Etiologic heterogeneity among non-Hodgkin lymphoma subtypes

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Understanding patterns of etiologic commonality and heterogeneity for non-Hodgkin lymphomas may illuminate lymphomagenesis. We present the first systematic comparison of risks by lymphoma subtype for a broad range of putative risk factors in a population-based case-control study, including diffuse large B-cell (DLBCL; N = 416), follicular (N = 318), and marginal zone lymphomas (N = 106), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; N = 133). We required at least 2 of 3 analyses to support differences in risk: (1) polytomous logistic regression, (2) homogeneity tests, or (3) dichotomous logistic regression, analyzing all 7 possible pairwise comparisons among the subtypes, corresponding to various groupings by clinical behavior, genetic features, and differentiation. Late birth order and high body mass index ($\geq$ 35) kg/m^2) increased risk for DLBCL alone. Autoimmune conditions increased risk for marginal zone lymphoma alone. The tumor necrosis factor G-308A polymorphism (rs1800629) increased risks for both DLBCL and marginal zone lymphoma. Exposure to certain dietary heterocyclic amines from meat consumption increased risk for CLL/SLL alone. We observed no significant risk factors for follicular lymphoma alone. These data clearly support both etiologic commonality and heterogeneity for lymphoma subtypes, suggesting that immune dysfunction is of greater etiologic importance for DLBCL and marginal zone lymphoma than for CLL/SLL and follicular lymphoma. (Blood. 2008;112:5150-5160)

Introduction

Non-Hodgkin lymphoma (NHL) comprises a group of closely related yet heterogeneous diseases, each characterized by the malignant transformation of lymphoid cells but with distinctive morphologic, immunophenotypic, genetic, and clinical features.[1] The strongest known NHL risk factor is severe immunodeficiency, but the etiologies of most lymphomas remain unknown.[1] Other factors possibly associated with NHL include a variety of medical conditions (eg, autoimmune diseases), infections (eg, hepatitis C virus), occupations (eg, farming), occupational and environmental risk factors (eg, polychlorinated biphenyls [PCBs], pesticides, solvents, hair dyes), and inherited genetic variations, all with moderate to weak strength of association or inconsistency in the literature.[2,3]

Descriptive and analytic epidemiologic studies increasingly point to both heterogeneity and commonality in the etiology of lymphoma subtypes. Population registry data reveal striking differences in incidence among lymphoma subtypes by age, sex, race, and calendar year.[4-6] Analytic studies link specific infections to individual lymphoma subtypes, for example, human T-lymphotropic virus type I (HTLV-I) inducing adult T-cell leukemia/lymphoma[7]

and *Helicobacter pylori* inducing gastric mucosa-associated lymphoid tissue (MALT) NHL.[8] However, other viruses apparently affect lymphoma in general. For example, human immunodeficiency virus (HIV) infection markedly elevates risk for diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma, but it also weakly or moderately elevates risks for virtually all other types of lymphoma.[1,9] Hepatitis C virus similarly affects multiple NHL subtypes, but not all.[10] Emerging evidence from analytic studies reveals differences in genetic susceptibility by lymphoma subtype, with some commonality in risk among certain subtypes.[11,12]

Understanding patterns of commonality and heterogeneity in the etiology of NHL subtypes may illuminate mechanisms of lymphomagenesis. We therefore systematically examined risks by NHL subtype across a broad range of putative environmental and genetic risk factors among 1321 NHL cases and 1057 population controls in a US multicenter study. In our analyses, we consider both individual lymphoma subtypes and combinations of subtypes. The rationale for considering combinations of NHL subtypes is founded in similarities in the morphologic, immunophenotypic, genetic, and clinical features used to define each subtype, and in the

limited previous evidence of commonality in risk for some subtypes. Examples include the observations that (1) the t(14;18) chromosomal translocation, which has been suggested to have etiologic importance,[13-16] is present only in follicular lymphoma and DLBCL; (2) the postulated cells of origin for follicular lymphoma DLBCL and marginal zone lymphoma are germinal center or post–germinal center B cells, whereas the postulated cell of origin for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is not thought to have undergone germinal center transit[1]; and (3) DLBCL is typically more aggressive than follicular lymphoma, marginal zone lymphoma, or CLL/SLL.[1]

Methods

Study population

The study population, described in detail previously,[17] included 1321 NHL cases diagnosed during 1998-2000, 20 to 74 years of age, from 4 Surveillance Epidemiology and End Results (SEER) registries (Iowa, Detroit, Los Angeles, and Seattle). Known HIV-positive cases were excluded. Population controls (N = 1057) were selected from residents of the same 4 SEER areas using random digit dialing (< 65 years) or Medicare eligibility files (≥ 65 years), frequency matching to cases by age (within 5-year groups), sex, race, and SEER area. Controls with a history of NHL or known HIV infection were excluded. Participation (percentage interviewed among those approached) was 76% in cases and 52% in controls. Institutional Review Boards at the National Cancer Institute and each SEER center approved the study protocol. Written informed consent was obtained from participants before interview in accordance with the Declaration of Helsinki.

Histopathology

All cases were histologically confirmed by the local diagnosing pathologist and assigned codes from the *International Classification of Diseases for Oncology*, *2nd edition* (ICD-O-2) by the SEER registries.[18] We grouped cases into NHL subtypes according to the World Health Organization classification[1] using the International Lymphoma Epidemiology Consortium (InterLymph) guidelines.[19]

In the present analyses, we evaluated NHL subtypes with at least 100 cases in our study: DLBCL (ICD-O-2: 9680-84, 9688; N = 417), follicular lymphoma (9690-91, 9695-98; N = 318), marginal zone lymphoma (9710-11, 9715; N = 106), and CLL/SLL (9670, 9823; N = 133). Our study primarily included SLL (N = 116) rather than CLL (N = 17) cases. Additional histologic types excluded from this analysis were mantle cell lymphoma (9673; N = 50), lymphoplasmacytic lymphoma (9671; N = 28), Burkitt lymphoma/leukemia (9687, 9826; N = 13), mycosis fungoides/Sézary syndrome (9700-01; N = 26), peripheral T-cell lymphoma (9702-09, 9714; N = 55), and not otherwise specified/unknown (N = 175).

Exposure assessment

From the numerous suggested risk factors for NHL or NHL subtypes that we have investigated,[17,20-34] we included in the present analyses those risk factors that were associated with NHL or NHL subtypes in our study and for which there was some supporting evidence in the literature (Table S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

Questionnaire data and environmental samples. We used a split-sample questionnaire design, with core questions for all respondents and additional questions for either group A (all black and 50% of non-black participants) or group B (50% of non-black participants). Before the interview, participants were mailed questionnaires regarding residential and job history, and either family and medical history (group A) or diet and lifestyle (group B). During the home visit, the interviewer administered a computer-assisted personal interview (Table S1, interview topics). Dust samples from about half the participants' vacuum cleaners were collected to measure residential exposure to pesticides, PCBs, and other chemicals.[21,23]

DNA extraction and genotyping. We conducted genotyping for 1172 (89%) cases and 982 (93%) controls. As previously described,[34] DNA was extracted from blood clots, buffy coats, or buccal cell samples, and genotyping with quality control duplicates was conducted at the National Cancer Institute Core Genotyping Facility (Advanced Technology Center, Gaithersburg, MD; http://snp500cancer.nci.nih.gov).[35]

In the present analyses, we included genetic polymorphisms in 7 genes that were associated with NHL or NHL subtypes in our study (Table S1). Agreement for quality control samples was more than 99% for all assays. Successful genotyping was achieved for more than 98% of DNA samples, and the genotype frequencies among white, non-Hispanic controls were in Hardy-Weinberg equilibrium for all polymorphisms ($P > .05$). We also assessed *N*-acetyltransferase 1 (*NAT1*) genotypes and *N*-acetyltransferase 2 (*NAT2*) phenotypes as described previously.[36]

Statistical analysis

For each risk factor, odds ratios (ORs) and 95% confidence intervals (CIs) were derived from polytomous unconditional logistic regression models. P values for the linear trend were computed using ordinal variables.

To evaluate heterogeneity among the 4 NHL subtypes, we used 2 statistical approaches. First, we conducted a homogeneity test in the polytomous model, testing the null hypothesis that the regression coefficient for each risk factor was the same for all 4 subtypes. Values of P less than .05 were considered to provide evidence of heterogeneity. The test for homogeneity has the greatest power to detect risk differences when the risks for the subtypes all vary slightly from one another. Second, we analyzed all 7 possible case-case pairwise comparisons using dichotomous logistic regression models (controls were excluded): (1) DLBCL versus follicular lymphoma, marginal zone lymphoma, and CLL/SLL; (2) follicular lymphoma versus DLBCL, marginal zone lymphoma, and CLL/SLL; (3) marginal zone lymphoma versus DLBCL, follicular lymphoma, and CLL/SLL; (4) CLL/SLL versus DLBCL, follicular lymphoma, and marginal zone lymphoma; (5) DLBCL and follicular lymphoma versus marginal zone lymphoma and CLL/SLL; (6) DLBCL and marginal zone lymphoma versus follicular lymphoma and CLL/SLL; and (7) DLBCL and CLL/SLL versus follicular lymphoma and marginal zone lymphoma. For each of the 7 models, we computed a Wald χ^2 P value, testing the null hypothesis that the particular risk factor does not discriminate between the 2 disease groups modeled. To account for the 7 comparisons within the pairwise analysis, we applied a Bonferroni correction and considered P values less than .007 to be statistically significant. In contrast to the test for homogeneity, the pairwise analysis has the greatest power to detect risk differences when the risk for one disease group is distinct from the other(s). For risk factors with more than 2 categories, we used the ordinal variable for the homogeneity test and pairwise analysis.

All models included sex, age (< 45, 45-64, 65+ years), race (non-Hispanic white, black, other), SEER area, and education (< 12, 12-15, 16+ years) as covariates. We excluded one DLBCL case from all analyses because of missing data on education. Statistical analyses were performed using the SAS system, version 9.1 (SAS Institute, Cary, NC).

Results

The study population was predominantly white and non-Hispanic (Table S2). The median ages at diagnosis for NHL cases and at interview for controls were 58 and 61 years, respectively. Compared with controls, DLBCL and follicular lymphoma cases were younger whereas CLL/SLL cases were older. The control group had a higher proportion of blacks than any of the NHL subtype case groups.

We highlight herein those risk factors for which we inferred etiologic heterogeneity among the NHL subtypes, as evidenced by at least 2 of 3 analyses supporting differences in risk (magnitude of

Table 1. Associations between family and medical history risk factors and non-Hodgkin lymphoma, by lymphoma subtype

Exposure	Controls, N†	All NHL combined*		DLBCL		Follicular lymphoma		Marginal zone lymphoma		CLL/SLL		P homo-geneity	Lowest P value from pairwise analysis§
		N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡		
Family history of NHL													
No	969	1185	1.0 (reference)	370	1.0 (reference)	284	1.0 (reference)	98	1.0 (reference)	121	1.0 (reference)		
Yes	32	56	1.3 (0.8, 2.0)	18	1.3 (0.7, 2.3)	16	1.5 (0.8, 2.8)	4	1.4 (0.5, 4.1)	3	0.6 (0.2, 2.0)	.5	CLL/SLL vs DLBCL, FL, MZ; P = .2
Autoimmune conditions													
No	996	1225	1.0 (reference)	392	1.0 (reference)	298	1.0 (reference)	90	1.0 (reference)	126	1.0 (reference)		
Yes	61	95	1.3 (0.9, 1.9)	24	1.0 (0.6, 1.7)	20	1.1 (0.7, 1.9)	16	2.9 (1.6, 5.4)	7	0.9 (0.4, 2.0)	.01	MZ vs DLBCL, FL, CLL/SLL; P > .001
Asthma													
No	523	684	1.0 (reference)	202	1.0 (reference)	151	1.0 (reference)	61	1.0 (reference)	76	1.0 (reference)		
Yes	66	74	0.9 (0.6, 1.3)	21	0.9 (0.5, 1.5)	21	1.2 (0.7, 2.0)	4	0.4 (0.2, 1.3)	5	0.6 (0.2, 1.6)	.3	MZ vs DLBCL, FL, CLL/SLL; P = .2
Allergy													
No	173	225	1.0 (reference)	83	1.0 (reference)	60	1.0 (reference)	17	1.0 (reference)	22	1.0 (reference)		
Yes	289	326	0.9 (0.7, 1.2)	106	0.8 (0.5, 1.1)	84	0.8 (0.6, 1.3)	21	0.8 (0.4, 1.6)	29	0.9 (0.5, 1.7)	.9	DLBCL, FL vs MZ, CLL/SLL; P = .1
Surgeries, total no.													
0-6	112	97	1.0 (reference)	29	1.0 (reference)	17	1.0 (reference)	7	1.0 (reference)	11	1.0 (reference)		
7-12	123	148	1.4 (1.0, 2.1)	44	1.5 (0.9, 2.7)	28	1.6 (0.8, 3.1)	10	1.3 (0.5, 3.5)	11	0.8 (0.3, 2.0)		
13-17	118	170	1.6 (1.1, 2.3)	56	1.8 (1.0, 3.2)	38	2.0 (1.0, 4.0)	17	2.1 (0.8, 5.5)	19	1.1 (0.5, 2.5)		
18-25	114	166	1.6 (1.1, 2.4)	43	1.6 (0.9, 2.8)	46	2.5 (1.3, 4.9)	12	1.5 (0.6, 4.3)	23	1.4 (0.6, 3.2)		
26+	122	177	1.6 (1.1, 2.4)	51	1.7 (1.0, 3.1)	43	2.1 (1.1, 4.2)	19	2.2 (0.8, 6.0)	17	0.9 (0.4, 2.1)		
P trend			.1		.1		.01		.1		.7	.5	DLBCL, FL vs MZ, CLL/SLL; P = .02
Transfusion													
No	876	1108	1.0 (reference)	352	1.0 (reference)	265	1.0 (reference)	83	1.0 (reference)	117	1.0 (reference)		
Yes	170	199	1.0 (0.8, 1.3)	58	1.0 (0.7, 1.4)	50	1.1 (0.7, 1.5)	22	1.4 (0.9, 2.4)	16	0.7 (0.4, 1.2)	.2	CLL/SLL vs DLBCL, FL, MZ; P = .1
Birth order													
First/middle	327	402	1.0 (reference)	104	1.0 (reference)	100	1.0 (reference)	35	1.0 (reference)	43	1.0 (reference)		
Last	105	173	1.3 (1.0, 1.8)	64	1.9 (1.2, 2.8)	36	1.1 (0.7, 1.7)	13	1.2 (0.6, 2.3)	18	1.3 (0.7, 2.4)	.2	DLBCL vs FL, MZ, CLL/SLL; P = .003

CLL/SLL indicates chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; and NHL, non-Hodgkin lymphoma.

*Includes all NHL cases in the study, regardless of histologic subtype (N = 1320, excludes one DLBCL case resulting from missing data on education).

†Counts may not sum to the total because of missing data. For some exposures, a split-sample design was used so that only approximately 50% of participants were expected to provide information.

‡Odds ratios (95% CIs) estimated using polytomous logistic regression models, adjusted for age, sex, race, study center, and education.

§To account for the seven comparisons within the pairwise analysis, we applied a Bonferroni correction and considered P < .007 to be statistically significant.

the OR in comparison with other subtypes, P homogeneity $< .05$, or lowest P from the pairwise analysis $< .007$; Tables 1-4). The full results of the pairwise analysis for all environmental and genetic risk factors are presented in Table S3.

Risks for a single NHL subtype

DLBCL. Late birth order increased the risk of DLBCL more than other NHL subtypes (P homogeneity $= .2$; DLBCL vs other subtypes, pairwise analysis $P = .003$; Table 1). Among people with at least one sibling, being last born elevated risk of DLBCL 1.9-fold (95% CI, 1.2-2.8). High BMI ($35+$ vs < 25 kg/m^2, OR $= 1.7$, 95% CI, 1.1-2.5) also increased the risk of DLBCL but not of the other NHL subtypes (P homogeneity $= .008$; pairwise analysis $P = .01$; Table 2).

Marginal zone lymphoma. A reported history of an autoimmune condition increased risk of marginal zone lymphoma (OR $= 2.9$; 95% CI, 1.6-5.4) but not of other NHL subtypes (P homogeneity $= .01$; marginal zone vs others, pairwise analysis $P < .001$; Table 1). Risk estimates were also higher for marginal zone lymphoma than for other NHL subtypes for patients in the highest tertile of PCB180 levels in carpet dust (OR $= 3.0$; 95% CI, 1.5-6.1; P homogeneity $= .04$; pairwise analysis $P = .01$; Table 3).

CLL/SLL. Intake of heterocyclic amines formed when meat is cooked well done by high-temperature cooking techniques increased risk of CLL/SLL but not of other NHL subtypes (Table 2). High levels of 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx) elevated CLL/SLL risk 3-fold (OR $= 3.0$; 95% CI, 1.5-5.9; P homogeneity $< .001$; CLL/SLL vs others, pairwise analysis $P < .001$). Similar results were observed for analyses of 2-amino-3,4,8-trimethylimidazo(4,5-f)quinoxaline (DiMeIQx), another heterocyclic amine, and a continuous measure of total mutagenic potential, derived from a database (http://charred.cancer.gov/) constructed from meat cooking methods and the Ames *Salmonella* test[37] (data not shown).

Follicular lymphoma. Using the criterion that at least 2 of 3 analyses must support differences in risk to infer etiologic heterogeneity, risk estimates were not significantly different for follicular lymphoma compared with other NHL subtypes for any of the risk factors we evaluated. The pairwise analysis did suggest that several risk factors were more pronounced for follicular lymphoma than other NHL subtypes, including height, use of permanent hair dyes before 1980, the variant allele of the *MGMT* I143V polymorphism, and *NAT2* acetylation phenotype (follicular lymphoma vs others, pairwise analysis $P = .05, .07, .05,$ and $.02$, respectively), but none was at the Bonferroni correction level of less than .007 (Tables 2-4). In addition, the ORs and test for homogeneity did not clearly support these findings.

Risks for multiple NHL subtypes

DLBCL and marginal zone lymphoma. Persons possessing the variant allele of the *TNF* G-308A polymorphism had significantly higher risk estimates for DLBCL and marginal zone lymphoma than for follicular lymphoma or CLL/SLL (P homogeneity $= .04$; pairwise analysis $P = .002$; DLBCL OR$_{GA/AA} = 1.6$; 95% CI, 1.2-2.1; marginal zone lymphoma OR$_{GA/AA} = 1.5$; 95% CI, 0.9-2.4; Table 4). Risk estimates for residential termite treatment before 1988 and increasingly dark eye color were also higher for DLBCL and marginal zone lymphoma than for follicular lymphoma and CLL/SLL, although the pairwise analysis P value was not statistically significant after the Bonferroni correction (termite treatment $P = .009$, eye color $P = .01$; Table 3).

DLBCL and CLL/SLL. Persons consuming higher levels of dietary vitamin B$_6$ had significantly lower risk estimates for DLBCL and CLL/SLL than for follicular or marginal zone lymphoma (P homogeneity $= .2$; pairwise analysis $P = .002$; DLBCL OR $= 0.6$; 95% CI, 0.4-0.8; CLL/SLL OR $= 0.5$; 95% CI, 0.3-1.0; Table 2).

All NHL subtypes. We observed no clear pattern of significant heterogeneity among individual NHL subtypes or combinations of subtypes for the remaining environmental and genetic risk factors evaluated (Tables 1-4). Risk estimates were strikingly consistent among all 4 NHL subtypes for decreased risk with ethanol consumption, exposure to sunlight, dietary lutein/zeaxanthin, and consumption of cruciferous vegetables, and increased risk with the genetic polymorphisms *FCGR2A* R165H, *RAG1* K820R, and *XRCC1* R194W.

Discussion

We present here the first broad evaluation of risk factor patterns for the 4 most common NHL subtypes. Our analysis included a wide range of putative environmental and genetic risk factors. Our data strongly support the growing body of evidence that there is both distinctiveness and commonality in the etiology of NHL subtypes. Although all lymphomas fundamentally result from immune dysfunction (including immune dysregulation, immunosuppression, immune stimulation, or inflammation), and all cancers fundamentally result from genomic dysregulation, these data also suggest that immune dysfunction is of greater etiologic importance for DLBCL and marginal zone lymphoma than for CLL/SLL and follicular lymphoma.

Understanding of etiologic heterogeneity advances as disease subtypes are increasingly recognized by various characteristics, such as histology, site, or molecular features. However, studies that consider disease subtype require formal statistical tests to evaluate the likelihood that variation in risk estimates arise by chance. Because simple case-case comparisons are not sufficient for testing etiologic heterogeneity when there are greater than 2 disease subtypes, we used 3 methods to evaluate patterns of risk among the 4 most common NHL subtypes: magnitude of the ORs, test for homogeneity across the 4 subtypes, and analysis of all possible pairwise comparisons.

The combination of results from all 3 of our analyses revealed a fairly consistent portrait of etiologic heterogeneity among NHL subtypes. Specifically, our data were suggestive that 7 risk factors (the *TNF* G-308A polymorphism, reported history of autoimmune conditions, late birth order, obesity, increasingly dark eye color, residential termite treatment before 1988, and exposure to PCB180) increase risk for DLBCL and/or marginal zone lymphoma but not follicular lymphoma or CLL/SLL. We hypothesize that these risk factors contribute to lymphomagenesis via immune dysfunction. The *TNF* G-308A polymorphism and history of autoimmune conditions, both established risk factors for NHL, are the strongest surrogates for immune dysfunction. The *TNF* G-308A polymorphism was shown to increase risk of DLBCL but not follicular lymphoma in a pooled analysis of 8 studies, including ours.[11] Risk estimates for marginal zone lymphoma have not been published in studies other than ours.[34] *TNF* encodes an immunoregulatory cytokine (TNF-α) that mediates inflammation by activating the nuclear factor-κB pathway.[38] The variant allele of the G-308A polymorphism may be associated with higher levels of TNF-α,

Table 2. Associations between anthropometric, lifestyle, and dietary risk factors and non-Hodgkin lymphoma, by lymphoma subtype

Exposure	Controls, N†	All NHL combined*		DLBCL		Follicular lymphoma		Marginal zone lymphoma		CLL/SLL		P homogeneity	Lowest P value from pairwise analysis§
		N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡		
BMI, kg/m²													
< 25	305	398	1.0 (reference)	117	1.0 (reference)	104	1.0 (reference)	29	1.0 (reference)	50	1.0 (reference)		
25-< 35	578	688	0.9 (0.8, 1.1)	215	1.0 (0.7, 1.3)	161	0.9 (0.6, 1.1)	60	1.1 (0.7, 1.8)	66	0.6 (0.4, 0.9)		
35+	94	132	1.1 (0.8, 1.5)	57	1.7 (1.1, 2.5)	23	0.7 (0.4, 1.2)	9	1.0 (0.5, 2.3)	12	0.7 (0.4, 1.4)		
P trend			.4		.06		.2		.8		.06	.008	DLBCL vs FL, MZ, CLL/SLL; P = .01
Height, in													
< 65	283	308	1.0 (reference)	93	1.0 (reference)	71	1.0 (reference)	29	1.0 (reference)	29	1.0 (reference)		
65-70	472	602	1.2 (0.9, 1.5)	186	1.1 (0.8, 1.6)	142	1.4 (1.0, 2.0)	50	1.2 (0.7, 2.1)	69	1.3 (0.7, 2.2)		
71+	232	319	1.3 (0.9, 1.8)	112	1.3 (0.8, 2.1)	76	1.8 (1.1, 2.9)	19	1.1 (0.5, 2.4)	33	1.1 (0.6, 2.3)		
P trend			.3		.2		.02		.8		.9	.5	DLBCL, FL vs MZ, CLL/SLL; P = .04
Cigarette smoking‖													
Never	184	219	1.0 (reference)	83	1.0 (reference)	56	1.0 (reference)	15	1.0 (reference)	23	1.0 (reference)		
Former	161	161	0.9 (0.6, 1.2)	54	0.8 (0.5, 1.2)	37	0.9 (0.5, 1.4)	10	0.8 (0.3, 1.9)	18	0.8 (0.4, 1.6)		
Current	61	89	1.1 (0.7, 1.6)	29	1.0 (0.6, 1.6)	24	1.1 (0.6, 2.1)	6	1.1 (0.4, 3.0)	9	1.1 (0.5, 2.6)	.9	DLBCL, MZ vs FL, CLL/SLL; P = .5
Ethanol													
Nondrinkers	156	236	1.0 (reference)	83	1.0 (reference)	65	1.0 (reference)	15	1.0 (reference)	24	1.0 (reference)		
Ever drinkers	233	228	0.6 (0.4, 0.7)	83	0.6 (0.4, 0.8)	52	0.5 (0.3, 0.7)	16	0.6 (0.3, 1.4)	24	0.6 (0.3, 1.2)	.8	DLBCL, FL vs MZ, CLL/SLL; P = .002
Dietary vitamin B6, mg/1000 kcal													
0.97	197	286	1.0 (reference)	110	1.0 (reference)	68	1.0 (reference)	17	1.0 (reference)	32	1.0 (reference)		
0.97+	192	178	0.7 (0.5, 0.9)	56	0.6 (0.4, 0.8)	49	0.8 (0.5, 1.3)	14	1.1 (0.5, 2.3)	16	0.5 (0.3, 1.0)	.2	DLBCL, CLL/SLL vs FL, MZ; P = .002
Dietary lutein and zeaxanthin, µg/d													
< 1915	195	274	1.0 (reference)	99	1.0 (reference)	70	1.0 (reference)	20	1.0 (reference)	31	1.0 (reference)		
1915+	194	190	0.8 (0.6, 1.1)	67	0.8 (0.5, 1.2)	47	0.8 (0.5, 1.3)	11	0.6 (0.3, 1.3)	17	0.6 (0.3, 1.2)	.8	CLL/SLL vs DLBCL, FL, MZ; P = .2
Dietary zinc, mg/d													
< 16	196	269	1.0 (reference)	96	1.0 (reference)	67	1.0 (reference)	16	1.0 (reference)	29	1.0 (reference)		
16+	193	195	0.8 (0.6, 1.0)	70	0.8 (0.5, 1.1)	50	0.8 (0.5, 1.2)	15	1.1 (0.5, 2.3)	19	0.6 (0.3, 1.1)	.7	DLBCL, CLL/SLL vs FL, MZ; P = .1
Green leafy vegetables, servings/wk													
< 4	195	297	1.0 (reference)	116	1.0 (reference)	74	1.0 (reference)	21	1.0 (reference)	29	1.0 (reference)		
4+	194	167	0.6 (0.5, 0.8)	50	0.5 (0.3, 0.7)	43	0.6 (0.4, 1.0)	10	0.4 (0.2, 1.0)	19	0.8 (0.4, 1.5)	.5	DLBCL, MZ vs FL, CLL/SLL; P < .001
Cruciferous vegetables, servings/wk													
< 2	196	269	1.0 (reference)	96	1.0 (reference)	66	1.0 (reference)	20	1.0 (reference)	29	1.0 (reference)		
2+	193	195	0.8 (0.6, 1.1)	70	0.8 (0.6, 1.2)	51	0.9 (0.6, 1.3)	11	0.6 (0.3, 1.4)	19	0.8 (0.4, 1.4)	.9	MZ vs DLBCL, FL, CLL/SLL; P = .4
Dietary MelQx, ng/d													
< 33.4	235	262	1.0 (reference)	86	1.0 (reference)	77	1.0 (reference)	20	1.0 (reference)	15	1.0 (reference)		
33.4+	154	202	1.0 (0.8, 1.4)	80	1.2 (0.8, 1.8)	40	0.7 (0.4, 1.1)	11	0.8 (0.3, 1.7)	33	3.0 (1.5, 5.9)	< .001	CLL/SLL vs DLBCL, FL, MZ; P < .001
Dietary PhIP, ng/d													
< 105.6	234	279	1.0 (reference)	102	1.0 (reference)	74	1.0 (reference)	18	1.0 (reference)	25	1.0 (reference)		
105.6+	155	185	0.8 (0.6, 1.1)	64	0.7 (0.5, 1.1)	43	0.7 (0.4, 1.1)	13	0.9 (0.4, 2.0)	23	1.2 (0.6, 2.3)	.4	DLBCL, FL vs MZ, CLL/SLL; P = .03

BMI indicates body mass index; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZ, marginal zone lymphoma; MelQx, 2-amino-3,8-dimethylimidazo-[4,5-f]quinoxaline; NHL, non-Hodgkin lymphoma; and PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine.

*Includes all NHL cases in the study, regardless of histologic subtype (N = 1320, excludes one DLBCL case resulting from missing data on education).

†Counts may not sum to the total because of missing data. For some exposures (Table 1), a split-sample design was used so that only approximately 50% of participants were expected to provide information.

‡Odds ratios (95% CIs) estimated using polytomous logistic regression models, adjusted for age, sex, race, study center, and education.

§To account for the seven comparisons within the pairwise analysis, we applied a Bonferroni correction and considered P < .007 to be statistically significant.

‖For cigarette smoking, the homogeneity test and pairwise analysis were conducted comparing current smokers to never smokers; former smokers were excluded from these analyses.

Table 3. Associations between sun exposure and environmental risk factors and non-Hodgkin lymphoma, by lymphoma subtype

Exposure	Controls, N†	All NHL combined* N†	All NHL combined* OR (95% CI)‡	DLBCL N†	DLBCL OR (95% CI)‡	Follicular lymphoma N†	Follicular lymphoma OR (95% CI)‡	Marginal zone lymphoma N†	Marginal zone lymphoma OR (95% CI)‡	CLL/SLL N†	CLL/SLL OR (95% CI)‡	P homogeneity	Lowest P value from pairwise analysis§
Sun in teens, h/wk													
< 7	46	62	1.0 (reference)	23	1.0 (reference)	18	1.0 (reference)	4	1.0 (reference)	5	1.0 (reference)		
7–< 14	68	89	1.0 (0.6, 1.7)	26	0.8 (0.4, 1.6)	24	1.0 (0.5, 2.0)	7	1.1 (0.3, 4.1)	4	0.5 (0.1, 2.2)		
14–< 28	155	185	0.8 (0.5, 1.3)	67	0.8 (0.4, 1.4)	44	0.7 (0.4, 1.3)	13	0.8 (0.2, 2.6)	13	0.7 (0.2, 2.2)		
28+	187	211	0.8 (0.5, 1.2)	73	0.7 (0.4, 1.2)	56	0.7 (0.4, 1.4)	14	0.7 (0.2, 2.3)	28	1.2 (0.4, 3.5)		
P trend			.5		.2		.3		.3		.3	.3	CLL/SLL vs DLBCL, FL, MZ; P = .1
Sun in past 10 y, h/wk													
< 7	159	216	1.0 (reference)	71	1.0 (reference)	58	1.0 (reference)	14	1.0 (reference)	18	1.0 (reference)		
7–< 14	126	145	0.8 (0.6, 1.2)	43	0.7 (0.5, 1.2)	43	0.9 (0.6, 1.4)	12	1.0 (0.5, 2.4)	12	0.8 (0.4, 1.7)		
14–< 28	123	131	0.7 (0.5, 1.0)	44	0.7 (0.5, 1.2)	29	0.6 (0.4, 1.0)	9	0.7 (0.3, 1.8)	18	1.1 (0.6, 2.4)		
28+	51	59	0.7 (0.4, 1.1)	31	1.1 (0.6, 1.9)	14	0.6 (0.3, 1.2)	3	0.5 (0.1, 1.9)	3	0.4 (0.1, 1.4)		
P trend			.3		.7		.05		.3		.5	.5	FL vs DLBCL, MZ, CLL/SLL; P = .1
Eye color													
Green/blue-green	64	59	1.0 (reference)	17	1.0 (reference)	19	1.0 (reference)	2	1.0 (reference)	8	1.0 (reference)		
Blue	180	188	1.3 (0.8, 2.0)	71	1.7 (0.9, 3.1)	53	1.2 (0.7, 2.3)	10	1.8 (0.4, 8.7)	15	0.6 (0.2, 1.6)		
Hazel	84	96	1.4 (0.9, 2.2)	28	1.4 (0.7, 2.8)	29	1.4 (0.7, 2.7)	9	3.7 (0.8, 18.0)	13	1.3 (0.5, 3.2)		
Light brown	41	50	1.7 (0.9, 2.9)	20	2.4 (1.1, 5.4)	11	1.3 (0.5, 3.0)	3	2.1 (0.3, 13.5)	3	0.7 (0.2, 2.8)		
Dark brown	93	158	2.2 (1.4, 3.4)	53	2.6 (1.3, 4.9)	32	1.4 (0.7, 2.8)	14	4.7 (1.0, 22.4)	12	1.1 (0.4, 2.8)		
P trend			.009		.005		.3		.01		.4	.2	DLBCL, MZ vs FL, CLL/SLL; P = .01
Termite treatment before 1988													
Not treated before 1988	717	852	1.0 (reference)	261	1.0 (reference)	218	1.0 (reference)	59	1.0 (reference)	96	1.0 (reference)		
None or DK treated	176	244	1.1 (0.9, 1.4)	80	1.1 (0.8, 1.6)	59	1.0 (0.7, 1.5)	21	1.4 (0.8, 2.4)	20	1.0 (0.6, 1.6)		
1+ homes treated before 1988	162	220	1.3 (1.0, 1.6)	74	1.6 (1.1, 2.3)	41	1.0 (0.7, 1.5)	26	1.8 (1.0, 3.1)	17	0.9 (0.5, 1.6)	.1	DLBCL, MZ vs FL, CLL/SLL; P = .009
Alpha-chlordane (dust), ng/g													
ND	317	409	1.0 (reference)	128	1.0 (reference)	99	1.0 (reference)	29	1.0 (reference)	50	1.0 (reference)		
20.8–60.1	98	116	0.9 (0.7, 1.3)	31	0.9 (0.5, 1.4)	26	0.9 (0.6, 1.5)	16	1.5 (0.8, 3.0)	10	0.7 (0.3, 1.4)		
60.3–5870	98	157	1.3 (1.0, 1.9)	50	1.5 (1.0, 2.3)	34	1.3 (0.8, 2.1)	16	1.5 (0.7, 3.1)	9	0.6 (0.3, 1.3)		
P trend			.07		.9		.06		.004		.9	.1	CLL/SLL vs DLBCL, FL, MZ; P = .04
PCB180 (dust), ng/g													
< 20.8	395	499	1.0 (reference)	162	1.0 (reference)	115	1.0 (reference)	41	1.0 (reference)	52	1.0 (reference)		
20.8–44.3	60	92	1.3 (0.9, 1.9)	27	1.2 (0.7, 2.0)	20	1.3 (0.7, 2.2)	6	1.2 (0.5, 3.1)	11	1.3 (0.6, 2.8)		
44.4+	58	91	1.4 (1.0, 2.0)	20	0.9 (0.5, 1.6)	24	1.6 (1.0, 2.8)	14	3.0 (1.5, 6.1)	6	0.8 (0.3, 2.0)		
P trend			.07		.9		.06		.004		.9	.04	MZ vs DLBCL, FL, CLL/SLL; P = .01
Pre-1980 hair dye use													
Never	98	101	1.0 (reference)	34	1.0 (reference)	24	1.0 (reference)	13	1.0 (reference)	10	1.0 (reference)		
Permanent	123	169	1.3 (0.9, 1.9)	42	0.9 (0.5, 1.7)	49	1.9 (1.0, 3.4)	16	0.9 (0.4, 2.0)	18	1.5 (0.6, 3.5)	.2	FL vs DLBCL, MZ, CLL/SLL; P = .07

CLL/SLL indicates chronic lymphocytic leukemia/small lymphocytic lymphoma; DK, don't know; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZ, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; and PCB180, polychlorinated biphenyl congener 180.

*Includes all NHL cases in the study, regardless of histologic subtype (N = 1320, excludes one DLBCL case resulting from missing data on education).

†Counts may not sum to the total because of missing data. For some exposures (Table 1), a split-sample design was used so that only approximately 50% of participants were expected to provide information.

‡Odds ratios (95% CIs) estimated using polytomous logistic regression models, adjusted for age, sex, race, study center, and education.

§To account for the seven comparisons within the pairwise analysis, we applied a Bonferroni correction and considered P < .007 to be statistically significant.

Table 4. Associations between genetic polymorphisms and non-Hodgkin lymphoma, by lymphoma subtype

Exposure	Controls, N†	All NHL combined* N†	All NHL combined* OR (95% CI)‡	DLBCL N†	DLBCL OR (95% CI)‡	Follicular lymphoma N†	Follicular lymphoma OR (95% CI)‡	Marginal zone lymphoma N†	Marginal zone lymphoma OR (95% CI)‡	CLL/SLL N†	CLL/SLL OR (95% CI)‡	P homogeneity	Lowest P value from pairwise analysis§
TNF G-308A, rs1800629													
GG	696	799	1.0 (reference)	236	1.0 (reference)	196	1.0 (reference)	64	1.0 (reference)	94	1.0 (reference)		
GA	207	298	1.3 (1.0, 1.6)	102	1.5 (1.1, 2.0)	67	1.1 (0.8, 1.6)	23	1.3 (0.8, 2.2)	23	0.8 (0.5, 1.3)		
AA	18	38	2.0 (1.1, 3.6)	16	2.9 (1.4, 5.8)	7	1.4 (0.6, 3.5)	5	3.6 (1.3, 10.2)	1	0.4 (0.1, 3.1)		
P trend			.002		<.001		.3		.03		.2		
GA+AA	225	336	1.3 (1.1, 1.6)	118	1.6 (1.2, 2.1)	74	1.2 (0.9, 1.6)	28	1.5 (0.9, 2.4)	24	0.8 (0.5, 1.2)	.04	DLBCL, MZ vs FL, CLL/SLL; P = .002
IL10 T-3575A, rs1800890													
TT	379	446	1.0 (reference)	134	1.0 (reference)	98	1.0 (reference)	44	1.0 (reference)	49	1.0 (reference)		
TA	401	518	1.1 (0.9, 1.4)	165	1.2 (0.9, 1.6)	129	1.2 (0.9, 1.7)	38	0.9 (0.5, 1.4)	45	0.9 (0.6, 1.3)		
AA	130	164	1.1 (0.8, 1.4)	54	1.1 (0.8, 1.7)	41	1.2 (0.8, 1.8)	10	0.7 (0.4, 1.5)	23	1.3 (0.7, 2.2)		
P trend			.4		.3		.3		.3		.6		
TA+AA	531	682	1.1 (0.9, 1.3)	219	1.2 (0.9, 1.5)	170	1.2 (0.9, 1.6)	48	0.8 (0.5, 1.3)	68	1.0 (0.6, 1.4)	.3	DLBCL, FL vs MZ, CLL/SLL; P = .08
FCGR2A Ex4-120G>A, R165H, rs1801274													
GG	242	237	1.0 (reference)	78	1.0 (reference)	51	1.0 (reference)	19	1.0 (reference)	23	1.0 (reference)		
AG	430	539	1.3 (1.0, 1.6)	164	1.2 (0.8, 1.6)	135	1.4 (1.0, 2.1)	40	1.2 (0.7, 2.1)	60	1.5 (0.9, 2.4)		
AA	227	335	1.5 (1.1, 1.9)	102	1.3 (0.9, 1.9)	79	1.5 (1.0, 2.3)	31	1.7 (0.9, 3.1)	32	1.5 (0.8, 2.7)		
P trend			.004		.1		.04		.08		.2		
AG+AA	657	874	1.3 (1.1, 1.6)	266	1.2 (0.9, 1.6)	214	1.5 (1.0, 2.1)	71	1.4 (0.8, 2.3)	92	1.5 (0.9, 2.4)	.8	FL vs DLBCL, MZ, CLL/SLL; P = .09
RAG1 Ex2+2473A>G, K820R, rs2227973													
AA	695	810	1.0 (reference)	258	1.0 (reference)	190	1.0 (reference)	59	1.0 (reference)	86	1.0 (reference)		
AG	179	246	1.1 (0.9, 1.4)	73	1.1 (0.8, 1.5)	57	1.2 (0.8, 1.7)	29	1.7 (1.1, 2.8)	26	1.2 (0.8, 2.0)		
GG	17	35	1.8 (1.0, 3.4)	7	1.4 (0.5, 3.4)	10	2.8 (1.2, 6.4)	4	2.0 (0.6, 6.5)	3	1.8 (0.5, 6.7)		
P trend			.05		.4		.05		.02		.3		
AG+GG	196	281	1.2 (1.0, 1.5)	80	1.1 (0.8, 1.5)	67	1.3 (0.9, 1.8)	33	1.8 (1.1, 2.8)	29	1.3 (0.8, 2.0)	.3	MZ vs DLBCL, FL, CLL/SLL; P = .03
LIG4 Ex3+54C>T, T9I, rs1805388													
CC	611	788	1.0 (reference)	247	1.0 (reference)	197	1.0 (reference)	67	1.0 (reference)	70	1.0 (reference)		
CT	267	299	0.9 (0.7, 1.0)	89	0.8 (0.6, 1.1)	67	0.8 (0.6, 1.0)	23	0.8 (0.5, 1.3)	39	1.3 (0.8, 2.0)		
TT	26	18	0.5 (0.3, 1.0)	6	0.6 (0.2, 1.4)	2	0.2 (0.1, 0.9)	0	~	5	1.7 (0.6, 4.6)		
P trend			.02		.07		.01		.09		.1		
CT+TT	293	317	0.8 (0.7, 1.0)	95	0.8 (0.6, 1.0)	69	0.7 (0.5, 1.0)	23	0.7 (0.4, 1.2)	44	1.3 (0.9, 2.0)	.06	DLBCL, FL vs MZ, CLL/SLL; P = .02
XRCC1 Ex6-22C>T, R194W, rs1799782													
CC	782	911	1.0 (reference)	287	1.0 (reference)	217	1.0 (reference)	72	1.0 (reference)	91	1.0 (reference)		
CT	112	186	1.4 (1.1, 1.8)	52	1.2 (0.9, 1.8)	41	1.3 (0.9, 1.9)	19	1.8 (1.0, 3.0)	24	2.0 (1.2, 3.3)		
TT	7	9	1.2 (0.4, 3.2)	4	1.7 (0.5, 6.0)	4	2.6 (0.7, 9.0)	0	~	0	~		
P trend			.01		.2		.07		.2		.03		
CT+TT	119	195	1.4 (1.1, 1.8)	56	1.3 (0.9, 1.8)	45	1.4 (0.9, 2.0)	19	1.6 (0.9, 2.8)	24	1.9 (1.1, 3.1)	.5	CLL/SLL vs DLBCL, FL, MZ; P = .06

CLL/SLL indicates chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IL10, interleukin-10; MZ, marginal zone lymphoma; MGMT, O-6-methylguanine DNA methyltransferase; NAT, N-acetyltransferase; NHL, non-Hodgkin lymphoma; RAG1, recombination-activating gene 1; TNF, tumor necrosis factor; and XRCC1, X-ray repair cross-complementing 1.

*Includes all NHL cases in the study, regardless of histologic subtype (N = 1320, excludes one DLBCL case resulting from missing data on education).

†Counts may not sum to the total because of missing data. For some exposures (see Table 1), a split-sample design was used so that only approximately 50% of participants were expected to provide information.

‡Odds ratios (95% CIs) estimated using polytomous logistic regression models, adjusted for age, sex, race, study center, and education.

§To account for the seven comparisons within the pairwise analysis, we applied a Bonferroni correction and considered P values < 0.007 to be statistically significant.

Table 4. Associations between genetic polymorphisms and non-Hodgkin lymphoma, by lymphoma subtype (continued)

Exposure	Controls, N†	All NHL combined*		DLBCL		Follicular lymphoma		Marginal zone lymphoma		CLL/SLL		P homogeneity	Lowest P value from pairwise analysis§
		N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡	N†	OR (95% CI)‡		
MGMT Ex7+13A>G, I143V, rs2308321													
AA	722	861	1.0 (reference)	271	1.0 (reference)	192	1.0 (reference)	76	1.0 (reference)	91	1.0 (reference)		
AG	166	234	1.1 (0.9, 1.4)	67	1.0 (0.7, 1.4)	67	1.4 (1.0, 1.9)	13	0.7 (0.4, 1.4)	23	1.0 (0.6, 1.7)		
GG	10	14	1.1 (0.5, 2.4)	4	0.9 (0.3, 3.0)	5	1.6 (0.5, 4.7)	1	1.0 (0.1, 7.9)	2	1.5 (0.3, 7.0)		
P trend			.4		.9		.06		.4		.8		
AG+GG	176	248	1.1 (0.9, 1.4)	71	1.0 (0.7, 1.4)	72	1.4 (1.0, 1.9)	14	0.8 (0.4, 1.4)	25	1.0 (0.6, 1.7)	.3	FL vs DLBCL, MZ, CLL/SLL; P = .05
NAT1													
Any/any	454	546	1.0 (reference)	166	1.0 (reference)	137	1.0 (reference)	41	1.0 (reference)	57	1.0 (reference)		
*10/any	251	303	1.1 (0.9, 1.3)	106	1.2 (0.9, 1.7)	59	0.9 (0.6, 1.2)	25	1.1 (0.6, 1.8)	36	1.2 (0.8, 1.9)		
*10/*10	41	66	1.6 (1.0, 2.4)	18	1.4 (0.8, 2.6)	19	2.0 (1.1, 3.6)	5	1.4 (0.5, 4.0)	4	0.9 (0.3, 2.7)		
P trend			.1		.1		.4		.5		.6		
*10/any + *10/*10	292	369	1.1 (0.9, 1.4)	124	1.3 (0.9, 1.7)	78	1.0 (0.7, 1.4)	30	1.1 (0.7, 1.9)	40	1.2 (0.8, 1.9)	.6	DLBCL, CLL/SLL vs FL, MZ; P = .07
NAT2													
Slow	452	522	1.0 (reference)	172	1.0 (reference)	113	1.0 (reference)	37	1.0 (reference)	59	1.0 (reference)		
Intermediate	306	390	1.2 (1.0, 1.4)	114	1.0 (0.8, 1.4)	103	1.5 (1.1, 2.0)	44	1.8 (1.1, 2.8)	39	1.0 (0.7, 1.6)		
Rapid	50	72	1.4 (1.0, 2.2)	25	1.5 (0.9, 2.6)	16	1.5 (0.8, 2.8)	1	0.2 (0.0, 1.8)	7	1.4 (0.6, 3.3)		
P trend			.03		.2		.02		.4		.5		
Intermediate/rapid	356	462	1.2 (1.0, 1.5)	139	1.1 (0.8, 1.5)	119	1.5 (1.1, 2.0)	45	1.6 (1.0, 2.5)	46	1.1 (0.7, 1.7)	.3	FL vs DLBCL, MZ, CLL/SLL; P = .02

CLL/SLL indicates chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; *LIG4*, DNA ligase IV; *FCGR2A*, Fc-gamma receptor IIA; FL, follicular lymphoma; *IL10*, interleukin-10; MZ, marginal zone lymphoma; *MGMT*, O-6-methylguanine DNA methyltransferase; *NAT*, *N*-acetyltransferase; NHL, non-Hodgkin lymphoma; *RAG1*, recombination-activating gene 1; *TNF*, tumor necrosis factor; and *XRCC1*, X-ray repair cross-complementing 1.

*Includes all NHL cases in the study, regardless of histologic subtype (N = 1320, excludes one DLBCL case resulting from missing data on education).

†Counts may not sum to the total because of missing data. For some exposures (see Table 1), a split-sample design was used so that only approximately 50% of participants were expected to provide information.

‡Odds ratios (95% CIs) estimated using polytomous logistic regression models, adjusted for age, sex, race, study center, and education.

§To account for the seven comparisons within the pairwise analysis, we applied a Bonferroni correction and considered *P* values less than .007 to be statistically significant.

contributing to chronic inflammation.[39] Similarly, some autoimmune conditions, such as lupus erythematosus or Sjogren syndrome, may increase risk of NHL through chronic immune stimulation and B-cell proliferation.[40] Previous studies of autoimmunity have observed greater increased risks for marginal zone lymphoma and DLBCL than for other B-cell lymphomas.[40-42]

The associations between NHL or specific NHL subtypes and obesity, late birth order, increasingly dark eye color, residential termite treatment before 1988, and exposure to PCB180 are less well established.[3] The data for NHL subtypes are inconsistent for birth order[24,43-46] and limited for residential termite treatment before 1988,[23] exposure to PCBs,[47] and eye color[27,48]; nevertheless, hypothesized mechanisms are clearly immune-related for late birth order and exposure to PCBs. Late birth order may be a surrogate for earlier exposure to infections, resulting in an earlier shift from a Th2 to a Th1 immune response,[24] and PCBs have been shown to be immunotoxic and to alter immune function.[47] Obesity has been associated with DLBCL in some studies[49,50] and has been hypothesized to lead to inflammation.[51,52] Exposure to residential termite treatments before 1988, when chlordane was banned, may alter immune function,[53] but the data are sparse. We measured eye color as an indicator of host susceptibility to sunlight, which protects against NHL; however, we observed no heterogeneity in risk estimates by lymphoma subtype for our direct measures of sun exposure. We recently reported that only persons with at least one variant allele for the *TNF* G-308A and *IL10* T-3575A polymorphisms had elevated risk of NHL associated with history of autoimmune conditions, late birth order, obesity, dark eye color, and residential termite treatment before 1988,[54] supporting the hypothesis that these risk factors act partly through immune dysfunction.

One reason to suspect that immune dysfunction could be particularly important for the development of DLBCL and marginal zone lymphoma is the pattern of risk in patients with severe immunodeficiency. Their most marked elevation in risk occurs for DLBCL and Burkitt lymphoma.[1,9,55,56] However, risk estimates from severe immunodeficiency are unknown for marginal zone lymphoma, which was only recently recognized by lymphoma classification systems in 1994.[57]

A second pattern emerging from our systematic evaluation is that there may be increased risk for CLL/SLL, but not for the other NHL subtypes, among people with higher levels of dietary heterocyclic amines and mutagens from meat consumption, including MeIQx and DiMeIQx, but not PhIP. Animal studies have demonstrated that lymphomas can be induced by exposure to various carcinogenic and genotoxic aromatic and heterocyclic amines formed when meats are cooked at high temperatures.[58-61] However, epidemiologic investigations of NHL in relation to these exposures have yielded conflicting results,[62] possibly because few studies have evaluated risks by NHL subtype. Whether, as these data suggest, direct DNA damage from environmental carcinogens influences the development of CLL/SLL needs further testing in other studies.

Follicular lymphoma did not present a distinct risk factor profile. However, several risk factors appeared to increase risk of follicular lymphoma more than other NHL subtypes, including height; use of permanent hair dyes before 1980, when hair dye formulations changed and several putative carcinogens were removed; the I143V polymorphism in *MGMT*, a DNA repair gene; and *NAT2* acetylation phenotype, which modifies heterocyclic and aromatic amine metabolism. The specific association for follicular lymphoma has been reported in other studies for both hair dyes[63,64]

and *MGMT*,[65] but NHL subtype risk estimates for *NAT2* acetylation phenotype have not been published in studies other than ours.[36] The published literature on height is inconsistent. As with CLL/SLL, our findings are consistent with the role of direct DNA damage from environmental carcinogens in the development of follicular lymphoma, but do not provide strong evidence and require replication in other studies.

The interpretation of our finding for vitamin B_6 is unclear. We observed that persons consuming higher levels of dietary vitamin B_6 had significantly lower risk estimates for DLBCL and CLL/SLL than for follicular or marginal zone lymphoma. Vitamin B_6 protects against DNA damage and has been implicated in various cancers,[66] but its role in lymphomagenesis is not well established.[62]

Finally, we observed no clear pattern of heterogeneity among NHL subtypes for numerous risk factors. Risk estimates most strikingly consistent for decreased risk among the 4 NHL subtypes were ethanol consumption, exposure to sunlight, dietary lutein/zeaxanthin, and consumption of cruciferous vegetables, whereas increased risks were observed with genetic polymorphisms in *FCGR2A*, *RAG1*, and *XRCC1*. It is possible that we did not observe heterogeneity for risk factors that do differ by subtype because of chance, insufficient sample size particularly for rare exposures, exposure misclassification, or effect modification. Alternatively, it is plausible that these risk factors are common to all NHL subtypes.

The observation that B-cell lymphomas appear to be "frozen" at specific stages of B-cell development is a key element of their classification and nomenclature.[1] The postulated cell of origin for CLL/SLL is not thought to have undergone germinal center transit. In contrast, follicular lymphoma DLBCL and marginal zone lymphoma correspond to germinal center or post–germinal center B cells. Specifically, follicular lymphoma arises primarily in centrocytes, germinal center B cells undergoing somatic hypermutation to increase antigen affinity; DLBCL arises in centroblasts (rapidly proliferating germinal center B cells) or post–germinal center B cells; and marginal zone lymphoma arises in memory B cells. We note the relative importance of risk factors that may induce lymphomagenesis via immune dysfunction for DLBCL and marginal zone lymphoma, which is consistent with our understanding that both subtypes arise in phases of B-cell differentiation that are most dependent on immune stimulation.

The main strength of this analysis is the comprehensive, systematic analysis of a broad range of putative environmental and genetic risk factors in a population-based study with detailed information on both exposure and disease. Interpretation of our results should also take into account several limitations. Our risk estimates may have been biased because of differential recall of exposure between cases and controls. It is also possible that our risk estimates were biased against finding an association for the more aggressive NHL subtypes for those risk factors also associated with prognosis because we excluded deceased cases. Although we queried participants on their dietary habits before 1 year before diagnosis or interview, our findings may represent reverse causality because of recent changes in diet reported by patients with insidious types of NHL, rather than true etiologic differences. Some exposures, such as autoimmune conditions, are heterogeneous entities themselves and may have differential effects on lymphoma risk, but power considerations necessitated collapsing them together. We could not assess the independence of the risk factors we identified as being important because we did not have sufficient power to simultaneously model multiple risk factors, particularly for rare exposures. Because the statistical approaches we used have greater power in different circumstances, the results

of the tests were not always consistent. The pairwise analysis is also sensitive to differences in sample size among the comparison groups, giving more weight to larger groups. We did not control for the number of risk factors for which we evaluated heterogeneity because this was an exploratory analysis. Our results reflect just one individual study, and we did not include analyses of all possible risk factors for which we had data; thus, we may have missed specific patterns because of either false-positive or false-negative results in our study. In addition, because many of the risk factors we evaluated only modestly affect lymphoma risk, most of the differences among subtypes we observed were small. Finally, there may have been misclassification among the lymphoma subtypes.

In conclusion, careful dissection of risk factor patterns by disease subtype reveals important clues about lymphomagenesis. Replication of our results is required with larger sample sizes, such as in pooled and/or meta-analyses, and in other studies with high-quality, detailed data on both exposure and disease. Nevertheless, these data clearly support both commonality and heterogeneity in the etiology of lymphoma subtypes, and suggest that immune dysfunction is of greater etiologic importance for DLBCL and marginal zone lymphoma than for CLL/SLL and follicular lymphoma.

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Authorship

Contribution: P.H., J.S.C., J.R.C., W.C., S.D., and R.K.S. obtained funding and oversaw data collection; P.H., J.S.C., J.R.C., W.C., S.D., R.K.S., M.S.L., N.R., A.B., L.B., C.F.L., M.S., S.H.Z., and M.A.V. oversaw data collection; L.M.M., P.H., N.C., and S.S.W. designed analysis; L.M.M., N.C., and S.W. performed statistical analysis; L.M.M., P.H., and S.S.W. drafted the manuscript; and all authors created exposure variables and revised the manuscript.

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