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Contents

Epidemiology and Etiology of Non-Hodgkin Lymphoma

Brian C.-H. Chiu and Ningqi Hou

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

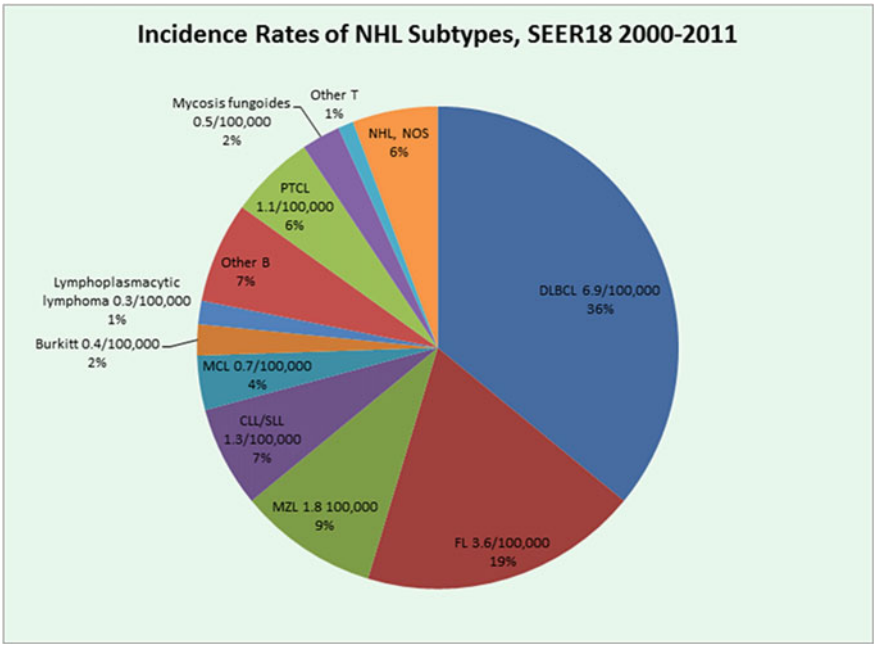

Fig. 1 Incidence Rates of NHL subtypes in the USA, 2000–2011, Surveillance, Epidemiology, and End-Results Program (Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat), Version 8.1.5. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)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

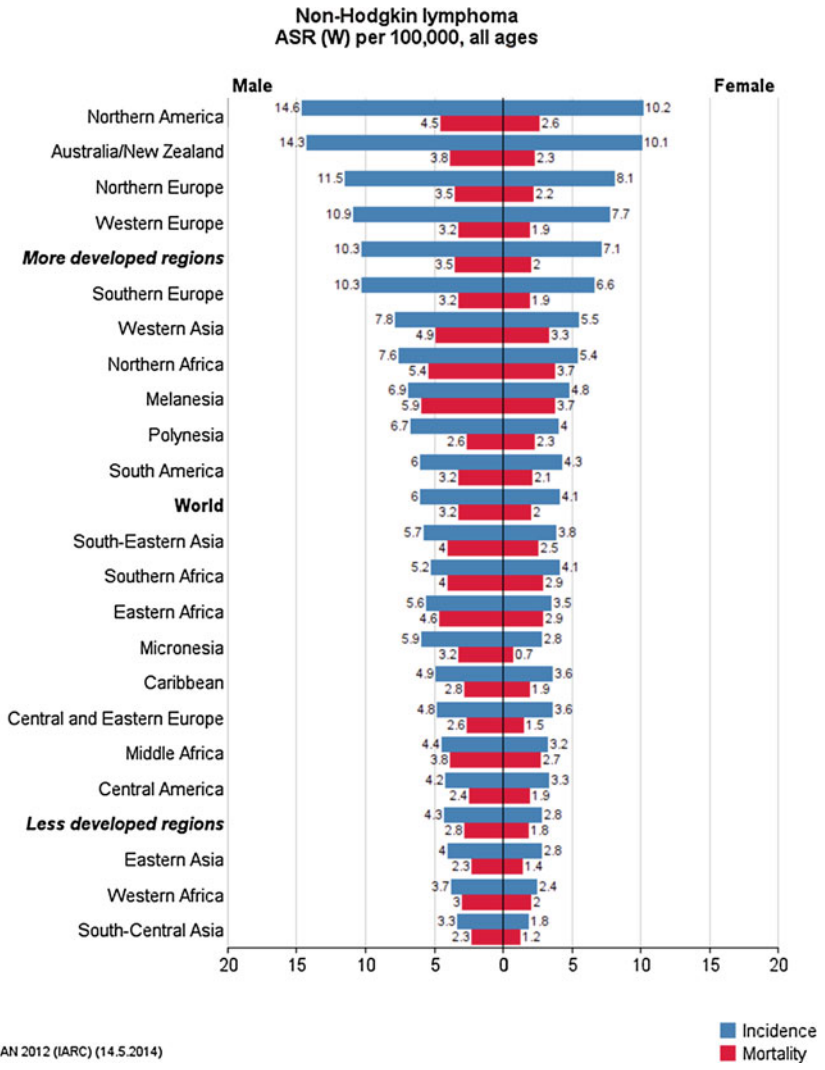

Fig. 2 Incidence and mortality of NHL in different parts of the world (Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International 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

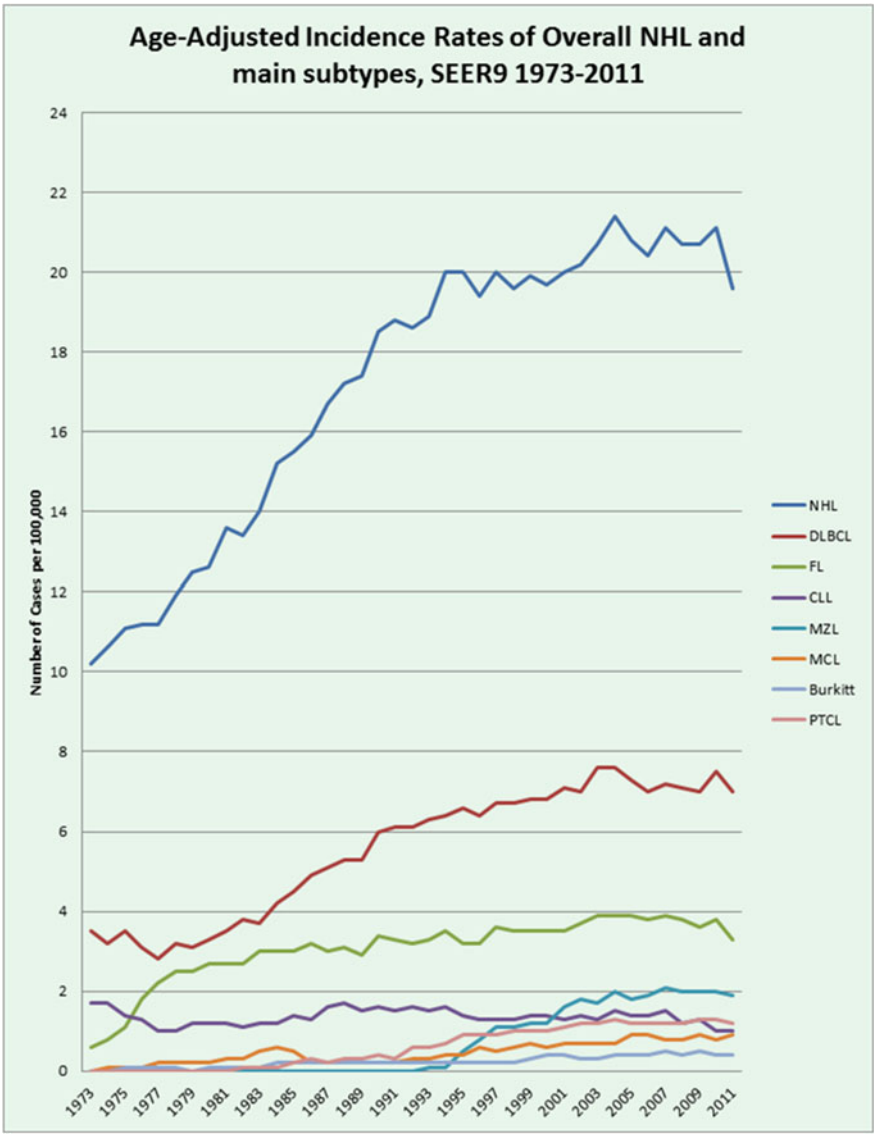

Fig. 3 Incidence rates of overall NHL and main histologic subtypes in the USA, 1973-2011, Surveillance, Epidemiology and End-Results Program (Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat), Version 8.1.5. Surveillance, Epidemiology, and End-Results (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).