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ORIGINAL RESEARCH

Tumor necrosis factor-308 polymorphism with the risk and prognosis of non-Hodgkin lymphomas: a meta-analysis study

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Background: Tumor necrosis factor-308 (TNF-308) was implied to be associated with the development of non-Hodgkin lymphoma (NHL). The aim of this meta-analysis study was to investigate the association of TNF-308A polymorphism with the susceptibility to, and prognosis of, NHL.

Methods: PubMed, Web of Science, Elsevier, HighWire, Scopus, and Google Scholar were searched up to May 2015. The association of TNF-308 polymorphism with the risk of NHL and prognosis was assessed by odds ratio and hazard ratio, respectively.

Results: Overall, TNF-308G>A polymorphism increased the risk of NHL, B-cell lymphomas (BCL), and T-cell lymphomas and decreased the risk of follicular lymphomas. In stratified analysis, increased risk of BCL and diffuse large B-cell lymphomas (DLBCL) were observed in Caucasians and population-based studies, whereas decreased risk of NHL, BCL, and DLBCL were detected in Asians and hospital-based studies. Furthermore, pooled results of 1,192 patients with NHL from five studies suggested that TNF-308A was correlated with shorter progression-free survival and overall survival in patients with NHL, BCL, and DLBCL.

Conclusion: Current evidence indicated that TNF-308A polymorphism was significantly associated with the risk and prognosis of NHL. Future studies should further confirm these associations in other NHL subtypes and ethnicities.

Keywords: tumor necrosis factor, polymorphism, rs1800629, lymphomas, susceptibility, survival outcome

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of neoplasms, developing from B-cell, T-cell, and natural killer (NK)/T-cell, with various clinical and biological features.[1] There were ~355,900 new cases and 191,400 deaths from NHL worldwide in 2008.[2] The numbers continued to increase with estimated 385,700 new cases and 199,700 deaths in 2012.[3] Epidemiologic studies have examined the etiology of NHL, identifying smoking, alcohol use, infectious agents, family history of lymphoma, autoimmune disease, asthma, and radiation exposure as risk factors.[1,4–6]

Tumor necrosis factor-alpha (TNF-α) is the activator of canonical pathway of nuclear factor kappa B and is associated with the process of cellular growth, differentiation, and apoptosis.[7] It is also noted that TNF-α is involved in the pathogenesis of inflammatory, autoimmune, and malignant diseases.[8] Accumulating evidence indicates that the variation in the promoter of TNF-α polymorphism (rs1800629) is correlated with the susceptibility to and progression and prognosis of NHL.[9–11]

The association between TNF-308G>A and the risk of NHL was examined in the previous three reviews and meta-analyses.[12–14] A previous study published in 2006

pooled the data of eight studies from an International Lymphoma Epidemiology Consortium,[12] which only examined patients with diffuse large B-cell lymphomas (DLBCL) and follicular lymphomas (FL) in Caucasians, the most common forms of NHL.[15] In 2010, Skibola et al extended the previous study and examined the risk of TNF-308G>A in NHL and other subtypes in different ethnicities.[13] The recent study by Zhai et al further pooled the data of 18 studies and examined this association in a larger population.[14]

However, odds ratio (OR) was either estimated using unconditional logistic regression models in the previous two meta-analyses[12,13] or only examined in additive model (A vs G) in the recent one.[14] Besides, this association was merely analyzed in ethnicity subgroups in the previous meta-analyses without stratification by the source of controls. Moreover, the prognosis value of TNF-308A in patients with NHL had not been examined in the previous meta-analyses.

We, therefore, performed this meta-analysis, aiming to further evaluate the association between TNF-308G>A and the susceptibility to NHL under five genetic models and exploring the potential difference among ethnicities and sources of controls, as well as its correlation with survival outcome in patients with NHL.

Materials and methods
Publication search
The databases of PubMed, Web of Science, Elsevier, HighWire, Scopus, and Google Scholar were searched up to May 2015 using the following terms: "TNF-308G>A polymorphism, rs1800629, or tumor necrosis factor-alpha" and "non-Hodgkin lymphomas, NHL, or lymphomas." Additional studies in the reference list of key articles and relevant reviews were also identified manually to further refine our research results. All the articles were retrieved independently by two researchers (S Gao and G Zhu).

Selection criteria
The articles included should meet the following criteria: 1) the study should be a case–control design; 2) the study should have investigated the association of TNF-308 with the risk of NHL or prognosis; 3) data should be available to calculate OR or hazard ratio (HR); and 4) subjects included in the study should not be a human immunodeficiency virus (HIV)-negative population. In addition, the data of the same population reported in more than one study should be used only once.

Data extraction
A standard data collection form was used to extract the relevant information by two investigators (S Gao and Y Lin)

independently, which included the first author, year of publication, sample size, ethnicity, source of control, and the genotype distribution of cases and controls or HRs with corresponding 95% confidence intervals (CIs). If HR was not reported in the article, Engauge Digitizer Version 4.1 was used to estimate the HR and 95% CI. The ethnicities were categorized as Caucasian or Asian, and the source of controls was categorized as population based or hospital based. Any discrepancies were discussed to reach an agreement.

Statistical analysis
For susceptibility analysis, Hardy–Weinberg equilibrium (HWE) of each study was assessed by chi-square test in controls with $P<0.05$, which was considered a departure from HWE. OR was used to measure the strength of the association between TNF-308G>A and the risk of NHL. Pooled OR was assessed under the allelic (A vs G), dominant (AA/GA vs GG), recessive (AA vs GA/GG), homozygous (AA vs GG), and heterozygous models (GA vs GG). The heterogeneity among the studies was estimated by Q-test and I^2 value; if $I^2 >50\%$, which was considered significant heterogeneity, a random- or fixed-effect model was used. Subgroup analysis was implemented, which was stratified by ethnicity and the source of controls. When a large amount of heterogeneity was exhibited, meta-regression analysis or sensitivity analysis was performed to explore the source of heterogeneity. Funnel plots and Egger's test were applied to estimate the potential publication bias.

For survival outcome, HR with 95% CI was used to estimate the association between TNF-308A and prognosis in patients with NHL. The heterogeneity among studies was evaluated by Q-test and I^2 value. If $I^2 >50\%$, which was considered significant heterogeneity, a random- or fixed-effect model was employed. Sensitivity analysis was also conducted to examine the influence of single study on pooled estimate. Publication bias was evaluated by funnel plots and Egger's test.

All the analyses were implemented with Stata Version 11.0. $P<0.05$ was considered statistically significant, and all P-values were two sided.

Results
The titles and abstracts of 221 records from the databases and another 18 articles from the reference lists were screened for eligibility. Eventually, 17 articles met the abovementioned criteria,[9,16–31] where nine studies were further excluded because of the following reasons: insufficient data in six articles,[5,6,10,32–34] the subjects were HIV-positive patients,[35] or studies focused on the risk of relapse (Figure 1).[11] Among
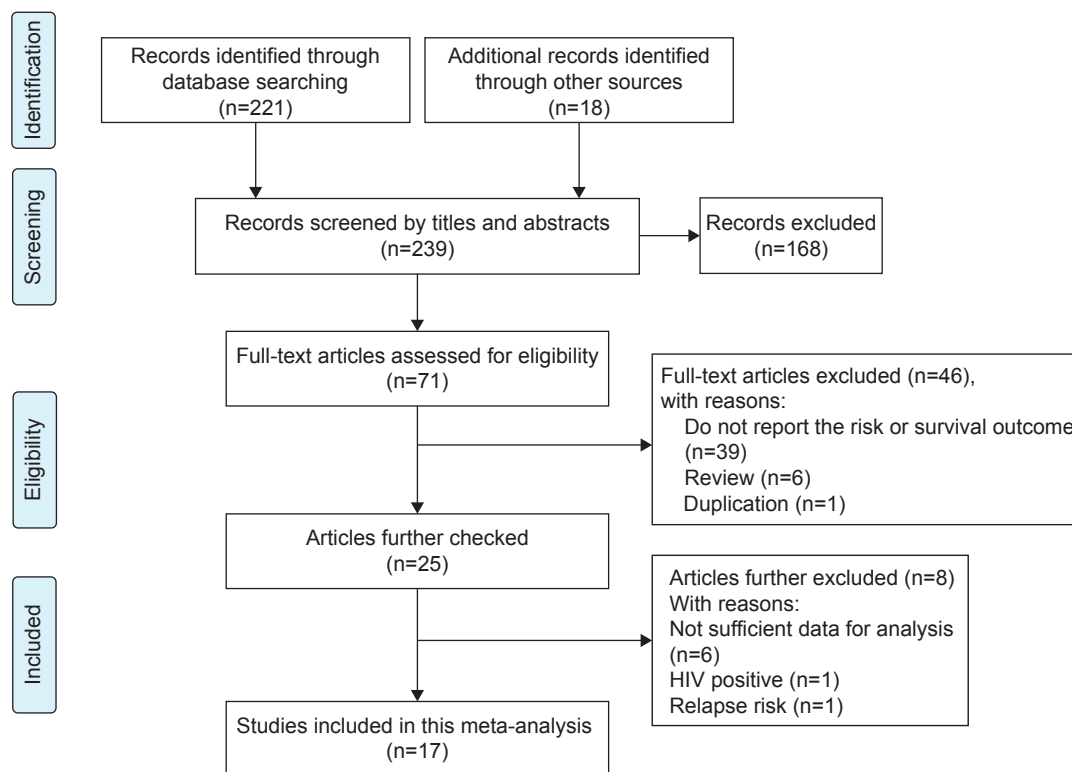
Figure 1 Flow diagram of the study selection process.
Abbreviation: HIV, human immunodeficiency virus.

the 17 pooled studies, 15 studies were used to analyze the association between TNF-308G>A and the risk of NHL and five studies to investigate the prognostic values of TNF-308A in patients with NHL.

Susceptibility analysis
Characteristics of 15 pooled studies
A total of 15 eligible studies, which included 10,609 cases and 10,660 controls, were included to evaluate the association between TNF-308G>A (rs1800629) and the genetic susceptibility to NHL.[9,16–29] Of these, there were eleven studies of Caucasian descendants and four studies of Asian descendants. The source of controls was population based in eleven studies and hospital based in another four studies. None of the genotype distributions in control groups were deviated from HWE. The characteristics of 15 pooled studies are summarized in Table 1.

TNF-308G>A polymorphism and overall risk of NHL
Among the enrolled 10,609 NHL cases and 10,660 controls, significantly increased risks were observed in recessive genetic (AA vs GA/GG, OR =1.42, 95% CI: 1.021–1.974, P=0.037; Figure 2) and homozygous models (AA vs GG, OR =1.434, 95% CI: 1.017–2.021, P=0.04) when all the

eligible data were pooled together (Table 2). In the stratification analysis by ethnicity, consistent results were detected in allelic (A vs G, OR =1.148, 95% CI: 0.007–1.309, P=0.039), homozygous (AA vs GG, OR =1.591, 95% CI: 1.098–2.306, P=0.014), and recessive models (AA vs GA/GG, OR =1.564, 95% CI: 1.094–2.236, P=0.014) in Caucasians. However, the risk was reduced under heterozygous model (GA vs GG, OR =0.816, 95% CI: 0.704–0.947, P=0.007; Figure 3A). In the subgroup analysis based on the source of controls, the risk was only reduced in hospital-based studies when GA genotype was compared with GG genotype (OR =0.838, 95% CI: 0.732–0.961, P=0.011; Figure 3B).

TNF-308G>A polymorphism and the risk of B-cell lymphomas and its subtypes
TNF-308G>A was associated with significantly increased risk of B-cell lymphomas (BCL) in recessive (AA vs GA/GG, OR =1.498, 95% CI: 1.038–2.163, P=0.031) and homozygous models (AA vs GG, OR =1.518, 95% CI: 1.035–2.225, P=0.033; Table 2). When stratified by ethnicity, a statistically significant association between TNF-308G>A and the increased risk of BCL was observed in Caucasians under recessive (AA vs GA/GG, OR =1.581, 95% CI: 1.051–2.377, P=0.028) and homozygous models (AA vs GG, OR =1.611,
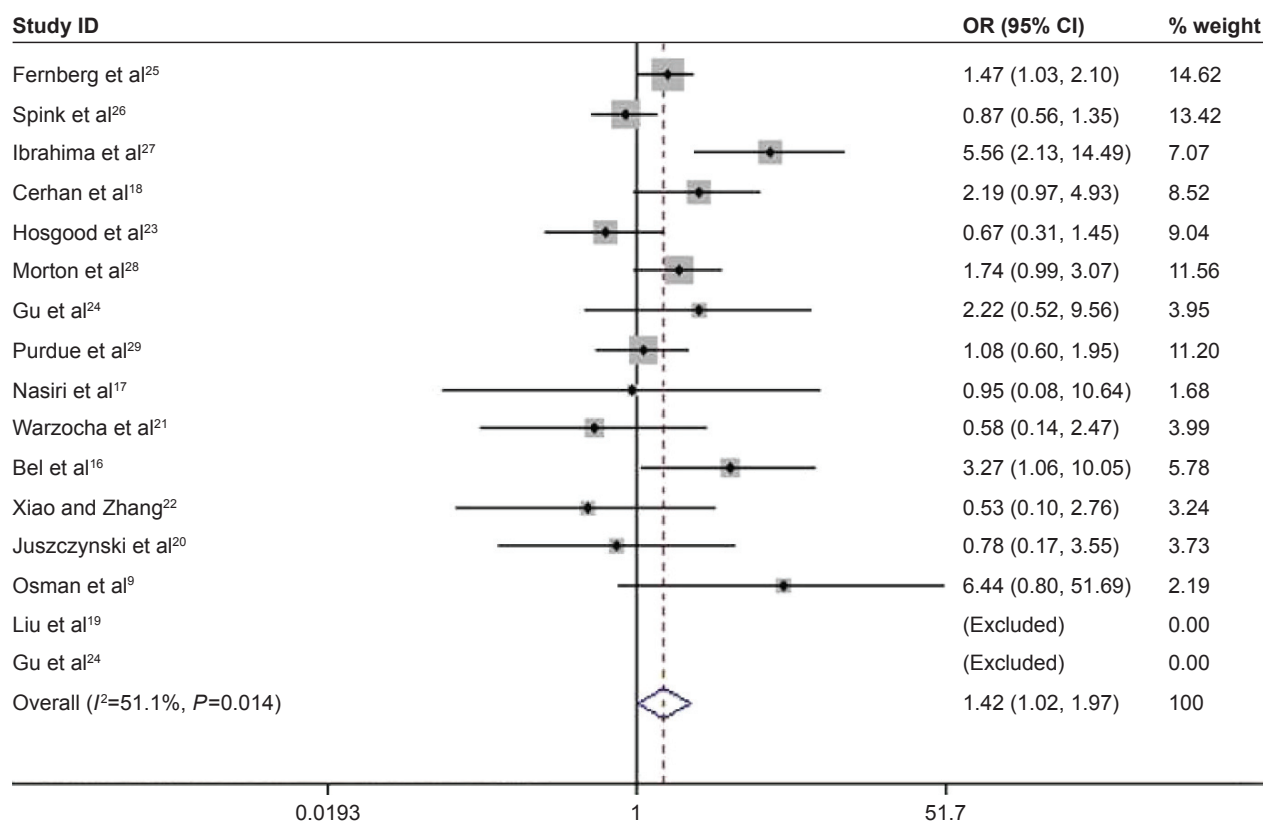
Table 1 Characteristics of 15 pooled studies evaluating the association between TNF-308G>A polymorphism and the risk of NHL

References	Year	Ethnicity	Source	Genotype distribution (case/control)						
				GG	AG	AA	GG	AG	AA	HWE
Osman et al[9]	2009	Caucasian	HB	59	34	1	79	51	9	0.26
Bel et al[16]	2006	Caucasian	PB	107	49	4	120	59	15	0.84
Nasiri et al[17]	2013	Caucasian	PB	105	22	2	58	9	1	0.8
Cerhan et al[18]	2008	Caucasian	HB	332	129	9	304	117	18	0.68
Liu et al[19]	2013	Asian	HB	260	40	0	264	27	0	0.47
Juszczynski et al[20]	2002	Caucasian	PB	85	32	3	151	49	4	1
Warzocha et al[21]	1998	Caucasian	PB	69	24	3	203	65	5	1
Xiao and Zhang[22]	2010	Asian	PB	174	35	5	138	20	2	0.16
Hosgood et al[23]	2013	Asian	HB	3,091	506	25	1,702	221	9	0.69
Gu et al[24]	2014	Asian	PB	186	40	5	49	12	3	0.29
Gu et al[24]	2014	Asian	PB	190	14	0	78	13	0	0.88
Fernberg et al[25]	2010	Caucasian	PB	1,007	431	46	1,490	675	102	1
Spink et al[26]	2006	Caucasian	PB	590	312	44	627	317	40	0.95
Ibrahima et al[27]	2012	Caucasian	PB	67	27	6	41	21	22	0.38
Morton et al[28]	2008	Caucasian	PB	696	207	18	799	298	38	0.85
Purdue et al[29]	2007	Caucasian	PB	318	143	21	345	164	25	0.63

Abbreviations: HB, hospital based; HWE, Hardy–Weinberg equilibrium; NHL, non-Hodgkin lymphoma; PB, population based; TNF, tumor necrosis factor.

95% CI: 1.054–2.496, $P=0.028$; Table 2). Conversely, there was a significant lower risk in Asians under heterozygous model (GA vs GG, OR =0.799, 95% CI: 0.669–0.954, $P=0.013$; Figure 4A). In the stratified analysis by the source of controls, a significant increased risk of BCL was found in population-based studies under the allelic model (A vs G, OR =1.2, 95% CI: 1.003–1.437, $P=0.047$), whereas decreased risk was found in hospital-based studies under heterozygous model (GA vs GG, OR =0.832, 95% CI: 0.751–0.967, $P=0.017$; Figure 4B).

Study ID		OR (95% CI)	% weight
Fernberg et al[25]		1.47 (1.03, 2.10)	14.62
Spink et al[26]		0.87 (0.56, 1.35)	13.42
Ibrahima et al[27]		5.56 (2.13, 14.49)	7.07
Cerhan et al[18]		2.19 (0.97, 4.93)	8.52
Hosgood et al[23]		0.67 (0.31, 1.45)	9.04
Morton et al[28]		1.74 (0.99, 3.07)	11.56
Gu et al[24]		2.22 (0.52, 9.56)	3.95
Purdue et al[29]		1.08 (0.60, 1.95)	11.20
Nasiri et al[17]		0.95 (0.08, 10.64)	1.68
Warzocha et al[21]		0.58 (0.14, 2.47)	3.99
Bel et al[16]		3.27 (1.06, 10.05)	5.78
Xiao and Zhang[22]		0.53 (0.10, 2.76)	3.24
Juszczynski et al[20]		0.78 (0.17, 3.55)	3.73
Osman et al[9]		6.44 (0.80, 51.69)	2.19
Liu et al[19]		(Excluded)	0.00
Gu et al[24]		(Excluded)	0.00
Overall ($I^2=51.1\%$, $P=0.014$)		1.42 (1.02, 1.97)	100

| 0.0193 | 1 | 51.7 |

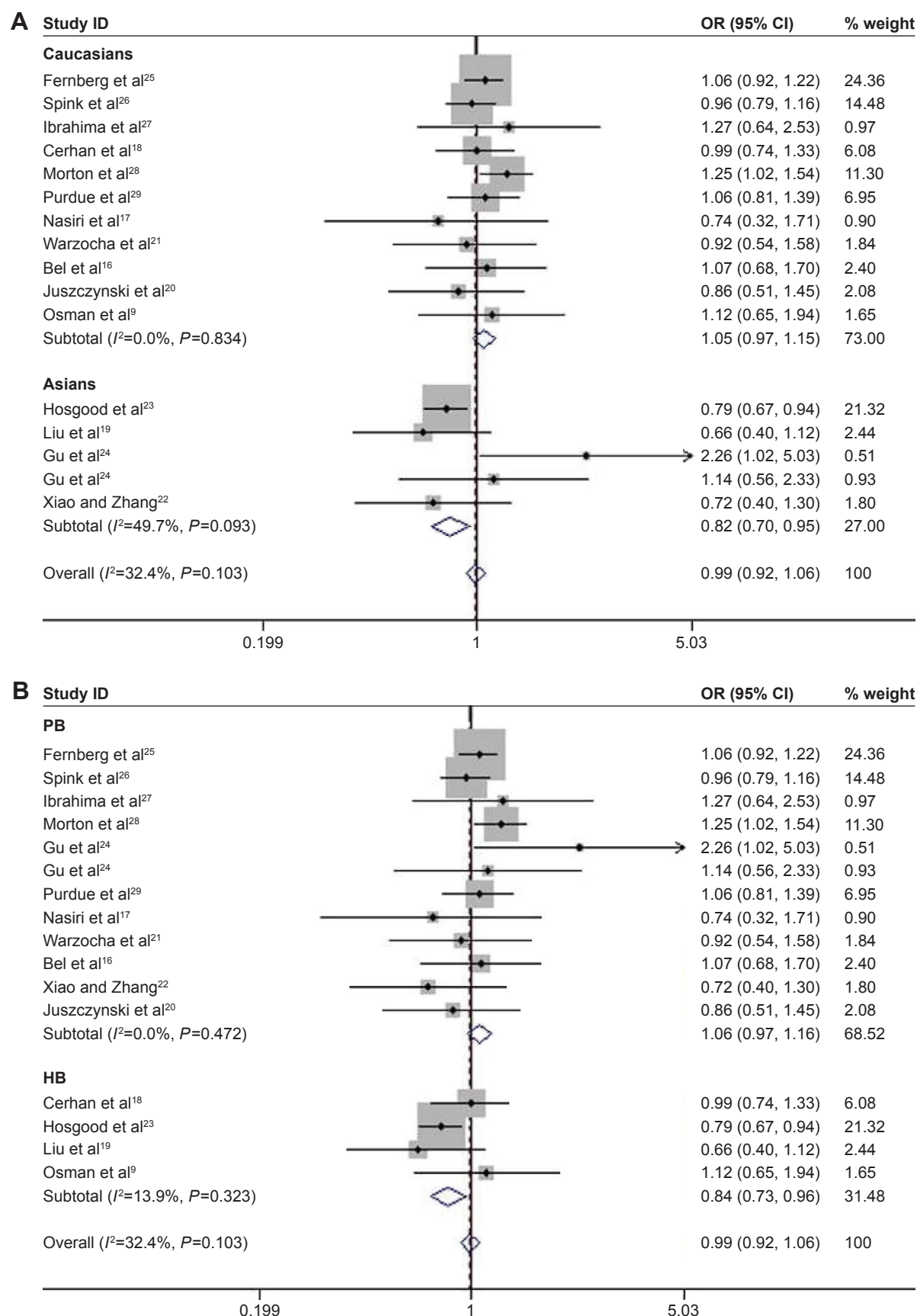**Figure 2** Association between TNF-308G>A polymorphism and the risk of NHL in recessive model.
Note: Weights are from random effects analysis.
Abbreviations: CI, confidence interval; NHL, non-Hodgkin lymphoma; OR, odds ratio; TNF, tumor necrosis factor.

Table 2 Results of the overall and subgroup analyses for TNF-308 polymorphism and the risk of NHL

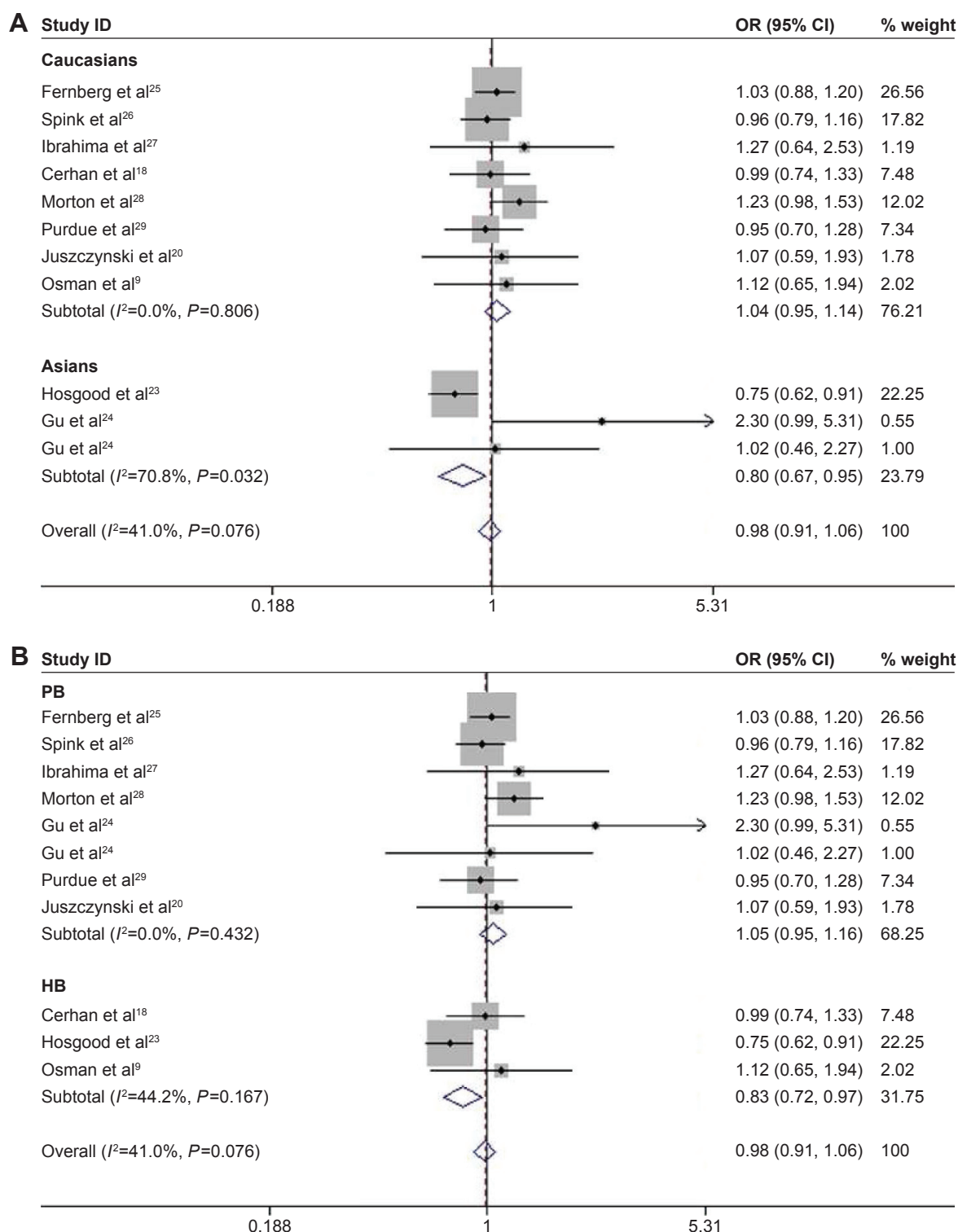| Type	Groups	N	A vs G OR (95% CI)	P-value	I²	AA/GA vs GG OR (95% CI)	P-value	I²	AA vs GA+GG OR (95% CI)	P-value	I²	AA vs GG OR (95% CI)	P-value	I²	GA vs GG OR (95% CI)	P-value	I²
NHL	Overall	15	1.805 (0.948–1.242)	0.238	70.6	1.04 (0.916–1.182)	0.543	56.7	1.42 (1.021–1.974)	0.037	51.1	1.434 (1.017–2.021)	0.04	54.1	0.99 (0.921–1.065)	0.787	32
	Caucasian	11	1.148 (0.007–1.309)	0.039	61.2	1.1 (0.991–1.221)	0.075	25.2	1.564 (1.094–2.236)	0.014	53.5	1.591 (1.098–2.306)	0.014	55.9	1.054 (0.97–1.146)	0.215	0
	Asian	4	0.922 (0.668–1.272)	0.621	59.9	0.904 (0.625–1.255)	0.547	55.7	0.836 (0.407–1.716)	0.626	14.2	0.829 (0.385–1.789)	0.663	21.1	0.816 (0.704–0.947)	0.007	0
	PB	11	1.137 (0.979–1.32)	0.092	64.9	1.1 (0.964–1.255)	0.158	41.7	1.413 (0.991–2.015)	0.056	49.6	1.432 (0.988–2.076)	0.058	52.8	1.06 (0.972–1.155)	0.188	0
	HB	4	0.958 (0.721–1.273)	0.766	72	0.901 (0.707–1.148)	0.4	53.3	1.642 (0.536–5.029)	0.385	70.3	1.645 (0.521–5.196)	0.396	71.7	0.838 (0.732–0.961)	0.011	14
DLBCL	Overall	8	1.116 (0.92–1.353)	0.264	70.8	1.115 (0.905–1.373)	0.307	67.1	1.225 (0.934–1.605)	0.142	34.8	1.269 (0.966–1.667)	0.088	38.9	1.088 (0.894–1.325)	0.399	61
	Caucasian	6	1.172 (1.035–1.325)	0.012	26.5	1.18 (1.047–1.33)	0.007	3.4	1.308 (0.986–1.736)	0.063	32.4	0.591 (0.209–1.675)	0.062	32.3	1.155 (1.023–1.304)	0.02	0
	Asian	2	1.206 (0.507–2.87)	0.672	75.6	1.221 (0.494–3.017)	0.665	72	0.604 (0.213–1.711)	0.343	47.9	1.366 (1.026–1.817)	0.323	60.8	1.188 (0.507–2.787)	0.691	67
	PB	6	1.2 (1.038–1.387)	0.014	36.7	1.215 (1.058–1.395)	0.006	16.1	1.269 (0.951–1.694)	0.105	13.3	1.331 (0.995–1.782)	0.054	22.1	1.185 (1.048–1.339)	0.007	0
	HB	2	0.853 (0.54–1.346)	0.495	68.8	0.751 (0.577–0.987)	0.033	16.4	0.938 (0.418–2.109)	0.878	80.7	0.898 (0.399–2.022)	0.795	80.4	0.73 (0.589–0.905)	0.004	0
BCL	Overall	10	1.145 (0.977–1.342)	0.096	75.1	1.078 (0.928–1.252)	0.324	62.6	1.498 (1.038–2.163)	0.031	56.6	1.518 (1.035–2.225)	0.033	59.3	0.981 (0.905–1.064)	0.649	41
	Caucasian	8	1.164 (0.999–1.356)	0.051	68.4	1.094 (0.969–1.235)	0.164	35.1	1.581 (1.051–2.377)	0.028	61.1	1.611 (1.054–2.496)	0.028	63.3	1.038 (0.948–1.138)	0.418	0
	Asian	2	1.2 (0.637–2.259)	0.572	77.2	1.59 (0.602–2.23)	0.659	74.2	1.238 (0.372–4.119)	0.728	54.8	1.222 (0.352–4.235)	0.572	57.1	0.799 (0.669–0.954)	0.013	71
	PB	7	1.2 (1.003–1.437)	0.047	71.1	1.129 (0.967–1.317)	0.124	48.5	1.481 (0.973–2.252)	0.067	60.7	1.508 (0.973–2.338)	0.066	63.2	1.051 (0.955–1.157)	0.31	0
	HB	3	1.026 (0.72–1.462)	0.887	80.6	0.952 (0.694–1.305)	0.761	68.9	1.694 (0.613–4.681)	0.309	63.1	1.694 (0.951–4.854)	0.326	65.3	0.832 (0.751–0.967)	0.017	44
FL	Overall	6	0.908 (0.812–1.014)	0.087	16.1	0.876 (0.772–0.996)	0.043	6.1	1.026 (0.74–1.422)	0.878	32.8	0.979 (0.705–1.36)	0.9	34.8	0.862 (0.755–0.985)	0.029	2.1
	Caucasian	5	0.911 (0.813–1.021)	0.111	37.1	0.884 (0.776–1.008)	0.067	20.5	0.884 (0.776–1.008)	0.98	37	0.95 (0.679–1.329)	0.764	39.2	0.874 (0.763–1.003)	0.055	11
	Asian	1	0.842 (0.511–1.386)	0.498	NA	0.759 (0.44–1.311)	0.323	0	0.759 (0.44–0.311)	0.274	NA	2.15 (0.503–9.187)	0.301	NA	0.691 (0.386–1.235)	0.212	NA
	PB	4	0.899 (0.798–1.012)	0.079	42.4	0.881 (0.768–1.011)	0.07	40	0.901 (0.623–1.285)	0.565	0	0.859 (0.601–1.228)	0.405	0	0.882 (0.765–1.017)	0.083	31
	HB	2	0.97 (0.713–1.319)	0.844	0	0.847 (0.597–1.201)	0.351	0	2.267 (1.146–6.249)	0.223	0	2.533 (1.08–5.938)	0.033	0	0.747 (0.153–1.086)	0.127	0
CCL	Overall	3	1.074 (0.926–1.246)	0.347	17.6	1.078 (0.908–1.279)	0.39	4.1	1.156 (0.726–1.839)	0.514	0	1.181 (0.74–1.885)	0.485	0	1.069 (0.869–1.276)	0.459	0
TCL	Overall	3	1.047 (0.759–1.445)	0.778	61.9	1.029 (0.755–1.403)	0.858	50.6	1.294 (0.228–7.346)	0.771	65.7	1.326 (0.321–7.609)	0.752	65.9	16.759 (7.909–35.477)	<0.001	69
NK/TCL	Overall	2	1.54 (0.592–2.492)	0.079	20.7	0.743 (0.459–1.203)	0.227	29.6	NA	NA	NA	NA	NA	NA	0.766 (0.473–1.239)	0.277	39

Abbreviations: BCL, B-cell lymphomas; CCL, chronic lymphocytic leukemias; CI, confidence interval; DLBCL, diffuse large B-cell lymphomas; FL, follicular lymphomas; HB, hospital based; N, number of studies; NA, not applicable; NHL, non-Hodgkin lymphoma; NK/TCL, natural killer/T-cell lymphomas; OR, odds ratio; PB, population based; TCL, T-cell lymphomas; TNF, tumor necrosis factor.

A Study ID | OR (95% CI) | % weight

Caucasians

Study	OR (95% CI)	% weight
Fernberg et al[25]	1.06 (0.92, 1.22)	24.36
Spink et al[26]	0.96 (0.79, 1.16)	14.48
Ibrahima et al[27]	1.27 (0.64, 2.53)	0.97
Cerhan et al[18]	0.99 (0.74, 1.33)	6.08
Morton et al[28]	1.25 (1.02, 1.54)	11.30
Purdue et al[29]	1.06 (0.81, 1.39)	6.95
Nasiri et al[17]	0.74 (0.32, 1.71)	0.90
Warzocha et al[21]	0.92 (0.54, 1.58)	1.84
Bel et al[16]	1.07 (0.68, 1.70)	2.40
Juszczynski et al[20]	0.86 (0.51, 1.45)	2.08
Osman et al[9]	1.12 (0.65, 1.94)	1.65
Subtotal (I^2=0.0%, P=0.834)	1.05 (0.97, 1.15)	73.00

Asians

Study	OR (95% CI)	% weight
Hosgood et al[23]	0.79 (0.67, 0.94)	21.32
Liu et al[19]	0.66 (0.40, 1.12)	2.44
Gu et al[24]	2.26 (1.02, 5.03)	0.51
Gu et al[24]	1.14 (0.56, 2.33)	0.93
Xiao and Zhang[22]	0.72 (0.40, 1.30)	1.80
Subtotal (I^2=49.7%, P=0.093)	0.82 (0.70, 0.95)	27.00
Overall (I^2=32.4%, P=0.103)	0.99 (0.92, 1.06)	100

0.199   1   5.03

B Study ID | OR (95% CI) | % weight

PB

Study	OR (95% CI)	% weight
Fernberg et al[25]	1.06 (0.92, 1.22)	24.36
Spink et al[26]	0.96 (0.79, 1.16)	14.48
Ibrahima et al[27]	1.27 (0.64, 2.53)	0.97
Morton et al[28]	1.25 (1.02, 1.54)	11.30
Gu et al[24]	2.26 (1.02, 5.03)	0.51
Gu et al[24]	1.14 (0.56, 2.33)	0.93
Purdue et al[29]	1.06 (0.81, 1.39)	6.95
Nasiri et al[17]	0.74 (0.32, 1.71)	0.90
Warzocha et al[21]	0.92 (0.54, 1.58)	1.84
Bel et al[16]	1.07 (0.68, 1.70)	2.40
Xiao and Zhang[22]	0.72 (0.40, 1.30)	1.80
Juszczynski et al[20]	0.86 (0.51, 1.45)	2.08
Subtotal (I^2=0.0%, P=0.472)	1.06 (0.97, 1.16)	68.52

HB

Study	OR (95% CI)	% weight
Cerhan et al[18]	0.99 (0.74, 1.33)	6.08
Hosgood et al[23]	0.79 (0.67, 0.94)	21.32
Liu et al[19]	0.66 (0.40, 1.12)	2.44
Osman et al[9]	1.12 (0.65, 1.94)	1.65
Subtotal (I^2=13.9%, P=0.323)	0.84 (0.73, 0.96)	31.48
Overall (I^2=32.4%, P=0.103)	0.99 (0.92, 1.06)	100

0.199   1   5.03

Figure 3 Association between TNF-308G>A polymorphism and the risk of NHL in heterozygous model.
Notes: (**A**) Stratified by ethnicity. (**B**) Stratified by the source of control.
Abbreviations: CI, confidence interval; HB, hospital based; NHL, non-Hodgkin lymphoma; OR, odds ratio; PB, population based; TNF, tumor necrosis factor.
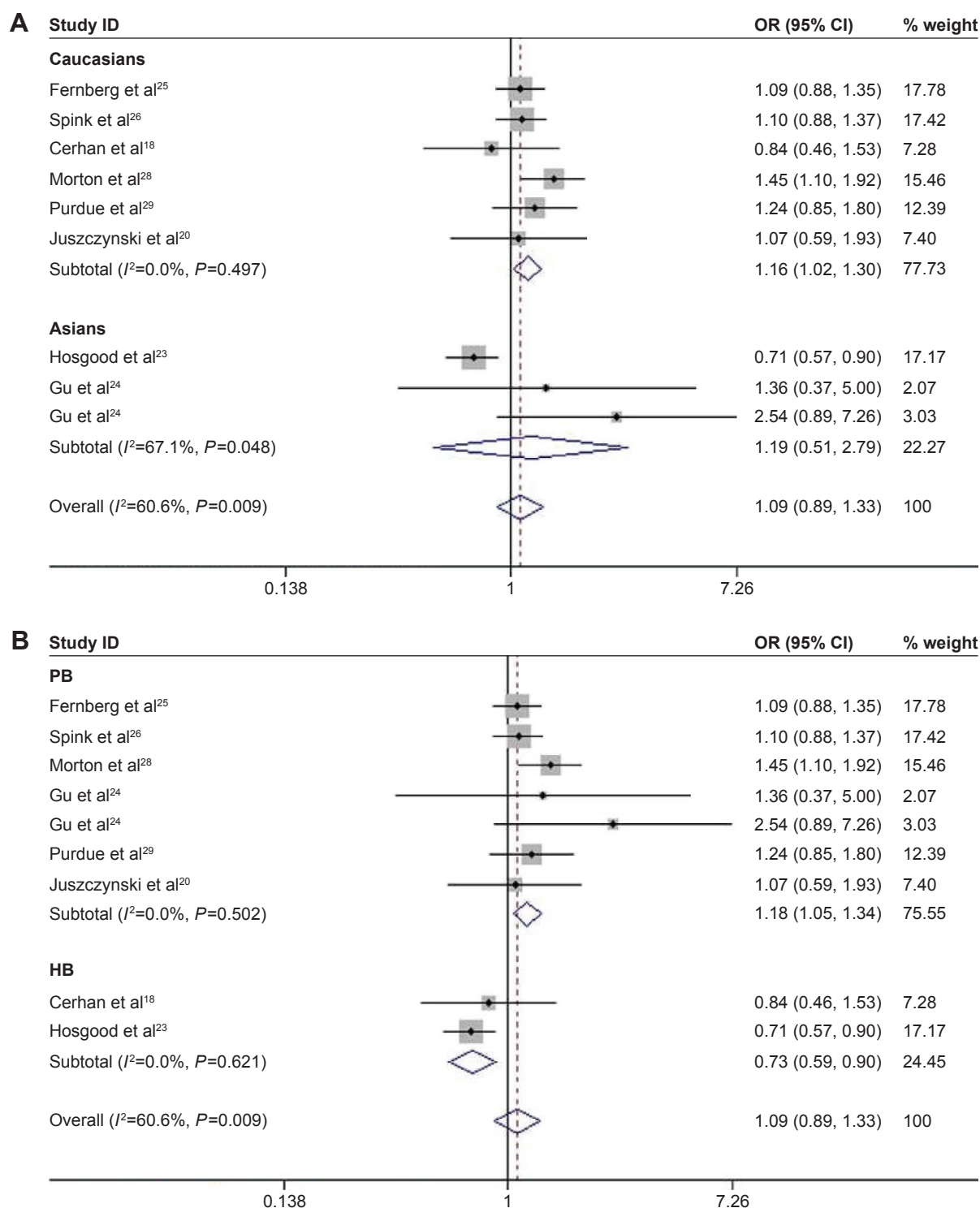
A Study ID   OR (95% CI)   % weight

Study ID	OR (95% CI)	% weight
Caucasians		
Fernberg et al[25]	1.03 (0.88, 1.20)	26.56
Spink et al[26]	0.96 (0.79, 1.16)	17.82
Ibrahima et al[27]	1.27 (0.64, 2.53)	1.19
Cerhan et al[18]	0.99 (0.74, 1.33)	7.48
Morton et al[28]	1.23 (0.98, 1.53)	12.02
Purdue et al[29]	0.95 (0.70, 1.28)	7.34
Juszczynski et al[20]	1.07 (0.59, 1.93)	1.78
Osman et al[9]	1.12 (0.65, 1.94)	2.02
Subtotal (I^2=0.0%, P=0.806)	1.04 (0.95, 1.14)	76.21
Asians		
Hosgood et al[23]	0.75 (0.62, 0.91)	22.25
Gu et al[24]	2.30 (0.99, 5.31)	0.55
Gu et al[24]	1.02 (0.46, 2.27)	1.00
Subtotal (I^2=70.8%, P=0.032)	0.80 (0.67, 0.95)	23.79
Overall (I^2=41.0%, P=0.076)	0.98 (0.91, 1.06)	100

0.188   1   5.31

B Study ID   OR (95% CI)   % weight

Study ID	OR (95% CI)	% weight
PB		
Fernberg et al[25]	1.03 (0.88, 1.20)	26.56
Spink et al[26]	0.96 (0.79, 1.16)	17.82
Ibrahima et al[27]	1.27 (0.64, 2.53)	1.19
Morton et al[28]	1.23 (0.98, 1.53)	12.02
Gu et al[24]	2.30 (0.99, 5.31)	0.55
Gu et al[24]	1.02 (0.46, 2.27)	1.00
Purdue et al[29]	0.95 (0.70, 1.28)	7.34
Juszczynski et al[20]	1.07 (0.59, 1.93)	1.78
Subtotal (I^2=0.0%, P=0.432)	1.05 (0.95, 1.16)	68.25
HB		
Cerhan et al[18]	0.99 (0.74, 1.33)	7.48
Hosgood et al[23]	0.75 (0.62, 0.91)	22.25
Osman et al[9]	1.12 (0.65, 1.94)	2.02
Subtotal (I^2=44.2%, P=0.167)	0.83 (0.72, 0.97)	31.75
Overall (I^2=41.0%, P=0.076)	0.98 (0.91, 1.06)	100

0.188   1   5.31

Figure 4 Association between the risk of BCL and TNF-308G>A polymorphism in heterozygous model.
Notes: (**A**) Stratified by ethnicity. (**B**) Stratified by the source of control.
Abbreviations: BCL, B-cell lymphomas; CI, confidence interval; HB, hospital based; OR, odds ratio; PB, population based; TNF, tumor necrosis factor.

There was no significant association between TNF-308G>A polymorphism and the susceptibility to DLBCL, when all the data of DLBCL were pooled together. This association was only identified in Caucasians under the allelic (A vs G, OR =1.172, 95% CI: 1.035–1.325, P=0.012), dominant (AA/GA vs GG, OR =1.18, 95% CI: 1.047–1.33, P=0.007), and heterozygous models (GA vs GG, OR =1.155, 95% CI: 1.023–1.304, P=0.02; Figure 5A and Table 2).

A **Study ID** OR (95% CI) % weight

Caucasians
Fernberg et al[25] 1.09 (0.88, 1.35) 17.78
Spink et al[26] 1.10 (0.88, 1.37) 17.42
Cerhan et al[18] 0.84 (0.46, 1.53) 7.28
Morton et al[28] 1.45 (1.10, 1.92) 15.46
Purdue et al[29] 1.24 (0.85, 1.80) 12.39
Juszczynski et al[20] 1.07 (0.59, 1.93) 7.40
Subtotal (I^2=0.0%, P=0.497) 1.16 (1.02, 1.30) 77.73

Asians
Hosgood et al[23] 0.71 (0.57, 0.90) 17.17
Gu et al[24] 1.36 (0.37, 5.00) 2.07
Gu et al[24] 2.54 (0.89, 7.26) 3.03
Subtotal (I^2=67.1%, P=0.048) 1.19 (0.51, 2.79) 22.27

Overall (I^2=60.6%, P=0.009) 1.09 (0.89, 1.33) 100

0.138   1   7.26

B **Study ID** OR (95% CI) % weight

PB
Fernberg et al[25] 1.09 (0.88, 1.35) 17.78
Spink et al[26] 1.10 (0.88, 1.37) 17.42
Morton et al[28] 1.45 (1.10, 1.92) 15.46
Gu et al[24] 1.36 (0.37, 5.00) 2.07
Gu et al[24] 2.54 (0.89, 7.26) 3.03
Purdue et al[29] 1.24 (0.85, 1.80) 12.39
Juszczynski et al[20] 1.07 (0.59, 1.93) 7.40
Subtotal (I^2=0.0%, P=0.502) 1.18 (1.05, 1.34) 75.55

HB
Cerhan et al[18] 0.84 (0.46, 1.53) 7.28
Hosgood et al[23] 0.71 (0.57, 0.90) 17.17
Subtotal (I^2=0.0%, P=0.621) 0.73 (0.59, 0.90) 24.45

Overall (I^2=60.6%, P=0.009) 1.09 (0.89, 1.33) 100

0.138   1   7.26

Figure 5 Association between the risk of DLBCL and TNF-308G>A polymorphism in heterozygous model.
Notes: (**A**) Stratified by ethnicity. (**B**) Stratified by the source of control. Weights are from random effects analysis.
Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphomas; HB, hospital based; OR, odds ratio; PB, population based; TNF, tumor necrosis factor.

When stratified by the source of controls, the risk was increased in population-based studies under allelic (A vs G, OR =1.2, 95% CI: 1.038–1.387, P=0.014), dominant (AA/GA vs GG, OR =1.215, 95% CI: 1.058–1.395, P=0.006), and heterozygous models (GA vs GG, OR =1.185, 95% CI: 1.048–1.339, P=0.007), while it was decreased in hospital-based studies under dominant (AA/GA vs GG, OR =0.751, 95% CI: 0.577–0.987, P=0.033) and heterozygous models (GA vs GG, OR =0.73, 95% CI: 0.589, 0.905, P=0.004; Figure 5B and Table 2).
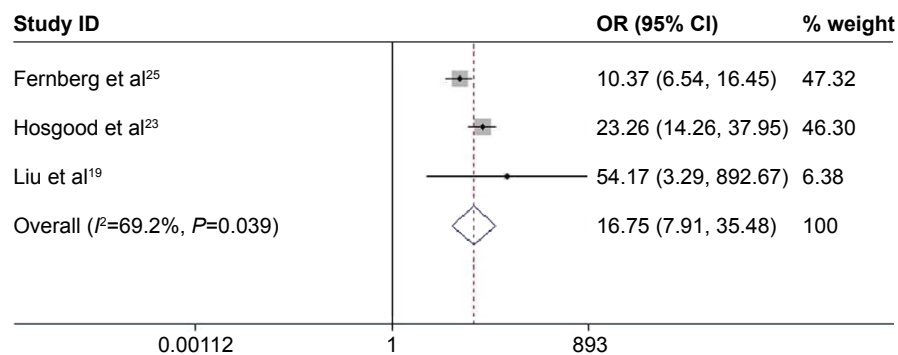
Figure 6 Association between the risk of FL and TNF-308G>A polymorphism in homozygous model.
Note: Weights are from random effects analysis.
Abbreviations: CI, confidence interval; FL, follicular lymphomas; OR, odds ratio; TNF, tumor necrosis factor.

Pooled results from six studies showed that people with TNF-308>A polymorphism had a decreased risk of FL under dominant (AA/GA vs GG, OR =0.876, 95% CI: 0.772–0.996, P=0.043; Figure 6) and heterozygous models (GA vs GG, OR =0.862, 95% CI: 0.755–0.985, P=0.029). However, no significant association between TNF-308G>A polymorphism and the risk of FL was observed when stratified by ethnicity. Further subgroup analysis based on the source of controls indicated that the risk of FL was only increased in hospital-based studies under homozygous model (AA vs GG, OR =2.533, 95% CI: 1.08–5.938, P=0.033; Table 2).

Based on the results of three studies, there was no significant association between TNF-308G>A polymorphism and the susceptibility to chronic lymphocytic leukemia (Table 2).

TNF-308G>A polymorphism and the risk of T-cell lymphomas and NK/T-cell lymphomas

The pooled results of three studies indicated that a significantly increased risk of T-cell lymphomas (TCL) was observed, when GA genotype was compared with GG genotype (OR =16.759, 95% CI: 7.909–35.477, P<0.001; Figure 7). There were no significant correlations between TNF-308G>A and the risk of NK/TCL based on the data of two studies.

Evaluation of heterogeneity and publication bias

There were some heterogeneities in the outcomes of overall NHL, BCL, DLBCL, and TCL. We performed subgroup analysis and meta-regression to investigate the sources of heterogeneity among studies. As shown earlier, the heterogeneity was decreased in some of the outcomes after the stratification of ethnicity and source of controls (Table 2). Furthermore, ethnicity (allelic model, P=0.044; recessive model, P=0.029) and publication years (recessive model, P=0.039) were identified as the sources of heterogeneity based on the results of meta-regression. Therefore, the publication year, ethnicity, and source of controls all may contribute to the heterogeneity exhibited in this meta-analysis. Sensitivity analysis was also performed, and the studies of
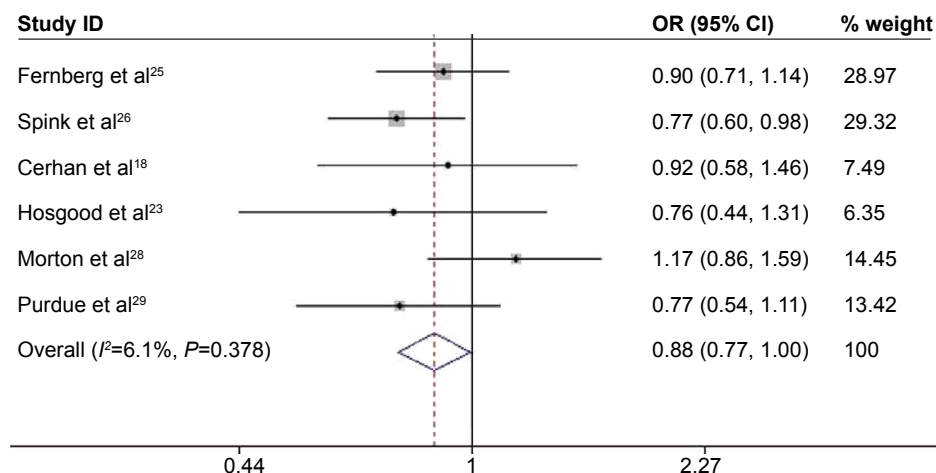
Figure 7 Association between the risk of TCL and TNF-308G>A polymorphism in homozygous model.
Abbreviations: CI, confidence interval; OR, odds ratio; TCL, T-cell lymphomas; TNF, tumor necrosis factor.

Table 3 Characteristics of five pooled studies evaluating the correlation between TNF-308 and the survival outcome in patients with NHL

References	Year	Ethnicity	Case (n)	Control (n)	Type	Outcome	HR (95% CI)	Risk factor
Osman et al[9]	2009	Caucasian	60	79	BCL	PFS	6.5 (1.9830, 21.3059)	TNF-308A
Juszczynski et al[20]	2002	Caucasian	53	151	NHL	PFS	1.63 (1.4155, 1.877)	TNF-308A
		Caucasian	53	151	NHL	OS	1.51 (1.3557, 1.6819)	TNF-308A
		Caucasian	32	72	DLBCL	PFS	1.52 (1.2893, 1.7920)	TNF-308A
		Caucasian	32	72	DLBCL	OS	1.43 (1.2442, 1.6435)	TNF-308A
Warzocha et al[21]	1998	Caucasian	76	197	NHL	PFS	1.96 (1.4, 2.73)	TNF/LT-α
		Caucasian	76	197	NHL	OS	2.08 (1.26, 3.43)	TNF/LT-α
		Caucasian	42	84	DLBCL	PFS	2.33 (1.17, 4.64)	TNF/LT-α
		Caucasian	42	84	DLBCL	OS	1.92 (0.63, 5.80)	TNF/LT-α
		Caucasian	18	78	FL	PFS	3.08 (2.1, 4.52)	TNF/LT-α
Seidemann et al[30]	2005	Caucasian	74	137	BCL	pEFS	2.34 (1.01, 5.43)	TNF/LT-α
Habermann et al[31]	2008	Caucasian	121	244	DLBCL	OS	1.44 (0.95, 2.18)	TNF-308A

Abbreviations: BCL, B-cell lymphomas; CI, confidence interval; DLBCL, diffuse large B-cell lymphomas; FL, follicular lymphomas; HR, hazard ratio; LT-α, lymphotoxin-α; NHL, non-Hodgkin lymphoma; OS, overall survival; pEFS, probability of event-free survival; PFS, progression-free survival; TNF, tumor necrosis factor.

Hosgood et al[23] and Morton et al[28] were identified as outliers in the outcomes of NHL, DLBCL, and BCL. Publication bias was evaluated using Egger's test and funnel plots, and obvious asymmetry was detected only in the recessive and homozygous models of FL.

Prognosis analysis
Characteristics of five pooled studies
We collected the data of five studies,[9,20,21,30,31] including 1,192 patients with NHL to analyze the correlation of TNF-308A with the survival outcomes in patients with NHL. Three studies evaluated the independent prognostic role of TNF-308A (the presence of one or more mutant alleles), and another two studies assessed TNF-308/LT-α+252 polymorphic high-producer alleles (at least two variant alleles). The progression-free survival (PFS) was reported as a survival outcome in three studies, overall survival (OS) in three studies, and probability of event-free survival in one study. The characteristics of the five studies are shown in Table 3.

TNF-308A and survival outcomes
The pooled results of five studies, involving 1,192 patients with NHL, suggested that TNF-308A was significantly related to poor OS and PFS in patients with NHL, where the pooled HR was 1.526 (95% CI: 1.378–1.690, $P<0.001$; Figure 8A) and 1.967 (95% CI: 1.438–2.689, $P<0.001$; Figure 8B), respectively. Furthermore, the PFS was shorter among patients with BCL with TNF-308A (HR =2.451, 95% CI: 1.536–3.912, $P<0.001$; Figure 9). The presence of TNF-308A was also associated with worse outcomes in patients with DLBCL (OS: HR =1.437, 95% CI: 1.260–1.638, $P<0.001$; PFS: HR =1.555, 95% CI: 1.325–1.826, $P<0.001$; Table 4).

Sensitivity analysis and publication bias
With substantial heterogeneity in the results of PFS in patients with NHL and BCL, the sensitivity analysis was performed to evaluate the influence of single study on the overall estimate, and the study of Osman et al was identified as an outlier. No publication bias was observed except OS in patients with NHL ($P=0.044$).

Discussion
The research suggested that TNF-308A could be utilized to identify the potential susceptible population of NHL.[36] We extended the previous meta-analyses and reviews to further assess the association of TNF-308A with the risk of NHL in different ethnicities and the source of controls. Our results showed that TNF-308A may be a risk factor of overall NHL, BCL, and DLBCL in Caucasians and healthy population, but not in Asian and hospital population. Besides, the risk of FL was also decreased in the carriers of TNF-308A.

In line with the previous two meta-analyses and reviews,[13,14] our analysis confirmed the associations of TNF-308G>A with the increased risks of all NHL and BCL in Caucasians and decreased risks in Asians. The different risks of NHL in Caucasians and Asians suggested that ethnic background and genetic structure played a critical role in the susceptibility to NHL.[37] Contrary to Zhai et al's study,[14] this significant association was observed only when GA genotype was compared with GG genotype, rather than the additive model (A vs G) in the recent one, which may be explained by the fact that AA genotype of TNF-308 was unlikely to influence the risk of NHL, as indicated in a pooled analysis.[13] Besides, there was no significant association between TNF-308G>A and the decreased risk of DLBCL in Asians, which was consistently reported in the previous two meta-analyses.[13,14] It is possible
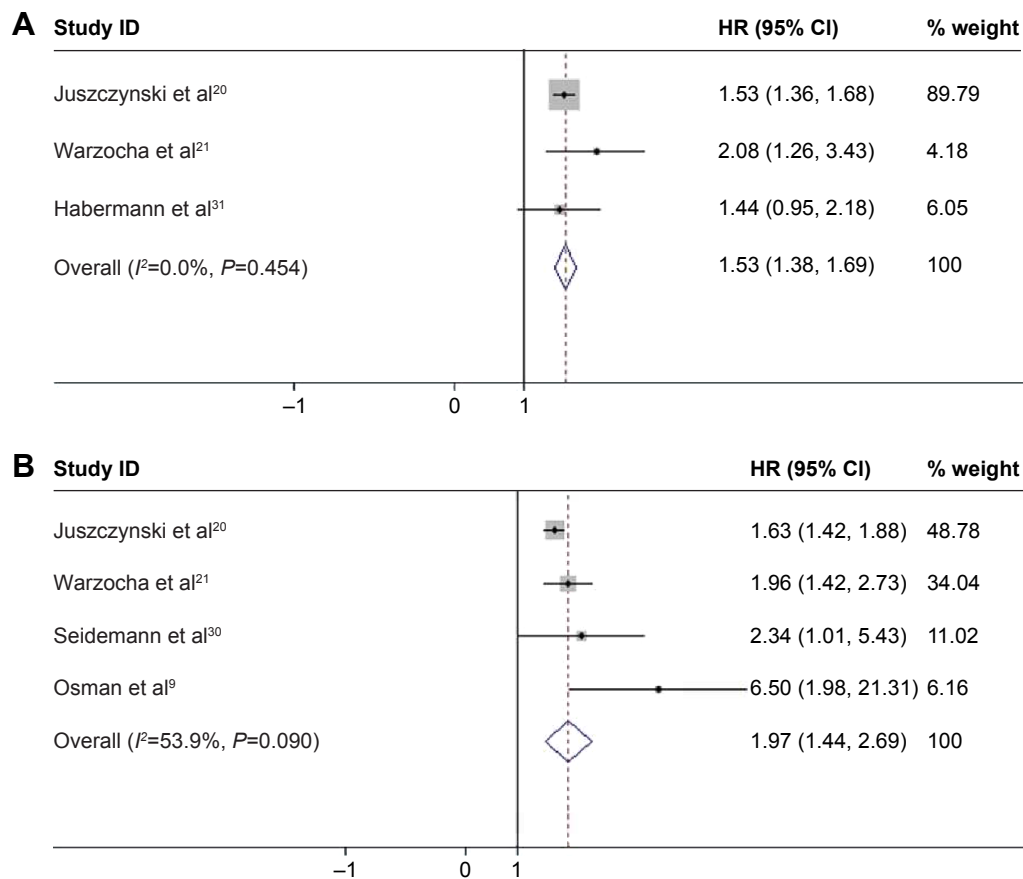
Figure 8 Association between TNF-308A and the progression-free survival and overall survival in patients with NHL.
**Notes:** (**A**) Progression-free survival. (**B**) Overall survival. Weights are from random effects analysis.
Abbreviations: CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin lymphoma; TNF, tumor necrosis factor.

that the substantial heterogeneity among Asian subgroups makes it insignificant in our meta-analysis.

Contrary to the previous results of meta-analysis, our results showed that TNF-308G>A reduced the risks of FL among 1,559 cases and 10,669 controls. However, the previous meta-analysis, based on the data of eight studies from the International Lymphoma Epidemiology Consortium, suggested that no significant association was detected between TNF-308G>A and the risk of FL.[12] Similarly, no pronounced association was observed neither in the extended meta-analysis
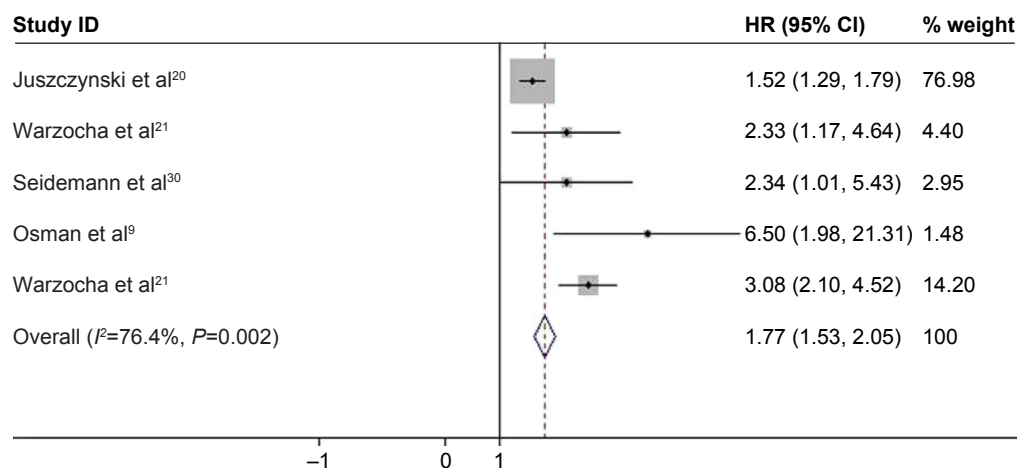
Figure 9 Association between TNF-308A and the PFS in patients with BCL.
Abbreviations: BCL, B-cell lymphomas; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TNF, tumor necrosis factor.

Table 4 Results of the correlation of TNF-308 with survival outcomes in patients with NHL

Sample size							
Type	Outcome	N	Case/control	I^2	P-value	HR	95% CI
NHL	PFS	4	263/564	53.90	<0.001	1.967	(1.438–2.689)
NHL	OS	3	250/259	0	<0.001	1.526	(1.378–1.690)
BCL	PFS	4	226/450	76.4	<0.001	2.451	(1.536–3.912)
DLBCL	OS	3	195/400	0	<0.001	1.437	(1.260–1.638)
DLBCL	PFS	2	74/156	28.4	<0.001	1.555	(1.325–1.826)

Abbreviations: BCL, B-cell lymphomas; CI, confidence interval; DLBCL, diffuse large B-cell lymphomas; HR, hazard ratio; N, number of studies; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; TNF, tumor necrosis factor.

published in 2010[13] nor in the recent one.[14] This could largely be attributed to the small number of cases in the previous two studies. Besides, the insignificant association may also be the results of the genetic models used in the recent one in which this association was assessed only in the additive model (A vs G), whereas this correlation was shown in dominant and heterozygous models in the present meta-analysis.

We also performed the subgroup analysis based on the source of controls, which demonstrated a significantly decreased risk of NHL, BCL, and DLBCL in hospital-based studies, whereas increased risk of DLBCL and BCL in population-based studies. The plausible explanation may be that many risk factors of NHL are relatively common in hospital patients, such as smoking,[38] obesity,[39] and immune system disease,[34] compared with healthy population. This contrary conclusion also suggested that the source of controls should be taken into account when the association of TNF-308G>A with the susceptibility to NHL was interpreted. However, the stratified analysis by the source of controls had not been performed in the previous three meta-analyses.[12–14]

According to the results of sensitivity analysis, the studies of Hosgood et al[23] and Morton et al[28] were identified as outliers in the susceptibility analysis of NHL, BCL, and DLBCL. It is noted that the risk of NHL in Asian populations was contrary to Caucasians. However, the study of Hosgood et al focused on three Asian populations, including Hong Kong, South Korea, and People's Republic of China, which enrolled 2,635 NHL cases and 4,234 controls, while other studies of Asian populations were in smaller numbers. As such, the result of this larger Asian population may be one of the resources of heterogeneity among the pooled population. The control group of Morton et al's study consisted of a small percentage of African–Americans, while the population was mainly Caucasians in the study of Morton et al.[28] The research

showed that the risk of NHL was higher in African–Americans than in other ethnicities. This mixed ethnicity may also be a source of difference in overall outcomes.

In addition to the results of genetic susceptibility to TNF-308G>A, we examined the potential correlation between TNF-308A and the survival outcome in patients with NHL, which had not been examined in the previous meta-analyses. The PFS and OS were shorter in patients with NHL with TNF-308A, based on the data of 1,192 patients with NHL. Besides, the present results indicated that TNF-308A was a risk factor for the survival outcome in patients with BCL and DLBCL. Consistent with the study of Cerhan et al,[32] no significant association of TNF-308A with survival was detected in patients with FL in the study of Warzocha et al.[21]

Lymphotoxin-α (LTA) 252A>G was in linkage disequilibrium with TNF-308G>A, which led to the inseparable effect of survival in the studies of Seidemann et al[30] and Warzocha et al.[21] Both of the studies suggested that the high-risk haplotype (the presence of two or more alleles, either TNF-A or LTA-α) was associated with poorer survival outcome (Table 4). Nevertheless, previous studies indicated that TNF-308 is the primary contributor of worse survival outcome of patients with NHL, and its association with LTA 252 was insignificant.[40] Therefore, we may conclude that the presence of TNF-308A is a predictor of worse prognosis of NHL.

According to the results of sensitivity analysis of survival outcomes, hazard ratio (HR) was much higher than the HR in the other four studies in the study of Osman et al.[9] It is likely that this higher risk leads to the substantial heterogeneity exhibited in the result of PFS in NHL and BCL.

Limitations and future directions

We searched only six databases for all available full texts and failed to include all the studies from the International Lymphoma Epidemiology Consortium due to the unavailable access to full text, which had been repeatedly used in the previous meta-analyses. Besides, the less common histological subtypes were reported in few studies, limiting the statistical power of pooled estimated OR and hindering a more thorough interpretation of the associations between TNF-308G>A and NHL subtypes. Moreover, we acknowledged that the population selection bias may exist in our study, with only Asians and Caucasians in the susceptibility analysis and Caucasians in prognosis analysis. Finally, only five studies were included to evaluate the correlation of TNF-308G>A and NHL survival. It is hard to exclude the possibility that this correlation may become insignificant after pooling the results of more studies.

Future expanded studies that would investigate the correlation of TNF-308 with other rare NHL subtypes may be warranted. Similarly, future efforts are also needed to assess the role of TNF-308A with the risk of NHL in larger Asian and African populations. Considering the small number of prognosis analyses, future studies that would explore the prognosis value of TNF-308 in patients with NHL may further refine our current outcomes.

Conclusion

Overall, our study found that TNF-308G>A polymorphism was associated not only with increased risks of NHL, BCL, and TCL and decreased risk of FL but also with shorter PFS and OS in patients with NHL, BCL, and DLBCL. However, those associations varied among different ethnicities and the source of controls, in which increased risk of NHL, BCL, and DLBCL was observed in Caucasians, whereas decreased risk of NHL and BCL in Asians. Meanwhile, the risk of NHL, BCL, and DLBCL was decreased in hospital-based population, while the risk of BCL and DLBCL was increased in population-based studies. Future studies focused on other NHL subtypes, and ethnicity groups may further our understanding of the association of TNF-308 with the susceptibility to and prognosis of NHL and its subtypes.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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