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Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph)

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Recent evidence suggests that there is etiologic heterogeneity among the various subtypes of lymphoid neoplasms. However, epidemiologic analyses by disease subtype have proven challenging due to the numerous clinical and pathologic schemes used to classify lymphomas and lymphoid leukemias over the last several decades. On behalf of the International Lymphoma Epidemiology Consortium (InterLymph) Pathology Working Group, we present a proposed nested classification of lymphoid neoplasms to facilitate the analysis of lymphoid neoplasm subtypes in epidemiologic research. The proposed classification is based on the World Health Organization classification of lymphoid neoplasms and the International Classification of Diseases–Oncology, Third Edition (ICD-O-3). We also provide a translation into the proposed classification from previous classifications, including the Working Formulation, Revised European-American Lymphoma (REAL) classification, and ICD-O-2. We recommend that epidemiologic studies include analyses by lymphoma subtype to the most detailed extent allowable by sample size. The standardization of groupings for epidemiologic research of lymphoma subtypes is essential for comparing subtype-specific reports in the literature, harmonizing cases within a single study diagnosed using different systems, as well as combining data from multiple studies for the purpose of pooled analysis or meta-analysis, and will probably prove to be critical for elucidating etiologies of the various lymphoid neoplasms. (Blood. 2007;110:695-708)

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Introduction

Lymphoid neoplasms, including lymphoma, myeloma, and lymphoid leukemia, arise from the malignant transformation of normal lymphoid cells at various stages of differentiation. Together, lymphoid neoplasms comprise the sixth most common group of malignancies worldwide in men and women.[1] Although some lymphoid neoplasms have been linked to certain infections and severe immunosuppression, the etiologies of most lymphoid neoplasms remain largely unknown, and evidence from descriptive and analytical epidemiologic studies increasingly points to etiologic heterogeneity among the lymphoid neoplasm subtypes.[2,3]

Changes in our understanding of lymphoid neoplasms have resulted in the evolution of numerous clinical and pathologic classification schemes over the past 50 years, particularly for non-Hodgkin lymphomas (NHL).[4-7] Throughout much of this time, lymphomas were categorized predominantly by morphology according to the Rappaport classification,[8] by morphology and clinical prognosis according to the Working Formulation,[9] or by cell lineage and differentiation according to the Lukes and Collins[10] or Kiel[11,12] classifications. These lymphoma classification schemes were largely replaced in 1994 by the Revised European-American Lymphoma (REAL) classification, which incorporated morphologic, immunophenotypic, genotypic, and clinical features into disease subtype definitions[13]; in 1995, some REAL classification subtypes were incorporated into the International Classification of Diseases for Oncology, Second Edition (ICD-O-2).[14,15] Leukemias were categorized by histology according to the French-American-British (FAB) classification from 1976 to 2000.[16,17]

In 2001, the World Health Organization (WHO) introduced a new classification built on the REAL and FAB classifications that represents the current "gold standard" for classifying all hematopoietic neoplasms.[18] Within the lymphoid neoplasms, the WHO system distinguishes Hodgkin lymphoma from NHL based on morphologic and immunologic characteristics. Stage of differentiation and additional morphologic, phenotypic, genotypic, and

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clinical features are used to distinguish the various NHL subtypes. Some lymphomas and corresponding lymphoid leukemias are recognized as different phases (solid and circulating, respectively) of the same disease entity. Importantly, the WHO classification represents a consensus classification for clinical and pathologic use and has been adopted worldwide, including the incorporation of WHO terminology into ICD-O-3.[19]

Implementation of the WHO classification in epidemiologic research has been slow, however, for several reasons. First, current analyses of many studies include cases diagnosed prior to the WHO classification and, thus, classified according to various older schemes, but there is no standard for translating from these historical classifications. Second, the WHO classification stratifies lymphoid neoplasms into approximately 40 categories, precluding analysis of individual WHO subtypes for all but the most common disease entities due to a lack of adequate sample size in many individual studies. Finally, it is not clear whether the WHO definitions of individual lymphoid neoplasm subtypes are optimal for discovering the elusive etiologies of these diseases. Recent studies suggest that some risk factors are related to specific lymphoma subtypes,[3,20-23] whereas other risk factors appear to be related to multiple subtypes[24,25] or to virtually all lymphomas,[26] yet there exists no standard methodology for combining various disease entities for epidemiologic research.

To overcome these obstacles and, thereby, facilitate the analysis of lymphoid neoplasm subtypes in epidemiologic research, we propose a nested classification for the study of lymphoid neoplasms that is based on the WHO classification and provides a translation from previous classifications.

Materials and methods

The Institutional Review Board at each institution where cases were identified approved the protocols for each study.

Development of a nested classification

The proposed nested classification, based on the WHO classification, was developed by the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph) (http://epi.grants.cancer.gov/InterLymph/). InterLymph is an open organization of international investigators conducting epidemiologic research on lymphoid neoplasms. The Pathology Working Group within InterLymph is composed of expert hematopathologists, epidemiologists, and other investigators with an interest in disease classification.

Originally, 3 nested classification schemes from individual studies (contributed by M. M. from the European multicenter case-control study EPILYMPH, L.M.M. and D.D.W.,[2] and W.C. and D.D.W.) were combined to develop a comprehensive WHO-based nested classification for all lymphoid neoplasms. The hierarchical groupings within this classification were defined by numerous parameters, including morphology, immunophenotype, genotype, stage of differentiation, and clinical features, including the site of occurrence. A hierarchical design was chosen for the proposed classification in order to explore etiologic similarities and differences among lymphoma subtypes, as defined by the various class parameters.[27] The proposed nested classification was circulated to all Pathology Working Group participants, who submitted comments and questions for discussion via e-mails, conference calls, and the InterLymph annual meetings in July 2005 and March 2006 until a consensus classification was reached.

Although we considered addressing immunodeficiency disorders using our nested classification approach, because of the complex nature of the relationship between the broad array of immunodeficiency conditions and lymphoid neoplasms, we decided to exclude consideration of the special problems posed by immunodeficiency disorders in our proposed classification scheme.

Descriptive analyses

In order to estimate the incidence of lymphoid neoplasm subtypes within the proposed nested classification, descriptive analyses were conducted using population-based data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registries.[28] Our analyses considered the incidence of malignant lymphoid neoplasms diagnosed during 2001 to 2003, the 3 years for which cases were directly coded using ICD-O-3 and complete data were available (based on the November 2005 SEER data submission, released April 2006). Data were compiled from 17 SEER registries, including 8 states (Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah), 6 metropolitan areas (Detroit, MI; Los Angeles County, San Jose/Monterey, and San Francisco/Oakland, CA; Seattle/Puget Sound, WA; and Atlanta, GA), the remainder of California, rural Georgia, and the Alaska Native Tumor Registry.[29] The combined population from these regions is approximately 78% white, 11% black, 9% Asian, and 1% American Indian/Alaska Native, and accounts for 26% of the total US population.[30]

For each newly identified case of a lymphoid neoplasm, SEER registries report patient demographic data, information on the tumor subtype using the WHO terminology and ICD-O-3,[19] primary site, clinical behavior, and immunophenotype (B cell, T/natural killer [NK] cell, or unknown). The distribution of lymphoid neoplasms within each hierarchical category of the proposed nested classification was described by computing for each category the number of cases and incidence rate using SEER*Stat software, version 6.2.3 (National Cancer Institute, Bethesda, MD).[31] Incidence rates, computed by aggregating county resident population estimates from the US Census Bureau, were directly age adjusted to the 2000 US standard population and are expressed per 100 000 person-years.[28]

Incorporation of historical classifications

Incorporating historical classifications into the proposed classification is essential for the analyses of lymphoma subtypes from epidemiologic studies conducted before 2001 when the WHO classification was introduced, comparing subtype-specific reports in the literature, harmonizing cases within a single study diagnosed during different time periods and classified in different systems, as well as combining data from multiple studies for the purpose of pooled analysis or meta-analysis. We therefore provide a translation into the proposed classification from ICD-O-2, the REAL classification, and the Working Formulation.

ICD-O-2. Categories of the ICD-O-2[15] were translated into the proposed nested classification using the SEER ICD-O-2 to ICD-O-3 conversion algorithm.[14] The reliability of this conversion algorithm has been evaluated previously.[32] Conversion from ICD-O-2 is more valid for cases diagnosed after 1995, when additional ICD-O-2 codes for marginal zone lymphomas were added, than for cases diagnosed before 1995. ICD-O-1 codes may be translated to ICD-O-2 for cases diagnosed before 1992,[33] but the reliability of this translation has not been evaluated.

REAL classification. Because the WHO classification was largely based on the REAL classification, REAL categories could be directly translated into the proposed nested classification scheme, with 2 exceptions. The REAL provisional entity, "high-grade B-cell lymphoma, Burkitt-like," is heterogeneous, including Burkitt lymphoma with atypical morphology and diffuse large B-cell lymphoma (DLBCL) with high-grade histology,[13,34] and it was not included as a separate category in the WHO classification.[18] As suggested in the WHO classification, this REAL category will only be accepted as Burkitt lymphoma in the nested classification if strict criteria are met (Table 3). The REAL provisional entity, "anaplastic large cell lymphoma, Hodgkin-like," also was not included as a separate category in the WHO classification because it includes cases of both Hodgkin lymphoma and anaplastic large cell lymphoma; this entity is included in the nested classification as lymphoid neoplasm, not otherwise specified (NOS), unknown lineage.

Working Formulation. Categories of the Working Formulation were translated into the proposed nested classification using data from

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4 studies.[34-38] In each study, cases were classified according to both the Working Formulation and the REAL/WHO classification. Agreement between Working Formulation categories and lymphoid neoplasm subtypes in the nested classification was assessed by computing the positive predictive value (PPV) for all groups with at least 5 cases.[39]

In the first study (A), participants included 694 cases of NHL recruited for a population-based epidemiologic study in Australia during 2000 to 2001.[37,38] The Working Formulation category was assigned to each case from the morphologic description in the original pathology report, which was reviewed by an anatomical pathologist with an interest in hematopathology. The immunophenotype was ignored for this exercise. A WHO category was then assigned to each case by the same pathologist after review of all the pathology reports (including immunophenotype, available in 96% of cases), and review of slides and further immunostains for a subset of 315 cases. In another study (B), participants included 601 cases of NHL recruited for a population-based epidemiologic study in Connecticut during 1995 to 2001.[35] Pathology reports and materials were reviewed independently by 2 pathologists with an interest in hematopathology, and cases were classified by Working Formulation and REAL classification categories. Disagreements were resolved by joint review. In the third study (C), 1375 cases of NHL identified consecutively during 1988 to 1990 in 9 institutions from 8 countries were used for evaluation of the clinical relevance of the REAL classification.[34] Our analysis of this study includes separate data from 2 expert hematopathologists (D.D.W. and B. N. Nathwani, University of Southern California, Los Angeles, CA), who independently reviewed pathology reports and slides and classified cases by the Working Formulation and REAL classification categories. In the fourth study (D), participants included 670 cases of NHL recruited for 2 clinical trials during 1985 to 1991.[36] During the trials, cases were assigned a Working Formulation category by an expert hematopathologist. Pathology materials were re-examined during 1994 to 1995, and a REAL classification category was assigned by 2 expert hematopathologists. Immunophenotype was available in 71% of cases, and mandatory only in the diagnosis of T-cell lymphoma and anaplastic large-cell lymphoma. Cases from each of the 4 studies were predominantly white (70%-95%).

Although the availability of immunophenotype data for cases is known to substantially improve the diagnosis of numerous lymphoma subtypes,[34] it is not known whether the incorporation of immunophenotype data would improve the translation of the Working Formulation categories into the proposed nested classification. We therefore also computed the PPV between Working Formulation categories and lymphoid neoplasm subtypes in the nested classification by immunophenotype.

Results

Proposed nested classification

Figure 1 schematically presents our proposed nested classification of lymphoid neoplasms for use in epidemiologic research. The ICD-O-3 codes corresponding to each WHO subtype are presented in Table 1. Hierarchical group 1 defines the scope of this nested classification, including all malignant neoplasms of lymphoid origin. Similar to the WHO classification, the proposed nested classification first distinguishes Hodgkin lymphomas from all other malignant lymphoid neoplasms (hierarchical group 2).

Among the Hodgkin lymphomas, hierarchical group 3 distinguishes classic Hodgkin lymphoma from nodular lymphocyte predominant Hodgkin lymphoma. In studies with sufficient sample size, classic Hodgkin lymphomas can be further classified as lymphocyte-rich, mixed cellularity, lymphocyte-depleted, and nodular sclerosis subtypes (hierarchical groups 4 and 5). The subcategorization of classic Hodgkin lymphoma was driven by evidence that the categories are epidemiologically meaningful. Specifically, the incidence of mixed cellularity classic Hodgkin lymphoma is higher among males than females and peaks at ages older than 75 years, and the risk is highest among those with low socioeconomic status; in contrast, the incidence of nodular sclerosis classic Hodgkin lymphoma is similar among males and females and peaks at 15 to 34 years of age, and the risk is highest among those with high socioeconomic status.[2,20]

Among the NHLs, similar to the WHO classification, the proposed nested classification distinguishes among B-cell NHL, T-cell NHL (including NK-cell NHL), and NHL of unknown cell lineage (hierarchical group 3). These categories are then classified by stage of differentiation into mature B-cell NHL, mature T-cell NHL, and precursor cell NHL (ie, lymphoblastic leukemia/lymphoma; hierarchical group 4). Finally, the mature B- and T-cell NHLs are further characterized based on similarities in morphologic, genotypic, and clinical features into major NHL subtypes (hierachical group 5) and more detailed NHL subtypes (hierarchical group 6). In level 5 of the T-cell neoplasm category, we separated several entities that present with leukemic/disseminated disease (adult T-cell leukemia/lymphoma [ATLL], large granular lymphocytic leukemia, and T-prolymphocytic leukemia) and the distinct clinicopathologic entities of mycosis fungoides/Sézary syndrome and NK/T-cell lymphoma. Although not ideal, this will allow grouping the other mature T-cell lymphomas together as "peripheral T-cell lymphoma," analogous to some of the heterogeneous B-cell categories in level 5 (eg, chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL]/prolymphocytic leukemia [PLL]/mantle cell lymphoma [MCL]), because few epidemiologic studies will have adequate numbers of the T-cell entities in level 6 for meaningful analysis. In addition, this allows us to separate several entities known to have a strong viral association (human T-lymphotrophic virus 1 [HTLV-1] and ATLL; Epstein-Barr virus [EBV] and NK/T-cell lymphoma) from the "peripheral T-cell lymphoma" group for epidemiologic analyses.

Incidence of lymphoid neoplasm subtypes as defined by the proposed nested classification

During 2001 to 2003, a total of 71 762 lymphoid neoplasms was diagnosed among residents of the 17 SEER registries (Table 2), of which 87.8% were NHL, 8.5% were Hodgkin lymphoma, and 3.7% were composite NHL/Hodgkin lymphoma or NOS (hierarchical group 2).

The vast majority (96.7%) of the 6103 Hodgkin lymphomas diagnosed were classic Hodgkin lymphomas, with nodular lymphocyte predominant Hodgkin lymphoma accounting for the remaining diagnoses (3.3%) (hierarchical group 3). The classic Hodgkin lymphomas included nodular sclerosis type (64.5%), lymphocyte-rich/mixed cellularity/lymphocyte-depleted types (18.6%), and cases not otherwise specified (16.9%) (hierarchical group 4).

Among the 62 982 NHLs, B-cell NHL accounted for 90.4%, T-cell NHL 6.8%, and NHL of unknown cell lineage 2.8% (hierarchical group 3). Regardless of cell lineage, precursor NHL was a small percentage of NHL (6.0%) (hierarchical group 4). The major NHL subtypes (hierarchical group 5) of mature B-cell origin consisted of CLL/SLL/PLL/MCL (19.4%), lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (2.1%), DLBCL (23.1%), Burkitt lymphoma/leukemia (1.4%), marginal zone lymphoma (5.7%), follicular lymphoma (12.0%), hairy cell leukemia (1.0%), and plasma-cell neoplasms (18.3%), whereas the major NHL subtypes of mature T-cell origin consisted of mycosis fungoides/Sézary syndrome (1.5%), peripheral T-cell lymphoma (3.8%), and several other rare subtypes (0.4%).

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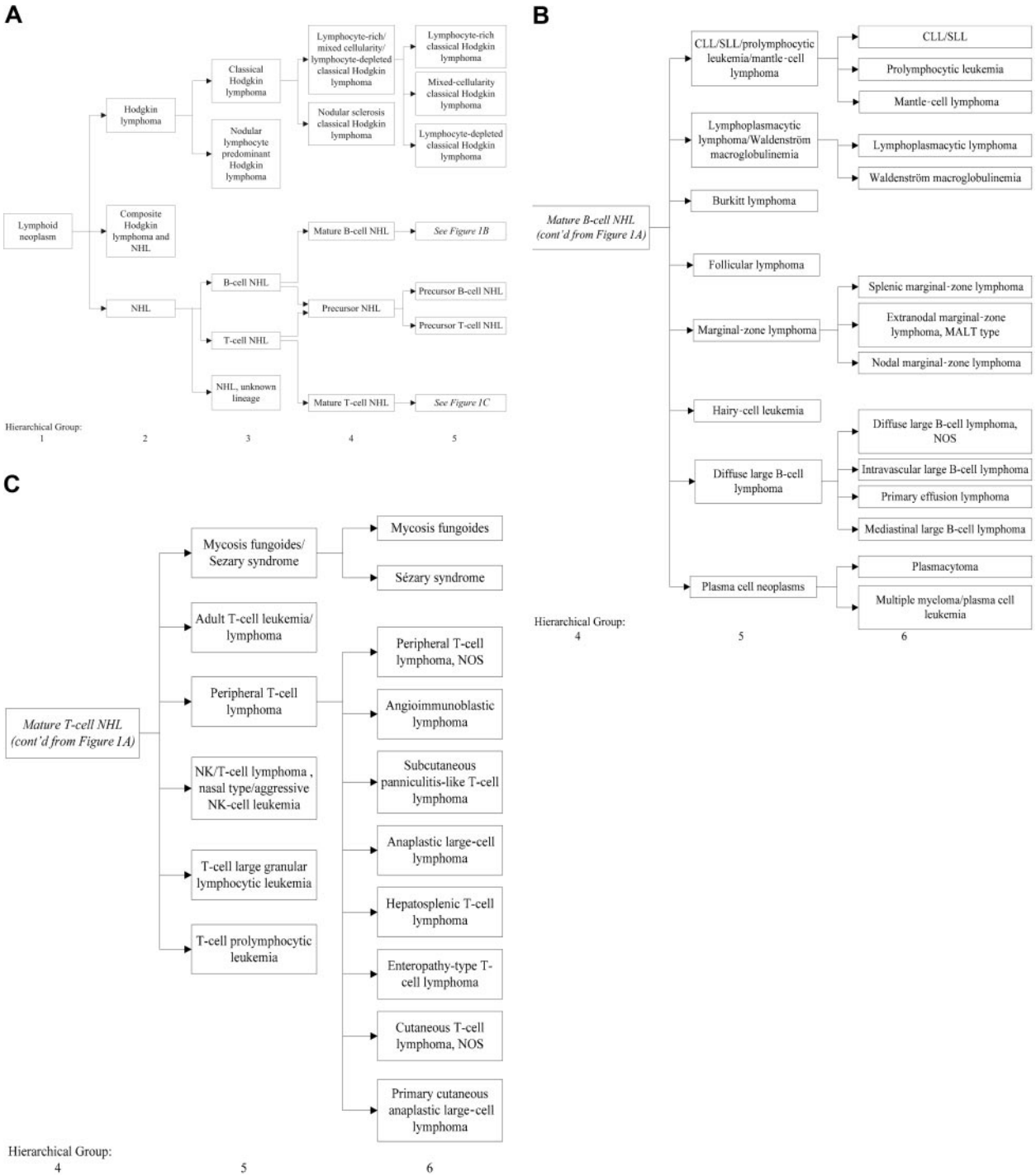

Figure 1. Proposed WHO-based nested classification of malignant lymphoid neoplasms. (A) Proposed WHO-based nested classification of malignant lymphoid neoplasms for epidemiologic research. (B) Proposed WHO-based nested classification of malignant lymphoid neoplasms: mature B-cell subtypes. (C) Proposed WHO-based nested classification of malignant lymphoid neoplasms: mature T-cell subtypes.

Incorporation of historical classifications

ICD-O-2. The ICD-O-2 codes corresponding to each WHO subtype and the proposed nested classification groupings are presented in Table 1. The ICD-O-2 codes included in each grouping were derived from the SEER ICD-O-2 to ICD-O-3 conversion algorithm,[14] the reliability of which has been evaluated previously.[32]

REAL classification. Cases classified using the REAL classification were grouped into the proposed nested classification based on the close relationship between the disease definitions in the REAL and WHO classifications (Table 3), with the exception of the provisional REAL categories "high-grade B-cell lymphoma, Burkitt-like" and "anaplastic large cell lymphoma, Hodgkin-like," as explained in "Materials and methods, REAL classification."

Working formulation. Cases classified using the Working Formulation were translated into the proposed nested classification using data from 4 studies (Tables 4-6; Tables S1-S5, available on the *Blood* website; see the Supplemental Materials link at the top of the online article). These data suggest that the lymphoblastic

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lymphomas (Working Formulation category I) can be reliably designated as precursor lymphoid neoplasms and, thus, be distinguished from mature NHLs (overall reliability in the 4 studies, 90.4%; n = 83).

Immunophenotyping was not routinely performed during the Working Formulation era; therefore, T-cell lymphoid neoplasms cannot be distinguished for most cases classified in the Working Formulation. However, because approximately 90% of NHLs among whites are of B-cell origin, most cases classified in the Working Formulation in studies of white populations can be reliably designated as B-cell NHLs (Table 4). Our data from the 4 studies combined (Table 6) show that the reliability of assuming all cases to be of B-cell origin was 97.1% for small lymphocytic lymphoma (A), 97.1% for follicular lymphoma (B-D), 82.8% for diffuse small cleaved cell lymphoma (E), 92.3% for diffuse large cell lymphomas (G), and 96.9% for small noncleaved cell lymphoma (J). Assuming all cases to be of B-cell origin was much less reliable for diffuse mixed small and large cell lymphoma (F) (50.3%) and immunoblastic lymphoma (H) (61.5%).

Cases classified into certain Working Formulation categories can be further classified into some of the specific mature B-cell NHL subtypes in the proposed nested classification (Table 4). The most consistent relationships occurred for translation of follicular lymphomas (B-D), which maintain the same designation of follicular lymphoma in the proposed nested classification (overall reliability, 88.9%; n = 1381), and diffuse large cell lymphomas (G) into DLBCL (overall reliability, 88.2%; n = 1165). Small noncleaved cell lymphomas (J) could be translated into the REAL combined categories of Burkitt lymphoma/leukemia and high-grade B-cell lymphoma, Burkitt-like (overall reliability, 90.6%; n = 159). However, the reliability of translation into the specific category of Burkitt lymphoma was substantially lower (22.0% for one pathologist and 21.8% for the other in study C, the only study with sufficient sample size for detailed analysis). Therefore, we require that small noncleaved cell lymphoma should be coded as Burkitt lymphoma only if the growth fraction is nearly 100% and the lymphoma is B-cell phenotype, $CD10^+$ and $Bcl2^-$, with proven or strong presumptive evidence of MYC translocation; otherwise, cases should be coded as DLBCL. Without these data, cases of small noncleaved cell lymphoma cannot be classified beyond mature B-cell NHL. Lower reliability was also observed for translation of immunoblastic lymphomas (H) into DLBCL (overall reliability, 60.9%; n = 447) and small lymphocytic lymphoma (A) into the combined grouping of CLL/SLL/PLL/MCL (overall reliability, 57.3%; n = 513). Diffuse small cleaved cell lymphoma (E) and diffuse mixed small and large cell lymphoma (F) were too heterogeneous for translation into a specific mature B-cell NHL subtype in the proposed nested classification.

The availability of basic immunophenotype data (ie, B-cell and T-cell typing only) for cases substantially improved the translation of certain Working Formulation categories into the proposed nested classification (Table 5). In particular, immunophenotype data improved the translation of B-cell immunoblastic lymphomas (H) into DLBCL (overall reliability, 98.9%; n = 275) and allowed for the identification of T-cell immunoblastic lymphomas (H) as peripheral T-cell lymphoma (overall reliability, 88.1%; n = 159). The incorporation of immunophenotype data resulted in much smaller improvements for those Working Formulation categories that could be reliably translated without immunophenotype data. Specifically, the translation of B-cell follicular lymphomas (B-D) into follicular lymphoma improved from 88.9% to 91.6%, and translation of B-cell diffuse large-cell lymphomas (G) into DLBCL improved from 88.2% to 95.5% (Table 6). Immunophenotype data also allowed the identification of diffuse large T-cell lymphomas (G) as peripheral T-cell lymphomas (overall reliability, 62.8%; n = 43), although diffuse large T-cell lymphomas were very rare (< 5%) in comparison with those of B-cell origin. Immunophenotype data also allowed for the identification of diffuse mixed small and large T-cell lymphomas (F) as peripheral T-cell lymphoma (overall reliability, 90.3%; n = 62); diffuse mixed small and large T-cell lymphomas accounted for more than one-third of the lymphomas in category F.

Immunophenotype data did not improve the translation of small lymphocytic lymphoma (A) into the proposed nested classification because this category was largely composed of CLL/SLL/PLL/MCL (57.3%), the marginal zone lymphomas (25.3%), and LPL/Waldenström macroglobulinemia (13.6%), all mature B-NHL subtypes. Similarly, immunophenotype data did not resolve the heterogeneity of the Working Formulation categories of B-cell and T-cell diffuse small cleaved cell lymphoma (E) or diffuse mixed small and large B-cell lymphoma (F), because these categories are also composed of several mature NHL subtypes.

Discussion

On behalf of the Pathology Working Group of the InterLymph Consortium, we present a proposed nested classification for the analysis of lymphoid neoplasm subtypes in epidemiologic research. Our proposal has 3 critical elements. First, the proposed classification is based on the new WHO classification, which is the first consensus classification that has been adopted worldwide. Second, the proposed classification is nested with hierarchical groupings defined according to clinical and pathologic features, which is critical for subtype-specific analyses within epidemiologic studies of limited sample size. Finally, the proposed classification provides a translation from previous lymphoma classifications, allowing for subtype analyses of cases from epidemiologic studies conducted prior to 2001 when the WHO classification was introduced. The standardization of groupings for epidemiologic analysis of lymphoma subtypes is essential for comparing subtype-specific reports in the literature, harmonizing cases within a single study classified in different systems, as well as combining data from multiple studies for the purpose of pooled analysis or meta-analysis,[21,25] and thereby will probably prove to be critical for elucidating the etiologies of various lymphoid neoplasms.

We propose that most large epidemiologic studies focus their analyses on the major NHL subtypes as defined by hierarchical group 5, and the major Hodgkin lymphoma subtypes as defined by hierarchical groups 3 and 4 (nodular lymphocyte predominant, nodular sclerosis, and lymphocyte-rich/mixed cellularity/lymphocyte-depleted Hodgkin lymphoma). Pooled analyses, meta-analyses, and individual studies with sufficient sample size should further examine risk factors associated with more specific subtypes.

Incorporation of historical classifications

The translation from previous lymphoma classifications into the proposed nested classification is particularly important for harmonizing lymphoid neoplasm subtype definitions from epidemiologic studies with cases diagnosed during different time periods and classified in different systems. In particular, numerous case-control studies have been conducted in recent years in an effort to explain the rising rate of NHL observed over the last half-century, and a

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Table 1. Proposed WHO-based nested classification of malignant lymphoid neoplasms for epidemiologic research

WHO categories	ICD-O-3 codes	ICD-O-2 codes*	Hierarchical group 1	2	3	4	5	6
Classic Hodgkin lymphoma								
Lymphocyte-rich	9651	9657, 9658	LN	HL	HL-C	HL-C-LR/MC/LD	HL-C-LR	
Mixed cellularity	9652	9652	LN	HL	HL-C	HL-C-LR/MC/LD	HL-C-MC	—
Lymphocyte-depleted	9653-9655	9653-9655	LN	HL	HL-C	HL-C-LR/MC/LD	HL-C-LD	—
Nodular sclerosis	9663-9667	9663-9667	LN	HL	HL-C	HL-C-NS	—	—
NOS	9650, 9661, 9662	9650, 9661, 9662	LN	HL	HL-C	—	—	—
Nodular lymphocyte predominant Hodgkin lymphoma	9659	9659, 9660	LN	HL	HL-NLP	—	—	—
Precursor lymphoblastic leukemia/lymphoma, B-cell	9727(B), 9728, 9835(B), 9836	9685(B), 9821(B), 9828(B)	LN	NHL	B-NHL	Precursor	Precursor B-NHL	—
Small lymphocytic lymphoma	9670	9670	LN	NHL	B-NHL	Mature B-NHL	CLL/SLL/ PLL/MCL	CLL/SLL
Chronic lymphocytic leukemia	9823	9823	LN	NHL	B-NHL	Mature B-NHL	CLL/SLL/ PLL/MCL	CLL/SLL
Prolymphocytic leukemia, B-cell	9833, 9832(B)	9825(B)	LN	NHL	B-NHL	Mature B-NHL	CLL/SLL/ PLL/MCL	B-PLL
Mantle-cell lymphoma	9673	9673, 9674, 9677	LN	NHL	B-NHL	Mature B-NHL	CLL/SLL/ PLL/MCL	MCL
Lymphoplasmacytic lymphoma†	9671	9671	LN	NHL	B-NHL	Mature B-NHL	LPL/ Waldenström	LPL
Waldenström macroglobulinemia†	9761	9761	LN	NHL	B-NHL	Mature B-NHL	LPL/ Waldenström	Waldenström
Diffuse large B-cell lymphoma, NOS	9680 (excl. site C49.9), 9684(B)	9680-9683 (excl. site C49.9), 9684(B), 9712, 9688§	LN	NHL	B-NHL	Mature B-NHL	DLBCL	DLBCL, NOS
Intravascular large B-cell lymphoma	9680 (site C49.9)	9680 (site C49.9)	LN	NHL	B-NHL	Mature B-NHL	DLBCL	Intravascular
Primary effusion lymphoma	9678	—	LN	NHL	B-NHL	Mature B-NHL	DLBCL	PEL
Mediastinal large B-cell lymphoma	9679	—	LN	NHL	B-NHL	Mature B-NHL	DLBCL	MLBCL
Burkitt lymphoma/leukemia	9687, 9826	9687, 9826	LN	NHL	B-NHL	Mature B-NHL	BL	—
Splenic marginal zone lymphoma	9689	—	LN	NHL	B-NHL	Mature B-NHL	MZL	SMZL
Extranodal marginal zone lymphoma, MALT type	9699 (excl. site C77.0-77.9), 9760, 9764	9710, 9711, 9715 (excl. site C77.0-77.9), 9760, 9764	LN	NHL	B-NHL	Mature B-NHL	MZL	EMZL, MALT
Nodal marginal zone lymphoma	9699 (site C77.0-77.9)	9710, 9711, 9715 (site C77.0-77.9)	LN	NHL	B-NHL	Mature B-NHL	MZL	NMZL
Follicular lymphoma	9690, 9691, 9695, 9698	9690-9693, 9695-9698	LN	NHL	B-NHL	Mature B-NHL	FL	—
Hairy-cell leukemia	9940	9940, 9941	LN	NHL	B-NHL	Mature B-NHL	HCL	—
Plasmacytoma	9731, 9734	9731	LN	NHL	B-NHL	Mature B-NHL	PCN	Plasmacytoma
Multiple myeloma/plasma-cell leukemia	9732, 9733	9732, 9830	LN	NHL	B-NHL	Mature B-NHL	PCN	MM
Heavy chain disease‡	9762	9762, 9763	LN	NHL	B-NHL	Mature B-NHL	—	
NHL, NOS, B-cell	9591(B), 9675(B)	9591-9593(B), 9595(B), 9672(B), 9675(B), 9676(B), 9686(B), 9694(B)	LN	NHL	B-NHL	—	—	—
Precursor lymphoblastic leukemia/lymphoma, T-cell	9727(T), 9729, 9835(T), 9837	9685(T), 9821(T), 9828(T)	LN	NHL	T-NHL	Precursor	Precursor T-NHL	—
Mycosis fungoides	9700	9700	LN	NHL	T-NHL	Mature T-NHL	MF/SS	MF
Sézary syndrome	9701	9701	LN	NHL	T-NHL	Mature T-NHL	MF/SS	SS
Peripheral T-cell lymphoma, NOS	9702, 9675(T)	9702, 9703, 9704, 9706, 9707, 9675(T), 9676(T)	LN	NHL	T-NHL	Mature T-NHL	PTCL	PTCL, NOS
Angioimmunoblastic T-cell lymphoma	9705	9705	LN	NHL	T-NHL	Mature T-NHL	PTCL	Angioimmunoblastic
Subcutaneous panniculitis-like T-cell lymphoma	9708	9708	LN	NHL	T-NHL	Mature T-NHL	PTCL	Subcutaneous panniculitis

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Table 1. Proposed WHO-based nested classification of malignant lymphoid neoplasms for epidemiologic research (continued)

WHO categories	ICD-O-3 codes	ICD-O-2 codes*	Hierarchical group 1	2	3	4	5	6
Anaplastic large-cell lymphoma, T-cell or null-cell type	9714	9714	LN	NHL	T-NHL	Mature T-NHL	PTCL	Anaplastic large cell
Hepatosplenic T-cell lymphoma	9716	9716	LN	NHL	T-NHL	Mature T-NHL	PTCL	Hepatosplenic
Enteropathy-type T-cell lymphoma	9717	9717	LN	NHL	T-NHL	Mature T-NHL	PTCL	Enteropathy
Cutaneous T-cell lymphoma, NOS	9709	9709	LN	NHL	T-NHL	Mature T-NHL	PTCL	Cutaneous T, NOS
Primary cutaneous anaplastic large-cell lymphoma	9718	—	LN	NHL	T-NHL	Mature T-NHL	PTCL	Primary cutaneous anaplastic
Adult T-cell leukemia/lymphoma	9827	9827	LN	NHL	T-NHL	Mature T-NHL	ATLL	—
NK/T-cell lymphoma, nasal-type/aggressive NK-cell leukemia	9719, 9948	9713	LN	NHL	T-NHL	Mature T-NHL	NK/T-cell lymphoma	—
T-cell large granular lymphocytic leukemia	9831	—	LN	NHL	T-NHL	Mature T-NHL	Large granular lymphocytic leukemia	—
Prolymphocytic leukemia, T-cell	9834, 9832(T)	9825(T)	LN	NHL	T-NHL	Mature T-NHL	T-PLL	—
NHL, NOS, T-cell	9591(T), 9684(T)	9591-9593(T), 9595(T), 9672(T), 9684(T), 9686(T), 9694(T)	LN	NHL	T-NHL	—	—	—
Precursor lymphoblastic leukemia/lymphoma, unknown lineage	9727(U), 9835(U)	9685(U), 9821(U), 9828(U)	LN	NHL	—	Precursor	—	—
Prolymphocytic leukemia, unknown lineage	9832(U)	9825(U)	LN	NHL	—	—	—	—
NHL, NOS, unknown lineage	9591(U), 9675(U), 9684(U)	9591-9593(U), 9595(U), 9672(U), 9675(U), 9676(U), 9686(U), 9694(U)	LN	NHL	—	—	—	—
Composite Hodgkin/NHL								
B-cell	9596(B)	—	LN	HL/NHL	—	—	—	—
T-cell	9596(T)	—	LN	HL/NHL	—	—	—	—
Unknown lineage	9596(U)	—	LN	HL/NHL	—	—	—	—
Lymphoid neoplasm, NOS								
B-cell	9590(B), 9594(B), 9820(B), 9970(B)	9590(B), 9594(B), 9820(B), 9822(B), 9824(B), 9850(B)	LN	—	—	—	—	—
T-cell	9590(T), 9594(T), 9820(T), 9970(T)	9590(T), 9594(T), 9820(T), 9822(T), 9824(T), 9850(T)	LN	—	—	—	—	—
Unknown lineage	9590(U), 9594(U), 9820(U), 9970(U)	9590(U), 9594(U), 9820(U), 9822(U), 9824(U), 9850(U)	LN	—	—	—	—	—

Cases of composite lymphoma with more than one type of NHL should be classified according to the low-grade component. Codes followed by parentheses indicate that immunophenotyping data (B-cell, T-/NK-cell, or unknown) should be used to assign cases to that lymphoid neoplasm subtype. Tables organized by ICD-O-2 and ICD-O-3 code are available from the author.

BL indicates Burkitt lymphoma/leukemia; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; HCL, hairy-cell leukemia; HL, Hodgkin lymphoma; HL/NHL, composite Hodgkin/non-Hodgkin lymphoma; HL-C, classical Hodgkin lymphoma; HL-C-LD, classical Hodgkin lymphoma, lymphocyte-depleted; HL-C-LR, classical Hodgkin lymphoma, lymphocyte rich; HL-C-MC, classical Hodgkin lymphoma, mixed cellularity; HL-C-NS, classical Hodgkin lymphoma, nodular sclerosis; HL-NLP, nodular lymphocyte predominant Hodgkin lymphoma; LN, lymphoid neoplasm; MALT, extranodal marginal-zone lymphoma of mucosa-associated lymphoid tissue; MF, mycosis fungoides; MLBCL, mediastinal large B-cell lymphoma; MM, multiple myeloma; MZL, marginal-zone lymphoma; NMZL, nodal marginal-zone lymphoma; PCN, plasma-cell neoplasm; PEL, primary effusion lymphoma; PTCL, peripheral T-cell lymphoma; SMZL, splenic marginal-zone lymphoma; and SS, Sézary syndrome; and —, category cannot be assigned.

*Conversion from ICD-O-2 is more valid for cases diagnosed after 1995, when additional ICD-O-2 codes for marginal-zone lymphomas were added, than for cases diagnosed before 1995. ICD-O-1 codes can be converted to ICD-O-2 using a SEER conversion algorithm.[33]

†Lymphoplasmacytic lymphoma and Waldenström macroglobulinemia are recognized as a single entity in the WHO classification; however, Waldenström macroglobulinemia may occur with other B-cell types and should be grouped as such when possible.

‡Heavy chain diseases share a single ICD-O-3 code, but the WHO classification considers γ heavy chain disease (associated with lymphoplasmacytic lymphoma), μ heavy chain disease (associated with CLL), and α heavy chain disease (associated with EMZL, MALT) to be distinct. Such cases should be grouped with specific histological types when possible.

§ICD-O-2 codes 9680-9683 (excl. site C49.9), 9684(B), 9712, and 9688 can be categorized as DLBCL in hierarchical group 5, but should be excluded from analyses in hierarchical group 6.

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Table 2. Incidence of lymphoid neoplasm subtypes as defined by the proposed nested classification, 17 SEER registries, 2001-2003

Lymphoid neoplasms	No. cases	Rate*	% of total	% of HL	% of NHL
Lymphoid neoplasms, total	71 762	33.42			
Hodgkin lymphoma	6 103	2.71	8.5		
Classic Hodgkin lymphoma	5 900	2.62	8.2	96.7	
Lymphocyte-rich/mixed cellularity/lymphocyte-depleted	1 097	0.50	1.5	18.0	
Lymphocyte-rich	171	0.08	0.2	2.8	
Mixed cellularity	858	0.39	1.2	14.1	
Lymphocyte-depleted	68	0.03	0.1	1.1	
Nodular sclerosis	3 806	1.67	5.3	62.4	
NOS	997	0.45	1.4	16.3	
Nodular lymphocyte predominant Hodgkin lymphoma	203	0.09	0.3	3.3	
NHL	62 982	29.46	87.8		
NHL, B-cell†	56 907	26.68	79.3		90.4
Mature NHL, B-cell	52 208	24.53	72.8		82.9
CLL/SLL/PLL/MCL	12 200	5.78	17.0		19.4
CLL/SLL	10 751	5.10	15.0		17.1
Prolymphocytic leukemia, B-cell	57	0.03	0.1		0.1
Mantle-cell lymphoma	1 392	0.66	1.9		2.2
LPL/Waldenstrom	1 333	0.63	1.9		2.1
Lymphoplasmacytic lymphoma	595	0.28	0.8		0.9
Waldenström macroglobulinemia	738	0.35	1.0		1.2
Diffuse large B-cell lymphoma	14 543	6.80	20.3		23.1
Diffuse large B-cell lymphoma, NOS	14 474	6.77	20.2		23.0
Intravascular large B-cell lymphoma	15	0.01	0.0		0.0
Primary effusion lymphoma	10	0.00	0.0		0.0
Mediastinal large B-cell lymphoma	44	0.02	0.1		0.1
Burkitt lymphoma/leukemia	863	0.39	1.2		1.4
Marginal-zone lymphoma	3 563	1.67	5.0		5.7
Splenic marginal-zone lymphoma	230	0.11	0.3		0.4
Extranodal marginal-zone lymphoma, MALT type	2 371	1.11	3.3		3.8
Nodal marginal-zone lymphoma	962	0.45	1.3		1.5
Follicular lymphoma	7 543	3.51	10.5		12.0
Hairy cell leukemia	645	0.30	0.9		1.0
Plasma cell neoplasms	11 510	5.45	16.0		18.3
Plasmacytoma	785	0.37	1.1		1.2
Multiple myeloma/plasma-cell leukemia	10 725	5.08	14.9		17.0
Heavy chain disease	8	~	~		~
NHL, NOS, B-cell	2 351	1.11	3.3		3.7
NHL, T-cell†	4 286	1.96	6.0		6.8
Mature NHL, T-cell	3 645	1.68	5.1		5.8
Mycosis fungoides/Sézary syndrome	957	0.44	1.3		1.5
Mycosis fungoides	934	0.43	1.3		1.5
Sézary syndrome	23	0.01	0.0		0.0
Peripheral T-cell lymphoma	2 405	1.11	3.4		3.8
Peripheral T-cell lymphoma, NOS	857	0.40	1.2		1.4
Angioimmunoblastic T-cell lymphoma	177	0.08	0.2		0.3
Subcutaneous panniculitis-like T-cell lymphoma	20	0.01	0.0		0.0
Anaplastic large-cell lymphoma, T-cell or null-cell type	629	0.29	0.9		1.0
Hepatosplenic T-cell lymphoma	13	0.01	0.0		0.0
Enteropathy-type T-cell lymphoma	18	0.01	0.0		0.0
Cutaneous T-cell lymphoma, NOS	501	0.23	0.7		0.8
Primary cutaneous anaplastic large-cell lymphoma	190	0.09	0.3		0.3
Adult T-cell leukemia/lymphoma	79	0.04	0.1		0.1
NK/T-cell lymphoma, nasal-type/aggressive NK-cell leukemia	130	0.06	0.2		0.2
T-cell large granular lymphocytic leukemia	25	0.01	0.0		0.0
Prolymphocytic leukemia, T-cell	49	0.02	0.1		0.1
NHL, NOS, T-cell	55	0.03	0.1		0.1
Precursor NHL	3 805	1.68	5.3		6.0
Precursor lymphoblastic leukemia/lymphoma, B-cell	2 348	1.04	3.3		3.7
Precursor lymphoblastic leukemia/lymphoma, T-cell	586	0.26	0.8		0.9
Precursor lymphoblastic leukemia/lymphoma, unknown lineage	871	0.39	1.2		1.4
NHL, unknown lineage†	1 789	0.82	2.5		2.8
Prolymphocytic leukemia, unknown lineage	40	0.02	0.1		0.1
NHL, NOS, unknown lineage	878	0.41	1.2		1.4

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Table 2. Incidence of lymphoid neoplasm subtypes as defined by the proposed nested classification, 17 SEER registries, 2001-2003 (continued)

Lymphoid neoplasms	No. cases	Rate*	% of total	% of HL	% of NHL
Composite Hodgkin/NHL	35	0.02	0.0		
Composite Hodgkin/NHL, B-cell	19	0.01	0.0		
Composite Hodgkin/NHL, T-cell	1	199	~		
Composite Hodgkin/NHL, unknown lineage	15	0.01	0.0		
Lymphoid neoplasm, NOS, B-cell	631	0.30	0.9		
Lymphoid neoplasm, NOS, T-cell	104	0.05	0.1		
Lymphoid neoplasm, NOS, unknown lineage	1 907	0.89	2.7		

Abbreviations are explained in Table 1.
~ indicates statistic was not calculated when fewer than 10 cases occurred.
*Incidence rates were age adjusted to the 2000 US population and are expressed per 100 000 person-years.
†Includes both mature and precursor neoplasms.

number of large cohort studies have ascertained lymphoma cases during follow-up over the last 10 to 15 years when multiple lymphoma classifications and versions of ICD-O were in use. Use of the proposed nested classification will not only resolve the variation in diagnoses within individual studies but also provide a guide for pooling data from different studies.

A previous study evaluated the reliability of the SEER ICD-O-2 to ICD-O-3 code conversion algorithm for 2 groups of cases diagnosed during 1988 to 1994 and 1998 to 2000.[32] That study found an overall reliability of 77% for the translation of individual codes from ICD-O-2 to ICD-O-3, with substantially higher reliability for some codes than others. When the codes were grouped into subtypes, reliability was generally high (> 80%) for the major NHL subtypes, including DLBCL, follicular lymphoma, Burkitt lymphoma/leukemia, marginal zone lymphoma, CLL/SLL/PLL/MCL, mycosis fungoides/Sézary syndrome, and peripheral T-cell lymphoma. We based our translation of cases coded in ICD-O-2 into the proposed nested classification on the SEER conversion algorithm, taking into account the findings of Clarke et al.[32,40] For example, ICD-O-3 code 9675 (malignant lymphoma, mixed small and large cell, diffuse) was placed in the category NHL, NOS, in the proposed nested classification. Although this code has previously been considered DLBCL, it has been shown to be heterogeneous[13] and Clarke et al[32] demonstrated that it is poorly reproducible. With the availability of the SEER conversion algorithm and an assessment of its reliability, we believe that all cases classified in ICD-O-2 can be translated into the proposed nested classification.

Our data suggest that, in studies of predominantly white populations, cases classified by the Working Formulation as follicular lymphoma (Working Formulation categories B-D), diffuse large cell lymphoma (G), and lymphoblastic lymphoma (I) can be reliably translated into major NHL subtypes in the proposed nested classification, even without the incorporation of immunophenotype data. However, small noncleaved cell lymphoma (J) can only be translated into Burkitt lymphoma if strict pathologic requirements are met because of overlap between the morphologic features of Burkitt lymphoma and DLBCL[18,41]; many of these cases will require pathology review with detailed phenotyping to achieve accurate translation. Together, the cases that can be translated (Working Formulation categories B-D, G, and I) account for approximately two-thirds of NHL (excluding plasma-cell neoplasms, which typically were not included in studies of NHL conducted during the Working Formulation era).

The availability of basic immunophenotype data (ie, B-cell and T-cell typing only) for cases substantially improves the translation of the Working Formulation categories into the proposed nested classification in several ways. First, the availability of immunophenotype data increases the accuracy of translating some Working Formulation categories into specific B-cell NHL subtypes in the nested classification, particularly immunoblastic lymphoma (Working Formulation category H). Second, it allows the translation of some Working Formulation categories into certain specific T-cell NHL subtypes. Finally, the availability of immunophenotype data makes the nested classification applicable to all population groups, including Asians in whom T-cell and NK-cell lymphomas account for a larger proportion of cases compared with whites.[42-45]

In some studies, it may be possible to obtain tumor tissue blocks to conduct basic immunophenotyping. Our data suggest that the inclusion of immunophenotyping data would greatly benefit the translation of immunoblastic lymphomas (Working Formulation category H) into DLBCL and peripheral T-cell lymphoma. Immunophenotyping the diffuse mixed small and large cell lymphomas (category F) would also enable the identification of peripheral T-cell lymphomas, and those of B-cell origin could be further categorized by more detailed phenotyping. The same is true for the small lymphocytic (category A) and diffuse small cleaved cell (category E) lymphomas. Obtaining tumor tissue for immunophenotyping lymphomas from the other Working Formulation categories would be substantially less cost effective in predominantly white populations. Although immunophenotyping diffuse large cell lymphomas (G) would enable the identification of peripheral T-cell lymphomas in this category, diffuse large T-cell lymphomas are very rare compared with those of B-cell origin. Immunophenotyping did not result in substantially improved translation of the other Working Formulation categories (B-D, J) into the proposed nested classification in the predominantly white populations we analyzed. In more diverse or nonwhite populations, however, the incorporation of immunophenotype would be critical for the translation of cases classified in the Working Formulation into a WHO-based classification.

Conclusions

The scope of the nested classification is restricted to all malignant neoplasms of lymphoid origin. Thus, the nested classification excludes malignancies of myeloid origin, including histiocytic and dendritic-cell neoplasms (ICD-O-3 9750-9758), and lymphoid proliferations of uncertain malignant potential, including monoclonal gammopathy (ICD-O-3 9765), angiocentric immunoproliferative lesion/lymphomatoid granulomatosis (9766), angioimmunoblastic lymphadenopathy (9767), T-γ lymphoproliferative disease (9768), and immunoglobulin deposition disease/systemic light chain disease/primary amyloidosis (9769). Due to the rare occurrence of these entities, their inclusion or exclusion should not substantially impact the analysis of lymphoid neoplasm subtypes in epidemiologic research.

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Table 3. Incorporation of lymphoid neoplasm subtypes defined by the REAL classification into the proposed WHO-based nested classification of malignant lymphoid neoplasms

REAL classification categories	Hierarchical group 1	2	3	4	5	6
B-cell neoplasms						
I. Precursor B-cell neoplasm: precursor B-lymphoblastic leukemia/lymphoma	LN	NHL	B-NHL	Precursor	Precursor B-NHL	—
II. Peripheral B-cell neoplasms						
A. B-cell chronic lymphocytic leukemia/prolymphocytic leukemia/small lymphocytic lymphoma	LN	NHL	B-NHL	Mature B-NHL	CLL/SLL/PLL/MCL	CLL/SLL
B. Lymphoplasmacytoid lymphoma/immunocytoma	LN	NHL	B-NHL	Mature B-NHL	LPL/Waldenström	LPL
C. Mantle-cell lymphoma	LN	NHL	B-NHL	Mature B-NHL	CLL/SLL/PLL/MCL	MCL
D. Follicle center-cell lymphoma, follicular	LN	NHL	B-NHL	Mature B-NHL	FL	—
E. Marginal-zone B-cell lymphoma						
1. Extranodal (MALT-type)	LN	NHL	B-NHL	Mature B-NHL	MZL	EMZL, MALT
2. Provisional subtype: nodal	LN	NHL	B-NHL	Mature B-NHL	MZL	NMZL
F. Provisional entity: splenic marginal-zone lymphoma	LN	NHL	B-NHL	Mature B-NHL	MZL	SMZL
G. Hairy-cell leukemia	LN	NHL	B-NHL	Mature B-NHL	HCL	—
H. Plasmacytoma/plasma-cell myeloma	LN	NHL	B-NHL	Mature B-NHL	PCN	—
I. Diffuse large B-cell lymphoma	LN	NHL	B-NHL	Mature B-NHL	DLBCL	DLBCL
1. Subtype: primary mediastinal (thymic) B-cell lymphoma	LN	NHL	B-NHL	Mature B-NHL	DLBCL	MLBCL
J. Burkitt's lymphoma	LN	NHL	B-NHL	Mature B-NHL	BL	—
K. Provisional entity: high-grade B-cell lymphoma, Burkitt-like*	LN	NHL	B-NHL	Mature B-NHL	BL	—
T-cell and putative NK-cell neoplasms						
I. Precursor T-cell neoplasm: precursor T-lymphoblastic lymphoma/leukemia	LN	NHL	T-NHL	Precursor	Precursor T-NHL	—
II. Peripheral T-cell and NK-cell neoplasms						
A. T-cell chronic lymphocytic leukemia/prolymphocytic leukemia	LN	NHL	T-NHL	Mature T-NHL	T-PLL	—
B. Large granular lymphocyte leukemia						
1. T-cell type	LN	NHL	T-NHL	Mature T-NHL	T-LGL	—
2. NK-cell type	LN	NHL	T-NHL	Mature T-NHL	—	—
C. Mycosis fungoides/Sezary's syndrome	LN	NHL	T-NHL	Mature T-NHL	MF/SS	—
D. Peripheral T-cell lymphomas, unspecified						
1. Combine all provisional cytologic categories (medium-sized cell, mixed medium and large large-cell, large-cell, lymphoepithelioid cell)	LN	NHL	T-NHL	Mature T-NHL	PTCL	PTCL, NOS
2. Provisional subtype: hepatosplenic γ/δ T-cell lymphoma	LN	NHL	T-NHL	Mature T-NHL	PTCL	Hepatosplenic
3. Provisional subtype: subcutaneous panniculitic T-cell lymphoma	LN	NHL	T-NHL	Mature T-NHL	PTCL	Subcutaneous panniculitis
E. Angioimmunoblastic T-cell lymphoma	LN	NHL	T-NHL	Mature T-NHL	PTCL	Angioimmunoblastic
F. Angiocentric lymphoma	LN	NHL	T-NHL	Mature T-NHL	NK/T-cell lymphoma	—
G. Intestinal T-cell lymphoma (+/− enteropathy associated)	LN	NHL	T-NHL	Mature T-NHL	PTCL	Enteropathy
H. Adult T-cell lymphoma/leukemia	LN	NHL	T-NHL	Mature T-NHL	ATLL	—
I. Anaplastic large-cell lymphoma						
1. Primary cutaneous (CD30+) type	LN	NHL	T-NHL	Mature T-NHL	PTCL	Primary cutaneous anaplastic
2. T-cell type	LN	NHL	T-NHL	Mature T-NHL	PTCL	Anaplastic large-cell
3. Null-cell type	LN	NHL	T-NHL	Mature T-NHL	PTCL	Anaplastic large-cell
J. Provisional entity: anaplastic large-cell lymphoma, Hodgkin's-like	LN	—	—	—	—	—
Hodgkin's disease						
I. Lymphocyte predominance	LN	HL	HL-NLP	—	—	—
II. Nodular sclerosis	LN	HL	HL-C	HL-C-NS	—	—
III. Mixed cellularity	LN	HL	HL-C	HL-C-LR/MC/LD	HL-C-MC	—
IV. Lymphocyte depletion	LN	HL	HL-C	HL-C-LR/MC/LD	HL-C-LD	—
V. Provisional entity: lymphocyte-rich classical Hodgkin's disease	LN	HL	HL-C	HL-C-LR/MC/LD	HL-C-LR	—

Abbreviations are explained in Table 1.

— indicates category cannot be assigned.

*High-grade B-cell lymphoma, Burkitt-like should be coded as Burkitt lymphoma only if the growth fraction is nearly 100%, $CD10^+$, $Bcl2^-$, and proven or strong presumptive evidence of MYC translocation; otherwise code to DLBCL. Without these data, cases of high-grade B-cell lymphoma, Burkitt-like cannot be classified beyond mature B-NHL.

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Table 4. Incorporation of lymphoid neoplasm subtypes defined by the Working Formulation into the proposed WHO-based nested classification of malignant lymphoid neoplasms, without immunophenotype data

Working Formulation categories	Hierarchical group					
	1	2	3	4	5	6
A. Small lymphocytic	LN	NHL	B-NHL	Mature B-NHL	—	—
B. Follicular, small cleaved cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
C. Follicular, mixed small cleaved and large cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
D. Follicular, large cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
E. Diffuse, small cleaved cell	LN	NHL	B-NHL	Mature B-NHL	—	—
F. Diffuse, mixed small and large cell	LN	NHL	—	—	—	—
G. Diffuse, large cell	LN	NHL	B-NHL	Mature B-NHL	DLBCL	—
H. Large cell, immunoblastic	LN	NHL	—	—	—	—
I. Lymphoblastic	LN	NHL	—	Precursor	—	—
J. Small noncleaved cell	LN	NHL	B-NHL	Mature B-NHL	—	—
K. Unclassified	LN	NHL	—	—	—	—

Without immunophenotype data, this translation is appropriate for predominantly white populations only. Abbreviations are explained in Table 1.
— indicates category cannot be assigned.

The WHO classification recognizes several immunodeficient states in which the incidence of lymphoid malignancies is markedly elevated, including primary immunodeficiency syndromes, HIV infection, and iatrogenic immunosuppression after organ transplantation or due to methotrexate treatment.[18] Each of these conditions carries varying prevalence of and risks for particular lymphoid neoplasm subtypes. Because etiologic pathways for a given subtype may be different for patients with concurrent immunodeficiency disorders than for those without such disorders, we generally advise excluding or separating them for epidemiologic study. However, stratification of these cases can be complicated by circumstances affecting the availability of information regarding concurrent immunodeficiency (eg, in cancer registry data). Although this scheme does not speak to the allocation of cases occurring in persons with immunodeficiency disorders, we hope that others will undertake

Table 5. Incorporation of lymphoid neoplasm subtypes defined by the Working Formulation into the proposed WHO-based nested classification of malignant lymphoid neoplasms, with basic immunophenotype data (ie, B-cell versus T-cell)

Working Formulation categories	Hierarchical group					
	1	2	3	4	5	6
A. Small lymphocytic, B-cell	LN	NHL	B-NHL	Mature B-NHL	—	—
A. Small lymphocytic, T-cell	LN	NHL	T-NHL	Mature T-NHL	—	—
A. Small lymphocytic, unknown cell	LN	NHL	—	—	—	—
B. Follicular, small cleaved cell, B-cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
B. Follicular, small cleaved cell, unknown cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
C. Follicular, mixed small cleaved and large cell, B-cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
C. Follicular, mixed small cleaved and large cell, unknown cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
D. Follicular, large cell, B-cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
D. Follicular, large cell, unknown cell	LN	NHL	B-NHL	Mature B-NHL	FL	—
E. Diffuse, small cleaved cell, B-cell	LN	NHL	B-NHL	Mature B-NHL	—	—
E. Diffuse, small cleaved cell, T-cell	LN	NHL	T-NHL	Mature T-NHL	—	—
E. Diffuse, small cleaved cell, unknown cell	LN	NHL	—	—	—	—
F. Diffuse, mixed small and large cell, B-cell	LN	NHL	B-NHL	Mature B-NHL	—	—
F. Diffuse, mixed small and large cell, T-cell	LN	NHL	T-NHL	Mature T-NHL	PTCL	—
F. Diffuse, mixed small and large cell, unknown cell	LN	NHL	—	—	—	—
G. Diffuse, large cell, B-cell	LN	NHL	B-NHL	Mature B-NHL	DLBCL	—
G. Diffuse, large cell, T-cell	LN	NHL	T-NHL	Mature T-NHL	PTCL	—
G. Diffuse, large cell, unknown cell	LN	NHL	—	—	—	—
H. Large cell, immunoblastic, B-cell	LN	NHL	B-NHL	Mature B-NHL	DLBCL	—
H. Large cell, immunoblastic, T-cell	LN	NHL	T-NHL	Mature T-NHL	PTCL	—
H. Large cell, immunoblastic, unknown cell	LN	NHL	—	—	—	—
I. Lymphoblastic, B-cell	LN	NHL	—	Precursor	Precursor B-NHL	—
I. Lymphoblastic, T-cell	LN	NHL	—	Precursor	Precursor T-NHL	—
I. Lymphoblastic, unknown cell	LN	NHL	—	Precursor	—	—
J. Small noncleaved cell, B-cell*	LN	NHL	B-NHL	Mature B-NHL	BL	—
J. Small noncleaved cell, T-cell	LN	NHL	T-NHL	Mature T-NHL	PTCL	—
J. Small noncleaved cell, unknown cell	LN	NHL	—	—	—	—
K. Unclassified, B-cell	LN	NHL	B-NHL	—	—	—
K. Unclassified, T-cell	LN	NHL	T-NHL	—	—	—
K. Unclassified, unknown cell	LN	NHL	—	—	—	—

Abbreviations are explained in Table 1.
— indicates category cannot be assigned.
*Small noncleaved cell lymphoma should be coded as Burkitt lymphoma only if the growth fraction is nearly 100%, $CD10^+$, $Bcl2^-$, and proven or strong presumptive evidence of MYC translocation; otherwise code to DLBCL. Without these data, cases of small noncleaved cell lymphoma cannot be classified beyond mature B-NHL.

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Table 6. Categorization of lymphoma subtypes according to the Working Formulation and proposed nested classification for 4685 cases from four studies

Nested classification categories	Working Formulation categories, %								
	A: Small lymphocytic; n = 513	B-D: Follicular lymphoma; n = 1381	E: Diffuse small cleaved cell; n = 244	F: Diffuse mixed small and large cell; n = 167	G: Diffuse large cell; n = 1165	H: Large cell Immunoblastic; n = 447	I: Lymphoblastic; n = 83	J: Small noncleaved cell; n = 159	K: Unknown (n = 526)
Precursor lymphoblastic leukemia/lymphoma, B- and T-cell	0	0	0	0	2	1	75	2	0
B-NHL	498	1341	202	84	1075	275	27	154	259
Mature B-NHL	498	1341	202	84	1073	274	6	152	259
CLL/SLL/PLL/MCL	294	65	103	6	8	0	6	1	40
LPL/Waldenström	70	0	1	2	0	0	0	0	4
DLBCL	1	10	4	40	1027	272	0	5	13
BL*	0	0	0	0	3	0	0	144	1
MZL	130	38	64	21	21	2	0	2	158
FL	3	1228	30	15	14	0	0	0	11
T-NHL	2	0	19	62	41	159	54	3	31
Mature T-NHL	2	0	19	62	41	159	0	3	31
MF/SS	0	0	6	0	0	0	0	0	10
PTCL	1	0	10	56	27	140	0	3	8
Unknown	13	40	23	21	49	13	2	2	236

Abbreviations are explained in Table 1.
*BL refers to the combined categories of Burkitt lymphoma and high-grade B-cell lymphoma, Burkitt-like.

an effort to suggest how these cases could be incorporated within our proposed nested classification.

The hierarchical groupings within the proposed nested classification were defined by numerous parameters (including morphology, immunophenotype, genotype, stage of differentiation, and clinical features, including the site of occurrence), which primarily reflect a pathologic perspective of disease. However, it is not known whether these parameters are, in fact, the most relevant for etiologic research. Because recent studies suggest that some risk factors are related to specific lymphoma subtypes,[3,20-23] we recommend that epidemiologic studies include analyses by lymphoma subtype to the most detailed extent allowable by sample size. However, there is also evidence that other risk factors may be related to multiple subtypes[24,25] or to virtually all lymphomas.[26] In addition, it is possible that other parameters should be used to combine various entities for etiologic research. For example, it is possible that lymphoplasmacytic lymphoma/Waldenström macroglobulinemia should be grouped with marginal zone lymphoma, because they are all postfollicular B-cell neoplasms with a tendency toward plasmacytic differentiation and secretion of clonal immunoglobulin. Therefore, we encourage empirical testing of all the hierarchical groupings of the proposed nested classification using both descriptive and analytical epidemiologic data to facilitate discovery of the etiologically relevant categories of lymphomas.

Finally, it should be emphasized that the proposed classification is limited by our current understanding of lymphoid malignancies. The WHO classification includes molecular characteristics in the definition of certain subtypes, including the t(11;14) translocation in mantle cell lymphoma and the t(8;14) and variant translocations in Burkitt lymphoma. However, other important WHO categories, such as DLBCL, CLL/SLL, and anaplastic large cell lymphoma, have been shown to be heterogeneous with respect to molecular characteristics and gene expression profiles.[46–50] Although the relevance of this heterogeneity to etiologic research is as yet unknown, preliminary evidence suggests that certain subgroups as defined by molecular characteristics such as the t(14;18) translocation, may be etiologically distinct.[51-54] Future research, particularly research focused on the molecular characteristics of lymphoid neoplasms, may therefore necessitate changes to the proposed nested classification.

In conclusion, we present a proposed nested classification of lymphoid neoplasms for epidemiologic research on behalf of the Pathology Working Group of the InterLymph Consortium. We are committed to better understanding the etiologic heterogeneity of the various lymphoid neoplasm subtypes. Accordingly, this proposed nested classification will be periodically reviewed and updated by InterLymph as future research efforts define the usefulness of the proposed classification for etiologic research, and as our understanding of the biology of the various lymphoma subtypes continues to evolve.[55]

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Authorship

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A complete list of the members of the International Lymphoma Epidemiology Consortium (InterLymph) study group is provided in Document S1.

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