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New insights into the epidemiology of non-Hodgkin lymphoma and implications for therapy

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Abstract

Non-Hodgkin lymphoma (NHL) comprises numerous biologically and clinically heterogeneous subtypes, with limited data examining risk factors for these distinct disease entities. Many limitations exist when studying lymphoma epidemiology, therefore until recently little was known regarding the etiology of NHL subtypes. This review highlights the results of recent pooled analyses examining risk factors for NHL subtypes. We outline heterogeneity and commonality among risk factors for NHL subtypes, with proposed subtype-specific as well as shared etiologic mechanisms. In addition, we describe how the study of lymphoma epidemiology may translate into prevention or therapeutic targeting as we continue to explore the complexities of lifestyle and genetic factors that impact lymphomagenesis.

Keywords

non-Hodgkin lymphoma; epidemiology; risk factors

Introduction

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in the world [1]. It is more common in developed countries, with an estimated 70,800 new cases in the United States (U.S.) in 2014. Accounting for 4.3% of all cancers in the U.S., NHL ranks as the 7th most common cancer among males and the 6th most common cancer among females [2,3]. NHL consists of more than 40 major subtypes with distinct genetic, morphologic, and clinical features. The incidence of NHL subtypes also varies by age, sex, ethnicity, and geographic region. However, since relatively fewer patients are affected by each NHL subtype, elucidating risk factors responsible for such variation in the development of lymphomas by subtype has been challenging,(4) since such studies often lacked the statistical power necessary to detect differences in risk factors by NHL subtype. Whereas the epidemiology of NHL as an entire entity has been well-characterized using population-based

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cancer registry data [4–6], the epidemiology of NHL subtypes is less well understood, and little is known regarding the etiology of rarer subtypes.

The International Lymphoma Epidemiology Consortium (InterLymph) was formed in 2001 to overcome this problem. InterLymph has performed several large pooled case-control studies in order to maximize statistical power toward identifying risk factors both shared by and particular to specific NHL subtypes, with the ultimate goal of uncovering subtype-specific or shared mechanisms of lymphomagenesis. To date, InterLymph has been successful in identifying numerous environmental, lifestyle, medical, and genetic risk factors by examining pooled studies of epidemiological surveys and single nucleotide polymorphisms [7–22]. These studies also have revealed etiologic commonality and heterogeneity among NHL subtypes. For example, family history of hematologic malignancy, autoimmune diseases, atopic conditions, and alcohol consumption are associated with risk or prevention across several subtypes [23–27], while smoking has been identified as a risk factor primarily in follicular lymphoma (FL) [26]. Although previous studies have focused on the relationships between exposure history and NHL as a single entity, few prior studies evaluated the weight of risk factors in a comprehensive fashion that allowed comparisons across NHL subtypes. Therefore, InterLymph undertook the "InterLymph NHL Subtype Project," investigating the contribution of environmental, medical, and lifestyle factors on NHL subtype-specific risk among large numbers of pooled cases and controls [23–35].

This project harmonized individual subject-level data for many exposures of interest, such as medical history, family history, lifestyle, and occupational factors, and analyzed risk factors for developing each NHL subtype using unconditional logistic regression models adjusted for age, race/ethnicity, sex, and study. Occupations (ascertained by complete work history in 8 studies and longest held occupation in 2 studies) were coded according to the International Standard Classification of Occupations, Revised Edition 1968 [36]. Evaluated risk factors in these studies are summarized elsewhere [31]. To quantify the strength of association between exposures and diseases, odds ratios (OR) with 95% confidence intervals (95% CI) were reported. For binary exposures the OR reported is the increase in the odds of cancer among exposed individuals, while for categorical and ordinal variables, the OR is a summary value approximating the increase in odds among individuals in the highest category, compared to those in the lowest category. To evaluate effect heterogeneity among the studies included in each analysis, InterLymph investigators performed a separate logistic regression within each study and then quantified the variability of the coefficients by the H statistic [37]. The authors then performed stratified analyses to evaluate possible effect modification. Additional details of the statistical methods and the exposures evaluated including occupations are summarized elsewhere [31]. By pooling large numbers of cases and controls, this project was the first attempt to comprehensively evaluate risk factor profiles and quantitatively assess etiologic heterogeneity among NHL subtypes, including the rarer subtypes. The purpose of this review is to summarize the recent series of the "InterLymph NHL Subtypes Project" and to discuss the preventive and therapeutic implications of these epidemiologic studies.

Risk factors by NHL subtype

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, constituting 25–30% of adult NHL in Western countries [38,39]. The age-standardized incidence rate ranges from 4 to 7 per 100,000 person-years in Western countries, with a median age at diagnosis in the 70s [5,6]. To determine risk factors for developing DLBCL, pooled analyses of 4,667 cases and 22,639 controls from 19 studies in Europe, North America and Australia were performed [27]. Multivariable analyses revealed that B-cell activating autoimmune diseases (OR: 2.36, 95% CI: 1.80–3.09), hepatitis C virus (HCV) positivity (OR: 2.02, 95% CI: 1.47–2.76), first-degree family history of NHL (OR: 1.95, 95% CI: 1.54–2.47), and higher body mass index (BMI) as a young adult (OR for ≥30 kg/m^2: 1.58, 95% CI: 1.12–2.23) were associated with increased DLBCL risk, while high socioeconomic status (measured by years of education for studies in North America or by dividing measures of education or socioeconomic status into tertiles for studies in Europe or Australia, OR: 0.86, 95% CI: 0.79–0.94), any atopic disorder (OR: 0.82, 95% CI: 0.76–0.89), and increased recreational sun exposure (OR for 4^{th} quartile: 0.78, 95% CI: 0.69–0.89) were associated with decreased risk of DLBCL. For females, work as a field crop/vegetable farmer (OR: 1.78, 95% CI: 1.22–2.60), seamstress/embroider (OR: 1.49, 95% CI: 1.13–1.97), or hairdresser (OR: 1.65, 95% CI: 1.12–2.41) were associated with increased DLBCL risk, while hormone therapy (HT) use starting at ≥50 years of age (OR: 0.68, 95% CI: 0.52–0.88), oral contraceptive (OC) use before 1970 (OR: 0.78, 95% CI: 0.62–1.00), and adult BMI ≤18.5 kg/m^2 (OR 0.46, 95% CI: 0.29–0.74) were associated with decreased DLBCL risk. In males, work as a driver/material handling equipment operator (OR: 1.58, 95% CI 1.02–2.44) was associated with increased DLBCL risk, while prior blood transfusion (OR: 0.69, 95% CI: 0.57–0.83) and increased lifetime alcohol consumption (OR for >400 kg: 0.57, 95% CI 0.44–0.75) were associated with decreased DLBCL risk. With regard to specific anatomical sites of DLBCL, smoking was found to be associated with central nervous system, testicular, and cutaneous DLBCL; inflammatory bowel disease was found to be associated with gastrointestinal DLBCL; and farming and hair dye use were found to be associated with mediastinal DLBCL. Most of these risk or preventive factors have been previously reported. However, this study demonstrated that these risk factors are mutually exclusive by multivariable analyses, suggesting that DLBCL has a multifactorial etiology. The results of this study also suggest that DLBCL risk factors vary by sex and anatomical site (Table 1). Integrating these findings with studies of host [40] and tumor [41] genomics will be critical to define novel treatment and prevention strategies for DLBCL in the future.

Burkitt lymphoma

Burkitt lymphoma (BL) is a highly aggressive lymphoma with an extremely short doubling time characterized by deregulation of MYC [42]. BL constitutes 1–5% of adult NHL, and the age-standardized incidence rate ranges from 0.1 to 0.3 per 100,000 person-years in Western countries [6]. There are three histologically indistinguishable subtypes of BL: sporadic, endemic, and immunodeficiency-associated BL. Since endemic BL is clearly associated with Epstein-Barr virus (EBV) infection and immunodeficiency-associated BL is associated with human immunodeficiency virus (HIV) infection as well as solid organ

transplant, the InterLymph study focused on sporadic BL, for which risk factors have been largely unknown. To determine risk factors for sporadic BL, 295 cases and 21,818 controls from 18 case-control studies were analyzed [25]. Since the incidence of BL has two age peaks (during childhood and during the 60s), age-stratified analyses were performed (dividing individuals into categories <50 years and ≥50 years). In the population <50 years old, multivariable analyses revealed that eczema without other atopic conditions (OR: 2.54, 95% CI: 1.20–5.40), highest quartile of height (OR: 2.17, 95% CI: 1.08–4.36), and work as a charworker/cleaner (OR: 3.49, 95% CI: 1.13–10.7) were associated with the increased risk of BL. In the population ≥50 years old, multivariable analyses revealed that history of HCV infection (OR: 4.19, 95% CI: 1.05–16.6) was associated with increased risk of BL, while ≥1 alcoholic beverage per month (OR: 0.63, 95% CI: 0.40–0.98) were associated with decreased risk of BL. Also, BMI of 18.5 or over demonstrated a trend towards an inverse association with risk of BL ($P_{trend} = 0.049$). These differences in risk factors between younger and older populations suggest that the etiology of sporadic BL may vary by age. Risk and preventive factors associated with aggressive B-cell NHL subtypes (DLBCL and sporadic BL) are summarized in Table 1.

Lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia

Lymphoplasmacytic lymphoma (LPL) is a rare, indolent subtype of NHL existing in the biological spectrum of plasmacytic differentiation from small lymphocytes to true plasma cells. Patients with LPL often have IgM paraproteins, and a minority produce IgM and IgG or other paraproteins. Waldenström's macroglobulinemia (WM) is a clinicopathological subset of LPL, defined by the 4th edition of the World Health Organization (WHO) classification system as LPL with bone marrow involvement and monoclonal IgM gammopathy [38]. In the U.S., the age-standardized incidence rate of LPL and WM is 0.27 and 0.35 per 100,000 person-years, respectively [6]. To determine risk factors for LPL/WM, 374 cases (LPL: 371, WM: 3) and 23,096 controls from 11 case-control studies were analyzed [32]. Multivariable analyses revealed that history of Sjögren's syndrome (OR: 14.0, 95% CI: 3.60–54.6), systemic lupus erythematosus (OR: 8.23, 95% CI: 2.69–25.2), HCV infection (OR: 2.51, 95% CI: 1.03–6.17), first-degree family history of hematologic malignancy (OR: 1.64, 95% CI: 1.02–2.64), cigarette smoking for ≥40 years (OR: 1.46, 95% CI: 1.04–2.05), and occupation as a medical doctor (OR: 5.54, 95% CI: 2.19–14.0) were associated with increased risk of LPL/WM, while history of hay fever (OR: 0.73, 95% CI: 0.54–0.99) and increased adult body weight (OR: 0.61, 95% CI: 0.44–0.85, quartile 4) were associated with decreased risk of LPL/WM. These results confirm that chronic immune stimulation and family history of hematologic malignancy are associated with LPL/WM, while identifying new associations with smoking, medical occupation, weight, and hay fever.

Follicular lymphoma

FL accounts for approximately 15–20% of adult NHL in Western countries and is characterized by an indolent clinical course [38,43–45]. The age-standardized incidence rate ranges from 2 to 3 per 100,000 person-years in Western countries, with a median age at diagnosis in the 60s [5,6]. To determine risk factors for FL, 3,530 cases and 22,639 controls from 19 case-control studies were analyzed via logistic regression [26]. First-degree family

history of NHL (OR: 1.99, 95% CI: 1.55–2.54), higher BMI as a young adult (OR: 1.21, 95% CI: 1.09–1.35 per 5 kg/m^2 increase), and work as a spray painter (OR: 2.66, 95% CI: 1.36–5.24) were associated with increased risk of FL, while any atopic disorder (OR: 0.87, 95% CI: 0.80–0.94), previous blood transfusion (OR: 0.78, 95% CI: 0.68–0.89), increased sun exposure (OR for highest quartile: 0.74, 95% CI: 0.65–0.86), occupation as a baker or miller (OR: 0.51, 95% CI: 0.28–0.93), and occupation as a university/higher education teacher (OR: 0.58, 95% CI: 0.41–0.83) were associated with decreased risk of FL. In females, Sjögren's syndrome and history of cigarette smoking were associated with increased FL risk, while history of alcohol consumption, hay fever, and food allergies were associated with decreased risk of FL. These results suggest that FL has a multifactorial etiology, and that cigarette smoking may be a stronger risk factor in females.

Chronic lymphocytic leukemia/Small lymphocytic lymphoma

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is one of the most common subtypes of NHL, with an age-standardized incidence rate of 4 to 8 per 100,000 person-years and a median age at diagnosis of 65 years in Western countries. In contrast, CLL/SLL is very rare in Asian countries, with an age-standardized incidence rate of 0.1 to 0.5 per 100,000 person-years [4–6]. Despite this low incidence rate, studies have shown that the incidence of CLL/SLL in Asian populations is increasing [46]. The incidence of CLL/SLL in people of Asian descent living in the U.S. is higher than that of Asians living in their native countries [47], suggesting that Westernized lifestyles may be risk factors for developing CLL/SLL. To determine risk factors for CLL/SLL, 2,440 cases and 15,186 controls from 13 case-control studies were analyzed [24]. Multivariate logistic regression analyses revealed that first-degree family history of any hematologic malignancy (OR: 2.16, 95% CI: 1.76–2.65), HCV infection (OR: 1.99, 95% CI: 1.16–3.41), occupation or residence on a farm (OR: 1.20, 95% CI: 1.06–1.35), occupation as a hairdresser (OR: 1.77, 95% CI: 1.05–3.01), and increased height (OR: 1.09, 95% CI: 1.01–1.17, per 10cm increase) were associated with the increased risk of CLL/SLL, while any atopic disorder (OR: 0.85, 95%CI: 0.77–0.94), blood transfusions (OR: 0.79, 95%CI: 0.66–0.95) and high total sun exposures (hours per week, Quartile 4 to Quartile 1, OR: 0.71, 95%CI: 0.55–0.92) were associated with decreased risk of CLL/SLL. Associations with atopic disorders, sun exposure, HCV infection, residence or work on a farm, height, and family history of hematologic malignancy have been previously identified. This study confirmed these associations and identified novel associations with previous blood transfusion and work as a hairdresser as risk factors for CLL/SLL. Together, these risk factors suggest that genetics (e.g. family history), the immune system (e.g. atopic disorders and sun exposure), and infection (e.g. HCV), play a role in CLL/SLL etiology.

Marginal zone lymphoma

Marginal zone lymphoma (MZL) is a common indolent subtype that accounts for about 5–10% of NHL. The age-standardized incidence rate ranges from 0.4 to 1.0 per 100,000 person-years in Western countries. In the current WHO classification, three distinct diseases comprise MZL: extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), splenic MZL (SMZL), and nodal MZL (NMZL). [38] Several inflammatory pathological states are associated with specific subtypes of extranodal MZL: *H. pylori* infection is

associated with gastric MALT lymphoma, *Chlamydia psittaci* infection with ocular adnexal MALT lymphoma, *Borrelia burgdorferi* infection with cutaneous MALT lymphoma, Sjögren's syndrome with salivary gland MALT lymphoma and Hashimoto thyroiditis with thyroid MALT lymphoma.[34] However, no large epidemiological studies of MZL subtypes have been previously published. To determine risk factors for MZL, 1052 MZL cases (EMZL=633, NMZL=157, SMZL=140, MZL-not otherwise specified=120) and 13766 controls from 12 case-control studies were analyzed [34]. Several factors were found to be associated with increased risk of EMZL, NMZL and/or SMZL, including B-cell activating autoimmune conditions, hepatitis C infection, peptic ulcers, asthma without other atopic disorder, family history of hematologic malignancy, permanent hair dye use, and occupation as a metal worker. On the other hand, alcohol consumption and occupation as a teacher were both associated with a lower risk of certain MZL subtypes. B-cell activating autoimmune conditions (EMZL OR: 6.40, 95%CI: 4.24–9.68; NMZL OR: 7.80, 95%CI: 3.32–18.33; SMZL OR: 4.25, 95%CI: 1.49–12.14), hepatitis C infection (EMZL OR: 5.29, 95%CI: 2.48–11.28), peptic ulcers (EMZL OR: 1.83, 95%CI: 1.35–2.49), asthma without other atopic disorder (SMZL OR: 2.28, 95%CI: 1.23–4.23), family history of hematologic malignancy (EMZL OR: 1.90, 95%CI: 1.37–2.62), family history of NHL (NMZL OR: 2.82, 95%CI: 1.33–5.98), permanent hair dye use (SMZL OR: 6.59, 95%CI: 1.54–28.17) and occupation as a metal worker (NMZL OR: 3.56, 95%CI: 1.67–7.58) were associated with the increased risk of MZL. Alcohol consumption (EMZL OR: 0.48, 95%CI: 0.28–0.82) and occupation as a teacher (EMZL OR: 0.58, 95%CI: 0.37–0.88; SMZL OR: 0.33, 95%CI: 0.12–0.91) were associated with the lower risk of EMZL or SMZL. Of note, Sjögren's syndrome was highly associated with the risk of parotid EMZL (OR: 506, 95%CI: 165–1554) and peptic ulcer was significantly associated with the risk of gastric EMZL (OR: 3.97, 95%CI: 2.38–6.64). Although this analysis examined a large number of total MZL cases, 60% of the cases were EMZL. Thus, the results from analyses of NMZL and SMZL were based on a relatively small number of cases and should be interpreted with caution.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma with poor prognosis that remains essentially incurable with conventional chemotherapy. Although the incidence of MCL appears to be increasing, it remains a rare disease, accounting for only 2–4% of NHL cases [38]. The age-standardized incidence rate is approximately 0.5 per 100,000 person-years in Western countries [5,6]. Due to its rarity, epidemiological studies for MCL are scarce and little is known about its risk factors apart from a male predominance of 2:1 or greater. To determine risk factors for MCL, 557 MCL cases and 13,766 controls from 13 case-control studies were analyzed [29]. First-degree family history of hematological malignancy (OR: 1.99, 95%CI: 1.39–2.84) and having lived on a farm (OR: 1.40, 95%CI: 1.03–1.90) were associated with the increased risk of MCL, while any history of atopic disorder (OR: 0.74, 95%CI: 0.61–0.89), especially hay fever (OR: 0.63, 95%CI: 0.48–0.82) was associated with lower risk of MCL. Risk and preventive factors associated with B-cell NHL subtypes: LPL/MM, FL, CLL/SLL, MZL, and MCL are summarized in Table 2.

Peripheral T-cell lymphoma

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of lymphomas derived from mature T-cells. Currently, WHO classification defines PTCLs as "Mature T- and NK-cell neoplasms," which are composed of more than 20 distinct entities based on differences in morphologic, phenotypic, molecular and clinical presentation, including site of disease [38]. PTCL comprises 5–10% of all NHL, and the age-standardized incidence is around 0.5 per 100,000 person-years in Western countries [5,6]. The most common histologic subtype is classified as PTCL-not otherwise specified (PTCL-NOS), followed by angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large cell lymphoma (ALCL). To determine risk factors for PTCL, 584 cases (PTCL-NOS: 234, AITL: 81, ALCL: 164, others: 57) and 15912 controls from 15 case-control studies were analyzed [28]. Multivariable analyses revealed that first degree family history of hematologic malignancy (PTCL-NOS OR: 1.92, 95%CI: 1.05–3.49; AITL OR: 2.55, 95%CI: 1.10–5.89), history of psoriasis (PTCL-NOS OR: 2.41, 95%CI: 1.15–5.04), smoking history for ≥40 years (PTCL-NOS OR: 1.76, 95%CI: 1.14–2.72; ALCL OR: 2.46, 95%CI: 1.30–4.65), and working as an electrical fitters (ALCL OR: 4.08, 95%CI: 1.36–12.2; AITL OR: 5.45, 95%CI: 1.20–24.7) or textile workers (ALCL OR: 2.60, 95%CI: 1.21–5.58) were associated with higher risk of PTCL subtypes. History of allergy (PTCL-NOS OR: 0.67, 95%CI: 0.46–0.98), ever drinking alcohol (PTCL-NOS OR: 0.65, 95%CI: 0.45–0.93) and high sun exposure (ALCL OR: 0.48, 95%CI: 0.26–0.88, 4^{th} quartile) were associated with lower risk of PTCL-NOS or ALCL. Of note, history of Celiac disease was associated with the risk of enteropathy-associated T-cell lymphoma (OR: 215, 95%CI: 44–1041) as well as PTCL-NOS (OR: 17.8, 95%CI: 8.61–36.8) and ALCL (OR: 8.66, 95%CI: 1.97–38.1).

Mycosis fungoides/Sezary syndrome

Mycosis fungoides (MF) is a most common type of cutaneous T-cell lymphoma, accounting for nearly half of all cutaneous lymphomas [38]. Sezary syndrome (SS) is a rare type of systemic cutaneous lymphoma characterized by erythroderma, generalized lymphadenopathy and peripheral blood involvement. MF commonly has an indolent clinical course but may progress to SS. The age-standardized incidence of MF/SS is around 0.5 per 100,000 person-years in Western countries [5,6]. Genetic susceptibility is suggested by the fact that a higher incidence rate of MF is observed among African Americans, with a black-to-white incidence rate ratio approximately 1.5:1. To determine risk factors for MF/SS, 324 cases (MF: 271, SS: 13, MF/SS: 40) and 17217 controls from 14 case-control studies were analyzed [35]. Multivariable analyses identified that smoking history for ≥40 years (OR: 1.55, 95%CI: 1.04–2.31), adult BMI greater than 30kg/m^2 (OR: 1.57, 95%CI: 1.03–2.40), history of eczema (OR: 2.38, 95%CI: 1.73–3.29), history of multiple myeloma (OR: 8.49, 95%CI: 3.31–21.8), and working as a crop and vegetable farmer (OR: 2.37, 95%CI: 1.14–4.92), painter (OR: 3.71, 95%CI: 1.94–7.07), woodworker (OR: 2.20, 95%CI: 1.18–4.08) or general carpenter (OR: 4.07, 95%CI: 1.54–10.8) were associated with higher risk of MF/SS. Of note, the association between eczema and the risk of MF/SS was even stronger (OR: 4.87, 95%CI: 2.15–11.02) for those who were diagnosed with eczema within 10 years of MF/SS diagnosis. This may suggest that early MF could have been misdiagnosed as eczema in some cases, and this association should be interpreted with caution. Family history of multiple myeloma also was significantly associated with the risk of MF/SS. However, both

diseases have significantly higher incidence in African Americans, which may confound the association. Risk and preventive factors associated with T-cell NHL subtypes (PTCL and MF/SS) are summarized in Table 3.

Etiologic Commonality and heterogeneity—To assess risk factor heterogeneity among NHL subtype and identify subtypes sharing similar risk factors, Morton LM et al. evaluated the variability of the estimated OR for a given exposure among subtypes. A total of 17471 NHL cases and 23096 controls from 20 case-control studies were analyzed and organized into hierarchical clusters with similar risk factor profiles [32]. The estimated ORs among subtypes for major exposures are summarized in Table 4. The majority of risk factors showed differences in risk among NHL subtypes, whereas family history of NHL, recreational sun exposure, hay fever, allergy, and socioeconomic status were homogenous in risk among subtypes. The greatest difference in risk factor patterns was seen between B-cell and T-cell lymphomas, as might be expected. Eczema, T-cell activating autoimmune disease such as celiac disease and cigarette smoking were more strongly associated with the risk of PTCL and/or MS/SS, whereas HCV infection, blood transfusion and B-cell activating autoimmune disease were more strongly associated with B-cell lymphomas. The clustering by association between exposures revealed three distinct major sub-groups based on shared risk factors: PTCL and MF/SS; MZL and BL; and a third subgroup including DLBCL, FL, CLL/SLL, MCL and LPL/WM. Within this last subgroup, DLBCL, CLL/SLL and LPL/WM showed a significantly different risk profile from FL and MCL, with key differentiating risk factors including B-cell activating autoimmune diseases, hay fever, allergy, alcohol consumption, HCV seropositivity, cigarette smoking, and occupation as a teacher or general farm worker.

The risk and preventive factors identified in this series of studies warrant further investigation. Several factors such as alcohol consumption, blood transfusion, sun exposure and occupation as teacher were associated with the reduced risk of certain types of NHL. The potential protective effects of alcohol could be due to its immune-modulatory effects. Heavy alcohol consumption impairs immune function. In contrast, light to moderate alcohol use might improve immune responses, although the mechanism is not well known [48]. Sun exposure is associated with the production of vitamin D, and Vitamin D has been shown to have anti-proliferative and pro-differentiating effects in lymphoma cell lines [49]. Occupation often is a proxy for related exposures. The mechanisms for the reduced risk of NHL by working as a teacher are difficult to speculate and investigate. With the best speculation, however, teachers, especially in elementary school, are frequently exposed to infections by students and frequent immune responses may be associated with the reduced risk of NHL. A previous study has described that blood transfusion increases the risk of NHL[50], which was inconsistent with the presented study. Therefore, validation of the results summarized in a large cohort is crucial to investigate further for lymphomagenesis. Nordic countries such as Sweden provide universal medical health care for the entire population, and have well established population-based cancer registry data. These cohort data are less likely to have limitations such as recall bias and would be very interesting and feasible to validate the results described from these studies.

This series of studies provides the most robust evidence yet of associations between major NHL subtypes and important risk factors such as family history, medical conditions, environmental and lifestyle factors, and occupation. However, several limitations warrant discussion. First, 30% of the cases were not originally diagnosed according to WHO classification, and central review was not performed. These shortcomings may be partly explained by the fact that classification of NHL has evolved over time [38,51]. Furthermore, since central review of 17000 NHL cases was not realistic or feasible, each study's determination of pathologic diagnosis was reviewed by InterLymph members to ensure that methodology remained consistent among studies. In addition, self-reported data are likely to be associated with recall bias, particularly with risk factors such as family history. Self-reported questionnaire data also can introduce selection bias, since patients with aggressive disease may be too ill to participate and are thereby more likely to be excluded. As in many analyses, the study populations were predominantly of Caucasian descent. In light of the fact that race and ethnicity themselves are associated with differential risk of certain NHL subtypes, the risk factors reported here may not be generalizable to non-Caucasian populations. Moreover, risk factors for NHL among racial/ethnic minorities and their impact on survival remain poorly characterized [43,52–58].

Several important risk factors are not analyzed by these studies, including infection other than HCV, diet and genetic background. Additional studies are needed to investigate the association of such factors with risk of NHL. Further characterization of the specific interactions between genetic and environmental factors that contribute to lymphoma risk could provide a more complete picture of the complex molecular events that underlie lymphomagenesis. Future studies also should focus on the impact of these risk factors on NHL survival.

Preventive and therapeutic implications

This review summarizes the most comprehensive case-control studies examining risk factors associated with NHL subtypes, which may provide insight into lymphomagenesis and potential preventive interventions. However, extracting modifiable risk factors and therapeutic implications from these results remains challenging. Several studies have suggested that lifestyle factors affect prognosis in patients with NHL. Geyer et al evaluated the survival of 1,286 patients who were diagnosed with NHL from 1998 through 2000, in relation to lifestyle factors such as cigarette smoking, alcohol use, and obesity [59]. Compared with never-smokers, former smokers (hazard ratio [HR]: 1.59, 95% CI: 1.12–2.26) and current smokers (HR: 1.50, 95% CI: 0.97–2.29) had inferior survival. However, the relationship between smoking and survival did not meet statistical significance, confounding clear interpretation of these results. Perhaps predictably, inferior survival also was observed with increased smoking duration, increased number of cigarettes smoked per day, increased pack-year smoking history, and shorter time since quitting (all p-values for trend < 0.01). Alcohol use >43.1 g/week (HR: 1.55, 95% CI: 1.06–2.27) and BMI ≥30 kg/m^2 (HR: 1.32, 95% CI: 1.02–1.70) also were associated with inferior survival. The relationship between smoking and survival also was examined in a Swedish population-based study, which included 1,523 NHL patients diagnosed from 1999 through 2002 [60]. Current smokers had inferior survival in comparison to never-smokers (HR: 1.5, 95% CI:

1.2–1.8), although the significant difference disappeared when cause of death was limited to lymphoma. Ollberding et al. performed a meta-analysis using a random effects model to assess the impact of smoking on NHL prognosis [61] in five studies including 3,464 patients [59,61–63]. This work identified that smoking ≥20 cigarettes per day, ≥30 years or ≥30 pack-years was significantly associated with inferior survival in comparison to non-smokers. These studies indicate that certain modifiable lifestyle factors, particularly cigarette smoking history, contribute to NHL prognosis. However, these studies lack important data such as lymphoma treatment administered and International Prognostic Index (IPI) score, and thus should be interpreted with caution. Of course, smoking also increases the risks of competing causes of death, including other cancers and cardiovascular disease; therefore, inferior survival in smokers may not be primarily related to lymphoma.

In the InterLymph NHL Subtype Project studies, increased sun exposure was associated with decreased risk of DLBCL, FL, CLL/SLL, and ALCL. These results suggest that vitamin D deficiency or sunlight-mediated immune modulation may play a role in non-Hodgkin lymphomagenesis [64]. Although a recent meta-analysis did not confirm a protective role for vitamin D in NHL[65], there is evidence that vitamin D deficiency may adversely impact NHL treatment and/or survival. In a Norwegian population-based study investigating the relationship between 25-hydroxyvitamin D levels and risk of death in cancer patients, higher levels were associated with superior survival in 145 patients with lymphoma [66]. In patients with CLL, Shanafelt et al. found that 25-hydroxyvitamin D deficiency was associated with inferior time-to-treatment and overall survival [67]. Additionally, Drake et al. found that in DLBCL and T-cell lymphoma patients, 25-hydroxyvitamin D deficiency was associated with inferior event-free and overall survival [68]. Bittenbring et al evaluated the impact of 25-hydroxyvitamin D deficiency in DLBCL patients enrolled in a prospective clinical trial RICOVER-60 [69]. In patients who received R-CHOP-14 (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone given every two weeks), multivariable regression analysis revealed that vitamin D deficiency (≤8 ng/ml) was significantly associated with inferior overall survival (HR: 1.8, 95% CI: 1.1–3.0), independent of IPI. Comparing DLBCL patients treated with R-CHOP with and without vitamin D deficiency, 3-year progression-free survival was 64% (95% CI 54%-75%) and 81% (95% CI 73%-89%), and 3-year overall survival was 70% (95% CI 60%-80%) and 82% (95% CI 74%-90%), respectively. In addition, the authors reported *in vitro* studies suggesting that these differences in survival were due to differences in rituximab-related cytotoxicity in vitamin D deficient versus replete individuals. However, additional studies are needed to provide a clearer explanation for these observed differences in survival. These provocative data provided the rationale to open a Phase III trial to test whether vitamin D replacement impacts tumor response and prognosis in DLBCL, T-cell lymphoma and CLL (NCT01787409) involving investigators from the Mayo Clinic, Emory, Iowa, and Wisconsin. A schema for the arms of the trial is shown in Figure 1.

Conclusions

This review highlights risk factors that are both shared by and particular to specific NHL subtypes emerging from the unique opportunity for analysis of large numbers of pooled cases and controls afforded by the InterLymph NHL Subtype Project. These findings and

others suggest that a number of medical history, family history, lifestyle, and occupational factors are associated with the risk of specific NHL subtypes. These data provide initial insights for examining whether the survival of patients with specific NHL subtypes may be dependent not only on treatment, clinical and tumor genetic factors, but also may be influenced by a complex interplay between medical, lifestyle, environmental, and host genetic factors. With this comprehensive assessment of NHL risk factors, including heterogeneity and commonality of risk factors across NHL subtypes, we are beginning to learn more about potential mechanisms underlying lymphomagenesis. We believe that this knowledge may translate into preventive and therapeutic targets for NHL in the future.

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Expert commentary

This review discusses NHL subtype-specific risk and preventive factors identified via InterLymph pooled case-control studies. The risk of developing specific NHL subtypes is associated with a number of medical history, family history, lifestyle, and occupational factors. These associations suggest that host genetics (e.g. family history of hematologic malignancy), immune conditions (e.g. autoimmune and atopic disorders), infection (e.g. HCV and H. pylori), modifiable risk factors (e.g. BMI, alcohol consumption, and cigarette smoking), occupation (e.g. farm or medical worker), and other factors play a role in non-Hodgkin lymphomagenesis. Increased sun exposure is associated with decreased risk of DLBCL, FL, CLL/SLL, and ALCL, suggesting that vitamin D deficiency or sunlight-mediated immune modulation may play an etiologic role in some NHL subtypes, which also appears to be a modifiable factor related to survival for certain NHL subtypes.

Five-year view

These risk and preventive associations with specific subtypes of NHL suggest that there is etiologic commonality and heterogeneity among NHL subtypes. Further studies are needed to determine potential genetic contributions to these associations, particularly in non-Caucasian populations. Additional studies are also needed to elucidate specific exposures associated with increased occupational risk, examine the effect of risk and preventive factors on NHL survival, and determine the mechanism underlying the association between increased sun exposure and decreased risk of DLBCL, FL, CLL/SLL, and ALCL. Improved understanding of these factors could support the development of prevention strategies for high-risk populations.

Key issues

1. Pooled case-control analyses from the InterLymph NHL Subtypes Project have identified a number of medical history, family history, lifestyle, and occupational associations with NHL subtypes.
2. There is variation in DLBCL risk and preventive factors by sex and anatomical site of disease.
3. Differences in sporadic BL risk factors between younger and older populations suggest that etiology of this disease may vary with age.
4. Cigarette smoking has been found to be associated with FL in other studies. The results from the InterLymph NHL Subtypes Project for FL suggest that this risk factor may be more prominent in females.
5. T-cell NHL subtypes are more strongly associated with T-cell activating autoimmune diseases such as celiac disease, cigarette smoking, and eczema.
6. B-cell NHL subtypes are more strongly associated with B-cell activating autoimmune diseases such as systemic lupus erythematosus, HCV infection, and history of blood transfusion.
7. Three distinct subgroups of NHL can be identified based on similarities of risk and preventive factors: 1) PTCL and MF/SS, 2) MZL and BL, and 3) DLBCL, FL, CLL/SLL, MCL, and LPL/WM.
8. DLBCL, CLL/SLL, and LPL/WM show a significantly different risk profile from FL and MCL, with the key differentiating risk factors of B-cell activating autoimmune diseases, hay fever, allergy, alcohol consumption, HCV seropositivity, cigarette smoking, and occupation as a teacher or general farm worker.
9. The highest quartile of sun exposure is associated with decreased risk of DLBCL, FL, CLL/SLL, and ALCL, suggesting a possible role for vitamin D deficiency or sunlight-mediated immune modulation in non-Hodgkin lymphomagenesis.
10. Identifying NHL risk factors may lead to discoveries of disease etiology as well as preventive and therapeutic targets.

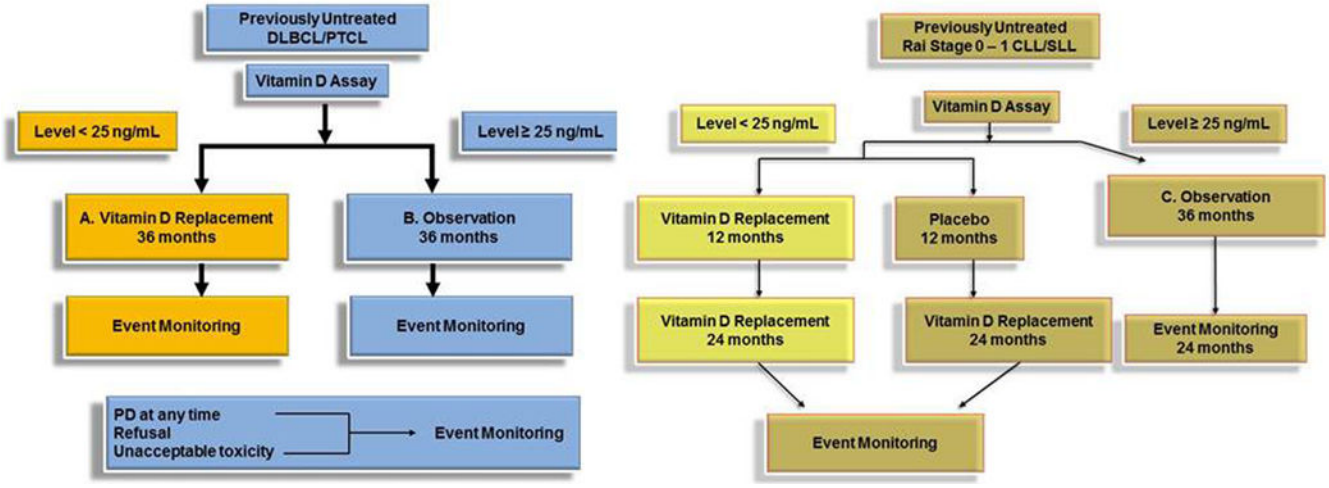

Figure 1.

Schema for a clinical trial evaluating to benefit of vitamin D in conjunction with treatment for nonHodgkin lymphoma

Table 1

Risk Factors for Aggressive B-Cell NHL

Factors that Increase Risk of DLBCL	Factors that Decrease risk of DLBCL
B-cell activating conditions	High SES
Seropositive for hepatitis C virus	Any atopic disorder
1st degree family history of NHL	Increased recreational sun exposure
Higher BMI as a young adult	Low adult BMI,<18.5 (females)
Cigarette smoking (CNS, testicular, and cutaneous DLBCL)	Hormone therapy use starting at ≥ 50 years of age (females)
Living on a farm (mediastinal DLBCL)	Oral contraceptive use before 1970 (females)
Inflammatory bowel disease (gastrointestinal DLBCL)	History of blood transfusion (males)
Hair dye use (mediastinal DLBCL)	Alcohol consumption (males)
Employment as: Field crop and vegetable farmer (females) Seamstress and embroider (females) Hairdresser (females) Driver/material handling equipment operator (male)	
Factors that Increase Risk of Sporadic BL	**Factors that Decrease Risk of Sporadic BL**
< 50 years of age	< 50 years of age
Eczema without other atopic conditions	Allergies
Highest quartile of height	Alcohol consumption
Employment as a cleaner	
Adult height, highest quartile	
≥ 50 years of age	≥ 50 years of age
Seropositive for hepatitis C virus	Alcohol consumption
Adult height, highest quartile	

Note: NHL=non-Hodgkin lymphoma, DLBCL=diffuse large B-cell lymphoma, HCV=hepatitis C virus, BMI=body mass index, CNS=central nervous system, SES=socioeconomic status, BL=Burkitt lymphoma, Q4=4th quartile.

Table 2

Risk Factors for Indolent B-Cell NHL

Factors that Increase Risk of LPL/WM	**Factors that Decrease Risk of LPL/WM**
Sjögren's syndrome	Hay fever
Systemic lupus erythematosus	Increased adult weight (Q4)
HCV infection	
1st degree family history of any hematologic malignancy	
Cigarette smoking for ≥ 40 years	
Employed as a medical doctor	
Factors that Increase Risk of FL	**Factors that Decrease Risk of FL**
1st degree family history of NHL	Any atopic disorder
High BMI as a young adult	Prior blood transfusion
Employed as a spray painter	Increased sun exposure
Sjögren's syndrome (female)	Employed as: baker or miller university/higher education teacher
Cigarette smoking (female)	Alcohol consumption (female)
Factors that Increase Risk of CLL/SLL	**Factors that Decrease Risk of CLL/SLL**
1st degree family history of any hematologic malignancy	Any atopic disorder
HCV infection	Prior blood transfusion
Occupation or residence on a farm	Increased sun exposure
Employed as a hairdresser	
Increased height	
Factors that Increase Risk of MZL	**Factors that Decrease Risk of MZL**
B-cell activating conditions	Alcohol consumption
HCV infection	Employed as a teacher
Peptic ulcers	
Asthma without other atopic condition	
1st degree family history of any hematologic malignancy	
Hair dye use	
Employed as a metal worker	
Factors that Increase Risk of MCL	**Factors that Decrease Risk of MCL**
1st degree family history of any hematologic malignancy	Any atopic disorder
Residence on a farm	

Note: NHL=non-Hodgkin lymphoma, MZL=marginal zone lymphoma, HL=Hodgkin lymphoma, SLL/CLL=small lymphocytic lymphoma/chronic lymphocytic leukemia, Q4=4th quartile, cm=centimeters, FL=follicular lymphoma, BMI=body mass index, kg=kilograms, m^2=meters squared, LPL/WM=lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, Q2=2nd quartile, Q3=3rd quartile.

Table 3

Risk Factors for T-Cell NHL

Factors that Increase Risk of PTCL	**Factors that Decrease Risk of PTCL**
1st degree family history of any hematologic malignancy	Allergies
Psoriasis	Alcohol consumption
Cigarette smoking for ≥ 40 years	High sun exposure
Employed as an electrical fitter or textile worker	
Celiac disease	
Factors that Increase Risk of MF/SS	**Factors that Decrease Risk of MF/SS**
Cigarette smoking for ≥ 40 years	Moderate physical activity
High adult BMI, >30	
Eczema	
Multiple myeloma or family history of multiple myeloma	
Employed as: crop/vegetable farmer painter woodworker or general contractor	

Note: NHL=non-Hodgkin lymphoma, PTCL=peripheral T-cell lymphoma, Q3=3rd quartile, Q4=4th quartile, PTCL-NOS=peripheral T-cell lymphoma not otherwise specified, MF/SS=mycosis fungoides/Sezary syndrome, BMI=body mass index, kg=kilograms, m^2=meters squared, ALCL=anaplastic large cell lymphoma.

Table 4

Odds ratios for all risk factors affecting one or more non-Hodgkin lymphoma subtypes

	Overall NHL	DLBCL	FL	CLL/SLL	MZL	MCL	BL	LPL/WM	PTCL	MF/SS	
Exposure category	**OR (95%CI)**										**P-homogeneity <0.05**
Family history of hematologic malignancy											
None (Reference)											
Any	1.72 (1.54–1.93)	1.57 (1.34–1.83)	1.48 (1.25–1.75)	2.17 (1.77–2.65)	1.73 (1.33–2.25)	1.99 (1.39–2.84)		1.65 (1.03–2.65)	1.86 (1.26–2.74)	1.16 (0.68–1.98)	*
HL	1.65 (1.18–2.29)	2.08 (1.38–3.15)			2.74 (1.36–5.51)						
NHL	1.79 (1.51–2.13)	1.84 (1.46–2.33)	1.99 (1.55–2.54)	1.92 (1.42–2.61)	1.65 (1.10–2.46)	1.95 (1.14–3.34)					
Leukemia	1.51 (1.29–1.77)			2.41 (1.85–3.14)	1.66 (1.15–2.38)	1.98 (1.21–3.24)		2.19 (1.21–3.96)	1.84 (1.09–3.13)		*
Multiple myeloma	1.77 (1.15–2.72)		1.93 (1.06–3.51)			3.10 (1.05–9.10)			2.86 (0.98–8.37)	6.11 (2.36–15.8)	*
Autoimmune disease											
None (Reference)											
Any B-cell acivating disease	1.96 (1.60–2.40)	2.45 (1.91–3.16)			5.46 (3.81–7.83)			2.61 (1.34–5.08)			*
Sjogren syndrome	7.52 (3.68–15.4)	8.77 (3.94–19.5)	3.32 (1.19–8.80)		38.1 (16.9–85.6)			12.1 (3.16–46.6)			*
Systemic lupus erythematosus	2.83 (1.82–4.41)	2.49 (1.42–4.37)			6.54 (3.10–13.8)			8.41 (2.81–25.2)	3.90 (1.24–12.3)	5.03 (1.17–21.6)	
Any T-cell activating disease		1.08 (1.09–1.28)							1.95 (1.37–2.77)	1.66 (1.00–2.75)	*
Celiac disease	1.77 (1.05–2.99)	2.09 (1.04–4.18)							14.8 (7.27–30.2)		*
Systemic sclerosis/scleroderma							20.2 (2.44–166)			8.87 (1.11–71.3)	
HCV seropositivity											
Negatie (Reference)											
Positive	1.81 (1.39–2.37)	2.33 (1.71–3.19)		2.08 (1.23–3.49)	3.04 (1.65–5.60)			2.70 (1.11–6.56)			*
Atopic disease											
None (Reference)											
Hay fever	0.82 (0.77–0.88)	0.78 (0.70–0.86)	0.82 (0.73–0.91)	0.88 (0.76–1.01)		0.63 (0.48–0.82)	0.64 (0.44–0.95)	0.70 (0.52–0.96)			
Eczema										2.31 (1.68–3.17)	*
Allergy	0.86 (0.81–0.92)	0.82 (0.74–0.90)	0.88 (0.79–0.98)	0.87 (0.77–0.98)		0.79 (0.63–0.98)			0.75 (0.60–0.94)		
Blood transfusion											
None (Reference)											

	Overall NHL	DLBCL	FL	CLL/SLL	MZL	MCL	BL	LPL/WM	PTCL	MF/SS	
Exposure category	**OR (95%CI)**										**P-homogeneity <0.05**
Any	0.83 (0.77–0.91)	0.84 (0.75–0.95)	0.78 (0.68–0.89)	0.79 (0.66–0.94)							*
Anthropometric factors											
BMI 18.5 to 22.5 (Reference)											
Usual adult BMI ≥ 25		1.32 (1.11–1.57)						0.40 (0.23–0.69)		1.95 (1.10–3.46)	*
Height, first quartile (Reference)											
Height, third and fourth quartile	1.20 (1.08–1.32)	1.16 (1.01–1.33)	1.20 (1.02–1.40)	1.29 (1.06–1.57)			2.43 (1.37–4.31)				*
Alcohol consumption (≥ 1 drink per month)											
None (Reference)											
Any alcohol	0.87 (0.81–0.93)	0.81 (0.73–0.89)	0.86 (0.77–0.96)		0.75 (0.62–0.91)		0.64 (0.48–0.87)		0.68 (0.53–0.87)		
Cigarette smoking											
None (Reference)											
Duration ≥ 20 years			1.19 (1.06–1.33)	0.84 (0.74–0.96)	1.27 (1.03–1.57)	1.24 (0.96–1.61)	0.77 (0.51–1.17)	1.50 (1.10–2.04)	1.75 (1.33–2.30)	1.22 (0.84–1.77)	*
Recreational sun exposure											
First quartile (Reference)											
Third and fourth quartile	0.74 (0.66–0.83)	0.75 (0.64–0.88)	0.70 (0.58–0.84)	0.79 (0.64–0.96)	0.65 (0.48–0.87)	0.70 (0.48–1.01)			0.67 (0.46–1.00)		
Socioieconomic status											
High (Reference)											
Low	0.88 (0.83–0.93)	0.82 (0.76–0.90)					0.65 (0.48–0.90)				
Occupational history											
Without the history (Reference)											
Teacher	0.86 (0.77–0.95)	0.87 (0.75–1.00)			0.50 (0.35–0.70)		0.27 (0.09–0.87)				*
Painter	1.22 (0.99–1.51)									3.42 (1.81–6.47)	
General farm worker	1.28 (1.10–1.50)			1.46 (1.15–1.85)						2.07 (1.06–4.07)	

Abbreviations: HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MZBCL, marginal zone B-cell lymphoma; MCL, mantle cell lymphoma; BL, Burkitt lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Wardenstrom macroglobulinemia; PTCL, peripheral T-cell lymphoma; MF/SS, mycosis fungoides/Sezary syndrome