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# I. Epidemiology of adult non-Hodgkin lymphoma

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The non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies arising from lymphoid tissue, with varied clinical and biological features. Many systems have been developed over time to classify NHL, reflecting the increased understanding of features of different types of the disease [1]. The extent to which the epidemiology of NHL may differ from one type to another is important to determine. The ability to address this issue depends on the use of an accurate and consistent classification system for these malignancies. Recent reviews of the epidemiology of NHL are available [2, 3].

## descriptive epidemiology

There were an estimated 356 000 new cases of NHL and 192 000 deaths from NHL worldwide in 2008 [4]. NHL is the 8th most commonly diagnosed cancer in men and the 11th in women. The disease accounts for ~5.1% of all cancer cases and 2.7% of all cancer deaths. Areas with highest incidence of NHL include North America, Europe, Oceania, as well as several African countries (Figure 1). The occurrence of NHL is higher in men [worldwide age-standardized rate (ASR) 6.1/100 000] then women (ASR 4.2/100 000). Incidence increased in many high-income countries between the 1950s and 1990s, but no further increase has been observed during the past decade [5]. For example, during the 1970s and 1980s in the USA, the age-adjusted incidence rate of NHL increased by 3%–4% annually in the USA, resulting in a near doubling of the rate [6]. The reasons for this pattern are largely unknown, although at least part of the increase has been attributed to diagnostic improvements [7], in particular for extra-nodal lymphomas [8], as well as to acquired immunodeficiency syndrome (AIDS)-related neoplasms following the human immunodeficiency virus (HIV) epidemic. Other factors that have been considered as potential contributors to the increase in incidence are discussed below.

There is a large variation in the geographical distribution of NHL types, with a higher proportion of follicular and diffuse lymphoma in North America and Europe, and a higher proportion of T-cell lymphoma in Asia [5]. Part of the difference might be due to a greater variability in the incidence of B-cell NHL compared with T-cell NHL, which is consistent with the results of a study reporting that increase in NHL rates from 1973 to 1988 in the USA was accounted for by B-cell NHL [8].

## family history and genetic factors

Increased risk of NHL among persons with relatives previously diagnosed with NHL has been reported [9, 10], but hereditary factors are hypothesized to account for a small percentage of NHL cases.

In a pooled analysis of eight European, Canadian and US case–control studies of NHL, single nucleotide polymorphisms (SNPs) in tumor necrosis factor (TNF) and interleukin-10 (IL-10) genes, encoding key cytokines involved in the inflammatory response and immune balance, were associated with risk of NHL, especially diffuse large B-cell lymphoma [11, 12]. A genome-wide association study of 1465 cases of follicular lymphoma and 6958 controls identified two variants associated with increased risk at 6p21.32 (rs10484561, rs7755224) [13]. A similar study of 1529 cases of chronic lymphocytic leukemia and 3115 controls identified six risk loci at 2q13 (rs17483466), 2q37.1 (rs13397985), 6p25.3 (rs872071), 11q24.1 (rs735665), 15q23 (rs7176508) and 19q13.32 (rs11083846) [14]. The biological and clinical significance of these loci remains unclear. Variations in genes involved in the folate metabolism and transport pathway, which affects DNA synthesis and methylation, have been examined in several case–control studies [15]. Although results are not fully consistent, there is a suggestion of an association between genetic variation in methionine synthase and thymidylate synthase and risk of NHL. Results for other genes are not consistent.

## medical conditions

Several autoimmune disorders have been associated with increased risk of NHL, including rheumatoid arthritis (RA), celiac disease, systemic lupus erythematosus (SLE) and Sjögren's syndrome; however, the proportion of cases of NHL associated with autoimmune disease is small, due to the low prevalence of autoimmune disorders in the general population. In a series of NHL patients included in a population-based lymphoma registry, 7.8% of patients exhibited clinical autoimmune phenomena, including RA (2.7%), Graves' disease (1.4%) and Sjögren's syndrome (1.0%) [16]. A meta-analysis of autoimmune diseases and risk of NHL produced strong summary associations with SLE [meta-relative risk (RR) 7.4, 95% confidence interval (CI) 3.3–17.0], RA (meta-RR 3.9, 95% CI 2.5–5.9) and Sjögren's syndrome (meta-RR 18.8, 95% CI 9.5–37.3) [17]. The excess risk of NHL in these patients may be a result of the disease or its treatment; in particular, immunosuppressive therapy for autoimmune disease may contribute to the risk of NHL [18].

An increased relative risk of NHL among persons with a history of type II diabetes has been reported in cohort and

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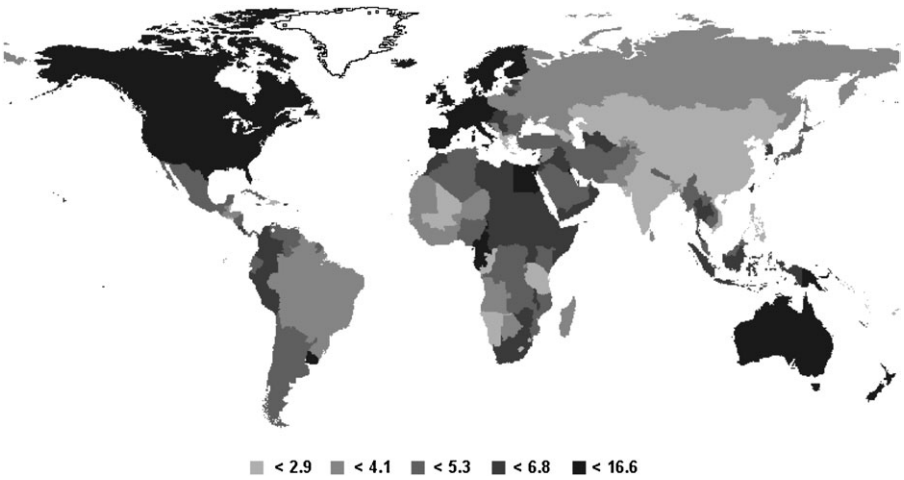


**Figure 1.** Estimated incidence (age-standardized rate/100 000) of NHL by country, 2008 [4].

case–control studies (RR range: 1.1–3.3) [19]. The causal nature of this association remains to be established, and the underlying mechanisms are unclear. The possible association between allergy, whether as a broad category or response to specific allergens, and development of NHL has been examined in numerous studies [20]; the overall evidence suggests that allergy does not increase the risk of NHL; rather, inverse associations with some allergies, including allergic reactions to medications, food and plant allergies and bee and wasp stings, have been reported. These studies mainly relied on self-reported conditions, which are subject to misclassification.

Several studies have reported associations between history of malignancy and NHL risk. In particular, an increased risk has been reported for individuals with history of Hodgkin lymphoma, breast cancer and skin cancer. Possible explanations for the positive associations that have been observed include inherited susceptibility to malignancy, exposure to an agent that is causally associated with both cancers, or an immunosuppressive or direct effect resulting from chemotherapy or radiation.

## medications and medical interventions

The association between medication use and the development of NHL has been examined in several studies. A complicating factor in studies of associations with medication use is that the underlying medical conditions that prompt treatment, rather than the medications themselves, may explain observed associations with risk of NHL (confounding by indication). Medications for which an association with NHL has been reported include phenytoin, a commonly used anticonvulsant drug; cimetidine, a histamine-2 receptor antagonist used to treat gastroesophageal disorders including ulcers; various antibiotics; and benzodiazepine. The most consistent associations have been reported for immunosuppression therapy including non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants for conditions such as inflammatory bowel disease and autoimmune disorders (see above) [2].

Several studies have examined the risk of NHL among persons who have received blood transfusions. Results from cohort studies have varied, while case–control studies have generally observed no associations between prior blood transfusions and NHL risk [2]. An increased risk of NHL due to diminished immune capacity after organ or bone marrow transplantation has been reported consistently. In the most informative study of 45 141 kidney and 7634 heart transplant patients, the incidence of NHL was dramatically higher in both groups during the first year following surgery, compared with the general population [21]. Among kidney transplant recipients, 101 NHL cases were observed (2.7 expected), and among heart recipients, 93 cases were observed (0.6 expected).

Results of studies that evaluated the association between Bacille Calmette–Guerin (BCG) vaccination and risk of NHL have varied, with most studies reporting positive associations [2]. The possible underlying mechanism of the association is unclear. Other vaccinations, such as those for smallpox, cholera, yellow fever, influenza, measles, tetanus and polio, have been associated inversely with risk of NHL.

## infectious agents

The relationship between HIV/AIDS and the risk of developing NHL has been examined in numerous studies, with strong positive associations observed [22]. The relative risk of NHL among persons infected with HIV has been reported to be >100, with the greatest risk for lymphomas of B-cell origin and high-grade histology. Chronic antigenic stimulation and immune deficiency may be responsible for the increased risk of NHL among HIV-infected individuals. HIV may act by inducing immunodysregulation, affecting genes responsible for cell regulation and control and/or failing to control other viruses, which may result in opportunistic infection and replication of oncogenic viruses [23]. NHL has been reported as an AIDS-defining disease in ~2%–3% of persons with AIDS, but AIDS accounts for only a small fraction of all NHL cases. Highly active antiretroviral therapy (HAART) for HIV infection was introduced in 1996, changing the natural history of HIV infection and altering the epidemiology of HIV-associated lymphomas [24]. The incidence of NHL has decreased since the advent of HAART; however, considerable risk still remains. In an international collaboration on HIV and cancer, incidence data from 23 prospective studies were used to

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compare incidence rates of NHL in HIV-infected persons in 1997–99 with those in 1992–96 [25]. The incidence rates for NHL declined from 6.2 per 1000 person-years to 3.6 per 1000 person-years (rate ratio 0.58, 99% CI 0.45–0.74).

Human herpesvirus 8 (HHV8) is accepted to be associated with development of primary effusion lymphoma (PEL), a rare B-cell lymphoma that almost exclusively affects HIV-positive patients [26]. This lymphoma, however, is often associated also with Epstein–Barr virus (EBV), limiting the understanding of the pathogenic role of HHV8. A role of HHV8 in other types of B-cell lymphoma is not established.

EBV is a ubiquitous human herpesvirus that infects >90% of the population worldwide, usually during childhood, and persists latently throughout life. EBV has been implicated as a cofactor in the development of several malignancies, including primary effusion lymphoma and high-grade B-cell NHL in immunodeficient patients [27]. Other B-cell and T-cell lymphomas have also been linked with EBV, mostly in the context of immunosuppression because of organ transplantation (see above), HIV infection or congenital immunodeficiency syndromes, any of which can lead to the reactivation of latent EBV infection. EBV is causally linked to Hodgkin lymphoma [28] but a direct role of EBV in NHL etiology remains in question. EBV is believed to be a cofactor with host immune defects in uncontrolled infection and proliferation of B lymphocytes that lead to NHL.

Hepatitis C virus (HCV) infection is prevalent worldwide, with a seroprevalence of >2–3% in much of Asia and Africa, ~2% in the USA and Italy, and >1% in many other high-income countries [29]. HCV is implicated in the development of hepatocellular carcinoma, and its role in the pathogenesis of NHL has recently been established [30]. In a pooled analysis of seven case–control studies, the overall RR for HCV infection was 1.78 (95% CI 1.40–2.25) [30]. The percentage of NHL cases attributable to HCV infection could be as high as 10% in countries with a high prevalence of HCV infection in the general population [31].

Adult T-cell leukemia/lymphoma (ATL) is a disease of mature T cells and is endemic in parts of Japan, the Caribbean Basin, Central and West Africa, and South America, and can account for >50% of NHL cases in these areas [32]. There is strong evidence that ATL is caused by the human retrovirus human T-cell lymphotropic virus (HTLV-I) [33], for which the international pattern of endemicity parallels that of ATL incidence worldwide [34]. HTLV-I has been found to be associated with other NHL types, although uncommonly, and the etiological fraction of overall NHL associated with HTLV-1 is likely to be small [35].

Gastric infection with *Helicobacter pylori*, a cause of peptic ulcer disease and gastric carcinoma, may also cause B-cell lymphomas, particularly mucosa-associated lymphoid tissue (MALT) tumors in the stomach [37]. *H. pylori* has been detected in >90% of patients with low-grade gastric MALT lymphoma, and in 40%–75% of high-grade gastric lymphomas [37]. More than 60% of MALT lymphomas regress with *H. pylori* eradication following treatment with antibiotics [37].

Other infectious agents that have been suggested to cause NHL include *Borrelia burgdorferi*, a tick-borne spirochete that causes Lyme disease and has been inconsistently linked with cutaneous lymphoma, and Simian virus 40, for which DNA sequences have been detected in a relatively large proportion (30–50%) of some series of NHL cases, but no association has been consistently detected in analytical studies [36]. Inconsistent results have been reported for other agents, including tuberculosis, parasites, influenza, measles, chicken pox and rubella. In addition, the hypothesis that exposure to animal viruses increases the risk of NHL has been examined among abattoir workers, meat cutters and veterinarians, with inconsistent results [2].

## lifestyle and personal factors

Results from studies on tobacco smoking do not support a causal association with NHL. In a pooled analysis of nine datasets, Morton and colleagues [38] evaluated the associations between cigarette smoking and risk of NHL and of types of NHL. Of all NHL types, the only one that was significantly associated with current smoking was follicular lymphoma (pooled RR 1.31, 95% CI 1.12–1.52); however, the test for trend for pack-years of smoking was not statistically significant (*P* value of test for linear trend 0.60).

Most studies of alcohol drinking and NHL have reported inverse associations. In a pooled analysis of nine case–control studies, Morton and coworkers [39] reported a significant inverse association with alcohol (pooled RR 0.83, 95% CI 0.76–0.89), which did not vary with frequency or duration of intake, or by type of alcoholic beverage. Results varied across NHL types, although all RR were <1.0 for current drinkers compared with non-drinkers. The potential protective effects of alcohol consumption may be due to improved cellular and humoral immune responses [40].

Concurrent increases in the prevalence of obesity and the incidence of NHL over the past few decades have contributed to the hypothesis that there is an association between obesity and NHL, but findings from epidemiological studies have been inconsistent. In a pooled analysis of 18 case–control studies, no overall effect of body mass index (BMI) on NHL risk was observed [41], although an association with NHL mortality was detected in a prospective mortality study of >900 000 US adults [42]. The discrepancy can be explained by the different outcome (incidence versus mortality) in case high BMI leads to poorer survival following NHL.

Personal use of hair dyes has been inconsistently linked with NHL risk. In a pooled analysis of four case–control studies, a weak association has been reported for use of hair dyes before 1980 (pooled RR 1.3, 95% CI 1.1–1.4), but not for more recent use [43].

No consistent associations with NHL risk were observed for other lifestyle factors, including diet and physical activity [2, 3]. Two possible exceptions are fish intake, which has been associated with a non-significantly decreased risk of NHL in several studies (although intake of omega-3 fatty acids from fish was not associated with reduced risk of NHL), and red meat intake, for which several, but not all, studies have reported positive associations, although results have not been consistent for associations with specific types of red meat or with preparation or cooking methods. Biological mechanisms for these dietary factors have not been established. Similarly, no

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association has been established between reproductive or hormonal factors and NHL risk, including age at menopause, age at menarche, age at first birth, use of oral contraceptives and use of menopausal hormone therapy [2].

## occupational and environmental factors

Occupational and environmental exposure to pesticides has been addressed as a possible cause of NHL in a large number of epidemiological studies. Recent detailed reviews are available [2, 3, 44]. Overall, these studies have not identified consistent associations with pesticides as a general category, or with classes of pesticides or specific chemicals. Furthermore, no consistent exposure–response patterns supporting a causal interpretation have been observed. Mixed and generally non-significant results were observed in studies of farmers, pesticide manufacturing workers, pesticide applicators and Vietnam veterans who sprayed herbicides. The main limitation in many of the available studies is the lack of information on the specific type of exposure, and limited information on intensity and duration of use.

In a meta-analysis of 54 cohort studies and 718 observed NHL deaths among chemical workers, Greenberg and colleagues [45] reported no significant excess mortality from NHL overall (meta-RR 1.09, 95% CI 0.97–1.23); however, a significant elevation in risk of NHL death was reported among workers after ≥10 years of follow-up (meta-RR 1.50, 95% CI 1.06–2.13). Risks attributable to individual chemical exposures were not evaluated, as there were limited data on worker-specific exposures.

In a pooled analysis of 26 cohorts of petroleum workers in the USA, UK, Canada, Australia, Italy and Finland, a significant deficit of NHL mortality was reported among benzene-exposed subjects (pooled RR 0.90, 95% CI 0.82–0.98) [46]. In a study of 74 828 chemical workers with benzene exposure and 35 805 unexposed workers from China, a non-significant positive association was reported for NHL mortality (RR 3.0, 95% CI 0.9–10.5). The RR for workers with ≥10 years of benzene exposure was 4.2 (95% CI 1.1–15.9; *P* value of test for linear trend 0.01); however, there was no dose–response pattern for average or cumulative benzene exposure [47].

Several studies have investigated the association between exposure to solvents, and in particular to tricholoroethylene (TCE), and NHL risk. Solvents as a general category have been inconsistently associated with NHL [48]. Results from studies of TCE have been heterogeneous, and although some European studies reported positive associations, there was no consistent exposure–response pattern within or across the studies. There appears to be no association of NHL with exposure to asbestos or other dusts. Although some studies reported significant positive associations with metal exposure, these results were not reproduced in other studies.

A large number of studies on occupational risk factors of NHL were based on occupation or job title: these studies have many limitations, most notably the lack of specific individual-level exposure information, and, in most instances, the lack of information on potential confounding factors. The most consistent finding is an association between occupation as a schoolteacher and risk of NHL. Findings from a meta-analysis of 14 studies (RR range: 0.31–3.60) indicated a significantly elevated relative risk of NHL in this occupational group (meta-RR 1.36, 95% CI: 1.13–1.62); however, results may have been affected by publication bias [49]. Significantly elevated associations have been reported among firefighters, but specific exposures have not been identified or evaluated in this occupational group. Results for other occupational groups have been inconsistent.

Occupational and wartime exposure to ionizing radiation has not been associated with an increased risk of NHL. Several studies have reported positive associations with therapeutic or diagnostic radiation exposure, but results are inconsistent and in general dose–response patterns have not been observed. A number of studies have reported an inverse association between ultraviolet (UV) radiation from sunlight and NHL risk: in a pooled analysis of ten case–control studies, the risk of NHL fell with the composite measure of increasing recreational sun exposure (pooled RR 0.76, 95% CI 0.63–0.91, for the highest exposure category; *P* value of test for linear trend 0.01) [50]. However, assessing lifetime exposure to sunlight is challenging, and several studies have relied on geographical latitude of residence or prior history of skin cancer as markers of potential exposure. Neither electromagnetic radiation nor radiofrequency exposure appears to be causally related to NHL [2].

## conclusions

Although factors related to altered immune function and several infectious agents appear to play a role in the etiology of NHL, these factors neither explain the majority of the cases, nor are they likely to account for the rapid increase in incidence observed over the last decades of the 20th century. There have been numerous epidemiological studies of occupational and environmental exposure to chemicals, but results from these studies have not identified any consistent positive associations with NHL risk or mortality. There is evidence that alcohol intake and UV exposure are associated inversely with NHL. Fish intake may also be associated inversely with NHL whereas meat intake may be associated positively with NHL. Little is known about the etiological role of potential susceptibility factors such as genetic markers or polymorphisms, immunologic characteristics because of prior or chronic illnesses, or results of environmental insults (e.g. UV damage to skin). There is growing evidence of etiological heterogeneity among types of NHL, with different incidence patterns according to age, sex, race and geography. The extent to which these differences reflect differences in etiology needs further study. Hence, future epidemiological research on NHL will be enhanced by analyses of types of NHL, improved reliability and validity of exposure assessment tools to evaluate occupational, environmental and personal exposures, and evaluation of susceptible subgroups of individuals whose risk of NHL may differ from that of the general population.

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