Original Article
Association of the four common polymorphisms in interleukin-10 (rs1800890, rs1800896, rs1800871, and rs1800872) with non-Hodgkin's lymphoma risk: a meta-analysis

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Abstract: Interleukin-10 (IL-10) single nucleotide polymorphisms (SNPs) have been indicated to be correlated with Non-Hodgkin's lymphoma (NHL) susceptibility. However, the results of these studies on the association remain inconsistent. This meta-analysis was conducted to derive a more accuracy estimation of the association between the common SNPs (rs1800890, rs1800896, rs1800871 and rs1800872) in IL-10 and NHL risk. Meta-analyses were performed on 21 studies with 7,749 cases and 8584 controls. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the NHL risk. Meta-analyses showed that rs1800890, rs1800871 and rs1800872 polymorphisms had no association with NHL risk. However, rs1800896 polymorphism has association with NHL risk based on the following comparison models (G vs. A: OR = 1.14, 95% CI = 1.00-1.29; AG vs. AA: OR = 1.20, 95% CI = 1.05-1.37; GG+AG vs. AA: OR = 1.22, 95% CI = 1.08-1.39). In the ethnic subgroup analysis, rs1800896 had an increased NHL risk in Caucasians based on the heterozygote model (OR = 1.21, 95% CI = 1.04-1.41) and dominant model (OR = 1.22, 95% CI = 1.00-1.48). When stratified by subtypes, rs1800890, rs1800896 and rs1800872 polymorphisms were found significant association with an increased risk of diffuse large B-cell Lymphoma (DLBCL) in different comparison models, whereas negative results were obtained for Follicular Lymphoma (FL) and chronic lymphocytic Leukemia/small lymphocytic Lymphoma (CLL/SLL) in all genetic models. Our meta-analysis suggested that the rs1800896 polymorphism had an increased risk with NHL susceptibility, where as the rs1800890, rs1800871 and rs1800872 had no association with NHL risk. Among the common subtypes of NHL, three polymorphisms (rs1800890, rs1800896 and rs1800872) had significant association with DLBCL risk.

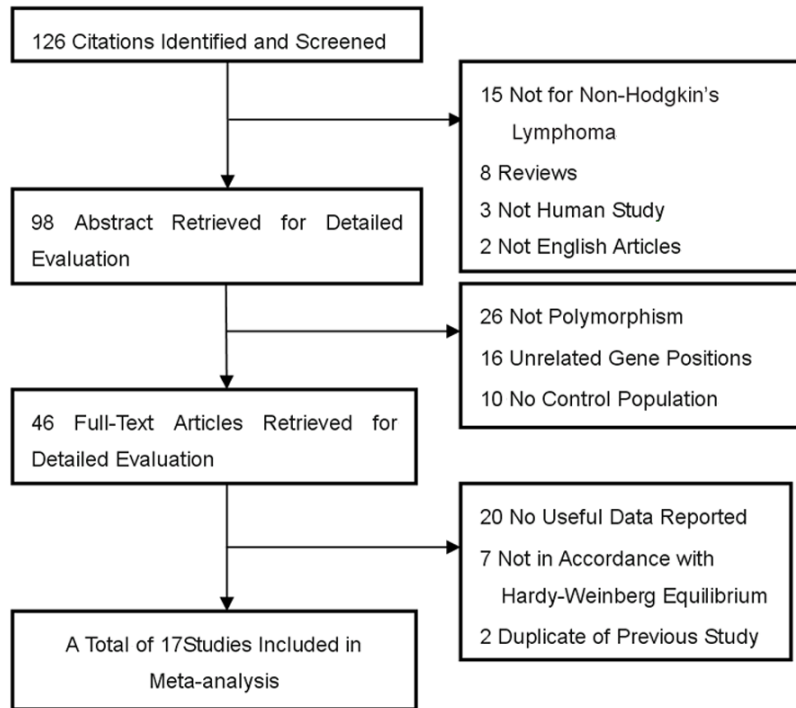Keywords: Non-Hodgkin's lymphoma, interleukin-10, polymorphism, meta-analysis

Introduction

Non-Hodgkin's lymphoma (NHL) is a group of heterogeneous disorders that origin of the lymphatic system. In the past 20 years, the incidence of NHL rose rapidly to become one of the major diseases that threaten human health. Immune dysfunction is considered to be related to NHL [1], suggesting that immune-related genes play an important role in the pathogenesis of NHL. Genetic variation of some immunomodulatory cytokine may lead to different subtypes of lymphoma predisposition [2, 3], respectively, these cytokine polymorphisms gradu-

ally become a hot topic in etiology, progression and prognosis of NHL.

Interleukin-10 (IL-10) is a Th2 cytokine that has strong anti-inflammatory effect and it mainly produced by immune cells, such as Th2 cells, Tr1 cells, monocytes, some subsets of dendritic cells and appropriately stimulated macrophages [4, 5]. Studies have shown that IL-10 could regulate Th1 cells [6], promote B cell proliferation and antibody production [7]. Numerous studies show that IL-10 single nucleotide polymorphisms (SNPs) and lymphoma susceptibility [8-25], which often involves four functional

Figure 1. Studies identified with criteria for inclusion and exclusion.

June 30, 2014. In order to identify the relevant publications, reference lists of research papers were also reviewed by manual search.

Selection criteria

The inclusion criteria for the meta-analysis study: (1) association studies between IL-10 SNPs (rs-1800890, rs1800896, rs-1800871, rs1800872) and NHL risk; (2) case-control studies; (3) full-text published articles and published in English; (4) included detailed genotype distribution data; (5) fulfilling Hardy-Weinberg equilibrium (P>0.05).

Data extraction

SNPs, -3575 T>A (rs1800890), -1082 A>G (rs1800896), -819 T>C (rs1800871), and -592 A>C (rs1800872).

Although previous studies have shown that IL-10 gene promoter polymorphisms play an important immunoregulatory role on non-Hodgkin's lymphoma [26], the results were inconsistent and conflicted. Some studies have found associations between IL-10rs1800890 as well as rs1800896 and the NHL predisposition [8, 13, 14], while other investigations have failed to identify these correlations [10, 11, 19]. Therefore, we conduct the present meta-analysis on all eligible case-control studies to evaluate the association between IL10 SNPs (rs-1800890, rs1800896, rs1800871 and rs-1800872) and susceptibility of NHL.

Materials and methods

Publication search

Check all the literature published by online electronic databases (PubMed, Embase, Web of Science and CNKI), keyword searched for: interleukin-10 or IL10 or IL-10, polymorphism or mutation or variant, Non-Hodgkin's lymphoma OR lymphoid neoplasm OR lymphoid malignancy. All qualified studies were searched up to

Two investigators independently extracted the information from all eligible publications according to the inclusion criteria and reached a consensus on all items. The following information were collected: first author, year of publication, country of origin, ethnicity, study design, genotype methods, source of control, numbers of cases and controls, total number of cases and controls, as well as number of cases and controls with the different genotypes. Different ethnicities were categorized as Caucasian, Asian, African and mixed. The controls had no present evidence of any malignant disease. The Newcastle-Ottawa Scale (NOS) is developed to assess the quality of nonrandom studies with its design, including case-control and cohort studies, content and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results [27]. Five independent researches from Rothman's report, including Rothman-Canada, Rothman-Italy, Rothman-UCSF and Rothman-UK, Rothman-Spain case-control researches, were selected respectively [13]. Pathology histologic subtypes of NHL, including diffuse large B-cell Lymphoma (DLBCL), Follicular Lymphoma (FL), chronic lymphocytic Leukemia/small lymphocytic Lymphoma (CLL/SLL), were classified for analyses based on the

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

First author	Year	Country	Ethnicity	Study design	Genotyping method	Source of control	Total sample size (case/control)	SNP No.	NOS score
Cunningham	2003	Australia	Caucasian	CC	SSOP	PB	109/164	2	8
Lech-Maranda	2004	France	Caucasian	CC	PCR-RFLP	PB	199/112	2;3;4	8
Guzowski	2005	USA	Mix	CC	Taqman	PB	17/25	2;3;4	8
Berglund	2005	Sweden	Caucasian	CC	NR	PB	244/195	2	6
Wang	2006	USA	Mix	CC	Taqman	PB	1133/936	1	9
Lan	2006	USA	Mix	CC	Taqman	Female	510/597	1;2;3	7
Nieters	2006	Germany	Caucasian	CC	Taqman	PB	507/661	1	9
Rothman	2006a	Canada	Caucasian	CC	Taqman	PB	85/349	1	8
	2006b	Italy	Caucasian	CC	Taqman	PB	59/112	1	8
	2006c	Spain	Caucasian	CC	Taqman	HB	77/554	1	7
	2006d	USA	Caucasian	CC	Taqman	PB	93/677	1	8
	2006e	UK	Caucasian	CC	Taqman	PB	262/459	1	8
Purdue	2007	USA	Caucasian	CC	Taqman	PB	524/475	1;2;3;4	9
Lech-Maranda	2007	France	Caucasian	CC	PCR-RFLP	PB	175/112	2;3;4	8
Kube	2008	Germany	Caucasian	CC	Taqman	HB	500/236	1;2;4	7
Maria	2008	Italy	Caucasian	CC	Taqman	PB	39/112	1;2	7
Liang	2009	USA	Caucasian	CC	OPA	PB	39/102	1	7
Fernberg	2010	Sweden	Caucasian	CC	MassArray	PB	2312/1838	1	9
Zhang	2012	China	Asian	CC	Taqman	PB	514/557	4	8
Lech-Maranda	2013	Poland	Caucasian	CC	Taqman	PB	290/192	1;2	8
Talaat	2014	Egypt	Caucasian	CC	SSP-PCR	PB	100/119	2;3	7

CC: case-control; SNP: single-nucleotide polymorphisms; SNP No.1: -3575 T>A (rs1800890); 2: -1082 A>G (rs1800896); 3: -819 T>C (rs1800871); 4: -592 A>C (rs1800872); PB: population based; HB: hospital based; NR: not reported; PCR-RFLP: polymerase chain reaction and restriction fragment length polymorphism; OPA: Oligo Pool Assay; SSOP: sequence specific oligo probing; SSC-PCR: sequence-specific primers polymerase chain reaction; NOS: the Newcastle-Ottawa Scale.

World Health Organization classification for lymphoma diagnoses [28].

Statistical analysis

Based on the genotype frequencies in cases and controls of each study, odds ratios (ORs) together with their 95% confidence intervals (95% CIs) were calculated to assess the association strength. The significance of the pooled ORs was determined by the Z test. Statistical heterogeneity between studies was evaluated by chi-square based Q-test and I^2 statistics [29]. If the *p* value of the heterogeneity test was more-than 0.1, the pooled OR estimate of the study was calculated by the fixed effects model. Otherwise, the random-effects model was used. Sensitivity analysis was performed to assess the stability of the final results. In order to assess the influence of each study to the pooled OR, risk assessment was tested by sequentially omitting one individual study at a time. Sensitivity analysis determines whether the individual data in fact have a major effect on the results of the review. Publication bias was evaluated by the visual inspection of asymmetry in Begg's funnel plots and further assessed by the method of Egger's test [30]. The meta-analysis assessed the following genetic models: dominant model (BB+AB vs. AA), recessive model (BB vs. AA+AB), homozygote comparison (BB vs. AA), heterozygote comparison (AB vs. AA) and allele comparison (B vs. A), the A represents the major allele, and the B represents the minor allele. All statistical analyses were calculated with the Review Manage 5.0 (The Cochrane Collaboration, Oxford, United Kingdom) and STATA 12.0 (Stata Corp, College Station, TX). A *P* value less-than 0.05 was considered statistically significant.

Results

Characteristics of eligible studies

There were 126 articles relevant to the search words and manual search. The flow chart for

Table 2. IL-10 polymorphisms Genotype Distribution and Allele Frequency in Cases and Controls

| First author | Genotype (N) | | | | | | | | | | | MAF |
| | Case | | | Control | | | Case | | Control | | | |
	total	AA	AB	BB	total	AA	AB	BB	A	B	A	B	
rs1800890													
Wang 2006	1133	447	521	165	936	387	417	132	1415	851	1191	681	0.38
Lan 2006	510	188	244	78	597	261	280	56	620	400	802	392	0.39
Nieters 2006	507	223	207	77	661	262	306	93	653	361	830	492	0.36
Rothman 2006a	85	28	48	9	349	119	179	51	104	66	417	281	0.39
Rothman 2006b	59	34	22	3	112	73	37	2	90	28	183	41	0.24
Rothman 2006c	77	34	39	4	554	271	233	50	107	47	775	333	0.31
Rothman 2006d	93	35	41	17	677	238	343	96	111	75	819	535	0.40
Rothman 2006e	262	82	128	52	459	174	212	73	292	232	560	358	0.44
Purdue 2007	524	165	255	104	475	159	233	83	585	463	551	399	0.44
Kube 2008	500	177	249	74	236	81	122	33	603	397	284	188	0.40
Maria 2008	37	18	18	1	112	73	37	2	54	20	183	41	0.27
Liang 2009	39	19	16	4	102	33	48	21	54	24	114	90	0.31
Fernberg 2010	2312	847	1092	373	1838	695	865	278	2786	1838	2255	1421	0.40
Lech-Maranda 2013	290	112	132	46	192	69	85	38	356	224	223	161	0.39
rs1800896													
Cunningham 2003	109	37	46	26	164	41	82	41	120	98	164	164	0.45
Lech-Maranda 2004	199	55	100	44	112	45	47	20	210	188	137	87	0.47
Guzowski 2005	17	4	9	4	25	9	12	4	17	17	30	20	0.50
Berglund 2005	244	70	136	38	195	60	89	46	276	212	209	181	0.43
Lan 2006	510	137	260	113	587	184	305	98	534	486	673	501	0.48
Purdue 2007	532	108	269	155	477	111	239	127	485	579	461	493	0.54
Lech-Maranda 2007	175	56	87	32	112	45	47	20	210	188	137	87	0.43
Kube 2008	500	134	253	113	236	81	122	33	521	479	284	188	0.48
Maria 2008	39	15	20	4	111	61	43	7	50	28	165	57	0.36
Lech-Maranda 2013	292	82	152	58	192	48	94	50	316	268	190	194	0.46
Talaat 2014	100	28	54	18	119	43	61	15	110	90	147	91	0.45
rs1800871													
Lech-Maranda 2004	199	11	81	107	112	13	46	53	103	295	72	152	0.74
Guzowski 2005	17	2	6	9	25	1	10	14	10	24	10	40	0.71
Lan 2006	491	26	191	274	574	34	211	329	243	739	279	869	0.75
Purdue 2007	538	21	175	342	488	23	170	295	217	859	216	760	0.80
Lech-Maranda 2007	175	15	68	92	112	13	46	53	98	252	72	152	0.72
Talaat 2014	100	6	54	40	119	5	52	62	66	134	62	176	0.67
rs1800872													
Lech-Maranda 2004	199	11	81	107	112	13	46	53	103	295	72	152	0.74
Guzowski 2005	17	2	5	10	25	2	11	12	9	25	15	35	0.74
Wang 2006	1120	93	426	601	938	81	342	515	612	1628	504	1372	0.73
Purdue 2007	540	21	176	343	489	23	169	297	218	862	215	763	0.80
Lech-Maranda 2007	175	15	68	92	112	13	46	53	98	252	72	152	0.72
Kube 2008	500	26	196	278	236	14	98	124	248	752	126	346	0.35
Zhang 2012	514	60	228	226	557	53	235	269	348	680	341	773	0.66

A represents the major allele, B represents the minor allele. MAF: minor allele frequencies.

studies search strategy was showed as **Figure 1**. Finally, 17 research literatures selected for this meta-analysis [8-25], including a total of 21 researches (which included five independent researches from Rothman's report). Among of these studies, 17 studies based on
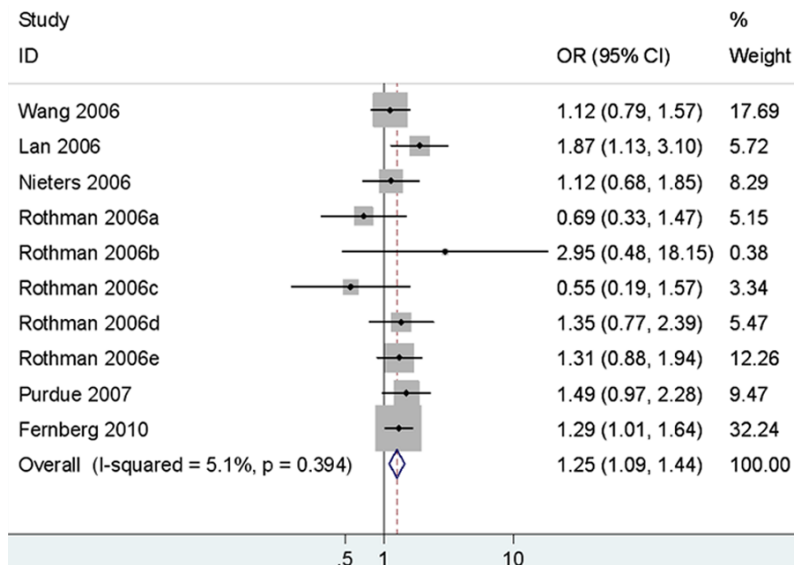
Figure 2. Forest plots of IL-10 rs1800890 polymorphism and diffuse large B-cell lymphoma risk (AA vs. TT+TA).

Caucasian, 1 Asian and 3 mixed ethnicities. There were a total with 7749 cases and 8584 controls enrolled for this analysis (**Table 1**), in which fourteen studies with 6428 cases and 7300 controls for rs1800890, eleven studies with 2637 cases and 2410 controls for rs1800896, seven studies with 2565 cases and 2233 controls for rs1800872 and six studies with 1520 cases and 1430 controls for rs1800871, respectively.

The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of each included literature, the results was showed as the last column of **Table 1**. The NOS score of all articles are not less than 6scores that mean each included literature was a high-quality study. The genotype distributions for four SNPs of IL-10 are shown in **Table 2**, and the frequency of the minor allele was diverse widely across the twenty-one eligible studies, ranging from 0.24 to 0.44 (rs1800890), 0.36 to 0.54 (rs1800896), 0.67 to 0.80 (rs1800871), 0.35 to 0.80 (rs1800872). The average frequency of the minor allele in the four polymorphisms was 0.37, 0.46, 0.73, and 0.34, respectively.

Meta-analysis results

IL-10-3575T>A polymorphism (rs1800890)

There was no association between rs1800890 and NHL susceptibility in any comparison

model. In the subgroup analysis by ethnicity, no significant correlation was observed between rs1800890 and an increased risk of NHL in Caucasians. According the origin of lymphoma cell, there were significantly associated in different comparison models (AA vs. TT+TA: OR = 1.15, 95% CI = 1.03-1.28; AA+TA vs. TT: OR = 1.11, 95% CI = 1.03-1.20; A vs. T: OR = 1.09, 95% CI = 1.01-1.19) between rs1800890 and B-NHL risk, where as there were no significant association between rs1800890 and T-NHL predisposition. Among the common subtypes, the rs1800890 was found significant association with an increased risk of DLBCL in all different comparison models (TA vs. TT: OR = 1.15, 95% CI = 1.03-1.28, **Figure 2**; AA vs. TT: OR = 1.35, 95% CI = 1.16-1.57; AA vs. TT+TA: OR = 1.25, 95% CI = 1.09-1.44; AA+TA vs. TT: OR = 1.20, 95% CI = 1.08-1.33; A vs. T: OR = 1.16, 95% CI = 1.08-1.25), whereas there were no statistical significance between rs1800890 and CLL/SLL or FL risk (**Table 3**).

IL-10-1082A>G polymorphism (rs1800896)

Significant increased risk of NHL was observed in different comparison models (AG vs. AA: OR = 1.20, 95% CI = 1.05-1.37, **Figure 3**; GG+AG vs. AA: OR = 1.22, 95% CI = 1.08-1.39; G vs. A: OR = 1.14, 95% CI = 1.00-1.29). When stratified by ethnicity, statistically significant was examined in two comparison models in Caucasians (AG vs. AA: OR = 1.21, 95% CI = 1.04-1.41; GG+AG vs. AA: OR = 1.22, 95% CI = 1.00-1.48). In addition, the association was detected between rs1800896 and risk of B-NHL and DLBCL (B-NHL: AG vs. AA: OR = 1.22, 95% CI = 1.06-1.40; GG+AG vs. AA: OR = 1.23, 95% CI = 1.08-1.41; DLBCL: AG vs. AA: OR= 1.26, 95% CI = 1.05-1.52; GG+AG vs. AA: OR = 1.29, 95% CI = 1.08-1.53). However, there were no significant increased CLL/SLL and FL risk in any gene distribution model of rs1800896. The results are presented in **Table 3**.

Table 3. Meta-analysis results Between IL-10 Polymorphisms and NHL Risk

Compari-sons	B vs. A		BB vs. AA		AB vs. AA		BB vs. AA+AB		AB+BB vs. AA	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
rs1800890	1.06 (0.98-1.14)	0.15	1.12 (0.96-1.31)	0.16	1.04 (0.97-1.13)	0.29	1.10 (1.00-1.22)	0.06	1.06 (0.99-1.14)	0.10
Caucasian	1.03 (0.97-1.10)	0.29	1.07 (0.94-1.21)	0.29	1.02 (0.93-1.11)	0.74	1.07 (0.95-1.20)	0.26	1.03 (0.95-1.12)	0.50
B-NHL	1.09 (1.01-1.19)	0.03	1.18 (0.99-1.41)	0.06	1.08 (1.00-1.18)	0.06	1.15 (1.03-1.28)	0.01	1.11 (1.03-1.20)	0.008
T-NHL	0.91 (0.76-1.08)	0.27	0.78 (0.53-1.16)	0.22	0.97 (0.75-1.24)	0.80	0.79 (0.55-1.14)	0.21	0.93 (0.73-1.17)	0.52
DLBCL	1.16 (1.08-1.25)	0.0001	1.35 (1.16-1.57)	0.0001	1.15 (1.03-1.28)	0.02	1.25 (1.09-1.44)	0.001	1.20 (1.08-1.33)	0.001
CLL/SLL	0.99 (0.90-1.10)	0.91	0.97 (0.79-1.20)	0.81	1.00 (0.86-1.16)	0.96	0.99 (0.82-1.20)	0.92	0.99 (0.86-1.14)	0.94
FL	1.07 (0.97-1.18)	0.19	1.14 (0.93-1.40)	0.19	1.04 (0.90-1.21)	0.57	1.12 (0.93-1.35)	0.22	1.07 (0.93-1.23)	0.34
rs1800896	1.14 (1.00-1.29)	0.02	1.26 (0.96-1.64)	0.09	1.20 (1.05-1.37)	0.007	1.12 (0.90-1.40)	0.313	1.22 (1.08-1.39)	0.002
Caucasian	1.12 (0.96-1.30)	0.16	1.20 (0.88-1.64)	0.25	1.21 (1.04-1.41)	0.01	1.07 (0.83-1.38)	0.62	1.22 (1.00-1.48)	0.048
B-NHL	1.12 (0.98-1.29)	0.09	1.23 (0.93-1.62)	0.15	1.22 (1.06-1.40)	0.007	1.09 (0.86-1.38)	0.49	1.23 (1.08-1.41)	0.002
DLBCL	1.15 (0.97-1.36)	0.11	1.32 (0.91-1.91)	0.14	1.26 (1.05-1.52)	0.01	1.14 (0.83-1.56)	0.41	1.29 (1.08-1.53)	0.004
CLL/SLL	1.17 (0.70-1.94)	0.55	0.84 (0.53-1.35)	0.48	1.15 (0.80-1.66)	0.45	0.81 (0.54-1.20)	0.29	1.08 (0.76-1.52)	0.67
FL	1.14 (0.97-1.34)	0.12	1.27 (0.92-1.76)	0.15	1.07 (0.81-1.41)	0.64	1.25 (0.95-1.63)	0.11	1.14 (0.88-1.47)	0.33
rs1800871	1.05 (0.93-1.18)	0.43	1.24 (0.90-1.70)	0.19	1.22 (0.88-1.69)	0.23	1.03 (0.89-1.19)	0.69	1.24 (0.91-1.69)	0.18
Caucasian	1.11 (0.95-1.29)	0.18	1.38 (0.92-2.06)	0.12	1.29 (0.86-1.94)	0.23	1.09 (0.91-1.32)	0.36	1.35 (0.91-2.00)	0.13
B-NHL	1.04 (0.91-1.18)	0.56	1.33 (0.94-1.87)	0.10	1.36 (0.96-1.93)	0.08	1.00 (0.85-1.16)	0.96	1.35 (0.96-1.88)	0.08
DLBCL	1.03 (0.79-1.35)	0.80	1.43 (0.89-2.30)	0.14	1.52 (0.94-2.47)	0.08	0.97 (0.70-1.34)	0.84	1.48 (0.93-2.36)	0.10
FL	0.99 (0.82-1.20)	0.95	1.16 (0.70-1.95)	0.56	1.18 (0.70-1.98)	0.53	0.96 0.76-1.21)	0.71	1.17 (0.71–1.92)	0.54
rs1800872	1.02 (0.93-1.11)	0.71	1.05 (0.85-1.29)	0.66	1.07 (0.86-1.32)	0.55	1.01 0.91-1.13)	0.85	1.06 (0.87-1.29)	0.59
Caucasian	1.06 (0.97-1.17)	0.21	1.18 (0.93-1.50)	0.17	1.17 (0.91-1.49)	0.22	1.05 (0.93–1.19)	0.39	1.18 (0.93-1.48)	0.17
B-NHL	1.18 (0.99-1.40)	0.06	1.55 (1.00-2.41)	0.05	1.36 (0.87-2.14)	0.17	1.17 (0.95-1.44)	0.15	1.47 (0.96-2.26)	0.08
DLBCL	1.28 (1.01-1.62)	0.04	2.06 (1.06-3.99)	0.03	1.77 (0.91-3.48)	0.10	1.26 (0.95-1.68)	0.11	1.95 (1.02-3.72)	0.04
FL	1.08 (0.85-1.36)	0.54	1.19 (0.65-2.16)	0.58	1.03 (0.56-1.91)	0.92	1.09 (0.82-1.44)	0.57	1.12 (0.62-2.01)	0.71

A: the major allele; B: the minor allele; CI: confidence interval; OR: odds ratio; B-NHL: B-cell non-Hodgkin's Lymphoma; T-NHL: T-cell non-Hodgkin's Lymphoma; DLBCL: diffuse large B-cell Lymphoma; FL: Follicular Lymphoma; CLL/SLL: chronic lymphocytic Leukemia/small lymphocytic Lymphoma.
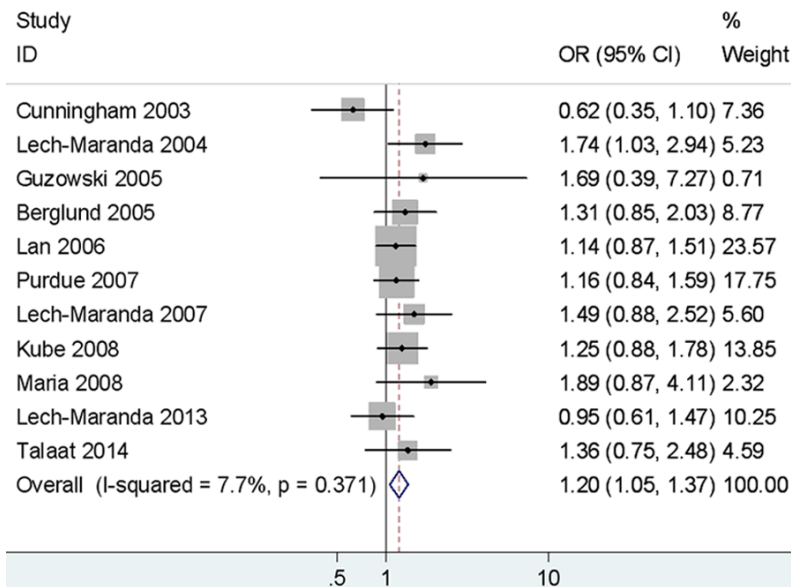
Figure 3. Forest plots of IL-10 rs1800896 polymorphism and non-Hodgkin's lymphoma risk (AG vs. AA).

IL-10-819T>C polymorphism (rs1800871)

As shown in **Table 3** and **Figure 4**, the rs1800871 variant was found no significant association with NHL susceptibility, whether it is stratified by ethnicity, or in the classification by NHL subtypes.

*IL-10-592A>C polymorphism (rs1800872)*

The rs1800872 polymorphism had no association with NHL predisposition based on all genetic models. Similarly, negative results were obtained for Caucasians in all genetic models when carried out stratified analysis by ethnicity. However, there was significant association between the rs1800872 polymorphism and DLBCL risk in homozygote, dominant and haploid models (CC vs. AA: OR = 2.06, 95% CI = 1.06-3.99, **Figure 5**; CC+AC vs. AA: OR = 1.95, 95% CI = 1.02-3.72; C vs. A: OR = 1.28, 95% CI = 1.01-1.62), whereas there was no
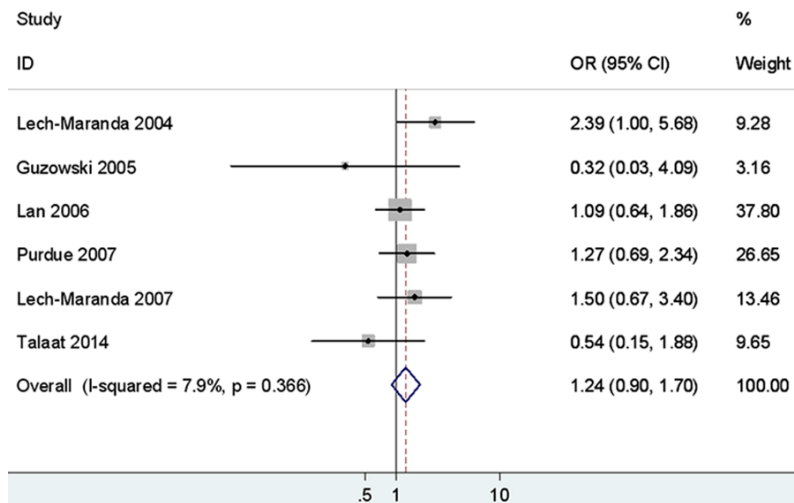
Figure 4. Forest plots of IL-10 rs1800871 polymorphism and non-Hodgkin's Lymphoma risk (CC vs. TT).
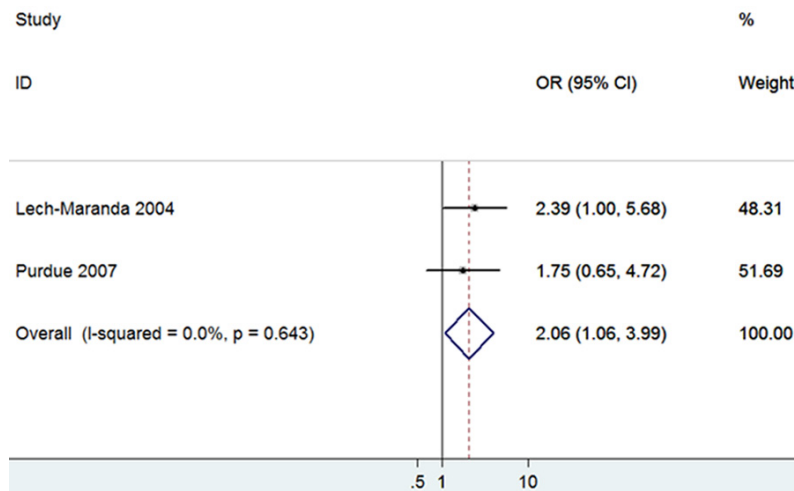
Figure 5. Forest plots of IL-10 rs1800872 polymorphism and non-Hodgkin's Lymphoma risk in Caucasians (CC vs. AA).

association between the rs1800872 variation and FL susceptibility. The results are showed as **Table 3**.

Tests of heterogeneity and sensitivity analysis

Statistically significant heterogeneity was observed between trials of the following analyses using Q statistic. As show in **Table 4**, when the *p* value of the heterogeneity test was more than 0.1, a fixed-effects model was performed. Otherwise, the random-effects model was used.

Sensitivity analysis was performed by sequentially omitting one individual study at a time, in order to reflect the influence of each study on the overall meta-analysis. As show in **Figure 6**, sensitivity tests suggested that no single study greatly influenced the estimates of overall risk for the four IL-10 polymorphisms respectively and the results of our meta-analysis were stable.

Publication bias

In this meta-analysis, we performed Begg's funnel plot and Egger's test to access the publication bias. As show in **Figure 7**, the funnel plots could not show any obvious asymmetry in all genotypes in the overall population. Therefore, the results of Egger's test revealed that publication bias was not significant in this meta-analysis (P>0.05).

Discussion

Malignant diseases of the lymphoid system, which originated in the process of lymphocyte proliferation and differentiation, was a multifactorial disease caused by complex inherited genetic variations and environmental factors. Immune dysfunction was expected to be the potential basis of lymphomagenesis, expression of key cytokines might play an important part in the pathogenesis of NHL. IL-10, an immunoregulatory cytokine, was considered promoting the occurrence of cancer by immunosuppression effects and suppressing the occurrence of cancer by anti-angiogenic functions, therefore, which were double-edged properties of immunosuppression and immune stimulation [31]. Genotypic variations in the promoter sequences of the IL-10 gene may influence in IL-10 production of different individual [32, 33] and play a certain role in the susceptibility and clinical progression of lymphoma [34, 35].

Table 4. Heterogeneity-analysis results

Comparisons	B vs. A			BB vs. AA			AB vs. AA			BB vs. AA+AB			AB+BB vs. AA		
	I^2	P	EM	I^2	P	EM	I^2	P	EM	I^2	P	EM	I^2	P	EM
Rs1800890	39%	0.07	R	35%	0.09	R	14%	0.30	F	23%	0.21	F	30%	0.14	F
Caucasian	25%	0.20	F	8%	0.36	F	18%	0.27	F	0%	0.50	F	25%	0.20	F
B-NHL	37%	0.09	R	38%	0.08	R	0%	0.57	F	28%	0.16	F	16%	0.28	F
T-NHL	0%	0.75	F	11%	0.34	F	0%	0.42	F	49%	0.12	F	0%	0.76	F
DLBCL	0%	0.71	F	2%	0.42	F	0%	0.95	F	5%	0.39	F	0%	0.91	F
CLL/SLL	41%	0.13	F	17%	0.31	F	4%	0.39	F	3%	0.40	F	28%	0.23	F
FL	29%	0.23	F	26%	0.25	F	22%	0.27	F	3%	0.39	F	29%	0.23	F
rs1800896	52%	0.02	R	53%	0.02	R	8%	0.37	F	50%	0.03	R	29%	0.17	F
Caucasian	59%	0.01	R	58%	0.01	R	24%	0.23	F	59%	0.03	R	42%	0.09	R
B-NHL	52%	0.02	R	52%	0.02	R	0%	0.58	F	51%	0.03	R	23%	0.23	F
DLBCL	56%	0.04	R	59%	0.02	R	0%	0.44	F	59%	0.02	R	30%	0.20	F
CLL/SLL	65%	0.06	R	49%	0.14	F	23%	0.27	F	18%	0.30	F	53%	0.12	F
FL	0%	0.86	F	0%	0.82	F	0%	0.57	F	0%	0.99	F	0%	0.64	F
rs1800871	38%	0.16	F	8%	0.37	F	0%	0.72	F	21%	0.28	F	0%	0.52	F
Caucasian	48%	0.12	F	22%	0.28	F	0%	0.64	F	44%	0.15	F	0%	0.44	F
B-NHL	37%	0.16	F	1%	0.41	F	0%	0.70	F	24%	0.25	F	0%	0.55	F
DLBCL	59%	0.06	R	26%	0.26	F	0%	0.73	F	58%	0.07	R	0%	0.46	F
FL	25%	0.27	F	0%	0.91	F	0%	0.71	F	53%	0.12	F	0%	0.95	F
rs1800872	26%	0.23	F	20%	0.27	F	0%	0.66	F	3%	0.41	F	2%	0.41	F
Caucasian	0%	0.40	F	0%	0.44	F	0%	0.75	F	0%	0.56	F	0%	0.55	F
B-NHL	0%	0.80	F	0%	0.68	F	0%	0.59	F	0%	0.88	F	0%	0.63	F
DLBCL	0%	0.70	F	0%	0.64	F	0%	0.61	F	0%	0.88	F	0%	0.64	F
FL	0%	0.33	F	0%	0.67	F	0%	0.84	F	22%	0.26	F	0%	0.87	F

A: the major allele; B: the minor allele; EM: Effects model; F: fixed effects model; R: random effects model; B-NHL: B-cell non-Hodgkin's Lymphoma; T-NHL: T-cell non-Hodgkin's Lymphoma; DLBCL: diffuse large B-cell Lymphoma; FL: Follicular Lymphoma; CLL/SLL: chronic lymphocytic Leukemia/small lymphocytic Lymphoma.
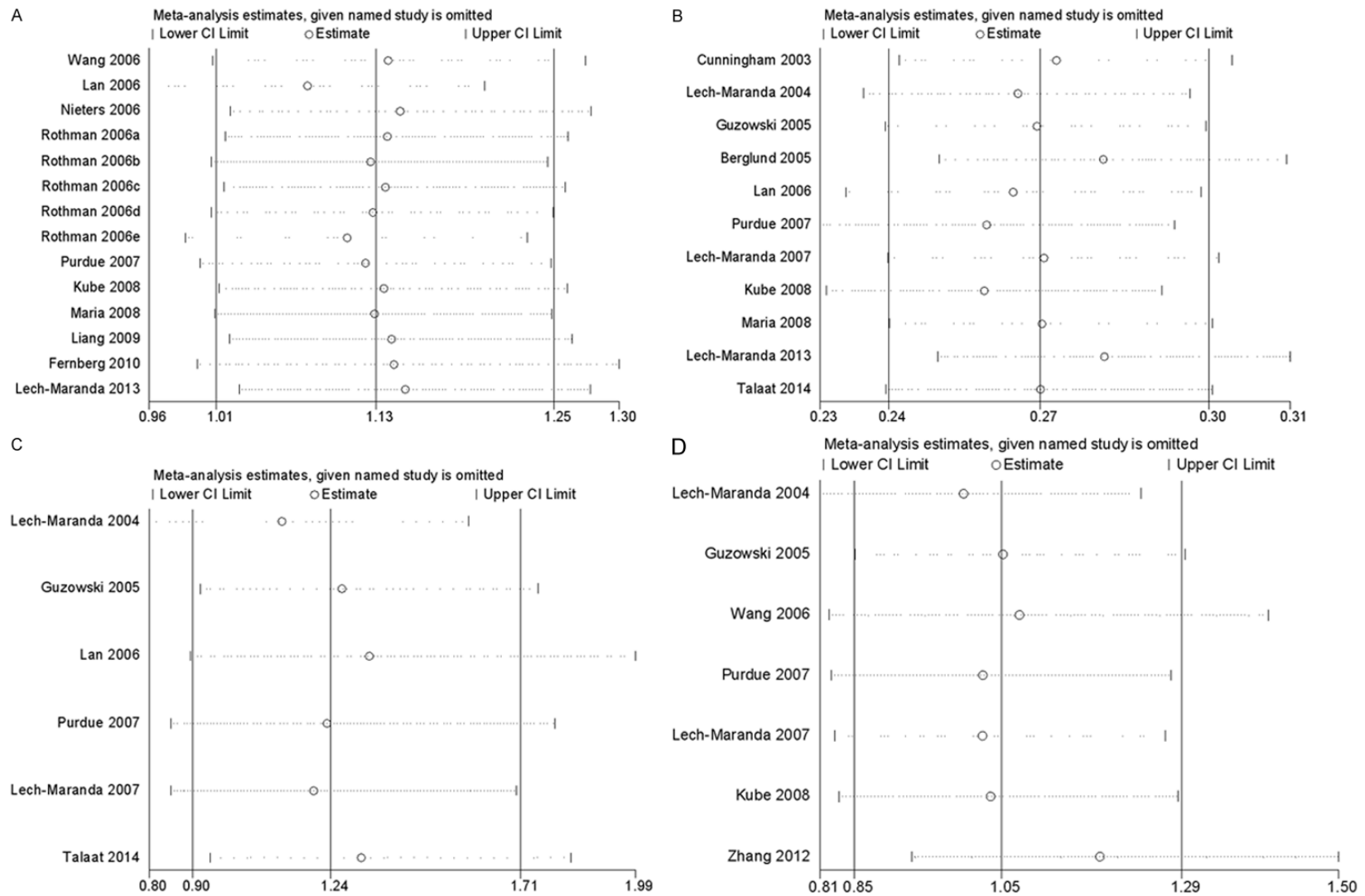
In present meta-analysis, we analyzed the relationship between the four common IL-10 SNPs (rs1800890, rs1800896, rs1800871 and rs1800872) and NHL susceptibility including twenty-one studies with 7749 cases and 8360 controls for this meta-analysis. To our known, this was the first meta-analysis which researched the association between the four common IL-10 SNPs and risk of NHL.

Overall, our research indicated, populations with IL-10 rs1800896 G allele were associated with a 14% increased risk of NHL (P = 0.02). Similarly, rs1800896 was found 20% increased (P = 0.007) and 22% increased (p = 0.002) susceptibility of NHL in heterozygote and dominant genetic model in the overall population, respectively. However, statistically significant was not examined between the three polymorphisms (rs1800890, rs1800871 and rs1800872) and NHL susceptibility. Our results were inconsistent with a previous single study, which found

aggressive lymphoma had a higher frequency of IL-10-3575A and IL-10-1082A haploid genotype [8]. The reason may be that it included fewer cases and controls. Ethnic origin analysis, significant association was detected between rs1800896 variation and NHL susceptibility in heterozygote and dominant models in Caucasians (AG vs. AA: OR = 1.21, P = 0.01; GG+AG vs. AA: OR = 1.21, p = 0.008), whereas other three SNPs (rs1800890, rs1800872 and rs1800871) did not find statistical significance with NHL risk in Caucasians. Previous studies found IL-10 gene polymorphisms associated with the risk of NHL [9, 13, 36], others shown that IL-10 was relative to the NHL's course [8, 37], IL-10 genetic loci haplotypes AGCC/TATA (-3575, -1082, -819, -592) and ATA/ACC (-1082, -819, -592) was relative to NHL predisposition and invasiveness [10, 19]. That supported IL-10 polymorphisms was associated with NHL susceptibility.
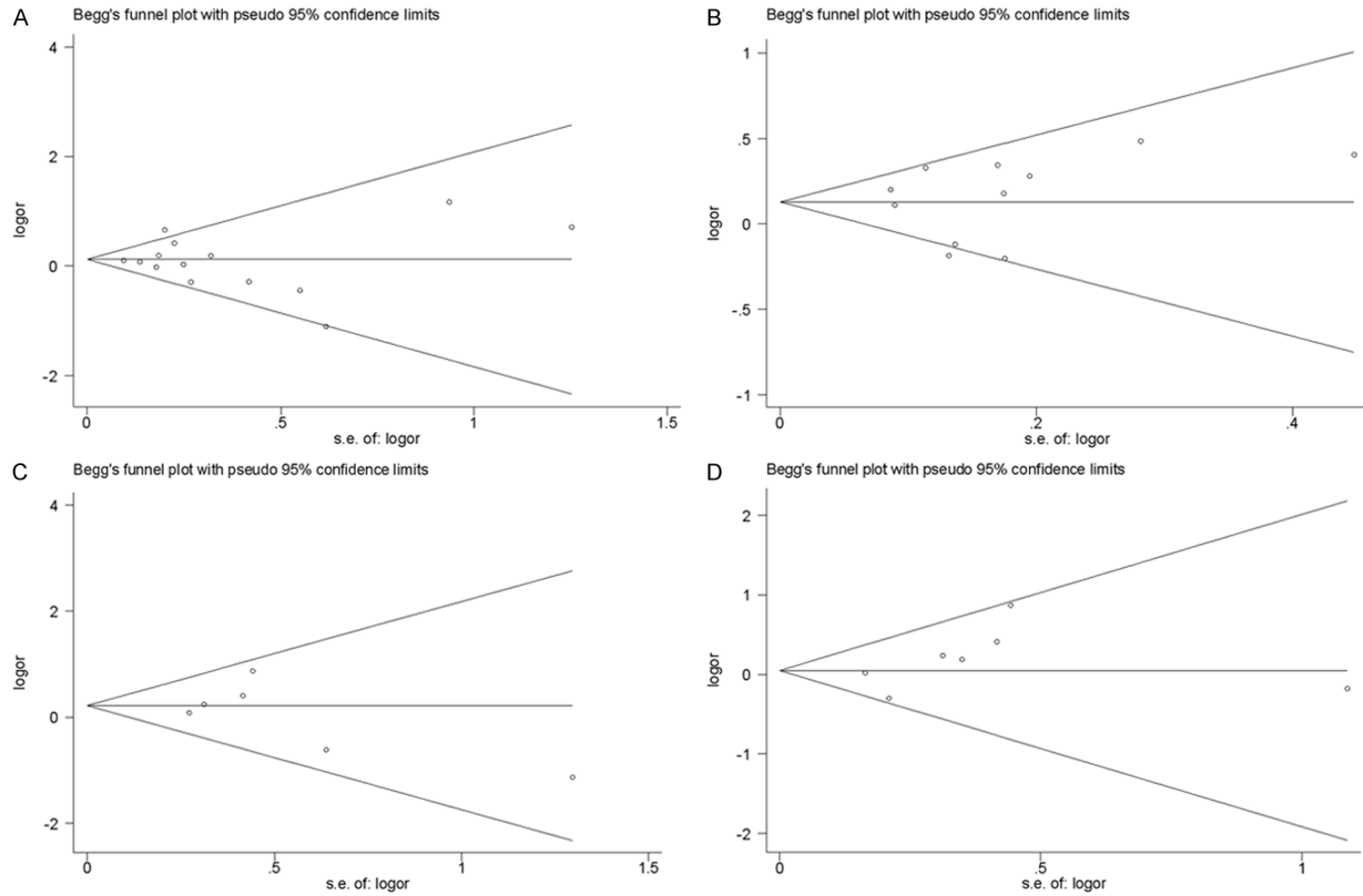
Figure 6. Sensitivity analysis of association between the polymorphisms and non-Hodgkin's Lymphoma risk. A. rs1800896; B. rs1800896; C. rs1800871; D. rs1800872.

Figure 7. Funnel plot assessing evidence of publication bias from the eligible studies. A. rs1800896; B. rs1800896; C. rs1800871; D. rs1800872.

According the origin of lymphoma cell, the rs1800890 variation had increased B-NHL risk in recessive and dominant comparison models (AA vs. TT+TA: OR = 1.15, P = 0.01; AA+TA vs. TT: OR = 1.11, P = 0.008), whereas the rs1800896 polymorphism had increased B-NHL risk in heterozygote and dominant comparison models (AG vs. AA: OR = 1.22, P = 0.007; GG+AG vs. AA: OR = 1.23, P = 0.002), respectively. Our study also studied the rs1800890 variation and T-NHL predisposition, no correlation was observed in end, which may be related to involve less number of subjects. In addition, the current meta-analysis results indicated that the rs1800871 and rs1800872 polymorphisms had no association with B-NHL predisposition based on all genetic models.

Among the common subtypes of NHL, there were significant association between the three polymorphisms (rs1800890, rs1800896 and rs1800872) and DLBCL risk in different genetic models. Specifically, the rs1800890A allele may be associated with substantial increased DLBCL risk in overall populations, our results was consistent with a previous meta-analysis by Rothman [13]. The rs1800896 variant were found to be significantly associated with an increased DLBCL risk in heterozygote and dominant comparison models (AG vs. AA: OR = 1.26, P = 0.01; GG+AG vs. AA: OR = 1.29, P = 0.004), respectively. In addition, the rs1800872 polymorphism was showed statistical significance with DLBCL risk in the following comparison models (homozygote model: CC vs. AA: OR = 2.06, P = 0.03; dominant model: CC+AC vs. AA: OR = 1.95, P = 0.04; allele comparison: C vs. A: OR = 1.28, P = 0.04). However, no significant association was detected between rs-1800871 polymorphism and DLBCL risk in any comparison model. The results of the meta-analysis [36] suggested that there were significant association between the three polymorphisms (rs1800890, rs1800896 and rs18-00872) and DLBCL risk, which was consistent with our investigation. In addition, the four polymorphisms (rs1800890, rs1800896, rs180-0871 and rs1800872) were found no correlation with FL predisposition. Studies suggested that FL has a familial aggregation [2, 39], that mean FL was associated with genetic factor. However, case-control studies were not found IL-10 SNPs increase the risk of FL [10, 20]. Similarly, this study also found that the rs1800890 and rs1800896 polymorphisms

unrelated with CLL/SLL susceptibility, which was consistent with previous data [14, 21]. Whereas a previous cohort study, CLL/SLL patients with the IL-10-1082AA genotype have better over survival (OS) compared with those individuals with AA and AC carriers [22], which indicated rs1800896 variant may predict clinical prognosis of CLL/SLL.

In summary, our study include the meta-analysis approach we took to evaluating the four important genetic polymorphisms (rs1800890, rs1800896, rs1800871 and rs1800872) and NHL predisposition in the present study that IL-10 polymorphisms had an association with the risk of NHL subtypes, particularly B-cell malignancy, and may contribute to the pathogenesis of DLBCL.

Several limitations of our meta-analysis should be attention. First, our meta-analysis was based on unadjusted estimates; thus, we could not assess the risk of lymphoma according to stratification of age, environmental factors, and other risk factors of NHL. The lack of such data for the analysis may cause serious confounding bias. Second, there was only one eligible study researched the association of IL-10 polymorphisms and risk of NHL in Asian. Therefore, more case-control studies are needed to further identify the association among Asians. Third, since some of the studies had a relatively small sample size, the results did not have adequate power to definitely confirm the association. Further large-scale studies with more detailed individual data, with different environmental factors are warranted to further precise gene-gene and gene-environment interactions on IL-10 polymorphisms and NHL risk.

Conclusion

In conclusion, our present meta-analysis indicated that IL-10 rs1800896 polymorphism was associated with NHL risk, further studies showed that rs1800896 polymorphism had an increased risk of NHL in Caucasians. Among the common NHL subtypes, significant association was found between rs1800890, rs18-00896 as well as rs1800872 polymorphisms and the susceptibility of DLBCL. Further large-scale multicenter epidemiological studies were needed to confirm our findings of IL-10 polymorphisms in Non-Hodgkin lymphoma carcinogenesis.

Disclosure of conflict of interest

None.

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