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Research Paper

Association of *IL10* -819C>T and -592C>A Polymorphisms with Non-Hodgkin Lymphoma Susceptibility: Evidence from Published Studies

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Abstract

Numerous studies have investigated the association of *IL10* -819C>T and -592C>A polymorphisms with non-Hodgkin lymphoma (NHL) susceptibility, and yet reported conflicting results. With this in mind, we performed the current meta-analysis with an aim to verify actual causative variants underlying lymphomagenesis. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the associations. Moreover, to explore the biological function of these polymorphisms, we also performed genotype-based mRNA expression analysis using online database derived from 270 subjects within three ethnicities. The final analysis included 11 studies with a total of 5859 NHL cases and 6893 controls for the *IL10* -819C>T polymorphism, and 11 studies with 6277 cases and 7350 controls for the *IL10* -592C>A polymorphism. No significant association was observed for these two polymorphisms in either the overall analysis or the stratification analyses by ethnicity and source of controls. Nevertheless, stratification analyses demonstrated a significant decreased risk associated with the *IL10* -819C>T polymorphism (homozygous: OR=0.81, 95% CI=0.66-0.99, and recessive model: OR=0.80, 95%CI=0.65-0.98) and *IL10* -592C>A polymorphism (homozygous: OR=0.80, 95% CI=0.66-0.99, and recessive model: OR=0.80, 95%CI=0.66-0.97) among patients with diffuse large B-cell lymphoma (DLBCL). Despite some limitations, this meta-analysis indicates that polymorphisms in *IL10* gene may contribute to DLBCL susceptibility.

Key words: IL10; NHL; polymorphism; susceptibility; meta-analysis

Introduction

Cancer is a major public health problem and burden worldwide, which cause remarkable cancer-associated death and disability. Cancer-related deaths account for one eighth of deaths overall - more than combined death toll caused by AIDS, tuberculosis and malaria together. Non-Hodgkin lymphoma (NHL) originated from hematological system is one of the most malignant tumors. According to

GLOBOCAN 2008 estimates, approximately 355,900 new cases and 191,400 deaths from NHL occurred that year [1, 2]. The developed areas such as North America, Australia/New Zealand, and Northern, Western, and Southern Europe were found with the highest incidence rates, while South-Central and Eastern Asia and the Caribbean with the lowest incidence rates [1]. NHL is a heterogeneous group of lymphoproliferative malignancies, with more than 60 recognized specific NHL subtypes. Mostly commonly, NHLs are classified into B-cell and T-cell lymphomas based on cell origins. In particular, B-cell lymphomas account for about 80%-85% of NHL cases.

Although the clear etiology of NHL is warranted extensive investigation, there are some well-documented NHL risk factors, such as immune dysfunction and stimulation, infection, high doses of radiation, family history, and occupational exposures to pesticides and chlorinated organic compounds [3]. Numerous studies have indicated that altered immunity may also play important roles in the development and prognosis of NHL [4-6]. Besides environmental exposures, chromosomal and genetic alterations that affect immune function may modulate the risk of developing NHL [7-10].

Multifunctional cytokines [e.g., tumor necrosis factor-alpha and interleukin 10 (IL10)] that regulate the immunological development and inflammatory responses have been suggested to partake in carcinogenesis [11]. IL10 is a well-known anti-inflammatory cytokine whose principal biologic function includes, but not limited to, the suppression of cytokine synthesis in Th1 cells and down-regulation of cell-mediated and cytotoxic inflammatory responses [12, 13]. Interestingly, accumulating evidence has shown that IL10 is also involved in the pathogenesis of lymphoid malignancies [14]. Increased serum levels of IL10 were found in NHL patients, which were correlated with adverse clinicopathological features and poor outcomes [15].

The *IL10* gene is located on chromosome 1q31-1q32 [16]. It is highly polymorphic, and there are at least 189 reported single nucleotide polymorphisms (SNPs) in the IL10 gene region (http://www.ncbi.nlm.nih.gov/projects/SNP). Among all the indentified SNPs, *IL10* -819C>T (rs1800871) and -592C>A (rs1800872) in the promoter region have been widely investigated [17]. Previous study have found that the -819C>T and -592C>A polymorphisms were associated with increased serum level of IL10 in NHL patients and may influence NHL susceptibility and clinical outcomes [18]. Given potential influence on gene transcription and expression, the promoter polymorphisms have undergone the most extensive scrutiny. Numerous studies have investigated the associations of *IL10* -819C>T [18-28] and -592C>A [18-25, 27-29] polymorphisms with NHL susceptibility, but the conclusions of these studies remains conflicting rather than conclusive. The disagreements may be ascribed to relatively small sample size in each study as well as ethnic difference. Hence, we performed the present meta-analysis to provide a more precise estimation of the associations of *IL10* -819C>T and -592C>A with NHL susceptibility.

Materials and methods

Identification of relevant studies

In order to track down all relevant studies for the given topic to limit bias, we conducted a comprehensive and systematical literature searched in PubMed and Embase, using the following items: "*interleukin-10* or *IL-10* or *IL10*", "polymorphism or variant or variation" and "non-Hodgkin lymphoma or non-Hodgkin's lymphoma or NHL" (prior to December 18, 2014). Reference lists of original articles and review articles were also checked manually to identify additional pertinent studies. The search was limited to investigations written in English. If more than one article was published with the same patient population, only the latest or the largest study would be used in this study.

Inclusion and exclusion criteria

Studies included had to meet the following criteria: (a) evaluating of the association between *IL10* -819C>T and/or -592C>A polymorphisms and cancer risk, (b) using a case-control or cohort design (retrospective or prospective and nested case-control), (c) providing sufficient information to estimate odds ratios (ORs) and their corresponding 95% confidence intervals (CIs), and (d) containing available genotype frequency.

Exclusion criteria were: (a) cases only or healthy subjects only studies, (b) duplicate publication, or (c) the genotype frequency distribution in the controls was not in accordance with Hardy-Weinberg equilibrium (HWE).

Data extraction

Two investigators (Ting Zhang and Shang Xie) assessed all retrieved studies following the inclusion criteria, reached a consensus on all items, and then extracted the following information independently from all eligible publications: the first author's surname, year of published, country of origin, ethnicity, source of control [population based (PB) and hospital based (HB)], genotyping methods, subtype of NHL [diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL)], total number of cases and controls, as well as genotype counts of *IL10* -819C>T (CC,

CT, and TT) and -592C>A (CC, AC, and AA) polymorphisms in cases and controls.

Correlation analysis between Genotype and gene expression

The genotype data for *IL10* polymorphisms (rs1800871C>T and rs1800872C>A) were available online from HapMap (http://hapmap.ncbi.nlm.nih.gov/), while corresponding *IL10* mRNA expression levels derived from 270 subjects of three ethnicity (Caucasians, Asians and Africans) were located in SNPexp (http://app3.titan.uio.no/biotools/tool.php?app=snpexp) website as described previously [30-32].

Statistical methods

The strength of association between *IL10* gene polymorphisms and NHL risk was assessed by calculating ORs with their corresponding 95% CIs. The pooled ORs and 95% CIs were performed for -819C>T using different genetic models: homozygous (TT vs. CC), heterozygous (CT vs. CC), recessive (TT vs. CT+CC), dominant (TT+CT vs. CC) and allele comparing (T vs. C). Likewise, the same models were applied to *IL10* -592C>A: homozygous (AA vs. CC), heterozygous (AC vs. CC), recessive (AA vs. AC+CC), dominant (AA+AC vs. CC) and allele comparing (A vs. C). The Chi square-based Q test was performed to calculate the between-study heterogeneity. If $P<0.1$, the random-effects model would be adopted; otherwise, the fixed-effects model was used. Stratification analysis was performed by race (Asians, Caucasians, and mixed), source of control (PB or HB) and subtype (DLBCL and FL). The chi-square goodness-of-fit test was evaluated for HWE, with a *P*-value below 0.05 indicating the departure from HWE. Furthermore, we conducted sensitivity analyses by excluding each investigation individually to evaluate the influence of each individual study on summary ORs. Funnel plot and Egger's test were used to assess publication bias. Differences in mRNA expression levels were determined by Student's t test. Moreover, the linear trend of mRNA expression levels among genotypes (0, 1 and 2 variant alleles) was tested by linear regression models. All statistical data manipulations were conducted by using the STATA software (Version 11.0, Stata, College Station, TX). A *P*-value less than 0.05 was defined as statistical significant.

Results

Study characteristics

As shown in **Figure 1**, a total of 63 publications were retrieved from PubMed and Embase database. After the assessment of abstracts and texts, 43 irrelevant publications were excluded, and the remaining 20 publications that met the crude inclusion criteria and were subjected to further evaluation. Among them, eight investigations were excluded, for five [33-37] were case only studies, one [38] was covered by another study [22], and two [39, 40] without detailed data available. Finally, 12 investigations [18-29] met the inclusion criteria and were included in the final meta-analysis (**Table 1**). Overall, 11 studies with 5859 cases and 6893 controls investigated the *IL10* -819C>T polymorphism, and 11 studies with 6277 cases and 7350 controls investigated the *IL10* -592C>A polymorphism. Of the remaining studies, six studies provided detailed genotype frequency data for the DLBCL and FL subtype for these two polymorphisms (**Supplemental Table S1**).

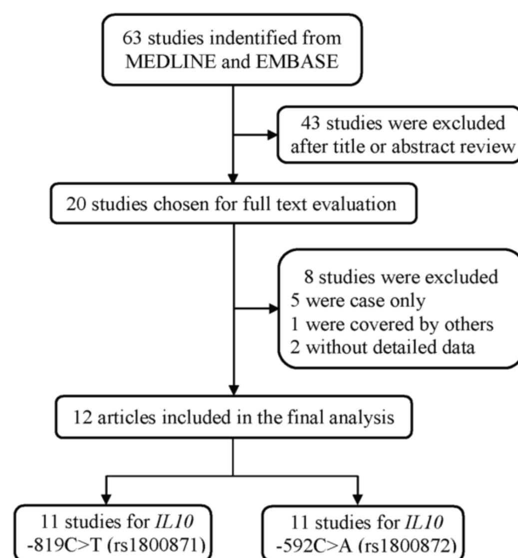

Figure 1. The flowchart of included studies.

For the *IL10* -819C>T polymorphism, sample sizes of cases ranged from 17 to 2401, and those of controls from 25 to 4097. There were seven studies focused on Caucasians, one study on Asians, and three studies on mixed ethnic group. Of these 11 studies, four were PB, six were HB designed and last one did not provide the source of control. As to the *IL10* -592C>A polymorphism, sample sizes ranged from 17 to 2401 for the cases, and those of controls from 25 to 4088. There were six studies conducted among Caucasians, two studies among Asians, and three studies among mixed ethnic group. Four studies were PB, and six were HB designed.

Meta-analysis results

As shown in **Table 2**, pooled analysis did not yield a significant association between *IL10* -819C>T polymorphism and overall NHL risk (homozygous: OR=0.97, 95% CI=0.76-1.22; heterozygous: OR=0.97, 95% CI=0.90-1.04; recessive: OR=1.04, 95%

CI=0.92-1.19; dominant: OR=0.98, 95% CI=0.91-1.05 and allele comparing: OR=0.99, 95% CI=0.94-1.05). The subgroup analysis found no significant association by either ethnicity or source of control. However, stratified analysis by tumor subtype demonstrated a significant decreased risk associated with *IL10* -819C>T polymorphism for DLBCL (homozygous: OR=0.81, 95% CI=0.66-0.99 and recessive: OR=0.80, 95% CI=0.65-0.98) (**Figure 2**).

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

Surname	Year	Country	Ethnicity	Source	Genotype method	Case				Control				MAF	HWE
-819C>T (rs1800871) polymorphism						CC	CT	TT	All	CC	CT	TT	All		
Lech-Maranda	2004	France	Caucasian	HB	PCR-RFLP	107	81	11	199	53	46	13	112	0.321	0.536
Guzowski	2005	USA	Caucasian	HB	DHPLC	9	6	2	17	14	10	1	25	0.24	0.629
Lan	2006	USA	Mixed	PB	TaqMan	274	191	26	491	329	211	34	574	0.243	0.982
Persico	2006	Italy	Caucasian	PB	PCR-RFLP	138	100	12	250	53	51	6	110	0.286	0.159
Wang	2006	USA	Mixed	PB	TaqMan	625	427	92	1144	514	339	81	934	0.268	0.021
Kube	2007	Germany	Caucasian	NA	NA	230	167	21	418	111	81	10	202	0.25	0.325
Lech-Maranda	2007	France	Caucasian	HB	PCR-RFLP	92	68	15	175	53	46	13	112	0.321	0.536
Purdue	2007	Australia	Caucasian	PB	TaqMan	342	175	41	558	295	170	23	488	0.221	0.813
Andrie	2009	Greece	Caucasian	HB	ARMS-PCR	22	20	6	48	45	35	5	85	0.265	0.594
Wong	2010	USA	Mixed	HB	TaqMan	109	47	2	158	88	57	9	154	0.244	0.954
Hosgood	2013	Asia	Asian	HB	TaqMan	1193	971	237	2401	2033	1700	364	4097	0.296	0.749
-592C>A (rs1800872) polymorphism						CC	AC	AA	All	CC	AC	AA	All		
Lech-Maranda	2004	France	Caucasian	HB	PCR-RFLP	107	81	11	199	53	46	13	112	0.321	0.536
Guzowski	2005	USA	Caucasian	HB	DHPLC	10	5	2	17	13	10	2	25	0.280	0.968
Lan	2006	USA	Mixed	PB	TaqMan	273	174	35	482	331	189	43	563	0.244	0.032
Persico	2006	Italy	Caucasian	PB	PCR-RFLP	138	100	12	250	53	51	6	110	0.286	0.159
Wang	2006	USA	Mixed	PB	TaqMan	601	426	93	1120	515	342	81	938	0.269	0.027
Kube	2007	Germany	Caucasian	NA	NA	226	165	21	412	111	81	10	202	0.250	0.325
Lech-Maranda	2007	France	Caucasian	HB	PCR-RFLP	92	68	15	175	53	46	13	112	0.321	0.536
Purdue	2007	Australia	Caucasian	PB	TaqMan	343	176	21	540	297	169	23	489	0.22	0.868
Wong	2010	USA	Mixed	HB	TaqMan	107	49	11	167	88	57	9	154	0.244	0.954
Zhang	2012	China	Asian	HB	TaqMan	226	228	60	514	269	235	53	557	0.306	0.872
Hosgood	2013	Asia	Asian	HB	TaqMan	1204	961	236	2401	2041	1685	362	4088	0.295	0.593

PB, Population based; HB, Hospital based; PCR-RFLP, polymorphism chain reaction-restriction fragment length polymorphism; DHPLC, denaturing high-performance liquid chromatography; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

Table 2. Meta-analysis of the association between *IL10* polymorphisms and NHL risk

Variables	No. of studies	Sample size Case/control	Homozygous		Heterozygous		Recessive		Dominant		Allele comparing	
			OR (95% CI)	P_{het}	OR (95% CI)	P_{het}	OR (95% CI)	P_{het}	OR (95% CI)	P_{het}	OR (95% CI)	P_{het}
-819C>T (rs1800871)			TT vs. CC		CT vs. CC		TT vs. (CT + CC)		(CT + TT) vs. CC		T vs. C	
All	11	5859/6893	0.97 (0.76-1.22)	0.094	0.97 (0.90-1.04)	0.821	1.04 (0.92-1.19)	0.108	0.98 (0.91-1.05)	0.558	0.99 (0.94-1.05)	0.184
Ethnicity												
Caucasian	7	1665/1134	0.99 (0.63-1.55)	0.118	0.90 (0.76-1.06)	0.964	1.07 (0.79-1.46)	0.132	0.92 (0.79-1.07)	0.800	0.96 (0.85-1.09)	0.365
Asian	1	2401/4097	1.10 (0.93-1.33)	/	0.97 (0.88-1.08)	/	1.12 (0.95-1.33)	/	1.00 (0.90-1.10)	/	1.02 (0.95-1.11)	/
Mixed	3	1793/1662	0.80 (0.48-1.32)	0.124	1.01 (0.88-1.17)	0.190	0.86 (0.66-1.12)	0.177	0.99 (0.86-1.13)	0.086	0.97 (0.87-1.08)	0.047
Source of control												
PB	4	2443/2106	1.02 (0.80-1.29)	0.392	0.99 (0.87-1.12)	0.430	1.02 (0.81-1.29)	0.306	1.00 (0.88-1.12)	0.603	1.00 (0.91-1.10)	0.689
HB	6	2998/4585	0.80 (0.44-1.46)	0.022	0.95 (0.86-1.05)	0.712	1.05 (0.90-1.24)	0.034	0.97 (0.88-1.06)	0.244	0.99 (0.92-1.06)	0.031
Subtype												
DLBCL	5	1997/6205	**0.81 (0.66-0.99)**	0.510	1.02 (0.92-1.14)	0.396	**0.80 (0.65-0.98)**	0.535	0.99 (0.89-1.09)	0.369	0.95 (0.88-1.03)	0.374
FL	5	932/6205	1.00 (0.76-1.32)	0.258	1.03 (0.88-1.20)	0.223	1.00 (0.76-1.31)	0.333	1.02 (0.89-1.19)	0.161	1.02 (0.90-1.14)	0.140
-592C>A (rs1800872)			AA vs. CC		AC vs. CC		AA vs. (AC + CC)		(AC + AA) vs. CC		A vs. C	
All[a]	11	6277/7350	1.04 (0.91-1.18)	0.565	0.98 (0.92-1.06)	0.652	1.04 (0.92-1.18)	0.652	0.99 (0.93-1.06)	0.542	1.00 (0.95-1.06)	0.435
Ethnicity												
Caucasian	6	1593/1050	0.74 (0.52-1.04)	0.743	0.89 (0.75-1.05)	0.946	0.78 (0.55-1.09)	0.739	0.87 (0.74-1.02)	0.915	0.88 (0.77-1.00)	0.824
Asian	2	2915/4645	1.14 (0.97-1.34)	0.385	0.99 (0.90-1.10)	0.206	1.14 (0.98-1.34)	0.603	1.02 (0.93-1.12)	0.169	1.04 (0.97-1.12)	0.196
Mixed	3	1769/1655	0.99 (0.76-1.27)	0.999	1.04 (0.90-1.20)	0.235	0.97 (0.75-1.24)	0.936	1.03 (0.90-1.18)	0.329	1.01 (0.91-1.13)	0.565
Source of control												
PB	4	2392/2100	0.94 (0.74-1.19)	0.902	1.01 (0.89-1.15)	0.366	0.93 (0.74-1.17)	0.974	1.00 (0.89-1.12)	0.367	0.99 (0.90-1.09)	0.492
HB	6	3473/5048	1.08 (0.93-1.26)	0.209	0.97 (0.88-1.06)	0.508	1.09 (0.94-1.27)	0.286	0.99 (0.91-1.08)	0.336	1.01 (0.94-1.08)	0.187
Subtype												
DLBCL	5	1986/6190	**0.80 (0.66-0.99)**	0.510	1.02 (0.91-1.13)	0.363	**0.80 (0.66-0.97)**	0.498	0.98 (0.88-1.08)	0.399	0.95 (0.87-1.03)	0.448
FL	5	934/6190	1.08 (0.83-1.42)	0.164	1.02 (0.88-1.19)	0.375	1.08 (0.83-1.40)	0.258	1.03 (0.89-1.19)	0.199	1.03 (0.92-1.16)	0.098

HB, Hospital based; PB, Population based; DLBCL, Diffuse large B-cell lymphomas; FL, Follicular lymphoma.

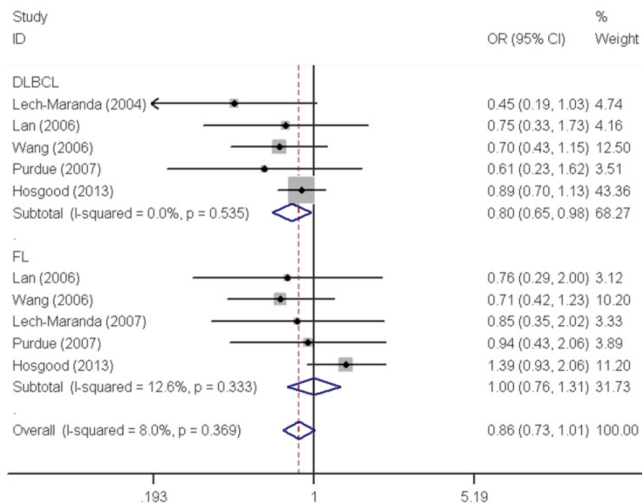

Figure 2. Forest plot of NHL risk associated with the *IL10* -819C>T polymorphism by subtypes under recessive model. For each study, the estimates of OR and their corresponding 95% CI were plotted with a box and a horizontal line. The symbol filled diamond indicates pooled OR and its corresponding 95% CI.

Similar results were observed for the *IL10* -592C>A polymorphism. We did not find any significant association with overall NHL risk (homozygous: OR=1.04, 95% CI=0.91-1.18; heterozygous: OR=0.98, 95% CI=0.92-1.06; recessive: OR=1.04, 95% CI=0.92-1.18; dominant: OR=0.99, 95% CI=0.93-1.06 and allele comparing: OR=1.00, 95% CI=0.95-1.06). Moreover, no any significant association was observed between *IL10* -592C>A polymorphism and NHL risk either, when data were stratified by ethnicity and source of control. In contrast, a significant decreased DLBCL risk was found with *IL10* -592C>A polymorphism in the stratification analysis by tumor subtype (homozygous: OR=0.80, 95% CI=0.66-0.99 and recessive: OR=0.80, 95% CI=0.66-0.97) (**Figure 3**).

The correlation between the mRNA expression and genotypes

We explored the correlation between *IL10* mRNA expressions levels and the genotypes of *IL10* polymorphisms among Caucasians, Africans and Asians as well as the whole group (**Table 3**). We failed to find any significant difference in the *IL10* mRNA expression levels among subjects with three genotypes (wild-type, heterozygote, and homozygote) of either the *IL10* -819C>T or -592C>A polymorphism in the Africans, Asians and the whole group. However, among the Caucasians, *IL10* mRNA expression level in *IL10* -819C>T polymorphism heterozygotes was significantly higher than wild-types (heterozygous: *P*=0.041), while *IL10* mRNA expression levels in heterozygous carriers or combined heterozygous and homozygous carriers of *IL10* -592C>A polymorphism were significantly increased, when compared with wild-type control (heterozygous: *P*=0.030 and dominant model: *P*=0.023).

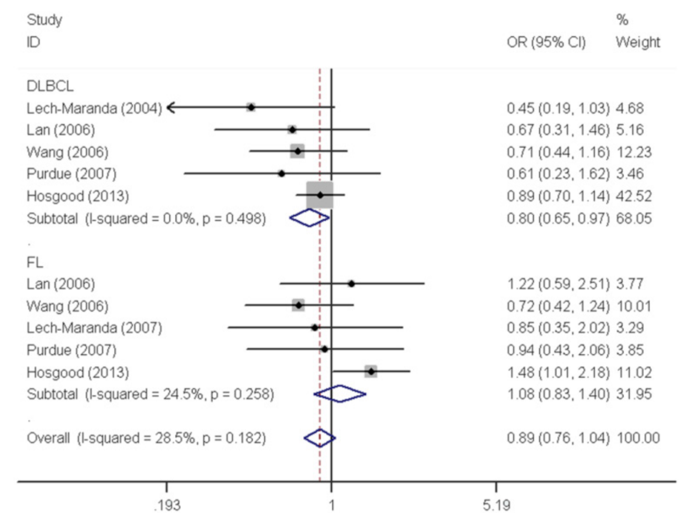

Figure 3. Forest plot of NHL risk associated with the *IL10* -592C>A polymorphism by subtypes under recessive model. For each study, the estimates of OR and their corresponding 95% CI were plotted with a box and a horizontal line. The symbol filled diamond indicates pooled OR and its corresponding 95% CI.

Heterogeneity and sensitivity analyses

As shown in **Table 2**, no heterogeneities were observed among all studies, while evaluating the association between *IL10* -819C>T polymorphism and NHL susceptibility (heterozygous: *P*=0.821, recessive: *P*=0.108, dominant: *P*=0.558, and allele comparing: *P*=0.184), except for the homozygous model with moderate heterogeneity (*P*=0.094). Likewise, for the *IL10* -592C>A polymorphism, no heterogeneity were detected, either (homozygous: *P*= 0.565, heterozygous: *P*=0.652, recessive: *P*=0.652, dominant: *P*=0.542, and allele comparing: *P*=0.435).

Publication bias

The shape of the funnel plot seemed symmetrical, indicating that there was no evidence of publication bias. Moreover, the Egger's test further demonstrated the absence of publication bias in this meta-analysis with statistical evidence (for the *IL10* -819C>T polymorphism, homozygous: *P*=0.365; heterozygous: *P*=0.249; recessive: *P*=0.413; dominant: *P*=0.215 and allele comparing *P*=0.246, and for the *IL10* -592C>A polymorphism, homozygous: *P*=0.099; heterozygous: *P*=0.225; recessive: *P*=0.128; dominant: *P*=0.127 and allele comparing *P*=0.074).

Table 3. *IL10* mRNA expression by the genotypes of SNPs, using data from the HapMap[a]

Population	-819C>T (rs1800871)					-592C>A (rs1800872)				
	genotypes	No.	Mean ± SD	P^b	P_{trend}^c	genotypes	No.	Mean ± SD	P^b	P_{trend}^c
Caucasian[d]	CC	52	7.77 ± 0.49		0.106	CC	54	7.78 ± 0.50		0.070
	CT	28	8.02 ± 0.59	**0.041**		AC	33	8.04 ± 0.61	**0.030**	
	TT	1	7.55	0.668		AA	2	8.21 ± 0.93	0.246	
	Dominant	29	8.00 ± 0.58	0.053		Dominant	35	8.05 ± 0.61	**0.023**	
African[d]	CC	24	7.60 ± 0.53		0.369	CC	24	7.60 ± 0.53		0.449
	CT	43	7.76 ± 0.46	0.196		AC	48	7.75 ± 0.45	0.219	
	TT	17	7.64 ± 0.43	0.793		AA	18	7.68 ± 0.44	0.617	
	Dominant	60	7.73 ± 0.45	0.269		Dominant	66	7.73 ± 0.45	0.252	
Asian[d]	CC	6	7.41 ± 0.52		0.217	CC	6	7.41 ± 0.52		0.151
	CT	33	7.57 ± 0.40	0.373		AC	39	7.57 ± 0.40	0.375	
	TT	40	7.70 ± 0.45	0.153		AA	44	7.71 ± 0.45	0.133	
	Dominant	73	7.64 ± 0.43	0.207		Dominant	83	7.64 ± 0.43	0.200	
All[d]	CC	82	7.69 ± 0.51		0.403	CC	84	7.70 ± 0.52		0.575
	CT	104	7.77 ± 0.50	0.283		AC	120	7.77 ± 0.52	0.334	
	TT	58	7.68 ± 0.44	0.889		AA	64	7.72 ± 0.46	0.843	
	Dominant	162	7.74 ± 0.48	0.475		Dominant	184	7.75 ± 0.50	0.433	

[a] Genotyping data and mRNA expression levels for *IL10* by genotypes were obtained from the HapMap phase II release 23 data from EBV-transformed lymphoblastoid cell lines from 270 individuals.

[b] Two-side Student's *t* test within the stratum.

[c] *P* values for the trend test of *IL10* mRNA expression among 3 genotypes for each SNP from a general linear model.

[d] There were missing data because genotyping data were not available.

Discussion

We performed this meta-analysis to comprehensively estimate the association between *IL10* gene polymorphisms and NHL risk, including 11 studies with 5859 NHL cases and 6893 controls for the *IL10* -819C>T polymorphism, and 11 studies with 6277 cases and 7350 controls for the *IL10* -592C>A polymorphism. Overall, we did not observe any significant association between either of two polymorphisms and NHL susceptibility. However, both of these two polymorphisms showed a trend to decrease DLBCL risk.

The *IL10* gene is comprised of five exons and four introns. Its protein product is an important anti-inflammatory cytokine that is involved in the regulation of inflammatory responses through directly influencing tumor necrosis factor production [41]. IL10 is also a critical immunoregulatory cytokine that regulates many aspects of the immune response. Moreover, it has been implicated in the tumorigenesis of various types of cancers [42, 43]. For instance, it might protect malignant cells by inhibiting cytotoxic T lymphocyte-mediated tumour-specific cell lysis [44]. Given IL10's important role in carcinogenesis, it is biologically plausible that the genetic variations in its coding gene may modulate the risk of cancers. It has been reported that *IL10* gene promoter may influence the IL10 expression, consequentially alter NHL susceptibility and clinical outcomes [18].

There were two recently published meta-analyses focusing on NHL risk and *IL10* gene polymorphisms [45, 46]. In one study carried out by Wang et al. [45], the association of *IL10* -1082A>C polymorphism with general cancer risk was investigated. The stratified analysis by cancer type found that the -1082A>C polymorphism was associated with overall NHL susceptibility, with a total of 2338 NHL cases and 1999 controls from eight studies. However, this study did not investigate the *IL10* -819C>T and -592C>A polymorphisms. Moreover, the other study by Cao et al. [46] merely focused on DLBCL, and included only three studies for either of *IL10* -819C>T or -592C>A polymorphisms. In the end, no significant association was observed between *IL10* -819C>T polymorphism and DLBCL risk under all genetic models, except that a modestly decreased DLBCL risk was observed under recessive model. Furthermore, they found that a significantly decreased DLBCL risk was associated with *IL10* -592C>A polymorphism under the recessive and homozygous models. The findings in the present meta-analysis were consistent with the results derived from Cao's meta-analysis. Moreover, we also investigated the associations between IL10 polymorphisms and follicle lymphoma as well as all other types of NHL, though no significant associations were observed. Carcinogenesis is a quite complex multi-step process, and different types of cancer may have different mechanisms. One possible explanation for the discrepancy in the cancer susceptibility between DLBCL and FL is that carcinogenic mechanisms under these two NHL subtypes may be different, and *IL10* genetic variants may exert differential effects in different cancers. Additionally, it is possible that the total sample size for the current meta-analysis is not sufficient enough to detect some potential association.

The current study has several merits: first, we included the latest studies, and this is the largest and most comprehensive meta-analysis for the association

of *IL*10 -819C>T and -592C>A polymorphisms with NHL susceptibility; second, we collected data for NHL subtype and performed subgroup analysis by subtype; third, we performed genotype-based mRNA expression analysis to further explore the potential function of these two polymorphisms which are located in the promoter region of *IL10* gene. Despite these merits, there remained some limitations in this meta-analysis to be addressed. First, we mainly searched published studies in PubMed and EMBASE, thus, we might have missed some publications, especially the unpublished negative studies. As a result, some degree of bias may occur. Second, due to lacking of original data, our meta-analysis was based on unadjusted estimates. A more precise analysis could have be performed if individual data were available such as age, gender, smoking status, body mass index, environment exposure, and lifestyles, which would allow us to further evaluate adjusted OR and gene-environment interactions. Third, the numbers of studies for these two polymorphisms were relatively small. Moreover, the individual sample sizes for cases in most studies included in the current meta-analysis were relatively small (<500) except for four studies [22, 25, 28, 29], which may lead to a limited statistical power to detect the real association. Finally, meta-analysis is a retrospective study that is subject to methodological limitations.

In conclusion, this meta-analysis indicates that both the *IL10* -819C>T and -592C>A polymorphisms may be associated with decreased DLBCL risk. However, well-designed large prospective studies using standardized genotyping methods, enrolling precisely diagnosed NHL patients, especially DLBCL patient, and strictly matched controls are warranted to validate the current findings.

Supplementary Materials

Supplementary Table S1. http://www.jcancer.org/v06p0709s1.pdf

Abbreviations

NHL, non-Hodgkin lymphoma; IL10, interleukin 10; SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PB, population based; HB, hospital based.

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Conflict of interest

The authors declare no conflicts of interest.

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