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Common Immune-Related Risk Factors and Incident Non-Hodgkin Lymphoma: The Multiethnic Cohort

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Abstract

Severe immune dysfunction is an established risk factor of lymphoma, but the role of moderate alterations of immunity is not clear and prospective investigations are needed. We examined several immune-related disorders and medications in relation to non-Hodgkin lymphoma (NHL) in the Multiethnic Cohort. Over 215,000 subjects of African American, Caucasian, Japanese American, Latino, and Native Hawaiian ancestry aged 45–75 years completed a questionnaire, including information on medical history, in 1993–1996. After exclusions, we performed Cox regression among 193,050 cohort members including 939 incident NHL cases while adjusting for sex, age, ethnicity, education, body mass index, and alcohol intake. Self-reported diabetes was not associated with NHL overall, but was positively associated with risk among Japanese Americans (hazard ratio (HR) = 1.55; 95% confidence interval (CI): 1.10–2.17). Participants with a history of blood transfusion were at increased risk with HR = 1.39 (95% CI: 1.06–1.84) in men and HR = 1.22 (95% CI: 0.94–1.58) in women, especially for the diffuse large B-cell lymphoma subtype. History of asthma or other allergies was associated with elevated risk only among Latinos (HR = 1.46; 95% CI: 1.07–2.00) who also showed a significant relation between current use of antihistamines and NHL (HR = 1.80; 95% CI: 1.09–2.97). Use of non-steroidal anti-inflammatory drugs was not associated with NHL. Our findings from this large prospective study support a moderate risk for NHL related to blood transfusions, current long-term antihistamine use, and diabetes, but the associations were limited to a certain ethnic groups and require further replications.

Keywords

allergy; blood transfusion; diabetes mellitus; lymphoma, non-Hodgkin; NSAIDs

Introduction

Immune dysfunction is thought to be the basis of non-Hodgkin lymphoma (NHL) etiology; in particular human immunodeficiency virus infection and immunosuppressive therapy after organ transplants are well known to increase the risk of NHL.1 Autoimmune diseases with chronic immune stimulation and inflammation are also established risk factors, as best described for rheumatoid arthritis and systemic lupus erythematosus.2 More common conditions with less prominent effects on immunity may also affect lymphoma risk in cumulative exposures and might have contributed to the decades-long upward trend in NHL incidence.3;4 Such common immune disorders as diabetes and atopic conditions and those reflected by a history of a blood transfusion have shown less consistent associations with NHL.5–7 Use of over-the-counter treatments for common immune disorders, namely non-

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steroidal anti-inflammatory drugs (NSAIDs) and antihistamines, may also be associated with risk. The treatments, as a proxy for underlying immune disorders, may be linked to elevated NHL risk[8¯11] or they may reduce risk[12¯16] by suppressing chronic inflammation.

To date, most epidemiologic studies examining common immunologic factors and NHL have been case-control studies which might have been biased from immune-altering effects of preclinical NHL.[17] For example, NHL patients have been reported to experience fewer allergic symptoms.[18] Based on the overall lack of consistent evidence and the need for results from prospective studies that collect data on exposure before onset of disease, we examined common conditions and medications related to immunity for their association with NHL risk within different ethnic groups in a large prospective cohort in the U.S.

Methods

Study Population

The Multiethnic Cohort (MEC) Study was assembled between 1993 and 1996 in Hawaii and Los Angeles with the purpose of providing prospective data on diet and other lifestyle exposures related to cancer risk in diverse ethnic groups (African American, Caucasian, Japanese American, Latino, Native Hawaiian, and Other). Details on recruitment and baseline information have been published previously.[19] A self-administered questionnaire was mailed to people between the ages 45–75 years who were part of the five main ethnic groups in the study region, identified primarily through the drivers' license files for the state of Hawaii and the county of Los Angeles, California, supplemented with other information sources. Japanese Americans had the highest response rate (49%), whereas Latinos had the lowest (20%). Response rates were 3–8% higher among women than men across ethnic groups. A comparison of the cohort with census data indicated that the MEC represents all levels of educational although cohort members, in particular men, were somewhat better educated than the general population.[19] From the 215,820 initial respondents who returned the questionnaire, 13,992 individuals were excluded because they did not belong to one of the five main ethnic groups, 8,264 subjects due to invalid dietary information, and 514 patients for NHL diagnosis before entry into the cohort, leaving 87,078 men and 105,972 women for the current analysis. The Institutional Review Boards at the University of Hawaii and at the University of Southern California approved the study, and all study participants provided informed consent.

Data Collection

The baseline questionnaire collected information on demographics, medical and reproductive history, medication use, family history of various cancers, and physical activity and included an extensive quantitative food frequency questionnaire. History of diabetes, blood transfusion, and allergies (“asthma, hay fever, skin allergy, food allergy, or any other allergy”) was assessed with the question, “Has your doctor ever told you that you had any of the following?”. The use of anti-inflammatory or anti-allergic medications was evaluated by the question, “Have you ever taken any of the following medications at least two times per week (for one month or longer)?”, for each of the following items – aspirin, other NSAIDs (ibuprofen, naproxen, indomethacin or other), and antihistamines (in the form of “pills or shots”) – with example brand names provided. Study participants responded by checking either “no”, “yes, but not at this time”, or “yes, currently”, and ever users were asked to indicate the length of medication use, categorized as ≤1 year, 2–3 years, 4–5 years, 6–10 years, or >10 years. Based on these responses, we created categories for each medication use: never users, past users of three duration levels (≤1 year, 2–5 years, and ≥6 years), or current users of the same three duration levels. For past users, the two highest categories had to be collapsed for some analyses due to small numbers. The categories were based on the

answers allowable in the questionnaire. A variable for total use of NSAIDs was generated by summing up the years of aspirin and other NSAIDs. Data on medication use was missing in 5–6% of subjects and missing slightly more often in women than in men. Information on diabetes, blood transfusion, and allergies was complete.

Ascertainment and Classification of NHL Cases

Linkages of the MEC with the Hawaii Tumor Registry, the Los Angeles County Cancer Surveillance Program, and the State of California Cancer Registry were performed to identify incident cancer cases. These Surveillance, Epidemiology, and End Results (SEER) registries ascertain all primary cancer diagnoses among residents in their area and provide information on site, stage, histology, differentiation, grade, and disease-specific survival. Based on the low out-migration rate observed in the cohort (3.7% after an average follow-up of 7 years; with 2.5% California participants having moved to Hawaii and 4.9% Hawaii participants having moved to California), we expect case identification within the MEC to be close to complete.19 The follow-up ended at the earliest of the following events: diagnosis of NHL, death, or December 31, 2003, the last date of follow-up. NHL was defined and classified into the most common subtypes according to the proposed adaptation20 of the World Health Organization classification21 for epidemiologic studies using the International Classification of Disease Oncology version 3 (ICD-O-3): diffuse large B-cell lymphoma (DLBCL; 9675–9680, 9684), follicular lymphoma (FL; 9690, 9691, 9695, 9698), T-cell lymphomas (9700–9719, 9827, 9831, 9948), chronic lymphocytic leukemia (CLL; 9823) or small lymphocytic lymphoma (SLL; 9670), and other NHL subtypes (9590–9590, 9687, 9671–9675, 9689, 9699, 9727–9729, 9731–9734, 9760–9764, 9820, 9826, 9832–9837, 9940, 9970). Deaths in the cohort were identified by linkage to the state death certificate files in Hawaii and California and to the National Death Index for deaths occurring in other states.

Statistical Methods

All statistical analyses were performed using the SAS statistical software, version 9.1 (SAS Institute, Inc., Cary, NC). We used Cox proportional hazards regression (PROC PHREG) to estimate the risk of NHL due to immune-related conditions and medications (diabetes, blood transfusion, allergies, antihistamines, and NSAIDs). We calculated hazard ratios (HR) and 95% confidence intervals (CI) using age as the underlying time metric.22 The final models were stratified by follow-up time, categorized as ≤2 years, 2–5 years, and >5 years, and were adjusted for age at cohort entry (continuous), education (<12 or ≥12 years), body mass index (BMI; <25, 25–30, or ≥30 kg/m^2), and alcohol use (never or rare drinkers with <0.1 drinks/week, 0.1–2.9 drinks/week, or ≥3 drinks/week). BMI and alcohol intake were included in the model because they have known pro- and anti-inflammatory effects, respectively, and have been associated with NHL risk in previous studies.23;24 Other factors, such as smoking, physical activity, and reproductive history, were examined for potential confounding effects but were ruled out because they produced a less than 10% change in the HR estimates for the main association. Linear trend for the duration of past and current medication use was tested using ordinal variables that included the median value for each duration category. We also conducted stratified analyses by ethnicity and common NHL subtypes. However, a few small subgroups (Native Hawaiians, T-cell NHL, and “other” subtypes) were excluded from the analyses because of limited sample sizes. No major violations of the proportional hazards assumption were observed when examined with Kaplan-Meier survival curves and Schoenfeld residuals.25

Results

During the median 10 years of follow-up, 939 subjects (514 men and 425 women) were newly diagnosed with NHL (Table 1). NHL cases were more likely to be older, Caucasian, and former smokers and drink more alcohol compared to non-cases at baseline. All ethnic groups had a relatively high proportion of DLBCL (Japanese 37%, Latinos 45%, Caucasians 25%, African-Americans 24%, and Native Hawaiians 34%), whereas the percentage of SLL/CLL cases was highest in Caucasians (32%), African-Americans (28%), and Native Hawaiians (24%) and low in Japanese (10%) and Latinos (14%). The proportions of FL and T cell tumors were relatively similar; they varied between 13–19% and 2–12%.

A diagnosis of diabetes, reported by 13% of the cohort participants, was not related to the risk of developing NHL in men and women (Table 2). A history of blood transfusions as present in 8% of men and 13% of women was associated with an increased NHL risk in men (HR = 1.39; 95% CI: 1.06–1.84), while a suggestive positive relation was observed in women (HR = 1.22; 95% CI: 0.94–1.58). The positive association did not change materially when the first two years of follow-up were excluded: the HR for men and women combined changed from 1.30 (95% CI: 1.08–1.57) to 1.27 (95% CI: 1.03–1.56). NHL risk was not modified among 30% of the cohort participants who reported asthma or other forms of allergies, but it was elevated among current long-term users of antihistamines when compared to never users. The respective risk estimates in men and women were 1.88 (95% CI: 1.20–2.95; P_{trend} for increasing duration = 0.02) and 1.42 (95% CI: 0.91–2.21; P_{trend} = 0.07). Use of aspirin or other NSAIDs did not show a significant association with NHL risk, except for past use of other NSAIDs in women; women with at least 2 years of past use had a HR = 0.61 (95% CI: 0.38–0.99; P_{trend} = 0.04).

Due to the similar results for diabetes and asthma in men and women and the non-significant findings for NSAIDs, we combined results for men and women when we stratified by ethnic group and NHL subtype. Among the four large ethnic groups in the MEC study (Table 3), the association for diabetes was positive among Japanese Americans (HR = 1.55; 95% CI: 1.10, 2.17). The significant risk observed for blood transfusions in the total population was limited to Japanese Americans (HR = 1.51; 95% CI: 1.06, 2.17) and Latinos (HR = 1.71; 95% CI: 1.17, 2.49). Both the associations of allergies and antihistamines with NHL were strongest among Latinos: the HR for allergies was 1.46 (95% CI: 1.07, 2.00) and the HR for current antihistamine use was 1.80 (95% CI: 1.09, 2.97). Neither total nor individual NSAIDs showed a significant or consistent pattern of association with NHL across by ethnic group.

DLBCL was the most common NHL subtype in both men and women, followed by CLL/SLL and FL (Table 1). The positive association for blood transfusions was only significant for DLBCL (HR = 1.55; 95% CI: 1.10, 2.17), whereas the null associations of diabetes and allergies were consistent across the common NHL subtypes (Table 4). The elevated risk associated with current antihistamine use was limited to DLBCL (HR = 2.34; 95% CI: 1.21, 4.55). NSAID use showed mostly null associations, though past use of non-aspirin types was associated with a reduced risk for FL only (HR = 0.56; 95% CI: 0.34, 0.90).

Discussion

The development of NHL itself alters immune functions.4 Therefore, prospective cohorts offer the optimal research design, especially for investigations addressing the role of mild immune factors in NHL etiology, although they tend to lack detailed information on diverse exposure items.4 In this analysis, one of the largest prospective investigations of common immune-related exposures, we found several associations with NHL risk. In particular, a

history of blood transfusion and current long-term use of antihistamines were related to a higher risk of NHL. Other findings were limited to specific ethnic groups or NHL subtypes. Diabetes was associated with elevated NHL risk only among Japanese Americans. A history of allergies was positively linked to NHL among Latinos who also experienced a significant risk related to the use of antihistamines. The association with blood transfusion and antihistamine use was limited to DLBCL, which is consistent with previous reports that have provided more evidence for altered immunity as a risk factor for DLBCL than for FL.[26–28]

Our finding of a positive association between blood transfusion and NHL is consistent with previous reports.[7;29] For example, a large population-based case-control study[29] reported an odds ratio (OR) of 1.26 (95% CI: 0.91–1.73). In that study, the risk was significantly higher for cases with a longer duration since the first transfusion and for transfusions given for a medical condition than for trauma, surgery, or obstetrics.[29] Therefore, it was postulated that blood transfusion may reflect the risk associated with immunity-altering medical conditions (e.g., anemia, ulcer, hemorrhage)[29;30] rather than a direct immunosuppressive effect of transfusion.[31] Unfortunately, our study did not record reasons for transfusions, but ethnic differences in the indications for transfusion seem plausible. Data are sparse for Asian Americans, but in Japan, low iron intake and anemia continue to be a prevalent health concern (above 15% of women in a national survey).[32;33] Therefore, anemia and other medical conditions that require blood transfusion may compromise immune function and in turn raise the risk of NHL. Alternatively, hepatitis C transmitted by infected donors may be responsible for the risk associated with transfusions.[1] Although blood banks are required to test blood donations for viral markers, blood transfusions are suspected to cause about 6% of all Hepatitis C infections.[34;35] Hepatitis C infection appears to be mainly associated with B-cell NHL, which might explain the positive association between blood transfusion and DLBCL in our study.[36–38] Although some earlier case-control studies did not find an association with transfusions, other cohort studies and our findings support this hypothesis.[7]

The positive association between antihistamine use and NHL in the MEC is inconsistent with previously reported inverse associations[39;40] and needs to be examined in light of the allergy-NHL relation in general. Studies on the link between atopic conditions and NHL have been equivocal,[6;41;42] involving two contradictory hypotheses. Allergic individuals with hypersensitive Th2-dominant immunity may either develop more efficient tumor immunosurveillance and, thus, be protected from lymphomagenesis or they may suffer from greater immune cell proliferation and malignant transformation.[43] Based on a number of case-control studies and a few small cohort studies,[44] the association remains inconclusive, reflecting the following complexities: (i) NHL itself suppresses reactions to allergens;[4] (ii) heterogenous findings on allergens, e.g., more consistent reports of protection from hay fever,[45;46] elevated risk from medication allergies,[6] and mostly null findings on asthma; [6;45] and (iii) unreliable self-reports of allergy that were not medically confirmed.[46] Thus, it is not surprising that the self-reported history of diverse types of allergies in our data did not show an association with NHL. Similarly, the only prospective study of NHL and immunoglobulin E reactivity found an inverse association that was limited to cases diagnosed shortly after blood collection, which suggests that findings of a protective effect might have been due to reverse effects of latent disease.[46] The persistent positive association in our analysis after excluding cases diagnosed during two years after baseline likely precludes such reverse causal bias. Nevertheless, replications in a cohort setting with immunological biomarkers as well as with detailed medical and treatment histories are needed. The associations for allergy history and medications in Latinos, although intriguing, could have been a chance finding; we do not have a plausible explanation for them.

Unlike rarer autoimmune disorders with more severely altered immune status, common autoimmune conditions such as diabetes have shown null or inconsistent associations of smaller magnitude.4;17 Although our study did not distinguish between diabetes types, more than 95% are expected to be type 2 given the age of the MEC participants. Type 2 diabetes with its insulin resistance and chronic inflammatory state was associated with an 28% higher risk of NHL, but the substantial heterogeneity among studies prevented a firm conclusion in a meta-analysis.5 Our null overall findings might have resulted from attenuations due to undiagnosed diabetes cases since we relied on self-reports.47 The positive association with NHL among Japanese Americans is consistent with the stronger risk estimates from previous case-control studies conducted in East Asia.5 While it is not clear whether this association has a biological basis related to the higher susceptibility to insulin resistance observed in Asian populations,48 further investigations of the diabetes-NHL association may be needed considering rapidly increasing central obesity and type 2 diabetes in this ethnic group.49

We find it difficult to resolve the controversy as to whether the presence of inflammatory conditions or the use of anti-inflammatory medications themselves constitute a risk factor for NHL, or these medications may even protect against the disease.50 The epidemiologic studies to date have shown both positive9–11 and negative14;15 associations. We did not detect significant or consistent associations with risk for total NSAIDs, aspirin specifically, or other NSAIDs, but long-term use of other NSAIDs in time appeared to be protective in women.

In this large prospective investigation, past exposure to immune-related conditions and medications was assessed prior to NHL diagnosis, minimizing selection and recall bias, the most serious limitation in most previous studies.4 In addition, the MEC study had nearly complete follow-up, utilized linkages to SEER registries which have standardized ascertainment procedures and a high rate of histologically-confirmed cases, and included detailed demographic and lifestyle information that allowed controlling of confounding or modifying effects in the analysis. The inclusion of different ethnic groups is novel and likely to have contributed to a wider range of exposures to the immune factors examined. The differential risk estimates across ethnic groups may be due to differences in subtypes. DLBCL, the most common subtype among Japanese Americans and Latinos, may have a stronger association with diabetes and allergies. Genetic susceptibility might also contribute to the diverse findings; hopefully, genetic investigations will provide new insights.1 However, caution is advised; the low response rates among some ethnic groups may have biased the ethnic specific results.

The main limitation of our study, like any other prospective cohort set up to investigate diverse etiologic factors, was lack of detailed exposure information. However, our aim was to put to test the consistency of some of the prior observations from retrospective study design, and we were able to do so for some of the associations as described above. The small numbers of cases in some ethnic and NHL subtype categories resulted in a lack of statistical power. The different response rates by sex and ethnicity, especially the low response rate in Latinos, are of concern. However, it has been shown that our study sample is quite comparable in terms of education and marital status to persons living in the study area.19

In summary, this large prospective cohort supports a moderate NHL risk related to a history of blood transfusions and long-term antihistamine use. The association with transfusions was observed primarily in Japanese Americans and Latinos. Japanese Americans also experienced a higher NHL risk related to diabetes, whereas antihistamine use and allergies conferred a higher NHL risk only among Latinos. Given the current sample sizes, the ethnic- and subtype-specific findings will need to be reexamined after a longer follow-up.

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Table 1

Baseline characteristics of incident non-Hodgkin lymphoma cases and non-cases in the Multiethnic Cohort Study, 1993 – 2003[1]

Characteristic		Cases (N = 939)	Non-cases (N = 192,111)	p-value
Age	45–54	138 (15)	60,306 (31)	
	55–64	294 (31)	63,538 (33)	
	≥65	507 (54)	68,267 (35)	*< 0.0001*
Ethnicity	African American	156 (17)	33,102 (16)	
	Caucasian	270 (29)	47,118 (23)	
	Japanese American	242 (26)	54,516 (26)	
	Latino	212 (23)	43,575 (21)	
	Native Hawaiian	59 (6)	13,800 (7)	*0.04*
Education (years)	≤12	427 (46)	84,458 (45)	
	>12	503 (54)	105,452 (55)	*0.96*
BMI (kg/m^2)	<25	450 (49)	88,695 (47)	
	25–30	332 (35)	68,630 (35)	
	>30	141 (17)	32,261 (17)	*0.26*
Cigarette Smoking	Never	374 (40)	83,231 (44)	
	Former	418 (45)	75,574 (40)	
	Current	136 (15)	30,354 (16)	*0.01*
Alcohol (drinks/week)	<0.1	560 (43)	119,288 (45)	
	0.1–2.9	319 (31)	61,900 (33)	
	≥3	60 (26)	10,923 (22)	*0.05*

[1] Number and percentages are shown; number of subjects might not add up due to missing values

Table 2

Association of immune-related conditions and medications with non-Hodgkin lymphoma in the Multiethnic Cohort Study, 1993-2003

Immune Factors		Men (N[1] = 514)		Women (N[1] = 425)	
		N	HR (95% CI)[2]	N	HR (95% CI)[2]
Diabetes	No	442	1.00	373	1.00
	Yes	72	1.12 (0.87–1.44)	52	1.08 (0.80–1.46)
Blood transfusion	No	455	1.00	354	1.00
	Yes	59	**1.39 (1.06–1.84)**	71	1.22 (0.94–1.58)
Allergies	No	406	1.00	289	1.00
	Yes	108	1.10 (0.89–1.37)	136	1.10 (0.89–1.35)
Antihistamines (years)[3]	Never	428	1.00	309	1.00
	Past	34	1.03 (0.73–1.46)	49	1.16 (0.86–1.57)
	≤ 1	16	1.56 (0.95–2.57)	15	1.08 (0.64–1.81)
	≥ 2	12	0.72 (0.41–1.28)	22	1.11 (0.72–1.71)
	p-trend		*0.30*		*0.65*
	Current	28	1.28 (0.87–1.89)	39	1.26 (0.90–1.77)
	≤ 1	3	1.00 (0.32–3.12)	4	0.88 (0.33–2.37)
	2 – 5	5	0.63 (0.24–1.70)	14	1.42 (0.81–2.47)
	≥ 6	20	**1.88 (1.20–2.95)**	21	1.42 (0.91–2.21)
	p-trend		***0.02***		*0.07*
Aspirin (years)[3]	Never	269	1.00	259	1.00
	Past	98	1.17 (0.92–1.48)	66	0.79 (0.60–1.03)
	≤ 1	31	1.07 (0.74–1.57)	18	0.65 (0.40–1.07)
	2 – 5	23	1.10 (0.72–1.69)	17	0.86 (0.53–1.41)
	≥ 6	32	1.25 (0.86–1.82)	20	0.78 (0.49–1.23)
	p-trend		*0.23*		*0.29*
	Current	126	0.99 (0.79–1.22)	78	0.87 (0.68–1.13)
	≤ 1	24	1.08 (0.71–1.64)	14	0.84 (0.49–1.45)
	2 – 5	48	0.91 (0.67–1.25)	24	0.73 (0.47–1.13)
	≥ 6	51	1.01 (0.75–1.37)	39	1.06 (0.75–1.48)
	p-trend		*0.95*		*0.95*

Immune Factors		Men (N[1] = 514)		Women (N[1] = 425)	
		N	HR (95% CI)[2]	N	HR (95% CI)[2]
Other NSAIDs (excluding Aspirin) (years)[3]	Never	348	1.00	263	1.00
	Past	83	1.11 (0.87–1.41)	71	0.80 (0.61–1.05)
	≤ 1	36	1.01 (0.71–1.44)	36	0.88 (0.62–1.26)
	≥ 2	31	1.21 (0.84–1.75)	18	**0.61 (0.38–0.99)**
	p-trend		*0.32*		***0.04***
	Current	55	1.18 (0.88–1.58)	60	0.90 (0.67–1.20)
	≤ 1	17	1.29 (0.78–2.13)	14	0.74 (0.42–1.30)
	2 – 5	24	1.16 (0.76–1.75)	23	0.79 (0.51–1.22)
	≥ 6	13	1.25 (0.72–2.18)	20	1.46 (0.92–2.31)
	p-trend		*0.29*		*0.34*

[1] Number of NHL cases. May not add up to total (n = 939) due to missing values.

[2] Hazards ratios (HR) and 95% confidence intervals (CI) were adjusted for ethnicity (Caucasian as the reference group), education (≥12 *vs.* <12 years), BMI (overweight (25–29.9), obese (≥30) *vs.* normal), and alcohol intake (0.1–2.9 drinks/week, ≥3 drinks/week *vs.* <0.1 drinks/week).

[3] Regular use is defined as two times per week (for one month or longer)

Table 3

Association of immune-related conditions and medications with non-Hodgkin lymphoma by ethnicity in the Multiethnic Cohort Study, 1993–2003

Immune Factors		Caucasian (N[1] = 270)		African American (N[1] = 156)		Japanese American (N[1] = 242)		Latino (N[1] = 212)	
		N	HR (95% CI)[2]	N	HR (95% CI)[2]	N	HR (95% CI)[2]	N	HR (95% CI)[2]
Diabetes	No	254	1.00	132	1.00	200	1.00	173	1.00
	Yes	16	0.98 (0.59–1.65)	24	1.00 (0.64–1.56)	42	**1.55 (1.10–2.17)**	39	1.05 (0.74–1.51)
Blood transfusion	No	239	1.00	135	1.00	207	1.00	178	1.00
	Yes	31	0.97 (0.66–1.41)	21	1.06 (0.66–1.69)	35	**1.51 (1.06–2.17)**	34	**1.71 (1.17–2.49)**
Allergies	No	182	1.00	123	1.00	186	1.00	157	1.00
	Yes	88	1.17 (0.90–1.52)	33	0.86 (0.58–1.27)	56	1.02 (0.75–1.38)	55	**1.46 (1.07–2.00)**
Antihistamines[3]	Never	208	1.00	117	1.00	206	1.00	157	1.00
	Past	28	1.11 (0.74–1.64)	12	0.91 (0.50–1.64)	19	1.23 (0.77–1.97)	21	1.20 (0.76–1.89)
	Current	25	1.21 (0.78–1.86)	10	1.00 (0.52–1.91)	10	0.93 (0.49–1.75)	17	**1.80 (1.09–2.97)**
Aspirin[3]	Never	127	1.00	83	1.00	168	1.00	115	1.00
	Past	50	1.11 (0.80–1.55)	33	0.86 (0.57–1.29)	24	0.86 (0.56–1.32)	46	0.99 (0.70–1.41)
	Current	84	1.07 (0.81–1.42)	29	0.80 (0.52–1.22)	40	0.80 (0.56–1.13)	39	0.95 (0.66–1.37)
Other NSAIDs excluding Aspirin[3]	Never	175	1.00	86	1.00	196	1.00	122	1.00
	Past	39	0.92 (0.65–1.31)	33	0.85 (0.57–1.27)	25	1.03(0.68–1.56)	41	0.84 (0.58–1.19)
	Current	41	1.13 (0.80–1.59)	20	0.87 (0.53–1.42)	11	0.71 (0.39–1.31)	34	1.02 (0.68–1.52)

[1] Number of NHL cases. May not add up to total due to missing values.

[2] Hazards ratios (HR) and 95% confidence intervals (CI) were adjusted for sex (women vs. men), education (≥ 12 *vs.* < 12 years), BMI (overweight (25–29.9), obese (≥ 30) *vs.* normal (< 25)), and alcohol intake (0.1–2.9 drinks/week, ≥ 3 drinks/week *vs.* < 0.1 drinks/week).

[3] Regular use is defined as two times per week (for one month or longer)

Table 4

Association of immune-related conditions and medications with common subtypes of non-Hodgkin lymphoma in the Multiethnic Cohort Study, 1993–2003[1]

Immune Factors		DLBCL (N[2] = 310)		FL (N[2] = 152)		CLL/SLL (N[2] = 198)	
		N	HR (95% CI)[3]	N	HR (95% CI)[3]	N	HR (95% CI)[3]
Diabetes	No	259	1.00	132	1.00	173	1.00
	Yes	52	0.87 (0.62–1.21)	20	1.03 (0.59–1.81)	25	0.85 (0.52–1.38)
Blood transfusion	No	262	1.00	141	1.00	172	1.00
	Yes	49	**1.55 (1.10–2.17)**	11	1.21 (0.54–2.70)	26	1.09 (0.67–1.78)
Allergies	No	239	1.00	107	1.00	141	1.00
	Yes	72	1.01 (0.76–1.35)	45	0.97 (0.64–1.47)	57	0.91 (0.64–1.30)
Antihistamines[4]	Never	238	1.00	117	1.00	155	1.00
	Past	38	0.95 (0.65–1.38)	11	0.78 (0.39–1.55)	17	0.85 (0.48–1.53)
	Current	13	**2.34 (1.21–4.55)**	18	0.92 (0.49–1.72)	16	0.60 (0.32–1.13)
Aspirin[4]	Never	177	1.00	87	1.00	106	1.00
	Past	51	0.88 (0.62–1.24)	26	0.82 (0.50–1.35)	34	0.81 (0.53–1.23)
	Current	64	1.06 (0.77–1.45)	35	1.09 (0.70–1.71)	51	0.72 (0.50–1.06)
Other NSAIDs excluding Aspirin[4]	Never	207	1.00	100	1.00	128	1.00
	Past	39	0.92 (0.63–1.35)	30	**0.56 (0.34–0.90)**	37	0.93 (0.60–1.44)
	Current	40	0.73 (0.50–1.07)	13	0.96 (0.47–1.96)	23	1.41 (0.82–2.43)

[1] DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

[2] Number of NHL cases. May not add up to total due to missing values.

[3] Hazards ratios (HR) and 95% confidence intervals (CI) were adjusted for sex (women vs. men), ethnicity (African Americans, Japanese Americans, Latinos, and Native Hawaiians *vs.* Caucasians), education (≥ 12 *vs.* < 12 years), BMI (overweight (25–29.9), obese (≥ 30) vs. normal (< 25)), and alcohol intake (0.1–2.9 drinks/week, ≥ 3 drinks/week *vs.* < 0.1 drinks/week).

[4] Regular use is defined as two times per week (for one month or longer).