Published in final edited form as:

Int J Hematol. 2013 June ; 97(6): 793–799. doi:10.1007/s12185-013-1345-5.

***IL10* and *TNF* variants and risk of non-Hodgkin lymphoma among three Asian populations**

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Electronic supplementary material The online version of this article (doi:10.1007/s12185-013-1345-5) contains supplementary material, which is available to authorized users.

Conflict of interest None.

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Abstract

Genetic variation in immune-related genes, such as *IL10* and *TNF*, have been associated with the development of non-Hodgkin lymphoma (NHL) in Caucasian populations. To test the hypothesis that *IL10* and *TNF* polymorphisms may be associated with NHL risk in Asian populations, we genotyped 20 single nucleotide polymorphisms (SNPs) within the *IL10* and *TNF/LTA* loci in three independent case-control studies (2635 cases and 4234 controls). *IL10* rs1800871, rs1800872, and rs1800896 were genotyped in all three studies, while 5 of the remaining SNPs were genotyped in two studies, and 12 in a single study. *IL10* rs1800896 was associated with B cell lymphoma [per-allele odds ratio (OR) = 1.25, 95 % confidence interval (CI) 1.08–1.45; $p_{\text{trend}} = 0.003$], specifically diffuse large B cell lymphoma (DLBCL) (per-allele OR = 1.29, 95 % CI 1.08–1.53; $p_{\text{trend}} = 0.004$), as well as T cell lymphoma (per-allele OR = 1.44, 95 % CI 1.13–1.82; $p_{\text{trend}} = 0.003$). *TNF* rs1800629, which was genotyped in only two of our studies, was also associated with B cell lymphoma (per-allele OR = 0.77, 95 % CI 0.64–0.91; $p_{\text{trend}} = 0.003$), specifically DLBCL (per-allele OR = 0.69, 95 % CI 0.55–0.86; $p_{\text{trend}} = 0.001$). Our findings suggest that genetic variation in *IL10* and *TNF* may also play a role in lymphomagenesis in Asian populations.

Keywords

NHL; DLBCL; Subtype; Asia; IL10; TNF

Introduction

Non-Hodgkin lymphoma (NHL) is the 8th leading incident cancer among men worldwide and the 10th among women [6]. There are few known risk factors for NHL beyond family history of NHL [15] and altered immune-function [11]. As such, many candidate-gene association studies of NHL have focused on cytokines, which are secreted proteins that play a critical role in regulating the immune system [4].

Interleukin 10 (IL10) and tumor necrosis factor (TNF) are cytokines that have been the subject of extensive epidemiological investigations into whether genetic variation in these genes is associated with NHL risk [12, 13]. These analyses, however, have included primarily only Caucasians. Rothman et al. [12] initially reported associations between *IL10* and *TNF* single nucleotide polymorphisms (SNPs) in ~3600 cases of NHL and ~4000 controls from North American and European studies participating in the InterLymph Consortium. Skibola et al. [13] extended these findings by pooling additional InterLymph-participating studies for a total of ~8000 cases and ~8500 controls. While Skibola et al. was able to perform analyses by ethnicity, including Asians, these analyses were considered exploratory due to limited sample size.

Given the previous findings in Caucasians, and the lack of sufficient data exploring these relationships in Asian populations to date, we investigated the possible associations of genetic variants in *IL10* and *TNF* with NHL risk by pooling data from three independent Asian case-control studies (2635 cases; 4234 controls) that genotyped SNPs in these two gene regions.

Methods

Our study population comprised three independent case-control studies carried out in Hong Kong, South Korea, and mainland China (Jinan, China). Subjects in the case-control study in Hong Kong were recruited from patients of the Queen Mary and Queen Elizabeth Hospitals in Hong Kong, using similar methods as a previous study of chronic lymphocytic leukemia [7]. Cases were patients with NHL diagnosed according to the World Health Organization Classification of Tumors of the Hematopoietic and Lymphoid Tissues. Patients with non-cancer diagnoses in the Queen Mary Hospital were used as controls. In Jinan, patients were recruited from the Shandong Cancer Hospital and Institute and the Shandong University Qilu Hospital. The case group comprised patients newly diagnosed with NHL according to the World Health Organization criteria. Controls were selected from the patient population without evidence of any personal or family history of cancer or other serious illness. In the case-control study carried out in South Korea, cases and controls were recruited from the Chonnam National University Hwasun Hospital in Jeollanam-do, South Korea. All three studies included only newly diagnosed NHL cases. To ensure the protection

of human subjects, the protocol for each study was approved by the local Institutional Review Board.

In total, 20 SNPs in the *IL10* and *TNF/LTA* gene regions were genotyped (Supplemental Table 1). SNPs were genotyped in blood samples by TaqMan as described at <http://snp500cancer.nci.nih.gov/>. Samples from Hong Kong were genotyped at the National Cancer Institute Core Genotyping Facility (CGF) in Gaithersburg, MD. Samples from South Korea and Jinan were genotyped at their local institutions. Hardy–Weinberg equilibrium (HWE) for each SNP was tested in controls using Fisher’s exact test. None of the SNPs deviated substantially from HWE ($p < 0.0001$) (Supplemental Table 1).

Associations of each SNP with NHL risk were estimated by odds ratios (OR) and 95 % confidence intervals (CI) calculated using unconditional logistic regression adjusted for age (reference group, <40 years old), gender (reference group, male), and study center (reference group, Hong Kong). The homozygote of the common allele was used as the reference group. Gene–dose effects were estimated by a linear trend test based on the number of variant alleles present (0, 1, 2). Polytomous regression models were used to evaluate SNP effects among B cell lymphoma subtypes [diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT), mantle cell lymphoma (MCL), chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL)] and T cell lymphoma subtypes [natural killer lymphoma (NK), peripheral T cell lymphoma (PTCL)]. For *IL10* rs1800896 and *TNF* rs1800629, differences between DLBCL and FL were determined by case–case analyses comparing the gene–dose effects.

Results

Our pooled population of subjects from Hong Kong (1174 cases, 2034 controls), South Korea (949 cases, 1700 controls), and Jinan (512 cases, 500 controls) was composed of 2635 NHL cases and 4234 controls (Table 1). Cases and controls were similar in age in our pooled population.

In total, 20 SNPs were genotyped in *IL10* and *TNF/LTA* (Supplemental Table 1). The NHL risk associated with all SNPs, as well as the allele distributions, is provided in Supplemental Table 2. The associations of each SNP with B cell lymphoma subtypes are provided in Supplemental Table 3. The associations of each SNP with T cell lymphoma subtypes are provided in Supplemental Table 4. Of the 13 SNPs genotyped in *IL10*, three (rs1800871, rs1800872, and rs1800896) were genotyped in all three of the studies included in our analysis. *IL10* rs1800896 was associated with increased risk of NHL ($OR_{\text{per-allele}} = 1.28$, 95 % CI 1.12–1.46; $p_{\text{trend}} = 0.0003$), as well as B cell ($OR_{\text{per-allele}} = 1.25$, 95 % CI 1.08–1.45; $p_{\text{trend}} = 0.003$) and T cell ($OR_{\text{per-allele}} = 1.44$, 95 % CI 1.13–1.82; $p_{\text{trend}} = 0.003$) lymphomas (Table 2; Supplemental Table 2). These associations were consistent across the studies. When exploring NHL subtypes further, the association between *IL10* rs1800896 and B cell lymphoma was restricted to DLBCL ($OR_{\text{per-allele}} = 1.29$, 95 % CI 1.08–1.53; $p_{\text{trend}} = 0.004$) (Table 2; Supplemental Table 3). The association between *IL10* rs1800896 and T cell lymphoma was restricted to NK T cell lymphoma ($OR_{\text{per-allele}} = 1.52$, 95 % CI 1.04–2.23; $p_{\text{trend}} = 0.030$) (Table 2; Supplemental Table 4). Heterogeneity was observed when

comparing the per-allele risks associated with *IL10* rs1800896 and DLBCL and FL ($p_{\text{heterogeneity}} = 0.01$).

Of the 7 SNPs genotyped in *TNF/LTA*, four (rs1800629, rs1799724, rs1800630, rs909253) were genotyped in two studies (Hong Kong, South Korea). Both *TNF* rs1800629 and rs1800630 were associated with risk of NHL ($\text{OR}_{\text{per-allele}} = 0.79$, 95 % CI 0.67–0.92; $p_{\text{trend}} = 0.003$ and $\text{OR}_{\text{per-allele}} = 1.19$, 95 % CI 1.05–1.35; $p_{\text{trend}} = 0.005$, respectively), specifically B cell lymphoma ($\text{OR}_{\text{per-allele}} = 0.77$, 95 % CI 0.64–0.91; $p_{\text{trend}} = 0.003$ and $\text{OR}_{\text{per-allele}} = 1.17$, 95 % CI 1.03–1.34; $p_{\text{trend}} = 0.019$, respectively) (Table 3; Supplemental Table 2). *TNF* rs1800629 was associated with DLBCL ($p_{\text{trend}} = 0.001$) (Table 3; Supplemental Table 3). No heterogeneity was observed when comparing the per-allele risks associated with *TNF* rs1800629 and DLBCL and FL ($p_{\text{heterogeneity}} = 0.67$).

Discussion

We have extended the previous observations that NHL risk is associated with *IL10* and *TNF* variants in Caucasians by evaluating these associations in three independent populations from Hong Kong, South Korea, and mainland China. Our study suggests that genetic variation in *IL10* and *TNF* may play a role in lymphomagenesis in these previously understudied populations.

We found *IL10* rs1800896 to be associated with B cell lymphoma, specifically DLBCL, as well as T cell lymphoma. Similar to our findings, previous studies in Caucasians observed an association between the G allele at *IL10* rs1800896 and increased risk of DLBCL but not FL [12, 13]. Of note, however, the risks observed by Rothman et al. [12] were not significantly different by histological type (DLBCL vs. FL). Exploratory analyses with limited power and in a relatively small number of Asians (<300 cases; <300 controls) found the association between *IL10* rs1800896 and DLBCL to be suggestive, but not statistically significant [13]. By conducting our analyses with an order of magnitude larger sample size, we have been able to confirm this observation, finding that the G allele at *IL10* rs1800896 infers about a 25 % increased risk of DLBCL in Asian populations.

The A allele at *TNF* rs1800629 was associated with a decreased risk of DLBCL in our study populations. This is inconsistent with Rothman et al.'s [12] and Skibola et al.'s [13] findings among Caucasians. However, similar to our findings, Asian-specific analyses carried out by Skibola et al. found the A allele at *TNF* rs1800629 to be associated with a decreased risk of B cell lymphoma ($\text{OR}_{\text{AG/AA vs GG}} = 0.50$, 95 % CI 0.30–0.85; $p_{\text{trend}} = 0.016$) and DLBCL ($\text{OR}_{\text{AG/AA vs GG}} = 0.60$, 95 % CI 0.30–1.18; $p_{\text{trend}} = 0.24$) [13]. The allelic distributions in both the current study and Skibola et al.'s are consistent with Asian HapMap populations (JPT: G allele = 0.977, A allele = 0.023; HCB: G allele = 0.965, A allele = 0.035). The opposing observations by ethnicity may be due to variation in genetic structure by population [8], such as *TNF* rs1800629 possibly tagging a different functional SNP and/or haplotype in the Asian populations compared to Caucasians in North America and Europe [10, 14].

Our pooled analysis of studies carried out in Asia provides evidence that variation in *IL10* and *TNF* influence lymphoma susceptibility beyond Caucasian populations. These findings have translational relevance as adverse prognosis of NHL has been observed in patients with altered IL10 [1] and TNF [16] concentrations, and genetic variation leading to altered IL-10 expression has been associated with the development of lymphoma in both the general population [3] and AIDS patients [2]. The main strength of our analysis is the large sample size, pooled from three independent case-control studies. While previous analyses have had larger samples sizes, this report is the largest to date in non-Caucasian populations. The strong a priori hypotheses of these SNPs and the fact that our strongest association remains significant after applying a Bonferroni correction lend strength to our findings. One possible limitation of our study is potential population stratification. However, it is unlikely that this would explain our results given that we adjusted for study center and that the populations within each center are relatively homogenous. Finally, given the exposure levels in Asia to suspected or known lymphomagens with immunotoxic properties, such as trichloroethylene [5] and benzene [9], and that interactions between loci involved in immunologic regulation and these chemicals may exist [9], high-quality genetic association studies that integrate cutting edge environmental and occupational exposure assessments are warranted. It is also the case that our results should be viewed as exploratory until confirmed in larger studies in Asia, especially given some of the low allelic frequencies we observed in these populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institutes of Health (NIH) [National Cancer Institute (NCI)], by Science Technology of Shandong Province grants ZR2009CM093 and 2011GSF11820, and by a grant from the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (A01-0385-A70604-07M7-00000A).

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Demographics of the three independent case-control studies carried out in Asia included in our pooled analysis of genetic variation in *IL10* and *TNF/LTA*

Table 1

Hong Kong				South Korea				Jinan, China				Total				
Cases (n = 1174)		Controls (n = 2034)		Cases (n = 949)		Controls (n = 1700)		Cases (n = 512)		Controls (n = 500)		Cases (n = 2635)		Controls (n = 4234)		
n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Age [mean (SD)]	57.7 (16.3)	52.5 (17.8)	56.1 (14.9)	52.2 (14.3)	51.3 (13.7)	51.9 (12.3)	55.9 (15.5)	52.3 (15.9)								
Gender																
Males	654	55.7	1104	54.3	574	60.5	821	48.3	322	62.9	300	60.0	1550	58.8	2225	52.6
Females	520	44.3	930	45.7	375	39.5	879	51.7	190	37.1	200	40.0	1085	41.2	2009	47.4
NHL subtype ^a																
B cell lymphoma	924	78.7	-	-	727	76.6	-	-	410	80.1	-	-	2061	78.2	-	-
DLBCL	488	41.6	-	-	513	54.1	-	-	204	39.8	-	-	1205	45.7	-	-
FL	128	10.9	-	-	20	2.1	-	-	124	24.2	-	-	272	10.3	-	-
MALT	101	8.6	-	-	0	0.0	-	-	0	0.0	-	-	101	3.8	-	-
MCL	45	3.8	-	-	16	1.7	-	-	36	7.0	-	-	97	3.7	-	-
CLL/SLL	162	13.8	-	-	16	1.7	-	-	0	0.0	-	-	178	6.8	-	-
Other B ^b	0	0.0	-	-	162	17.1	-	-	46	9.0	-	-	208	7.9	-	-
T cell lymphoma	179	15.2	-	-	196	20.7	-	-	102	19.9	-	-	477	18.1	-	-
NK	62	5.3	-	-	53	5.6	-	-	48	9.4	-	-	163	6.2	-	-
PTCL	0	0.0	-	-	63	6.6	-	-	35	6.8	-	-	98	3.7	-	-
Other T ^b	117	10.0	-	-	80	8.4	-	-	19	3.7	-	-	216	8.2	-	-
Other	71	6.0	-	-	26	2.7	-	-	0	0.0	-	-	97	3.7	-	-

^a B cell lymphoma subtypes: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL) mucosa-associated lymphoid tissue (MALT), mantle cell lymphoma (MCL), chronic lymphocytic leukemia/small lymphoma (CLL/SLL). T cell lymphoma subtypes: natural killer lymphoma (NK), peripheral T cell lymphoma (PTCL)

^b Includes cases with additional subtypes as well as those not fully characterized

Table 2

Risk of NHL, and NHL subtypes, associated with *IL10* rs1800896 in Asia

Gene	dbSNP ID	Subtype	Genotype	Controls		Cases		Odds ratio	95 % confidence interval	
				n	%	n	%		Lower	Upper
<i>IL10</i>	rs1800896	All NHL	AA	3598	88.2	2107	85.7	1.00	Reference	
			AG	452	11.1	312	12.7	1.17	1.00	1.37
			GG	29	0.7	40	1.6	2.48	1.52	4.04
			AG+GG	481	11.8	352	14.3	1.25	1.08	1.45
			Trend	4079		2459		1.28	1.12	1.46
		B cell lymphomas	AA	3598	88.2	1651	85.9	1.00	Reference	
			AG	452	11.1	241	12.6	1.16	0.98	1.37
			GG	29	0.7	29	1.5	2.32	1.37	3.94
			AG+GG	481	11.8	270	14.1	1.22	1.04	1.44
			Trend	4079		1921		1.25	1.08	1.45
		DLBCL	AA	3598	88.2	978	85.7	1.00	Reference	
			AG	452	11.1	145	12.7	1.18	0.96	1.45
			GG	29	0.7	18	1.6	2.57	1.41	4.69
			AG+GG	481	11.8	163	14.3	1.26	1.04	1.53
			Trend	4079		1141		1.29	1.08	1.53
		FL	AA	3598	88.2	215	85.3	1.00	Reference	
			AG	452	11.1	33	13.1	1.14	0.77	1.68
			GG	29	0.7	4	1.6	2.16	0.73	6.40
			AG+GG	481	11.8	37	14.7	1.20	0.83	1.75
			Trend	4079		252		1.22	0.88	1.70
		T cell lymphomas	AA	3598	88.2	380	84.4	1.00	Reference	
			AG	452	11.1	59	13.1	1.21	0.90	1.63
			GG	29	0.7	11	2.4	3.85	1.89	7.84
			AG+GG	481	11.8	70	15.6	1.36	1.04	1.80
			Trend	4079		450		1.44	1.13	1.82
		NK T cell	AA	3598	88.2	130	85.0	1.00	Reference	
			AG	452	11.1	17	11.1	1.03	0.61	1.74

Gene	dbSNP ID	Subtype	Genotype	Controls		Cases		Odds ratio	95 % confidence interval		p value
				n	%	n	%		Lower	Upper	
			GG	29	0.7	6	3.9	6.01	2.41	15.01	0.0001
			AG+GG	481	11.8	23	15.0	1.32	0.83	2.09	0.234
			Trend	4079		153		1.52	1.04	2.23	0.030

Odds ratios (OR) and 95 % confidence intervals (CI) adjusted for age, gender, and study center. B cell lymphoma subtypes: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), T cell lymphoma subtypes: natural killer lymphoma (NK)

Table 3

Risk of NHL and NHL subtypes, associated with *TNF* rs1800629 and rs1800630 in Asia

Gene	dbSNP ID	Subtype	Genotype	Controls		Cases		Odds ratio	95 % confidence interval	
				n	%	n	%		Lower	Upper
TNF	rs1800629	All NHL	GG	3091	85.3	1702	88.1	1.00	Reference	
			GA	506	14.0	221	11.4	0.78	0.66	0.93
			AA	25	0.7	9	0.5	0.69	0.32	1.49
			GA+AA	531	14.7	230	11.9	0.78	0.66	0.92
			Trend	3622		1932		0.79	0.67	0.92
		B cell lymphomas	GG	3091	85.3	1332	88.6	1.00	Reference	
			GA	506	14.0	164	10.9	0.74	0.61	0.90
			AA	25	0.7	8	0.5	0.80	0.36	1.80
			GA+AA	531	14.7	172	11.4	0.75	0.62	0.90
			Trend	3622		1504		0.77	0.64	0.91
		DLBCL	GG	3091	85.3	829	89.2	1.00	Reference	
			GA	506	14.0	97	10.4	0.69	0.54	0.87
			AA	25	0.7	3	0.3	0.48	0.14	1.61
			GA+AA	531	14.7	100	10.8	0.68	0.54	0.86
			Trend	3622		929		0.69	0.55	0.86
		FL	GG	3091	85.3	115	88.5	1.00	Reference	
			GA	506	14.0	13	10.0	0.74	0.41	1.33
			AA	25	0.7	2	1.5	2.25	0.51	9.87
			GA+AA	531	14.7	15	11.5	0.81	0.47	1.41
			Trend	3622		130		0.90	0.55	1.48
		T cell lymphomas	GG	3091	85.3	287	83.9	1.00	Reference	
			GA	506	14.0	54	15.8	1.10	0.81	1.50
			AA	25	0.7	1	0.3	0.43	0.06	3.22
			GA+AA	531	14.7	55	16.1	1.07	0.79	1.45
			Trend	3622		342		1.03	0.77	1.38
		NK T cell	GG	3091	85.3	89	86.4	1.00	Reference	
			GA	506	14.0	14	13.6	0.92	0.52	1.63
										0.775

Gene	dbSNP ID	Subtype	Genotype	Controls		Cases		Odds ratio	95 % confidence interval	
				n	%	n	%		Lower	Upper
TNF	rs1800630	All NHL	AA	25	0.7	0	0.0		Not applicable	
			GA+AA	531	14.7	14	13.6	0.88	0.50	1.56
			Trend	3622		103		0.85	0.49	1.47
			CC	1899	72.7	1079	69.5	1.00	Reference	
			CA	660	25.3	420	27.0	1.14	0.98	1.32
			AA	54	2.1	54	3.5	1.71	1.15	2.54
			CA+AA	714	27.3	474	30.5	1.18	1.03	1.36
			Trend	2613		1553		1.19	1.05	1.35
			CC	1899	72.7	832	69.3	1.00	Reference	
			CA	660	25.3	328	27.3	1.14	0.97	1.34
		B cell Lymphomas	AA	54	2.1	40	3.3	1.54	1.00	2.37
			CA+AA	714	27.3	368	30.7	1.17	1.01	1.37
			Trend	2613		1200		1.17	1.03	1.34
			CC	1899	72.7	556	70.6	1.00	Reference	
			CA	660	25.3	203	25.8	1.07	0.89	1.29
			AA	54	2.1	29	3.7	1.70	1.06	2.75
			CA+AA	714	27.3	232	29.4	1.12	0.94	1.34
			Trend	2613		788		1.15	0.98	1.35
			CC	1899	72.7	70	76.1	1.00	Reference	
			CA	660	25.3	20	21.7	0.79	0.47	1.31
		FL	AA	54	2.1	2	2.2	0.71	0.17	3.05
			CA+AA	714	27.3	22	23.9	0.77	0.47	1.27
			Trend	2613		92		0.80	0.52	1.24
			CC	1899	72.7	203	69.5	1.00	Reference	
			CA	660	25.3	76	26.0	1.09	0.83	1.45
			AA	54	2.1	13	4.5	2.25	1.20	4.24
			CA+AA	714	27.3	89	30.5	1.18	0.91	1.54
			Trend	2613		292		1.24	0.99	1.55
			CC	1899	72.7	61	74.4	1.00	Reference	
			CA	660	25.3	17	20.7	0.81	0.47	1.40
		T cell lymphomas	CC	1899	72.7	203	69.5	1.00	Reference	
			CA	660	25.3	76	26.0	1.09	0.83	1.45
			AA	54	2.1	13	4.5	2.25	1.20	4.24
			CA+AA	714	27.3	89	30.5	1.18	0.91	1.54
			Trend	2613		292		1.24	0.99	1.55
			CC	1899	72.7	61	74.4	1.00	Reference	
			CA	660	25.3	17	20.7	0.81	0.47	1.40
			AA	54	2.1	2	2.2	0.71	0.17	3.05
			CA+AA	714	27.3	22	23.9	0.77	0.47	1.27
			Trend	2613		92		0.80	0.52	1.24
		NK T cell	CC	1899	72.7	203	69.5	1.00	Reference	
			CA	660	25.3	76	26.0	1.09	0.83	1.45
			AA	54	2.1	13	4.5	2.25	1.20	4.24
			CA+AA	714	27.3	89	30.5	1.18	0.91	1.54
			Trend	2613		292		1.24	0.99	1.55
			CC	1899	72.7	61	74.4	1.00	Reference	
			CA	660	25.3	17	20.7	0.81	0.47	1.40
			AA	54	2.1	2	2.2	0.71	0.17	3.05
			CA+AA	714	27.3	22	23.9	0.77	0.47	1.27
			Trend	2613		92		0.80	0.52	1.24

Gene	dbSNP ID	Subtype	Genotype	Controls		Cases		Odds ratio	95 % confidence interval		p value
				n	%	n	%		Lower	Upper	
			AA	54	2.1	4	4.9	2.15	0.74	6.22	0.157
			CA+AA	714	27.3	21	25.6	0.92	0.55	1.52	0.739
			Trend	2613		82		1.04	0.67	1.60	0.864

Odds ratios (OR) and 95 % confidence intervals (CI) adjusted for age, gender, and study center. B cell lymphoma subtypes: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), T cell lymphoma subtypes: natural killer lymphoma (NK)