

## CHAPTER 2 EPIDEMIOLOGY AND AETIOLOGY

### 2.1 Introduction

#### 2.1.1 Lymphoma in Australia

Lymphoma is an increasingly common cancer with serious health consequences. It includes more than 20 lymphoproliferative malignant diseases that originate from T and B cells in the lymphatic system. The majority (70–80%) arise from lymph nodes; the remainder are extranodal. Lymphoma is primarily a disease of adults, with the highest number of new diagnoses in the seventh decade of life. It affects around 3500 people per year nationally and constitutes 4% of all newly diagnosed cancers. In men, lymphoma is the sixth most common cancer, after prostate, colorectal, lung, melanoma and bladder.<sup>1</sup> In women, it is the fifth most common cancer, after breast, colorectal, melanoma and lung.<sup>1</sup> Among children aged 0–14 years, lymphoma is the third most common cancer, after lymphoid leukaemia and brain and CNS.<sup>1</sup>

Lymphoma is more common in men than women (sex ratio 1.4:1 in 2001), with a lifetime risk of 1 in 64 men and 1 in 88 women in 2001.<sup>1</sup> In 2001, the annual incidence was 16.1 per 100,000 men and 11.3 per 100,000 women, with relatively high mortality rates of 6.3 per 100,000 for men and 4.4 per 100,000 for women.<sup>1</sup> Over the past several decades the incidence of lymphoma has increased dramatically in both men and women in Australia, and in a number of other countries. Reasons for this trend are incompletely understood.

Hodgkin lymphoma (HL), previously known as Hodgkin's disease, is a form of lymphoma distinguished histopathologically by the presence of Hodgkin or Reed Sternberg cells. There are four subtypes, in order of decreasing frequency: nodular sclerosis, lymphocyte predominance, mixed cellularity, and lymphocyte depletion.<sup>2</sup> HL is uncommon, making up only 0.5% of all newly diagnosed cancers. It predominantly manifests during young adulthood, but also peaks in advanced age. HL is more common in males than females (sex ratio 1.2:1 in 2001), especially before puberty. In 2001, the lifetime risk was 1 in 559 for men and 1 in 766 for women.<sup>1</sup> There were 401 cases diagnosed nationally in 2001, at an annual rate of 2.2 per 100,000 men and 1.8 per 100,000 women.<sup>1</sup> Unlike lymphoma, modern treatments are generally curative, resulting in an annual mortality rate of 0.2 per 100,000 for men and women.<sup>1</sup> The incidence of HL has remained relatively stable over time.

#### 2.1.2 Impact of diagnostic classification on epidemiological research

Advances in diagnostic procedures and changes in disease classification over time greatly complicate interpretation of the epidemiology of lymphoma. The increasing availability of molecular tests has aided the diagnosis of lymphoma, in particular the differential diagnosis of HL and other haematologic malignancies. Changes in classification systems have resulted in an increasing number of distinct disease entities. The revised European–American classification of lymphoid neoplasms (REAL classification)<sup>3</sup> was proposed in 1993 and updated to the WHO classification<sup>4</sup> in 2001, allowing categorisation by postulated cell of origin (B cell, T/NK cell). Earlier classifications included the Working Formulation<sup>5</sup> and the Kiel classification.<sup>6</sup> Lymphoma classification is complex; the WHO classification incorporates information on morphology, immunophenotype, genetic features, clinical features, race, geographic distribution and microbiologic features. Some subtypes are inherently difficult to diagnose and the WHO classification recognises the increasing importance of immunophenotyping. Despite the changes in classification over time, diagnostic error does not explain the continuing upward trend in incidence, especially in the younger population.

The classification of HL has remained relatively stable over time. As a consequence, a recent investigation of the reliability of diagnosis and classification of HL in women diagnosed in the United States from 1988 to 1994 found very good agreement between cancer registry and expert review diagnoses.<sup>7</sup>

## 2.2 Descriptive epidemiology

Lymphoma is a heterogeneous disease covering a diverse range of subtypes and anatomical sites, making interpretation of data for all lymphoma types combined somewhat difficult.

### 2.2.1 Trends in incidence and mortality

#### *Age and sex*

Incidence and mortality rates in men and women increase steadily with increasing age, peaking after the seventh decade.<sup>8</sup> In Australia and elsewhere, males predominate.

In Australia and other developed countries, the age-specific incidence of HL is bimodal, with peaks in young adulthood (15–34 years) and then again after the seventh decade.<sup>8</sup> Around 5% of all cases are diagnosed in children less than 15 years of age. In the younger years, the nodular sclerosis subtype is most common, while the mixed cellularity subtype predominates from age 50.<sup>2</sup> Males predominate in both age peaks. Mortality rates are highest in the older age groups. In developing countries, HL is more common in children than young adults.<sup>9</sup>

#### *Trends over time*

Since the 1970s, the incidence of non-Hodgkin's lymphoma (NHL) has increased worldwide and progressively across all age groups in both sexes. Rates increased by 20% to 50% every five years during the 1970s and 1980s<sup>10</sup>, but rates of increase have slowed in recent years. In Australia, rates increased by an average of 0.7% per year in men and 1.2% in women between 1991 and 2001.<sup>1</sup> These increases are largely independent of AIDS-associated diagnoses and changes in diagnostic practices and disease classification.<sup>11,12</sup> There is some evidence of a recent flattening of incidence rates. Population-based registry data in England and Wales from 1986 to 1993 show significant increases over time in the incidence of all extranodal lymphoma as well as lymphoma of the gastrointestinal tract, skin, central nervous system and male genital organs.<sup>13</sup> The greatest proportional increases were observed for middle-aged men and women and for cutaneous lymphomas. In the United States, the incidence of high-grade lymphoma has increased more than low-grade lymphoma.<sup>11</sup>

In Australia, the mortality rate for lymphoma decreased an average of 0.4% a year in males between 1991 and 2001.<sup>1</sup> Over the same period, the mortality rate in females increased on average 0.2% per annum.<sup>1</sup>

Since the 1980s, the incidence of all HL has declined slightly in many countries. Time trend analyses by age at diagnosis show a decrease in incidence for older adults, and an increase in incidence for young adults in some industrial countries.<sup>2</sup> In parallel, rates of the nodular sclerosis subtype have increased and the mixed cellularity subtype have decreased.<sup>9</sup> HL mortality rates have steadily decreased over time due to the increasing effectiveness of treatments.<sup>10</sup>

#### *Ethnic variation*

The incidence of lymphoma is lowest in Asian and African countries, at intermediate levels in European countries and highest in North America and Australia (see Table 2.1). A similar picture is seen for HL, with low rates in Asia and Africa, intermediate rates in Australia, and high rates in Europe and North America (see Table 2.1).<sup>14</sup> The incidence of HL among Asians across varying levels of economic development is consistently low, suggesting a low genetic predisposition or protective lifestyle factors. In the United States, incidence rates for lymphoma and HL are higher in white than black populations, but socioeconomic status is believed to be more important than ethnicity alone.<sup>2,15</sup>

**Table 2.1** Average annual age-standardised (world) incidence rates per 100,000 population for lymphoma and Hodgkin lymphoma in select countries and regions, 1993–1997

Country or region	Lymphoma		Hodgkin lymphoma	
	Men	Women	Men	Women
<i>Oceania</i>				
Australia, ACT	12.8	10.6	2.1	2.4
Australia, NSW	14.2	10.0	2.0	1.5
Australia, NT	9.2	6.7	0.8	0.6
Australia, QLD	12.8	8.9	1.9	1.5
Australia, SA	14.2	11.3	2.3	1.7
Australia, TAS	12.7	10.6	2.3	2.0
Australia, VIC	14.9	10.3	2.5	1.8
Australia, WA	11.4	8.7	1.4	1.5
New Zealand	11.8	8.7	1.8	1.1
<i>North America</i>				
Canada	13.8	10.1	2.8	2.2
USA, SEER: White	16.7	10.6	3.0	2.6
USA, SEER: Black	15.3	7.4	2.6	2.0
<i>Europe</i>				
Denmark	10.3	7.3	2.5	1.6
Sweden	10.1	6.9	2.1	1.7
The Netherlands	10.9	7.1	2.2	1.7
UK, England, Oxford Region	10.8	8.1	2.8	2.0
Spain, Granada	7.6	6.0	1.7	1.5
<i>Africa</i>				
Uganda, Kyadondo County	5.7	4.3	1.1	0.7
Zimbabwe, Harare: African	6.5	5.3	0.5	0.5
<i>Asia</i>				
China, Taiwan	5.9	4.5	0.4	0.2
India, Mumbai	4.5	3.2	0.8	0.4
Japan, Nagasaki Prefecture	8.2	4.4	0.3	0.2
Thailand, Bangkok	5.0	3.7	0.2	0.1
Viet Nam, Hanoi	7.2	3.0	1.7	0.7

Source: Parkin et al.<sup>14</sup>

### **Geographic variation**

A latitude gradient, or positive correlation between lymphoma incidence and ambient solar ultraviolet radiation (UVR), has been demonstrated in several Caucasian populations<sup>16</sup> and in England and

Wales<sup>17</sup>, but not in the United States for lymphoma mortality<sup>18</sup>, lymphoma incidence<sup>16</sup>, or cutaneous lymphoma incidence.<sup>19</sup>

### 2.2.2 Correlations with other neoplasms

Patients with lymphoma are at increased risk of skin cancer and patients with skin cancer are at increased risk of lymphoma. The evidence is consistently strong for both cutaneous melanoma and non-melanocytic skin cancer, and suggests solar UVR may be a risk factor.<sup>20</sup> Excesses of acute non-lymphocytic leukaemia, HL, lung, kidney and bladder cancer also occur in lymphoma patients.<sup>21</sup> An increased risk of lip and tongue cancer after lymphoma has also been reported in NSW.<sup>22</sup> These associations may be due to shared aetiological factors or therapy- or disease-induced immunosuppression.

Correlations in lymphoma incidence and incidence rate trends with those for cutaneous melanoma and non-melanocytic skin cancer are also indirect evidence of a positive association with solar UVR.<sup>16,23</sup>

As for lymphoma, the risk of skin cancer is significantly elevated after HL diagnosis.<sup>24</sup> Excesses of breast cancer, thyroid cancer, leukaemia and lymphoma also occur.<sup>25</sup>

## 2.3 Analytical epidemiology

Numerous epidemiological studies have been conducted to examine the role of putative risk factors. It is difficult to summarise their findings due to the generally poor exposure classification, poorly defined study populations, small sample sizes, and lack of adjustment for confounding by known risk factors. Furthermore, very few studies have examined interactions between risk factors. Moreover, lymphoma, and to some extent HL, consists of a diverse group of neoplasms and few studies have examined risk factors by lymphoma subtype.

### 2.3.1 Immunodeficiency

Immunodeficiency risk	Level of evidence			
	NHL	Ref.	HL	Ref.
Post-transplant immunosuppression is a strong risk factor for lymphoma and a weak risk factor for Hodgkin lymphoma.	III-2	26	III-2	27
Immunodeficiency in HIV/AIDs infection is a strong risk factor.	III-2	28	III-2	29
Congenital immune deficiency is a strong risk factor.	IV	30	IV	2
Acquired autoimmune disease is a moderate risk factor.	III-2	31	III-2	31

#### *Post-transplant immunosuppression*

There is strong evidence that lymphoma risk is increased in patients undergoing immunosuppression therapy to prevent rejection after transplantation with donor organs or tissues. Data from United States and Australian population-based transplant registries indicate a relative risk (RR) of at least 20 following kidney transplantation and 120 following heart transplantation.<sup>26</sup> Risk increases with increasing degree of post-transplant immunosuppression. The risk of lymphoma following bone marrow transplantation is low, but significant.<sup>32</sup> Lymphoma in transplant recipients is typically diagnosed within a few years of transplant, and is usually high grade, often extranodal, and positive for Epstein-Barr virus (EBV) infection.<sup>33</sup>

An excess of HL is not found in organ transplant recipients<sup>34</sup>, but when it does occur it is usually in association with EBV infection. There is evidence of an excess (RR 5) of HL in bone marrow recipients.<sup>27</sup>

### ***HIV/AIDS***

HIV infection is characterised by a specific deficiency of CD4 positive T cells and the chronic stimulation of B-cells. There is clear evidence from cohort and linkage studies that HIV infection markedly increases the risk of lymphoma, with estimates ranging from 14 (low-grade lymphoma) to 350 (high-grade lymphoma) times that of the general population in developed countries.<sup>28,35</sup>

Lymphoma risk in people with HIV infection is independently predicted by degree of immunodeficiency, duration of immunodeficiency, and chronic B-cell stimulation.<sup>36</sup> Risk of lymphoma is highest when CD4 count is less than 50 in late-stage HIV infection. More than 90% of HIV-associated lymphoma is derived from B-cells, and the majority are high-grade and extranodal. Around half are EBV positive.<sup>15</sup> The pathological spectrum includes Burkitt lymphoma, diffuse large B-cell lymphoma, immunoblastic lymphoma, primary CNS lymphoma, and primary effusion lymphoma.

Cohort and linkage studies in developed countries also consistently show increased risk of HL (RR 4–22) in association with HIV/AIDS infection, with risk generally increasing with increasing degree of immunodeficiency.<sup>28,29,35,37</sup> The median CD4 count at diagnosis is approximately 200. Nearly all cases are EBV positive, and the mixed cellularity and lymphocytic depletion subtypes predominate. Risk of HL is highest within six months of AIDS diagnosis.<sup>28</sup>

### ***Congenital/primary immunodeficiency***

Case series data show a predominance of lymphoma in patients with congenital immune deficiencies. An excess of lymphoma occurs in children with congenital X-linked immunodeficiency, severe combined system immunodeficiency and young people with ataxia telangiectasia or Wiskott-Aldrich syndrome.<sup>30</sup> Children with ataxia telangiectasia or Wiskott-Aldrich syndrome, and adults with common variable immunodeficiency, are also at increased risk of HL.<sup>2</sup> Cofactors include defective host immunoregulation, EBV infection (50%), and genetic defects.<sup>30</sup>

### ***Autoimmune diseases***

Autoimmune diseases characterised by persistent antigenic stimulation confer an increased risk of lymphoma. The excess risk associated with these conditions may also be due to treatment with immunosuppressive agents, although evidence from recent cohort study suggests an effect independent of treatment for rheumatoid arthritis.<sup>38</sup> Risk of lymphoma and HL is increased two to three-fold in rheumatoid arthritis patients.<sup>31</sup> Risk of lymphoma, especially T-cell lymphoma and primary gut lymphoma, is increased in celiac disease, although the magnitude of the association is unclear (RR 3–100).<sup>39</sup> Lymphoma risk is also increased in systemic lupus erythematosus (RR 3–7)<sup>40</sup> and Sjogren's (sicca) syndrome (RR 5–8).<sup>41</sup>

### 2.3.2 Infectious organisms

Infectious organism risk	Level of evidence			
	NHL	Ref.	HL	Ref.
Epstein-Barr virus (EBV) infection is a weak risk factor for lymphoma in the general population, a strong risk factor for lymphoma in the immune deficient, and a strong risk factor for Hodgkin lymphoma.	III-2	33	III-2	42
<i>Helicobacter pylori</i> ( <i>H. pylori</i> ) infection is a moderate risk factor for gastric lymphoma.	III-2	43	-	
Human T-lymphotrophic virus types I (HTLV-I) infection is a moderate risk factor for adult T-cell leukaemia/lymphoma (ATL).	IV	33	-	
Human herpesvirus-8 (HHV8) infection is a moderate risk factor for primary effusion lymphoma (PEL).	IV	44	-	
Proxy measures of delayed exposure to childhood infection are a moderate risk factor for Hodgkin lymphoma.	-		III-2	2

#### ***Epstein-Barr virus (EBV)***

EBV, a herpes virus with B-cell-transforming activity, is ubiquitous worldwide. The primary EBV infection usually occurs in childhood and latent infection persists throughout life. As noted in preceding sections, there is strong evidence that EBV infection in conjunction with immune dysfunction, such as post-transplant or HIV/AIDS, is associated with increased risk of lymphoma.<sup>33</sup> EBV infection is more frequent in T-cell than B-cell lymphoma, and the most consistent association is with sinonasal angiocentric T-cell lymphoma.<sup>42</sup> EBV infection is consistently associated with Burkitt's lymphoma, a lymphoma subtype, in African children<sup>42</sup>, and primary CNS lymphoma in people with immune deficiency.

The association between EBV infection and HL is regarded as causal.<sup>42</sup> Cohort and case-control studies indicate a three-fold excess of HL in people with serologically confirmed or self-reported history of infectious mononucleosis, a condition caused by delayed exposure to EBV.<sup>2</sup> Serologic studies suggest that endogenous EBV activation, coupled with an unusual host response, precedes diagnosis of HL.<sup>2</sup> Furthermore, molecular studies have detected EBV DNA in 30–50% of HL cases in developed countries.<sup>2</sup> EBV positivity increases with increasing histopathological grade, and a greater proportion are of the mixed cellularity subtype.<sup>2</sup> Males (OR 2.5), and cases in Asian and Latin American countries, rather than the United States and Europe, are also more likely to be EBV-positive. EBV positivity is more common in HL diagnosed in early childhood and older adulthood than it is in young adulthood.<sup>45</sup> Recent evidence suggests that delayed exposure to EBV and/or another as yet unidentified common infectious agent is a risk factor for the development of HL in young adulthood.<sup>45</sup>

#### ***Helicobacter pylori (H. pylori)***

In Australia, the prevalence of infection with the bacteria *H. pylori* is around 30%. Infection is almost always acquired in childhood and persists unless specifically treated. *H. pylori* infection is associated with a six-fold increase in risk of gastric B-cell lymphoma, known as mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>43</sup> The relationship is regarded as causal; eradication of *H. pylori* results in the complete regression of the majority of low-grade MALT lymphomas.<sup>46</sup>

### ***Human T-lymphotrophic virus types I and II (HTLV-I, HTLV-II)***

Infection with the human retrovirus HTLV-I or II is rare in Australia. In regions where HTLV-I is endemic, such as southern Japan and the Caribbean, infection, especially in early childhood and in males, is associated with increased risk of adult T-cell leukaemia/lymphoma (ATL), a form of lymphoma.<sup>33,47</sup> The cumulative risk of ATL in those infected with HTLV-I is 1–5% over a 70-year life span. Relative risk estimates are not available. HTLV-II has not been consistently associated with lymphoma. HTLV is not associated with HL.

### ***Hepatitis C virus (HCV)***

In Australia, at least 80% of HCV infection occurs in injecting drug users. HCV infection is the main cause of mixed cryoglobulinemia, a benign lymphoproliferation that can evolve into B-cell lymphoma.<sup>48</sup> There is mixed evidence for an association between HCV infection and lymphoma. Two cohort studies found no significant association<sup>49</sup>; one studied young Californian adults with HCV infection over 30 years, while the other followed Japanese HCV-positive patients for an average of six years. In contrast, the majority of case-control studies from areas of high HCV prevalence show a positive association with B-cell lymphoma (RR 2–4). However, these findings have not been replicated in some case-control studies from nonendemic areas elsewhere in Europe or from North America.<sup>48</sup> HCV infection is not associated with T-cell lymphoma or HL.

### ***Human herpesvirus-8 (HHV8)/Kaposi's sarcoma herpesvirus***

HHV8 is a human herpesvirus that is widespread in homosexual men in Australia.<sup>50</sup> In addition to Kaposi's sarcoma, it is associated with a rare form of B-cell lymphoma — primary effusion lymphoma (PEL) — in adults with immunosuppression related to HIV infection or organ transplantation.<sup>44</sup> Relative risk estimates are not available. Primary effusion lymphomas typically contain both HHV8 and EBV DNA and are located predominantly in serous body cavities. HHV8 is not associated with HL.

### ***Simian virus 40 (SV40)***

Australian children were inadvertently exposed to SV40, a macaque polyomavirus, via contaminated polio vaccines in the 1950s and 1960s. No prevalence estimates are available. SV40 causes B-cell lymphomas in rodents, but there are very limited data to suggest a role in human oncogenesis. Age-specific trends in lymphoma incidence are not consistent with a cohort effect, and laboratory data are inconsistent. SV40 DNA sequences have been detected in around 40% (n=222) of lymphoma samples from the United States<sup>51,52</sup>, but none of 152 samples from the United Kingdom<sup>53</sup>, despite evidence of similar levels of exposure in both nations.

There has been very limited investigation into the role of SV40 infection in HL. A United States study isolated SV40 DNA in 9% (n=30) of HL samples.<sup>52</sup>

### ***Other viruses***

There is inconsistent evidence of a positive association between HL and infection with other members of the herpesvirus family, including cytomegalovirus (CMV) and human herpesvirus type 6 (HHV-6).<sup>2</sup>

### ***Proxies for exposure to infection***

There is limited evidence of an association between lymphoma risk and factors indicating potential for infection and immunological stimulation, such as socioeconomic status and childhood crowding. Socioeconomic status was not identified as an independent risk factor in two cohorts<sup>38,54</sup>, while the association was not reported for other cohorts.<sup>55</sup> A case-control study found that having five or more siblings was a risk factor (OR 3.6) for lymphoma in homosexual men<sup>56</sup>, while others have reported both increased and decreased risk of lymphoma in association with higher educational level.<sup>57,58</sup> A

recent population-based case-control study found an increased risk of lymphoma in those with later age onset of common infectious diseases, which was limited to those from small-size families.<sup>59</sup>

Risk of HL in young adulthood is consistently associated with indicators of higher childhood social class, such as single-family housing, small family size, early birth order, and high maternal education.<sup>2</sup> These associations generated the hypothesis that HL in young adults is caused by delayed exposure to common childhood infections. Infections experienced during adulthood are usually more clinically severe than those normally encountered during childhood, and may alter the immunological control of a latent oncogenic infection, resulting in chronic antigenic stimulation.<sup>2</sup> In support of this hypothesis, risk of HL in young adults is decreased in those reporting fewer childhood infections<sup>60</sup>, and risk of HL at all ages is non-significantly and modestly increased in those reporting older age at first infection.<sup>57</sup> A similar mechanism is likely for HL in middle age, with increased risk for those of higher education, while risk of childhood and older adult HL is increased in those of lower social class.<sup>2</sup> It is important to note there is no evidence that patients with lymphoma as such, can transmit lymphoma to other individuals.

### 2.3.3 Occupational and environmental toxins

Most studies of occupational exposures have been based on job title, making interpretation with respect to specific exposures problematic.

Occupational risk	Level of evidence			
	NHL	Ref.	HL	Ref.
Exposure to pesticides or herbicides is a weak risk factor for lymphoma.	III-2	61	-	
Farming as an occupation is a weak risk factor.	III-2	62	III-2	63
Work in a wood-related industry is a moderate risk factor for Hodgkin lymphoma.	-		III-2	64

#### *Pesticides, herbicides and agricultural exposures*

Chemical exposure to both the use and production of pesticides and herbicides has been examined in relation to risk of lymphoma and HL. The balance of evidence suggests an increased risk of lymphoma,<sup>15,61</sup> but an inconclusive relationship with HL.<sup>64</sup> A nested case-control study utilising serum collected prior to lymphoma diagnosis found a positive association between lymphoma risk and total PCBs (polychlorinated biphenyls), but not DDT (dichlorodiphenyltrichloroethane) and related compounds, or organochlorines.<sup>65,66</sup> The authors noted, however, that the possibility of a weak association with organochlorines in highly exposed populations could not be excluded.

Farmers are at increased risk of lymphoma and may be at slightly increased risk of HL. A meta-analysis of lymphoma among farmers found a relative risk of 1.10 (95% CI 1.03–1.19) for all studies and 1.26 (95% CI 1.15–1.37) for studies conducted on farmers in the United States.<sup>62</sup> A meta-analysis of HL among farmers found a relative risk of 1.25 (95% CI 1.11–1.42) for all studies and 1.08 (95% CI 0.97–1.20) for cohort studies.<sup>63</sup> It is unclear which agent or agents are aetiologically important. Farmers may be exposed to pesticides, herbicides, fungicides, infectious microorganisms, solvents, paints, fuels, oils, and dusts; each of these agents has been inconsistently positively associated with risk of lymphoma and HL. Farmers' diet and level of physical activity may also differ from that of the general population.

Other occupations that involve work with animals, such as meat (abattoir) workers, meat inspectors, and veterinarians, have been inconsistently associated with increased risk of both lymphoma and HL. Exposure to animal-born viruses has been implicated.

### ***Other chemicals***

The relationship between occupational exposure to solvents and lymphoma<sup>15</sup> or HL<sup>64</sup> is not clear. However, a meta-analysis of cohort study data from five countries found no excess lymphoma mortality in workers exposed to benzene or benzene-containing petroleum products (standardised mortality ratio: 0.90, 95% CI 0.82–0.98).<sup>67</sup>

Occupational exposure to hair dyes, or the personal use of hair dyes, is inconsistently associated with increased risk of both lymphoma and HL.<sup>68,69</sup> Examination of the risk associated with occupational exposure to chemical compounds in hair dyes is probably confounded by the potential for increased exposure to infectious agents through personal contact with clients.

### ***Sun exposure***

Limited analytical evidence on the relationship between ambient solar UVR, a measure of potential sun exposure, and risk of lymphoma is contradictory. Cohort data suggest increased risk<sup>54</sup>; and mortality case-control study data, decreased risk<sup>70</sup>, with residence in areas of higher ambient UVR.

None of the analytical studies performed to-date obtained recalled estimates of personal occupational sun exposure; all were crudely based on job title. The only cohort study to examine sun exposure found no association between occupational sun exposure and lymphoma.<sup>54</sup> Results from three case-control studies were equivocal<sup>70–72</sup> with the exception of increased risk for farmers. Several other case-control studies that examine a range of occupations have not consistently identified outdoor occupations, other than farmers, as being at increased risk of lymphoma. The relative contribution of sunlight exposure and exposure to herbicides and pesticides in farmers is not known.

The association between sun exposure and risk of HL has not been examined.

### ***Other occupational exposures***

Although mixed, the balance of evidence favours a moderate positive association between occupation in a wood-related industry and HL.<sup>2,64</sup> The evidence with respect to such an association for lymphoma is weak and inconsistent.

Epidemiological studies have inconsistently identified increased risk of lymphoma in industries with exposure to asbestos particles and welding, as well as metal workers, rubber workers, those in electrical occupations, and to those in occupations of higher socio-economic class.

#### **2.3.4 Medical procedures and medical history**

Medical and comorbidity risk	Level of evidence			
	NHL	Ref.	HL	Ref.
Childhood appendectomy is a moderate risk factor for lymphoma.	III-2	73	-	
Skin cancer is a strong risk factor for lymphoma.	III-2	20	-	
Diabetes is a weak risk factor for lymphoma.	III-2	74	-	
Tuberculosis is a moderate risk factor for lymphoma.	III-2	75	-	
Infectious mononucleosis is a moderate risk factor for Hodgkin lymphoma.	-		III-2	2

### ***Ionising radiation***

There is little convincing evidence of a relationship between ionising radiation and lymphoma.<sup>15</sup>

### ***Blood transfusion***

Blood transfusions may expose recipients to oncogenic viruses and other immune-modulating antigenic substances. Three cohort studies are consistent in showing a two-fold increase in risk of lymphoma with prior receipt of a blood transfusion; with the most recent indicating strongest associations for low-grade lymphoma.<sup>76</sup> However, seven of eight case-control studies found no increased risk, and there is evidence that the inclusion of transfusions in the 12-month period before diagnosis artificially inflates the risk.<sup>77</sup> It is unclear whether the association is related to the condition(s) leading to the blood transfusion, or the transfusion itself.

The association between blood transfusion and HL has not been examined.

### ***Vaccinations and medications***

There are no cohort data on the association between vaccination history and risk of lymphoma. One case-control study found a significant protective effect (OR 0.7) on lymphoma risk from the receipt of six or more vaccinations;<sup>78</sup> subsequent analyses have shown this effect is confined to the diffuse large-cell type.<sup>79</sup> Two case-control studies found increased risk of lymphoma (OR 2–3) in association with immunisation against tuberculosis.<sup>31,79</sup> The only HL case-control study found a protective effect from immunisation against tetanus (OR 0.5) and diphtheria (OR 0.6), and no association with immunisation against smallpox or poliomyelitis.<sup>31</sup>

The association between nonsteroidal anti-inflammatory drugs (NSAIDs) and lymphoma risk is inconclusive and may be confounded by indication for use.<sup>38</sup> Some studies have reported a significant increase in risk, while others have found a significant decrease in risk.

### ***Tonsillectomy and appendectomy***

Tonsillectomy is not a risk factor for lymphoma. Although mixed, the epidemiological evidence suggests that risk of HL in young and middle-aged adulthood is unrelated to tonsillectomy, but the association with disease onset among older persons is unknown.<sup>2</sup>

A recently published cohort study from Sweden and Denmark reported a 20–50% excess of lymphoma after childhood appendectomy, but no increase in HL.<sup>73</sup>

### ***Medical conditions***

Risk of lymphoma is increased following melanoma and non-melanocytic skin cancers, and vice versa. This provides further indirect evidence of a positive association with sun exposure.<sup>20</sup>

Data from cohort, but not all case-control studies, show an increased risk of lymphoma in those with adult-onset diabetes, although the magnitude of the increase in risk is unclear (RR 1.2–2.2).<sup>74,80</sup>

Cohort and case-control study data are mostly in agreement in showing a doubling of risk of lymphoma in individuals with a history of tuberculosis.<sup>75</sup> Cohort results indicate a significant association only for those with severe infection, diagnosed many years before.<sup>75</sup> The increased risk may be due to the infection itself, an underlying susceptibility, or an associated exposure.

Despite the requirement for immunosuppressive therapy, inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, appears unrelated to risk of lymphoma, but may increase the risk of HL as much as four-fold.<sup>81</sup>

The evidence linking lymphoma with allergic diseases such as eczema, asthma, hay fever, general allergies and allergies to plants, dust, food, animals, medications, and insect bites/stings is weak and inconsistent.<sup>82</sup> Significant increases in risk, as well as significant decreases in risk, have been reported, but most studies have found no association.

The relationship between history of infectious mononucleosis (IM) and risk of lymphoma is uncertain; with two case-control studies reporting a significant positive association<sup>59,83</sup> and another a significant protective effect for diffuse large-cell lymphoma.<sup>79</sup> As noted above (2.3.2 Infectious organisms), IM increases the risk of HL by two to three-fold<sup>2</sup>, and the association is unlikely to be explained by confounding by social class.

### 2.3.5 Lifestyle

Lifestyle risk	Level of evidence			
	NHL	Ref	HL	Ref
Cigarette smoking doubles risk of follicular lymphoma and Hodgkin lymphoma.	III-2	84	III-2	82
Use of vitamin supplements does not affect risk of lymphoma.	III-2	55	-	

#### *Smoking*

The relationship between cigarette smoking and risk of lymphoma is unclear.<sup>85</sup> However, findings from recent, well-designed studies are consistent in showing a doubling of risk for the follicular lymphoma subtype.<sup>84</sup>

On balance, the results from cohort and case-control studies support a positive association (OR 1.5–2.0) between cigarette smoking and HL. A recent population-based case-control study of men found the strongest association for the mixed cellularity subtype.<sup>86</sup>

#### *Alcohol*

A number of studies have found a protective effect of alcohol consumption, in particular wine, on risk of lymphoma<sup>87</sup>; however, the precise relationship remains equivocal, particularly with respect to the amount and type of alcohol and the subtype of lymphoma.

There have been no cohort studies of alcohol consumption and risk of HL, while a hospital-based case-control study of alcohol and other dietary factors identified no significant associations.<sup>88</sup>

#### *Physical activity*

Physical activity and obesity are likely to influence immune function. Physical activity appears unrelated to risk of lymphoma<sup>89</sup>, while cohort and case-control study data with respect to excess weight are equivocal.<sup>89</sup> A single cohort study examining all cancers found a significant association between obesity and HL in men (SIR 3.3),<sup>90</sup> but there have been no studies of physical activity and risk of HL.

#### *Nutrition*

Diets high in fat or meat products appear to double the risk of lymphoma<sup>91,92</sup>, however, the data are inconsistent and may be confounded by an association with herbicides and pesticides. A single case-control study examined fish consumption and found no association with lymphoma.<sup>93</sup>

Results from two cohort and four case-control studies show no clear association between fruit and vegetable intake and risk of lymphoma, but there is a tendency towards a protective effect.<sup>94</sup> In addition, the balance of evidence from three cohort studies and one case-control study suggest there is no protective or harmful effect with respect to lymphoma from vitamin supplement use.<sup>55,95</sup>

Cohort and case-control studies are largely consistent in showing no association between risk of lymphoma and tea<sup>96</sup> and coffee<sup>88</sup> consumption. The association with milk consumption is unclear.<sup>91</sup> Nitrate, a contaminant in drinking water, can break down into carcinogenic compounds. None of the cohort studies and case-control studies conducted to date have found any association with nitrate levels in drinking water and lymphoma risk.<sup>97</sup>

There is no pattern of risk for diet and HL; two cohort studies and four hospital-based case-control studies typically examined a single food or vitamin type.<sup>88,93</sup>

### **2.3.6 Reproductive and hormonal factors**

Sex hormones have immuno-modulatory effects. Evidence from cohort studies indicates a weakly protective or zero effect of pregnancy on risk of lymphoma.<sup>98</sup> The only study to examine it found a significantly protective effect (RR 0.5) for breast-feeding more than two children versus none.<sup>89</sup> In contrast, data from the same cohort of women show a weak positive association with use of hormone replacement therapy (HRT), and a strong positive association for the follicular subtype.<sup>99</sup>

While results from an early cohort study supported the hypothesis that childbearing is protective of HL<sup>100</sup>, it has not been confirmed in more recent cohort studies.<sup>101,102</sup> No studies have examined use of HRT and HL.

### **2.3.7 Genetic susceptibility**

There is no evidence that lymphoma occurs more commonly than expected in members of the same family<sup>15</sup>, except in families with a history of lymphoma, HL or leukaemia among first-degree relatives (RR 3–4).<sup>103</sup> The very strong association between rare forms of genetic immune deficiency and lymphoma risk suggests that polymorphisms of genes controlling immune function may influence lymphoma risk, but genetic polymorphisms that independently predict risk of lymphoma have not yet been identified.

There is some evidence of genetic susceptibility in HL. There is a higher than expected incidence of HL among siblings but not spouses, and monozygotic but not dizygotic twins, suggesting a role for both genetic factors associated with immune competence and common childhood environmental exposures.<sup>2</sup> There is also a weak positive association between risk of HL and genes whose products play a role in the regulation of the immune response, the human leucocyte antigen (HLA) genes.<sup>9</sup> The oncogene *bcl-2* and the p53 gene have also been implicated.<sup>9</sup> Of importance for both lymphoma and HL is an understanding of the interaction between genetic polymorphisms and environmental factors.

## **2.4 Conclusions**

The only accepted strong risk factors for lymphoma are immune deficiency and specific infections, but these account for only a small proportion of all cases. The question of whether mild sub-clinical immune deficiency is an important cause has not been adequately addressed. Other less well-established risk factors include cigarette smoking, farming, herbicides/pesticides, specific medical conditions and animal fat or meat consumption. Solar UVR is a putative risk factor for lymphoma, however, the evidence is only indirect and awaits verification from studies where lifetime personal sun exposure has been comprehensively quantified.

The established risk factors for HL are immune deficiency and EBV infection. Other risk factors include proxy measures for childhood exposure to infectious agents, infectious mononucleosis, cigarette smoking, farming, work in a wood-related industry, and genetic susceptibility.

In summary, the aetiologies of lymphoma and HL are complex and, for the most part, poorly understood. While some important causes have been well described, these account for only a minority of cases.

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