aim of this study was to explore whether the IL-10 gene polymorphism contribute to the susceptibility of lung cancer. Method: We searched in PubMed, EMBASE, Cochrane Library as well as Chinese databases including China National Knowledge Infrastructure (CNKI) and Wan Fang database for all the relevant studies up to May 15, 2015. The data were extracted by two independent authors. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) under co-dominant model, dominant model and recessive model were estimated. Results: A total of 8 studies involving 2033 cases and 3100 controls were included in the meta-analysis. The results revealed that the IL-10 -592C/A polymorphism was related to lung cancer susceptibility under all models (C allele vs. A allele: OR=1.195, 95% CI=1.075-1.329; CC vs. AA: OR=1.651, 95%=1.290-2.113; CA vs. AA: OR=1.229, 95%=1.029-1.468; CA+AA vs. CC: OR=0.832, 95%=0.704-0.984; CC+CA vs. AA: OR=1.301, 95%=1.100-1.538) and IL-10 -819C/T polymorphism was associated with lung cancer susceptibility under three models (C allele vs. T allele: OR=1.441, 95% CI=1.228-1.691; CC vs. TT: OR=2.444, 95%=1.732-3.449; CC+CT vs. TT: OR=1.496, 95%=1.172-1.908). For IL-10 -1082G/A, there was no significant association between its polymorphism and lung cancer risk. Conclusions: This meta-analysis demonstrated that two polymorphisms (-592C/A and -819C/T) in the promoter region of IL-10 gene were significantly associated with the risk of lung cancer in general population, while -1082G/A polymorphism did not affect susceptibility to lung cancer.

Keywords: IL-10, polymorphism, lung cancer, systematic review, meta-analysis

Introduction

Lung cancer has become the most frequently occurring cancer worldwide, which accounts for 13% of the total cancer cases and 18% of total deaths each year [1]. Yet even now, the potential mechanism of lung carcinogenesis is still unclear. Tobacco smoking is considered to be the leading cause of lung cancer, but only about 15% of heavy tobacco smokers ultimately develop lung cancer [2]. It is established that lung cancer is a complex multifactorial disease resulting from the interactions between various genetic and environmental factors3. Chronic inflammation has long been deemed to be a crucial factor in the development of carcinogenesis [4]. Previous studies have suggested that many pro-inflammatory cytokines were involved in the pathogenesis of lung cancer [5, 6]. However, the molecular mechanisms underlying this relationship are not well explained.

Interleukin-10 (IL-10), mainly produced by many kinds of immune cells [7], is an anti-inflammatory cytokine involved in down-regulating cytotoxic and cell-mediated inflammatory responses [8]. And recent study has demonstrated that IL-10 has anti-angiogenic and immunosuppressive properties, which played an important role in the pathogenesis of cancer, including lung cancer [9].

The human IL-10 gene is located on chromosome 1q32 [10]. Promoter region polymorph-

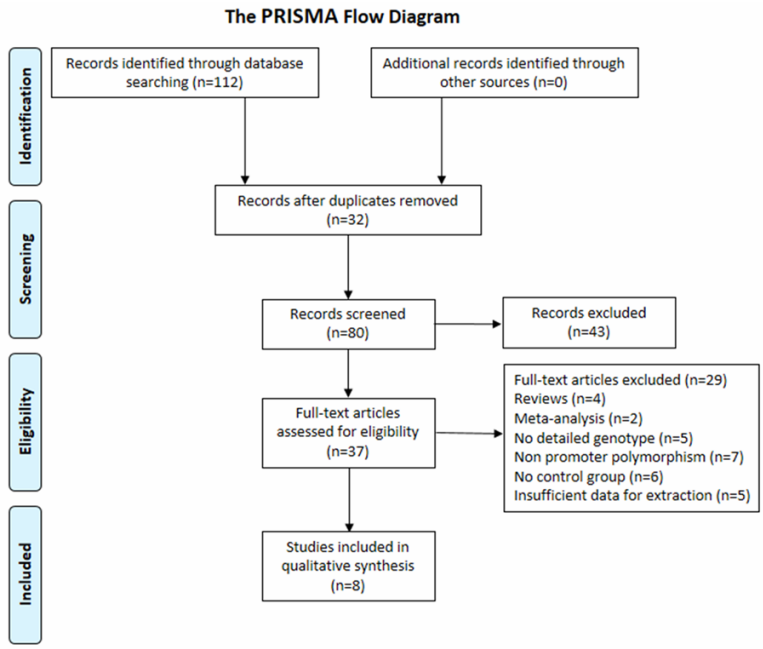


Figure 1. Flow chart of study selection.

isms appear to be correlated with variations in transcription. Three single nucleotide polymorphisms (SNPs), positioned at -1082G/A, -819C/T and -592C/A promoter regions, have been linked to effective production of IL-10. These polymorphisms have been investigated as potential susceptibility factors for lung cancer. Unfortunately, effects of IL-10 promoter polymorphisms on lung cancer genotypes in different studies are inconsistent and inconclusive [11-21]. Most studies used an inadequate sample sizes and lacked statistical power to obtain reliable conclusions. Therefore, we extensively reviewed literatures and conducted a meta-analysis to provide more credible evidence by systematically summarizing existed data.

Methods

Search strategy

An electronic search was performed in PubMed, EMBASE, Cochrane Library as well as Chinese databases including China National Knowledge Infrastructure (CNKI) and WanFang database for all the relevant studies utilizing the following search terms: “interleukin-10” or “IL-10”, “polymorphism” or “SNPs”, “lung cancer” or “lung carcinoma” (the latest research was updated to May 15, 2015). When more than one of the same patient population was included in several publications, only the most recent or complete study was used. Search and literature retrieval were completed independently by two investigators. Disagreements of the search result were settled by discussion among all the authors. No limitation was placed on publication status or language.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they met the following criteria: (1). the study assessed the association between lung cancer and IL-10 polymorphisms (-1082G/A, -819C/T and -592C/A); (2). using case-control or cohort design; (3). data in the studies were adequate to calculate odds ratio (OR) and 95% confidence interval (95% CI); (4). the genotype was tested in controls to ensure its fitting with the Hardy-Weinberg equilibrium (HWE). The major reasons for exclusion from our studies were: (1). family-based or sibling-based association studies; (2). the study without control group; (3). literature with insufficient data for evaluating OR and 95% CI; (4). reviews and abstracts. For overlapping studies, only the one with the largest sample numbers was included.

Data extraction

Two investigators independently extracted the data from all eligible studies according to the inclusion and exclusion criteria. We verified accuracy of data by comparing collection forms from each investigator. Any discrepancy was resolved by discussion. The following information was collected from each study: name of the first author, year of publication, country of origin, ethnicity of research population, experimental method, sample sizes of cases and controls, genotype distributions of cases and controls, and the Hardy-Weinberg equilibrium (HWE) results in controls.

Statistical analysis

We measure the strength of the association between IL-10 SNPs (-1082G/A, -819C/T and -592C/A) and lung cancer by pooled OR with its

Table 1. Characteristics of studies included in the systematic review and meta-analysis

	Study	Year	Country	Ethnicity	Genotyping method	Cases	Controls	Genotype frequency in cases			Genotype frequency in controls			P_{HWE}
-592C/A								CC	CA	AA	CC	CA	AA	
	Shih, C. M.	2005	Taiwan	Asian	PCR-RFLP	154	205	18	70	66	13	76	116	0.9
	Colakogullari, M.	2008	Turkey	Asian	PCR-SSP	44	59	19	23	2	27	25	7	0.74
	Vogel, U.	2008	Denmark	European	PCR	403	744	241	149	13	452	250	42	0.34
	Liang, H. G.	2011	China	Asian	PCR-RFLP	116	120	11	36	69	7	44	69	0.99
	Hsia, T. C.	2014	Taiwan	Asian	PCR-RFLP	358	716	40	145	173	71	277	368	0.08
	Zhang, Y. M.	2015	China	Asian	PCR-RFLP	330	336	110	156	64	75	176	85	0.37
-819C/T								CC	TC	TT	CC	TC	TT	
	Seifart, C.	2005	German	European	PCR-RFLP	77	242	42	31	4	140	88	14	0.97
	Shih, C. M.	2005	Taiwan	Asian	PCR-RFLP	154	205	30	58	66	15	86	104	0.63
	Colakogullari, M.	2008	Turkey	Asian	PCR-SSP	44	59	19	23	2	26	26	7	0.9
	Zhang, Y. M.	2015	China	Asian	PCR-RFLP	330	336	87	135	108	47	144	145	0.25
-1082G/A								AA	AG	GG	AA	AG	GG	
	Seifart, C.	2005	German	European	PCR-RFLP	115	243	30	54	31	86	115	42	0.74
	Colakogullari, M.	2008	Turkey	Asian	PCR-SSP	44	59	11	30	3	33	21	5	0.53
	Hart, K.	2011	Norway	European	TaqMan	436	435	120	207	109	104	226	105	0.41
	Hsia, T. C.	2014	Taiwan	Asian	PCR-RFLP	358	716	273	69	16	561	130	25	0.07

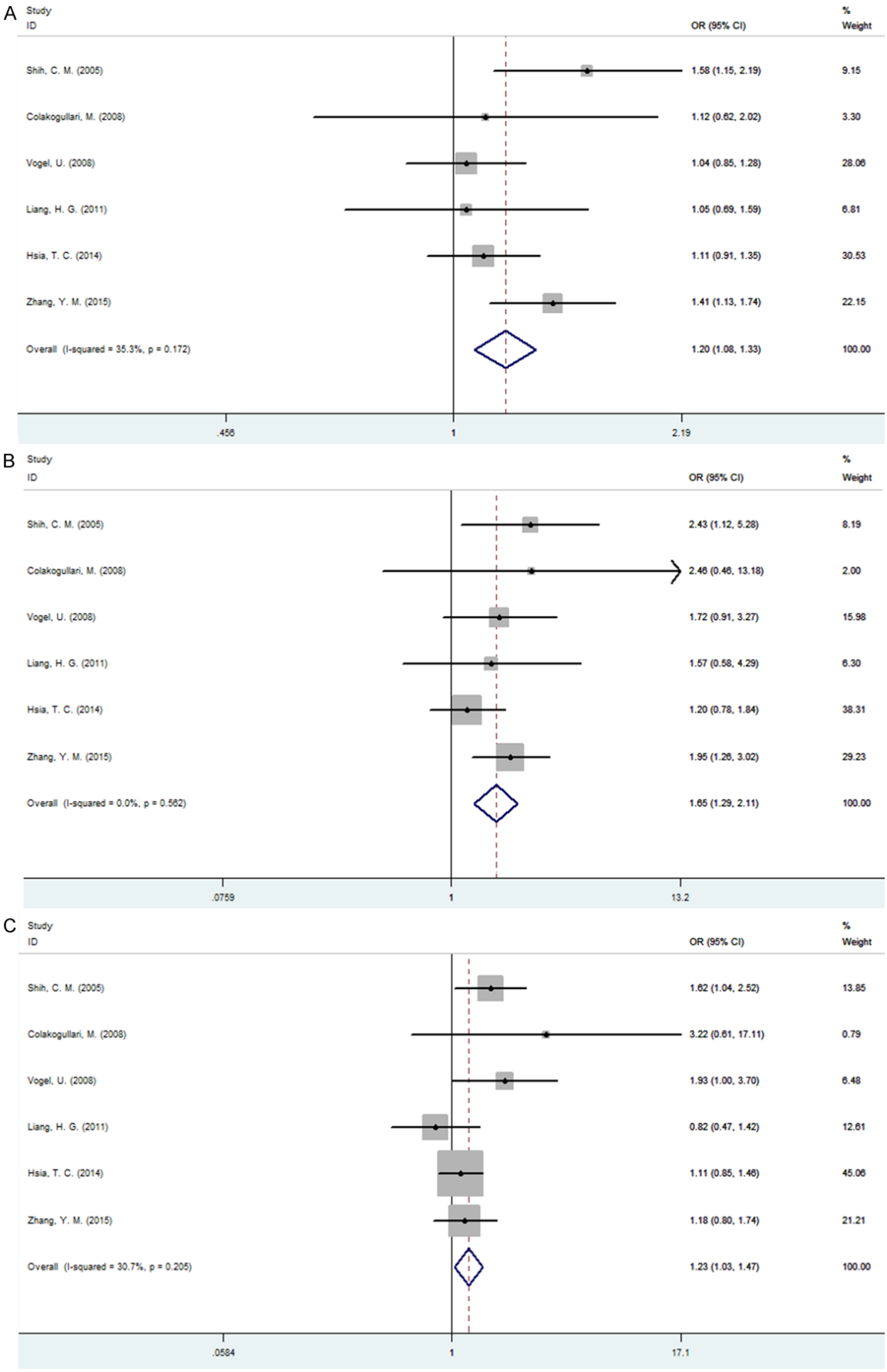
P_{HWE}, *p* value for Hardy-Weinberg Equilibrium test in controls.

Table 2. The meta-analysis results of association between IL-10 polymorphisms and lung cancer

SNPs	Contrast model	OR (95% CI)	P	Test for heterogeneity		Publication bias (Egger's test)	
				I^2 (%)	P	t	P
-592C/A	C vs. A	1.195 (1.075-1.329)	0.001	35.3	0.172	0.25	0.813
	CC vs. AA	1.651 (1.290-2.113)	0.000	0.0	0.562	1.01	0.372
	CA vs. AA	1.229 (1.029-1.468)	0.023	30.7	0.205	1.89	0.132
	CA+AA vs. CC	0.832 (0.704-0.984)	0.032	51.2	0.069	-0.83	0.452
	CC+CA vs. AA	1.301 (1.100-1.538)	0.002	25.6	0.242	1.69	0.167
-819C/T	C vs. T	1.441 (1.228-1.691)	0.000	49.7	0.114	-1.83	0.210
	CC vs. TT	2.444 (1.732-3.449)	0.000	0.0	0.446	-0.47	0.683
	CT vs. TT	1.220 (0.939-1.586)	0.137	0.0	0.663	1.25	0.337
	CT+TT vs. CC*	0.638 (0.354-1.151)	0.136	77.0	0.005	0.50	0.667
	CC+CT vs. TT	1.496 (1.172-1.908)	0.001	0.0	0.785	0.51	0.661
-1082G/A	A vs. G*	0.815 (0.626-1.061)	0.128	67.6	0.026	-3.05	0.093
	AA vs. GG	0.849 (0.641-1.126)	0.256	48.0	0.124	-1.30	0.322
	AG vs. GG	0.843 (0.651-1.091)	0.193	0.0	0.426	1.07	0.397
	AG+GG vs. AA*	1.340 (0.855-2.100)	0.201	77.6	0.004	1.78	0.145
	AA+AG vs. GG	0.839 (0.658-1.070)	0.158	4.7	0.369	-0.17	0.881

*Random-effect model was used.

corresponding 95% CI, which were estimated for allelic comparison, homozygote comparison, heterozygote comparison, dominant model and recessive model respectively. The *P* value of the pooled OR was considered significant if less than 0.05, which was examined by Z test. Heterogeneity across studies was determined by Chi-square test based Q statistic test and I [2] statistic and the presence of heterogeneity was confirmed if the result was $P<0.05$ and $I^2 \geq 50\%$. In the condition of existence of heterogeneity, a random-effect model was utilized [22]; otherwise the fixed-effect model was employed to pool the results [23]. Additionally, in order to evaluate the stability of results, a sensitivity analysis was conducted. Both Begg's test and Egger's test were performed to test whether publication bias existed or not. All the


A
Study ID
OR (95% CI)
% Weight
Shih, C. M. (2005) 1.58 (1.15, 2.19) 9.15
Colakogullari, M. (2008) 1.12 (0.62, 2.02) 3.30
Vogel, U. (2008) 1.04 (0.85, 1.28) 28.06
Liang, H. G. (2011) 1.05 (0.69, 1.59) 6.81
Hsia, T. C. (2014) 1.11 (0.91, 1.35) 30.53
Zhang, Y. M. (2015) 1.41 (1.13, 1.74) 22.15
Overall (I-squared = 35.3%, p = 0.172) 1.20 (1.08, 1.33) 100.00
.456
1
2.19
B
Study ID
OR (95% CI)
% Weight
Shih, C. M. (2005) 2.43 (1.12, 5.28) 8.19
Colakogullari, M. (2008) 2.46 (0.46, 13.18) 2.00
Vogel, U. (2008) 1.72 (0.91, 3.27) 15.98
Liang, H. G. (2011) 1.57 (0.58, 4.29) 6.30
Hsia, T. C. (2014) 1.20 (0.78, 1.84) 38.31
Zhang, Y. M. (2015) 1.95 (1.26, 3.02) 29.23
Overall (I-squared = 0.0%, p = 0.562) 1.65 (1.29, 2.11) 100.00
.0759
1
13.2
C
Study ID
OR (95% CI)
% Weight
Shih, C. M. (2005) 1.62 (1.04, 2.52) 13.85
Colakogullari, M. (2008) 3.22 (0.61, 17.11) 0.79
Vogel, U. (2008) 1.93 (1.00, 3.70) 6.48
Liang, H. G. (2011) 0.82 (0.47, 1.42) 12.61
Hsia, T. C. (2014) 1.11 (0.85, 1.46) 45.06
Zhang, Y. M. (2015) 1.18 (0.80, 1.74) 21.21
Overall (I-squared = 30.7%, p = 0.205) 1.23 (1.03, 1.47) 100.00
.0584
1
17.1

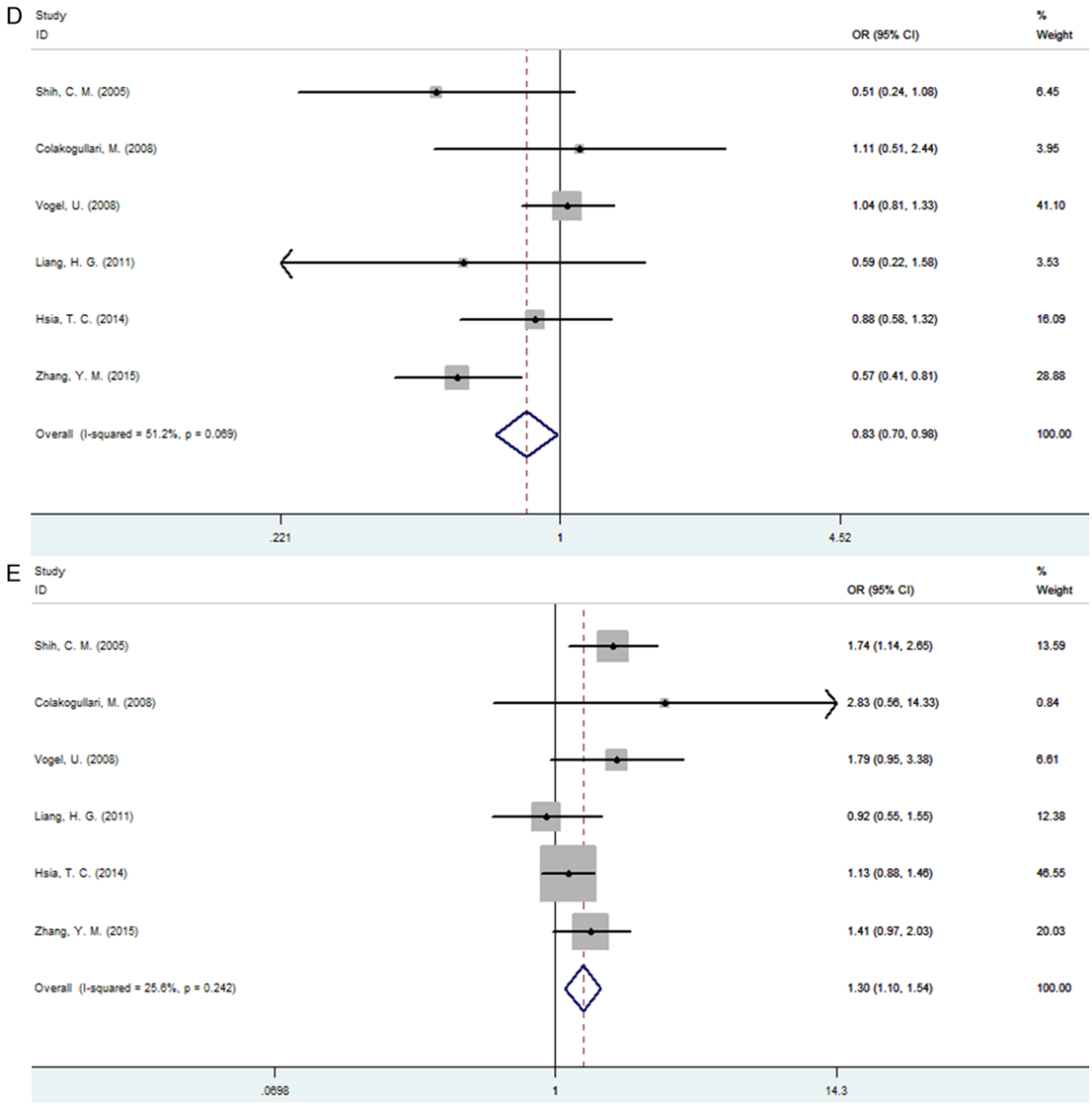


Figure 2. Forest plot of association between IL-10-5922C/A polymorphism and lung cancer. A. C allele vs. A allele; B. CC vs. AA; C. CA vs. AA; D. CA+AA VS. CC; E. CC+CA vs. AA.

analyses that have been mentioned were completed by STATA v.12.0.

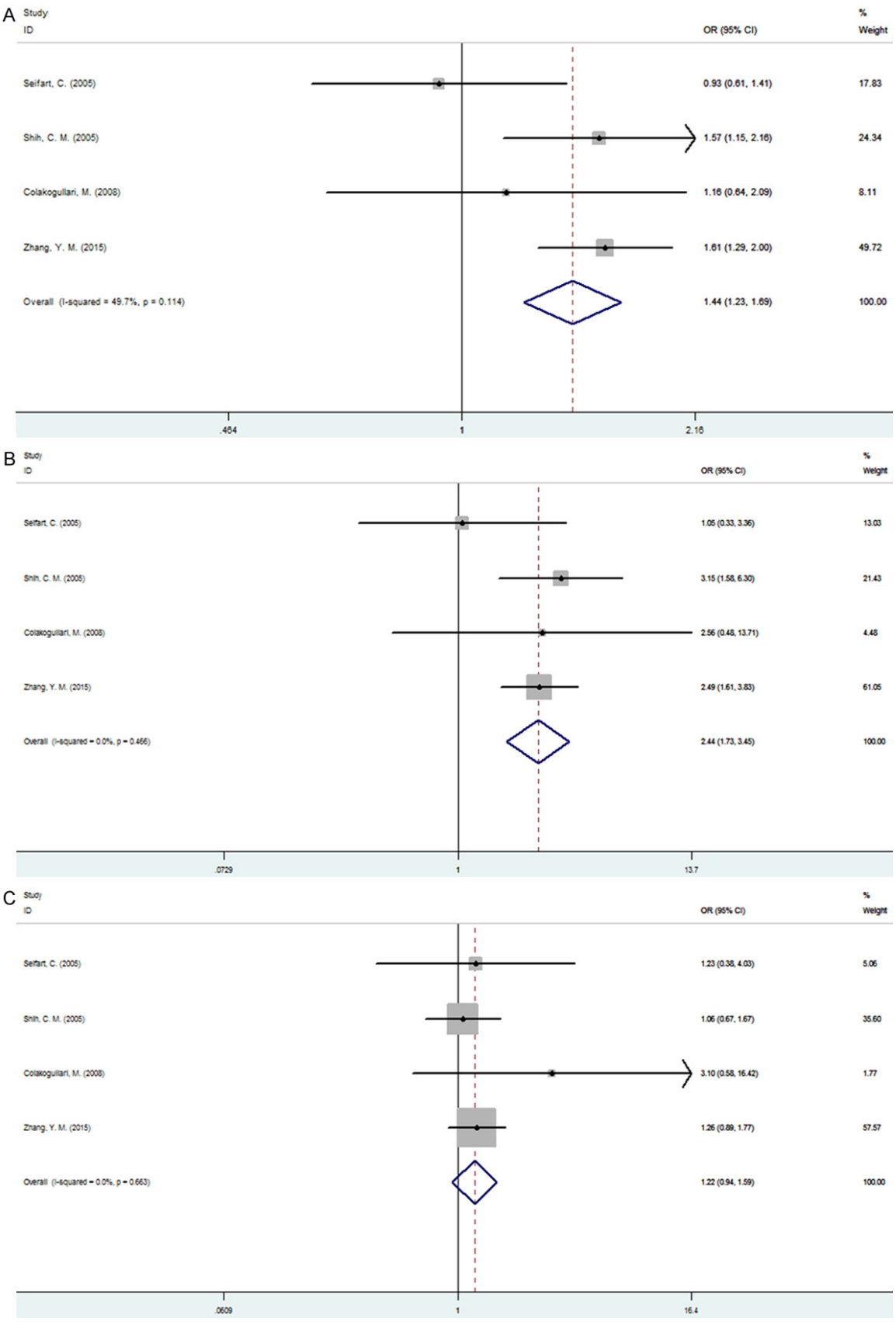
Results

Characteristics of included studies

As shown in the **Figure 1**, 112 articles were found according to the search strategy and then 32 duplicates are removed. Meanwhile, 43 records without full-text were excluded. After reading the abstracts and full-texts of the remaining 37 articles, 29 records not conforming to the inclusion criteria were further excluded. Eventually, 8 studies involving a total of 2033 cases and 3100 controls met the criteria were included in the meta-analysis of which 9 articles were in English and other 1 in Chinese. The characteristics of included articles were showed in **Table 1** and all of them were case-control study.

Quantitative data synthesis

A summary of this meta-analysis results concerning the relationships between IL-10 polymorphism and lung cancer is provided in **Table 2**. Six studies determined IL-10 -592C/A polymorphism were included in pooling. Total sample sizes for lung cancer and control groups


A
Study ID
OR (95% CI)
% Weight
Seifart, C. (2005)
0.93 (0.61, 1.41)
17.83
Shih, C. M. (2005)
1.57 (1.15, 2.16)
24.34
Colakogullari, M. (2008)
1.16 (0.64, 2.09)
8.11
Zhang, Y. M. (2015)
1.61 (1.29, 2.00)
49.72
Overall (I-squared = 49.7%, p = 0.114)
1.44 (1.23, 1.69)
100.00
.464
1
2.16
B
Study ID
OR (95% CI)
% Weight
Seifart, C. (2005)
1.05 (0.33, 3.36)
13.03
Shih, C. M. (2005)
3.15 (1.58, 6.30)
21.43
Colakogullari, M. (2008)
2.56 (0.48, 13.71)
4.48
Zhang, Y. M. (2015)
2.49 (1.61, 3.83)
61.05
Overall (I-squared = 0.0%, p = 0.466)
2.44 (1.73, 3.45)
100.00
.0729
1
13.7
C
Study ID
OR (95% CI)
% Weight
Seifart, C. (2005)
1.23 (0.38, 4.03)
5.06
Shih, C. M. (2005)
1.06 (0.67, 1.67)
35.60
Colakogullari, M. (2008)
3.10 (0.58, 16.42)
1.77
Zhang, Y. M. (2015)
1.26 (0.89, 1.77)
57.57
Overall (I-squared = 0.0%, p = 0.663)
1.22 (0.94, 1.59)
100.00
.0609
1
16.4

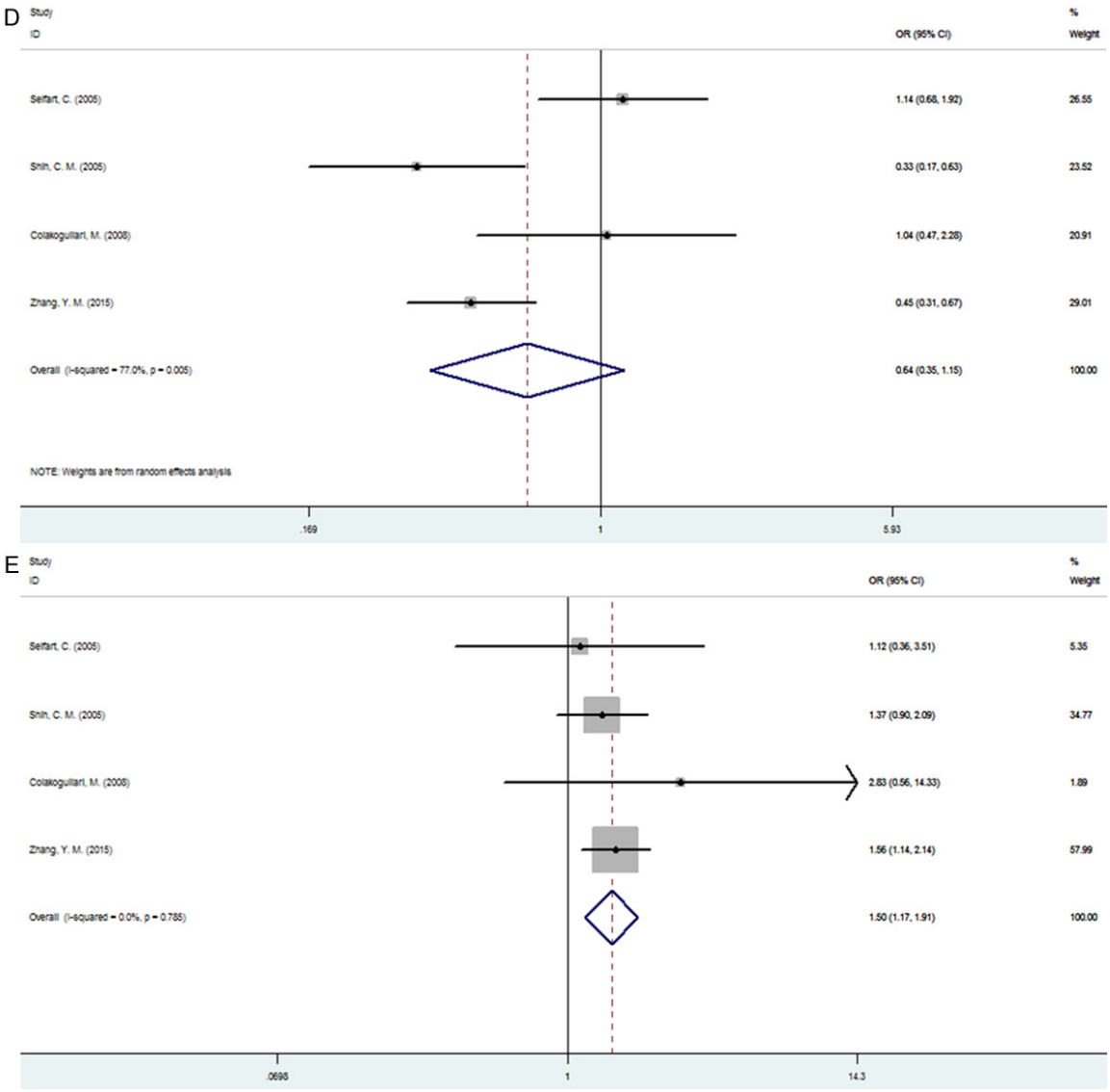
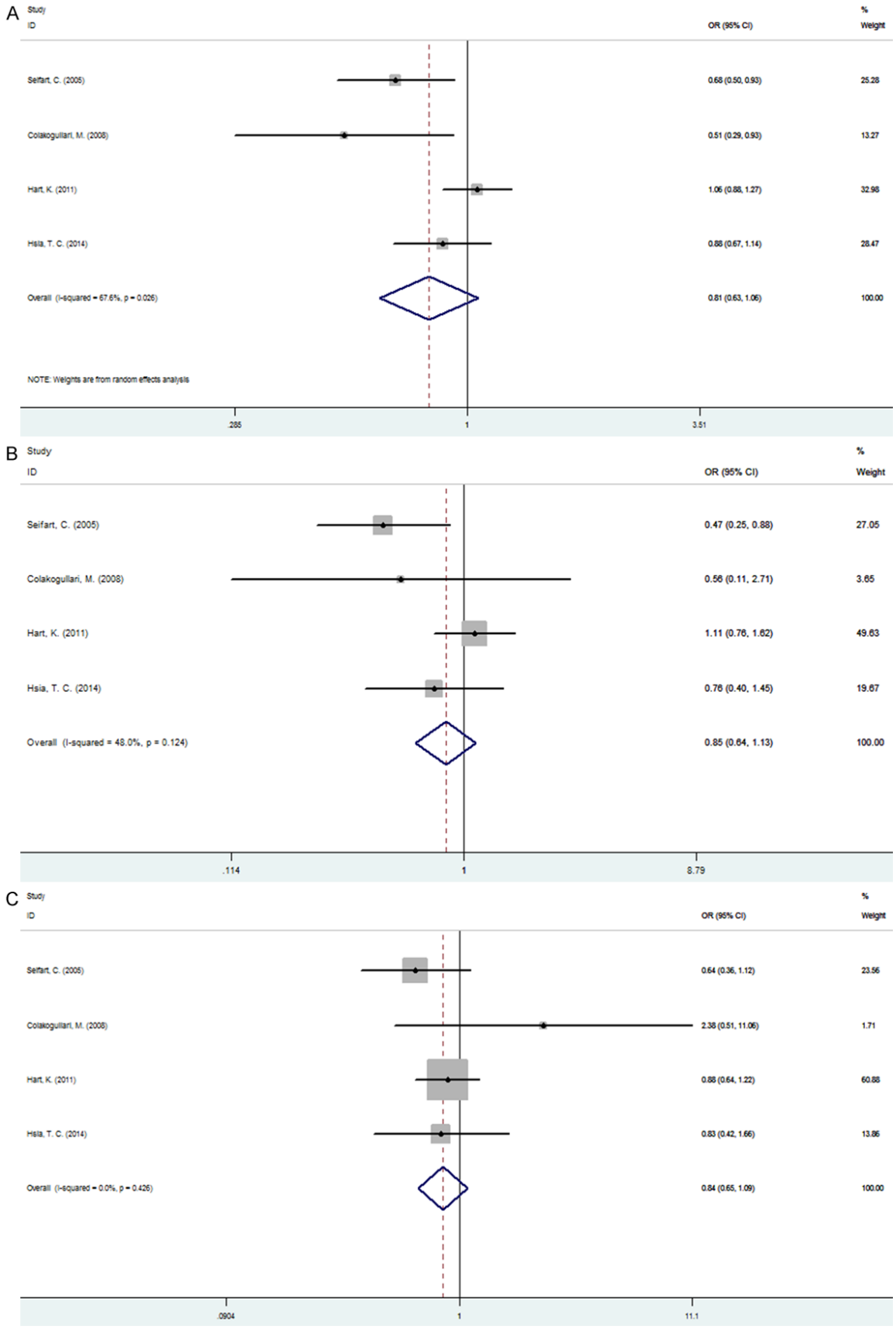


Figure 3. Forest plot of association between IL-10-8192C/T polymorphism and lung cancer. A. C allele vs. T allele; B. CC vs. TT; C. CT vs. TT; D. CT+TT VS. CC; E. CC+CT vs. TT.

were 1405 and 2180. Overall, the results of pooling all studies showed that IL-10 -592C/A polymorphism exhibited the obvious association with lung cancer susceptibility in general population under allelic, homozygous, heterozygous, recessive and dominant model (C allele vs. A allele: OR=1.195, 95% CI=1.075-1.329, P=0.001; CC vs. AA: OR=1.651, 95%=1.290-2.113, P<0.001; CA vs. AA: OR=1.229, 95%= 1.029-1.468, P=0.023; CA+AA vs. CC: OR= 0.832, 95%=0.704-0.984, P=0.032; CC+CA vs. AA: OR=1.301, 95%=1.100-1.538, P= 0.002) (**Figure 2**). No significant heterogeneity was found in all the five models. The fixed-effect model was therefore chosen to synthesize the data.

Four studies involving a total of 605 cases and 842 controls that identified the association between IL-10 -819C/T polymorphism and lung cancer risk were included in this meta-analysis. The results suggested that IL-10 -819C/T polymorphism was associated with lung cancer susceptibility under allelic, homozygous and dominant model (C allele vs. T allele: OR=1.441, 95% CI=1.228-1.691, P<0.001; CC vs. TT: OR=2.444, 95%=1.732-3.449, P<0.001; CC+ CT vs. TT: OR=1.496, 95%=1.172-1.908, P=


A
Study ID
OR (95% CI)
% Weight
Seifart, C. (2005) 0.68 (0.50, 0.93) 25.28
Colakogullari, M. (2008) 0.51 (0.29, 0.93) 13.27
Hart, K. (2011) 1.06 (0.88, 1.27) 32.98
Hsia, T. C. (2014) 0.88 (0.67, 1.14) 28.47
Overall (I-squared = 67.6%, p = 0.026) 0.81 (0.63, 1.06) 100.00
NOTE: Weights are from random effects analysis
.285
1
3.51
B
Study ID
OR (95% CI)
% Weight
Seifart, C. (2005) 0.47 (0.25, 0.88) 27.05
Colakogullari, M. (2008) 0.56 (0.11, 2.71) 3.65
Hart, K. (2011) 1.11 (0.76, 1.62) 49.63
Hsia, T. C. (2014) 0.76 (0.40, 1.45) 19.67
Overall (I-squared = 48.0%, p = 0.124) 0.85 (0.64, 1.13) 100.00
.114
1
8.79
C
Study ID
OR (95% CI)
% Weight
Seifart, C. (2005) 0.64 (0.36, 1.12) 23.56
Colakogullari, M. (2008) 2.38 (0.51, 11.06) 1.71
Hart, K. (2011) 0.88 (0.64, 1.22) 60.88
Hsia, T. C. (2014) 0.83 (0.42, 1.66) 13.86
Overall (I-squared = 0.0%, p = 0.426) 0.84 (0.65, 1.09) 100.00
.0904
1
11.1

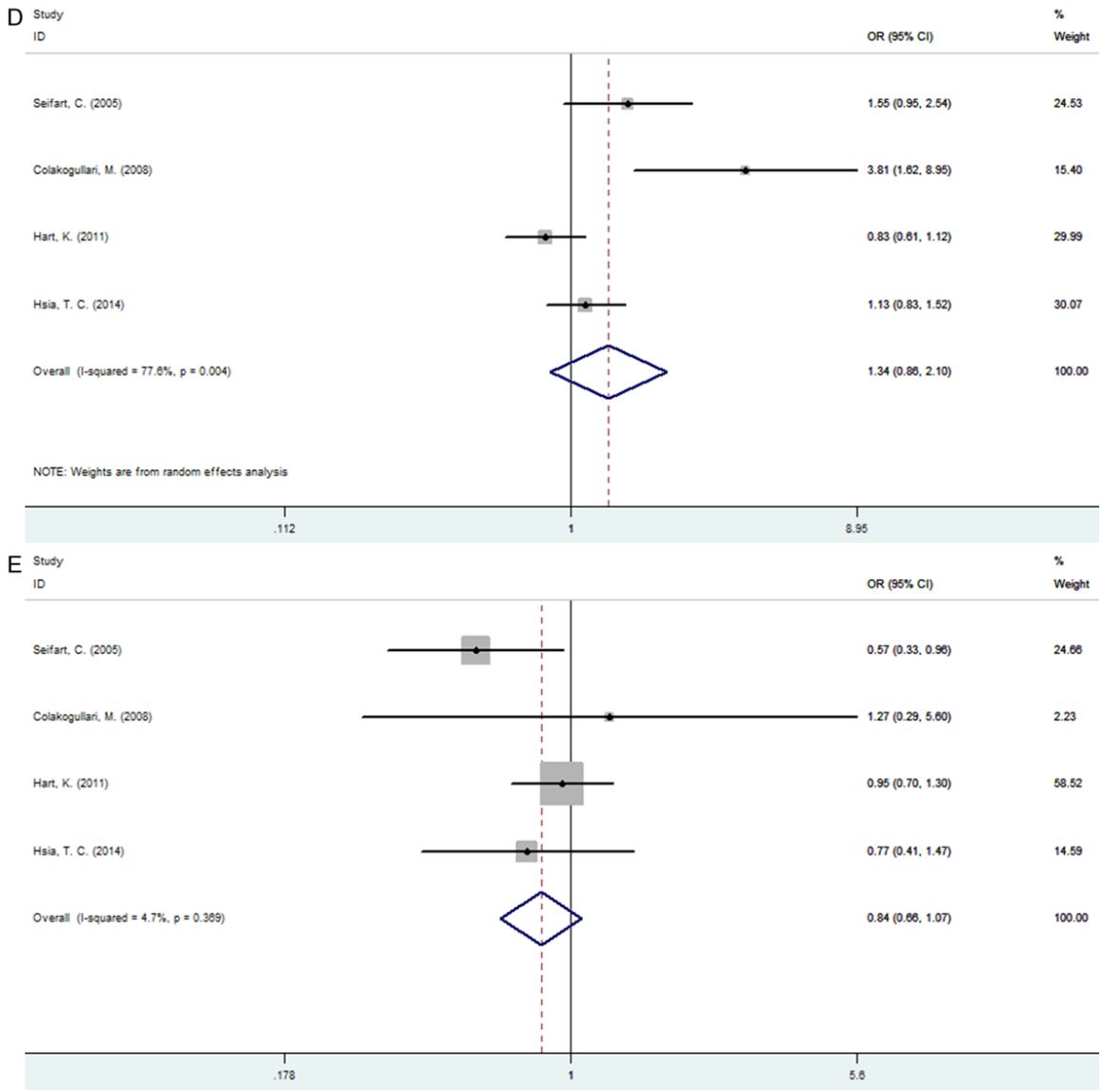


Figure 4. Forest plot of association between IL-10-1082G/A polymorphism and lung cancer. A. A allele vs. G allele; B. AA vs. GG; C. AG vs. GG; D. AG+GG VS. AA; E. AA+AG vs. GG.

0.001). However, under heterozygous and recessive model, we observed no association between IL-10 -819C/T polymorphism and lung cancer risk (CT vs. TT: OR=1.220, 95% CI= 0.939-1.586, P=0.137; CT+TT vs. CC: OR= 0.638, 95%=0.354-1.151, P=0.136) (**Figure 3**). Meanwhile, significant heterogeneity was detected under the recessive model and a random-effect model was utilized to pool the data.

For the IL-10 -1082G/A polymorphism, 4 studies (953 cases and 1453 controls) were pooled to perform the meta-analysis and the results indicated there was no significant between IL-10 -1082G/A polymorphism and lung cancer susceptibility under all the five models (A allele vs. G allele: OR=0.815, 95% CI=0.626-1.061, P=0.128; AA vs. GG: OR=0.849, 95%=0.641-1.126, P=256; AG vs. GG: OR=0.843, 95%= 0.651-1.091, P=0.193; AG+GG vs. AA: OR= 1.340, 95%=0.855-2.100, P=0.201; AA+AG vs. GG: OR=0.839, 95%=0.658-1.070, P= 0.158) (**Figure 4**). Under allelic and recessive model, because of significant between-study heterogeneity for the association, we used random-effect model to complete the synthesis of data.

Since there was above-mentioned significant heterogeneity for association between IL-10 polymorphism and risk of lung cancer, we performed a subgroup analysis to explore source of heterogeneity. We introduced variables including year of publication, ethnicity of research population, experimental method, sample sizes of cases and controls. Nevertheless, these variables cannot explain the source of heterogeneity.

Publication bias and sensitivity analysis

Begg's funnel plot and Egger's test were performed to assess the publication bias of included studies. The shapes of funnel plot were symmetrical, which have not implied the existence of publication bias. All the Egger's test results of three SNPs were demonstrated in **Table 2**, all *P* values were greater than 0.05 and thus there was no obvious publication bias in the meta-analysis.

Sensitivity analysis was performed to evaluate the stability of the result. Each data set was omitted individually to investigate the impact of a single study on the pooled ORs. The exclusion of any single study did not alter the overall conclusion, indicating that results were reliable.

Discussion

To date, convincing evidence indicate that the outcome of lung cancer is modulated by the environment and host genetic components. Many investigations have confirmed that cytokines appear to play the critical roles in the development of lung cancer. Polymorphisms in several cytokine genes have been described and demonstrated to influence gene transcription, leading to inter individual variations in cytokine [24].

IL-10 is a potent immunomodulatory molecule that inhibits the synthesis of pro-inflammatory cytokines, and upregulates of B cell production and differentiation [25]. IL-10 production has also been implicated in the development of various types of cancers, including lung cancer, and may also protect tumors by inhibiting cytotoxic T lymphocyte (CTL)-mediated tumor-specific cell lysis [12], suggesting that IL-10 gene may play an important role in the pathogenesis of lung cancer. Furthermore, Polymorphisms in the promoter of the IL-10 gene, consisting of three SNPs (-1082G/A, -819C/T and -592C/A), have been reported to influence its production capacity [26] and to be associated with the risk of different cancer types. Although a number of studies have investigated the association between the IL-10 promoter polymorphism and susceptibility to lung cancer, the results were controversial and unconvincing. Therefore, it is necessary to use a quantitative approach for combining the results of these studies, and for estimating and explaining their diversity.

This current meta-analysis of 8 case-control studies including 2033 cases and 3100 controls evaluated the association between IL-10 polymorphism and lung cancer risk. We found that -592C/A polymorphism was a risk factor for developing lung cancer between patients with lung cancer and control subjects. The results demonstrated that compared with homozygote (-592AA) genotype, both the variant (-592CC) genotype and the heterozygote (-592CA) genotype were significantly associated with lung cancer risk. In addition, the C allele carriers (CC+CA) had a 30% increased risk of lung cancer, as compared with those individuals with the AA homozygote. Overall, the -592C allele may contribute to the susceptibility of lung cancer. Similarly, -819C/T polymorphism was also significantly associated with lung cancer risk, with carriers of the C allele (CC+CT) having a 50 increased risk. However, compared with homozygote (-819TT) genotype, the heterozygote (-819CT) genotype was not associated with lung cancer risk, indicating that the statistical difference under the dominant model originated from the variant homozygote (-819CC) genotype which had a 140% increased risk of lung cancer. In terms of -1082G/A polymorphism, the results in pooling all studies presented no evidence to support the association between this polymorphism and susceptibility of lung cancer. Due to the limit of the number of studies, we should prudently consider the conclusions. The current consensus is that lung cancer is a multi-factorial disease that results from complex interactions between many environmental and genetic factors, and the interaction among some other SNPs might affect the relationship of each polymorphism included with the development of lung cancer. Hence, if we only consider suspected gene polymorphisms in lung cancer neglecting the role of environmental factors or other genes, we might fail to conclude a real association.

In addition, the existence of heterogeneity may potentially affect the interpretation of the results, which may be attributed to the year of publication, ethnicity of research population, experimental method, sample sizes of cases and controls, or the interaction with other risk factors. In our meta-analysis, there was significant heterogeneity for association between two IL-10 promoter polymorphisms (-819C/T and -1082G/A) and risk of lung cancer under certain genetic models. However, subgroup analysis in consideration of the potential confounders did not address the heterogeneity.

There are several limitations that should be considered when interpreting our results. Firstly, this meta-analysis was based on a relatively small number of studies, especially in the case of -819C/T and -1082G/A polymorphisms, which respectively included only four studies. Secondly, given that only published studies were included in this study, there may be publication bias, although our results of publication bias showed no significance. Thirdly, significant between study heterogeneity was detected in some comparisons, and as such, results may be distorted. Moreover, we included no prospective study to confirm the correlation between IL-10 promoter polymorphisms and risk of lung cancer, which can provide a higher credibility.

Conclusions

In conclusion, this meta-analysis demonstrated that two polymorphisms (-592C/A and -819C/T) in the promoter region of IL-10 gene were significantly associated with the risk of lung cancer in general population, while -1082G/A polymorphism did not affect susceptibility to lung cancer. However, taking above-mentioned shortcomings into consideration, more evidence of prospective, multi-centric and multi-populational trials are needed to further explore the association between the IL-10 promoter polymorphism and susceptibility to lung cancer.

Disclosure of conflict of interest

None.

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