Rationale and Design of the International Lymphoma Epidemiology Consortium (InterLymph) Non-Hodgkin Lymphoma Subtypes Project

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- Background** Non-Hodgkin lymphoma (NHL), the most common hematologic malignancy, consists of numerous subtypes. The etiology of NHL is incompletely understood, and increasing evidence suggests that risk factors may vary by NHL subtype. However, small numbers of cases have made investigation of subtype-specific risks challenging. The International Lymphoma Epidemiology Consortium therefore undertook the NHL Subtypes Project, an international collaborative effort to investigate the etiologies of NHL subtypes. This article describes in detail the project rationale and design.
- Methods** We pooled individual-level data from 20 case-control studies (17 471 NHL cases, 23 096 controls) from North America, Europe, and Australia. Centralized data harmonization and analysis ensured standardized definitions and approaches, with rigorous quality control.
- Results** The pooled study population included 11 specified NHL subtypes with more than 100 cases: diffuse large B-cell lymphoma (N = 4667), follicular lymphoma (N = 3530), chronic lymphocytic leukemia/small lymphocytic lymphoma (N = 2440), marginal zone lymphoma (N = 1052), peripheral T-cell lymphoma (N = 584), mantle cell lymphoma (N = 557), lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (N = 374), mycosis fungoides/Sézary syndrome (N = 324), Burkitt/Burkitt-like lymphoma/leukemia (N = 295), hairy cell leukemia (N = 154), and acute lymphoblastic leukemia/lymphoma (N = 152). Associations with medical history, family history, lifestyle factors, and occupation for each of these 11 subtypes are presented in separate articles in this issue, with a final article quantitatively comparing risk factor patterns among subtypes.
- Conclusions** The International Lymphoma Epidemiology Consortium NHL Subtypes Project provides the largest and most comprehensive investigation of potential risk factors for a broad range of common and rare NHL subtypes to date. The analyses contribute to our understanding of the multifactorial nature of NHL subtype etiologies, motivate hypothesis-driven prospective investigations, provide clues for prevention, and exemplify the benefits of international consortial collaboration in cancer epidemiology.

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Each year, more than 500 000 individuals worldwide are diagnosed with non-Hodgkin lymphoma (NHL), making it the most common hematologic malignancy (1). NHL is composed of numerous closely related yet heterogeneous diseases with distinctive morphologic, immunophenotypic, genetic, and clinical features (2,3). The strongest known risk factor for some NHLs is severe immunodeficiency, but this accounts for relatively few cases (4). Incidence

of NHL rose dramatically in most Western countries throughout the second half of the 20th century, independently of the AIDS epidemic, and appears to have plateaued in the last decade (5–11). A number of epidemiological studies were launched in the 1980s–1990s to identify potential causes of these long-standing increases and to understand NHL etiology more broadly, yet the “epidemic” of NHL remains poorly understood.

In 2001, the World Health Organization (WHO) introduced an international consensus-based classification for hematologic malignancies (2,3). This classification provided the first biologically based, integrated framework for consistently defining the subtypes of NHL, thereby greatly facilitating research on this heterogeneous group of diseases. Subsequent analyses of population-based registry data revealed striking differences in incidence among NHL subtypes by age, sex, race/ethnicity, and calendar year (11–14). Additionally, studies have reported that certain infectious agents are associated with risk of specific NHL subtypes, such as human T-cell lymphotropic virus, type I (HTLV-I) with adult T-cell leukemia/lymphoma (15), and *Helicobacter pylori* with gastric mucosa-associated lymphoid tissue NHL (16), whereas infection with the HIV (17–19) and hepatitis C virus (20,21) are associated with multiple NHL subtypes. Variation in risk among NHL subtypes also is clearly evident for

associations with autoimmune conditions (22), iatrogenic immunodeficiency associated with solid organ transplantation (23–25), and certain common genetic variants (26–31). In contrast, cumulative sun exposure appears to affect the risk of all NHL subtypes (32).

The International Lymphoma Epidemiology Consortium (InterLymph) is an open scientific forum for epidemiological research in NHL (<http://epi.grants.cancer.gov/InterLymph/>) (33). Formed in 2001, InterLymph's primary goal was to facilitate pooled analyses of individual-level data from lymphoid malignancy case-control studies with the purpose of increasing statistical power for examining associations with rare exposures and less common NHL subtypes. Collaborations among epidemiologists in Europe, North America, and Australia were initiated in the 1990s through formal (34) and informal meetings, where investigators shared draft protocols and questionnaires for recent

Table 1. Characteristics of studies included in the InterLymph NHL Subtypes Project*

Region	Study (reference)	Location	Years of diagnosis	Design	Participation, %†		Total No.	
					Cases	Controls	Cases	Controls
North America								
	British Columbia (43)	Vancouver, Victoria, British Columbia (Canada)	2000–2004	Population-based	79	46	833	845
	Iowa/Minnesota (44)‡	Iowa, Minnesota (US)	1981–1983	Population-based	87	81	866	1245
	Kansas (45)§	Kansas (US)	1976–1982	Population-based	96	94	170	948
	Los Angeles (46)§	Los Angeles, California (US)	1989–1992	Population-based	45	69	376	375
	Mayo Clinic (47,48)‡	Iowa, Minnesota, Wisconsin (US)	2002–2008	Clinic-based	69	69	1120	1314
	NCI-SEER (49)	Detroit, Michigan; Iowa; Los Angeles, California; Seattle, Washington (US)	1998–2000	Population-based	76	52	1316	1055
	Nebraska (older)‡ (50)	Nebraska (US)	1983–1986	Population-based	91	87	441	1432
	Nebraska (newer) (51)	Nebraska (US)	1999–2002	Population-based	73	77	387	533
	UCSF1 (52)	San Francisco, California (US)	1988–1995	Population-based	72	78	1302	2402
	UCSF2	San Francisco, California (US)	2001–2006	Population-based	70	68	487	457
	University of Rochester (53)	Rochester, New York (US)	2005–2007	Hospital-based	96	78	129	139
	Yale (54)	Connecticut (US)	1995–2001	Population-based	72	47–69	600	717
Europe								
	Engela (55)‡, §	Bordeaux, Brest, Caen, Lille, Nantes, Toulouse (France)	2000–2004	Hospital-based	97	93	567	722
	EpiLymph (56)‡, §	Spain; France; Germany; Italy; Ireland; Czech Republic	1998–2004	Population-based (Italy, Germany), otherwise hospital-based	82–93	44–96	1735	2460
	Italy multicenter (57)‡	Firenze, Forli, Imperia, Latina, Novara, Ragusa, Siena, Torino, Varese, Vercelli, Verona (Italy)	1990–1993	Population-based	82	74	1911	1771
	Italy (Aviano-Milan) (58,59)	Aviano, Milan (Italy)	1983–1992	Hospital-based	>97	>97	429	1157
	Italy (Aviano-Naples) (60)	Aviano, Naples (Italy)	1999–2002	Hospital-based	97	91	225	504
	SCALE (61)‡	Denmark; Sweden	1999–2002	Population-based	81	71	3055	3187
	United Kingdom (62)‡, §	Lancashire/South Lakeland, South England, Yorkshire (United Kingdom)	1998–2001	Population-based	75	71	828	1139
Australia								
	New South Wales (63)	New South Wales, Australian Capital Territory (Australia)	2000–2001	Population-based	85	61	694	694

* InterLymph = International Lymphoma Epidemiology Consortium; NCI-SEER = National Cancer Institute-Surveillance, Epidemiology, and End Results Program; NHL = non-Hodgkin lymphoma; SCALE = Scandinavian Lymphoma Etiology Study; UCSF = University of California, San Francisco.

† Participation was typically computed as number participating divided by the number contacted.

‡ Studies were designed to investigate other malignancies in addition to NHL: Engela: Hodgkin lymphoma, multiple myeloma, and lymphoproliferative syndromes; EpiLymph: Hodgkin lymphoma and multiple myeloma; Iowa/Minnesota: leukemia; Italy: Hodgkin lymphoma, multiple myeloma, and soft-tissue sarcoma; Mayo: Hodgkin lymphoma; Nebraska (older): Hodgkin lymphoma and multiple myeloma; SCALE: Hodgkin lymphoma; United Kingdom: Hodgkin lymphoma.

§ Studies individually matched controls to cases. The remaining studies frequency matched controls to cases, typically by age (5-y groups), sex, race/ethnicity, and geographic location where appropriate.

|| This recently completed study has not yet published results but had similar methodology to a previous study conducted in the same region (52).

and planned epidemiological studies. Since its official inception, InterLymph has expanded to become an interdisciplinary group of epidemiologists, pathologists, clinicians, geneticists, immunologists, and biostatisticians who have worked together to publish pooled analyses on a range of individual risk factors among NHL subtypes (20,22,27,28,32,35–42).

Despite advances in our understanding of NHL etiology, broad evaluation of risk factor profiles for specific NHL subtypes across a range of exposures is lacking, and little is known about risk factors for many of the less common NHL subtypes. We therefore undertook the “InterLymph NHL Subtypes Project,” a consortium-wide initiative with the aims of 1) evaluating associations for medical history, family history of hematologic malignancy, lifestyle factors, and occupation with specified NHL subtypes, and 2) quantitatively assessing etiologic heterogeneity among NHL subtypes. The project expands previous InterLymph pooled analyses (20,22,27,28,32,35–42) by examining a range of exposures in the same analysis for each NHL subtype, quantitatively assessing differences and commonalities in risk factor associations across a broader range of NHL subtypes, and including new studies that recently joined the consortium. In this article, we describe in detail the design and methods of the project.

Methods

Project Structure and Coordination

The InterLymph NHL Subtypes Project was governed by a Project Coordinating Committee, with representation from each contributing study and InterLymph working group (Immunity & Infection, Lifestyle & Environment, and Pathology). The Committee was led by an interdisciplinary group of epidemiologists (LMM, MSL, JRC), pathologists (DDW, JJT), and biostatisticians (SLS, JNS)

who initiated and/or led the project. Additional oversight of the analyses was provided by an analytic working group with biostatisticians from three participating studies (JNS, SLS, YB). Project coordinators corresponded regularly by e-mail and teleconference, and met in-person at four annual InterLymph meetings during 2010–2013. Working groups for each NHL subtype included in the project were formed with representation from participating studies and with other InterLymph members with expertise and interest in that particular subtype. Each group included at least one pathologist, clinician, and biostatistician, in addition to epidemiologists. Communication was facilitated by use of a password-protected web portal for posting study documents and results. Decisions were made by consensus or voting.

Study Population

Studies eligible for inclusion in these pooled analyses fulfilled the following criteria: 1) case-control design, with incident cases of NHL and information on NHL subtype, 2) availability of individual-level data by December 31, 2011, and 3) participation in InterLymph. A total of 20 studies fulfilled these criteria (Table 1). As described below, studies were included in specific analyses where cases were available with the subtype of interest and data were collected on the particular risk factor under evaluation. Contributing studies were approved by local ethics review committees, and all participants provided informed consent before interview.

Individuals with a known history of solid organ transplantation or HIV/AIDS were ineligible for most studies; any individual who reported a history of these conditions during patient interviews or via questionnaires was excluded from these pooled analyses. All studies conducted direct interviews with study participants, except Iowa/Minnesota and Italy multicenter, which used proxy respondents for deceased cases. In the six studies that used hospital- or

Figure 1. The power to detect an association between a characteristic (e.g., autoimmune disease) and a non-Hodgkin lymphoma subtype depends on the number of cases, the prevalence of that characteristic in the control group, and the odds ratio [OR] indicative of effect size. Each figure shows the power as a function of the number of cases in

the study for different effect sizes ($1.25 \leq \text{OR} \leq 4.0$), given the prevalence of the dichotomous characteristic among controls ($0.02 \leq \text{prevalence} \leq 0.2$). The top row includes up to 3000 cases, whereas the bottom row focuses on a smaller sample size (up to 500 cases). Calculations assume five controls:one case and $\alpha = 0.05$.

clinic-based controls, analyses included all controls used in the original study, regardless of reason for hospital admission.

NHL Subtype Ascertainment and Harmonization

Eligible cases were diagnosed with incident, histologically confirmed NHL. Most studies had centralized review of pathology reports and diagnostic slides by at least one expert hematopathologist to confirm the NHL diagnoses and assign an NHL subtype, except for the National Cancer Institute-Surveillance, Epidemiology, and End Results Program and Italy multicenter studies, in which cases were diagnosed by local pathologists.

Each participating study's pathology review procedures, rules for NHL subtype classification, and NHL subtype distribution were reviewed by an interdisciplinary team of hematopathologists and epidemiologists. We grouped cases into NHL subtypes according to the WHO classification (2,3) using guidelines from the InterLymph Pathology Working Group (64,65). NHL subtypes with more than 100 cases in the pooled dataset were eligible for inclusion in this project.

Because of the potential for risk factors to differ by primary site of disease for certain NHL subtypes (e.g., Sjögren's syndrome and salivary gland marginal zone lymphoma) (22), we further classified cases according to primary site of NHL for secondary analyses.

In most studies (N = 14), primary site of NHL was recorded if known, irrespective of disease stage. In some NHL subtypes, site is a diagnostic criterion. NHL site was categorized as nodal, extra-nodal lymphatic (Waldeyer's ring, thymus, or spleen), or extranodal extralymphatic (66). Specific primary sites (e.g., skin, gastrointestinal tract) also were recorded for further analysis in some NHL subtypes. Leukemias were classified as systemic by definition. Cases with widespread disease or primary site listed as bone marrow, blood, or cerebrospinal fluid, and in which subtype was not site-specific by definition, also were classified as systemic.

Risk Factor Ascertainment and Harmonization

Each study collected data on putative NHL risk factors in a standardized, structured format by in-person or telephone interviews and/or self-administered questionnaires. In some studies, participants also provided a venous blood sample. Risk factors selected for inclusion in this analysis were the available medical history, family history of hematologic malignancy, lifestyle factors, and occupations with data from at least four studies.

Each study contributed de-identified, individual-level data for the risk factors of interest. Data harmonization was conducted centrally at the Mayo Clinic under the leadership of SLS. Each

Table 2. Demographic characteristics of controls from participating studies in the InterLymph NHL Subtypes Project*

Region			Race/ethnicity, %					Age, y§	Socioeconomic status, %			
	Controls, No.	Male, %†	White	Black	Asian	Hispanic	Other ‡	Median (range)	Low	Medium	High	Missing
North America												
British Columbia	845	53	77	0	17	0	7	60 (20–80)	38	32	29	1
Iowa/Minnesota	1245	100	100	0	0	0	0	68 (30–97)	71	18	11	0
Kansas	948	100	96	0	0	1	3	63 (18–98)	36	32	24	8
Los Angeles	375	49	75	5	3	16	0	54 (17–79)	33	35	32	0
Mayo Clinic	1314	54	98	0	0	1	1	63 (21–94)	23	24	40	13
NCI-SEER	1055	52	78	14	2	5	1	61 (20–74)	37	31	31	0
Nebraska (older)	1432	51	99	0	0	0	1	68 (19–98)	66	17	12	6
Nebraska (newer)	533	53	96	2	1	1	1	59 (20–76)	45	26	29	0
UCSF1	2402	65	81	6	5	7	2	53 (21–74)	29	25	46	0
UCSF2	457	59	94	0	0	6	0	59 (20–84)	15	29	56	0
University of Rochester	139	44	88	6	1	3	1	52 (21–85)	40	25	32	4
Yale	717	0	92	3	0	4	1	64 (23–86)	37	31	32	1
Europe												
Engela	722	62	100	0	0	0	0	55 (18–76)	32	37	31	0
EpiLymph	2460	54	97	0	0	0	3	59 (17–76)	46	41	14	0
Italy multicenter	1771	52	100	0	0	0	0	58 (19–75)	53	24	23	0
Italy (Aviano-Milan)	1157	61	100	0	0	0	0	57 (17–85)	57	21	22	1
Italy (Aviano-Naples)	504	68	100	0	0	0	0	63 (18–83)	47	20	33	0
SCALE	3187	55	95	0	0	0	5	59 (18–76)	29	34	36	2
United Kingdom	1139	55	100	0	0	0	0	53 (16–69)	33	35	32	0
Australia												
New South Wales	694	57	87	0	2	0	11	57 (21–74)	34	35	31	0
Total	23 096	58	93	2	1	2	2	59 (16–98)	41	29	29	2

* InterLymph = International Lymphoma Epidemiology Consortium; NCI-SEER = National Cancer Institute-Surveillance, Epidemiology, and End Results Program; NHL = non-Hodgkin lymphoma; SCALE = Scandinavian Lymphoma Etiology Study; UCSF = University of California, San Francisco.

† The Yale study was restricted to women, whereas the Kansas and Iowa/Minnesota studies were restricted to men.

‡ Includes individuals with other specified races as well as unknown race. For studies with predominantly white, non-Hispanic populations, individuals with unknown race were assumed to be white (Iowa/Minnesota, Kansas, Mayo Clinic, NCI-SEER [Seattle, Iowa study centers], Nebraska [older], Nebraska [newer], UCSF2, University of Rochester, Yale, Engela, SCALE, United Kingdom).

§ Age at diagnosis for cases and interview for controls. All studies excluded children (with varying minimum ages), and most studies excluded the elderly (with varying maximum ages) population, except for the Iowa/Minnesota, Kansas, Mayo Clinic, Nebraska (older), and University of Rochester studies, which did not have an upper age limit.

|| Socioeconomic status was measured by years of education for studies in North America or by dividing measures of education or socioeconomic status into tertiles for studies in Europe or Australia.

exposure variable was harmonized individually and data were then reviewed for consistency among related exposure variables. A small subcommittee reviewed harmonization rules for each exposure, ensured consistency with previously published InterLymph pooled analyses, and advised the analytic approaches for that exposure.

Statistical Analysis

We defined a single analytical plan and applied it to each of the 11 NHL subtypes, with all analyses conducted centrally at the National Cancer Institute under the leadership of JNS and LMM. Here, we describe this plan in terms of a generic NHL subtype. Each analysis defined individuals with a specific NHL subtype as cases, individuals without any type of NHL as controls, and excluded cases with NHL subtypes other than the one of interest. For analyses of a particular subtype, we only included controls from studies that also contributed cases of that subtype. Analyses were conducted using SAS software, version 9.2 (SAS Institute, Inc, Cary, NC).

We examined the relationship between case/control status and each exposure variable individually using unconditional logistic regression models adjusted for age (<30, 30–39, 40–49, 50–59, 60–69, 70–79, ≥80 years), race/ethnicity (white, black, Asian, Hispanic, or other/missing), sex, and study. Confidence intervals (CIs) for the odds ratios (ORs) were estimated by asymptotic theory for maximum likelihood estimation. Statistical significance of each relationship was evaluated by a likelihood ratio test, comparing models with and without the exposure variable of interest, with *P* values less than .05 identifying putatively influential factors. We excluded individuals who had missing data for the exposure variable of interest, and we excluded both cases and controls from studies where only a single category of the exposure variable of interest was represented (e.g., no cases and no controls reported history of a particular autoimmune condition).

To evaluate effect heterogeneity among the studies included in each analysis, we performed a separate logistic regression within

Table 3. Distribution of the InterLymph NHL Subtypes Project study population by NHL subtype and study*

NHL subtype classification†	Cases													
Study	Total	DLBCL	FL	CLL/SLL	MZL	PTCL	MCL	LPL	MF/SS	BL	HCL	ALL	Other	NOS
WHO (total)	11 976	3320	2583	1982	1052	528	557	374	252	159	124	92	50	903
British Columbia	833	218	228	42‡	101	33	50	42	42	10	0§	6	3	58
Engela	567	174	101	132	20	18	25	21	0	11	36	8	0	21
EpiLymph	1735	516	251	414	138	78	67	44	38	24	15	46	13	91
Italy (Aviano-Naples)	225	112	36	18‡	14	9	2	10	2	9	0§	0§	2	11
Mayo Clinic	1120	210	271	376	68	32	56	22	9	7	0§	1	6	62
NCI-SEER	1316	413	318	133‡	106	55	50	28	26	12	0§	0§	1	174
Nebraska (newer)	387	103	123	29‡	35	12	16	5	7	12	0§	1	0	44
New South Wales	694	231	252	29‡	61	16	22	27	4	4	10	5	4	29
SCALE	3055	796	586	752	117	121	148	116	41	31	63	15	16	253
UCSF2	487	0¶	0¶	0¶	187	77	58	43	54	35	0§	7	3	23
University of Rochester**	129	32	45	7‡	24	8	7	0§	2	0	0§	0	0	4
United Kingdom	828	326	236	0‡	141	50	40	0§	15	0§	0§	0§	2	18
Yale	600	189	136	50‡	40	19	16	16	12	4	0§	3	0	115
Working Formulation (total)	5495	1347	947	458	0	56	0	0	72	136	30	60	0	2389
Iowa/Minnesota	866	112	195	244	0	0	0	0	0	18	0§	6	0	291
Italy multicenter	1911	407	159	214	0	55	0	0§	25	23	30	12	0	986
Italy (Aviano-Milan)	429	47	55	0	0	0	0	0§	0	9	0§	10	0	308
Kansas	170	27	34	0	0	0	0	0	0	2	0§	1	0	106
Los Angeles**	376	151	41	0	0	1	0	0§	0	50	0§	16	0	117
Nebraska (older)	441	94	111	0	0	0	0	0	0	6	0§	3	0	227
UCSF1	1302	509	352	0	0	0	0	0§	47	28	0§	12	0	354
Total	17 471	4667	3530	2440	1052	584	557	374	324	295	154	152	50	3292

* ALL = acute lymphoblastic leukemia; BL = Burkitt lymphoma/leukemia; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HCL = hairy cell leukemia; InterLymph = International Lymphoma Epidemiology Consortium; LPL = lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MCL = mantle cell lymphoma; MF/SS = mycosis fungoides/Sézary syndrome; MZL = marginal zone lymphoma; NCI-SEER = National Cancer Institute-Surveillance, Epidemiology, and End Results Program; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PTCL = peripheral T-cell lymphoma; SCALE = Scandinavian Lymphoma Etiology Study; UCSF = University of California, San Francisco; WHO = World Health Organization.

† We grouped cases into NHL subtypes according to the WHO classification (2,3) using guidelines from the InterLymph Pathology Working Group (64,65). NHL subtypes with more than 100 cases in the pooled dataset were eligible for inclusion in this project. “Other” includes subtypes with less than 100 cases: extranodal natural killer/T-cell lymphoma-nasal type (N = 29), prolymphocytic leukemia (N = 11), T-cell large granular lymphocytic leukemia (N = 8), and adult T-cell leukemia/lymphoma (N = 2). NOS represents poorly specified subtypes (N = 3292). The higher proportion of NOS cases from the Working Formulation studies is due to low correspondence between certain Working Formulation and WHO subtypes (64). NHL subtypes from the British Columbia, United Kingdom, Engela, and UCSF2 studies were classified using the International Classification of Diseases for Oncology, third edition (70), and from the NCI-SEER study using the second edition (71), allowing for translation to the WHO classification.

‡ Included SLL but not CLL based on original study eligibility criteria.

§ NHL subtype excluded based on original study eligibility criteria.

|| NHL subtypes were classified according to the Working Formulation with varying levels of additional pathology data, and certain subtypes could not be distinguished reliably.

¶ The three most common NHL subtypes were excluded from this recently completed study, pending publication of individual study results.

** Excluded cases with evident central nervous system involvement.

†† Restricted to intermediate- or high-grade NHL, as defined by the Working Formulation.

Table 4. Contribution of risk factor data for the InterLymph NHL Subtypes Project*

Risk factor	North America												Europe							
	British Columbia	Iowa/Minnesota	Kansas	Los Angeles	Mayo Clinic	NCI-SEER	Nebraska (newer)	Nebraska (older)	UCSF1	UCSF2	Univ. of Rochester	Yale	Engela	Epilymph	Italy multicenter	Italy (Aviano-Milan)	Italy (Aviano-Naples)	SCALE	United Kingdom	New South Wales
Family history of hematologic malignancy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medical history risk factors	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Autoimmune disease	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hepatitis C virus seropositivity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Peptic ulcer disease	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Atopy (allergy, asthma, hay fever, or eczema)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood transfusion	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reproductive history	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Oral contraceptive use	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hormonal replacement therapy use	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lifestyle risk factors	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anthropometric measures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical activity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alcohol consumption	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cigarette smoking	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Personal hair dye use	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sun exposure	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Farm exposure	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Occupation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

* Indicates the studies that contributed data for at least one variable in the particular risk factor category; — indicates studies that did not have any data in the risk factor category. The studies that contributed to each exposure variable are listed in [Supplementary Table 1](#). InterLymph = International Lymphoma Epidemiology Consortium; NCI-SEER = National Cancer Institute-Surveillance, Epidemiology, and End Results Program; SCALE = Scandinavian Lymphoma Etiology Study; UCSF = University of California, San Francisco.

Table 5. Harmonization of family history of hematologic malignancy and medical history risk factor data for the InterLymph NHL Subtypes Project*

Risk factor	Analytic variables	Notes
Family history of hematologic malignancy (37)	<ul style="list-style-type: none"> Family history of any hematologic malignancy Family history of NHL Family history of leukemia Family history of multiple myeloma Family history of Hodgkin lymphoma 	<ul style="list-style-type: none"> Self-reported family history of hematologic malignancy was limited to reports in a first-degree relative, including any hematologic malignancy (17 studies), NHL (16 studies), leukemia (15 studies), multiple myeloma (14 studies), or Hodgkin lymphoma (14 studies). Type of hematologic malignancy was coded according to ICD as NHL (ICD-9: 200, 202.0–202.2, 202.8–202.9; ICD-10: C82–C85, C96.3), Hodgkin lymphoma (ICD-9: 201, ICD-10: C81), leukemia (ICD-9: 202.4, 203.1, 204–208; ICD-10: C90.1, C91–C95), or multiple myeloma (ICD-9: 203, ICD-10: C90.0, C90.2). Note that the ICD includes both lymphoid and myeloid leukemias in the broad category of “leukemia,” and excludes lymphoid leukemias and plasma cell neoplasms from NHL, in contrast to the WHO classification (2,3) and InterLymph guidelines (64,65). Additional analyses considered the sex of the relative (14 studies). Mean correlation among family history variables = 0.21.
Autoimmune conditions (22)	<p><u>Conditions mediated by B-cell response</u></p> <ul style="list-style-type: none"> Hashimoto thyroiditis Hemolytic anemia Myasthenia gravis Pernicious anemia Rheumatoid arthritis Sjögren’s syndrome Systemic lupus erythematosus <p><u>Conditions mediated by T-cell response</u></p> <ul style="list-style-type: none"> Celiac disease Immune thrombocytopenic purpura Inflammatory bowel disorder Multiple sclerosis Polymyositis or dermatomyositis Psoriasis Sarcoidosis Systemic sclerosis or scleroderma Type 1 diabetes 	<ul style="list-style-type: none"> Self-reported history of specific autoimmune conditions occurring ≥ 2 y prior to diagnosis/interview (except the New South Wales study, which did not ascertain date of onset). Conditions were classified according to whether they are primarily mediated by B- or T-cell response (22,72–75). Any condition assessed by more than one study was eligible for inclusion (N = 16), although most studies did not contribute data on every condition. Reports of rheumatoid arthritis were accepted only in individuals who also reported receiving corticosteroid or immunosuppressive treatment. Studies that did not collect treatment data were excluded. For individuals reporting both rheumatoid arthritis and systemic lupus erythematosus, only the most recently diagnosed disorder was considered. Inflammatory bowel disorder included individuals reporting Crohn’s disease or ulcerative colitis. Type 1 diabetes included individuals reporting a history of diabetes with age of onset < 30 y. Mean correlation among B-cell-mediated conditions = 0.13, T-cell-mediated conditions = 0.07.
Hepatitis C virus (20)	<ul style="list-style-type: none"> Seropositivity 	<ul style="list-style-type: none"> Serum antibodies to hepatitis C virus were evaluated using a third-generation ELISA (76).
Peptic ulcer	<ul style="list-style-type: none"> Any history of peptic ulcer 	<ul style="list-style-type: none"> Self-reported history of gastric ulcer (three studies), peptic ulcer (seven studies), or any ulcer (one study).
Atopy (40)	<ul style="list-style-type: none"> Any atopic condition Any allergy Food allergy Asthma Hayfever Eczema 	<ul style="list-style-type: none"> Self-reported history of atopic conditions occurring before diagnosis/interview, including allergy (12 studies), asthma (18 studies), hayfever (15 studies), and eczema (16 studies). Any allergy included plant, food, animal, dust, insect, or mold. Sensitivity analyses were performed by excluding cases and controls with atopic conditions diagnosed within 2 y of NHL diagnosis/interview. Mean correlation among atopic condition variables (excluding any atopic condition) = 0.22.
Blood transfusion	<ul style="list-style-type: none"> Any blood transfusion Year of transfusion Total number of transfusions 	<ul style="list-style-type: none"> Self-reported history of blood transfusions occurring ≥ 1 y prior to diagnosis/interview. Mean correlation among transfusion variables = 0.86.
Reproductive history, use of OCs or HRT (41,42)	<ul style="list-style-type: none"> Number of children Age at first birth Any OC use OC use initiated before versus after 1970 Any HRT use HRT use initiated before versus after age 50 y 	<ul style="list-style-type: none"> Men were excluded from analysis. Analyses considered date of OC use initiation due to substantial changes in OC formulations. Age at initiation of HRT use was used as a proxy for premenopausal versus postmenopausal initiation. Mean correlation among variables = 0.25.

* HRT = hormone replacement therapy; ELISA = enzyme-linked immunosorbent assay; ICD = International Classification of Diseases; InterLymph = International Lymphoma Epidemiology Consortium; NHL = non-Hodgkin lymphoma; OC = oral contraceptive.

each study and then quantified the variability of the coefficients by the H statistic. Adapting the definition by Higgins and Thompson to categorical variables (67), we defined H as follows. Let $\hat{\beta}$ be the vector of size $n = \text{number of studies} \times (\text{number of categories} - 1)$ containing the estimated coefficients from all studies. Let S be the estimated block diagonal variance matrix for $\hat{\beta}$. Subtract the mean of each coefficient from $\hat{\beta}$ to obtain $\hat{B}$. Then, we defined $Q = \hat{B}^T \Sigma^{-1} \hat{B}$, which has a χ^2 with $n' = (n - \text{number of categories} - 1)$ degrees of freedom and $H = \sqrt{Q/n'}$. The lower and upper bounds for the 95% CI of H is $H \exp(-A)$ and $H \exp(A)$, where $A = 1.96 \sqrt{(1 - (1/(3k^2)))/(2k)}$ and $k = n' - 1$. In the absence of heterogeneity, H is expected to equal 1. Statistically significant heterogeneity among studies was identified by 95% CI for H that excluded 1. If a category within a particular study included no cases, suggesting that the disease risk was 0 or the $\log(\text{OR}) = -\infty$, we set the $\log(\text{OR})$ to -2 and estimated the standard deviation by rerunning the logistic regression with an additional case added into that category.

We then examined the relationship between case/control status and each putative risk factor considering possible effect modification and accounting for other potential confounders. To consider possible effect modification, we repeated the above logistic regression analyses, but now stratified individuals by age, sex, race/ethnicity, region (North America, Northern Europe, Southern Europe, and Australia), study, study design (i.e., population-based versus hospital- or clinic-based studies), or putative risk factors identified in the analysis. Forest plots illustrated the results from the stratified analyses to identify possible effect modifiers for each exposure variable. To account for potential confounding, we conducted two analyses. First, we evaluated the risk estimate for each putative risk factor in a series of models that adjusted for one other putative risk factor at a time (as well as age, race/ethnicity, sex, and study). Second, we conducted a single logistic regression analysis including all putative risk factors, age, sex, race, and study, this time including a separate missing category for each variable to ensure that the whole study population was included in the analysis (i.e., not excluded due to missing data). Note, however, that the likelihood ratio P values for a putative risk factor excluded the effect of this newly created missing category. Finally, we conducted a forward step-wise logistic regression with all putative risk factors, adjusting for age, sex, race/ethnicity, and study.

In most of the original studies, controls were frequency-matched to cases by age and sex. However, because some studies included cases with Hodgkin lymphoma, myeloma, leukemia, and/or soft-tissue sarcoma in addition to NHL (Table 1), each analysis included only a subset of cases causing the matching to be broken. Therefore, as a sensitivity analysis, we repeated the analyses described above using a subset of controls that were frequency-matched by age and sex to cases with that NHL subtype. The results from these sensitivity analyses were very similar to the results obtained using the full set of controls, thus we retained the full set of controls for our main analyses to increase statistical power.

The power to detect an association between a dichotomous characteristic and NHL subtype depends on the number of available cases, the prevalence of the characteristic, and the strength of the association. To understand the potential types of associations

detectable for each subtype, we calculated the power for varying combinations of those three parameters (Figure 1). The calculations assumed a 1:5 case:control ratio, an α level of 0.05, and that the estimated proportions of exposed cases and controls were normally distributed.

Results

Study Population

Twenty studies from North America ($N = 12$), Europe ($N = 7$), and Australia ($N = 1$) were included in the InterLymph NHL Subtypes Project, representing most of the large-scale case-control studies of NHL conducted over the last three decades in these regions (Table 1). The pooled dataset included a total of 17 471 NHL cases and 23 096 controls. More than 75% of participants were derived from the 14 population-based studies, with the remaining participants from hospital- or clinic-based studies. The pooled study controls were 58% male and 93% non-Hispanic white, and had a median age at interview of 59 years (range 16–98 years); 41% were classified in the lowest tertile of socioeconomic status (Table 2).

NHL Subtypes

Of the 17 471 NHL cases in the pooled analyses, 11 976 (69%) were derived from studies that classified NHL subtypes according to the WHO classification (2,3) or its closely related predecessor, the Revised European-American Lymphoma classification (68) (Table 3). The remaining 5 495 (31%) cases were classified according to the Working Formulation (69). Among cases originally defined by the WHO classification, 11 023 (92%) were assigned to one of the 11 subtypes included in this project (i.e., with >100 cases), with the remaining cases assigned to a rare ($N = 50$ total, $<1\%$) or unspecified ($N = 900$, 8%) NHL subtype. Where the Working Formulation was the original coding scheme, 3 106 (57%) cases were assigned to one of the 11 subtypes included in this project, with the remaining 2 389 (43%) considered poorly specified because certain Working Formulation subtypes do not reliably correspond to subtypes defined by the WHO (e.g., chronic lymphocytic leukemia/small lymphocytic lymphoma) or were not recognized in the Working Formulation (e.g., marginal zone lymphoma, mantle cell lymphoma) (64).

Risk Factors

Analyses included risk factors with data from at least four studies (Table 4, Supplementary Table 1). Details of the harmonization of exposure variables across studies are provided for medical history factors and family history of hematologic malignancy (Table 5), lifestyle factors (Table 6), and farming and occupation (Table 7).

Discussion

The InterLymph NHL Subtypes Project represents the largest and most comprehensive analysis of medical history, lifestyle factors, family history of hematologic malignancy, and occupation with risk for specific NHL subtypes conducted to date. Findings from this project, as described in subsequent articles in this issue (78–89), accomplish two of the primary goals of the consortium: investigation of the etiology of specific NHL subtypes and comparison of risk factors, including those of rare prevalence, among NHL

Table 6. Harmonization of lifestyle risk factor data for the InterLymph NHL Subtypes Project*

Risk factor	Analytic variables	Notes
Anthropometric measures (38)	<ul style="list-style-type: none"> • Height • Usual adult weight • Usual adult body mass index • Young adulthood body mass index 	<ul style="list-style-type: none"> • Usual adult weight was asked directly or derived from weight 1–5 y prior to diagnosis/interview. • Data on weight during young adulthood corresponded to ages 18–30 y. In seven studies, these data were collected directly by querying participants regarding their weight at specific ages during 18–30 y. For the studies that queried usual adult weight only (eight studies), weight during young adulthood was assigned from usual adult weight for individuals aged 18–30 y at diagnosis (cases) or interview (controls), or was left as missing otherwise. • Analyses of height and weight used sex-specific quartiles among controls. • Body mass index was computed as kg/m². • Mean correlation among anthropometric measures = 0.20.
Alcohol consumption (36)	<ul style="list-style-type: none"> • Any history of alcohol consumption • Current versus former consumption • Age at initiation of consumption • Frequency of consumption (drinks/wk) • Intensity of consumption (g ethanol/wk) • Duration of consumption • Lifetime consumption (kg) 	<ul style="list-style-type: none"> • Data were collected and analyzed separately by beverage type (e.g., beer, wine, and liquor) and then summed to evaluate total alcohol consumption (15 studies), or collected only for any alcohol consumption (two studies). • Alcohol consumption was defined as consumption of alcohol ≥1 time per month on average as an adult. • Former consumption was defined as stopping drinking within 2 y of diagnosis/interview (eight studies). • Frequency of consumption was defined as number of drinks per week of standardized portions by beverage type (beer: 12 ounces or 355 mL, wine: 4 ounces or 118 mL, and liquor: 1.5 ounces or 44 mL). • Intensity of consumption was defined as number of drinks per week × grams of ethanol per drink (beer: 12.9g, wine: 9.3g, and liquor: 15.9g). • Age at initiation and duration of consumption were limited to seven studies. • Mean correlation among alcohol consumption variables = 0.61.
Cigarette smoking (35)	<ul style="list-style-type: none"> • Any history of cigarette smoking • Current versus former smokers • Years since quitting for former smokers • Usual number of cigarettes per day • Duration of smoking • Lifetime exposure to smoking (pack-years) 	<ul style="list-style-type: none"> • Ever smokers were defined as having smoked >100 cigarettes in their lifetime or having smoked regularly (at least 1 cigarette per day) for at least 6 months. • Former smoking was defined as stopping smoking within 2 y of diagnosis/interview. • Some studies did not collect information on duration of smoking. • Mean correlation among smoking variables = 0.79.
Physical activity	<ul style="list-style-type: none"> • Recreational physical activity 	<ul style="list-style-type: none"> • Data on recreational physical activity were classified as vigorous, moderate, mild, or no regular activity.
Personal hair dye use (39)	<ul style="list-style-type: none"> • Ever personal hair dye use • Type of hair dye used • Color of hair dye used • Duration of hair dye use • Frequency of hair dye use • First hair dye use before versus after 1980 	<ul style="list-style-type: none"> • For each personal hair dye product used, data were collected on the color, type, age at first use, and frequency and duration of use. • Analyses were performed by calendar year of first use (before versus after 1980) due to substantial changes in hair dye formulations. • Men were excluded from analysis. • Mean correlation among hair dye variables = 0.52.
Sun exposure (32)	<ul style="list-style-type: none"> • Lifetime total sun exposure (hours/week) • Lifetime recreational sun exposure (h/wk) 	<ul style="list-style-type: none"> • Exposure was reported as recreational (three studies), recreational/nonrecreational (five studies), or total (three studies). • For studies that asked about sun exposures separately at different time periods (e.g., by decade of life or at certain time points before diagnosis/interview), a composite measure of “lifetime” exposure was computed using time-weighted averages of reported data. • Correlation between total and recreational sun exposure = 0.73.

* InterLymph = International Lymphoma Epidemiology Consortium; NHL = non-Hodgkin Lymphoma.

subtypes to better understand the etiologic heterogeneity within this common hematologic malignancy.

The primary strengths of the project are the large sample size, achieved by pooling data from 20 studies with a total of 17 471 NHL cases and 23 096 controls, and centralized data harmonization and analysis. For less common NHL subtypes, the relatively

large sample size enabled the first broad investigation of associations for medical history, lifestyle factors, family history of hematologic malignancy, and occupation, with sufficient statistical power to detect ORs < 2.0 for prevalent exposures (e.g., obesity) and ORs of 2.0–4.0 for rarer exposures (e.g., autoimmune conditions) or exposures ascertained in fewer studies (Figure 1). For common NHL

Table 7. Harmonization of farming and occupational risk factor data for the InterLymph NHL Subtypes Project

Risk factor	Analytic variables	Notes
Farm exposure	<ul style="list-style-type: none"> • Ever lived on a farm • Ever worked on a farm • Ever lived or worked on a farm 	<ul style="list-style-type: none"> • Self-reported history of working on a farm (six studies) or living or working on a farm (six studies separated a history of living and working, and four studies queried participants in a single question). • Mean correlation among farming variables (including occupations below) = 0.34.
Occupation	<ul style="list-style-type: none"> • Baker or miller • Chemist or chemical worker • Cleaner (+charworker) • Driver (+material handling equipment operator) • Drycleaner • Electrical/electronics worker (+electrical fitter) • Engine mechanic • Farmer or farm worker of any type (+animal, crop, field crop and vegetable, mixed/unspecified, and general farm worker) • Firefighter • Forestry worker • Hairdresser (+women's hairdresser) • General unspecified laborer • Leather worker • Meat worker • Medical worker • Metal processer • Metal worker • Painter (+spray painter except construction) • Pulp and paper worker • Petroleum worker • Printer • Teacher (+university and higher education, secondary education, and pre-primary education teacher) • Textile worker (+fiber preparer, sewer/embroiderer) • Undertaker or embalmer • Welder or flamecutter • Woodworker (+general carpenter) 	<ul style="list-style-type: none"> • A detailed work history was captured in eight studies, and an additional two studies collected information on the longest held occupation. • Occupations were coded according to the International Standard Classification of Occupations, Revised Edition 1968 (77). • Based on literature review, 26 categories of occupations were included in this analysis based on a priori evidence of an association with lymphoid malignancies. Certain subgroups with more specific occupations within these categories (specified in parentheses) also were included based on post hoc evidence of association in a recent pooled analysis. • Mean correlation among 24 occupations (excluding farming and hairdye) = 0.0.

InterLymph = International Lymphoma Epidemiology Consortium; NHL = non-Hodgkin Lymphoma.

subtypes, the large sample size facilitated evaluation of risk factors in multivariate models, allowing for consideration of potential confounding and effect modification among risk factors, with sufficient statistical power to detect ORs < 2.0 even for some rarer exposures.

By centralizing the data harmonization and analysis, we ensured rigorous quality control at all stages of the project and standardized approaches to defining exposures and conducting statistical models, which allowed both pooling and direct comparisons among studies and within subgroups. We also leveraged the vast interdisciplinary expertise of InterLymph collaborators to define and categorize both exposure and outcome variables for analysis.

Despite the strengths noted above, several weaknesses of the project should be taken into consideration when interpreting the results. A key complication of the analysis was the variability of available data on both exposures and outcomes from different studies (Tables 3–4, Supplementary Table 1). Although certain exposures (e.g., family history of hematologic malignancy, history of cigarette smoking) were ascertained by nearly all studies, data on other exposures (e.g., reproductive history, personal hair dye use) were collected in fewer than half the studies. Individual studies also had varying eligibility criteria for inclusion of specific NHL subtypes, particularly the inclusion of lymphoid leukemias in some but not all studies.

Another limitation was lack of centralized pathology review of all cases included in the pooled analysis, although nearly all studies individually conducted some form of pathology review by at least one expert hematopathologist to confirm the initial diagnoses and assign NHL subtypes. Insufficient pathology data were available to further subclassify certain histological subtypes, such as diffuse large B-cell lymphoma, which comprises numerous subentities (3).

Additional limitations of the project are similar to those inherent in pooled analyses of case-control studies with interview- or questionnaire-based (i.e., self-reported) ascertainment of exposures. Examples include potential bias of risk estimates due to biased selection of the study population, differential recall of exposures between cases and controls, and exclusion of cases with the most aggressive disease because studies could have missed cases who had died or were too ill to participate, although rapid case-ascertainment used by most studies should have minimized such effects. Exposure information was not ascertained uniformly in all studies, although centralized harmonization of data enabled us to apply standardized exposure definitions despite differences in questionnaire structure. Analyses were restricted to those exposures for which data were collected in the individual studies. Finally, the studies included in the project were predominantly conducted in non-Hispanic white populations

in Western countries, and thus the results may not be generalizable to individuals in with substantially different exposure prevalences (e.g., hepatitis C virus infection, autoimmune conditions).

The InterLymph NHL Subtypes Project demonstrates the benefits of long-term and large-scale international collaboration for advancing etiologic research. Results from the project identify important associations with specific NHL subtypes for some risk factors and shared among multiple NHL subtypes for others (78–89). Findings also suggest possible mechanisms of lymphomagenesis and provide clues for prevention with modifiable risk factors. Future research with complementary study designs (e.g., prospective cohort studies) will help confirm associations observed in these case-control data. Additionally, combining our findings with large-scale studies of genetic susceptibility will provide further insight into the interplay of environmental and genetic factors in the etiology of NHL.

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