Pathological Classification of Non-Hodgkin’s Lymphoma for Epidemiological Studies

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Abstract

Non-Hodgkin’s lymphoma (NHL) consists of a heterogeneous group of disorders which have been difficult to study by epidemiological means in the past. However, recent advances in knowledge of the biology of NHL and improvements in its classification will greatly improve the quality of epidemiological studies in the future. Use of the Working Formulation and the current International Classification of Diseases for Oncology, along with paraffin immunohistochemistry, allow the delineation of NHL subgroups with possible etiological significance based on the biology of the disease. The collaboration of epidemiologists with expert pathologists in the design, performance, and evaluation of epidemiological studies of NHL is essential for such studies to be meaningful.

Introduction

NHL has long been recognized as a heterogeneous group of disorders based on morphological appearance, clinical presentation, and response to therapy. In recent years, the use of immunological and molecular biological techniques has led to important advances in our knowledge of lymphocyte differentiation and has provided the basis for a better understanding of the cellular origin and pathogenesis of NHL. Currently, the various types of NHL are thought to represent neoplastic cells arrested at various stages in the normal differentiation scheme, although the key events in malignant transformation may actually occur in cells at an earlier stage of differentiation (1, 2).

A number of difficulties have been associated with the performance and review of epidemiological studies of NHL and related hematopoietic cancers (3). Foremost has been the constantly evolving nomenclature and confusing array of complex classification systems for NHL. These systems have evolved and improved the classification of NHL over the years as new scientific information has become available and been incorporated. However, epidemiologists and nosologists have traditionally relied on the ICD developed by the WHO to classify NHL. Unfortunately, the ICD has not kept up with the rapid changes in the state of the art of NHL classification over the years, and the ICD system has not been particularly useful for epidemiological studies (Table 1). However, in 1976, the WHO published the ICD-O-1 as a supplement to the ICD, Ninth Revision. At that time, six different classifications for NHL (WHO, Rappaport, Lukes/Collins, Dorfman, British, and Kiel) were in use, and the ICD-O-1 tried to incorporate all of the various histological terms of these classifications, with no preference given to any one classification scheme (4). However, no attempt was made to translate the terminology of one classification into another, and some of the outdated terminology (Table 1) was retained. Thus, difficulty with the use of the ICD system for epidemiological studies was compounded rather than improved.

Use of the Working Formulation for Histological Classification

In response to increasing confusion and controversy regarding the clinical usefulness of the six NHL classifications, the National Cancer Institute of the United States sponsored an international study in the late 1970s to determine whether one classification was more satisfactory than another (5). However, no one scheme was found to be superior to another and, instead, a WF for clinical usage was developed. The WF was not proposed as a new classification, but as a means of translation among the various systems. The establishment of ten major histological types and three clinical grades in the WF was primarily based upon morphology and differences in survival, although other clinical parameters such as age and potential for cure were also considered. However, major deficiencies of the WF include the lack of a provision for classification based on immunological type (i.e., B-cell, T-cell), the separation of some entities that are closely related biologically and the grouping together of others that are unrelated, and the lack of inclusion of new entities (i.e., mantle zone and intermediate lymphocytic lymphoma). Shortly after publication of the WF in 1982, temporary ICD-O codes were assigned to each of the WF histological types, and the utility of the new system for epidemiological studies was evaluated (6).

The lymphoma section in the ICD-10 is based on the WF, and the corresponding ICD-O-2 provides morphology codes for all of the major NHL classification schemes in current use (7). The ICD-O-2 system has been field tested by the Surveillance, Epidemiology, and End Results (SEER) Program and will be formally adopted by all cancer registries in the United States in 1992. The WF groups and ICD-O codes, as well as the corresponding Rappaport and Kiel terms and codes, are shown in Tables 2 and 3. Table 4 lists a number of special types of NHL not included in the WF, as well as codes for unclassifiable NHL. Cases of NHL are classified as having either a follicular (nodular) or diffuse growth pattern, and all lymphomas with an unspecified pattern are grouped in the diffuse category. Composite lymphomas, i.e., those with both a follicular and diffuse pattern, should be categorized as follicular for epidemiological studies, and the lowest grade morphology category should be used.

The ICD-O system also provides a section for coding by topography, thus allowing the distinction to be made between nodal and extranodal lymphomas. The majority of lymphomas (75%) arise in lymph nodes (topography code C77) or lymphatic tissues such as the tonsils, Waldeyer’s ring, spleen, or thymus, and these are considered “nodal” lymphomas. The rest of the lymphomas (25%) arise in extranodal sites such as the stomach, intestine, breast, or brain. When deciding whether a lymphoma is nodal or extranodal, it is the primary site of the tumor that is to be considered. This distinction is important...
Use of Paraffin-reactive Antibodies for Immunological Classification

The ICD-O-2 system also provides codes for the immunological classification of NHL. These codes are given as the sixth digit of the code for each case. Each NHL may be coded as T-cell type (code 5), B-cell type (code 6), or as immunological type not determined (code 9). Nearly all cases of NHL can be categorized as having either a B-cell or a T-cell phenotype if detailed immunological and molecular biological studies are performed on frozen tumor tissue. However, frozen tumor tissue is usually not available for use in epidemiological studies. Recently, the development of reliable and specific monoclonal antibodies for the immunophenotyping of NHL in paraffin sections has obviated the need for frozen tissue (8-15). A list of commonly used paraffin reactive antibodies and their sources is given in Table 5. These antibodies are best used as a panel, since none is entirely specific, and patterns of reactivity should be utilized for immunophenotypic interpretation. Only the diffuse NHLs need to be phenotyped, since follicular NHL is always of B-cell type. In a recent case-control study of 201 NHLs in eastern Nebraska (16), using only the antibodies L26 and UCHL-1, the authors found that 80% of the lymphomas were of B-cell type, 10% were of T-cell type, 5% were of indeterminant phenotype due to inconclusive staining, and tissue was unavailable for study in the other 5% of cases. Segal et al. (15) have recently reported on the reliability and cost effectiveness of an antibody panel including L26, UCHL-1, and Leu 22 in NHL. In that study, 96% (76 of 79) of the lymphomas were marked definitively using paraffin sections. These findings indicate that paraffin immunophenotyping of NHL is highly reliable and should be performed in future epidemiological studies of NHL.

The immunophenotypes of the various histological categories of NHL in the WF, based on frozen tissue data from 1160 cases in the Nebraska Lymphoma Study Group Registry, are given in Table 6. All of the lymphomas in WF categories A to D and J, and the vast majority in categories E and G, are of B-cell origin, whereas categories F and H consist of a mixture of B- and T-cell cases. T-cell lymphomas predominate in category I, but the total number of cases is small. Overall, 88% of the 1160 cases of NHL were of B-cell type, and only 12% were of T-cell type. These findings should be largely reproducible using the paraffin-reactive antibodies listed in Table 5. As such, the WF appears to be a good system for categorization of the B-cell lymphomas, but it is less than satisfactory for the T-cell lymphomas. With immunophenotyping, however, the special codes for peripheral T-cell lymphoma (Table 4) could be used and may result in the delineation of etiological entities.

Use of Expert Pathologists as Part of the Team

A major problem for epidemiological studies is the inaccuracy of NHL diagnoses by local pathologists (17-20), which can be further compounded by a high rate of nonconcurrency (23%) in abstracted diagnoses (21). In addition, death certificates typically under-report deaths due to NHL and are likely to be a poor source of more specific information with regard to classification (22). A number of comparative studies (17-20) have shown that the contributing pathologists' diagnosis of NHL is confirmed by expert pathologists in 86 to 93% of the cases, but complete agreement with regard to pattern and cytology occurs in only 49 to 56% of the cases. Major diagnostic discrepancies

Table 1 Eighth International Classification of lymphatic neoplasms

<table>
<thead>
<tr>
<th>ICD code</th>
<th>Histological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>200.0</td>
<td>Reticulum cell sarcoma</td>
</tr>
<tr>
<td>200.1</td>
<td>Lymphosarcoma</td>
</tr>
<tr>
<td>201.0</td>
<td>Hodgkin's disease</td>
</tr>
<tr>
<td>202.0</td>
<td>Giant follicular lymphoma</td>
</tr>
<tr>
<td>202.1</td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>202.2</td>
<td>Other primary lymphoid neoplasms (chloroma, compound lymphoma, leukaosarcoma, and malignant neoplasms not otherwise classifiable)</td>
</tr>
<tr>
<td>202.9</td>
<td>Other forms of lymphoma (benign lymphoma, benign or unspecified neoplasm of bone marrow, benign lymphoid polyp, ocular lymphoma)</td>
</tr>
</tbody>
</table>

Table 2 Working Formulation with related terms in the Rappaport and Kiel classifications and ICD-O code numbers

<table>
<thead>
<tr>
<th>Working Formulation</th>
<th>ICD-O code</th>
<th>Rappaport classification</th>
<th>Kiel classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. ML, small lymphocytic</td>
<td>9670/3</td>
<td>ML, lymphocytic, well differentiated 9670/3</td>
<td>ML, lymphocytic 9670/3</td>
</tr>
<tr>
<td>ML, plasmacytoid lymphocytic</td>
<td>9671/3</td>
<td>ML, lymphocytic, plasmacytoid 9671/3</td>
<td>ML, lymphoplasmacytic 9671/3</td>
</tr>
<tr>
<td>ML, consistent with chronic lymphocytic leukemia</td>
<td>9823/3</td>
<td></td>
<td>ML, consistent chronic lymphocytic leukemia 9823/3</td>
</tr>
<tr>
<td>B. ML, follicular small cleaved cell</td>
<td>9695/3</td>
<td>ML, nodular lymphocytic, well differentiated 9695/3, intermediate (mantle cell) 9694/3, poorly differentiated 9696/3</td>
<td>ML, centroblastic/centrocytic 9692/3</td>
</tr>
<tr>
<td>C. ML, follicular mixed small Cleaved and large cell</td>
<td>9691/3</td>
<td>ML, nodular mixed lymphocytic-histiocytic 9691/3</td>
<td>ML, centroblastic/centrocytic 9692/3</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. ML, follicular large cell</td>
<td>9698/3</td>
<td>ML, nodular histiocytic 9698/3</td>
<td>ML, centroblastic, follicular 9697/3</td>
</tr>
<tr>
<td>E. ML, diffuse small cleaved cell</td>
<td>9672/3</td>
<td>ML, diffuse lymphocytic, poorly differentiated 9672/3, intermediate (mantle cell) 9673/3</td>
<td>ML, centroblastic 9674/3</td>
</tr>
<tr>
<td>F. ML, diffuse mixed small and large cell</td>
<td>9675/3</td>
<td>ML, diffuse mixed lymphocytic-histiocytic 9675/3</td>
<td>ML, diffuse centroblastic-centrocytic 9676/3</td>
</tr>
<tr>
<td>G. ML, diffuse large cell</td>
<td>9680/3</td>
<td>ML, diffuse, histiocytic 9680/3</td>
<td>ML, diffuse centroblastic 9683/3</td>
</tr>
<tr>
<td>cleaved noncleaved</td>
<td>9681/3</td>
<td>ML, diffuse, histiocytic 9681/3</td>
<td>ML, diffuse centroblastic 9683/3</td>
</tr>
<tr>
<td>9682/3</td>
<td>ML, diffuse, histiocytic 9682/3</td>
<td>ML, diffuse centroblastic 9683/3</td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. ML, large cell, immunoblastic (diffuse)</td>
<td>9684/3</td>
<td>ML, diffuse, histiocytic 9680/3</td>
<td>ML, immunoblastic 9684/3</td>
</tr>
<tr>
<td>I. ML, lymphoblastic (diffuse)</td>
<td>9685/3</td>
<td>ML, lymphoblastic, convoluted/nonconvoluted 9685/3</td>
<td>ML, lymphoblastic 9685/3</td>
</tr>
<tr>
<td>J. ML, small noncleaved cell, Burkitt's (usually diffuse)</td>
<td>9687/3</td>
<td>ML, undifferentiated, Burkitt's 9687/3</td>
<td>Burkitt's lymphoma 9687/3</td>
</tr>
<tr>
<td>ML, small noncleaved cell (usually diffuse)</td>
<td>9686/3</td>
<td>ML, undifferentiated, non-Burkitt's 9686/3</td>
<td></td>
</tr>
</tbody>
</table>
PATHOLOGY OF NHL FOR EPIDEMIOLOGICAL STUDIES

Table 3  Interrelationships of the Rappaport and Kiel classifications of non-Hodgkin's lymphoma (ICD-O codes) and the Working Formulation groups

A to J denote Working Formulation groups (see Table 2).

Table 4  Special and unclassified non-Hodgkin's lymphomas and ICD-O code numbers

Table 5  Paraffin antibodies which are useful for immunophenotyping non-Hodgkin's lymphoma

between contributing pathologists and expert pathologists occurred in 21% of the cases in one study (19), and a diagnosis other than NHL is made by the experts in about 5% of cases (18, 19). In the only published study utilizing the WF, Dick et al. (20) found good concordance (80%) between the diagnoses of the contributing pathologists and the experts for follicular lymphoma and diffuse small lymphocytic lymphoma. However, concordance with regard to the other diffuse lymphomas was only 41%. Dick et al. (20) also found that contributing pathologists often underdiagnose follicular lymphoma, resulting in a false increase in diffuse lymphoma, and often include cases of chronic lymphocytic leukemia with small lymphocytic lymphoma. Other studies (18, 19) have also found a low rate of concordance (45 to 55%) for diffuse lymphoma, but they have also found a lower rate for follicular lymphoma (52 to 58%).

The above findings indicate that expert pathologists are needed in epidemiological studies of NHL to provide accurate and consistent histological classification of the cases and, thus, decrease the inordinately high rate of diagnosis misclassification which would tend to obscure any relationships between exposure and disease. Expert pathologists are also needed to interpret the immunohistochemical stains for B- and T-cell phenotyping and to correlate these results with the histological findings. In addition, expert pathologists often have a good working relationship with the contributing pathologists and clinicians involved in the care of patients in epidemiological studies, and they can facilitate the performance of such studies at the regional and community levels. Finally, expert pathologists have the knowledge and expertise to advise epidemiologists with regard to the design and evaluation of such studies, and they should be included from the start in the planning of such projects.

Understanding the Biology of Non-Hodgkin's Lymphoma

In order to use a histological classification of NHL for epidemiological purposes, one must first understand the biology of NHL and how the various histological types relate to one another in the normal differentiation scheme (1, 2). Pluripotent stem cells in the bone marrow give rise to both immature B-cells and immature T-cells in the adult human. These cells then migrate via the blood to the peripheral lymphoid organs (lymph nodes, spleen, thymus) where they differentiate into mature, functional cells of the immune system. Cancers of the immune system, i.e., NHL or lymphoid leukemia, arise when genetic events occur within immature lymphoid cells in the bone marrow or more mature cells in the peripheral organs (1, 23). These events result in chromosomal aberrations which turn key genes on or off and cause the cells to become malignant, proliferate in an uncontrolled manner, and spread to other sites. The causes of the cytogenetic events which result in lymphoid neoplasia are largely unknown, some being random events and others due to environmental genotoxins such as organic chemicals or ionizing radiation. Lymphoid malignancies of the bone marrow and peripheral blood are called leukemia, either acute or chronic, whereas those arising in the peripheral organs are called NHL. As such, the distinction between lymphoid leukemia and NHL is largely distributional with overlapping entities, such that a
particular lymphoid neoplasm may manifest both lymphomatous and leukemic features during the course of the disease. For example, lymphoid leukemias can sometimes spread to the peripheral lymphoid organs and present clinically like NHL, and the cells of NHL sometimes spread to the blood and manifest as leukemia. The tissue correlate of chronic lymphocytic leukemia is small lymphocytic NHL, and that of acute lymphoblastic leukemia is lymphoblastic NHL. The pathological classification of lymphoid neoplasia is usually based upon the clinical nature of the disease (i.e., acute, chronic, low grade) and the predominating cell type within the neoplastic proliferation, even though the key genetic events may occur in a cell at an earlier stage of differentiation.

Although the precise sequence of B-cell differentiation is unknown, considerable progress has recently been made in our understanding of the development and function of the normal humoral immune system (2). Currently, the various types of B-cell neoplasia are thought to represent cells arrested at various stages in the normal differentiation scheme. Simplified diagrams showing the various stages of the normal humoral immune response and their corresponding B-cell neoplasms are given in Fig. 1 to 3. Fig. 1 shows the overall scheme of B-cell differentiation, whereas Fig. 2 shows the cells of the germinal center reaction and Fig. 3 shows the cells of the plasma cell reaction which arise from mature (or memory) B-cells. The reader is encouraged to refer to a recent review of this topic (2) for the rationale behind and a more detailed description of this process.

Basically, the various B-cell neoplasms appear to recapitulate the normal stages of B-cell differentiation. The lymphocytic neoplasms consist predominantly of nondividing (resting) cells, whereas the blastic neoplasms consist of cells in the proliferative phase of the cell cycle. Partial blocks in differentiation are not uncommon and result in the development of "mixed cell" lymphomas consisting of cells at closely related stages of differentiation. However, some of the categories of B-cell NHL in the WF are not pure and consist of tumors corresponding to cells at different and sometimes distant stages of differentiation. However, there is currently no simple or practical means
by which to separate these latter tumors into more pure sub-
groups. The reader is again encouraged to refer to the above-
mentioned review (2) for a more detailed description of the
various types of B-cell neoplasia and their interrelationships. A
brief summary of the various NHL cell types, their ICD-O-2
codes, and their cells of origin and relationships is given in
Table 7, which can be correlated pictorially with the cells in Fig.
1 to 3.

In a similar manner, pluripotent stem cells in the bone mar-
row give rise to immature or pre-T-cells which then migrate via
the blood to the thymus (1). In the thymus, the cells migrate
from the cortex to the medulla during the process of differen-
tiation, and they then leave the thymus as mature T-cells and
migrate to the peripheral lymphoid organs. The lymphomas of
T-cell lineage can be divided into two categories based on their
origin from immature T-cells or mature T-cells. The lymphoid
neoplasms of immature T-cells are acute lymphoblastic leuke-
mia and lymphoblastic NHL (WF category I), whereas all of the
NHLs arising from mature T-cells can be grouped together as
peripheral T-cell NHL (WF categories E to H) or subdivided
into special subtypes (Table 4). However, our understanding of
the behavior of the T-cell system is not as complete as that of the
B-cell system, and the sequence and morphology of mature
T-cell activation and differentiation have not been well charac-
terized. However, mycosis fungoides and Sézary’s syndrome
correspond to mature T-cells which home to and reside in the
skin and, as such, represent a special subset of peripheral T-cell
lymphoma.

Use of the Working Formulation (ICD-O-2) for
Epidemiological Studies

Some epidemiologists have suggested that hematopoietic
cancers should be subdivided as finely as possible in epidemio-
logical studies in order to maximize the prospect that homoge-
neous etiological entities are studied, and they state that the
various types of hematopoietic cancer should only be grouped
together for investigative purposes when there is some indica-
tion that the cancers may share a common etiology. Unfortu-
nately, NHL cannot be subdivided into standard etiological
categories at the present time, since the etiologies and patho-
genesis of NHL are not well understood. Furthermore, since
the various types of NHL are related to one another and they all
arise from a common hematopoietic stem cell, it is valid to
group all of the various types of NHL together for epidemio-
logical study. This will ensure that diseases of similar etiology,
even those which are misclassified, be included in the study
and that useful information will not be lost. However, this may
dilute important data to the point that small increases in risk
associated with certain subtypes may be missed. On the other
hand, it is likely that any significant increases in risk that are
identified will actually underestimate the true risk due to dilu-
tion of the data. However, specific disease entities should also
be analyzed separately in order to distinguish important differ-
ences in target cell specificity for various exposures which may
be etiologically important. Obviously, NHL could be simply
subgrouped by immunophenotype (i.e., B-cell and T-cell types).
A variety of other possible etiological groups of NHL and re-
lated disorders is given in Table 8. The standard WF groups, the
codes for which are given in the second column of Table 2 under
ICD-O code, and some more specific ICD-O categories for the
various entities within each group are also given in Table 8. In
general, use of the standard WF groups will tend to dilute the
data more than use of the more specific categories since some of
the WF groups are heterogeneous (Table 7). However, either
approach should be useful for most types of epidemiological
study. Other group combinations may also be appropriate de-
pending on the nature of the study, and consultation with an
expert pathologist should always be obtained prior to any ag-
grenate analysis.

Latency Period of Non-Hodgkin’s Lymphoma

The latency period for the development of NHL following an
environmental exposure is largely unknown. One valid source
of information on the latency period of NHL can be found
in the literature on NHL developing after the treatment of
Hodgkin’s disease with chemotherapy and/or radiotherapy
(24, 25). In such studies, the median latency period for NHL is
about 5 to 6 yr (24, 25), not unlike that for secondary acute

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### Table 7 Histological types of B-cell non-Hodgkin’s lymphoma and their origins and interrelationships

<table>
<thead>
<tr>
<th>Working Formulation</th>
<th>ICD-O-2 codes</th>
<th>Cellular origin and relationships</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ML, small lymphocytic</td>
<td>9670/3</td>
<td>Majority correspond to immature virgin B-cells of the diffuse cortex; closely related to chronic lymphocytic leukemia; minority correspond to memory B-cells</td>
</tr>
<tr>
<td>ML, plasmacytoid lymphocytic</td>
<td>9671/3</td>
<td>Mature B-cells of the primary or secondary (memory) response with plasma cell differentiation</td>
</tr>
<tr>
<td>B. ML, follicular mantle cell, intermediate lymphocytic</td>
<td>9693/3, 9694/3</td>
<td>Corresponds to immature virgin B-cells of the primary follicle and mantle zone; closely related to small lymphocytic</td>
</tr>
<tr>
<td>B-D. ML, follicular center cell</td>
<td>9695/3, 9696/3, 9692/3, 9691/3, 9692/3, 9693/3, 9697/3</td>
<td>Corresponds to cells of the follicular germinal center; closely related to each other and to their diffuse follicular center cell counterparts</td>
</tr>
<tr>
<td>E. ML, diffuse small cleaved cell</td>
<td>9672/3</td>
<td>Diffuse counterpart of follicular small cleaved cell NHL; closely related to other follicular center cell NHL</td>
</tr>
<tr>
<td>ML, diffuse mantle cell, intermediate lymphocytic</td>
<td>9673/3, 9674/3</td>
<td>Diffuse counterpart of follicular mantle cell NHL; closely related to small lymphocytic</td>
</tr>
<tr>
<td>F. ML, diffuse mixed cell</td>
<td>9675/3, 9676/3</td>
<td>Diffuse counterpart of follicular mixed-cell NHL; closely related to other follicular center cell NHL</td>
</tr>
<tr>
<td>G. ML, diffuse large cell, cleaved and noncleaved</td>
<td>9780/3, 9681/3, 9682/3, 9683/3</td>
<td>About 40 to 50% are diffuse counterparts of follicular large-cell NHL; remainder correspond to transformed cells at earlier or later stages</td>
</tr>
<tr>
<td>H. ML, large cell, immunoblastic, plasmacytoid</td>
<td>9684/3, 9680/3</td>
<td>About 30% are closely related to diffuse large-cell NHL of follicular center cell origin; remainder likely correspond to transformed cells of the primary or secondary plasma cell reaction</td>
</tr>
<tr>
<td>I. ML, lymphoblastic</td>
<td>9685/3</td>
<td>Majority correspond to pre-B- or early bone marrow B-cells and are closely related to common and other types of acute B-lymphoblastic leukemia</td>
</tr>
<tr>
<td>J. ML, small noncleaved cell</td>
<td>9686/3, 9687/3</td>
<td>Rarely follicular; majority correspond to cells of the early germinal center reaction and are closely related to other follicular center cell NHL; minority may correspond to an earlier B-cell</td>
</tr>
</tbody>
</table>
Table 8 Possible etiologic groups of non-Hodgkin’s lymphoma and related disorders

<table>
<thead>
<tr>
<th>B-cell type (88%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Small lymphocytic lymphoma (A; or 9670/3) + chronic lymphocytic leukemia (9823/3)</td>
</tr>
<tr>
<td>2. Small lymphocytic lymphoma (A; or 9670/3 + 9693/3) + intermediate lymphocytic lymphoma (E; or 9694/3 + 9673/3)</td>
</tr>
<tr>
<td>3. Follicular lymphoma (B + C + D; or 9696/3 + 9691/3 + 9698/3)</td>
</tr>
<tr>
<td>4. Follicular center cell lymphoma (B + C + D + F + G + J; or 9696/3 + 9691/3 + 9698/3 + 9675/3 + 9680/3 + 9683/3 + 9687/3)</td>
</tr>
<tr>
<td>5. Diffuse large cell lymphoma (F + G + H; or 9675/3 + 9680/3)</td>
</tr>
<tr>
<td>6. Blastic lymphoma (G + H + J; or 9680/3 + 9682/3 + 9686/3 + 9687/3)</td>
</tr>
</tbody>
</table>

T-cell type (12%)  
1. Lymphoblastic lymphoma (I; or 9685/3) + acute lymphoblastic leukemia (9821/3)  
2. Peripheral T-cell lymphoma (E + F + G + H; or 9672/3 + 9675/3 + 9680/3)  
3. Mycosis fungoides/Sézary’s disease (9700/3 + 9701/3)

*A to J denote Working Formulation groups (see Table 2).

Fig. 4. Idealized latency curves for non-Hodgkin’s lymphoma associated with short-term, high-dose (A) and long-term, low-dose (B) carcinogenic exposures.

leukemia (26, 27). In these studies (24, 25), the latency of NHL in some cases was as short as 2 yr, but it may also be as long as ≥15 yr (28). In contrast, the average latency period for the development of malignant lymphoma (including Hodgkin’s disease) among young (<25 yr) atomic bomb survivors who received a radiation dose of >100 rads was about 9 yr, with a longer latency for those receiving smaller doses (29). Interestingly, the average latency was 14 yr in older survivors who received >100 rads (29), suggesting that the latency period may be dependent on age. In contrast, the median latency period for acute leukemia associated with chronic, low-dose exposure to benzene is 15 to 20 yr (27, 30), and the latency in similar situations would be expected to be similar for NHL.

An idealized graph of the above data showing latency curves for NHL due to short-term, high-dose (Curve A) and long-term, low-dose (Curve B) carcinogenic exposures is shown in Fig. 4. Based on these data, short-term, high-dose exposures would be expected to result in a short latency period, whereas long-term, low-dose exposures would be expected to result in a long latency period. This relationship of dose and exposure time to latency has also been demonstrated in numerous carcinogenesis studies in animals. For example, Melnick et al. (31, 32) have performed animal studies in which exposure to 1,3-butadiene was stopped after limited periods of time to assess the effects of exposure level and duration of exposure on the outcome of butadiene-induced NHL. In these studies, NHL was induced in mice exposed to 625 ppm of butadiene for only 13 wk. The incidence of lymphoma in mice exposed to 625 ppm of butadiene for 26 wk was approximately 2 times that in mice exposed for only 13 wk. However, when the exposure was reduced by one half to 312 ppm and exposure duration was extended to 52 wk, the incidence of NHL was reduced by 90%. Thus, the multiple of the exposure concentration times the exposure duration (cumulative dose) did not predict the incidence of lymphoma in mice. Peto (33) has also suggested that the cumulative dose of a carcinogen may be less predictive of an increased risk of cancer in humans than the intensity of the exposure. Thus, knowledge of the nature and timing of carcinogenic exposures should be considered in the design of epidemiological studies. For example, in the setting of an environmental carcinogen, the accepted belief that risk ratios should be higher for long-term workers than for short-term workers may not always be true, particularly if the short-term workers received the highest exposures. Also, short-term workers with high exposures are likely to have a shorter latency period than long-term workers with lower exposures. These considerations are important for the design and interpretation of epidemiological studies, since such studies may arbitrarily eliminate short-term workers from the study or attribute increased risks in such workers to prior exposures.

Conclusions

In summary, current knowledge and understanding of the biology and classification of NHL are important for the design and evaluation of epidemiological studies. Many of the problems of the past can be eliminated by the use of the WF and ICD-O-2 systems for the classification of NHL; the use of immunological markers; and the collaboration of epidemiologists and expert pathologists in the design, performance, and evaluation of such studies. Future studies which incorporate the concepts put forth herein will be more likely to identify endogenous and environmental factors which play a role in the etiology and pathogenesis of NHL.

References


Discussion

Mrs. Percy: I am an Editor of the ICD-O-2 and I want to bring you up to date on a few things. First of all, the SEER Program and most of the major registries in the United States following the SEER guidelines have been using the equivalent of ICD-O-2, i.e., the field trial edition since the beginning of 1988. Even before that, when Dr. O’Conor and myself and others here assigned ICD-O numerics to specific morphological categories of undifferentiated carcinomas and found—with mid-1970s to mid-1980s techniques—10% of those in fact were lymphomas of one sort or another.

Dr. O’Conor: This would appear then to be a significant group of tumors where misclassification could have some effect on trends.

Dr. Cartwright: Yes.

Participant: Dr. Cartwright, I’d like to ask you what other disease categories were examined? You said that you looked at eye diseases and some other diseases.

Dr. Cartwright: Yes. The main category of error was HD. When we looked at the so-called HD, we did indeed find 8–10% who were NHL.

Dr. O’Conor: I recall that in the studies that Dr. Correa and I did in Connecticut and California, we had a similar experience. Approximately 10% of cases that had been diagnosed as HD we reclassified as NHL.

Dr. Banks: May I ask what relative numbers we’re talking about? When we talk about undifferentiated carcinoma, 10% of that category being recruited, what is the absolute number of such reported cases in relation to the absolute number in percentage of NHL? Is this significant?

Dr. Cartwright: No. The numbers are low.

Dr. Banks: I think this is very important because, for the nonepidemiologists in the group this morning, having the socioeconomic and educational levels correlated with risk for NHL immediately makes one suspect that maybe they
Pathological Classification of Non-Hodgkin's Lymphoma for Epidemiological Studies

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