Part I

LYMPHOMA OVERVIEW

1 EPIDEMIOLOGY

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INTRODUCTION

Lymphomas, a heterogeneous group of malignancies arising in the lymphoid tissue, account for over 3% of cancers occurring worldwide. Most lymphomas are B-cell in origin, with a minority being T-cell. These cancers are primarily divided into Hodgkin's (HL) and non-Hodgkin's lymphomas (NHL), where HLs are B-cell malignancies distinguishable by the presence of Reed–Sternberg cells, and NHLs are of either B- or T-cell origin. A few inherited disorders, immunosuppressive drug therapies and certain viruses are known to be associated with specific types of lymphoma. However, for the most part, little is currently known about the etiology of lymphomas. The heterogeneous nature and inconsistent definitions of the specific lymphomas has hindered the identification of potential risk factors, but with the introduction of the Revised European–American Lymphoma (REAL) classification in 1994 and its 2001 successor, the World Health Organization Classification of Tumours of the Haematopoietic and Lymphoid Tissues, lymphomas are more consistently segregated on the basis of morphology, immunophenotype, and genetic and clinical features.

DESCRIPTIVE EPIDEMIOLOGY

With a view to elucidating potential causes of disease, descriptive epidemiological studies are routinely concerned with measures of disease incidence, prevalence, mortality and survival in well-defined populations and/or subgroups. For cancer, disease occurrence is commonly estimated from national, or specialist, cancer registries and the "population at risk" of disease from national, or local, census data.

Incidence estimates for NHL vary ten- to twelve-fold across countries, ranging from 1.6 to 17.1 cases per 100 000 persons per year among men and 0.7 to 11.7 cases per 100 000 persons per year among women. Among men, rates of NHL are highest in the United States, Canada and Australia and lowest in El Salvador, Mongolia and Fiji; for women, the highest NHL rates are observed in Israel, the United States and Canada and the lowest in El Salvador, Fiji and Bangladesh – although few reliable data are available from Africa (Fig. 1.1). In the UK, where the estimated incidence is relatively high compared to other parts of the world, NHL is diagnosed in 11.4 and 8.2 of 100 000 men and women respectively each year. Across all nations, more men than women are diagnosed with NHL, incidence increases with age, and data from the USA suggest that the incidence is greater among whites than blacks.

Hodgkin's lymphoma accounts for one-sixth of all lymphomas, with worldwide annual incidence estimates ranging from 0.2 to 5.7 and 0.1 to 4.9 per 100 000 men and women respectively. For both males and females, incidence is highest in the Middle East and eastern Europe, relatively high in other areas of Europe, North America and Australia, and lowest in East and South-East Asia (Fig. 1.2). Rates in the UK are 2.7 per 100 000 amongst men and 1.9 per 100 000 amongst women. Like NHL, HL tends to occur more often in men than women, and in whites more than blacks. The incidence of HL, however, has a bimodal pattern with age in developed countries, peaking at ages 15 to 34 and again at ages over 60, while in developing nations the higher rates are observed in the elderly (Fig. 1.3).

The estimated incidence of NHL has increased over time, whereas rates for HL have remained relatively constant. A rise in NHL occurrence has been reported

Lymphoma: Pathology, Diagnosis and Treatment, ed. Robert Marcus, John W. Sweetenham and Michael E. Williams. Published by Cambridge University Press.

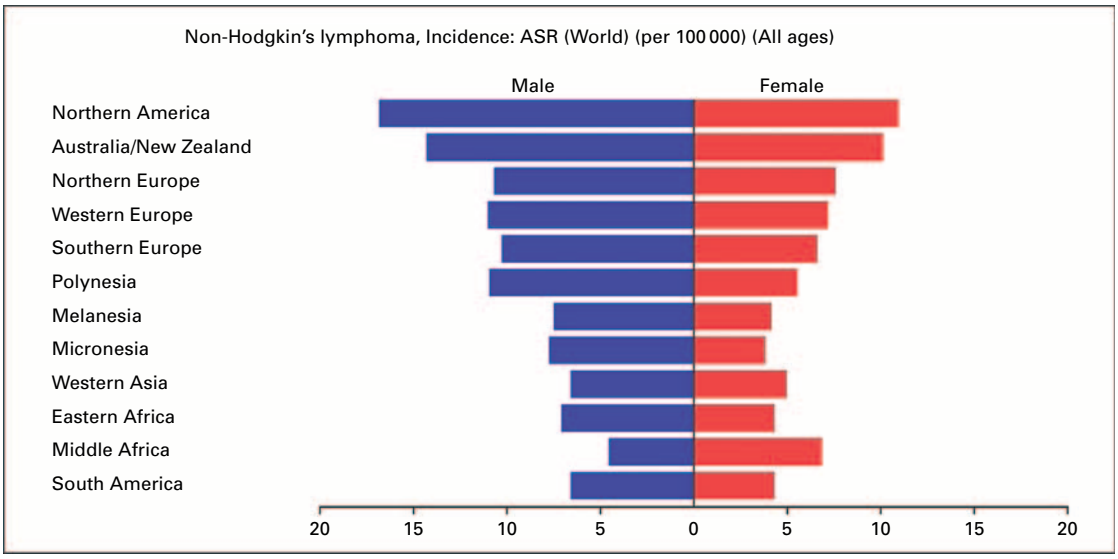

Figure 1.1. Incidence of non-Hodgkin's lymphoma by sex and region. (From *GLOBOCAN 2002*.)

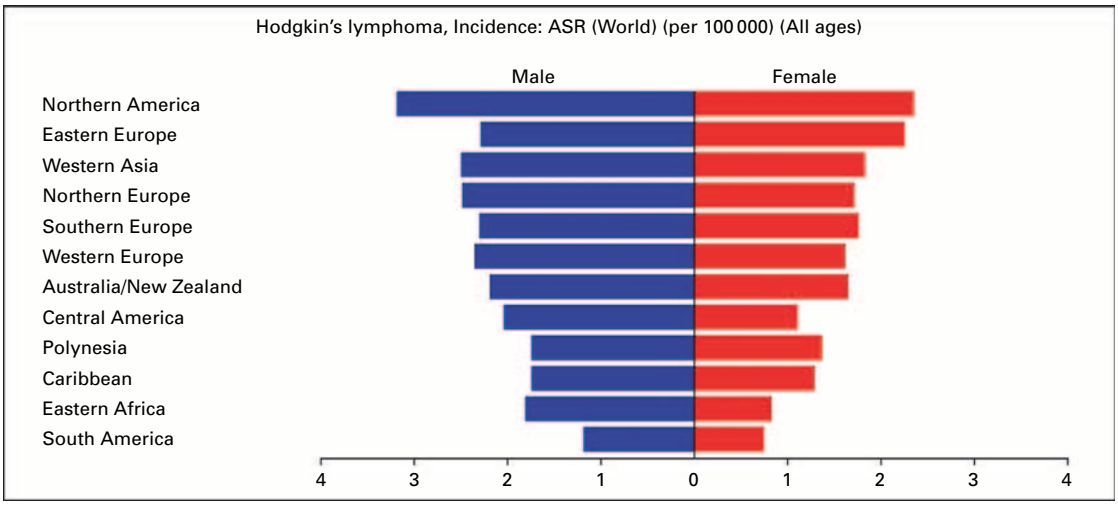

Figure 1.2. Incidence of Hodgkin's lymphoma by sex and region. (From *GLOBOCAN 2002*.)

for several countries, both sexes, all adult ages and ethnic groups, although the greatest increases have been observed among young white males and the elderly. Recent data suggest, however, that the rate of increase has begun to slow down. The increasing rates in the 1980s and 1990s have been attributed, at least in part, to improvements in diagnostic techniques, changes in the disease classification and completeness of cancer registration – as well as to the AIDS epidemic.

Current data suggest that the relative proportions of NHL subtypes vary worldwide. In the West, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma account for over 50% of NHL while other sub-entities, such as mantle cell lymphoma and peripheral T-cell lymphoma, are comparatively rare. The distribution in Eastern nations differs, with relative proportions of T-cell lymphomas being higher, and of follicular lymphoma and chronic lymphocytic

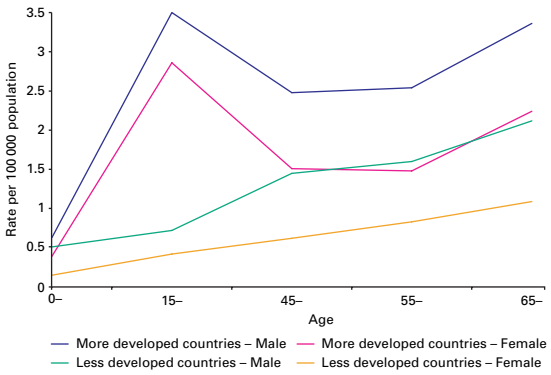

Figure 1.3. Incidence of Hodgkin's lymphoma in more and less developed countries by age and sex. (From *GLOBOCAN 2002*.)

leukemia being lower, than observed in the West. These disparities may reflect the under-presentation or detection of indolent lymphomas in the East, where access to diagnostic tools such as sensitive flow-cytometric methods for use on peripheral blood samples may be more limited. Among HL subtypes, nodular sclerosing HL is the most common, with mixed-cellularity/lymphocyte-depleted less common, and nodular lymphocyte-predominant HL being rare. Most NHL and HL subtypes are more common in men than women except for follicular lymphoma, marginal zone lymphoma and nodular sclerosing HL, where a slight female predominance is observed.

ETIOLOGY

The few known risk factors, such as particular inherited disorders, immunosuppressive drug therapies and certain viruses, are generally accepted to cause lymphoma through severe immunodeficiency. Mild immunosuppression and other alterations to immune function as a consequence of viruses, allergies, autoimmune disorders and ultraviolet light, for example – mediated by genes that influence immune response, such as interleukins and other cytokines – may lead to the development of lymphoma.

Genetics

A family history of lymphoma increases the risk of the disease, with the development of NHL or HL more likely if the relative affected is a sibling. These findings may imply a genetic component in lymphoma pathogenesis, and there is evidence that the human leukocyte antigens (HLA) are involved in HL. Other variants in genes involved in DNA repair, immune response, xenobiotic metabolism and folate metabolism have generally produced, at best, modest associations with little consistency. Probably the most robust associations – with narrow confidence intervals and evidence of heterogeneity between the two most common diagnostic subgroups – have arisen from a large pooled analysis of 3600 cases and 4000 controls from eight European and North American case–control studies of NHL (Rothman *et al.* 2006). The investigation of 12 single nucleotide polymorphisms (SNPs) in nine cytokine genes suggested that persons homozygous for the A allele at TNF-α-308G >A SNP in the tumor necrosis factor-α (TNF-α) gene were at a 60% increased risk of DLBCL compared to those who were homozygous for the G allele; an association was also suggested between DLBCL and interleukin-10-3575T >A polymorphism. However, the function of these two SNPs remains unknown and the possibility that either SNP is in linkage disequilibrium with other SNPs in the same or neighboring genes cannot be ruled out.

Some interesting findings have been observed in familial studies for chronic lymphocytic leukemia (CLL), now classified as an NHL. Similar risks of CLL among subjects with affected siblings, parents and offspring were reported in one registry linkage study. Further to these observations, unaffected members of families with multiple CLL cases had a monoclonal B-lymphocyte expansion, described as a "CLL-like" phenotype, more often than a randomly selected group of adults. The comparatively high prevalence of this "CLL-like" phenotype in comparison to the occurrence of CLL suggests that a relatively common event initiates the phenotype, but a much rarer one is required for the occult disease to progress to CLL.

Primary/acquired immunosuppression

Rare inherited disorders of the immune system, such as ataxia telangiectasia, Wiskott–Aldrich syndrome and common variable hypogammaglobulinemia, are known in some instances to lead to lymphoma. Since relatives carrying the specific gene (e.g. the *ataxia-telangiectasia mutated* [*ATM*] gene) but without immunodeficiency symptoms are not at risk of

Table 1.1. Human viruses associated with lymphoma.

Virus	Lymphoma	Consistency of association
Human T-cell leukemia virus 1	Adult T-cell leukemia/lymphoma	100%
Epstein–Barr virus	Burkitt's lymphoma	Endemic 98% Sporadic < 30% Human immunodeficiency virus (HIV) 40%
	Hodgkin's lymphoma	Developed countries 40% Developing countries and HIV > 90%
	Post-transplant lymphoproliferative disorder early polymorphic monomorphic	Highest frequency in early onset (<1 year)
Human herpesvirus 8	Plasmablastic non-Hodgkin's lymphoma	Higher frequency in HIV patients
	Primary effusion lymphoma	100%

Sources: M. K. Gandhi and R. Khanna, *Pathology* **37** (2005), 420–433; R. F. Jarrett, *J. Pathol.* **208** (2006), 176–186.

lymphoma, the associated severe immunodepression, rather than the underlying genetic trait, may cause the lymphoma.

The autoimmune conditions rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus (SLE), celiac disease, dermatitis herpetiformis, psoriasis, Crohn's disease and ulcerative colitis are associated with lymphoma. The suspected causal agents include the immunosuppressive therapies azathioprine and methotrexate and the tumor necrosis factor-α blockers infliximab and etanercept, but although an additional effect of these drugs on lymphoma risk cannot be excluded, the severity of the autoimmune disease could also be responsible. Little data are available by lymphoma subtype, but more diffuse large B-cell lymphomas than expected develop among patients with rheumatoid arthritis or SLE, while more T-cell lymphomas are diagnosed among those with celiac disease. Like some autoimmune diseases, atopic conditions stimulate the immune system and impair T-cell function, but little association between lymphoma and atopic dermatitis, hayfever or asthma has been reported.

Infections

Viruses have been implicated in the etiology of several cancers, including lymphoma. A minority of specific lymphoma subtypes are linked with human T-cell leukemia/lymphotropic virus 1 (HTLV-1), Epstein–Barr virus (EBV) and human herpesvirus 8 (HHV-8) (Table 1.1). Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) may be involved in lymphoma pathogenesis although it is likely that, for the most part, the roles of these viruses are indirect. Other suspected viral agents include simian virus 40 (SV40) but evidence is currently inconsistent.

HTLV-1, a deltaretrovirus, causes adult T-cell leukemia/lymphoma (ATLL). The geographical distribution of ATLL follows the regions where the virus is endemic, namely Japan, parts of South America, the Caribbean, central Africa, Melanesia, Papua New Guinea and the Solomon Islands. In other areas of the world, persons at risk of ATLL are immigrants from endemic areas and intravenous drug users positive for HTLV-1. It is suggested from Japanese data that 7% of male and 2% of female HTLV-1 carriers will develop ATLL, with the highest risks amongst those infected at a young age.

The ubiquitous herpesvirus EBV is involved in several types of lymphoma, particularly Burkitt's lymphoma (BL), HL and lymphomas in immunosuppressed individuals. EBV genomes are found in almost all cases of endemic BL, a childhood tumor prevalent in equatorial Africa and Papua New Guinea in areas with high exposure to malaria, in <30% of sporadic BL which occur elsewhere, and in 40% of

HIV-associated BL. EBV-positive HLs comprise 30–50% of HL tumors in developed, and 50–95% in developing, countries. In developing regions, primary exposure to EBV occurs in childhood, where the virus is usually asymptomatic, while in developed nations, first infection is often delayed until adolescence, resulting in infectious mononucleosis. However, EBV-positive HLs do not explain the young adult peak in HL incidence in industrialized nations but are diagnosed more often at younger and older ages. EBV infection is controlled by cytotoxic T-lymphocyte (CTL) responses and so, among persons with primary, acquired or iatrogenic immunosuppression where the CTL response is compromised, EBV-associated lymphomas can occur. Probably the most investigated of these are the post-transplant lymphoproliferative disorders (PTLD), a heterogeneous group of conditions that arise as a consequence of the associated or drug-induced immunosuppression following organ transplantation. EBV is found in the majority of PTLDs, with the greatest likelihood of EBV-positive disease within a year or two of transplantation. Other rarer lymphomas that are EBV-associated include primary effusion lymphoma (PEL) and T/NK-cell lymphoma, particularly of the nasal type. Within all EBV-associated lymphomas EBV is clonal, suggesting viral infection occurs prior to the proliferation of the malignant clone. A causal role for EBV is not necessarily implied, however, and given that the vast majority of adults have been exposed to EBV infection, the EBV-positive lymphomas, at least at older ages, may arise from some host : virus imbalance.

HHV-8 (also known as Kaposi's sarcoma herpesvirus) is associated with several benign and malignant lymphoproliferative disorders. It is detected in a plasmablastic variant of multicentric Castleman's disease, a benign condition which in some cases can transform into HHV-8-positive plasmablastic lymphoma. HHV-8 is also found in all cases of the rare lymphoma PEL. Many PEL tumor cells are co-infected with EBV, but HHV-8 is thought to be the main transforming virus. For the majority of NHLs, however, HHV-8 does not appear to be a major etiological factor, and while this virus and other human herpesviruses, type 6 (HHV-6) and type 7 (HHV-7), are present in HL biopsies, their low prevalence in HL tumors probably reflects impaired immunosurveillance rather than a role in pathogenesis.

The immunosuppressive retrovirus HIV substantially increases the risk of lymphoma. Monoclonal HIV is seldom integrated into lymphoma tumor cells and so, in most instances, HIV leads to lymphoma through immunosuppression or B-cell activation. Other viruses are observed in HIV-associated lymphomas, with EBV being present in more than 50% of cases and HHV-8 more rarely. HIV-associated NHLs are predominantly aggressive lymphomas such as BL with plasmacytoid differentiation, DLBCL, PEL and plasmablastic lymphoma of the oral cavity. HL also develops in some HIV patients, with almost all cases being EBV-positive and from the poorer prognostic subtypes of mixed-cellularity and lymphocyte-depleted. Since the introduction of highly active antiretroviral therapy, the risk of HIV-associated lymphomas, particularly those of the central nervous system, has declined.

An association between HCV and lymphoma was first suspected when some patients with essential mixed cryoglobulinemia, an autoimmune condition with 90% HCV seropositivity, developed lymphoplasmacytoid NHL. HCV prevalence is much lower in the general population but varies widely geographically, ranging from around 12% in Italy and Japan to 1% in other Western countries. Recent epidemiological studies conducted in areas of both high and low prevalence suggest HCV is associated with B-cell NHL. Since HCV is an RNA virus incapable of integrating into host-cell DNA, the virus is not directly oncogenic and its involvement in lymphoma is probably related to chronic antigenic stimulation.

Poliovirus vaccines administered to millions of people across the USA and Europe from 1955 to 1962 were contaminated with SV40, a primate polyomavirus. Involvement of SV40 in lymphoma etiology has been suspected since lymphomas, as well as other malignancies, can develop in rodents exposed to SV40. In humans, the virus has been detected in some series of NHL DNA, but not in others. These inconsistent observations could be explained by, for instance, differences in polymerase chain reaction (PCR) testing methods, and since the virus was detected with low copy number, PCR contamination or other laboratory artifact. Epidemiological studies have been more consistent in suggesting that SV40 is not a risk factor for lymphoma. Investigations of birth cohorts likely to have received the contaminated poliovirus vaccine reported similar lymphoma incidence to other birth

cohorts where SV40 exposure from the vaccine was unlikely. While a high proportion of individuals born during the 1955–62 period received the contaminated vaccine, specific antibody responses against SV40 were detectable after the injected formaldehyde inactivated (IPV) poliovirus vaccine but not with the oral attenuated live (OPV) vaccine; moreover, SV40 antibodies are present in persons born after this period, suggesting human-to-human SV40 transmission. Serological measurement of SV40 antibodies provides a direct measurement of SV40 exposure and two case–control studies found no difference in the SV40 seroprevalence among lymphoma cases and unaffected controls.

Bacterial, as well as viral, infections have been suspected in the etiology of lymphoma, particularly of extranodal marginal zone lymphomas that occur in mucosa-associated lymphoid tissue (MALT). Chronic inflammation caused by persistent bacterial infection is thought to encourage development of MALT, and so possibly lymphoma, in organs such as the gastrointestinal tract, ocular adnexa and skin which are normally devoid of native lymphoid tissue. The most established association is between gastric MALT lymphoma and *Helicobacter pylori*. Infection with *H. pylori* can persist for decades in the stomach, where the organism can cause lymphoid follicles and so MALT to develop. The link with these lymphomas was first made in 1991, when the majority of gastric MALT lymphomas in one case series were found to be infected with *H. pylori*. Although this study could not confirm that the infection preceded the lymphoma, it has subsequently been shown that lymphoma B-cell clones are present in biopsy specimens of chronic gastritis taken before the onset of lymphoma, and that lymphoma growth can be stimulated in cultured *H. pylori* strain-specific T cells when crude lymphoma cells were exposed to the organism in vitro. Case–control studies have also reported increased risks of gastric lymphoma following prior *H. pylori* infection. Furthermore, treating the organism with antibiotics has caused, in 75% of cases, the gastric lymphoma to regress, with many patients sustaining remission after several years of follow-up.

Immunoproliferative small intestinal disease (IPSID), a MALT lymphoma arising in the small intestine, can also be successfully treated in the early stages with antibiotics. This suggests that, like the majority of gastric MALT lymphomas, IPSID is bacterial in origin. Following identification of *Campylobacter jejuni* in intestinal tissue from an IPSID patient, Lecuit *et al.* found evidence of the infection in a further four of six cases. Unlike *H. pylori*, however, *C. jejuni* does not appear to persist in the host and future work is required to determine whether infection by this organism occurs as a consequence of altered immunity or whether it is truly a precursor for this rare lymphoma.

Borrelia burgdorferi has been suspected of causing primary cutaneous marginal zone lymphomas. Evidence of *B. burgdorferi* infection in lymphoma tissue has been reported in several European cases. *B. burgdorferi*, which is transmitted by tick bites, has some parallels with *H. pylori* in its potential to induce lymphoma. The organism is capable of persisting in the host despite immune response and it can induce the development of acquired lymphoid tissue in organs where lymphoid tissue is not normally present. Moreover, treatment of the *B. burgdorferi* infection with antibiotics has led to the regression of early-stage primary cutaneous marginal zone lymphomas. However, some US series of these lymphomas have not found *B. burgdorferi* DNA in lesional skin. The geographical difference between Europe and the USA may be explained by the epidemiology of the organism's genospecies as *B. burgdoferi sensu stricto*, *B. garinii* and *B. afzelli* have been isolated in Europe while only the first has been detected in the USA.

Another bacterial infection suspected of involvement in MALT lymphomas is *Chlamydophila psittaci* (formerly *Chlamydia psittaci*), although published data are preliminary. Ferreri *et al.* first detected this microorganism in 80% of ocular adnexal lymphomas in an Italian case series and reported evidence of lymphoma regression among a small sample of cases treated with antibiotics. Subsequent case series of ocular adnexal lymphomas from other parts of the world had lower proportions, and often no cases, with *C. psittaci* DNA.

Delayed exposure to infections has been proposed as a possible explanation of the young-adult peak in HL incidence. Recent studies show little association between HL and low number of childhood infections, low birth order, small sibship size and other surrogate markers for late exposure to infections, although few report risks among young adults. Without exposure to infections, T helper type 1 (Th1) lymphocyte reactions are not developed, and the human body instead mounts a Th2 immune response. The hypothesis of

delayed infection has now been considered for NHL, with a few preliminary reports examining similar proxy variables. Whether early exposure to a specific infection protects against lymphoma remains unanswered, but perhaps the most consistent decreased risks exist for measles, a virus which is present in some lymphoma tumors.

Other medical conditions and therapies

Hodgkin's and non-Hodgkin's lymphomas occur in patients diagnosed with a previous cancer, and both lymphomas can precede other malignancies. Although chemo- and radiotherapies are possible causes, some cancers were treated with neither, and genetic alterations or immunodepression from lymphoma or surgery may be responsible.

While long-term immunosuppressive drug therapy is an accepted risk factor for lymphoma, evidence for other medications remains inconclusive. Antibiotics and sulphonamides have been positively associated with lymphoma, although underlying infection could explain the increased risks with these drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are anticipated to protect against lymphoma since NSAIDs inhibit cyclooxygenase-catalysed synthesis of proinflammatory prostaglandins, and further, aspirin can block nuclear factor κB, a transcription factor essential for immune function and survival of lymphoma cells. The direction of risk estimates with aspirin and other NSAIDs have however been mixed. There has been little consistency too in published findings for steroids, drugs with both immunosuppressive and anti-inflammatory properties. Treatments for hypertension and high cholesterol have been linked with decreased risks while antidepressants, psychotropics and histamine-2 blockers have generally shown no association with lymphoma.

Since the greatest sex difference in HL incidence occurs between the ages of 25 and 44, with women having lower rates than men, high levels of estrogen exposure may protect young women from this lymphoma. Studies of reproductive histories have provided some support for this hypothesis, but the evidence is inconclusive. Incidence of NHL is also lower among women than men, but contraceptive use, hormone replacement therapy, parity and other reproductive factors have largely shown little association with NHL or its subtypes.

Several case reports have been published describing the occurrence of diffuse large B-cell lymphoma following replacement of hip and knee joints, although epidemiological studies have yet to support this association. The metallic implants are suspected of being carcinogenic, but it is also possible that inflammation or infection could be involved. It has also been suggested that hemophiliacs, and those who have undergone blood transfusions, may be at increased risk due to the transmission of viruses such as HCV.

Radiation

Lymphoma appears not to be associated with low-dose ionizing radiation, radiofrequency electromagnetic fields or power-frequency electromagnetic fields. Recently, the potential role of ultraviolet radiation in lymphomagenesis has received some attention since UV rays, particularly UVB, can cause immunosuppression. Contrary to the hypothesized positive association, protective effects have been reported with various proxy variables for UV exposure, including latitude, outdoor work, recreational exposure, number of vacations, use of sunlamps and sunbathing. Vitamin D is suggested to protect against other cancers, but this fails to explain the occasional occurrence of lymphoma among skin cancer patients, and vice versa.

Occupation

Certain occupations and related exposures have been extensively studied for NHL, but less so for HL. Farmers and agricultural workers may be at increased risk of NHL, possibly due to exposure to pesticides or animals. Several groups of pesticides, such as organophosphates, organochlorines, phenoxy herbicides, carbamates and atrazines, have been linked with NHL, but identification of a specific compound is difficult given the frequent use of multiple products. Positive associations with animal exposures are more consistent for cattle than for other livestock, perhaps suggesting a bovine viral agent, but butchers, meat processors and packers do not appear to be at risk of NHL.

Exposure to solvents may increase the risk of lymphoma. Benzene, a known leukemogen, is however probably not a risk factor for lymphoma. Recent studies of workers exposed to styrene, ethylene oxide, butadiene and tetrachloroethylene, as well as those employed in the synthetic rubber, chemical, printing,

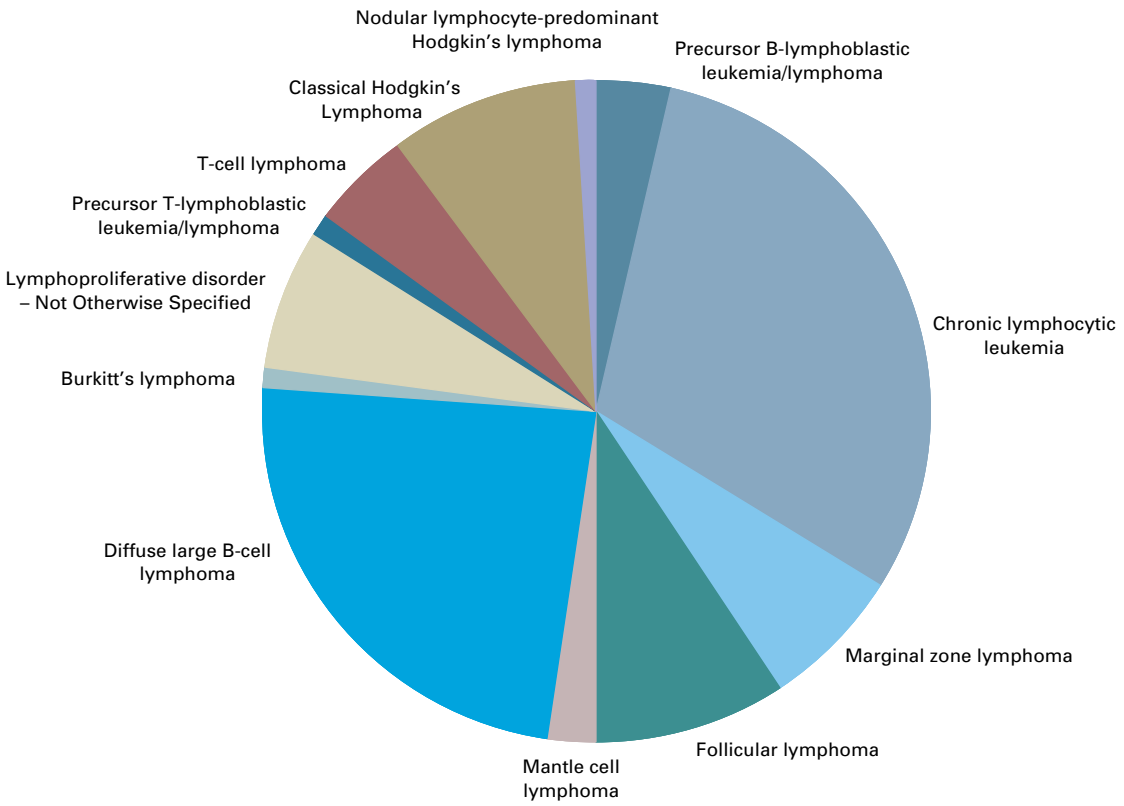

Figure 1.4. Distribution of WHO lymphoma subtypes, based on incidence data in the Yorkshire and Humberside Strategic Health Authority, 2004–5 (www.hmrn.org).

painting, leather and dry-cleaning industries could not definitely confirm associations between solvents and either NHL or HL.

HL may be associated with exposure to wood dust. Cotton dust may also increase the risk of HL as excesses of this lymphoma have been reported among textile workers, tailors, sewers and dressmakers. Organic dusts seem less likely to cause NHL.

Lifestyle

Tobacco smoke shows little consistent association with NHL, most NHL subtypes and HL. An increased risk of follicular lymphoma is suggested, although convincing dose–response trends have rarely been reported. Emerging epidemiological evidence supports a smoking relationship specific to EBV-positive, as opposed to EBV-negative, HL, possibly caused by CD95/CD95L (Fas/FasL)-mediated apoptosis of Hodgkin/Reed–Sternberg cells being inhibited by both EBV and tobacco smoke.

Alcohol, particularly wine, may decrease the risk of NHL and its subtypes, although evidence is inconsistent; studies of HL are fewer and inconclusive. Similarly, investigations of diet lack consistency, but some general patterns have been observed. Consumption of vegetables, fruit and grains may decrease the risk of lymphoma while dairy products, fat, animal protein and total food intake may elevate the risk; no associations were observed with intake of coffee, tea, folate or vitamin B12. Use of hair dyes has previously been associated with NHL, but more recent data suggest no effect for NHL, its subtypes or HL.

Several studies report positive associations between NHL and obesity, while others have not. Risks of diffuse large B-cell lymphoma generally rise with increasing body mass index, patterns for follicular lymphoma are less consistent, and little data are available for rarer

NHL subtypes. Findings for HL are inconsistent, although positive associations have been observed among men. Polymorphisms in genes involved in energy homeostasis which can also modulate immune response, such as leptin, leptin receptor, adiponectin and ghrelin, have been related to NHL but these polymorphisms do not modulate the risk of NHL associated with body mass index.

SUMMARY

While many agents have been proposed, there are few that have been accepted as risk factors for lymphoma. Most potential risk factors cause modulation to the immune system, either through immunodeficiency or chronic inflammation. Probably the largest area of interest for lymphoma etiology is infections, and, while several viral and bacterial agents have been proposed, further work is required to confirm observed associations. Few of the investigated environmental exposures appear to be involved in lymphoma, with perhaps the exception of pesticides. One of the major problems in identifying risk factors for lymphoma has been the heterogeneity of this group of malignancies. More consistent diagnostic techniques, which continue to be improved and modified, have identified more homogeneous subtypes of lymphoma (Fig. 1.4). Availability of these better-quality pathological diagnostic data has enabled the most recent epidemiological studies to explore risks by the distinct disease subtypes. The frequency of the rarer subtypes within some individual studies has been low and so sufficient power to detect risks may only be achieved through collaborative study.

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