# Epidemiology and Etiology of Non-Hodgkin Lymphoma

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**Abstract**

Non-Hodgkin lymphoma (NHL) consists of many histologically and biologically distinct lymphoid malignancies with poorly understood, but possibly distinct, etiologies. The patterns of incidence and time trend vary not only by age, sex, and race/ethnicity in the USA, but also show significant geographic differences, suggesting the potential role of infectious agents, environmental factors, and lifestyle factors in addition to host genetic status in the development of NHL. Important pathogenetic mechanisms include immune modulation and chronic antigen stimulation. Epidemiologic studies in the past two decades have provided intriguing new insights on the possible causes of lymphoma and support the idea that there is some mechanistic commonality of lymphomagenesis, but significant etiologic heterogeneity clearly exists. This review presents a summary of the current understanding of the descriptive epidemiology and etiology of NHL and suggests areas of focus for future epidemiologic research.

**Keywords**

Epidemiology · Lymphoma · Immunomodulation · Infections · Diet · Alcohol · Tobacco · Obesity · Reproductive factors · Occupation · Chemical exposures · Blood transfusion · Autoimmune disease · Allergy · Medications · Radiation · Hair dyes · Genetics

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## Contents



## 1 Introduction

Non-Hodgkin lymphomas (NHL) account for about 4.2 % of new cancer diagnoses in the USA [1]. It is the seventh most commonly diagnosed cancer in both men and women in the USA [2], with approximately 70,800 new cases (38,270 men and 32,530 women) expected in 2014 [1]. NHL is a heterogeneous group of malignancies that arises from two distinct lymphocyte types, B or T lymphocytes, at various stages of differentiation [3]. While 60–75 % of NHL develops or presents in the lymphoid tissues, such as lymph nodes, spleen, and bone marrow, it can occur in almost any tissue and ranges from the more indolent follicular lymphoma to the more aggressive diffuse large B-cell and Burkitt's lymphomas [4]. Incidence rates of NHL almost doubled between 1970 and 1990, but have stabilized since the late 1990s among general populations [2, 5]. The increases have been more pronounced in whites, males, the elderly, and those with NHL diagnosed at extranodal sites. Patterns of occurrence and intensive research efforts in the past two decades strongly suggest the role of environmental effects and considerable etiologic variation among NHL subtypes. This review presents the descriptive epidemiology of NHL and summarizes current knowledge about the possible etiology of NHL, with a focus on NHL subtypes for which data are available.

## 2 Descriptive Epidemiology

### 2.1 Histologic Classification and Disease Sites

NHL is presently classified according to the fourth edition of the World Health Organization (WHO) classification of tumors of hemopoietic and lymphoid tissues

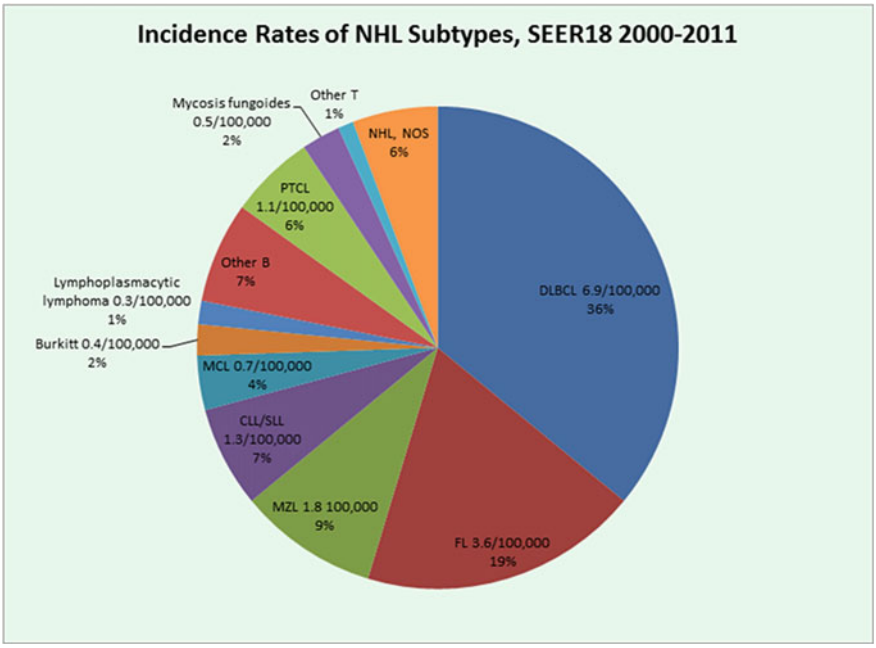


**Fig. 1** Incidence Rates of NHL subtypes in the USA, 2000–2011, Surveillance, Epidemiology, and End-Results Program (Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat), Version 8.1.5. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Database: Incidence-SEER 18 Registries Research Data, Nov 2013 Submission (2000–2011)

that distinguishes between precursor and mature neoplasms corresponding to stages of differentiation [3]. Approximately 85–90 % of all lymphomas arise from B lymphocytes and the remainder derives from T lymphocytes or NK lymphocytes [3]. The two most common types of NHL are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, accounting for approximately 35 and 20 % of all lymphomas, respectively (Fig. 1) [2, 3, 6]. Nodal disease accounted for approximately 65–70 % of all lymphomas in the USA [2]. The incidence of extranodal disease has increased rapidly during the 1980s and early 1990s and is now accounts for 20–30 % of all cases, with the most common sites of origin the skin, the gastrointestinal tract, and the central nervous system [2, 6–8].

## 2.2 Incidence

The annual incidence rate of NHL from 2007 to 2011, estimated from the Surveillance, Epidemiology, and End-Results (SEER) Program of the National Cancer Institute, was 19.7 cases per 100,000 persons, and it increased exponentially with age (9.3 per 100,000 persons under 65 years and 91.5 per 100,000 persons age

65 years and older) [2]. The overall incidence of NHL is about 50 % higher in men (23.9 per 100,000) than in women (16.4 per 100,000) in the USA [2], and this increased risk for men is seen in other countries as well [2, 6]. Male predominance in incidence was seen in most histologic subtypes with Burkitt lymphoma and mantle cell lymphoma exhibited the most marked excess among men (men vs. women rate ratios of 4 and 3, respectively) [6, 9]. The overall NHL incidence rates remained largely unchanged during 2001–2010 among women, but increased at the rate of 0.5 % per year among men.

In the USA, the incidence of NHL varies by race/ethnicity, with non-Hispanic whites (21 per 100,000 persons) at higher risk than blacks (14.3 per 100,000), Asian/Pacific Islanders (13.1 per 100,000) and Hispanics (17.8 per 100,000) during 2007–2011 [2]. Most histologies, particularly low-grade lymphoma and follicular lymphoma, are more common in whites than in blacks [9]. Only peripheral T-cell lymphoma (PTCL), mycosis fungoides, and Sezary syndrome are more common in blacks than in whites. There is also substantial variation in both incidence and histologic subtypes around the world. NHL is most common in developed countries, with the USA and Australia having one of the highest rates worldwide, followed by Europe (Fig. 2) [10]. In contrast, incidence rates are generally lowest in eastern and southern Asia (2–3 per 100,000). There are also marked differences in the distribution of lymphoma subtypes across geographic regions. Compared with North America and Western European countries, Asian countries tend to have higher incidences of mature T-/natural killer (NK)-cell lymphomas and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) and lower rates of follicular lymphoma, CLL/SLL, and Hodgkin lymphoma [11–15]. This geographic and racial/ethnic heterogeneity suggest that infectious, environmental, and lifestyle factors are important in addition to host factors in the etiology of certain subtypes of NHL [8, 16, 17].

## 2.3 Time Trends

The incidence of NHL has changed substantially in the past four decades in both the USA (Fig. 3) and in other countries [2, 6, 8, 18]. In the USA, the incidence almost doubled between 1970 (10.2 per 100,000) and 1990 (18.5 in 1990), and the increase has been more pronounced in whites, males, the elderly, and those with NHL diagnosed at extranodal sites [5, 7, 8]. Some of this increase may be due to improved diagnostic techniques, effect of the human immunodeficiency virus (HIV) epidemic, and immunosuppressive therapies. While the overall incidence rates stabilized between 1995 and 2010 (about 19 per 100,000), NHL rates among HIV-unaffected individuals increased 1.4 % per year during 1992 and 2003, before stabilizing in mid-2000s [19]. This slow increase of NHL incidence in HIV-unaffected individuals is largely unexplained.

Studies have reported diverse trends by NHL subtypes (Fig. 3). From 1992 to 2001, DLBCL and follicular lymphoma increased 1.4 and 1.8 % per year, respectively, whereas rates of CLL/SLL declined 2.1 % per year. The rates for

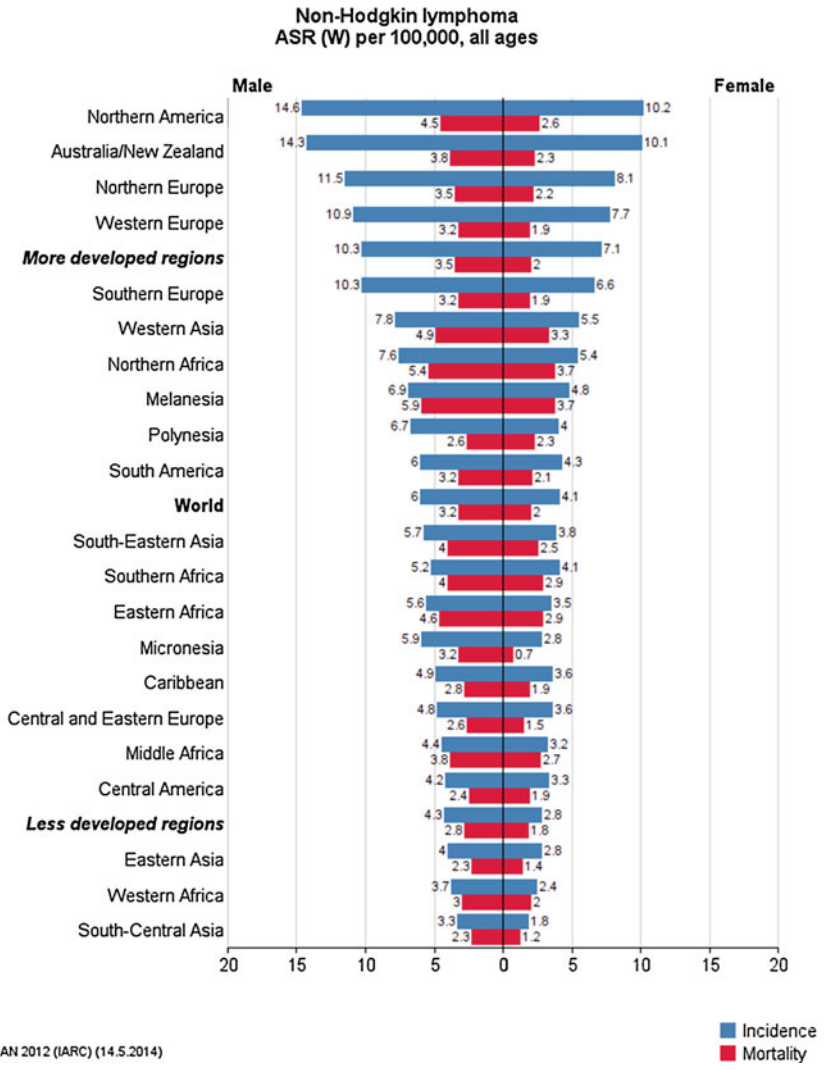


**Fig. 2** Incidence and mortality of NHL in different parts of the world (Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on day/month/year)

DLBCL and follicular lymphoma in the general population appear to have stabilized since mid-2000s, independent of HIV [19]. During 2002–2011, incidence rates increased significantly for marginal zone lymphoma (1.7 % per year) and mantle cell lymphoma (1.7 % per year), with white elderly men seeing the most

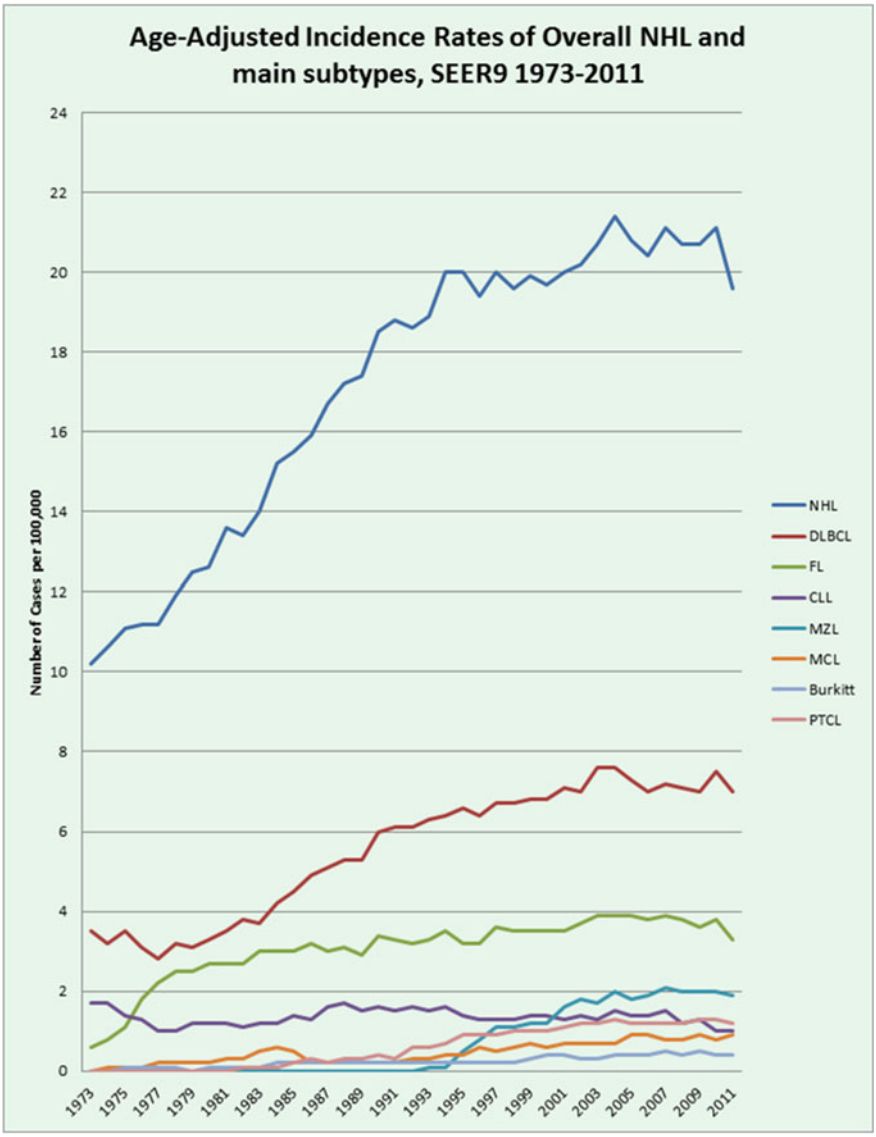


**Fig. 3** Incidence rates of overall NHL and main histologic subtypes in the USA, 1973-2011, Surveillance, Epidemiology and End-Results Program (Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat), Version 8.1.5. Surveillance, Epidemiology, and End-Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 9 Registries Limited-Use Data, Nov 2013 Submission (1973–2011)

striking increase [2, 20–22]. These time trends are difficult to assess due to the recent recognition of these two entities as distinct subtypes.

Primary extranodal disease has increased more rapidly than nodal disease since the 1970s [7, 23]. Incidence rates increased 3.0–6.9 % per year for extranodal cases compared to only 1.7–2.5 % per year for nodal cases, with the largest increase occurring in the brain and other areas of the central nervous system (224 %). The increase in extranodal lymphomas is, in part, a consequence of improved diagnostic tools and the application of modern immunophenotypic and molecular methods [24]. Although primary central nervous system lymphomas are rare, there has been a threefold increase in incidence. The dramatic increase in NHL of the central nervous system warrants investigation, although the rates have begun to decrease since the mid-1990s [25], most likely due to the decline in the incidence of acquired immunodeficiency syndrome (AIDS) [26].

Intensive research efforts have been made in the past two decades to understand factors that might account for the incidence patterns and trends. This effort is strengthened by the initiation of several consortia, such as a large International Lymphoma Epidemiology Consortium (InterLymph) and the EPILYMPH study in six European countries that have allowed a detailed examination of NHL subtype-specific association and the potential for etiologic heterogeneity as well as the assessment of less prevalent exposures [27–30]. The following section will review some of the established and postulated risk factors for the development of NHL with an emphasis on epidemiologic findings reported in the past two decades.

## 3 Etiology

### 3.1 Immune Modulation

Congenital and acquired states of immunosuppression are the strongest factor known to increase NHL risk [31]. These conditions include ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable hypogammaglobulinemia, X-linked lymphoproliferative syndrome, and severe combined immunodeficiency [32]. Epstein-Barr virus (EBV) appears to be an important cofactor, and host defects in immune regulation resulting in uncontrolled infection and proliferation of B-lymphocytes likely contribute to the development of NHL.

Acquired immunodeficiency states such as HIV infection are associated with 75- to 100-fold increased risk of NHL compared with the general population [19, 33], although recent data in the post-HARRT (highly active antiretroviral therapy) era suggest it has decreased [34, 35]. These NHLs are usually high-grade and often present with extranodal disease. Increased risk varied by NHL subtypes, ranging from 30-fold, 50-fold, and 1020-fold for DLBCL, Burkitt lymphoma, and central nervous system lymphoma, respectively [34]. The occurrence of NHL in HIV-infected persons has been attributed to deficient immune surveillance of oncogenic herpesviruses, such as EBV and human herpesvirus 8, as well as defective immune regulation and chronic antigenic stimulation due to other infections [36].

Patients who are treated with immunosuppressive drugs following solid organ transplant or hematopoietic stem cell transplant are at substantially increased risk (30–50 times) for NHL [37–39], particularly during the first year after transplant [40, 41]. The risk varied widely across subtypes and appeared markedly elevated for DLBCL, marginal zone lymphoma, lymphoplasmacytic lymphoma, and NK/T-cell lymphoma [37–39]. Chronic antigenic stimulation induced by the graft and significant immunosuppression associated with EBV infection are the probable mechanisms. Polyclonal or monoclonal B-cell proliferations are seen in transplant patients, but these often regress when immunosuppressive therapy is stopped. However, the proliferation may persist and evolve into an aggressive NHL. Loss of control of persistent EBV infection caused by the immunosuppressive therapy appears to be important to this process.

Patients who receive chemotherapy and/or radiation are also at increased risk for developing subsequent secondary NHL [42, 43]. In the SEER database, NHL risk was increased after initial radiotherapy for all solid cancers combined, non-small cell lung cancer, and prostate cancer [42]. Risk increased with longer latency after radiotherapy, but there was no clear pattern by NHL subtype or age.

Epidemiologic studies concerning a history of blood transfusion and the subsequent development of NHL have produced contradictory findings. A meta-analysis including 14 studies showed that blood transfusion was associated with a 20 % increase in the risk of NHL overall that was limited to cohort studies [44]. The association was similar for men and women as well as for transfusions given before or after 1992. In contrast, case–control studies have demonstrated no association of NHL with transfusion [45, 46]. A recent large pooled analysis from InterLymph found an inverse association between transfusion history and risk of DLBCL [47], follicular lymphoma [48], and CLL/SLL [49]. Bias cannot be ruled out because these results are inconsistent with the hypothesis that the immunosuppressive effects of allogeneic blood transfusion and infections caused by blood-borne organisms would likely increase the risk of NHL [50].

An increased incidence of gastrointestinal lymphomas is seen in patients with celiac (nontropical) sprue and inflammatory bowel disease, particularly Crohn's disease [5]. Sjogren's syndrome has been associated with NHL overall, particularly follicular lymphoma [48], DLBCL [51], marginal zone lymphoma [52, 53], and lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia (LPL/WM) [54]. Systemic lupus erythematosus and rheumatoid arthritis have also been associated with B-cell lymphoma [53]. It remains unclear whether the excess risk is due to immunosuppressive drugs to treat these autoimmune conditions or the condition itself.

## 3.2 Viruses

Several viruses have been implicated in the pathogenesis of NHL, including EBV, human T-cell lymphotrophic virus (HTLV-1), Kaposi sarcoma-associated herpesvirus (KSHV, also known as human herpesvirus 8), and hepatitis C virus (HCV).

### 3.2.1 Epstein-Barr Virus (EBV)

Infection with EBV is highly prevalent in the adult population, with approximately 90 % of individuals in developed countries having evidence of previous infection by age 40 years [31]. In healthy individuals, equilibrium exists between latent EBV infection and the host's immune system. In immunocompromised patients (i.e., organ transplant and HIV infection), however, control mechanisms are impaired which could lead to EBV-driven B-cell proliferation and ultimately the development of B-cell lymphoma [18, 55]. EBV has been associated with Burkitt lymphoma (particularly in areas of Africa where the virus is endemic), Hodgkin lymphoma, lymphoma in immunocompromised patients, sinonasal lymphoma in Asia and South America, and sporadically in other NK/T-cell lymphomas (predominantly occurring in Asia) [31].

### 3.2.2 Human T-Cell Lymphotrophic Virus (HTLV-1)

HTLV-1 is a human retrovirus that establishes a latent infection via reverse transcription in activated T-helper cells. Infection with HTLV-1, especially in early childhood, is strongly related to adult T-cell leukemia/lymphoma in the Caribbean and Japan, where infection is endemic [56]. The cumulative lifetime risk in infected individuals is estimated to be approximately 5 % [57], suggesting a multistage process of T-cell transformation and involvement of additional pathogenetic factors [58]. An HTLV-1-like provirus has been detected in some patients with mycosis fungoides, although findings have been inconsistent.

### 3.2.3 Kaposi Sarcoma-associated Herpesvirus (KSHV)

KSHV-like DNA sequences are frequently detected in primary effusion lymphomas, in patients with Kaposi sarcoma, and in those with multicentric Castleman disease-plasmablastic lymphoma [6] . These herpesvirus 8 (HHV-8)-related NHL subtypes are associated almost exclusively with HIV infection in settings of profound immunosuppression, particularly primary effusion lymphomas [59]. It has also been seen in the absence of immunodeficiency in areas of high HHV-8 seroprevalence, such as the Mediterranean [18].

### 3.2.4 Hepatitis C Virus (HCV)

Several studies have linked HCV to NHL, but results are not entirely consistent. A positive association between HCV and B-cell NHL was found in some studies [60, 61], but not others [62, 63]. A study in Southern Italy showed a higher incidence of HCV infection in high-grade NHL than in low-grade NHL [64], whereas other studies report a higher incidence in low-grade NHL [61]. A meta-analysis of 18 studies found positive associations for both B- and T-cell NHL [65], while pooled analyses of individual-level data in 20 case–control studies from InterLymph reported excess risk for DLBCL [47], marginal zone lymphoma [52], CLL/SLL [49], and LPL/WM [54], but not follicular lymphoma [48, 66]. EPILYMPH also reported a positive association with DLBCL [67]. Geographic variability in HCV seroprevalence may account for some of the inconsistency in that positive

associations tend to be reported from geographical areas with high HCV seroprevalence such as Italy and Japan, whereas no associations were noted mostly in studies from northern Europe, northern USA, or Canada where HCV seroprevalence is low [18].

## 3.3 Bacterial Infections

Chronic gastric infection with *H. pylori* has been linked to the development of low-grade, gastric mucosa-associated lymphoid tissue (MALT) lymphoma [68, 69]. A pooled analysis of 1,052 marginal zone lymphoma cases and 13,766 controls in 12 case–control studies from the InterLymph found a positive association between self-reported peptic ulcers and risk of extranodal marginal zone lymphoma, but not nodal or splenic marginal zone lymphoma [52]. Eradication of *Helicobacter pylori* has been shown to result in the regression of MALT lymphoma [70]. Infection with *B. burgdorferi,* the causative agent in Lyme disease, has been detected in about 35 % of patients with primary cutaneous B-cell lymphoma [71]. A near-complete remission of a primary marginal zone B-cell lymphoma was observed after eradication of *Borrelia burgdorferi* with antibiotic treatment [72]. Studies have also linked *C. psittaci* to ocular adnexal marginal zone lymphoma [73]. This infection, however, is highly specific and does not reflect a subclinical infection widespread among the general population [5]. Herpes zoster has also been associated with Hodgkin lymphoma and NHL [74–76]. Findings on infectious agents are consistent with the idea of chronic antigenic stimulation or inflammation in the pathogenesis of NHL.

## 3.4 Lifestyle Factors

### 3.4.1 Tobacco

Cigarette smoking appears to have no association [77–79] or only a weak association [80–82] with NHL. A meta-analysis of 50 studies reported that ever smoking was associated with a higher risk of NHL, mainly because of the association with T-cell NHL [83]. Some studies, however, have linked smoking with a higher risk of follicular lymphoma [82, 84–86] and high-grade NHL including diffuse large B-cell NHL [80, 82]. Pooled analyses of 20 case–control studies from the InterLymph found that cigarette smoking was positively associated with risk of central nervous system, testicular and cutaneous DLBCL [47], follicular lymphoma [48], LPL/WM [54], and mycosis fungoides and Sezary syndromes (MF/SS) [87], but inversely associated with risk of CLL/SLL [49] and hairy cell leukemia [88]. Because greater smoking exposure was found to be associated with a higher frequency of t(14;18), a translocation that occurs commonly in follicular lymphoma, in healthy individuals [89], two studies specifically evaluated cigarette smoking and risk of t(14;18)-positive NHL but found no clear association [90, 91]. A recent study suggested that

while exposure to environmental tobacco smoke is not associated with NHL overall, it was associated with a higher risk of follicular lymphoma for both children and adults, and a lowered risk of DLBCL in adults [92].

### 3.4.2 Alcohol Use

Several epidemiologic studies have evaluated alcohol use and risk of NHL, but the findings are not entirely consistent. Alcohol use has been linked to an increased risk [93], a lower risk [94–98], or no effect on the risk of NHL [99]. Studies that assessed the association by type of alcoholic beverages or by subtype of NHL have also reported conflicting results. A large InterLymph NHL subtypes project [30] found an inverse association between ever drinkers and risk of many subtypes of NHL, including DLBCL [47], follicular lymphoma [48], marginal zone lymphoma [52], peripheral T-cell lymphomas [100], and sporadic Burkitt lymphoma [101], but most findings lack clear dose-response. The EPILYMPH study did not observe an association for NHL overall or across histologic subtypes, but found an inverse association in men [79].

### 3.4.3 Diet

The role of dietary intake and NHL risk has been reviewed elsewhere [102, 103]. Some studies found positive associations with intake of meat [104, 105], particularly red meat [104, 106, 107], whereas no association was reported by others [108–110]. Fish consumption has been associated with a lower risk of NHL [111, 112], although null results were also reported [105, 106, 108]. There are multiple pathways through which meat intake might impact NHL risk, including modulating the immune response through meat and its constituents (e.g., fat and protein), carcinogens, and mutagens [104, 113]. An excess risk of NHL has been associated with a higher intake of dietary fat, including total fat, animal fat, saturated fat, and trans fatty acids [104–107, 111, 112]. Evidence for total and animal protein intakes was less consistent. Findings on meat mutagens and NHL risk are also not entirely consistent [107, 109]. One recent study reported that phytanic acid, a saturated fatty acid obtained primarily through the consumption of ruminant meat and dairy products, is positively associated with risk of NHL, especially follicular lymphoma and CLL/SLL [114].

Dietary intake of fruit and vegetables has received great attention in the prevention of NHL because antioxidants and other constituents in these foods are thought to influence immune function and to inhibit oxidative processes involved in carcinogenesis and cell proliferation [103, 115]. Epidemiologic studies have reported inverse associations between the risk of NHL and a higher intake of all vegetables combined [116, 117], green leafy vegetables [108, 116], or cruciferous vegetables [116], but others have found no associations [104, 105, 118, 119] or even a suggestive positive association with green leafy vegetables [118]. A recent study found that higher circulating carotenoids prior to diagnosis are associated with reduced risk of NHL [120].

Dietary patterns and NHL risk were evaluated in one cohort [121] and one case–control study [122]. The Multiethnic cohort reported that the vegetable pattern was inversely related to risk in Caucasian women, whereas the fat and meat pattern was associated with a fivefold higher risk of follicular lymphoma in men [121]. A population-based case–control study found that a dietary pattern high in meats, fats, and sweets is associated with an increased risk of overall NHL, follicular lymphoma, DLBCL, and marginal zone lymphoma [122].

### 3.4.4 Anthropometric Measures

Obesity is associated with chronic, low-grade inflammation, and specific immune modulations including changes in cytokine profiles that may predispose to NHL [123]. Several studies have found a significant positive association between obesity and NHL risk [96, 124, 125], whereas others reported null associations with body mass index [126–128] or central obesity [129–131]. Excess risk of DLBCL was linked to obesity [126, 132, 133] and severe obesity [131]. The InterLymph NHL Subtypes Project reported a positive association between higher young adult body mass index and risk of diffuse large lymphoma [47] and follicular lymphoma [48]. Usual adult height was linked to risk of CLL/SLL [49] and sporadic Burkitt lymphoma [101].

### 3.4.5 Hair Dyes

Hair coloring products contain compounds that are mutagenic and carcinogenic in animals [134]. Several studies reported excess NHL risk associated with the use of hair dyes, particularly long-term use of dark permanent dyes [135–137]. A pooled analysis from InterLymph found excess risk of follicular lymphoma and CLL/SLL, but not other subtypes, in women who started use before 1980 [137]. These findings were supported by recent reports from the InterLymph with more than four times as many cases and controls [48, 49].

### 3.4.6 Ultraviolet (UV) Radiation

Exposure to sunlight and other sources of UV radiation, with possible immunosuppressive effects, has been suggested as a risk factor for NHL [138]. Recent studies estimated personal sun exposure with questionnaires instead of using latitude as a proxy reported an inverse association in general [139–142], particularly with regard to recreational sun exposure [139]. Pooled analyses from InterLymph found that the inverse association with recreational sun exposure was more evident for follicular lymphoma [48, 143] and DLBCL [47, 143]. This inverse association has been suggested to be due partly to effects on the immune function from sun exposure [144] or vitamin D production [145]. While low serum concentration of the vitamin D metabolite, 25-hydroxyvitamin D, has been found as an independent poor prognostic factor in patients with NHL [146], particularly CLL [147], DLBCL, and T-cell lymphoma [148], circulating 25-hydroxyvitamin D was not associated with risk of NHL in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [149] and a pooled analysis of 10 cohorts in the cohort consortium [150].

## 3.5 Occupational Exposures

A number of occupations have been associated with increased risk for the development of NHL, including farmers, pesticide applicators, benzene workers, rubber workers, petroleum refinery workers, dry cleaners, firefighters, and chemists [6, 18, 151–153]. The InterLymph Subtypes Project reported excess risk of DLBCL in persons who worked as field crop/vegetables farmer, seamstress/embroiderer, and driver/material handling equipment operator [47], follicular lymphoma and employment as a spray painter [48], marginal zone lymphoma and metalworker occupation [52], CLL/SLL in persons worked as hairdresser [49], LPL/WM and occupation as medical doctor [54], sporadic Burkitt lymphoma and employment as a cleaner [101], adult acute lymphocytic leukemia in leather and sewing/embroidery workers [154], mycosis fungoides and Sezary syndrome in crop/vegetables farmers, painters, wood workers, and general carpenters [87], and PTCL in persons worked as textile worker and electrical fitter [100]. Common exposures in these occupations include benzene, pesticides, herbicides, and other organic solvents [6, 18, 155]. However, mechanisms linking these exposures to specific NHL subtypes remain to be determined.

Epidemiologic studies suggest that an excess risk of NHL among farmers is related to the use of phenoxyacetic acid herbicides, organophosphate insecticides, and fertilizers [151]. Pesticides have also been associated specifically with follicular NHL and small lymphocytic NHL [156–158]. Two studies evaluating the pesticide-NHL association according to the t(14;18) status of the NHL found that t(14;18)-positive NHL was associated with farming and pesticides, whereas there were no such associations with t(14;18)-negative NHL [159, 160]. Solvents have been associated with an increased risk of NHL, especially in occupational studies of rubber workers, aircraft maintenance workers, and dry cleaners [161]. A large EPILYMPH study found excess risk for follicular lymphoma and CLL [162]. A recent case–control study in Connecticut reported that polymorphism in IL10 (rs1800890) modified the association between occupational exposure to organic solvents and the risk of DLBCL [163].

## 3.6 Host Factors

### 3.6.1 Familial Aggregation

A history of NHL or other hematolymphoid cancer in close relatives has repeatedly been shown to increase the risk of NHL by 2- to 3-fold [164–166], a stronger association than is estimated for most of the other suspected risk factors. A pooled analysis from InterLymph reported that NHL risk was elevated for individuals who reposted a first-degree relative with NHL, especially among those who reported a brother with NHL [167]. A recent InterLymph pooled analysis with an additional cases and controls confirmed these earlier findings and further linked family history of NHL to risk of DLBCL [47], follicular lymphoma [48], and marginal zone

lymphoma [52]. Familial aggregation has been associated with an inherited defect of immune function in some instances, but no such abnormality can be discerned in most families [31]. Lymphomas may also cluster within families, not because of an inherited susceptibility, but because of shared environmental determinants [95, 164, 168].

### 3.6.2 Genetics

Numerous studies implicate the role of genetic variants that promote B-cell survival and growth with increased risk of NHL [169]. For example, NHL risk has been linked to genetic variation in various pathways, including one-carbon metabolism, cytokine, innate immunity, oxidative stress, and apoptotic and DNA repair pathways as well as in the HLA region [169, 170]. Two recent genome-wide association studies (GWAS) identified associations between FL risk and three variants within the HLA region, one at 6p21.33 (rs6457327) [171] and three at 6p21.32 (rs10484561, rs7755224, and rs2647012) [172]. Another study found that rs10484561 was also associated with risk of DLBCL [172], suggesting some shared biological mechanisms of susceptibility between these two common NHL subtypes. Another study reported that the TAP2 coding SNP rs2411447 at 6p21.4 was strongly associated with follicular lymphoma and, to a lesser extent, DLBCL [173]. Findings from the Population Architecture using Genomics and Epidemiology (PAGE) consortium further support a shared genetic susceptibility between follicular lymphoma and DLBCL, particularly involving variants in the major histocompatibility complex region [174]. The 6p21.3 also emerged as a potential susceptibility locus associated with familial CLL [175]. A GWAS of CLL further identified 4 highly correlated intronic variants within the IRF8 gene that were associated with CLL [176]. This association is specific to CLL, with little evidence for association across the other common NHL subtypes.

A large pooled InterLymph study reported that common polymorphisms of TNF and IL10, which are both key cytokines for inflammatory response and T-helper balance, were associated with risk of NHL, particularly for diffuse large B-cell lymphoma, but not for follicular lymphoma [177]. Studies evaluating the associations of SNPs in folate-metabolizing genes with NHL risk have reported inconsistent findings [178–180].

## 4 Conclusions

After two decades of steep increase in the incidence of NHL in the USA, the overall NHL incidence rates appear to have stabilized in the early 1990s due primarily to a decline in the AIDS incidence. NHL rates among HIV-unaffected individuals, however, continued to increase throughout the 1990–2009. The temporal trends varied by histologic subtypes. The incidence of NHL and the distribution of histologic subtypes not only show significant geographic differences and distinct time trends but also vary by age, sex, and race/ethnicity. These incidence patterns and

time trend, although poorly understood, strongly suggest that infectious, environmental, and lifestyle factors in addition to host factors are important in the etiology of NHL as well as certain NHL subtypes.

Intensive research efforts, including international consortia, in the past two decades, have led to a better understanding of the causes of NHL in that there is some mechanistic commonality of lymphomagenesis, but it has also become apparent that significant etiologic heterogeneity exists [8, 29, 181]. It is more likely that a compilation of immune function, genetic host susceptibility, and environmental and lifestyle factors will identify the most robust profiles for lymphoma risk [182]. Continued epidemiologic research to rigorously evaluate the interplay between these factors in NHL etiology is warranted and critically needed.

Cytogenetics, fluorescence in situ hybridization (FISH), immunophenotyping, and gene-rearrangement studies are increasingly being used to diagnose and characterize NHL [183]. New techniques, such as FISH and gene expression profiles, have made the identification of genetic abnormalities possible in routine paraffin-embedded tissue [184]. Because many WHO-defined NHL subtypes remain heterogeneous at the molecular level, future epidemiologic studies should collect not only peripheral blood but also tissues and incorporate these new technologies to investigate specific etiologic factors that are associated with well-defined homogeneous molecular subtypes of NHL.

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