

## Review Article

# Current Understanding of Lifestyle and Environmental Factors and Risk of Non-Hodgkin Lymphoma: An Epidemiological Update

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The incidence rates of non-Hodgkin lymphoma (NHL) have steadily increased over the last several decades in the United States, and the temporal trends in incidence can only be partially explained by the HIV epidemic. In 1992, an international workshop sponsored by the United States National Cancer Institute concluded that there was an “emerging epidemic” of NHL and emphasized the need to investigate the factors responsible for the increasing incidence of this disease. Over the past two decades, numerous epidemiological studies have examined the risk factors for NHL, particularly for putative environmental and lifestyle risk factors, and international consortia have been established in order to investigate rare exposures and NHL subtype-specific associations. While few consistent risk factors for NHL aside from immunosuppression and certain infectious agents have emerged, suggestive associations with several lifestyle and environmental factors have been reported in epidemiologic studies. Further, increasing evidence has suggested that the effects of these and other exposures may be limited to or stronger for particular NHL subtypes. This paper examines the progress that has been made over the last twenty years in elucidating the etiology of NHL, with a primary emphasis on lifestyle factors and environmental exposures.

## 1. Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous disease resulting from the malignant transformation of lymphocytes and includes multiple subtypes each with specific molecular and clinical characteristics [1]. The past several decades have seen a steady increase in incidence rates of NHL, with overall rates in the United States nearly doubling over the period 1975 to 2008 (Figure 1). Currently, incidence rates of NHL for both men and women in the United States are among the highest in the world (Figure 2) and, whereas rates of NHL associated with HIV infection have decreased with the use of antiretroviral therapy, there is evidence to suggest that rates from other causes have continued to increase [2, 3]. In particular, distinct incidence trends have been reported among different demographic groups, as incidence rates decreased in middle-aged men starting in the mid 1990s, but increased in middle-aged women, blacks  $\geq 55$  years old, and

in younger whites aged 15–24 [4]. In 1992, an international workshop sponsored by the United States National Cancer Institute concluded that there was an “emerging epidemic” of NHL and the panel recommended investigation of the potential risk factors that were responsible for the rapid increase in this deadly disease [5].

Subsequently, over the ensuing two decades, tremendous efforts have been made to understand the risk factors accounting for the increase of NHL particularly as related to potential environmental and lifestyle risk factors. This effort has been aided by the initiation of several consortia, including a large international consortium of case-control studies (InterLymph) that has enabled a closer examination of NHL subtype-specific associations and the potential for etiologic heterogeneity as well as the assessment of less prevalent exposures [1, 6]. Moreover, this research effort has been aided by the development of a uniform classification system for lymphoid neoplasms for use in epidemiologic

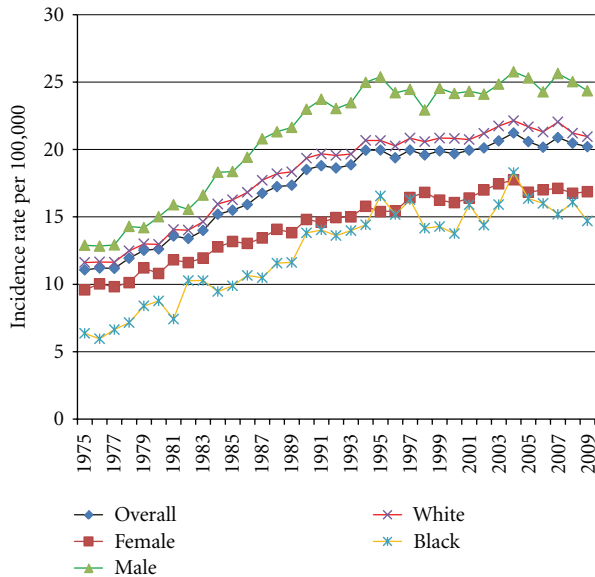


FIGURE 1: Temporal trends in the age-adjusted incidence rate of non-Hodgkin lymphoma in the United States based on SEER data, 1975–2009.

research by InterLymph, as several previous classifications have been developed and applied in studies including the Revised European-American Lymphoma classification in 1994 and the World Health Organization classification developed in 2001 and updated in 2008 [7]. Both the scientific community and the public must wonder where we are in terms of understanding the etiology of NHL after these twenty years of effort. Here, we summarize and review the epidemiological findings and progress that has been made over the past twenty years in terms of furthering our understanding of the etiology of NHL, with an emphasis on lifestyle and environmental risk factors that may contribute to NHL risk.

**1.1. Smoking.** Although the majority of epidemiologic studies do not support a major association between smoking and overall NHL [8–13], several studies which examined the risk for NHL subtypes suggest that smoking may increase the risk of follicular lymphoma (FL) [14–16]. The largest study that has examined an association with smoking to date, a pooled InterLymph analysis with 6,594 cases and 8,892 controls, reported an increased risk of FL in current smokers (OR 1.31, 95% CI 1.12–1.52), including a 45% increased risk in current heavy smokers, with some evidence for a dose-response effect according to longer duration of smoking [15]. However, there was limited evidence for an effect with overall NHL for ever smoking (OR 1.07, 95% CI 1.00–1.15; Table 1), and a significant FL association was not confirmed in the EpiLymph case-control study (Table 1) [17]. Cohort studies have been inconsistent with respect to the FL association, with three U.S. studies reporting elevated risks for either former, current smoking, or exposure to passive smoking [16, 18, 19], and others reporting null or curiously decreased risks [11, 20, 21].

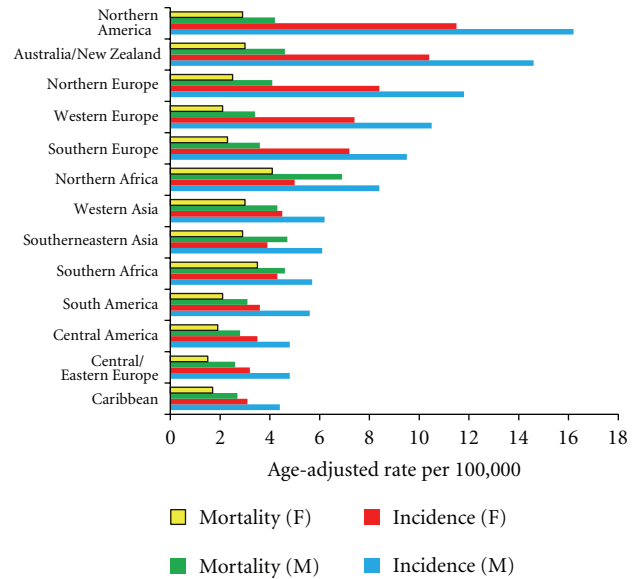


FIGURE 2: Age-adjusted incidence and mortality rates of non-Hodgkin lymphoma in selected world regions based on IARC GLOBOCAN 2008 data.

An association with smoking and FL specifically may be biologically plausible, as heavy smoking has been observed in some studies to increase the risk of NHL associated with t(14; 18) translocations, which are characteristic of FL and occur in up to 90% of cases [29, 30]. Chronic exposure to cigarette smoke has been demonstrated to have immunosuppressive effects by impairing proliferation of T cells and antibody responses [31], but available evidence does not suggest that smoking is an important determinant for overall NHL risk.

**1.2. Alcohol.** A number of studies have examined the association between alcohol consumption and NHL risk, with some suggesting that consumption of alcohol may be protective against NHL [8, 21, 22, 32–35], but consistent epidemiological evidence for this protective association is lacking [9, 10, 20, 36–42].

Large international pooling studies have suggested an overall reduced risk of NHL associated with alcohol consumption or in distinct subgroups. An InterLymph study that included 6,492 NHL cases and 8,683 controls (Table 1) reported a modest reduced risk of NHL in ever drinkers (OR 0.83, 95% CI 0.76–0.89) but no clear dose-response trends [22], and a large EpiLymph study including 1,742 cases and 2,465 controls reported a protective effect in male ever drinkers (OR 0.76, 95% CI 0.62–0.93), but no overall effect was observed (Table 1) [17]. Two large cohort studies have shown some evidence for an inverse association with the DLBCL subtype, but were conflicting with respect to overall NHL risk [20, 21]. Most recently, a systematic review of 29 studies has indicated an overall reduced risk of NHL for drinkers compared to nondrinkers (RR 0.85, 95% CI 0.79–0.91), with similar risk estimates for the level (i.e., light, moderate, and heavy) of consumption [43].

TABLE 1: Primary results from NHL consortia studies for selected environmental and lifestyle risk factors, for overall NHL and common subtypes.

Reference, consortium	Total cases	Total controls	Exposure	Exposure metric	Overall NHL (OR, 95% CI)	Diffuse (OR, 95% CI)	FL (OR, 95% CI)	CLL/SLL (OR, 95% CI)	Reference
Morton et al., InterLymph	6594	8892	Smoking	Ever smoker	1.07 (1.00–1.15)	1.09 (0.99–1.20)	1.15 (1.02–1.29)	1.01 (0.86–1.18)	
				≥31 cigs/day	1.07 (0.93–1.23)	1.13 (0.92–1.38)	0.95 (0.73–1.23)	0.82 (0.59–1.14)	[15]
				≥36 years	1.16 (1.05–1.28)	1.13 (0.97–1.31)	1.28 (1.08–1.53)	1.16 (0.95–1.42)	
				≥36 pack-yrs	1.21 (1.09–1.34)	1.24 (1.06–1.44)	1.30 (1.08–1.56)	1.11 (0.89–1.38)	
Besson et al., EpiLymph	1742	2465	Smoking	Ever smoker	1.06 (0.92–1.21)	0.88 (0.72–1.09)	1.16 (0.87–1.56)	1.08 (0.83–1.39)	
				≥20 cigs/day	1.05 (0.88–1.26)	0.95 (0.72–1.24)	1.21 (0.83–1.78)	0.89 (0.64–1.22)	[17]
				>32 years	1.15 (0.96–1.39)	0.91 (0.68–1.22)	1.39 (0.94–2.06)	1.10 (0.81–1.50)	
				≥27 pack-yrs	1.13 (0.94–1.37)	1.04 (0.78–1.38)	1.21 (0.81–1.82)	1.01 (0.73–1.39)	
Morton et al., InterLymph	6492	8683	Alcohol	Ever drinker	0.83 (0.76–0.89)	0.75 (0.66–0.84)	0.84 (0.73–0.97)	0.94 (0.79–1.13)	
				≥28 servings/week	0.87 (0.76–0.99)	0.73 (0.60–0.90)	0.82 (0.63–1.07)	1.16 (0.88–1.52)	[22]
				≥401 kg lifetime consumption	0.80 (0.68–0.95)				
				≥41 years	0.81 (0.69–0.95)	0.67 (0.53–0.85)	0.84 (0.63–1.12)	0.81 (0.58–1.15)	
Besson et al., EpiLymph	1742	2465	Alcohol	Ever regular drinker	0.99 (0.84–1.18)	0.89 (0.69–1.15)	0.96 (0.65–1.44)	1.18 (0.87–1.59)	
				>730 grams per month	0.90 (0.71–1.15)	0.74 (0.51–1.07)	1.15 (0.67–1.99)	0.94 (0.62–1.41)	[17]
				≥ 378 kg lifetime consumption	0.99 (0.78–1.26)	0.82 (0.57–1.19)	1.12 (0.63–2.00)	1.04 (0.69–1.55)	
				>42 years duration	0.88 (0.68–1.12)	0.68 (0.46–1.02)	1.20 (0.67–2.16)	1.06 (0.73–1.55)	

TABLE 1: Continued.

Reference, consortium	Total cases	Total controls	Exposure	Exposure metric	Overall NHL (OR, 95% CI)	Diffuse (OR, 95% CI)	FL (OR, 95% CI)	CLL/SLL (OR, 95% CI)	Reference
Krickler et al., InterLymph	8243	9697	Sun exposure	Composite total sun exposure	0.87 (0.71–1.05) <sup>1</sup>				
				Composite recreational sun exposure	0.76 (0.63–0.91)	0.69 (0.55–0.87)	0.73 (0.62–0.86)	0.83 (0.59–1.17)	
				Composite nonrecreational sun exposure	1.01 (0.89–1.15)				
				Lifetime, total exposure	0.88 (0.69–1.11)				
				Lifetime, recreational	0.79 (0.54–1.14)				
				Lifetime, nonrecreational	0.98 (0.84–1.15)				
				Age 10–17, total exposure	0.76 (0.56–1.03)				
				Age 10–17, recreational	0.85 (0.62–1.16)				
				Age 10–17, nonrecreational	0.87 (0.66–1.15)				
				Age 18–40, total exposure	0.93 (0.82–1.06)				
				Age 18–40, recreational	0.80 (0.68–0.94)				
				Age 18–40, nonrecreational	0.97 (0.85–1.10)				
				10 years before diagnosis, total	0.84 (0.72–0.97)				
10 years before diagnosis, recreational	0.74 (0.62–0.88)								
10 years before diagnosis, nonrecreational	0.98 (0.85–1.14)								

[23]

TABLE 1: Continued.

Reference, consortium	Total cases	Total controls	Exposure	Exposure metric	Overall NHL (OR, 95% CI)	Diffuse (OR, 95% CI)	FL (OR, 95% CI)	CLL/SLL (OR, 95% CI)	Reference
Boffetta et al., EpiLymph	1518	2124	UV radiation	Personal exposure, free days childhood	1.07 (0.81–1.43) <sup>1</sup>	0.88 (0.60–1.28)	1.35 (0.80–2.26)	1.17 (0.70–1.97)	[24]
				Personal exposure, school days childhood	1.01	0.71	0.90	1.44	
				Personal exposure, free days adulthood	0.76 (0.76–1.35)	0.62 (0.45–1.14)	0.78 (0.46–1.77)	0.76 (0.89–2.34)	
				Personal exposure, workdays adulthood	0.97 (0.61–0.95)	0.93 (0.44–0.87)	0.81 (0.47–1.27)	0.91 (0.44–1.31)	
				Occupational exposure, duration years (UV natural)	0.97 (0.73–1.30)	0.63 (0.37–1.04)	0.61 (0.33–1.11)	1.27 (0.89–1.82)	
				Occupational exposure, duration years (UV artificial)	1.14 (0.77–1.70)	0.90 (0.45–1.79)	1.92 (0.85–4.31)	0.90 (0.45–1.78)	
				Sunlamp use	0.69 (0.51–0.93)	0.63 (0.38–1.03)	0.71 (0.41–1.24)	0.99 (0.58–1.70)	
				Ever exposed	B-NHL: 1.1 (1.0–1.3); T-lymphoma: 0.9 (0.7–1.4)	1.0 (0.8–1.2)	1.3 (1.0–1.7)	1.3 (1.1–1.6)	
				Solvents	B-NHL: 1.5 (1.2–1.8); T-lymphoma: 1.7 (0.9–3.0)	1.1 (0.7–1.6)	2.0 (1.3–3.2)	1.5 (1.0–2.3)	
				Cocco et al., EpiLymph	2348	2462	Solvents	High frequency of exposure	
				High exposure intensity	B-NHL: 1.2 (1.0–1.4); T-lymphoma: 1.1 (0.6–1.8)	1.0 (0.8–1.4)	1.3 (0.8–1.9)	1.3 (1.0–1.8)	
				High duration of exposure	B-NHL: 1.3 (1.1–1.6); T-lymphoma: 1.2 (0.7–2.0)	1.3 (0.9–1.7)	1.7 (1.1–2.5)	1.5 (1.1–2.1)	
				High cumulative exposure					

TABLE 1: Continued.

Reference, consortium	Total cases	Total controls	Exposure	Exposure metric	Overall NHL (OR, 95% CI)	Diffuse (OR, 95% CI)	FL (OR, 95% CI)	CLL/SLL (OR, 95% CI)	Reference
				Ever use	1.1 (1.0–1.3) <sup>2</sup>	1.0 (0.9–1.2)	1.3 (1.0–1.6)	1.3 (1.0–1.6)	
				Permanent dye	1.1 (1.0–1.3)	1.0 (0.8–1.2)	1.3 (1.1–1.7)	1.2 (0.9–1.6)	
				Nonpermanent	1.2 (1.0–1.4)	1.1 (0.9–1.4)	1.3 (1.0–1.7)	1.3 (0.9–1.7)	
				Permanent dark	1.1 (0.9–1.3)	0.9 (0.7–1.1)	1.4 (1.1–1.8)	1.3 (0.9–1.7)	
				Permanent light	1.2 (1.0–1.4)	1.0 (0.8–1.3)	1.3 (1.0–1.7)	1.3 (0.9–1.8)	
				Nonpermanent dark	1.2 (1.0–1.5)	1.1 (0.9–1.4)	1.4 (1.0–1.8)	1.3 (0.9–1.8)	
				Nonpermanent light	1.2 (0.9–1.5)	1.1 (0.8–1.6)	1.2 (0.8–1.9)	1.7 (1.0–2.7)	
				<1980, ever	1.3 (1.1–1.4)	1.1 (0.9–1.3)	1.4 (1.1–1.9)	1.5 (1.1–2.0)	
Zhang et al., InterLymph	4461	5799	Hair dye	<1980, permanent dark	1.3 (1.0–1.5)	1.0 (0.8–1.3)	1.4 (1.0–1.9)	1.5 (1.0–2.2)	[26]
				<1980, permanent light	1.3 (1.1–1.6)	1.1 (0.9–1.5)	1.6 (1.2–2.2)	1.5 (1.0–2.2)	
				<1980, nonpermanent dark	1.2 (1.0–1.6)	1.0 (0.7–1.4)	1.2 (0.8–1.8)	1.6 (1.0–2.5)	
				<1980, nonpermanent light	1.3 (0.9–1.9)	1.0 (0.6–1.7)	1.7 (1.0–3.0)	1.9 (1.1–3.6)	
				≥1980, ever	1.1 (0.9–1.2)	1.0 (0.8–1.2)	1.3 (1.0–1.7)	1.1 (0.8–1.5)	
				≥1980, permanent dark	1.0 (0.8–1.2)	0.7 (0.5–1.0)	1.5 (1.1–2.1)	1.1 (0.7–1.8)	
				≥1980, permanent light	1.0 (0.8–1.3)	1.0 (0.7–1.3)	1.2 (0.8–1.8)	0.9 (0.5–1.7)	
				≥1980, nonpermanent dark	1.3 (1.0–1.6)	1.2 (0.9–1.6)	1.7 (1.1–2.4)	1.3 (0.8–2.1)	
				≥1980, nonpermanent light	1.1 (0.7–1.6)	1.1 (0.6–1.9)	1.0 (0.5–2.1)	1.8 (0.9–3.7)	

TABLE 1: Continued.

Reference, consortium	Total cases	Total controls	Exposure	Exposure metric	Overall NHL (OR, 95% CI)	Diffuse (OR, 95% CI)	FL (OR, 95% CI)	CLL/SLL (OR, 95% CI)	Reference
de Sanjosé et al., EpiLymph	2302	2417	Hair dye	Ever use	1.24 (1.01–1.53) <sup>3</sup>	0.96 (0.72–1.27)	1.33 (0.90–1.96)	1.43 (1.01–2.03)	[27]
				Dark dye	1.26 (1.00–1.58)				
				Light dye	1.27 (1.00–1.60)				
				Permanent	1.24 (1.00–1.53)				
				Wash-out (rinse)	1.38 (1.07–1.77)				
				≥18 years use	1.31 (1.02–1.67)				
				≥14 years use, dark	1.50 (1.10–2.05)				
				≥12 uses per year	1.33 (1.02–1.74)				
				Ever, <1980	1.37 (1.09–1.72) <sup>4</sup>				
				Ever, ≥1980	1.11 (0.92–1.34)				
				Dark, <1980	1.33 (1.01–1.75)				
				Dark, ≥1980	1.17 (0.93–1.47)				
				Light, <1980	1.27 (0.96–1.68)				
				Light, ≥1980	1.13 (0.88–1.45)				
				Permanent, <1980	1.27 (1.00–1.62)				
				Permanent, ≥1980	1.14 (0.92–1.41)				
				Wash-out, <1980	1.62 (1.16–2.27)				
Wash-out, ≥1980	1.14 (0.89–1.47)								
>10 years use, <1980	1.34 (1.04–1.71)								
>10 years use, ≥1980	1.24 (0.94–1.64)								

TABLE 1: Continued.

Reference, consortium	Total cases	Total controls	Exposure	Exposure metric	Overall NHL (OR, 95% CI)	Diffuse (OR, 95% CI)	FL (OR, 95% CI)	CLL/SLL (OR, 95% CI)	Reference
Willett et al., InterLymph	10453	16507	Obesity	<18.5 BMI	0.88 (0.71–1.08)	0.90 (0.65–1.24)	0.96 (0.62–1.48)	1.19 (0.69–2.03)	[28]
				25–29.99 BMI	0.95 (0.85–1.07)	0.97 (0.81–1.15)	0.99 (0.84–1.15)	0.96 (0.81–1.15)	
				30–39.99 BMI	0.97 (0.81–1.15)	1.02 (0.82–1.26)	1.07 (0.86–1.33)	1.09 (0.84–1.42)	
				≥40 BMI	0.99 (0.70–1.41)	1.80 (1.23–2.62)	1.34 (0.69–2.63)	1.11 (0.56–2.19)	
				Per 5 mg/k <sup>2</sup> +	0.96 (0.89–1.04)	1.00 (0.90–1.10)			

<sup>1</sup> ORs are for highest versus lowest categories; <sup>2</sup> results shown are for women, no significant effects in men; <sup>3</sup> results are for lymphoma overall and for women, unless indicated; <sup>4</sup> Stratified results for the year hair dye use was started include all study subjects.



The suggested reduced risk of NHL associated with alcohol consumption has varied in some studies by alcoholic beverage type. Studies conducted in Connecticut and among women living in Iowa, for instance, have suggested decreased risks of NHL associated with higher consumption of red wine [33, 44]. Higher consumption of wine has also been inversely associated with NHL in a large population-based case-control study [45], but other studies suggest null or elevated risks [10, 20, 40]. Red wine is a source of a variety of phytochemicals, including resveratrol which has anti-inflammatory properties and may aid in the inhibition of tumor proliferation [46], including for human lymphoma cells specifically [47].

Low-to-moderate alcohol intake may increase immunocompetence by improving humoral and cellular immunity [48], but an association with NHL to date has not yet been firmly established. Additional epidemiological evidence with respect to potential dose-response effects and the relevant quantity of consumption that may be most relevant in terms of risk is needed.

**1.3. Hair Dye.** Several case-control studies that have collected comprehensive exposure data and disease information have indicated that the risk of NHL associated with hair coloring product use may vary by the type of dye products, time period of use, and the duration and intensity of the products used [26, 27, 49, 50]. Further, the risk appears to vary by NHL subtype.

For example, several studies have indicated that an increased risk of lymphoma and/or NHL specifically is apparent in people who started using hair dye before the year 1980, with the highest risks for greater numbers of applications and at least 25 years of use [26, 27, 49]. An increased risk was seen among permanent or dark colored dye users and for the FL and CLL subtypes. These findings have been reported by a large pooled InterLymph study of 4,461 cases and 5,799 controls (Table 1), which found elevated risks of FL (ever use <1980, OR 1.4, 95% CI 1.1–1.9) and CLL/SLL (ever use <1980, OR 1.5, 95% CI 1.1–2.0), but not for other subtypes, primarily in women who started use before 1980 [26]. This observation, and given that patterns of use may vary over time, has underscored the need to comprehensively examine lifetime use of hair dye products, and studies which do so may provide the best assessment of its etiologic role.

Several studies, including prospective cohorts, which investigated this relationship have not reported an increased risk of NHL for hair dye use, but not all of these studies collected detailed information on lifetime hair dye use and the data usually did not allow for comprehensive examination of the risk by exposure features (such as by time period of use, type and color of products, and lifetime duration of use) and subtypes of the disease [38, 51, 52].

Hair dye formulations have long been known to contain mutagenic chemicals [53] including aromatic amines, and formulations prior to 1980 likely contained greater amounts of these chemicals. This is notable given that chromosomal aberrations which may arise from mutagenic exposures are

characteristic of both CLL and FL. While the absence of a consistent risk after 1980 may be reflective of regulatory requirements imposing stricter safety standards on hair dye products, it is also plausible that the induction period for carcinogenicity has not yet manifested to detect elevated risks in more recent users. This would suggest the urgent need for continued studies of more recent users to further characterize this risk.

#### 1.4. Radiation

**1.4.1. UV Radiation.** Several lines of evidence have emerged suggesting that exposure to ultraviolet (UV) radiation may be associated with NHL risk. In addition to parallel increases in incidence of NHL and cutaneous melanoma in the United States since the 1980s, several studies have reported an increased risk of NHL associated with a previous skin cancer, including melanoma, suggesting the possibility of a common risk factor [54–57]. Second, one of the highest incidence rates of NHL in the world is found in Australia, which has high UV exposure and also one of the highest rates of melanoma globally. Moreover, experimental evidence has demonstrated that UV radiation at high levels may suppress the immune response [58] and decrease levels of beta-carotene, which has immunostimulatory properties and may enhance lymphocyte functioning [59, 60]. Finally, a series of ecologic studies have noted positive correlations between NHL incidence and ambient UV radiation exposure [61, 62] though this evidence has been inconsistent [63, 64]. Moreover, increasing sun exposure and residence in southern most latitudes have been associated with an increased risk of NHL in a study of Connecticut women (OR 1.7, 95% CI 1.2–2.4) and in a Swedish cohort (RR 1.21, 95% CI 1.08–1.35), respectively [65, 66]. Similar results were suggested in a recent study from the Nurses' Health Cohort, which found an increased risk of NHL associated with high ambient UV radiation exposure [67].

Conversely, the majority of epidemiological studies have reported a decreased risk of NHL for various measures of sun exposure although differences in exposure assessment and constructs of sun exposure across studies may limit comparative interpretations [68–74]. A significantly reduced risk of NHL or specific B-cell subtypes with increasing recreational exposure to the sun was reported in both InterLymph (OR 0.76, 95% CI 0.63–0.91) and EpiLymph consortia studies (OR for DLBCL, 0.62, 95% CI 0.44–0.87), which had the power to consider multiple NHL subtypes and constructs of exposure (Table 1) [23, 24]. A further protective effect for DLBCL which was marginally significant was reported in the EpiLymph study for greater use of sunlamps (OR 0.63, 95% CI 0.38–1.03) and for longer duration of occupational sun exposure.

The primary hypothesis for a protective effect of sunlight, if real, has focused on the potential role of vitamin D absorbed from sunlight, which has been demonstrated to induce regression of low-grade NHL and possess antiproliferative effects in lymphoma cell lines [75]. There is no consistent evidence, however, suggesting that either dietary

vitamin D or circulating levels of 25-hydroxyvitamin D, the main vitamin D metabolite, is associated with NHL [67, 76–78]. Alternative hypotheses have focused on the role of ultraviolet radiation and its effect on the Th1-Th2 mediated immune response, but further elucidation of this potential mechanism is needed [76, 79]. Importantly, the underlying biological mechanism as well as clarification as to why regions with high UV radiation exposure report higher rates of NHL will require further study in order to support any epidemiological findings of a protective effect for sunlight.

**1.4.2. Ionizing Radiation.** There is limited evidence to suggest that exposure to ionizing radiation is a major risk factor for NHL. Analyses of cancer incidence and mortality within the U.S. radiologic technologists' cohort, which includes followup of more than 100,000 workers, have generally not reported an excess risk of NHL in these workers who are exposed to low-levels of radiation on a chronic basis [80–82]. Further, no consistent risk associated with diagnostic or therapeutic radiation [83–86] or occupational exposures has emerged [87–90].

The survivors of the Nagasaki and Hiroshima bombings, who received both large and acute doses of radiation, also showed no excesses of malignant lymphoma in all cases [91, 92], while excess relative rates of NHL mortality were recently observed for those with the longest time period since exposure, suggesting that any lymphomagenic effect of ionizing radiation may have a long induction period [93]. An elevated risk for mortality and NHL incidence has also been reported in a cohort of British radiologists [94] and in patients receiving radiotherapy for ankylosing spondylitis (RR 1.74, 95% CI 1.23–2.36), respectively [95]. NHL has been observed to occur as a second primary cancer; however, the relative contribution of radiotherapy, chemotherapy, or a general susceptibility to lymphoma has been debated [96]. Given limited evidence and the relatively infrequent exposures to high levels of ionizing radiation in the overall population, any contribution of this exposure to the overall rise in NHL rates is likely to be small.

## 1.5. Diet

**1.5.1. Macronutrients.** The role of dietary intake and lymphomagenesis has been reviewed elsewhere [97]. Briefly, of the macronutrients, a higher intake of dietary fat has been associated with NHL, including total, saturated, and animal fat, and to a lesser extent monounsaturated fat [98–101]. Two large cohort studies in the United States, including one of women in Iowa and the Nurses' Health Cohort, have reported an increased risk of NHL for higher levels of animal fat (RR 2.00, 95% CI 1.21–3.30), saturated fat (RR 1.69, 95% CI 1.07–2.67), monounsaturated fat (RR 1.90, 95% CI 1.18–3.04), and transunsaturated fat (RR 2.4, 95% CI 1.3–4.6) [99, 100]. The association for NHL with protein intake is inconclusive, as null results [98–100] have been reported in addition to two population-based case-control studies in the U.S. which have reported conflicting

findings for total protein [101, 102]. Intake of animal protein has been suggested to influence immune functioning, but epidemiologic evidence has not been consistent with respect to NHL risk [98–101]. There is limited evidence to suggest that higher intake of carbohydrates is associated with NHL, although a positive association has been observed for B-cell lymphoma specifically (OR 1.4, 95% CI 1.0–2.0) as well as for higher intake of dessert foods for overall NHL [98, 101].

**1.5.2. Micronutrients.** Antioxidants have a recognized benefit to the immune system including protection from the effects of free radicals and oxidative stress [103], and deficiencies in specific nutrients involved in one-carbon metabolism, in particular, may lead to disruption in DNA repair processes [104]. However, a series of epidemiological studies including prospective cohorts have not suggested consistent protective effects for NHL and intake of specific vitamins, or for multivitamin use [99, 101, 105–108]. It is possible that any protective effect of vitamin use may be subtype-specific, as a decreased risk of FL was observed with greater intake of dietary vitamin C (RR 0.55, 95% CI 0.30–1.00) in a large prospective study of Iowa women [109].

Associations with micronutrients involved in one-carbon metabolism have been shown, but have differed with respect to the specific nutrient. Whereas dietary B<sub>12</sub> was inversely associated with NHL risk in male smokers enrolled in the Alpha-Tocopherol Beta-Carotene prevention trial (HR 0.61, 95% CI 0.37–1.00) [110], this finding was not confirmed in three case-control studies each of which found protective associations for higher intake of either vitamin B<sub>6</sub>, methionine, and folate either overall or in specific subgroups (i.e., alcohol abstainers) [111–113]. It is likely that the risk associated with these micronutrients may be modified by other exposures, including consumption of alcohol [113], or by genetic susceptibility and/or gene-environment interactions involving one-carbon metabolism genes [114]. Relative to vitamin intake, the association between other micronutrients and NHL has received less attention, although evidence from the Iowa Women's Health Cohort has suggested a potential protective effect of other antioxidants including dietary manganese, proanthocyanidins, and alpha-carotene [109].

**1.5.3. Specific Food Items.** Overall, few dietary components have emerged as strong and consistent risk factors for NHL, although some suggestive associations have been identified and reviewed [97]. Briefly, some epidemiological studies have inconsistently reported an elevated risk of NHL for red meat intake, or specific types of meat, as well as for overall or specific types of dairy food, but these findings have not been consistent [97]. Depending on the preparatory method, red meat specifically is a source of several mutagenic compounds and, in the case of processed meat, of *N*-nitroso compounds. However, some studies which have considered associations with well-done meat and levels of specific mutagens have generally not supported a clear risk, but some evidence has indicated that intake of broiled meat may be associated with

a greater risk of NHL compared with other preparatory methods [100, 102].

Conversely, the strongest evidence for a decreased risk of NHL has been higher intake of some vegetables and fruits, particularly for cruciferous vegetables [97]. Several large cohorts, including one of over 35,000 women in Iowa and among 88,410 subjects enrolled in the Nurses' Health Cohort, have reported a decreased risk of NHL associated with the highest intake of all fruits and vegetables (RR 0.69, 95% CI 0.51–0.94) and greater consumption of fruits and cruciferous vegetables [106, 109]. These findings are biologically plausible given that cruciferous vegetables and some fruits are rich sources of antioxidants and folate, and constituents of cruciferous vegetables may aid in the metabolism of carcinogens via interaction with drug metabolizing enzymes [115].

*1.6. Occupation.* Conclusions from studies examining the role of occupational groups and NHL risk are generally limited by the small number of individuals in specific occupations as well as a general inability to collect individual level data on working patterns and potential exposure profiles. However, these studies can be useful in terms of gaining insight into potential etiological factors, particularly for chemical exposures.

The strongest evidence for an elevated risk of NHL for a specific occupational group is for farmers or agricultural workers [90, 116–121], suggesting a potential chemical or viral etiology. These associations have been subsequently observed in several, but not all [122] meta-analyses, with relatively modest elevated risks [116, 123, 124]. Aside from chemical exposures, some evidence has indicated that contact with animals and/or animal breeding may contribute to NHL risk or mortality [116, 119, 125, 126]. In a meta-analysis conducted by Boffetta and de Vocht, associations with NHL for farming were predominately limited to studies which examined animal breeding, suggesting a potential importance of viral exposures [116].

Both primary and secondary teachers have been reported to have elevated risks of NHL, which is thought to be due primarily to exposure to childhood infections [116, 118, 127]. However, effects for other occupational groups have been largely inconsistent. Inconsistently elevated risks have been reported for metal workers [117, 118, 128, 129], meat or food production workers [117, 130–132], mechanics/and or truck drivers [117, 118, 130], wood workers [116, 129], communication workers [118, 133, 134], workers in the printing industry [116, 118] as well as a variety of workers in the service industry or in white-collar professions [128, 133–136].

The meta-analysis conducted by Boffetta and de Vocht examined seven occupational groups that have emerged from epidemiological studies as potentially related to NHL risk [116]. In addition to farming and teaching, livestock workers (RR 1.31, 95% CI 1.08–1.50), printers (RR 1.86, 95% CI 1.37–2.52), and wood workers (RR 1.15, 95% CI 1.00–1.31) all had significantly increased associations with NHL. Further, in a recent examination of occupation in the European Prospective Investigation into Cancer and

Nutrition cohort, butchers and car repair workers were the only occupational groups that showed an increased risk of NHL [130]. Given the lack of established environmental risk factors for NHL, the implications of these findings are not yet clear, though exposures to solvents or other chemicals may be implicated.

### *1.7. Chemical Exposures*

*1.7.1. Solvents.* Results from several epidemiological studies have indicated that exposure to solvents may increase overall NHL risk or for specific subtypes [25, 131, 137–145]. A large pooled case-control study in Europe has reported elevated risks for FL (OR 1.3, 95% CI 1.0–1.7) and CLL (OR 1.3, 95% CI 1.1–1.6; Table 1) for ever solvent exposure with risks varying for specific chemicals [25]. Risk estimates for NHL and overall solvent exposure are likely to mask chemical specific associations, given that some but not all solvents may be associated with NHL.

Two of the most widely studied chemicals with respect to NHL risk have been benzene and trichloroethylene (TCE), which have a number of industrial uses and applications. Overall, some suggestive evidence has emerged for an association with NHL for benzene exposure based on animal studies, case-control studies of benzene exposure, and some occupational cohorts, but the evidence is inconsistent and several meta-analyses have reported conflicting findings [137, 146–149]. Findings from the Pliofilm cohort of rubber workers, which suggested a significantly elevated association with leukemia mortality and has played a role in the development of occupational benzene exposure standards, did not report an association with NHL mortality (SMR = 0.96, 95% CI 0.31–2.25) [150]. A common limitation of occupational studies of solvent exposure more generally and benzene in particular is the potential for exposure misclassification, which may arise from reliance on self-reported work histories or assigning levels of exposure based solely on job title. Furthermore, it is likely that any effect of benzene exposure on NHL risk could be subtype-specific, which may not be apparent in analyses which consider NHL overall. Some analyses have supported these possibilities, suggesting a significantly elevated risk of NHL after taking into account studies with likely exposure misclassification as well as for the CLL subtype specifically in an analysis of occupational cohorts which evaluated study quality [151, 152].

Similar methodologic issues have limited firm conclusions regarding the association between TCE exposure and NHL. Specifically, occupational cohorts that have examined this association have varied with respect to the quality of the exposure assessment with methods ranging from the use of urinary biomarkers of exposure and job exposure matrices (JEMs) to evaluations based solely on job title. Further, the majority of studies have not considered specific NHL subtypes, have had a relatively small number of exposed cases, and have used different NHL classification systems [153]. One of the larger occupational cohort studies which included 40,049 blue-collar workers (96 NHL cases) in Denmark reported a 50% elevated risk of NHL in a

subcohort of workers with the highest assumed exposures to TCE [154], while other cohorts including those which utilized urinary biomarkers of exposure have not consistently reported significantly elevated associations [155–158]. Meta-analyses that have stratified studies based on the quality of the exposure assessment or overall study quality provided some indication for an elevated risk of NHL in studies with more extensive exposure assessment, but clear dose-response trends were lacking and there was no assessment of subtype-specific associations [159, 160]. These studies which suggested a positive association tended to have more detailed exposure assessments such as having a subcohort of workers who were more likely to be exposed or utilized biomarkers or JEMs, compared to less specific studies which relied on occupation or lacked verification of TCE exposure specifically [159, 160]. More recently, findings from a NCI-Surveillance, Epidemiology and End Results case-control study which had detailed exposure assessment suggested a 2.5-fold increased risk of NHL in workers with the highest category of average weekly TCE exposure as well as for the highest cumulative exposure, and elevated associations were seen for both FL and CLL/SLL [161]. This study utilized job-specific exposure modules and evaluated multiple metrics of TCE exposure including duration, average weekly and cumulative exposure levels, in addition to considering the probability of exposure.

Recent molecular epidemiology studies of TCE and benzene exposures have suggested that each of these chemicals results in hematotoxic and/or immunotoxic effects that may be relevant to lymphomagenesis, indicating that an association with NHL may be biologically plausible. Specifically, declines in peripheral blood cell counts and lymphocyte subsets, including CD4<sup>+</sup> T cells, have been observed in workers exposed to both benzene and TCE, indicating the ability of these chemicals to result in immunosuppressive effects [162, 163]. Further, TCE exposure has been demonstrated to result in alterations in several immune parameters, including blood cytokine levels and markers of B-cell activation, and has been previously associated with the development of some autoimmune conditions [162, 164].

**1.7.2. Pesticides.** Epidemiological studies of pesticide exposure and NHL risk have generally focused on specific classes of pesticides, including organochlorine pesticides (OCPs), organophosphates (OPs), and carbamate insecticides. Some OCPs have been demonstrated to be genotoxic in animal and *in vitro* models [165, 166], but the epidemiological results for specific OCPs have been mixed. Specifically, whereas positive associations with NHL for use of DDT [167–169], oxychlordane [170, 171], and *p,p'*-DDE levels in serum and adipose tissue have been reported [170, 171], others have not observed an association with NHL for DDT or other OCPs [172–175]. An analysis of serum *p,p'*-DDE levels using data from three large cohorts provided some evidence for a positive association with NHL, but there were no clear dose-response trends and results were attenuated after adjustment for levels of PCBs [176].

These differences across studies may be partially explained by the use of different biologic specimens, as adipose tissue is thought to better reflect cumulative exposure levels than serum, particularly with respect to DDT and its metabolites. A recent Danish cohort study, for instance, found a positive association for NHL with increasing adipose tissue levels of DDT (IRR 1.35, 95% 1.10–1.66) in prediagnostic samples [177]. Another limitation inherent to studies of pesticide exposure is the potential for confounding by coexposures due to use of multiple chemicals. De Roos and colleagues analyzed a series of 47 pesticides simultaneously in a pooled study of 650 cases and 1933 controls using data from three case-control studies in the United States that assessed pesticide exposure using direct subject interviews. Among the OCPs, elevated but nonsignificant associations with NHL were reported for chlordane and dieldrin, but not for DDT or other OCPs [178].

Similarly inconsistent findings for NHL risk have been observed for other classes of pesticides. Experimental evidence has suggested that some OPs and carbamate insecticides may be genotoxic and potentially immunotoxic, and in the case of OPs may induce chromosomal damage at domestically sprayed levels [179, 180]. Evidence for an association with NHL for OP insecticides has come from a pooled study of 748 cases and 2,236 population-based controls (OR 1.5, 95% CI 1.2–1.9), although the highest risks were associated with cases who had proxy interviews [181], as well as in two population-based case-control studies [167, 168] where use of any OP insecticide was positively associated with NHL risk. Moreover, the pooled case-control study conducted by De Roos and colleagues has reported an elevated risk of NHL for the OP insecticides coumaphos (OR 2.4, 95% CI 1.0–2.58), diazinon (OR 1.9, 95% CI 1.1–3.6), and fonofos (OR 1.8, 95% CI 0.9–3.5) [178].

With respect to carbamate exposure, an elevated risk of NHL in farmers who used carbamate herbicides (OR 1.5, 95% CI 1.1–2.3) or insecticides (OR 1.6, 95% CI 1.2–2.2) was reported in a large pooled study, with the strongest evidence for carbaryl [182]. This finding is consistent with two studies in Canada and Italy, each of which reported about a twofold increased risk of NHL for carbaryl exposure [168, 183]. However, there was no clear association among over 21,000 subjects in the Agricultural Health Study [184]. Carbaryl has shown little genotoxic potential in humans; however, immunotoxic effects have been demonstrated in animal models [185].

Use of phenoxyacetic acid (PCA) and triazine herbicides has each been studied with respect to NHL risk, with inconsistent findings. In De Roos et al.'s evaluation of 47 pesticides, no association with individual PCA herbicides was observed, but an elevated risk of NHL for use of the triazine herbicide atrazine (OR 1.6, 95% CI 1.1–2.5) was reported [178]. Further, an elevated risk of NHL for exposure to 2,4-D and/or 2-methyl-4-chlorophenoxyacetic acid (MCPA), two PCA herbicides, has been observed [168, 186–188], including in a Swedish case-control study of 910 cases and 1,016 controls where an elevated risk of NHL for use of MCPA was reported (OR 2.81, 95% CI 1.27–6.22) in addition to the herbicide glyphosate (OR 2.02, 95% CI

1.10–3.71) [187]. However, the association with NHL for use of atrazine was not confirmed in the Agricultural Health Study nor in two large case-control studies [167, 183, 189, 190].

Overall, studies of pesticide use are generally limited by small sample sizes, the presence of multiple coexposures, lack of detailed information on exposure histories, and in some instances the use of a proxy for exposure assessment. These methodological challenges have likely contributed to the overall inconsistent findings concerning pesticide use and NHL risk, but reports of an elevated risk for some pesticide classes suggest that an association cannot be ruled out.

**1.7.3. Polychlorinated Biphenyls (PCBs).** Several studies have evaluated the association between total PCB exposure and NHL, as well as for specific congeners, and these associations have been reviewed elsewhere [191]. PCBs were used extensively in industry starting in the 1930s and continuing through the 1970s, after which their use was banned by the U.S. Environmental Protection Agency. However, the relative stability and bioaccumulation of these compounds, as well as the immunotoxic potential of some PCB congeners, has raised some concern about lasting health effects [191]. Currently, PCBs are classified as probable carcinogens (group 2A) by the International Agency for Research on Cancer.

Two nested case-control studies, including one which pooled data from three existing cohorts, have reported an increased risk of NHL associated with total serum or plasma levels of PCBs, or exposure-response trends for the congeners 118, 138, and 153 in all three cohorts [176, 192]. Further, a case-control study of 100 cases and 100 controls in the United States which evaluated NHL risk in relation to specific PCB congeners reported an elevated risk for PCBs 156 (OR 2.70, 95% CI 0.97–7.50), 180 (OR 3.50, 95% CI 1.34–9.15), and 194 (OR 3.52, 95% CI 1.30–9.52) [193]. However, a nested case-control study using data from the Nurses' Health Cohort, as well as two other case-control studies and a Danish cohort study, reported no association for total PCB exposure or for individual congeners in blood or adipose tissue samples [170, 172, 174, 177].

While several of the specific PCB congeners that have been reported to increase NHL risk are potentially immunotoxic [194], thus supporting a potential etiologic role, correlation between individual congeners and with some organochlorine pesticides as well as limited evidence concerning the most relevant time period of exposure necessitates further followup of these findings.

## 2. Medical Risk Factors

In addition to immune deficiency, and evidence suggesting that a family history of a hematologic cancer is positively associated with NHL risk [195–197], several other medical risk factors have been identified for NHL. Here, we provide a general and brief overview of these conditions that have been implicated in NHL risk.

**2.1. Infectious Agents.** Infectious causes of NHL have been extensively reviewed elsewhere [198]. Infection with HIV is the most well-characterized infectious risk factor for NHL, with elevated risks nearing four-hundred fold for certain subtypes although rates of AIDS-related NHL have declined with the emergence of antiretroviral therapy [199, 200]. AIDS-related NHL results from systemic immunosuppression and chronic B-cell stimulation, with the majority being high-grade tumors and involving extra nodal sites [201]. AIDS-NHL are pathologically heterogeneous and include high-grade B cell lymphomas that also manifest in HIV negative patients, and subtypes that are more specific to HIV, including primary effusion lymphoma and plasmablastic lymphoma of the oral cavity [202]. Levels of B-cell stimulatory biomarkers suggestive of immune activation are elevated preceding a systemic AIDS-NHL diagnosis, indicating that chronic stimulation of B cells associated with HIV/AIDS may contribute to AIDS-related tumors [203]. Overall, current CD4<sup>+</sup> T-cell count as well as the duration of time spent with a high viral load are important predictors of AIDS-NHL risk [204].

Other than HIV, infection with Epstein-Barr virus (EBV) is associated with NHL in the context of immunosuppression resulting in proliferation of transformed B cells normally controlled by T-cell-mediated immunity [205]. About half of DLBCL cases in the context of HIV infection are EBV positive, whereas about 30% of Burkitt's lymphoma are EBV associated [206]. In immunocompetent hosts, EBV is associated with rarer NK/T cell subtypes, and nearly all cases (>95%) of endemic Burkitt's lymphoma in Northern Africa are EBV positive [207]. Recently, a large InterLymph analysis with 12,585 NHL cases and 15,416 controls reported an excess risk of NHL associated with a self-reported history of infectious mononucleosis (OR 1.26, 95% CI 1.01–1.57), of which EBV is a major cause, and particularly for CLL and T-cell NHL, but this history was based on self-report and there was significant heterogeneity across studies [208]. A similar increase in risk for NHL, B-cell lymphoma, and CLL/SLL was reported for a self-reported history of infectious mononucleosis among 2,362 lymphoma cases and 2,458 controls in the EpiLymph study [209].

Moreover, infection with human T-lymphotropic virus 1 (HTLV-1) and human herpesvirus-8 (HHV-8) has been associated with rare NHL subtypes. Specifically, a lifetime cumulative risk of developing adult T-cell leukemia/lymphoma (ATL) on the order of 2–6% has been observed among HTLV-1 carriers in Japan [210], while infection with HHV-8 is associated with Kaposi's sarcoma as well as body cavity lymphoma and primary effusion lymphomas in the setting of immunodeficiency [211, 212].

Increasing evidence has suggested that hepatitis C infection (HCV) may increase the risk of NHL [213–215], but a causal relationship is not conclusive [216, 217], and some evidence also indicates a potential etiologic role of hepatitis B [209, 213]. An elevated risk of NHL as well as for several subtypes associated with HCV was observed in a large population-based SEER study of 61,464 cases of hematopoietic malignancies (OR 1.35, 95% CI 1.06–1.73), as well as in a meta-analysis of 18 studies which included

$\geq 100$  cases (RR 2.5, 95% CI 2.1–3.1), with consistent risks for B- and T-cell subtypes [218, 219]. Further, a large pooled InterLymph study including 4,784 cases and 6,269 controls found an elevated risk of primarily B-cell subtypes, including DLBCL and marginal zone lymphoma, associated with HCV infection [220]. Notably, complete or partial remission of lymphoproliferative disorder has been observed following antiviral therapy for HCV in up to 75% of cases, which provides some plausibility for the positive epidemiologic findings [221].

*H. pylori* infection is a causative agent of gastric MALT lymphoma, an indolent tumor arising from B cells and affecting the gastric mucosa. Chronic inflammation due to infection results in the colonization and proliferation of lymphocytes in the gastric mucosa; however, only a small percentage of *H. pylori* positive individuals develop MALT lymphoma [222]. *H. pylori* infection has been reported to increase the risk of gastric MALT lymphoma specifically by about sixfold [223]. A high percentage of patients with this rare subtype, up to 98%, are found to be infected with *H. pylori*, and eradication of infection leads to complete remission of early-stage lymphoma in up to 80% of cases [224]. As reported in a population-based study in Italy, the incidence of gastric MALT lymphomas may be declining particularly in developed countries where the prevalence of *H. pylori* infection is decreasing [225].

Some evidence from case-series data has further indicated that infection with certain bacterial agents is associated with specific subtypes of NHL. Infection with the bacteria *Campylobacter jejuni* and *Chlamydia psittaci*, which can infect humans via contact with animal feces and contact with birds, respectively, and the vector borne agent *Borrelia burgdorferi* has been associated with rare MALT lymphomas, including immunoproliferative small intestinal disease, ocular adnexal lymphoma, and cutaneous MALT lymphoma, respectively [226]. However, these agents are only variably found in the respective lesions and the magnitude of the risks associated with these exposures are not well defined [226].

**2.2. Obesity.** Increasing attention has been given to the potential relationship between cancer risk and obesity, given that obesity is associated with chronic, low-grade inflammation, and specific immune alterations including changes in cytokine profiles that may alter the immune response [227]. Moreover, the obesity-associated hormone leptin has been demonstrated to influence proinflammatory responses as well as have specific effects on helper T-lymphocyte function [227].

Some evidence has emerged suggesting that obesity or higher BMI may increase the risk of NHL, particularly for specific histological subtypes including DLBCL. DLBCL was positively associated with severe obesity (OR 1.80, 95% CI 1.24–2.62) in a pooled InterLymph analysis that included 10,453 cases and 16,507 controls (Table 1), and recent pooled and meta-analyses have indicated a marginally elevated association for NHL and DLBCL with either obesity (BMI  $\geq 30$ ) or per 5 kg/m<sup>2</sup> increase in BMI [28, 228, 229]. Prospective studies have generally supported these findings,

with evidence that higher BMI at both younger ages and during midlife may be relevant to NHL risk [20, 230, 231].

**2.3. Autoimmune Disease and Allergy.** Several epidemiologic studies that have examined the role of autoimmunity have reported an increased risk of NHL for specific conditions, particularly for Sjogren's syndrome [232–240], systemic lupus erythematosus [232–234, 241, 242], celiac disease [234, 243–245], and rheumatoid arthritis [239, 246, 247]. Moreover, positive associations with overall NHL or for specific subtypes have been reported less consistently for other inflammatory disorders including psoriasis, inflammatory bowel disease particularly for Crohn's disease, and Hashimoto's thyroiditis as reviewed elsewhere [248].

There is also evidence suggesting associations with specific NHL subtypes for some of these disorders, including enteropathy-associated T-cell lymphoma and celiac disease [249], marginal zone lymphoma of the parotid gland and Sjogren's syndrome [233], and MALT lymphoma of the thyroid gland associated with Hashimoto's thyroiditis from case-series data [250]. Whereas case reports and some observational studies suggest that treatment with antirheumatic drugs and some anti-inflammatory treatments, such as tumor necrosis factor antagonists, increase NHL risk, these associations are inconclusive given possible confounding by indication and the conflicting findings across studies [248]. Given the low prevalence of some autoimmune and atopic conditions in the general population, and the possibility that some but not all NHL subtypes may be associated with these conditions, large pooling studies may offer important insight into these associations.

Findings from InterLymph in a study of 12,984 cases and 16,441 controls have suggested an increased risk of overall NHL (OR 6.56, 95% CI 3.10–13.9) and specifically DLBCL and FL for patients with Sjogren's syndrome as well as an association with overall NHL (OR 2.69, 95% CI 1.68–4.30), DLBCL, and marginal zone lymphoma for systemic lupus erythematosus [233]. This same study reported positive findings for T-cell lymphoma associated with celiac disease and psoriasis. Conversely, a pooled InterLymph study including 13,535 cases and 16,388 controls has reported a modest reduction in risk of NHL for a history of any allergy (OR 0.80, 95% CI 0.68–0.94), particularly for B-cell subtypes, and two population-based case-control studies in Australia and the United States found a reduced risk of NHL associated with some allergic conditions, including hay fever, eczema, and/or food allergies specifically [251–253]. Findings from an EpiLymph case-control study with 2,480 cases of lymphoma and 2,540 controls have similarly suggested a reduced risk of overall NHL and specifically B-NHL for history of food allergies [254]. These collective findings are suggestive of a reduced risk of NHL associated with a Th2-dominated immune response, whereas chronic immune stimulation may increase risk.

**2.4. Family Size.** The relationship between NHL and atopy and viral infections may substantiate the "hygiene hypothesis," suggesting that delayed infection during childhood

may contribute to an over-activation of the Th2 mediated immune response, in turn promoting the development of atopy. Some epidemiological evidence suggests that children with fewer siblings or delayed first infection may have a reduced risk of NHL, and that household crowding and having a greater number of siblings increases risk, but not all studies have observed this association [209, 252, 255–257]. Further, about a twofold increased risk of DLBCL specifically was found to be associated with being the last born in those with at least one sibling [1]. However, a large InterLymph study with 13,535 NHL cases and 16,427 controls found limited evidence for an association with overall NHL for either birth order or sibship size, though positive associations were reported for some subtypes [258]. Number of older siblings was also not associated with NHL in a large population based study using data from the Swedish-Family Cancer Database [259].

**2.5. Reproductive Factors.** Several epidemiological studies have evaluated the association between reproductive factors and NHL, including for age at menarche, age at first birth, and use of oral contraceptives (OCs) and/or hormone replacement therapy (HRT). Collectively, these studies have not been suggestive of a major role of reproductive factors in NHL risk with respect to age at menopause [260–263] or menarche [260, 262, 264–266], although an elevated risk of NHL and particularly for the diffuse subtype was reported for age at menarche  $\geq 15$  years in a case-control study of Connecticut women [261]. However, other reproductive factors have been inconsistently associated with overall NHL or particular subtypes. Findings from an EpiLymph case-control study which included 847 cases of B- or T-cell neoplasms and 1,141 frequency-matched controls suggested a reduced risk of both mature B- (OR per 1 child increase = 0.87, 95% CI 0.81–0.93) and T-cell (OR per 1 child increase = 0.71, 95% CI 0.54–0.94) lymphoma associated with increasing parity, including for CLL/SLL and DLBCL [267]. A similar significant NHL risk reduction for the diffuse subtype has been observed for a higher number of pregnancies in two population-based case-control studies conducted in Connecticut and San Francisco [261, 265], while the association has been less consistent in cohort studies [260, 268, 269]. There is additionally limited evidence suggesting an inverse association with NHL for either age at first full-term pregnancy or for breastfeeding [260, 269], but other studies have not observed these associations [261, 268, 270].

Exposure to exogenous hormones through the use of OCs and HRT have also been investigated in relation to overall NHL risk and the findings have been equivocal, with generally either null findings [261, 262, 266] or an associated protective effect for NHL associated with OC use or menopausal hormone therapy [263, 265, 270]. Recent examination of contraceptive use in the large EpiLymph case-control study found no significant association with B-cell neoplasms for ever use of contraceptives, but women who used contraceptives for  $< 5$  years had significantly elevated risks of DLBCL and FL compared with never users

[267]. Most recently, reproductive factors and hormonal contraception use have been evaluated by InterLymph in a study of 4,263 NHL cases and 5,971 controls [266]. Whereas there was no evidence for an association for overall NHL or DLBCL with reproductive factors or hormonal contraception use, a decreased risk of FL was observed for increasing number of pregnancies (OR = 0.88, 95% CI 0.81–0.96), while ever use of hormonal contraception increased the risk of FL. The increased risk was particularly apparent in those who used hormonal contraceptives  $\leq 5$  years and who were  $> 22$  years of age at first use.

**2.6. Blood Transfusion and Organ Transplantation.** Three cohort studies have suggested an increased risk of NHL, particularly of low grade, associated with a previous history of having received a blood transfusion [271–273]; however, most case-control studies with the exception of one conducted in Sweden have reported no increase in risk [274–278]. In the Swedish case-control study, an overall increased risk of NHL was associated with having had a blood transfusion, particularly in the 6–15-year period before diagnosis (OR 2.83, 95% CI 1.60–4.99) with the highest risks observed for nodal B-CLL and high-grade extranodal lymphomas [279].

Recently, the first meta-analysis of this association, including 14 studies, found about a 20% increase in risk of NHL overall and CLL/SLL specifically for blood transfusions, though the overall association was limited to the included cohort studies [280]. Blood transfusions result in a decline in cell-mediated immunity, but a number of methodological challenges in these studies including potential biases and limited assessment of NHL subtypes have precluded firm conclusions regarding this relationship [281, 282].

Previous organ transplantation, including heart, kidney, and liver transplants, is associated with a subsequent increased risk of NHL and/or lymphoproliferative disease, with the highest risks generally observed during the first year aftertransplant [283–288]. Risks arise primarily due to the use of post-transplant immunosuppressive medications, and evidence suggests that risks differ according to the specific organ transplanted [283, 287, 288].

**2.7. Medications.** There is some evidence indicating an association with NHL for use of medications including for statins, NSAIDs, antibiotics, and antidepressants. The strongest evidence for an association with statin use has come from an EpiLymph case-control study which included 2,362 cases of B- and T-cell lymphoma and 2,206 controls and collected information on medication use through personal interviews [289]. Ever use of statins was associated with about a 40% reduced risk of lymphoma (OR 0.61, 95% CI 0.45–0.84), but there was limited evidence of a dose-response effect according to duration of use. A reduced risk of NHL for ever use of statins has similarly been reported in a population based case-control study in Connecticut [290], in a cohort of HIV-positive individuals [291], as well as in other cohorts [292], but not in all studies [293]. Experimental studies have suggested that statins may possess anti-inflammatory

properties and evidence suggests that these agents may inhibit tumor cell growth and metastases [294].

Some studies have indicated that greater use of NSAIDs [295, 296] or antibiotics [297–299] may result in an increased risk of NHL, but it is generally unclear as to what extent the underlying medical conditions for which these medications were taken may have contributed to the observed risk. Notably, a meta-analysis of nine epidemiologic studies which included a total 5,794 NHL cases and 34,707 controls for the NSAID analysis found no elevated risk of NHL for NSAID use or for use of corticosteroids [300], but this analysis did not consider duration of exposure or the possibility of an association in distinct subgroups. Whereas previous studies have suggested an increased risk of NHL associated with NSAID use overall or for specific NSAID medications specifically in women [296, 301] or for longer duration of use [296, 299], there is conflicting evidence from two population-based case-control studies in the United States which did not observe a significantly elevated risk of NHL for NSAID use [302, 303].

The associations between antibiotic use and NHL risk have been examined in population-based case-control studies which have evaluated antibiotic use either through direct interviews or utilizing pharmacy databases [298, 299, 304, 305] as well as in a recent nationwide register-based cohort study in Denmark [297]. Greater use of antibiotics has been reported to increase NHL risk in two of these case-control studies, both of which utilized personal interviews [298, 299], but no increase in risk was observed for NHL; however, in two additional population-based case-control studies one of which utilized pharmacy records for the antibiotic exposure assessment [304, 305]. The cohort study which included the entire adult population of Denmark aged 15 or older and utilized a national prescription registry in addition to evaluating multiple NHL subtypes found a marginally elevated risk of overall NHL for ever use of antibiotics (RR 1.13, 95% CI 1.08–1.19), with the highest risk estimates reported for anaplastic large T-cell lymphoma, CLL/SLL, and mantle cell lymphoma [297]. Overall, a limitation in the assessment of these studies which have observed elevated associations is the potential for confounding by indication and exposure misclassification in studies that have relied on personal interviews.

Evidence for an association with NHL for use of antidepressants is currently limited, but results from a population-based cohort study in Denmark have indicated an elevated association for NHL for higher use categories of tricyclic antidepressants [306, 307]. These studies have utilized pharmacy data for the exposure assessment but have provided limited assessment of subtype specific associations. Antidepressant use, including tricyclic antidepressants, was not significantly associated with NHL in a previous cohort of HIV-positive individuals or in a population-based case-control study in Canada which evaluated antidepressant use via self-administered questionnaires [308, 309].

**2.8. Genetics.** The observed increasing trend in NHL incidence is likely the result of environmental and/or lifestyle

factors, but an important consideration is that genetic factors may modify associations between environmental risk factors and NHL, and this may contribute at least in part to the inconsistencies between studies. Indeed, studies have suggested that polymorphisms in Th1/Th2 pathway genes modify the association between BMI and NHL [310], that NHL risk associated with hair dye use is modified by variation in *NAT1* and *NAT2* genes [311], and that the relationship between organochlorine exposure and NHL is influenced by variants in *IFNG* and interleukin genes [312]. Similar examples of gene-environment interactions involving NHL risk have included fruit and vegetable intake (*NOS1*) [313], solvent exposure and metabolic genes [314], and smoking (*NAT2*) [315], suggesting the importance of considering genetic influences when evaluating NHL risk in relation to environmental and lifestyle factors. However, this evidence for gene-environment interactions in relation to NHL risk is based on the results of single studies with limited power to evaluate the associations, particularly for specific NHL subtypes.

Numerous candidate gene studies of overall NHL and for specific NHL subtypes have been conducted, and these findings have been extensively reviewed elsewhere [316]. Overall, genetic variation in several pathways have been implicated in NHL risk, including in one-carbon metabolism, cytokine, innate immunity, oxidative stress, and apoptotic and DNA repair pathways as well as in the HLA region [316]. Pooled InterLymph analyses in particular have suggested an elevated risk of NHL and particularly DLBCL associated with the *TNF-308G* → *A* and *IL10-3575T* → *A* variants [317] and with the *LTA 252A* → *G/TNF-308G* → *A* haplotype for DLBCL [318]. Over the past several years, ongoing genome-wide association studies (GWAS) have been conducted for common NHL subtypes and the results of these studies have provided additional insight into the genetic basis of this disease [319–323]. Specifically, GWAS of FL have suggested a protective effect associated with rs6457327 on 6p21.33, which contains the HLA region and is located near psoriasis susceptibility region 1, and associations with rs10484561 and rs7755224 on 6p21.32 [320, 321]. Recently, a third GWAS of FL identified an additional variant on 6p21.32, rs2647012, associated with a reduced risk of FL and located 962 bp away from rs10484561, which was also associated with DLBCL [319]. These findings suggest the potential importance of the HLA class II region in NHL susceptibility and for FL in particular.

GWAS of CLL/SLL have identified several risk loci for this subtype, with the strongest associations observed for rs872071 on 6p25.3 which encompasses *IRF4*, and rs2456449 on 8q24.21 [322, 323]. *IRF4* regulates lymphoid development and proliferation, while the 8q24 genomic region has been implicated as a susceptibility locus for multiple cancer types [322, 323]. The 6p21.3 locus, which harbors HLA class II genes, has also emerged as a potential susceptibility locus associated with familial CLL [324]. Notably, several of the variants that have emerged from the GWAS of CLL/SLL have been subsequently validated in other case-control studies, including for variants at 15q25.2 (rs783540), 18q21.1 (rs1036935), 2q37.1 (rs13397985),



6p25.3 (rs872071), 11q24.1 (rs735665), 15q23 (rs7176508), and 19q13.32 (rs11083846) [325, 326]. Ongoing and future GWAS should clarify the many putative associations that have been previously reported in candidate gene studies.

### 3. Conclusion

Extensive epidemiological investigation has been devoted to postulated lifestyle and environmental risk factors that may explain the rise in NHL incidence over the past several decades. While some etiologic clues have emerged, patterns of NHL incidence remain largely unexplained and cannot be solely attributed to changes in rates of HIV infection. Whereas severe immunosuppression, resulting from immunodeficiency syndromes and postorgan transplantation, and some infectious agents are established risk factors for NHL or specific subtypes, the contribution of most environmental exposures and lifestyle or dietary components remain unclear.

Specifically, positive associations with NHL have been reported for the use of hair dye before 1980, diets high in fat and some dairy products, higher BMI, smoking for FL, as well as exposure to certain solvents and chemicals. However, the inconsistency in some of these associations across studies precludes their consideration as established NHL risk factors, and the associated risk estimates have generally been only marginally elevated. Moving forward, increased emphasis on potential etiologic differences for NHL subtypes, further examination of underlying mechanisms to establish biologic plausibility, exposure assessments which consider multiple metrics of exposure, and further consideration of potential gene-environment interactions will be critical in clarifying the role of putative environmental and lifestyle risk factors for NHL.

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