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REVIEW ARTICLE

Epidemiology and etiology of non-Hodgkin lymphoma – a review

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Abstract
The etiology of non-Hodgkin lymphoma, as well as its global dramatic rise in incidence during the past decades, remains largely unexplained. However, there is increasing awareness that this group of malignancies may entail not only clinical, morphological and molecular heterogeneity, but also considerable variations in terms of etiologic factors. In this review, epidemiologic patterns are summarized as well as current evidence of associations between various known or suspected risk factors for non-Hodgkin lymphoma overall or for any of its subtypes. Central pathogenetic mechanisms include immunosuppression, especially in relation to T-cell function and loss of control of latent EBV infection, and chronic antigen stimulation. Some degree of familiar aggregation also implies a role for genetic susceptibility. A number of recent investigations of non-Hodgkin lymphoma etiology will hopefully lead to a better understanding of the causes of these malignancies.

The malignant lymphomas entail considerable heterogeneity with regard to morphological and molecular characteristics as well as clinical course [1]. The non-Hodgkin lymphomas (NHL) make up around 90%, and Hodgkin lymphoma (HL) account for the remaining 10% percent of all malignant lymphomas. NHL arises, with few exceptions, from two distinct lymphocyte types, B or T cells, and the heterogeneity is at least in part related to the many stages of normal differentiation and maturation of these cells [1]. A dramatic rise in incidence of NHL worldwide during the past decades, surpassed only by lung cancer in women and malignant melanoma in both sexes [2], has sparked intense research efforts to reveal the causes of this group of malignancies as well as to explain the past increase. Although some strong risk factors have been identified (including primary immunodeficiency disorders, HIV-infection and organ transplantation), the causal factors behind most newly diagnosed NHL patients remain unknown. However, it has become clear that also etiologic variation among NHL subtypes may be considerable [2]. The aim of this review is to describe the epidemiology of NHL, to summarize current evidence of associations with an array of known and possible etiologic factors, and to outline established and potential biological mechanisms of lymphomagenesis. In addition, there is a brief description of a recent large Scandinavian initiative to investigate risk factors of malignant lymphomas.

Descriptive epidemiology

Classification

NHL is presently classified according to the universally accepted World Health Organization (WHO) classification where 36 subtypes (21 of B-cell and 15 of T-cell type) are recognised, excluding entities of uncertain malignant potential [1]. Chronic lymphocytic leukemia (CLL) now belongs to the NHL group, together with its non-leukemic counterpart small lymphocytic lymphoma [1]. Plasma cell malignancies are now also recognised as NHL subtypes according to WHO. This review focuses on NHL excluding CLL and plasma cell malignancies.

The variation in clinical presentation and course, treatment approaches and prognosis among NHL subtypes is considerable, to say the least. In spite of major advances in the understanding of lymphoma biology reflected in the WHO classification, a clinical subdivision into indolent, aggressive and very aggressive lymphoma types is still meaningful. Other

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aspects considered in the clinical setting are location and disease spread. The International Prognostic Index, published in 1993 [3] (based on age, performance status, serum lactate dehydrogenase, number of involved extranodal sites, Ann Arbor stage) separates patients into clinically distinct groups with varying prognoses. Newer technologies, such as cDNA microarrays, have further distinguished patients into distinct prognostic groups even within histologic subtypes. For example, there appears to be at least two subcategories of diffuse large B-cell lymphoma, a germinal center B-cell type and a less favorable activated B-cell type based on differences in gene expression profiling [4]. Thus, the lymphoma classification schemes currently in use will almost certainly be subject to further refinement in the future.

Incidence

NHL (excluding CLL and plasma cell malignancies) is more common in the developed world, with the highest incidence rates in the USA, Australia and New Zealand, and Europe, and the lowest in Eastern and South Central Asia [5]. Around the year 2000, the age standardized (world standard) incidence of NHL was estimated at approximately 14 per 100 000 person-years in the USA and Canada, 10 per 100 000 in Denmark and Sweden, and 3 per 100 000 in South Central Asia [5]. However, the rare T-cell neoplasms are more common in Asia than in other regions. Worldwide, NHL constitutes the tenth most commonly diagnosed malignancy, whereas in the developed world it ranks seven. In Sweden in 2003, malignant lymphomas (NHL and HL) were the eighth most common new cancer diagnoses among males and the tenth most common in females [6]. In the USA, NHL has climbed to the fifth most frequently diagnosed malignancy in recent years [7]. The most common NHL subtypes by far in developed countries (disregarding CLL and plasma cell entities) are diffuse large B-cell lymphoma (about 30%) and follicular lymphoma (about 20%). All other NHL subtypes have a frequency of less than 10% [1]. Many subtypes are characterised by a slight preponderance of males, most striking in mantle cell lymphoma (70% males), whereas females predominate in follicular lymphoma [1].

Time trends

For several decades, there has been a dramatic increase in NHL incidence worldwide, of about 2–4% annually [8]. The highest increase was observed in Denmark, where the rate doubled between 1970 and 1985 [9]. In Scandinavia in general the increase in incidence was apparent already in the 1950s [10], and in Connecticut, USA, even in the 1930s [11]. Interestingly, this increase is not limited to developed countries, but has been observed also in for example India, Japan, Brazil, Singapore and Puerto Rico [12]. In the beginning of the 1990s, the rise in incidence began to level off in Sweden (Figure 1) [6], and Denmark [13]. In the USA, data from the Surveillance, Epidemiology, and End Results (SEER) Program showed stabilization in overall NHL incidence rates in the early 1990s and then subsequent decline. However, in population groups at low risk of human immunodeficiency virus (HIV)-infection and acquired immunodeficiency syndrome (AIDS), such as men above the age of 55 years and women of all ages, rate increases were still evident through the 1990s [14].

Less is known about time trends for NHL subtypes. Available information comes from studies using USA SEER data [15]. Thus, between 1974 and 1992, a rapid increase was noted for diffuse large cell lymphoma, partly fuelled by the AIDS epidemic. More modest risk increases were observed for precursor lymphoblastic leukemia/lymphoma, Burkitt's or Burkitt-like lymphoma and follicular lymphoma, whereas no change was noted for CLL/small lymphocytic lymphoma or lymphoplasmacytic lymphoma. For several subtypes such as the mantle cell and marginal zone lymphomas, time trends are difficult to assess due to the recent recognition of these entities as distinct subtypes. Concerning the group of T-cell lymphomas, SEER data have shown an increase of mycosis fungoides, but otherwise epidemiological data are scarce [15]. Primary extranodal lymphoma, particularly located in the central nervous system, has increased more rapidly than nodal forms since the 1970s [12]. However, a decline in rates of central nervous system lymphomas has been noted since the mid-1990s in the USA,

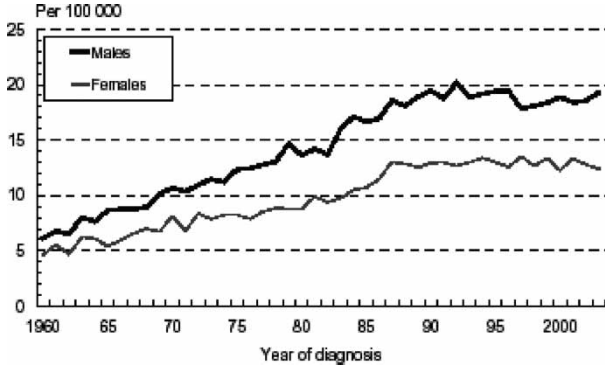

Figure 1. Non-Hodgkin lymphoma (NHL) incidence in Sweden 1960 to 2003 in males and females, age-standardized to the Swedish population in the year 2000 (ICD: 200).

in parallel with the decreasing incidence of AIDS [2].

In 1992, an assembly was organized by the USA National Cancer Institute to evaluate the time trends of NHL. At this meeting, it was concluded that the increasing temporal trend was indeed real [16], and that known and suspected risk factors could not explain the observed increase over time [17]. Thus, after accounting for the likely effects of misclassification of diagnoses, the inclusion of new entities of NHL, and for established risk factors (see below), it was estimated that close to 50% of the observed increase in both sexes remained unexplained [17]. In view of the absence of major breakthroughs concerning the etiology of NHL since then (with the exception of the role of a few infectious agents in specific lymphoma forms, most notably *Helicobacter pylori* in gastric lymphomas, however representing few cases in the population), the conclusions from the 1992 meeting appear still valid.

Etiology of non-Hodgkin lymphoma

Pathogenesis

B and T lymphocytes are important members of the immune system that above all serve to protect against infectious agents [18]. In general, B cells produce antibodies with antigen-binding capacity, whereas T cells recognize antigen presented by other cells. A variety of different secreted proteins, or cytokines, released by activated T cells (especially of the T helper cell, or CD4+, type) serve to alert and coordinate the local immune response. In light of the importance of the T cells in controlling B-cell as well as overall immune function, it is perhaps not surprising that the strongest and most well-established risk factors for malignant lymphomas are characterized by dysregulation or suppression of T-cell function (HIV/AIDS, organ transplantation, see below) that allow for Epstein-Barr virus (EBV)-driven B-cell proliferation and transformation.

As in cancer development in general, neoplastic transformation of T or B cells represents a multistep process with progressive accumulation of genetic lesions that result in clonal expansion and establishment of a solid or leukemic tumor. Mechanisms may involve dysregulation of cell growth, cell signaling pathways and programmed cell death (apoptosis). The intricate rearrangements in B-cell immunoglobulin or T-cell receptor genes during the normal differentiation and adaptation of these cells represent genetically vulnerable stages. During these processes, physiologically occurring DNA double-strand breaks pave the way for aberrant chromosomal translocations, which are typical of NHL tumors. In fact, chromosomal translocations have been observed in up to 90% of NHL cases [19,20]. These translocations, with or without additional genetic lesions, can precipitate the activation of oncogenes or inactivation of tumor suppressor genes [1]. Oncogenic viruses provide other possible mechanisms for genetic lesions, as well as direct carcinogenesis by environmental factors. Although the importance of genetic factors in lymphoma development is evident, the geographically uniform rise in NHL incidence implicates a crucial role of one or several environmental agents in the etiology of NHL.

Immunosuppression

Either primary or genetic disorders of immune dysfunction and acquired states of severe immunosuppression (HIV/AIDS and organ transplantation) constitute strong and well-established risk factors for NHL, but explain few new cases in the general population. Clinical features shared by the majority of immunodeficiency-related lymphomas are diffuse large B-cell histology, extra-nodal location especially in the gastrointestinal tract and central nervous system, aggressive clinical course, and an association with EBV. It has been suggested that minor degrees of immunodeficiency also may mediate the development of lymphoma. However, judging from lymphomas occurring in HIV/AIDS and after organ transplantation, it would be predicted that EBV-driven lymphoma most often would be the result. As most lymphomas occurring in the population are not EBV-positive, the HIV/AIDS and post-transplantation settings may not offer ideal causal models for the study of lymphoma etiology in the general population [21].

Primary disorders of immune dysfunction

Inherited disorders most commonly associated with an excess risk of NHL include ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, severe combined immunodeficiency, X-linked lymphoproliferative disorder, Nijmegen breakage syndrome, hyper-IgM syndrome and autoimmune lymphoproliferative syndrome [1]. It has been estimated that up to 25% of patients with these disorders will develop tumors, primarily B-cell lymphoma, during their lifetime and often already in childhood [22]. The mechanisms of lymphomagenesis are related to the underlying disorder and involve loss of T-cell control (Wiskott-Aldrich syndrome), apoptosis defects (autoimmune lymphoproliferative syndrome), abnormal DNA repair function (ataxia-telangiectasia, Nijmegen breakage

syndrome), defective T-cell/B-cell interactions (hyper-IgM-syndrome), and perhaps chronic antigen stimulation (common variable immune deficiency) [1]. Defective immune surveillance of EBV infection is an important co-factor in lymphoma development in these cases.

HIV/AIDS

Overall NHL risk has been estimated to be increased about 60- to 200-fold in HIV positive individuals relative to the general population, with low-range risk increases for indolent NHL types and higher excess risk for diffuse large cell NHL, in particular of the immunoblastic type [23]. A decline in the incidence of AIDS-related lymphomas has been noted since the introduction of highly active antiretroviral therapy (HAART) [24], nevertheless, NHL still accounts for more than 20% of AIDS-related deaths in developed countries [23]. The classic model of HIV-associated lymphomagenesis proposes chronic antigenic stimulation of B lymphocytes and macrophages induced mainly by EBV, but also human herpes virus 8 (HHV-8), in the presence of disturbed T-cell function and low CD4 cell counts. However, nearly 50% of AIDS-related lymphomas are negative for EBV or HHV8. Therefore, other factors must also influence HIV-related lymphomagenesis such as genetic abnormalities, cytokine dysregulation and dendritic cell impairment induced by HIV itself [23]. Although HIV is not characterized by typical oncogenic potential by insertional mutagenesis, occasional non-random integration of the viral genome could possibly contribute to oncogenic transformation in a subset of patients [25].

Organ transplantation

A greatly increased relative risk of NHL in conjunction with potent immunosuppressive therapy following renal, liver, heart or bone marrow transplantation has been reported consistently [8]. The relative risk of malignant lymphomas increases by about 10- to 20-fold in renal allograft recipients and up to about 200-fold in heart transplant recipients, compared to the general population [26]. Post-transplant lymphoproliferative disorders comprise a spectrum ranging from early EBV-driven polyclonal proliferations to EBV-positive (80–90%) or EBV-negative malignant lymphomas, predominantly of B-cell origin [27]. EBV-negative cases typically occur later than EBV-positive tumors: the majority of cases occurring more than five years after transplantation are EBV-negative. The pathogenesis of post-transplant lymphoproliferative disorders is most likely complex and multifactorial although drug-induced impaired T-cell immune surveillance in combination with chronic antigenic stimulation exerted by the graft is believed to have a central role [27]. Modulating factors include donor and recipient EBV serologic status, type of transplanted organ, underlying disease and type, duration and intensity of the immunosuppressive treatment [27].

Other genetic factors

Familial aggregation of hematopoietic malignancies has been consistently reported, thus implicating a role of genetic susceptibility in lymphoma development. The risk of NHL is increased about 2- to 3-fold in first-degree relatives of patients with lymphoma or hematopoietic cancer [28–32]. Higher excess risks of about 7-fold or more have been reported for CLL in first-degree relatives of CLL patients [33]. It cannot be excluded, however, that familial clustering is attributable to shared environmental exposures rather than genetic predisposition. A few studies have described a tendency towards differential lymphoma risks by type of first-degree relation [29,31,32], i.e., higher risk in siblings compared to parents and offspring of index persons with lymphoma or hematopoetic cancer. This may indicate that both shared genetic and environmental factors contribute to the observed overall association.

In recent years, several studies of common genetic variation that could confer susceptibility to malignant lymphomas in the general population have been published. Examples of specific genes investigated include those encoding for tumor necrosis factor alpha [34] and other cytokines [35], the p53 protein [36], DNA repair proteins [37], biotransformation enzymes [38], intermediates of the folate metabolism pathway [39], human leukocyte antigens (HLA) [40], and transcriptional factors (Bcl6 [41]). However, no strong susceptibility loci have yet been confirmed.

Infectious agents

Infectious agents consistently associated with malignant lymphomas include the herpesviruses EBV and HHV-8, and the retrovirus human T-cell lymphotrophic virus 1 (HTLV-1). More recent evidence also suggests a role for the hepatitis C virus (HCV), a single-strand RNA virus, whereas the role of simian virus 40 (SV40) of the polyoma virus family remains uncertain. Associated bacteria include *Helicobacter pylori* (*H. pylori*) and perhaps also *Borrelia burgdorferi*.

EBV

Widespread in all human populations, EBV persists in the vast majority of individuals as a lifelong asymptomatic infection of the B-lymphocyte pool. Primary infection with EBV usually occurs in childhood, but if it is delayed until adolescence it presents as infectious mononucleosis in about half of those infected [42]. In healthy individuals, equilibrium exists between latent EBV infection and the host's immune system, where continued T-cell surveillance is of special importance. However, with severe immunodeficiency, control mechanisms are impaired which may lead to EBV-driven B-cell proliferation and development of B-cell lymphoma [43]. Importantly, EBV-encoded latent genes are capable of transforming B lymphocytes *in vitro* by altering cellular gene transcription and key cell signaling processes [44]. Apart from a strong association with lymphomas in immuno-compromised hosts, early EBV infection is also associated with Burkitt lymphoma in Africa but infrequently in other parts of the world, and with a few rare but specific types of T- and NK-cell lymphomas (predominantly occurring in Asia). Occasionally, EBV DNA has been found in B-cell tumors other than Burkitt lymphoma in immunocompetent hosts, but only to a small extent (less than 5%), and without evidence of linkage to a specific B-cell NHL type [45].

HHV-8

Also called Kaposi sarcoma herpes virus (KSHV), HHV-8 is detected in the majority of primary effusion or body cavity lymphomas. This rare lymphoma type occurs almost exclusively in HIV-infected individuals, but can develop occasionally in the absence of immunodeficiency in areas of high HHV-8 seroprevalence, such as the Mediterranean. Because patients with primary effusion lymphoma are often coinfected with EBV, the delineation of the etiologic role of each virus is difficult [45]. However, observations of tumors being monoclonal expansions of a single infected cell support an etiologic role of HHV-8 [46].

HTLV-1

This human retrovirus is causally associated with adult T-cell leukemia/lymphoma in the Caribbean and Japan, where infection is endemic. The virus causes a latent persistent infection in circulating T lymphocytes. Adult T-cell leukemia/lymphoma develops in 2 to 5% of HTLV-1 infected individuals after a long latent period, suggesting a multistage process of T-cell transformation and involvement of additional pathogenetic factors [47]. HTLV-1 infection is rare in Europe and the USA, but some studies from the USA have indicated a possible association between HTLV-1 and mycosis fungoides or Sézary syndrome [1].

HCV

Investigators have reported 2- to 14-fold increased relative risk of B-cell NHL in association with hepatitis C infection, but results are inconsistent [48,49]. Positive associations are mostly reported from geographical areas with high HCV seroprevalence, such as southern and eastern Europe, Japan and southern USA, whereas no associations have generally been noted in studies from central and northern Europe, northern USA or Canada [49]. Thus, it has been estimated that the proportion of B-cell lymphoma cases potentially attributable to HCV infection in countries with a high seroprevalence is about 5 to 10%, but much lower if at all existent in other countries [49,50]. HCV is both lympho- and hepatotrophic and replicates in mononuclear blood cells. A specific HCV protein (E2) may be responsible for chronic antigen-driven polyclonal B-cell proliferation which may lead to lymphoma development in the presence of unidentified genetic or environmental cofactors [51]. Interestingly, case reports suggest that low-grade B-cell lymphomas associated with HCV infection may regress after successful antiviral and interferon therapy [52]. Mixed cryoglobulinemia, a vasculitic immune complex disorder, develops in a minority of HCV infected individuals and is frequently associated with benign lymphoproliferations in the liver and bone marrow. Overt malignant lymphoma occurs in about 10% of these cases [53].

SV40

The monkey polyoma virus SV40 is known to induce a variety of cancer types in laboratory animals, including lymphomas, by inactivation of the tumor suppressor genes *p53* and *pRB* [54]. This virus accidently contaminated the Salk polio vaccine administered during the years 1955 to 1962 [55]. However, the infection also exists among recipients of non-contaminated vaccines [56]. In a few studies in humans, SV40-specific DNA sequences have been detected in a higher proportion in NHL tumor tissue than in control samples of normal lymphoid tissue or other tumors [57–59], but several other studies have failed to confirm viral presence in lymphoma lesions [60–64]. Furthermore, serum levels of SV40 antibodies have not been associated with lymphoma risk [55,65]. Also, comparisons of lymphoma risk in recipients of contaminated versus

uncontaminated polio vaccine support no association [66,67]. In conclusion, available evidence for a role of SV40 in NHL etiology is weak.

Helicobacter pylori

This gastric pathogen causes chronic gastritis, and its association with primary gastric lymphoma of the low-grade MALT-type is well established. In one of the first and most important studies, *H. pylori* infection in gastric tissue was detected in over 90% of cases with gastric MALT lymphoma [68]. The relative risk of gastric MALT lymphoma has been estimated to be increased about six-fold in association with serologic evidence of *H. pylori* infection [69]. *In vitro* studies have shown that B-cell proliferation in response to *H. pylori* is mediated by tumor-infiltrating T cells [70]. Clinical trials further support a causal link, as about 75% of gastric MALT lymphomas regress upon eradication of *H. pylori* with antibiotic treatment [71].

Other pathogens

Infection with *Borrelia burgdorferi* has been associated with the development of primary cutaneous B-cell lymphoma in studies from European countries [72]. However, no association has been observed in North America [73]. The discrepancy may be due to genetic and phenotypic differences between *Borrelia burgdorferi* strains in Europe and the USA [73]. A bacterial etiology is also suspected for the uncommon immunoproliferative small intestinal disease (also known as alpha chain disease) arising from small intestinal mucosa-associated lymphoid tissue (MALT). Early-stage lesions may respond to antibiotic treatment, and isolation of *Campylobacter jejunei* from tumor tissue was recently reported in a small case series [74]. *Chlamydia psittaci* has been linked to ocular adnexal lymphomas [75]. In addition, a number of chronic infectious disorders including tuberculosis, malaria, pyelonephritis and herpes zoster have been associated with increased risk of NHL overall in epidemiological studies [76–79]. Hence, the number of specific infectious agents found to be associated with lymphoproliferative malignancies is clearly growing, consistent with the idea of chronic immune stimulation as a potential risk factor for lymphomagenesis.

Autoimmune and chronic inflammatory disorders

Excess risks of malignant lymphomas have been consistently reported in rheumatoid arthritis (RA), Sjögren's syndrome, systemic lupus erythematosus (SLE), celiac disease, dermatitis herpetiformis, polyand dermatomyositis, and chronic thyroiditis [80]. Other autoimmune and chronic inflammatory disorders, such as psoriasis [81,82] and inflammatory bowel disorders [83–85], have occasionally, but not invariably, been associated with increased lymphoma risks. Spurious positive associations could arise in this context due to misclassification, as lymphomas may mimic inflammatory disorders and be accompanied by autoimmune paraneoplastic phenomena [86].

Most well-documented is the association with NHL in patients with Sjögren's syndrome. Reported increases in relative risk range from 4.5- to 44-fold, with higher estimates for primary disease than when secondary to RA, SLE or myositis [80,87,88]. More severe disease characterized by parotid enlargement, hypocomplementemia and low CD4 cell counts has been associated with accentuated NHL risks [89,90], but no association has been reported with immunosuppressive treatment [80]. Case reports and case series have indicated a strong association with MALT lymphomas, especially in the parotid gland [91,92], but the risk of diffuse large B-cell lymphoma may also be increased [90,93]. Local pathogenesis in affected glandular tissue involves chronic inflammation and T-cell-dependent antigen stimulation. If these mechanisms are responsible also for development of non-organ specific lymphoma in Sjögren's syndrome is, however, not clear. A number of studies have also demonstrated increased risks of NHL in patients with RA [94–99]. On average, reported excess risks of NHL overall range between 1.5- and 4-fold increased [87,94–96]. The underlying reasons for the increased NHL risk in RA patients remain a matter of debate. Particular concern has been raised for treatment with immunosuppressants [80], and more recently also for the biological tumor necrosis factor-blocking agents [100]. In a few studies with information on markers of inflammatory activity as well as treatment [93,97,101], degree of inflammation was however suggested to be more important than treatment. EBV has been detected at low frequency in RA-related lymphomas [101,102] and is therefore not likely to be of major importance.

Skin cancer and ultraviolet radiation exposure

Numerous studies have described increased risks of HL, NHL and CLL following a diagnosis of skin cancer, including malignant melanoma, squamous cell carcinoma and basal cell carcinoma. Conversely, an increased risk of all three forms of skin cancer has been noted following a history of lymphoma [103–108]. These observations, along with parallel time

trends in incidence of skin cancer and NHL, gave rise to the former popular hypothesis that ultraviolet radiation exposure would increase risk, not only of skin cancer, but also NHL [11,109]. However, two recent studies in different parts of the world contrarily observed inverse associations between frequent UV radiation exposure and risk of NHL [110,111]. Thus, alternative explanatory mechanisms for the link between skin cancer and NHL needs to be considered, including common genetic susceptibility, post-treatment effects and/or detection bias [106–108]. The surprising finding that UV radiation exposure may be inversely associated with risk of NHL [110,111] first of all needs to be confirmed in additional studies. Possible mechanisms behind such an association include UV-induced systemic immune modulation [112] or photo-activation of vitamin D-production [113].

Allergy

Similar to the incidence of NHL, the incidence of allergic disorders has increased epidemically during the past decades. However, evidence suggests that several allergic conditions may be associated with a reduced risk of NHL. A decrease in risk has been observed repeatedly in case-control studies in individuals with allergic skin conditions or with a history of allergy to grass or pollen [114–118], but the majority of these studies have used self-reported history of allergy, and the distinction between non-allergic conditions and allergy has not always been clear. Also, recent cohort studies with prospectively collected data on allergy could not confirm a decreased lymphoma risk among these patients [119,120]. Allergic reactions have been suggested to be related to a reduced NHL risk through promotion of B-cell differentiation [121] and/or by skewing the T helper cell immune response towards increased T helper type 2 activity [122].

Occupational exposures

An increased risk of NHL has been suggested in a variety of occupational groups, such as farmers, pesticide applicators, grain millers, wood and forestry workers and workers in the petroleum, rubber, plastic, and synthetics industries [123]. Potentially hazardous exposures among these groups include pesticides (phenoxy acids, organophosphates, organochlorines and others), benzene and other organic solvents [123]. A positive association between pesticide exposures and NHL and CLL has been observed repeatedly, but not consistently [56,124–126]. However, pesticides include a large number of different substances, of which only some may be truly related to lymphoma risk [125]. Concern has been raised especially for the herbicide 2,4-dichlorophenoxyacetic acid [56]. However, in a review of the effects of this herbicide on cancer risk, Garabrant et al. concluded that epidemiological studies provide weak evidence that 2,4-dichlorophenoxyacetic acid is associated with NHL or HL, and that biologically plausible effect mechanisms are lacking [127]. Although the fraction of agricultural workers is small and decreasing in the developed world, domestic use of pesticides is widespread and increasing [2]. Therefore, even small risk increases could explain a significant number of NHL cases and thus, further investigations are indeed warranted [2]. According to another recent hypothesis, the leveling off of NHL incidence rates in several countries in recent years could be related to the banning of various organochlorine substances during the 1970s and 1980s in these countries [128].

Benzene is a well-known leukemogenic agent (primarily causing acute myeloid leukemia), but current evidence for a causal link with NHL or CLL is insufficient [129]. Other organic solvents, such as for example trichlorethylene, may be associated with increased risks of NHL [130,131], but study inferences are limited by low power or poor exposure assessment [130]. Another chemical compound of concern is dioxin, which is listed as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) [132]. However, this designation has been criticized partly for being based on observations of increased risks of cancer overall rather than one or a few specific cancer forms [133]. Some epidemiological studies have shown increased NHL risk in association with dioxin exposure, but available data are inconsistent [133].

Tobacco smoking

Study results on the possible role of tobacco smoking in NHL etiology are conflicting. Most reports have shown no excess risk of NHL overall in tobacco or cigarette smokers [134–137], but there are several exceptions [138–140]. Some studies have suggested a specific association with risk of the common follicular NHL subtype [139,141,142]. Tobacco smoking appears to induce the *bcl-2* oncogene translocation (14;18) in peripheral lymphocytes of healthy individuals [143]. This translocation is also present in the tumor tissue of 70–95% of follicular lymphomas [1]. However, one study that specifically evaluated tobacco use and risk of t(14;18)-positive NHL failed to show any clear association [144].

Alcohol and dietary factors

The role of alcohol in the development of NHL is uncertain. Previous studies of alcohol intake have shown no association, or increased or reduced risk of NHL overall [145,146]. Because dietary habits in western countries have changed dramatically over time, the potential influence of diet on NHL risk is of interest. Several investigations have suggested that higher consumption of meat, especially red meat, and dairy products may be associated with increased risk of NHL, and that increased intake of vegetables and fruits may reduce NHL risk [147–149]. Diet could influence NHL risk through changes in energy balance, through direct exposure to dietary carcinogens and anti-carcinogens or by modulating the immune system, although evidence for any biological mechanism is limited [149].

Blood transfusion

Interest in blood transfusions and NHL arose after findings of a positive association in a prospective cohort study in 1993 [150]. Blood transfusions may promote lymphomagenesis through transmission of oncogenic viruses, transfusion-associated immunosuppression and/or engraftment of lymphoma cells from a donor with subclinical lymphoma. Although several early studies identified an elevated risk of NHL associated with transfusion of blood products, subsequent and larger studies were unable to confirm this association [151–153]. Also, one large cohort study with adjustment for possible confounding by transfusion indication, reported no association with type of blood product, amount of blood transfused or latency period and risk of NHL or CLL [154]. Thus, although an association between NHL and blood transfusion is biologically plausible, epidemiologic evidence of an association is weak, at most.

Medication

The existing literature concerning use of different drugs and NHL risk is contradictory. Past studies have found a significantly elevated risk of lymphoma in association with use of antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics, corticosteroids, histamine$_2$-receptor antagonists, psychotropic drugs, anti-convulsants, estrogen replacement therapy, antidepressants or anti-anxiety drugs, amphetamines, and/or digitalis or digitoxin [114,115,155]. Conversely, perhaps just as many studies have detected no or even an inverse association between risk of NHL and these same medications [98,156–158]. As several diseases, including acquired immunosuppression, autoimmune disorders, allergies and infections also appear to be associated with NHL risk, it is difficult to determine whether apparent associations between medications and lymphoma risk are due to the effects of the medications themselves, or rather the underlying disorder. In a recent large Scandinavian case-control study, use of corticosteroids, histamine$_2$-receptor antagonists, NSAIDs or anti-convulsants were not associated with risk of NHL or its major subtypes [158]. However, lifetime use of antibiotics was positively associated with risk of NHL, but it is unclear whether the association was due to use of the antibiotic drugs *per se*, the infections they were intended to treat or, alternatively, to an underlying susceptibility to infections [158].

Anthropometric measures

The prevalence of obesity has expanded into a global epidemic over recent decades [159], in parallel with the rise in NHL incidence. Several studies have found a significant positive association between obesity and lymphoma incidence [115,160], but equally many studies have observed no association [161,162]. Recent results from the Scandinavian case-control study showed no association between usual adult body mass index and risk of NHL overall, but suggested an increased risk of diffuse large B-cell lymphoma among individuals with high body mass index [163]. However, in a prospective cohort study, no association was observed with risk of diffuse lymphomas (n = 137) [164]. Thus, based on available evidence, it appears unlikely that the escalation of overweight and obesity worldwide has contributed meaningfully to the increase in incidence of NHL.

Hair dyes

An excess risk of NHL has been proposed in association with use of hair dyes, especially in women and for dark dye colors, but results are not consistent [165,166]. In a recent population-based case-control study, an increased risk of NHL was noted only in relation to hair dye use before 1980 [167]. This observation may reflect long duration of use, but it may also relate to the removal of carcinogenic compounds in hair dyes after a warning from the USA Federal Drug Adminstration in 1979 [56].

Other environmental factors

Because pregnancy causes immunologic alterations, it has been suggested that reproductive factors could affect lymphoma incidence. However, no clear picture of any such relationship has emerged

[168,169]. Evidence is also inconclusive with regard to vaccination history [123]. Physical activity could be of importance in lymphomagenesis as exercise is accompanied by transient changes of lymphocyte function. However, neither positive nor negative associations between physical activity and NHL risk has been reported [2]. Exposure to ionizing radiation, either in individuals exposed to therapeutic, diagnostic or occupational radiation or in atomic bomb survivors, does not seem to increase risk of NHL, although it may increase risk of CLL [8,40]. Acute and chronic psychological stress have suppressive effects on immune function which may affect immune surveillance of developing tumors [170]. A relationship between stress and the development of breast cancer has been indicated [171], but if stressful life events affect the development of malignant lymphomas is not known.

Summary of non-Hodgkin lymphoma etiology

In spite of intense research efforts in recent years, the causes of many cases of NHL remain poorly understood. Established risk factors for NHL overall, or for one or several NHL subtypes, currently include hereditary immunodeficiency disorders, acquired states of strong immunosuppression (HIV/AIDS, organ transplantation), some infectious agents (EBV, HTLV-1, HHV-8, *H. pylori*), some autoimmune disorders (RA, Sjögren's syndrome, SLE, myositis, Hashimoto's thyroiditis, celiac disease/dermatitis herpetiformis) and a positive family history of hematolymphoproliferative malignancies. Although the list of probable and possible risk factors is clearly growing, evidence is still inconclusive for a number of potentially lymphomagenic exposures. Several recently conducted or ongoing studies of lymphoma etiology in different countries, as well as international efforts of pooling of results (http://epi.grants.cancer.gov/InterLymph), will hopefully arrive to straighten out some of these uncertainties. Perhaps the most important breakthrough in recent years was the finding that local *H. pylori* infection is involved in the development of gastric MALT lymphoma, a model that may serve to illustrate the importance of considering biologically plausible risk factors for separate lymphoma entities in current and future research.

A Scandinavian lymphoma etiology initiative

A large case-control study (the SCALE, Scandinavian Lymphoma Etiology, study) was undertaken in Denmark and Sweden between 1999 and 2002 in order to investigate risk factors for malignant lymphomas (previously described in [111]). In brief, individuals aged 18 to 74 years with a first, newly diagnosed malignant lymphoma (NHL, including CLL, or HL according to the WHO classification [1]) were eligible as case patients, and identified through a network of contact physicians in all hospital clinics where malignant lymphomas are diagnosed and treated (in total 157 departments in both countries). Control subjects were randomly sampled from the entire Danish and Swedish populations (18–74 years) using updated population registers, and were frequency-matched within each country on the expected distribution of NHL cases by sex and age (in 10-year intervals). Review of tumor material took place within the national Lymphoma Registry Organization (LYFO, [172]) in Denmark, and was performed by one of six especially appointed senior hematopathologists or cytologists in Sweden.

Information on potential risk factors for lymphoma was collected through a telephone interview based on a standardized questionnaire, and addressed a number of areas such as medical history,

Table I. Number of participants in the SCALE (Scandinavian Lymphoma Etiology) study according to malignant lymphoma status and the WHO classification.

Lymphoma subtype	No. of participants
Precursor B-cell lymphoblastic leukemia/lymphoma	3
Mature B-cell neoplasms	
Diffuse large B-cell lymphoma	796
Chronic lymphocytic leukemia/Small lymphocytic lymphoma	752
Follicular lymphoma	586
Mantle cell lymphoma	148
Marginal zone lymphoma	117
Lymphoplasmacytic lymphoma	116
Hairy cell leukemia	63
Burkitt lymphoma/leukemia	31
B-cell prolymphocytic leukemia	5
Unspecified B-cell lymphoma	195
Precursor T-cell lymphoblastic leukemia/lymphoma	12
Mature T- and NK-cell neoplasms	
Anaplastic large cell lymphoma	58
Peripheral T-cell lymphoma, unspecified	41
Mycosis fungoides/Sezary syndrome	41
Other specified T-cell lymphoma types	33
Unspecified T-cell lymphoma	19
Unspecified non-Hodgkin lymphoma	39
Hodgkin lymphoma	
Nodular sclerosis	414
Mixed cellularity	102
Lymphocyte rich classical	36
Lymphocyte depleted	3
Nodular lymphocyte predominant	7
Unspecified Hodgkin lymphoma	56
Unspecified lymphoma	67
Lymphoma-free control subjects	3187

medication and life-style habits. Altogether, close to 7 000 individuals (malignant lymphoma patients and controls) participated in the study (Table I). Most interview participants also gave blood. In Sweden, additional written questionnaires about dietary habits or occupational exposures were administered. The SCALE study constitutes the largest case-control study on etiology of malignant lymphomas hitherto performed internationally. Results from the study have so far been published regarding lymphoma risk and exposure to UV radiation [111], body mass [163], smoking [142], medication [158], autoimmunity [93], diet and alcohol [145,149] and family history of cancer [32] (see above).

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