Introduction

Epidemiology is the basic quantitative science of public health and, as such, is concerned with the distribution, determinants, treatment, management, and potential control of disease. Concentrating on the first two of these, this chapter reviews the epidemiology of lymphomas – a heterogeneous group of malignancies that is estimated to account for around 3–4% of cancers worldwide.

Epidemiological reports on lymphomas often begin, and sometimes end, by stating that little is known about the causes of the cancers under study. This is slowly changing, as evidence about the pathological diversity of the various lymphoma subtypes accumulates. At present, however, the issue of lymphoma classification continues to permeate much of the literature, since, in order to originate and test hypotheses about pathogenesis, it is vitally important to describe accurately and understand underlying descriptive disease patterns. Implicit in this is the need to use appropriate disease classifications; it is this requirement that has beleaguered epidemiological research into the lymphoid malignancies.

In short, the classification of hematological malignancies has changed markedly over recent decades, and will continue to do so as biological understanding increases and new diagnostic methods and techniques are developed. One problem for epidemiological research concerns the use of historical classifications emanating from the latter half of the nineteenth century – long before there were any effective treatments or real understanding of the relationships between lymphoid malignancies, the normal bone marrow and immune system, and before anything was known about the cellular and genetic basis of malignant transformation. The application of modern disease classifications is, however, now beginning to discriminate between subtypes, revealing many features that future etiological hypotheses will undoubtedly seek to address. Accordingly, the next few decades promise to be an exciting time for epidemiological research into lymphoid, as well as other hematological, malignancies.

Descriptive epidemiology

In 2001 the World Health Organization (WHO) produced, for the first time, a consensus classification that defined malignancies of the hematopoietic and lymphoid systems in terms of their immunophenotype, genetic abnormalities, and clinical features. Up until then, the use of competing classifications had tended to make meaningful comparison of results both between and within populations virtually impossible. For a variety of reasons, although WHO’s 2001 classification and its successor was adopted into clinical practice almost uniformly around the world, it did not have an immediate effect on population-based epidemiological research. This is because, unlike many other cancers, hematological neoplasms are diagnosed using multiple parameters, including a combination of histology, cytology, immunophenotyping, cytogenetics, imaging, and clinical data. This range and depth of data is difficult for cancer registries and other researchers to access routinely, forming a barrier both to complete ascertainment and to the collection of diagnostic data at the level of detail required to implement the latest classification systematically. Furthermore, in practice, even within some of the best defined WHO categories, there is a need to qualify the final diagnosis even further using additional clinical and biological prognostic factors before valid outcome comparisons can be made between clinical centers.
Chapter 1: Epidemiology

Gathering accurate information about disease burdens and patterns is central to any successful cancer information strategy. However, whilst cancer registration has a long history in many countries, particularly those in the more affluent regions of the world, nearly 80% of the world’s population is not covered by such systems (www.globocan.iarc.fr/). Furthermore, in some of these, even enumerating the population at risk (denominator) through census counts and vital registration is challenging. Even so, with a view to characterizing the global burden of disease, the WHO’s International Agency for Research on Cancer (IARC) routinely uses the available data to estimate worldwide cancer incidence and mortality levels.

Misdiagnosis and underenumeration are recognized as particularly problematic for hematological cancers. The acute and rapidly fatal presentation of some patients leads to underenumeration in those countries with less well-developed health service infrastructures and the intermittent and non-specific nature of symptoms associated with others poses problems even in countries with well-developed health service systems and cancer registration processes. In addition, population-based data continue to be reported in the broad anatomical-based categories of non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), myeloma, and leukemia since, for reasons outlined above, the laboratory data required to classify hematological cancers appropriately are hard for cancer registries to access in a timely and systematic fashion.

Geographic variation

Of the 12.68 million new cancers estimated to have occurred around the world in 2008, 6.64 were in men and 6.04 in women. Combined, hematological malignancies (lymphomas, leukemias, and myelomas) comprised 7.5% of the estimated cancers in males and 6.4% in females, with lymphomas accounting for around half of all newly diagnosed hematological neoplasms in both men and women.

Figure 1.1 shows the estimated global regional rates and numbers of cases of NHL and HL separately for men and women (www.globocan.iarc.fr/). In general, estimated lymphoma rates are higher in more economically developed regions of the world – North America, Europe, and Australasia – and lower in less affluent regions. This relationship with affluence is seen for both NHL and HL, with one or two interesting pockets such as the consistently low overall rates reported for Japan (www.globocan.iarc.fr/). Nevertheless, less than half of all NHL and HL diagnoses occurred in the three regions with the highest rates – Northern America, Europe, and Oceania (Figure 1.1) – largely reflecting the underlying world population distribution. The most striking disparity is seen for Asia, which has the lowest rates but more than a third of all of the estimated worldwide cases. To some extent these broad regional differences may well reflect, at least in part, underlying lymphoma subtype variations – with a relatively high proportion of mature T-/natural killer cell neoplasms being reported for several Asian populations. These issues are discussed in more depth in the later section on etiology.

Age and sex

That lymphoid malignancies are, overall, generally more common in men than in women in all areas of the world is evident from Figure 1.1, where for both NHL and HL the age-standardized rates and numbers are consistently higher for males than for females. Interestingly, these gender differences appear to be slightly more pronounced in less developed regions of the world (http://globocan.iarc.fr/) – the sex rate ratios (M:F) for HL, for example, range from 1.8 and 1.6, respectively, in Africa and Asia through to 1.2 and 1.1, respectively, in North America and Europe. Whether or not these gradations reflect genuine underlying incidence differences, either generally or within particular subtypes, or are in fact caused by enumeration biases cannot be investigated further from the available cancer registration data.

The NHL and HL age-specific incidence patterns seen in more economically developed regions of the world are all broadly similar to the pattern shown in Figure 1.2, which presents cancer registration data from the UK. For NHL, the age-specific male and female rates increase with increasing age, the divergence between the male and female rates becoming progressively more marked as age increases, but, despite this, more women than men are diagnosed over the age of 80 years. This apparent discrepancy reflects the fact that the UK, like other economically developed regions of the world, has an aging population structure within which more women than men survive to reach old age.

The relationship with age and sex is quite different for NHL and HL. In more affluent regions of the world HL tends to have a bimodal age distribution that is characterized by early age peak, within which females are often in excess but have a deeper following trough,
and a late age peak with a pronounced male excess (Figure 1.2). The earlier age peak is not clearly evident in less well developed regions of the world. Inspection of various case-series has revealed that these patterns are the result of differences in the age and gender frequencies of the various HL subtypes. Likewise, the comparatively smooth pattern seen when all NHLs are combined (Figure 1.2) conceals considerable age and sex subtype variability.

The diagnostic challenges posed by hematological malignancies means that subtype data can only be obtained from specialist registries. Furthermore, population-based data with clearly defined numerators and denominators (as opposed to hospital-based case-series) are required for epidemiological research. One such registry is the UK-based Haematological Malignancy Research Network (www.HMRN.org), and descriptive age and sex patterns for the lymphomas diagnosed within HMRN are presented in Figures 1.3 and 1.4. Established in 2004 and covering a population of 3.6 million with over 2100 diagnoses each year, HMRN comprises an ongoing population-based cohort of all newly diagnosed hematological malignancies (pediatric and adult). Importantly, as a matter of policy and irrespective of treatment intent, all diagnoses within HMRN are made and coded to the latest WHO classification by a single specialist hematopathology laboratory.

HMRN patients newly diagnosed with lymphoma in the 5 years from September 2004 to August 2009 are proportionately distributed by WHO diagnostic category in Figure 1.3, beginning with the B-cell NHLs, moving clockwise through the T-cell NHLs and ending with the HLs. Diffuse large B-cell (DLBCL), follicular (FL), and marginal zone lymphomas (MZL) dominate—together accounting for more than 70% of the total. The high proportion of DLBCL and MZL is a common feature evident in all reported series, including hospital-based registers in Asia. By contrast, in certain Asian and other population groups, diagnoses of the more indolent FL appear to occur far less frequently, whereas diagnoses of T-cell lymphomas are more common.
The corresponding HMRN box-and-whisker age distributions and sex rate ratios (male rate:female rate), together with their standard errors, are shown in Figure 1.4. Whilst most B-cell NHLs have a median diagnostic age over 70 years, a significant minority tend to be diagnosed at younger ages – follicular, Burkitt, and mediastinal lymphomas in HMRN having median ages of 65, 52, and 36 years, respectively. Furthermore, some subtypes have broad age ranges whilst others are narrow; with no patients diagnosed before the age of 48 years and a median of 74 years, the age distribution of mantle cell lymphoma shows the least variation. By contrast, with a median diagnostic age approaching 71 years, but with several sporadic pediatric cases, DLBCL covers the largest age range – the scatter of outliers at younger ages is indicative, perhaps, of diagnostic heterogeneity within this subtype category. Overall, in agreement with other reports, within HMRN T-cell NHLs tend to be diagnosed at younger ages than B-cell neoplasms. Nonetheless, within T-cell forms of the disease there is considerable subtype heterogeneity – the tight age band for enteropathy...
type T-cell contrasting with that seen for anaplastic large T-cell, for example. Lastly, with a pronounced pediatric component, HL tends to be diagnosed earlier still, but, again, there are differences between the subtypes – the median ages within the classical Hodgkin lymphoma (CHL) category, for example, ranging from 37 years for nodular sclerosis CHL to 60 years for mixed cellularity CHL. These subtype differences are largely responsible for the bimodal HL age and sex distributions shown in Figure 1.2.

That males are far more likely to develop lymphoma than females is conspicuously clear in Figures 1.1, 1.2, and 1.4 – but it is also evident that the gender disparity is much greater for some subtypes, whilst being almost absent for others. Among B-cell NHLs, roughly equal numbers of males and females were diagnosed with FL and with extranodal MZL; however, the sex rate ratio for all other B-cell lymphomas shows a male bias – the most striking being for Burkitt lymphoma which, in these and other series, is at least three times as likely to...
be diagnosed in males than in females. T-cell NHLs and HLs also exhibit a male bias, but again there is considerable subtype heterogeneity, with angioimmunoblastic T-cell lymphoma running counter to the trend by being more common in women.

The wide diversity of descriptive patterns shown in Figure 1.4 is indicative of different subtype etiologies, which many new and ongoing epidemiological studies are aiming to address. This, coupled with the geographic variations for T- and B-cell subtypes reported for various case-series, underscore the importance of using appropriate classifications. Indeed, the continued application of site-based classification systems for routine cancer registration severely limits the use of their data in epidemiological studies. Hopefully, in the future, new insights into lymphoma epidemiology will emerge as the WHO classification becomes more widely applied in a population-based context.

**Changes over time**

Monitoring disease trends over time is a fundamental activity of descriptive epidemiology, such analyses often yielding important etiological clues. Indeed, there are many examples in the field of cancer epidemiology where this has been the case, particularly in relation to the identification of hazardous occupational and environmental exposures. In this context, the temporal changes reported for NHL in recent decades are unquestionably dramatic, as can be seen from Figure 1.5, which shows the estimated age-adjusted incidence rates for NHL in recent decades.
Epidemiology and End Results (SEER) Program in the United States (www.seer.cancer.gov).

The sharp increase seen for NHL in the USA between the 1970s and the 1990s was reported in many countries with population-based cancer registration systems (both statutory and voluntary), and the magnitude and global scale of the effect naturally captured both scientific and public attention at the time (Figure 1.5). In males, the doubling of the NHL rate over a comparatively short 20-year period is particularly striking, and contrasts with the modest fall in HL seen among males over the same time period. These registrational trends coincided with a period of significant change in clinical understanding and consequent marked taxonomic alterations.

During the 1980s the working formulation dominated in North America, whilst Kiel gained ground in Europe. In 1994, the Revised European–American Lymphoma (REAL) classification was published, and this was followed by the WHO classifications of 2001 and 2008. Quantification of the likely impact of these diagnostic changes on the patterns seen in Figure 1.5 is almost impossible to achieve. Whilst it is generally recognized that shifting clinical diagnostic practice almost certainly fuelled the trends, there remains debate about whether such changes could have been responsible for all, or only part, of the dramatic increase in NHL registrations. In this context, for example, the potential etiological role of human immunodeficiency virus (HIV) and organ transplantation, as well as other viruses and environmental exposures, attracted considerable attention at the time – and these factors are discussed in more detail in the section on causes below.

Whatever the cause, the rate of change in NHL slowed in the USA towards the end of the twentieth century, and similar plateauing has now been reported for other developed regions of the world. Taken at face value, this would seem to support the notion that changes in disease detection, diagnostic practice, and cancer registration procedures are all likely to have contributed to the increase seen over the 1970s and 1990s. Indeed, a recent report examining incidence and survival trends across Europe concluded that ‘the evolving classification and poor standardization of data collected on hematological malignancies vitiate the comparisons of disease incidence and survival over time and across regions’ (Sant et al., 2009).

Importantly, with respect to the examination of future time-trends, the role of changing diagnostic practice will undoubtedly remain challenging to evaluate since hematological oncology is changing rapidly, with new approaches to treatment and diagnosis continually emerging as diverse patient pathways evolve. In this regard, the use of more reliable and sensitive diagnostic techniques continues to lower the threshold of disease detection – the ability of flow cytometry to detect small populations of abnormal cells, for example, as well as the introduction of the polymerase chain reaction (PCR) allowing the detection of disease at a molecular level. Hence, proportionately more of the patients diagnosed today have indolent or asymptomatic disease, and it remains possible that the increasing numbers of registrations may be the result, at least in part, of the recognition of new group(s) of patients that would not have been diagnosed in previous decades.

Etiology

For the reasons discussed above, etiological studies conducted in previous decades have often been hampered by the need to aggregate their data into the broad groupings of NHL or HL, either because primary source information was recorded in that way or because diagnostic standards were inconsistently applied. Hence, given the underlying variations in pathologies and prognosis, it is perhaps not surprising that epidemiological reports on lymphomas have often tended to produce inconsistent and conflicting results. Hopefully, this situation will improve in the near future as evidence about the pathological and clinical diversity of lymphoma subtypes continues to accumulate, not only revealing descriptive differences such as those outlined in the previous section, but also other associations.

With respect to the underlying causes of lymphoma, it is generally agreed that immune dysregulation plays a pivotal role in lymphogenesis, and most epidemiological research has concentrated on factors and exposures that interact with the immune system – particularly infection, immunosuppression, and autoimmune disease. These interrelated associations are discussed in the sections that follow.

Infection

In the context of immunodeficiency (see following section), the strong association between human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and several B-cell lymphomas has been examined in numerous studies – the increased risks reported range from 10- to 300-fold, the highest
risks generally been observed for the more aggressive NHL subtypes and the lowest risks for the HL subtypes. Unsurprisingly, the potential role of the HIV/AIDS epidemic was one of the factors evaluated in the context of the striking rise of NHL observed in the 1970s–90s discussed above. In this context it is important to note that NHL rates had begun to rise before the onset of the HIV/AIDS epidemic in the 1980s (Figure 1.5), and in the era of modern therapies the contribution of HIV/AIDS to the totality of lymphomas diagnosed in developed countries remains comparatively small.

In addition to HIV, a number of other viruses are either known or thought to impact on lymphoma risk, albeit by different mechanisms. The most accepted viral associations are those with human T-cell leukemia virus type 1 (HTLV-1) and the two herpesviruses Epstein–Barr virus (EBV) and human herpesvirus 8 (HHV-8) – also known as Kaposi’s sarcoma herpesvirus (KSHV). Infection with HTLV-1 is a necessary but not sufficient cause of adult T-cell leukemia/lymphoma (ATLL), with ATLL developing in around 3% of those infected. ATLL principally occurs in areas where HTLV-1 is endemic, including Japan, the Caribbean, and parts of central Africa and, like most other lymphomas, it is more common in males than females.

In contrast to the specific nature of the HTLV-1/ATLL association, the globally ubiquitous EBV features in several lymphoma subtypes, including Burkitt lymphoma and CHL, as well as those lymphomas occurring in immunosuppressed individuals. EBV is invariably associated with the endemic form of Burkitt lymphoma that occurs in equatorial Africa and New Guinea, where, with a median age of around 7 years and a male to female ratio of 2:1, it is the commonest pediatric malignancy. However, as can be seen from Figure 1.4, the median age at onset of the comparatively rare sporadic form of Burkitt lymphoma seen in other areas of the world is much later, and the male predominance is considerably greater. In contrast to endemic Burkitt’s, EBV is only associated with around a third of all sporadic cases, and the role of EBV in these tumors remains a continuing area of research. Likewise, the significance of the well-established association between EBV and CHL, observed most frequently in children and the elderly in around a third of all cases in resource-rich countries (but even more commonly in less affluent parts of the world), remains an area of current investigation. HHV-8 has been found in several comparatively rare tumor subtypes, where it sometimes occurs with EBV. The nature of these associations, as well as those with a number of other viruses, including both hepatitis B and C, are topics of much ongoing research.

Albeit by very different mechanisms, bacterial infection resulting in chronic inflammation has been consistently linked with a marked increase in the risk of some NHL subtypes – one of the best known associations being that between *Helicobacter pylori* and gastric mucosa-associated lymphoid tissue (MALT) extranodal MZL; the presence of the bacteria increase lymphoma risk by about sixfold. As with the viral associations (e.g. HTLV-1 and ATLL), bacterial infection often occurs many years before MALT lymphoma development, the median age of diagnosis of all extra-marginal zone lymphomas combined in the HMRN series being just under 70 years with no obvious sex bias (Figure 1.4). *H. pylori* infection, however, generally occurs in childhood – the prevalence being highest in developing countries and falling as socioeconomic status increases. In the future, the introduction of effective *H. pylori* treatments, coupled with increasing affluence in developed regions of the world, may well lead to a reduction in incidence of *H. pylori*-positive gastric MZLs.

Interestingly, with respect to the timing of infection and subsequent lymphoma development, detailed analysis of medical records collected during the course of a UK case-control study revealed significant increases in the frequency of non-specific infectious illness episodes more than 10 years before the diagnosis of CHL, but not of DLBCL and FL. No associations with specific infections were, however, found, and whether or not the excess seen for CHL was a consequence of an underlying immune abnormality or whether infection played a causal role could not be determined.

**Immunosuppression**

In addition to HIV/AIDS, it has been known for some time that both inherited and acquired immunodeficiency syndromes predispose towards lymphoproliferative disorders. A few rare inherited disorders of the immune system, including Wiskott–Aldrich syndrome and ataxia telangiectasia, are well known to be associated with marked increases in the risk of lymphoproliferative disorders. Such conditions are, however, exceedingly rare in the general population, and
the proportion of total lymphoma diagnoses for which they account is correspondingly small.

In addition to these rare inherited conditions, lymphoma risks in organ transplant recipients have been extensively investigated, and there are many ongoing patient cohorts. The spectrum of lymphoma subtypes that occur in immunosuppressed individuals tends to differ in important respects from those seen in the non-immunosuppressed, being more aggressive, less responsive to therapy, often EBV-associated, and more likely to occur at extranodal sites. Indeed, post-transplant lymphoproliferative disorders (PTLD) are generally considered separately, the latest WHO classification distinguishing several different malignant and benign PTLD disease forms. Immunosuppression is recognized as the major causal factor in PTLD, the likelihood of development varying with the patient’s age and type of transplant – the incidence being lowest following renal transplant and highest following heart and lung.

Organ transplantation is an increasingly successful therapy and, as with HIV/AIDS, it is one of the factors often considered to have contributed to the temporal increase in NHLs seen at the end of the last century (Figure 1.5). Nonetheless, organ transplantation remains comparatively rare and the proportion of the increase it could account for remains small.

Autoimmune disease

Several strong associations between autoimmune disease and subsequent lymphoma development have been described. In particular, links with autoimmune disease-based chronic inflammation and MALT lymphoma are well recognized – two of the strongest and most well-known relationships being those between Hashimoto thyroiditis and thyroid lymphoma and between Sjögren’s syndrome and salivary gland lymphoma. Consistent associations have also been reported for other chronic inflammatory rheumatic diseases; for example, rheumatoid arthritis and systemic lupus erythematosus with both MZL and DLBCL, and gastrointestinal inflammatory autoimmune conditions, such as celiac disease and Crohn’s disease, with the T-cell lymphomas. Indeed, evidence linking lymphoproliferative disorders with autoimmunity continues to accumulate, the strongest associations being seen for MZL, DLBCL, and T-cell lymphoma, and the weakest with the relatively indolent FL. Associations between chronic inflammatory rheumatic diseases and CHL, but not nodular sclerosis HL, have also been reported.

Taken as a whole, there is broad consensus that elucidating the mechanisms underpinning the link between autoimmune disease and the lymphomas could lead to fundamental insights into the biology of both groups of disorders, and there is considerable speculation about potential mechanisms in the literature. In this regard routine examination of sex-specific associations could provide valuable information since it has long been known that most autoimmune conditions are considerably more common in women than in men, whereas the reverse is true for the majority of lymphoproliferative malignancies. Furthermore, there are well-documented sex-specific variations in immune response that may well impact on the risk of these diseases.

Other environmental factors

The dramatic increase in lymphoma registrations seen at the end of the last century (Figure 1.5) resulted in a massive increase in epidemiological research. Accordingly, in addition to investigating the explicit immunological factors discussed above, many other putative risk factors have been examined, including genetic predisposition, associations with other comorbidities, and a wide range of occupational and other potentially hazardous environmental exposures. However, despite concentrated effort, many of the potentially hazardous associations identified have been weak or contradictory, with few consistent associations emerging. Indeed, at the present time, the lack of accepted environmental determinant(s) for lymphomas sits starkly against the accumulated knowledge about other cancers such as lung, stomach, skin, bladder, and breast.

With respect to the continued investigation of lymphoma determinants, the InterLymph consortium – a scientific forum for epidemiologic research on lymphoma – was established in 2001. InterLymph members have reviewed and published on several health-related states/events and environmental exposures – and their website includes all their reports and provides up-to-date information on many putative risk factors (http://epi.grants.cancer.gov/InterLymph/). Thus far, topics investigated by InterLymph have included self-reported obesity (rising levels being another potential factor suggested as contributing to temporal trends), smoking and alcohol (no consistent effects found); sun exposure and history of atopic infections (marginally reduced risks found); and family history of hematological cancers (increased risks confirmed). Finally, with a view to investigating genetic susceptibility, the majority of
Chapter 1: Epidemiology

InterLymph studies collected constitutional biological material from cases and corresponding controls, and findings here have, perhaps, been more informative. Thus far polymorphisms in two immune system-related genes have been identified using the candidate gene approach, associations being seen for both DLBCL and MZL, and genome-wide association studies are currently ongoing.

Further reading


