RESEARCH ARTICLE

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Correlation between rs1800871, rs1800872 and rs1800896 Polymorphisms at *IL-10* Gene and Lung Cancer Risk

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Abstract

Background: The tumorigenesis of lung cancer is complicated, and genetic factor may have the role in the malignant transformation of lung cells. *IL-10* gene polymorphisms have been evaluated for their potential roles in lung cancer. However, those studies results are controversial. To clarify the effects of *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms on the risk of lung cancer, a meta-analysis was performed with eligible individual studies. **Methods:** Eligible publications were gathered by retrieving PubMed, Web of Science, Embase, Wan Fang, and CNKI up to September 01, 2023. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of such association. **Results:** A total of 23 studies, including 5950 patients with lung cancer and 8046 healthy controls, were identified in this meta-analysis. Overall, there was no a significant association between the rs1800871, rs1800872 and rs1800896 polymorphisms at *IL-10* gene and susceptibility to lung cancer globally when all studies in the pooled into this meta-analysis. Stratified analysis by ethnicity showed that rs1800872 polymorphism was associated with lung cancer among Asians and Caucasians. However, no significant association was identified between the rs1800871 and rs1800896 and risk of lung cancer. **Conclusions:** Pooled data showed that *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms were not associated with lung cancer globally. Future well-designed large case-control studies with different ethnicities are recommended.

Keywords: Interleukin 10- Polymorphism- Lung neoplasms- Meta-analysis

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Introduction

Lung cancer is one of the most common types of human cancer, and it is additionally one of the leading causes of cancer associated mortality globally [1-3]. A meta-analysis revealed a statistically significant increase in mortality rate in lung cancer patients compared with other patients with cancer [4, 5]. It is estimated that Lung cancer remained the leading cause of cancer death and was responsible for 1.8 million deaths, or 18% of all deaths due to cancer in 2020 globally [6, 7]. However, it is noted that women were less than half as likely to die of lung cancer as men [6, 8]. Lung cancer is the most frequently occurring cancer and the leading cause of cancer death in men, followed by prostate and colorectal cancer for incidence and liver and colorectal cancer for mortality. According to the latest GLOBOCAN estimates, lung cancer ranks first (39 per 100,000) and prostate cancer ranks second (37.5 per 100,000) in higher HDI countries, and vice versa for lower HDI countries (11.3 per 100,000 for prostate cancer and 10.3 per 100,000 for lung cancer) [7, 9]. Lung cancer is categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC, which constitutes ~80% of all lung cancers, is further classified into three major pathologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell

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carcinoma [10-12].

Genetic susceptibility to lung cancer occurs mainly through rare germline pathogenic variants specifically associated with cancer risk [13-15]. Smoking and air pollution are the major causes of lung cancer; however, numerous studies have demonstrated that genetic factors also contribute to the development of lung cancer [16-18]. A decade after the first genome-wide association study (GWAS) published for of lung cancer was published approximately 45 genomic loci has now been significantly associated with lung cancer risk. These include the 5p15 locus (telomerase reverse transcriptase), the 6p21 locus (regulates G-protein signaling), and the 15q25-26 loci, which have been shown to increase nicotine dependence and lung cancer susceptibility [19, 20].

The biological significance of *IL-10* is extensive and diverse because of its role in many diseases [21-23]. *IL-10* is known to play a substantial role in inflammation and immune processes [24]. *IL-10* has been reported to inhibit the production of proinflammatory cytokines tumor necrosis factor alpha (TNFα), interleukin 1α and β (IL1α and β), interleukin IL-6 (IL-6), and interleukin-8 (IL-8), while stimulating B-cell proliferations, differentiation, and production [25-29]. *IL-10* is an immunomodulatory cytokine encoded by the *IL-10* gene on chromosome 1q31-32, containing five exons separated by four introns, and its receptor is located on chromosome 11 [30-32]. Polymorphisms located in the 5′-flanking region of the *IL-10* gene are known to be involved in regulating the production of *IL-10* [33, 24]. Among the cancer susceptibility studies, rs1800871 (-819C>T), rs1800872 (-592C>A) and rs1800896 (-1082A>G) polymorphisms are the most widely studied mutation point [34]. The promoter region polymorphisms of *IL-10* gene has been associated with susceptibility to several cancers including lung cancer [35, 36, 13, 37]. Many studies have reported the relationship between race and *IL-10* gene polymorphism and lung cancer risk in recent years. Zhang et al., reported a significant association of the *IL-10* rs1800871 and rs1800872 polymorphisms with lung cancer in a Chinese population [38], while Hsia et al., have reported that the *IL-10* rs1800871 polymorphism may have a protective effect on lung cancer risk among Taiwanese population [39]. Therefore, to estimate the effect of the rs1800871, rs1800872 and rs1800896 polymorphisms at *IL-10* gene with 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

The ethical approval was not required for this study, as it is a systematic review and meta-analysis. This work was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The identification and selection of articles were performed in the databases Science Direct, the National Library of Medicine National Institutes of Health of the USA (PUBMED), PubMed, EMBASE, Wed of Science, Elsevier, Google Scholar, Cochrane Library, SciELO, SID, WanFang, VIP, Chinese Biomedical Database (CBD) and Chinese National Knowledge Infrastructure (CNKI) to identify all relevant studies on the association of *IL-10* rs1800871 (-819C>T), rs1800872 (-592C>A) and rs1800896 (-1082A>G) polymorphisms with risk of lung cancer. The time cutoff was designated from the beginning of publications on the rs1800871, rs1800872 and rs1800896 polymorphisms until September 01, 2023. Combinations of the following MeSH terms and keywords were used in the search: (''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 (''Gene'' OR ''Single-Nucleotide Polymorphism'' or "SNP" OR ''Polymorphism'' OR ''Genotype' OR ''Allele'' OR ''Variation'' OR ''Mutation''). The search was limited to human studies published in English and Chinese language. We also reviewed the references list of relevant reviews and eligible publications to find other potentially sources.

Inclusion and exclusion criteria

Studies meeting the following criteria were included: 1) it was published by September 01, 2023; 2) studies with case-control or cohort design; 3) studies evaluated association of *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms with lung cancer; 4) studies with available and sufficient data for calculating an odds ratio (OR) with 95% confidence interval (CI). The following exclusion criteria were also used: 1) papers do not involve human subjects; 2) studies with in sufficient data on genotype frequencies; 3) unrelated to each of lung cancer and *IL-10* polymorphisms; 4) studies involving family members (including sibling, twins and trios-parents studies), because their analysis was based on linkage considerations; 5) abstracts, case reports, commentaries, editorials, conference articles, reviews, proceedings and meta-analyses; and 6) duplicates or overlapping studies. If more than one study was published by the same author(s) using repeated or overlapped data, the studies with the largest sample size or the most recently published study was included to the meta-analysis.

Data extraction

Two independent investigators who were co-authors of this meta-analysis were selected to screen the search results. After they found relevant publications, they searched the full text of those studies, read them carefully, and evaluated them to decide whether to include or exclude them. The whole process was done by two investigators independently. If there was any disagreement over whether to include an article, they would discuss it with a third reviewer to decide whether to include the article. 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).

Quality Score Assessment

The Newcastle-Ottawa Score (NOS) were performed to assess the quality of included studies in the meta-analysis and to assess the various aspects of the methodology used by the observational research, which are relevant to the quality of the study. This standard assessed 3 sections (selection of cases, comparability of groups, and determination of exposure) and 8 items. In the selection and exposure categories, a quality research item received 1 star, and a comparable category could receive at most 2 stars. The quality assessment values ranged from 0 stars (worst) to 9 stars (best), and studies with a score ≥7 were defined as high quality. Generally, the study which scored at least 5 points was considered to be included in meta-analysis and any discrepant opinions were resolved by discussion and consensus.

Statistical Analysis

The strength of the association between *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms and lung cancer risk was estimated by odds ratio (OR) with the corresponding 95% confidence intervals (CIs). The significance of pooled ORs was tested by Z-test, in which P<0.05 was considered significant. The association of *IL-10* rs1800871 (-819C>T), rs1800872 (-592C>A) and rs1800896 (-1082A>G) polymorphisms was estimated under five 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. The chi-square test was used to evaluate the between-study heterogeneity. If P <0.10, it was considered to have significant heterogeneity in statistics [40, 41]. Moreover, I2 test to quantify the heterogeneity, which ranges from 0 to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance (I2<25%, no heterogeneity; I2 25-50%, moderate heterogeneity; I2>50%, large or extreme heterogeneity) [42, 43]. When significant heterogeneity existed, we selected a random-effects model (the DerSimonian and Laird method) for statistics. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used [44, 35, 45, 41, 46]. The Hardy-Weinberg equilibrium (HWE) of the controls was evaluated by Fisher exact test and a p-value less than 0.05 was considered as significant disequilibrium (HWE-violating) [47-49]. Subgroup analyses by ethnicity, country, source of controls, and genotyping methods were performed to explore the potential sources of between-study heterogeneity in the meta-analysis [50, 33, 51]. One-way sensitivity analysis, by which a single study in the meta-analysis was omitted each time to reflect the influence of the individual data set for the pooled OR, was carried out to assess the stability of the results [31, 52, 53]. Moreover, sensitivity analysis was performed by excluding HWE-violating studies. To assess the potential influences of the publication bias on the results, Begg's funnel plots were generated. An asymmetrical plot usually indicates the existence of the publication bias [54-56]. Moreover, Egger's linear regression test which measures funnel plot asymmetry using a natural logarithm scale of OR was performed to evaluate the symmetry of the plot. All statistical tests were performed using Comprehensive Meta-Analysis (CMA) version 2.0 software (Biostat, USA). All P values in the meta-analysis were 2-sided, and P values less than 0.05 were considered significant.

Results

Characteristics of the Included Studies

The corresponding characteristics were seen in Table 1. The flow chart of literature search and study selection was illuminated in Figure 1. After a comprehensive literatures search we have identified 612 articles. Among them, 252 were excluded based on titles and abstracts. The full texts of the remaining 119 articles were screened and 69 studies were excluded based on inclusion and exclusion criteria. Finally, a total of 23 case-control studies in 12 publications [57-63, 39, 38, 64-66] on 5950 patients with lung cancer and 8046 healthy controls were included in the meta-analysis. The details of each study were shown in Table 1. Of those studies, six case-control studies [57, 58, 39, 38, 65] with 1543 cases and 2175 controls were on rs1800871, eight case-control studies [58-60, 62, 63, 39, 38, 65] with 2410 cases and 3234 controls on rs1800872, and nine case-control studies [57, 58, 60, 61, 63, 39, 64-66] with 1997 cases and 2637 controls on the rs1800896. The publication year of studies ranged from 2005 to 2018. Among the included studies, 12 were preformed among the Asians and eleven among the Caucasians. The countries of these studies included Germany, Taiwan, Turkey, China, United States, Denmark, Norway and India. The genotypes in the healthy control group for four studies were not consistent with HWE (P < 0.05).

Quantitative Synthesis

The summary of the meta-analysis of the association between *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms and susceptibility to lung cancer risk were listed in Tables 2-4. Pooled data showed that there was no a significant association between *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms and lung cancer risk under all five genetic models in overall population worldwide (Figure 2). Stratified analysis by ethnicity revealed that the *IL-10* rs1800872 polymorphism was associated with lung cancer risk in Asians under four genetic models, i.e., allele (C vs. A: OR= 1.261, 95% CI 1.112-1.430, p≤0.001), homozygote (CC vs. AA: OR= 1.615, 95% CI 1.229-2.214, p=0.001), dominant (CC+CA vs. AA: OR= 0.658, 95% CI 0.517-0.837, p=0.001), and recessive (CC vs. CA+AA: OR= 1.521, 95% CI 1.195-1.935, p=0.001), and Caucasians under the recessive model (CC vs. CA+AA: OR= 0.837, 95% CI 0.706-0.993, p=0.041, Table 3). However, stratified analysis by ethnicity also revealed that there was not a significant association between rs1800871 and rs1800896 polymorphisms of *IL-10* gene and lung cancer among Asians and Caucasians (Tables 2, 4).

Sensitivity Analysis

Meta-analyses were performed repeatedly when each eligible study had been removed. The results indicated that

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

First Author/Year	Ethnicity (Country)	Type	SOC	Genotyping Methods	Case/Control	Patients					Healthy Control					MAFs	HWE	NOS
						Genotypes			Alleles		Genotypes			Alleles				
rs1800871						TT	TC	CC	T	C	TT	TC	CC	T	C			
Seifart 2005	Germany(Caucasian)	NSCLC	HB	PCR-RFLP	40/242	24	14	2	62	18	140	88	14	368	116	0.76	0.972	7
Shih 2005	Taiwan(Asian)	NSCLC	HB	PCR-RFLP	154/205	66	58	30	190	118	104	86	15	294	116	0.283	0.627	7
Colakogullari 2008	Turkey(Caucasian)	LC	HB	PCR-SSP	44/59	19	23	2	61	27	26	26	7	78	40	0.661	0.898	7
Hsia 2014	Taiwan(Asian)	LC	HB	PCR-RFLP	358/716	212	128	18	552	164	372	265	79	1009	423	0.295	0.003	7
Zhang 2015	China(Asian)	LC	HB	PCR-RFLP	330/336	108	135	87	351	309	145	144	47	434	238	0.354	0.246	8
Eaton 2018	USA(Caucasian)	LC	PB	TaqMan	617/617	382	195	40	959	275	371	206	40	948	286	0.232	0.121	8
rs1800872						AA	AC	CC	A	C	AA	AC	CC	A	C			
Shih 2005	Taiwan(Asian)	NSCLC	HB	PCR-RFLP	154/205	66	70	18	202	106	116	76	13	308	102	0.249	0.907	7
Colakogullari 2008	Turkey(Caucasian)	LC	HB	PCR-SSP	44/59	19	23	2	61	27	27	25	7	79	39	0.669	0.743	7
Vogel 2008	Denmark(Caucasian)	LC	HB	PCR	403/744	241	149	13	631	175	452	250	42	1154	334	0.776	0.341	8
Liang 2011	China(Asian)	LC	HB	PCR-RFLP	116/120	69	36	11	174	58	69	44	7	182	58	0.242	0.996	7
Hart 2011	Norway(Caucasian)	NSCLC	HB	TaqMan	434/433	243	175	15	661	205	264	144	26	672	196	0.774	0.287	8
Hsia 2014	Taiwan(Asian)	LC	HB	PCR-RFLP	358/716	173	145	40	491	225	368	277	71	1013	419	0.293	0.079	7
Zhang 2015	China(Asian)	LC	HB	PCR-RFLP	330/336	110	156	64	376	284	75	176	85	326	346	0.485	0.373	8
Eaton 2018	USA(Caucasian)	LC	PB	TaqMan	572/620	382	175	15	939	205	375	206	39	956	284	0.229	0.14	8
rs1800896						AA	AG	GG	A	G	AA	AG	GG	A	G			
Seifart 2005	Germany(Caucasian)	NSCLC	HB	PCR-RFLP	39/243	6	21	12	33	45	86	115	42	287	199	0.409	0.738	7
Shih 2005	Taiwan(Asian)	NSCLC	HB	PCR-RFLP	154/205	115	39	0	269	39	194	11	0	399	11	0.027	0.693	7
Colakogullari 2008	Turkey(Caucasian)	LC	HB	PCR-SSP	44/59	11	30	3	52	36	33	21	5	87	31	0.263	0.532	7
Hao 2009	China(Asian)	LC	PB	TaqMan	43/52	36	7	0	79	7	46	6	0	98	6	0.066	0.606	7
Hart 2011	Norway(Caucasian)	NSCLC	HB	TaqMan	436/435	120	207	109	447	425	104	226	105	434	436	0.501	0.414	8
Hsia 2014	Taiwan(Asian)	LC	HB	PCR-RFLP	358/716	273	69	16	615	101	561	130	25	1252	180	0.126	≤0.001	7
Peddireddy 2016	India(Asian)	NSCLC	HB	PCR-RFLP	246/250	156	69	21	381	111	130	84	36	344	156	0.312	≤0.001	8
Eaton 2018	USA(Caucasian)	LC	PB	TaqMan	595/595	162	273	160	597	593	140	297	158	577	613	0.515	0.985	8
Nong 2018	China(Asian)	LC	HB	NA	82/82	28	29	25	85	79	28	26	28	82	82	0.5	≤0.001	8

NSCLC, Non-Small Cell Lung Carcinoma; LC,lung cancer; SOC, Source of Controls, HB, Hospital Based; PB, Population Based ; PCR-RFLP, Restriction Fragment Length Polymorphism; HWE, Hardy-Weinberg equilibrium; MAF, Minor Allele Frequency; NOS, Newcastle-Ottawa Scale.

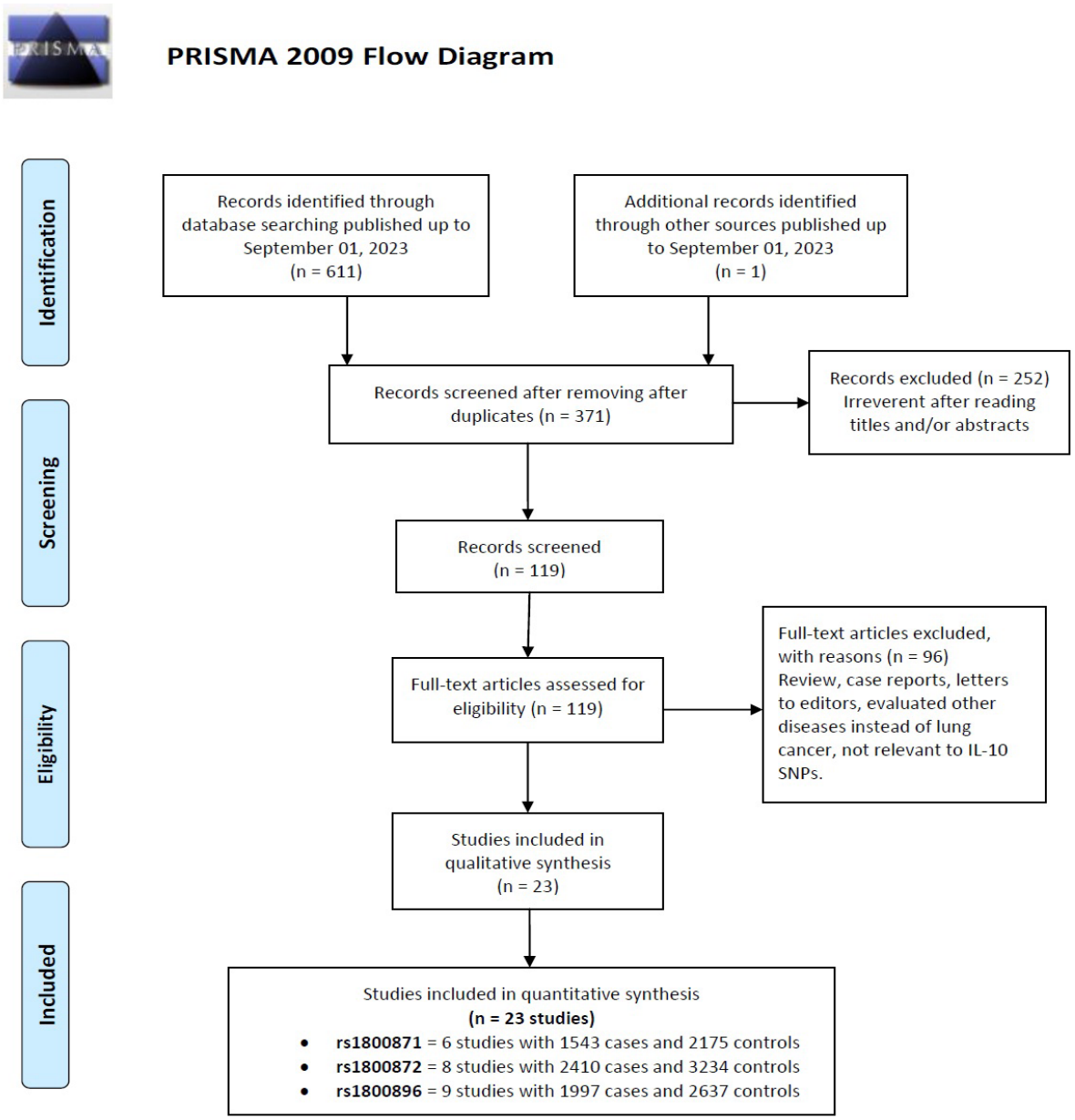

Figure 1. Flow Diagram of the Study Selection Process

fixed-effects estimates and/or random-effects estimates before and after the omission of each study were similar at large for each gene model, suggesting high stability of our pooled results. Moreover, we conducted 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. After excluding several studies inconsistent with HWE, we did not found substantial alteration under all five genetic models.

Heterogeneity test

Based on the generalized results found for this meta-analysis, a high level of heterogeneity was found between the included studies. Since there was significant heterogeneity for *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms under most genetic models, a subgroup analysis was conducted to explore the predefined possible source of heterogeneity. Subgroup analyses showed that ethnicity was significant source of heterogeneity for *IL-10* rs1800872 polymorphism (Table 3), but not for rs1800871 and rs1800896 polymorphisms (Tables 2, 4).

Publication Bias

Begger's funnel plot and Egger's test were used to assess the publication bias. The standard error of the logarithm of the OR (SE(log[OR])) was plotted against the OR for each study included to this meta-analysis. According to a widely accepted interpretation, when selection bias is present, the plot will become asymmetrical and the meta-analysis's overall impact will be skewed. The shapes of the Begger's funnel plots did not show any evidence of publication bias for *IL-10* rs1800871 and rs1800872 polymorphisms under all five genetic models and further confirmed by Egger test (Table 2, 3). For *IL-10* rs1800896 polymorphism, the results showed

Table 2. Summary Risk Estimates for association between *IL-10* rs1800871 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}
Overall	T vs. C	Random	86.14	≤0.001	1.067	0.780-1.460	0.406	0.685	1	0.875
	TT vs. CC	Random	58.17	0.026	0.997	0.700-1.420	-0.017	0.987	0.133	0.267
	TC vs. CC	Fixed	0	0.575	0.973	0.842-1.125	-0.369	0.712	0.452	0.4
	TT+TC vs. CC	Random	85.46	≤0.001	0.922	0.458-1.852	-0.229	0.819	0.452	0.608
	TT vs. TC+CC	Random	85.46	≤0.001	1.085	0.540-2.181	0.229	0.819	0.452	0.608
Asians	T vs. C	Random	94	≤0.001	1.208	0.682-2.140	0.647	0.518	1	0.651
	TT vs. CC	Random	93.88	≤0.001	1.455	0.407-5.200	0.576	0.564	1	0.964
	TC vs. CC	Fixed	38.35	0.197	1	0.825-1.211	-0.003	0.997	1	0.585
	TT+TC vs. CC	Random	93.29	≤0.001	0.706	0.222-2.243	-0.59	0.555	1	0.913
	TT vs. TC+CC	Random	93.29	≤0.001	1.416	0.446-4.495	0.59	0.555	1	0.913
Caucasians	T vs. C	Fixed	0	0.952	0.94	0.792-1.116	-0.707	0.48	0.296	0.306
	TT vs. CC	Fixed	0	0.588	0.905	0.590-1.387	-0.458	0.647	0.296	0.394
	TC vs. CC	Fixed	0	0.817	0.939	0.753-1.171	-0.559	0.576	0.296	0.477
	TT+TC vs. CC	Fixed	0	0.479	1.085	0.713-1.650	0.379	0.705	0.296	0.413
	TT vs. TC+CC	Fixed	0	0.479	0.922	0.606-1.403	-0.379	0.705	0.296	0.413

that a largely symmetrical distribution of Funnel plots, except for the heterozygote model (GA vs. AA: P_{Beggs} = 0.175 and P_{Eggers} = 0.030). Thus, we applied the Duval and Tweedie non-parametric ''trim and fill'' method to the publication bias (Figure 3). The results showed that the current meta-analysis with and without ''trim and fill'' did not draw different results, indicating that our results were statistically reliable. Overall, the results suggest this meta-analysis is not affected by publication biases.

Discussion

The molecular basis of lung cancer is the gradual accumulation of genetic and epigenetic changes in the cell nucleus [67]. Mutations are an inherent feature of lung cancer development, and their detection has significance in both the diagnostic and treatment stages of disease. To our best knowledge, several epidemiological studies have been performed to examine the association of *IL-10* polymorphisms with susceptibility to lung cancer, but their analysis is not comprehensive enough.

Previously, some meta-analyses have analyzed the association of *IL-10* gene polymorphisms and risk of lung cancer, but their analysis is not comprehensive enough. Because there are few studies included and the subgroup analyses is not accurate enough in their articles. The present meta-analysis was performed to examine the association of *IL-10* rs1800871 (-819C>T), rs1800872 (-592C>A) and rs1800896 (-1082A>G) polymorphisms with risk of lung cancer in different ethnic groups. Our

Table 3. Summary Risk Estimates for association between *IL-10* rs1800872 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}
Overall	C vs. A	Random	73.62	≤0.001	1.083	0.906-1.294	0.874	0.382	0.71	0.55
	CC vs. AA	Random	69.86	0.002	1.393	0.908-2.138	1.517	0.129	0.901	0.785
	CA vs. AA	Random	58.72	0.018	1.228	0.955-1.578	1.603	0.109	0.107	0.05
	CC+CA vs. AA	Random	72.12	0.001	0.949	0.703-1.281	-0.34	0.733	0.71	0.765
	CC vs. CA+AA	Random	72.6	0.001	1.05	0.776-1.421	0.318	0.751	0.71	0.755
Asians	C vs. A	Fixed	43.73	0.149	1.261	1.112-1.430	3.61	≤0.001	0.734	0.86
	CC vs. AA	Fixed	17.91	0.301	1.615	1.229-2.214	3.435	0.001	0.734	0.635
	CA vs. AA	Fixed	20.93	0.285	1.164	0.965-1.403	1.589	0.112	1	0.95
	CC+CA vs. AA	Fixed	0.00	0.402	0.658	0.517-0.837	-3.41	0.001	0.734	0.786
	CC vs. CA+AA	Fixed	0.00	0.402	1.521	1.195-1.935	3.41	0.001	0.734	0.786
Caucasians	C vs. A	Fixed	53.99	0.089	0.899	0.798-1.012	-1.758	0.079	0.734	0.661
	CC vs. AA	Fixed	80.66	0.001	1.016	0.709-1.454	0.084	0.933	1	0.655
	CA vs. AA	Fixed	75.92	0.006	1.029	0.806-2.989	1.315	0.188	0.734	0.077
	CC+CA vs. AA	Fixed	56.33	0.076	1.186	1.000-1.406	1.955	0.051	0.452	0.608
	CC vs. CA+AA	Fixed	56.60	0.075	0.837	0.706-0.993	-2.042	0.041	0.734	0.406

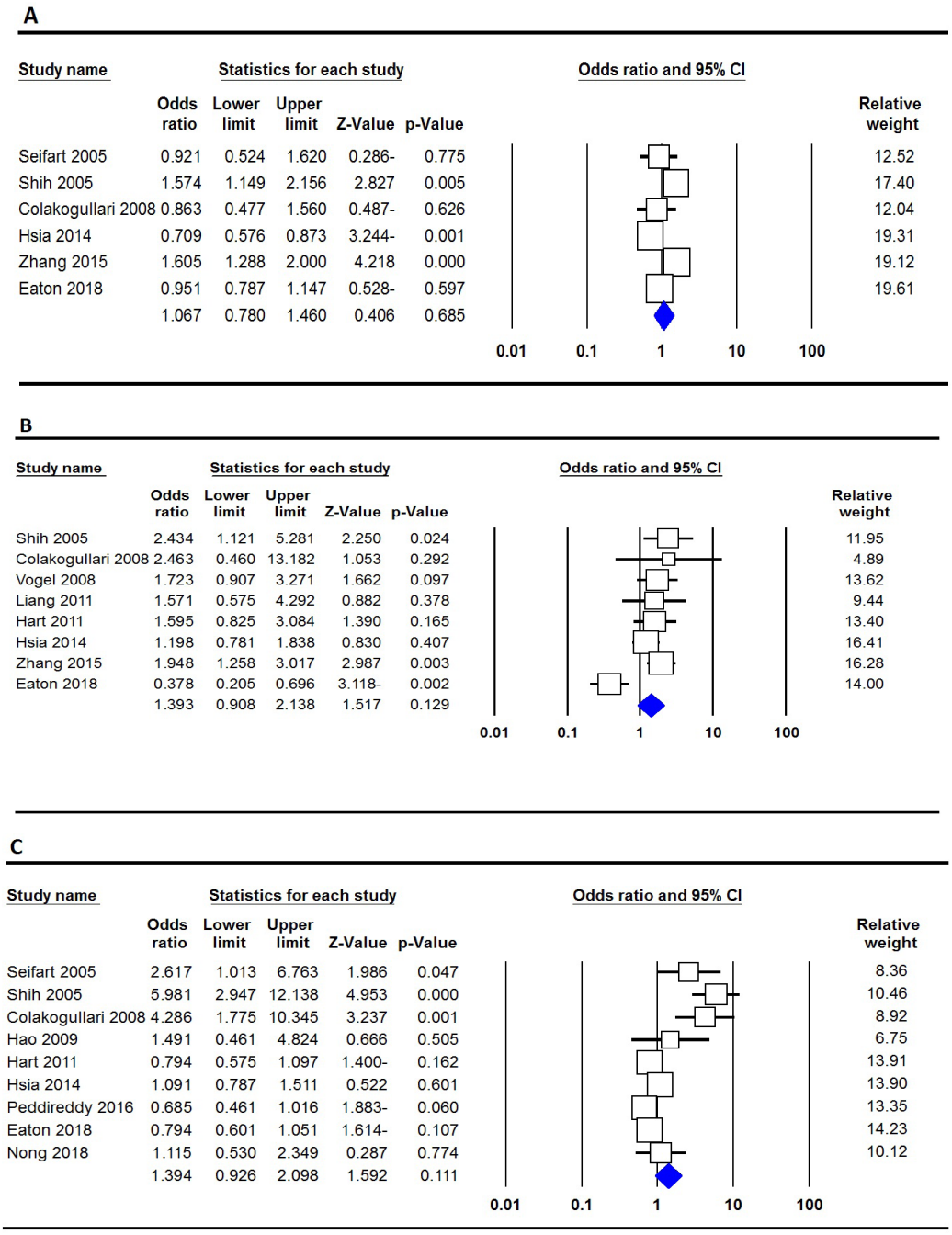

Figure 2. Forest Plots for the Association of *IL-10* Polymorphism with Lung Cancer Risk. A: rs1800871 (allele model: T vs. C); B: rs1800872 (homozygote model: CC vs. AA) ; and C: rs1800896 (heterozygote model: GA vs. AA).

pooled data indicated that *IL-10* -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). Moreover, our subgroup analysis revealed that this polymorphism was associated with lung cancer among Asians and Caucasians. However, there was no a significant association between the 819T>C and -1082A>G polymorphisms and lung cancer risk. Recently, Ding et al., in a meta-analysis evaluated the association of 11 variants at multiple interleukin including IL-1β, IL-4, IL-6, IL-8 and *IL-10* and IL proteins (IL-6, *IL-10*) relate with risk of lung cancer from 43 articles. Their pooled data showed that the IL-1β rs16944 and *IL-10* rs1800872 decreased while *IL-10* rs1800896 increased lung cancer risks. In 2020, Gao et al., in a meta-analysis examined the association between interleukin polymorphisms and lung cancer. Their pooled data showed that there was no significant association in distribution of IL-4 rs2070874, IL-6 rs1800795, IL-6 rs1800796, IL-8 rs4073, *IL-10* rs1800871, and *IL-10* rs1800896 polymorphisms among lung cancer patients and controls. However, their subgroup analysis showed that IL-4 rs2243250 might influence predisposition to lung cancer in Asians, whereas *IL-10* rs1800872 polymorphism might influence predisposition

Table 4. Summary Risk Estimates for Association between *IL-10* rs1800896 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}
Overall	G vs. A	Random	82.85	≤0.001	1.232	0.941-1.613	1.516	0.13	0.076	0.073
	GG vs. AA	Random	71.79	≤0.001	1.151	0.637-2.084	0.464	0.641	0.133	0.267
	GA vs. AA	Random	83.28	≤0.001	1.394	0.926-2.098	1.592	0.111	0.175	0.03
	GG+GA vs. AA	Fixed	33.17	0.175	0.989	0.837-1.170	-0.125	0.9	0.763	0.982
	GG vs. GA+AA	Fixed	33.17	0.175	1.011	0.855-1.195	0.125	0.9	0.763	0.982
Asians	G vs. A	Random	87.98	≤0.001	1.296	0.743-2.260	0.913	0.361	0.806	0.329
	GG vs. AA	Fixed	61.1	0.076	0.794	0.545-1.156	-1.206	0.228	1	0.651
	GA vs. AA	Random	85.59	≤0.001	1.435	0.739-2.789	1.066	0.286	1	0.396
	GG+GA vs. AA	Fixed	46.74	0.153	1.223	0.856-1.748	1.104	0.269	1	0.404
	GG vs. GA+AA	Fixed	46.74	0.153	0.832	0.509-1.359	-0.735	0.462	1	0.404
Caucasians	G vs. A	Random	77.5	0.004	1.207	0.894-1.628	1.23	0.219	0.308	0.017
	GG vs. AA	Random	64.34	0.038	1.187	0.721-1.955	0.675	0.5	0.308	0.167
	GA vs. AA	Random	83.54	≤0.001	1.372	0.754-2.498	1.035	0.301	0.308	0.033
	GG+GA vs. AA	Fixed	14.03	0.322	0.932	0.771-1.126	-0.728	0.467	0.734	0.567
	GG vs. GA+AA	Fixed	14.03	0.322	1.073	0.888-1.297	0.728	0.467	0.734	0.567

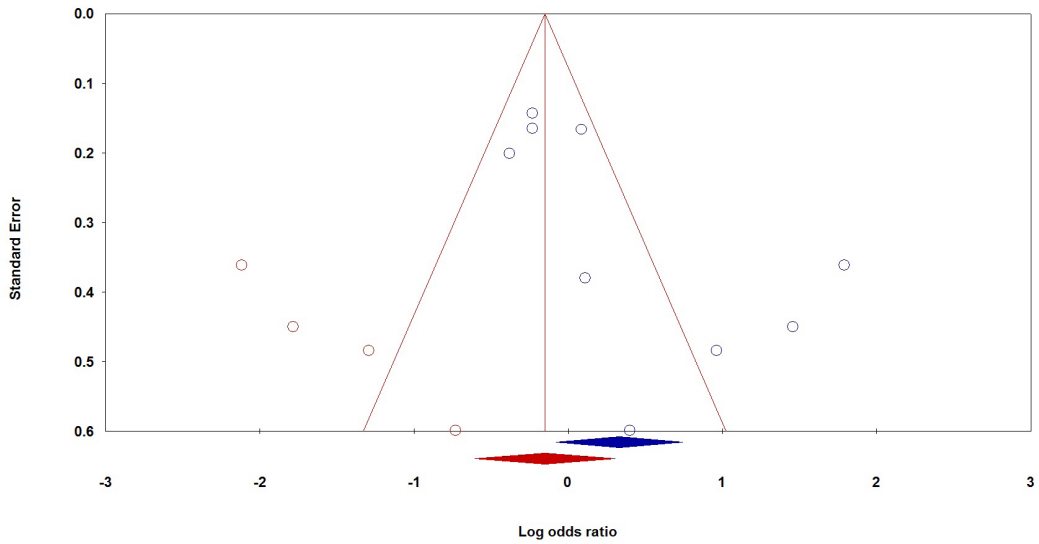

Figure 3. Begg's Funnel Plots of *IL-10* rs1800896 Polymorphism and Lung Cancer Risk for Publication bias Test under the Heterozygote Model (GA vs. AA). Before (blue) and after (red) ''Trim-and-Fill'' method.

to in Caucasians. Yu et al., in a meta-analysis based on 73 studies with 15,942 cancer cases and 22,336 controls evaluated the association between the *IL-10* -819C>T polymorphism and cancer risk. Their pooled results showed that this variant was not significantly associated with cancer risk in overall. Their stratified analysis showed that *IL-10* -819C>T polymorphism was not significantly associated with breast cancer, colorectal cancer, lung cancer, hepatocellular carcinoma, prostate cancer, lymphoma, or melanoma. The heterozygous variant (CT) and the dominant model (TT/CT vs. CC) were associated with an increased risk for cervical and ovarian cancer [68]. In 2012, Peng et al., in work based on 20 studies involving 6,467 cases and 8,320 controls evaluated the effects of eight polymorphisms including TNF-α 308G>A, IL-6 174G>C, IL-1β 31T>C, IL-1β 511C>T, COX-2 8473T>C, *IL-10* -1082G>A, *IL-10* -819C>T, and *IL-10* -592C>A with susceptibility to lung cancer. Their results revealed that the *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms might be risk factors for lung cancer. TNF-α -308G>A, IL-6 -174G>C, IL-1β 31 T>C, IL-1β -511C>T, COX-2 -8473T>C polymorphisms were not detected to be related to the risk for lung cancer [69].

The heterogeneity and publication bias are of importance which may affect the results of meta-analysis [44, 70, 42, 71, 72]. In the current meta-analysis, a significant heterogeneity existed for -819T>C and -1082A>G polymorphisms under almost genetic models in overall, but not for *IL-10* -592A>C. After subgroup analyses by ethnicity, the heterogeneity was not decreased by ethnicity, suggesting that other factors such as gene-environment factors or histological type cause the heterogeneity. In the meta-analysis, publication bias was analyzed by Begg's funnel plots and the Egger's test and

no significant publication bias was detected, suggesting the reliability of our results [73-75]. Our results showed a publication bias for *IL-10* -1082A>G polymorphism under the heterozygote model. However, the ''trim and fill'' method results did not draw different results, indicating that the results were statistically reliable. In summary, a significant heterogeneity among studies on the association between *IL-10* -819T>C and -1082A>G polymorphisms and lung cancer risk in overall population and by ethnicity was observed. However, the source of heterogeneity was not found in the meta-regression analysis, but the sensitivity analysis confirmed a robust association in this study.

Furthermore, the *IL-10* -592A>C polymorphism was sensitive to lung cancer susceptibility, and ethnic subgroup analysis obtained from our pooled data indicated that this polymorphism might be a promising biomarker in Caucasian and Asian populations. Nevertheless, there were still some limitations that need to be addressed in this meta-analysis. First, the number of studies for each *IL-10* polymorphisms and in the different ethnicity included was not abundant. The difference between ethnicities was smaller due to the limited number of studies included. Thus, whether the association between the *IL-10* polymorphisms and risk of lung cancer is dependent on ethnicity remains a matter of debate and more independent studies were needed to evaluate our results. Second, the effects of gender, age, smoking status, lifestyle, and other environmental factors on risk of lung cancer were not considered in the current meta-analysis due to the limitations or unavailable data. Moreover, the genotyping methods for *IL-10* polymorphisms genotyping were also inconsistent; all methods were based on PCR-RFLP, PCR-SSP, and each method had its own merits and limitations, so more appropriate methods and guidelines for genotyping required to be discussed. Third, there was clear heterogeneity for association between *IL-10* -819T>C and -1082A>G polymorphisms and the occurrence of lung cancer. The final pooled samples included Caucasian and Asian populations. The source of heterogeneity might be that the different ethnicities contained various genetic backgrounds. Fourth, we only selected eligible articles from those previously published, so some relevant unpublished works might be missed, generating certain publication bias, though not detected even with funnel plot or Egger test. Finally, this study did not reveal gene environment and gene-gene interactions, due to the original information of the included studies was not sufficient. Moreover, in this work, just three polymorphisms in the *IL-10* gene were analyzed, and information on these particular polymorphisms was limited. Many polymorphic loci have been reported to be involved in the etiology of lung cancer. The occurrence of lung cancer is usually thought to involve multiple genes and their interactions.

Collectively, our findings suggest that *IL-10* rs1800871, rs1800872 and rs1800896 polymorphisms might not be risk factor for lung cancer in overall population. However, *IL-10* rs1800872 polymorphism was associated with lung cancer risk in Asians and Caucasians. Nevertheless, future research on the subject with greater methodological rigor and sample sizes is mandatory to clarify the role of *IL-10* the rs1800871, rs1800872 and rs1800896 polymorphisms and its genetic profiles on risk of lung cancer.

Author Contribution Statement

All authors contributed equally in this study.

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