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Epidemiology and Etiology of Diffuse Large B-Cell Lymphoma (DLBCL)

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Abstract

As the most common non-Hodgkin lymphoma subtype, diffuse large B-cell lymphoma (DLBCL) incidence patterns generally parallel that for NHL overall. Globally, DLBCL accounts for a third of all NHLs, ranging between 20%−50% by country. Based on U.S. cancer registry data, age-standardized incidence rate for DLBCL was 7.2 per 100,000. DLBCL incidence rises with age and is generally higher in males than females; in the U.S., incidence is highest among non-Hispanic whites (9.2 per 100,000). Like NHL incidence, DLBCL incidence rose in the first half of the 20th century but has largely plateaued. However, there is some evidence that incidence rates are rising in areas of historically low rates, such as Asia; there are also estimates for rising DLBCL incidence in the near future due to the changing demographics in developed countries whose aging population is growing. Established risk factors for DLBCL include those that result in severe immune deficiency such as HIV/AIDS, inherited immunodeficiency syndromes, and organ transplant recipients. Factors that lead to chronic immune dysregulations are also established risk factors, and include a number of autoimmune conditions (e.g., Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis), viral infections (e.g., HIV, KSHV/HHV8, HCV, EBV), and obesity. Family history of NHL/DLBCL, personal history of cancer, and multiple genetic susceptibility loci are also well-established risk factors for DLBCL. There is strong evidence for multiple environmental exposures in DLBCL etiology, including exposure to trichloroethylene, benzene, and pesticides and herbicides, with recent associations noted with glyphosate. There is also strong evidence for associations with other viruses, such as HBV. Recent estimates suggest that obesity accounts for nearly a quarter of DLBCLs that develop, but despite recent gains in the understanding of DLBCL etiology, the majority of disease remain unexplained. An understanding of the host and environmental contributions to disease etiology, and concerted efforts to expand our understanding to multiple race/ethnic groups, will be essential for constructing clinically relevant risk prediction models and develop effective strategies for disease prevention.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patterns of Occurrence

DLBCL is the most common NHL subtype, accounting for approximately one-third of NHLs (Table 1); its incidence rates mirrors that of overall NHL and total lymphoid neoplasms (Figure 1). In the United States SEER data, for the time period 1992 through 2020, incidence rates for all lymphoid neoplasms, including NHL and DLBCL, have plateaued. In all three endpoints (all lymphoid neoplasms, NHL, and DLBCL), incidence is highest among white men, followed by Black men and Asian males. Although Asian females have the lowest rates of total lymphoid neoplasms and NHL, Black females have the lowest incidence of DLBCL in the U.S. (Figure 1 & Table 2). DLBCL risk monotonically with age (Figure 2) and its incidence is higher in men than women in all categories of race (Figure 2 and Table 3). In both men and women, Whites have the highest DLBCL incidence.

Global Distribution and Incidence

Global DLBCL incidence by country and region is not available, although overall NHL rates have exhibited notable differences. According to rates estimated based on the GLOBOCAN database, NHL ranks the 5th to 9th most common cancer in most countries[1]; highest incidence was observed in Australia, U.S. (Whites), and Canada. Although global incidence rates are lacking, numerous initiatives and studies have evaluated the distribution of NHL by subtypes. The International NHL Classification Project, initiated in 1995, evaluated the distribution of NHL subtypes across 24 countries, between 1995 and 2012[2]. Overall, and across all regions – Europe, Central/South America, North Africa/Middle East/India, Africa, and Asia – and countries, DLBCL was the most common NHL subtype.

North & South America.

In the International NHL Classification Project, DLBCL accounts for ~1/3 of NHLs among Whites, based on a population derived from Omaha, Nebraska and Vancouver, Canada [2]. This is consistent with recent U.S. SEER data (Table 1) and with prior evaluation of the U.S. National Cancer Data Base which reported 32.5% of NHL as DLBCL, and DLBCL as the most common NHL subtype[3, 4]. A recent estimate of trends projects that incident DLBCL in the U.S. will rise 11% from 2020–2025 based on the changing U.S. demographics that comprises a growing aging population [5].

DLBCL is also the most common NHL subtype in South and Central America, although the distribution was higher (40%)[6]. This is consistent with an independent evaluation of NHL subtypes in a reference center in Brazil (48%)[7]. While male to female ratios are similar to that of North America, the median ages of DLBCL diagnosis was younger overall[6].

Europe.

Among 595 confirmed NHLs reviewed from Southeastern Europe as part of the International Non-Hodgkin Lymphoma Classification Project, DLBCL was the most common subtype overall (39%) in all three countries included: Croatia (37%), Macedonia (40%), and Romania (41%)[8]. Among Western European countries (United Kingdom, Germany, France, Switzerland), the International NHL Classification Project reported slightly lower proportion of DLCL among NHL subtypes of 25–30%[3]. Based on demographic

characteristics, the number of incident DLBCL cases in Europe is also projected to increase from 2020 to 2025 at a rate of 7%[5].

Asia.

DLBCL is the most common NHL subtype in Asia, with reported NHL proportions of 30% in Korea[9] and ~35% across multiple populations in China[10]. Median ages also appear younger; a review of 2027 NHLs diagnosed between 2009–2014 in China yielded median age of 54 years, of which 41% were DLBCL[11]. In the International NHL Classification Project, nearly 50% DLBCL was observed in parts of China, Hong Kong, Thailand, and Jakarta based on the evaluation of 730 NHL cases[12]. Similarly in Taiwan, 48% (of 1257 NHLs) were DLBCL, based on review of 2000–2015 patients[13] and 33–38% DLBCL was observed in Japan[14, 15]. Of 194 NHL patients evaluated in India, 35.1% were DLBCL [16].

Although the incidence in Asia is lower than those reported for Europe and North America, there is some evidence of rising DLBCL incidence. Based on claims data from the National Health Insurance Service in Korea, Kim et al[17] reported DLBCL as the most common subtype (42–48% annually from 2011–2015) with standardized incidence rising for NHL overall and DLBCL (2.23 per 100,000 incidence for DLBCL). DLBCL incidence in Yogyakarta, Indonesia was also reported to rise between 2010–2014[18].

Middle East.

In the middle east, DLBCL is the most common NHL subtype, accounting for half of all NHL subtypes reported in a number of populations (e.g., 52% in Iraq [19], 51% in Saudi Arabia[19]; 54% in Lebanon[20]. Of NHL patients evaluated as part of the International NHL Classification Project, DLBCL accounted for 52.8% of NHL patients in Algeria[21], 41.5% in Egypt, 58.6% in Saudi Arabia, and 57.4% in Kuwait [16]. Studies in Kuwait have also reported similar distributions[22], and among Kuwaiti Arabs (46.5%) and non-Kuwaiti Arabs (48%)[23]. The proportion of DLBCL in Jordan was similarly high[24].

Africa.

DLBCL is the most common NHL subtype in Africa, accounting from 17% of DLBCLs in Zambia[25] to over 60% reported in the Tunisia cancer registry [26]. Data from the International NHL Classification Project [27] in Southern Africa on 487 consecutive NHL found 418 were B-cell lymphomas and DLBCL the most common subtype (38.2%). Trends in Tunisia showed rising DLBCL incidence from 2004–2007 and a projected increase, after a long period of plateau and slight decline [26].

Australia.

DLBCL incidence rose and plateaued in Australia from 1982–2014; having risen 6.2% annually prior to 1994, rates have stabilized with a 0.6% annual increase[28]. Based on Australian Cancer Registry data from 1982–2006, DLBCL accounted for 18% of all NHL. Consistent with DLBCL worldwide, DLBCL was marked by a male predominance[29].

Risk Factors for Diffuse Large B-cell Lymphoma

Epidemiologic studies conducted to uncover DLBCL risk factors have uniformly adopted the WHO definition for defining DLBCL and lymphoid malignancies[30–32]. This has enabled large pooled consortial efforts and meta-analyses of purported risk factors that include both genetic and non-genetic risk factors. At present, established DLBCL risk factors span hereditary, behavioral, infectious, and environmental exposures (Table 4). The strongest risk associations are those that result in severe immune deficiency such as HIV/AIDS, inherited immunodeficiency syndromes, and organ transplant recipients. Factors that lead to chronic immune dysregulations are also established risk factors, and include a number of autoimmune conditions (e.g., Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis), viral infections (e.g., HIV, KSHV/HHV8, HCV, EBV), and obesity. Family history of NHL/DLBCL, personal history of cancer, and multiple genetic susceptibility loci are also well-established risk factors for DLBCL. There is strong evidence for multiple environmental exposures in DLBCL etiology, including trichloroethylene, benzene, and pesticides and herbicides with recent associations noted with glyphosate. There is also growing evidence supporting a role for additional viruses in DLBCL etiology, such as HBV.

Hereditary risk factors

Family history.

Familial aggregation of NHL and elevated NHL (including DLBCL) risk among first degree relatives (parents, siblings, children) have long been established using nationwide registry data from Sweden and Denmark[33, 34]. Based on data from the Swedish Family-Cancer Database, a two-fold standard incidence ratio (SIR) in NHL risk was observed for those with family history (first-degree) of NHL; the SIR rose above two-fold (2.3) for DLBCL and when the first degree relative was a parent. When the NHL subtype of the parent was also DLBCL, the SIR increased to 11.8[35].

Population-based case control studies have also observed elevated DLBCL among those reporting a first degree relative with any hematopoietic malignancy. An international pooled study of studies across Northern America, Western Europe, and Australia conducted by the InterLymph Consortium reported a 1.4 fold increased risk of DLBCL among those reporting a family history of NHL; the risk increased to two if the relative was male[36]. In updated efforts that evaluated family history in multivariate models constructed with all DLBCL risk factors, a nearly two-fold increased DLBCL risk was observed among those reporting a family history of NHL (odds ratio, OR=1.95)[37].

Personal history.

Personal history of cancer is an established risk factor for NHL, and among the NHLs that arise as a second cancer, DLBCL is the most common NHL subtype. NHL/DLBCL risk is elevated among those who have had a lymphoid malignancy[38, 39], with a 20 year cumulative incidence rate of 3–5% for NHL after Hodgkin’s disease. Although less frequent, NHL/DLBCL has also been documented among childhood and adolescent cancer

survivors[39, 40]. DLBCL is also documented to occur after primary solid tumors; in a retrospective analysis of 809 DLBCL patients in Japan, over 10% of DLBCL patients had past cancer, with stomach cancer the most frequent[41]. 836 DLBCL patients in China evaluated for personal history of solid tumors were found to have had personal histories of a number of solid tumors[42].

Genetic Susceptibility.

Several large international consortia efforts have identified genetic susceptibility loci in DLBCL risk (Table 5) [43–45]. A large international effort across populations of European ancestry based on a meta-analysis of 3 genome-wide associations studies and one prior scan comprising 3,857 cases and 7,666 controls of European ancestry and further validation in 1,359 cases and 3,557 controls yielded five genome wide significant ($p<10^{8}$) and independent SNPs across four loci: chromosome 6p25.4 (EXOC2), 6p21.33 (HLA-B), 2p23.3 (NCOA1), and 2 SNPs in 8q24.21 (PVT1). Defining the candidate genes require further investigation and functional analyses, but the loci at 6p21.33 strongly supports the role of HLA-B*08:01 in DLBCL risk, an association also supported by case-control studies based on HLA allelotyping [46]. In Abdou et al [46], the HLA-B*0801 and HLA-A*01-B*08-DR*03-TNF-A ancestral haplotype (AH8.1) was associated with elevated DLBCL risk. In expanded GWAS efforts that included the meta-analysis of four original GWAS discovery scans and three replication studies, additional associations between 3q13.33 and 3p24.1 were observed with DLBCL risk [44],

Notably, confirmed DLBCL susceptibility loci are largely distinct from susceptibility loci that have been identified for other NHL subtypes. To date, only one loci appears to be pleiotropic; a three-stage genome-wide association study of follicular lymphoma among European ancestry reported associations between rs10484561, which tags the extended haplotype HLA-DQA1*0101-HLA-DQB1*0501-HLA-DRB1*0101, with both follicular lymphoma and DLBCL ($p<10^{7}$), [47, 48]. An evaluation of polygenic risk scores (PRS) for each NHL subtype with GWAS data (among European ancestry) found that PRS for DLBCL was also associated with increased risk for chronic lymphocytic leukemia (CLL), follicular lymphoma, and marginal zone lymphoma[49]. Alternatively, PRS for CLL, follicular lymphoma, marginal zone lymphoma, and Waldenstrom's macroglobulinemia were also associated with increased DLBCL risk with ORs of 1.17, 2.69, 1.28, 1.53 and 1.24, respectively, suggesting overlap in unmeasured shared heritability.

We note that early meta-analysis of candidate SNPs evaluated in populations of European ancestry yielded significant associations between rs3789068 (BCL2L11), rs3132453 (PRRC2A in HLA complex class III region) [50] and TNF-alpha [51]. Although reaching genome-wide significance in these early studies, the statistical significance of these loci in the larger pooled GWAS efforts became attenuated. It is possible that these associations were in linkage disequilibrium with the confirmed loci identified by GWAS efforts, but risk attenuation could also be due to differences in population sampling or chance.

GWAS efforts among non-European populations remain sparse. In a pooled study comprising 1124 DLBCL patients and 3596 controls from three Eastern Asian populations (Hong Kong, South Korea, and Thailand), 3 of the five GWAS SNPs from the European

ancestry GWAS were replicated, despite very different minor allele frequencies for each: EXOC2, PVST1, and HLAB [45]. A GWAS among Singapore Chinese reported a new DLBCL susceptibility locus, rs6773854, located between BCL6 and LPP in chromosome 3q27 [52]. Additional efforts that build upon these data in Asian and other non-European populations are needed to construct relevant and validated PRS across race/ethnic populations. The 3q27 association reported in Singapore Chinese population [52] was not observed in the Eastern Asian or European population-based GWAS, and it is unclear whether this is a function of sample size, population, or race/ethnic differences.

The DLBCL susceptibility loci identified by GWAS in European populations are estimated to contribute to ~16% of the overall variance for DLBC [43]. The confirmed DLBCL loci are also estimated to contribute 0.09 heritability, suggesting that the most susceptibility loci have not yet been identified [43]. The familial risk estimate based on these loci is calculated to be 1.40 [49, 53], which is consistent with prior studies of family history and DLBCL.

Organ transplants and primary immunodeficiencies.

Organ transplants and primary immunodeficiencies are well-established risk factors for elevated NHL and DLBCL risk. Elevated B-cell lymphoma risk, including DLBCL, is well-documented among populations with primary immunodeficiencies and disorders, including common variable immune deficiency (CVID), Wiskott Aldrich, and Nijmegen Breakage syndrome[54–57]. A number of studies among recipients of solid organ transplants demonstrate elevated DLBCL risk[58–61]. Among a U.S.-based population, risk of DLBCL after solid organ transplantation was 12.6-fold (standard incidence ratio) that of a non-transplant population[62], with the highest risk was observed among those who underwent organ transplantation at younger ages and those receiving a lung or pancreas/kidney-pancreas transplant. The risk was also higher among extranodal DLBCLs at the site of transplant, and highest in the first year following the transplant. In a large cohort of solid organ transplant recipients, elevated DLBCL risk followed solid organ transplantation in a U.S. population based on linkages to 14 state and regional cancer registries[63–65]. In the U.S. Transplant Cancer Match Study, DLBCL risk among solid organ transplant recipients was >13 times higher than the general population[63, 66]. By type of organ transplanted, risk was highest for pancreas or kidney/pancreas transplant (SIR=32.6), followed by heart and/or lung transplant (SIR=18.2), liver transplant (SIR=13.1), and kidney transplant (SIR=11.0). By age of transplant, DLBCL risk was highest among those receiving a transplant 19 years and under (SIR=379).

Autoimmune Conditions

There is substantial and consistent evidence supporting positive associations between autoimmune conditions and elevated NHL and DLBCL risk. A pooled analysis of autoimmune disorders and NHL subtypes across 12 participating InterLymph Consortium case-control studies[67] reported positive associations with DLBCL with the following autoimmune disorders: hemolytic anemia (OR=3.2), systemic lupus erythematosus (OR=2.74), Sjogren's syndrome (OR=8.92; primary Sjogren syndrome OR=6.57; Secondary Sjogren syndrome OR=12.8). Although autoimmune conditions from case control studies

are inherently limited based on self-report, these associations were corroborated in data using medical billing codes from the U.S. Surveillance Epidemiology and End Results-Medicare database[68] where elevated DLBCL risk was observed for those with Sjögren syndrome and autoimmune hemolytic anemia. A modest association between rheumatoid arthritis and DLBCL (OR=1.4) and borderline association between systemic lupus erythematosus and DLBCL was also observed[68]. In a cancer registry and hospital linkage-based studies of autoimmune disorders in Sweden, elevated standardized incidence ratios (SIRs) for Sjogren syndrome (SIR=5.5), systemic lupus erythematosus (SIR=6.6), and rheumatoid arthritis (SIR=2.2) were observed[69] Associations were also observed for a number of other conditions, including: celiac disease, chronic rheumatic heart disease, Crohn's disease, immune thrombocytopenic purpura, myasthenia gravis, primary biliary cirrhosis, sarcoidosis, systemic sclerosis, and ulcerative colitis.

Perhaps the most convincing evidence comes from studies derived of patient cohorts. A Swedish cohort reported a 16-fold NHL risk for those with Sjogren syndrome, with DLBCL the predominant NHL subtype[70]. In an international cohort of systemic lupus erythematosus (SLE) patients across 30 centers, DLBCL was the most common NHL to arise[71], and in a patient cohort of over 9500 patients with Sjogren Syndrome, DLBCL accounted for over half of the NHL subtypes that developed [72]. A Scandinavian cohort identified elevated risk among Crohn's disease patients and inflammatory bowel disease for NHL/DLBCL[73], an association that was similarly observed in an updated evaluation of InterLymph case control studies where inflammatory bowel disease was associated with gastrointestinal DLBCL[37].

It has been posited that immunosuppressive therapies used as treatment for autoimmune conditions may at least partially explain the risk or may further increase the risk for DLBCL/NHL. Epidemiologic studies to clarify this distinction have largely comprised cohorts of specific autoimmune conditions; a number of studies have evaluated the relationship between NHL and treatment among RA patients, but results remain inconsistent and largely null [74]. Importantly, the inherent bias in treatment associated with more severe autoimmune disease severity confounds the potential to delineate treatment-related elevation in NHL risk from the underlying RA. Other autoimmune conditions and treatments have also been explored, similarly resulting in mixed though largely null associations. A prospective study of 2,105 participants with inflammatory polyarthritis reported highest lymphoma incidence among those treated with methotrexate [75, 76], but another found little evidence of elevated risk among RA patients using methotrexate, beyond that from RA alone [77]. Large epidemiologic studies have also generally not found elevated NHL risk among those on anti-TNF drugs. Mercer and colleagues [78] reported no difference in lymphoma incidence between 11,931 TNF inhibitor-treated patients from 3,367 untreated patients with RA. In a SEER-based study [77], elevated NHL risk among RA patients were modestly higher among those on anti-TNF therapies but the differences were "slight"; the study authors suggested the results were due to bias due to patients with the highest risk of lymphoma preferentially receiving anti-TNF therapy. In a meta-analysis, inflammatory bowel disease patients in 22 placebo-controlled trials were evaluated and no difference in NHL risk was observed between IBD patients on TNF-a antagonists versus placebo [79].

Infections

There are robust epidemiologic data demonstrating associations between the following infectious agents and DLBCL risk: human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), Kaposi Sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8), hepatitis C virus (HCV). Evidence for an association between hepatitis B virus (HBV) and DLBCL continues to emerge.

Human immunodeficiency virus (HIV)

The association between HIV and NHL/DLBCL is well-established. NHL is an AIDS-defining cancer as defined by the U.S. Centers for Disease and Control[80, 81]. NHL is the second most common cancer that arises in HIV patients, but among specific AIDS subpopulations (e.g., intravenous drug users and hemophiliacs), NHL is the most frequent cancer[82]. Of NHLs, DLBCL is the most common NHL subtype that arises in HIV patients (accounting for ~50–75% of NHLs) [83, 84]. NHL DLBCL risk among HIV patients is high; compared to the general population (people without AIDS), NHL risk is 50–100-fold and DLBCL is 650-fold greater among those with HIV[80]. Standardized incidence ratios for DLBCL ranges from 100–140 per 100,000 [85]. However, this risk association has declined greatly in the era of modern antiretroviral therapy (ART) (e.g., post-ART). In the U.S., NHL risk was 11-fold greater, and DLBCL risk was 10.3-fold greater among people identified in HIV registries compared to the general population[86]. HIV is classified as a class I carcinogen by the International Agency for Research on Cancer (IARC)[87] but is believed to cause lymphoma through immunosuppression rather than oncogenic properties of the virus itself[85].

Kaposi sarcoma herpesvirus / Human Herpesvirus-8 (KSHV/HHV8)

Kaposi sarcoma herpesvirus (KSHV), also known as human herpesvirus 8 (HHV8), is also classified as a class I human carcinogen by IARC based on its role as a causative agent to Kaposi’s sarcoma (KS) and primary effusion lymphoma (PEL), a rare type of DLBCL also known as body cavity lymphoma[88–90]. KSHV-DLBCL has also been described but has overlapping clinical features with PEL and other KSHV-associated diseases[88]. KSHV preferentially occurs in immunocompromised populations such as HIV-infected or organ transplant recipienst; KSHV and EBV co-infection is also frequently seen[88].

Epstein Barr Virus (EBV)

EBV is an oncogenic virus; it is ubiquitous, infecting more than 90% of the world’s population at some point, but infection is largely asymptomatic[91]. Overall, ~10% of DLBCLs are EBV-positive, though this range varies by country and by method of EBV detection. EBV-positive DLBCL is often found among immunocompromised individuals, such as HIV/AIDS patients and organ transplant recipients[92, 93]. Over half of AIDS-related DLBCL are EBV-positive[92, 94] and standardized incidence ratios for EBV-related DLBCL is 100–140 per 100,000 [85]; among transplant recipients, EBV infection can range 70–100% [92]. EBV is posited to cause lymphoma by driving B cell hyperstimulation[92].

Hepatitis C Virus

Hepatitis C virus (HCV) is classified by IARC as a Group 1 carcinogenic agent in humans (https://gco.iarc.fr/causes/infections). HCV RNA and proteins have been identified in biopsy samples from lymphoma patients[95] and specifically in HCV-positive DLBCL [96, 97]; in addition to potential oncogenic properties, HCV is posited to contribute to NHL etiology through chronic antigenic stimulation[98, 99].

A number of case-control studies[100], cohort studies[98, 101], consortial efforts[37], and meta-analyses consistently report an association between HCV infection and elevated NHL risk[102–106], and specifically for DLBCL[37, 100]. In 2008, the InterLymph Consortium conducted a pooled analyses of 4784 NHL cases and 6260 controls across 7 studies with low HCV prevalence in North America, Europe, and Australia that measured HCV infection in serum using third-generation enzyme-linked immunosorbent assays to detect antibodies against HCV, reporting a 2.2-fold elevation in risk for DLBCL[100]. This association was robust in multivariate analysis that included other DLBCL risk factors[37]. In a meta-analysis of 8 case-control studies across populations with both high and low HCV prevalence, a 2.7-fold increased risk for DLBCL was estimated[102]. Aggregated data from 26 health care systems in the U.S compared the prevalence of DLBCL among patients with chronic hepatitis C infection between 2013–2020 to those negative for HCV, reporting a four-fold increased risk for DLBCL among those with chronic hepatitis C infection[98]. The associations are consistently supported by claims data from U.S. SEER-Medicare linkage [107] and from recent serology-based case-control studies [108]

Hepatitis B Virus

Hepatitis B virus (HBV) is classified by IARC as a Group 1 carcinogenic agent in humans (https://gco.iarc.fr/causes/infections). Although not a directly oncogenic virus, HBV infection is posited to result in chronic antigenic stimulation, the mechanism by which it would increase risk for NHL.

Multiple meta-analyses have concluded there is a positive association between HBsAg positivity and elevated NHL risk[109–112]. A 2013 meta-analysis evaluating 8 studies with NHL subtype information yielded a 2.73-fold increase in DLBCL risk among those who were HBsAg positive versus those who were HBsAg negative[110]; these studies included those with higher HBV prevalence, including Taiwan and Korea. These also included several large prospective cohort studies including the Korean Cancer Prevention Study where over 600,000 participants were followed for over a decade, yielding a 2-fold increase for DLBCL risk among HBsAg+ participants[113]. Another prospective cohort of >20,000 participants in Japan followed for other 16 years yielded a >7-fold increased risk of DLBCL[114]. A subsequent 2018 meta-analysis included 10 studies that evaluated DLBCL risk also reported a two-fold elevation in DLBCL risk among those HBsAg-positive[115]; this analysis included additional studies from non-HBV endemic regions, whose results varied. While case-control studies in Israel and Italy yielded elevated DLBCL risk[116, 117], null results were observed in a Danish cohort study with 30 years of follow-up[118]. At present,

the association between HBV and DLBCL, particularly in HBV-endemic regions, appears mostly consistent.

Anthropometric measures

Epidemiologic evidence consistently demonstrates a positive association between higher adult and young adult BMI / obesity with elevated DLBCL risk. A pooled analyses of over 10,000 NHL cases (including >3000 DLBCL) in 18 case-control studies participating in the InterLymph Consortium across North America and Europe yielded excess risk (OR=1.80) between grade 3 obesity (defined as BMI 40+ kg/m2) and DLBCL, compared to normal BMI (defined as 18.5–24.99 kg/m2) [119]. A meta-analysis of 6 case-control and 10 cohort studies conducted through 2012 also reported a positive association between overweight and obese individuals and DLBCL risk with RR of 1.14 and 1.29, respectively, with elevated DLBCL risk observed for both men and women, and for both case-control and cohort studies [120].

An updated pooled analyses conducted in the InterLymph Consortium comprising 4,667 DLBL cases and 22,639 controls across 19 case-control studies whose data were used to construct multivariate models for DLBCL risk, demonstrated positive associations between higher young adult body mass index (OR=1.58) with elevated DLBCL risk; although this measure was highly correlated with adult BMI, the group with higher young adult BMI was largely a subset of those with high adult BMI, thereby emphasizing the importance of obesity prevention early in life as avenue for DLBCL prevention [37]. The association between young adult BMI and elevated DLBCL risk has been further corroborated in a number of cohort studies, including among cohorts of U.S. physicians and nurses [121], across multiethnic populations [122], in U.S. nationwide cohorts [123], and in a cohort in the Netherlands [124]. In a recent pooled analysis of six prospective cohort studies in the United States[125], the strongest associations observed were for young adult BMI and elevated DLBCL risk, with the strong association observed among those who maintained a higher BMI from young adult into later adulthood which more than doubled their DLBCL risk (HR=2.67) compared those with a BMI of 18.5–22.9 kg/m2 [125]. Based on data from prospective cohort studies, it estimated that up to 23.5% of all DLBCLs may be preventable if young adult obesity were avoided [125].

Environmental and Occupational Exposures

Although there is relatively robust evidence linking occupations and environmental exposures to increased risk of hematopoietic malignancies, the evidence that links these exposures specifically to DLBCL remains limited due to the nature of the studies. Much of the epidemiologic data is derived from occupational cohorts that follow high-exposed populations for years but accrue relatively small numbers of NHLs, of which evaluating NHL subtypes is challenging. Nested case control studies are also used to directly measure environmental exposures in biospecimens, but due to the expense (in cost and biospecimen) of measuring exposures, these studies are also typically limited in sample size.

Trichloroethylene (TCE) is classified as a probable carcinogen (Group 2A) by IARC. A meta-analysis of 14 occupational cohort and four case-control studies linked TCE to elevated NHL risk but lacked NHL subtype data [126]. However, a pooled analysis of 3788 NHL cases and 4279 controls within four participating InterLymph Consortium studies evaluated the association between TCE based on occupation categories and NHL risk and found DLBCL risk to be elevated in the highest category of exposure intensity[127].

Benzene is classified by IARC as a human carcinogen that causes leukemia; evidence for benzene causing lymphoma has to date been considered “limited” [128]. In a 2021 meta-analysis of benzene exposure and NHL risk, data from 20 case-control studies and eight cohort studies, totaling 9587 NHL cases, yielded a 1.67-fold increased risk for DLBCL [129].

2,3,7,8-tetrachlordibenzo-p-dioxin (**TCDD**) is classified as a Group 1 carcinogen (Group B2) by IARC and has been linked to lymphomas [130]. However, evidence specifically linking TCDD to DLBCL risk remains lacking.

1,3-butadiene is considered a potential occupational carcinogen and teratogen by the National Institute for Occupational Safety and Health (NIOSH). Epidemiological evidence linking 1,3-butadiene to DLBCL risk is still lacking, though there is some suggestion that 1,3-butadiene may be associated with lymphoma mortality based on occupational studies of workers employed in facilities that produce styrene butadiene rubber [131, 132].

Polychlorinated Biphenyls (PCBs) are classified as a Group 1 carcinogen by IARC [133], but the evidence of association between overall PCBs and PCB congeners with NHL and DLBCL risk is inconsistent. In one of the largest studies of NHL and PCBs at the time, excess risk for NHL (and across subtypes including DLBCL) was observed for top quartiles of plasma concentrations for numerous congeners [134]. However, a comparable study in Europe of 9 PCB congeners in plasma samples yielded no overall association of PCBs with DLBCL risk [135]. Another study in Europe and Sweden measuring 6 PCB congeners in prediagnostic plasma measurements also found no overall association with NHL or DLBCL over 16 years of follow-up[136]. A 2019 case-control study of 33 PCB congeners measured in serum for NHL risk in Italy among a chemical factory similarly found no association between serum levels of total PCBs with NHL or DLBCL [137]. A 2017 meta-analysis [138] of 11 occupational cohort studies and a 2019 meta-analysis of [139] of 30 populations, including occupational cohorts, high-exposure populations, and standard populations found insufficient evidence to support an association.

The association between **herbicides and insecticides** and DLBCL is still developing. In a pooled analysis of nearly 8000 NHL cases from 9 case control studies across North America, Europe, and Australia in the InterLymph Consortium, long-term diazinon use (>8 years) was positively associated with DLBCL (OR=3.16). Use of insecticides, organochlorine insecticides, DDT, chlordane, organophosphate insectides and malathion were not associated with DLBCL risk [140, 141]. However, use of herbicides in a pooled analysis of 10 InterLymph case-control studies reported a positive association between 2,4-dichlorophenoxyacetic acid (2,4-D), glyphosate with DLBCL (>25.5 years, OR=1.47)

[140, 141]. Overall herbicide use was also found associated with DBLCL in an evaluation of data from the United States Geological Survey (USGS), United States Census, and the Surveillance, Epidemiology, and End Results (SEER) database[142]. Calculating the association between the area density of specific agricultural pesticides and the county level annual incidence of DLBCL, DLBCL incidence was positively associated with an area density of 14 of the pesticides, of which 13 were used as herbicides, including the organophosphate Methyl Parathion and glyphosate. In a pooled analysis of three large agricultural worker cohorts including 2430 NHL cases across the United States, France, and Norway, a positive association was reported between glyphosate and DLBCL (HR=1.48) [143], which was further supported in a meta-analysis of 7 studies with a 1.3-fold DLBCL risk for the highest category of glyphosate exposure[144].

Finally, in a pooled analysis of 10 case-control studies participating in the InterLymph Consortium, 10,046 cases and 12,025 controls were evaluated for the association between occupational exposures and NHL risk[145], based on occupational coding from **t**he 1968 International Standard Classification of Occupations (ISCO-1968). Positive associations with DLBCL were observed for the following occupations: hairdressers, textile workers, charworkers and cleaners, field crop and vegetable farm workers, metal melters and reheaters, special education teachers, and forestry workers with >10 years of employment. Further investigations are required to confirm these associations and understand the underlying biology.

Other Putative Risk Factors include atopic conditions (allergies, hay fever), smoking, alcohol consumption, sun / ultraviolet radiation exposure, hair dye use, oral contraceptives, hormone therapy, and blood transfusions. Decreased risk for atopic conditions, alcohol consumption, and sun/ultraviolet radiation exposure has been reported[37, 146–152], but discrepancy and/or inconsistent results require additional follow-up. Other risk factors such as blood transfusion and hair dye use appear to apply to specific population subsets[153, 154]. At present, there is insufficient evidence to conclude that these factors are associated with DLBCL risk.

Future Directions in Epidemiologic Research

Although there are some very strong risk factors for DLBCL, most patient's DLBCL will likely develop through multi-factorial etiology. Continued efforts to confirm and identify novel DLBCL risk factors in prospective cohort studies where survival bias is reduced and temporality can be established are thus needed; efforts to understand how genetic and environmental risk factors contribute to risk (e.g., synergistically, independently, etc.) and whether they interact are needed. Constructing risk prediction models that combine genetic and environmental risk factors may be beneficial for those at elevated risk due to personal histories, such as family history or among those with autoimmune conditions. Pooled and consortial efforts in diverse populations will be particularly important to reach sufficient power to identify modest associations and to clarify important differences by race/ethnicity. Prospective studies further offer the ability to identify pre-diagnostic biomarkers of exposure and/or risk, a critical step for understanding the underlying biology and for constructing risk prediction models. Understanding whether DLBCL risk factors differ further by

molecular subtypes, of which there are now seven[155], may also aid in understanding the multifactorial etiology of DLBCL. Preliminary data linking high body mass index and germinal center B-cell-like GCB DLBCL, have been reported [156], and new and purported risk factors may be uncovered or clarified with these molecular delineations. Data from the InterLymph Subtypes Project noted specific associations by tumor site, including positive association between heavy smoking and CNS DLBCL, and between autoimmune conditions and gastrointestinal DLBCL. Larger sample sizes will be required to confirm these results. Other DLBCL characteristics that warrant future investigations include FL-transformed DLBCL as a distinct outcome.

As genetic susceptibility loci are uncovered, it will be particularly important to interrogate gene-environment interactions to understand their joint contribution to disease risk[157–160]; further understanding whether purported environmental exposures exert their effects in the presence of susceptibility loci, or vice versa, will add to our understanding of this complex disease. To date, large population sample sizes are available for Caucasian populations, but effort is required to understand whether susceptibility loci identified to date are applicable to non-Caucasian race groups and whether risk prediction models that are constructed can be applied to non-Caucasian race groups. Finally, new and continued efforts for identifying environmental risk factors or novel infectious agents responsible for DLBCL etiology are needed. A study on HLA zygosity that demonstrated positive association with DLBCL risk suggested a role for infectious etiologies[161]. Pinpointing environmental contributions to DLBCL risk should also expand to a broader definition as defined by social and built environment, and to multi-mixture models as environmental exposures do not occur in isolation.

Although much progress on uncovering DLBCL risk factors has been made over the last two decades, early detection and screening does not yet exist. Continued efforts to identify risk factors that can explain the causes of DLBCL are thus needed to construct risk prediction models, tailored to identify those at highest risk for disease. Critically, continued efforts to identify precursor conditions for early detection efforts are needed. Potentially promising precursors include clonal hematopoiesis; while studies have largely reported CH in myeloid, follicular, and CLL/SLL as endpoints, continued discovery efforts to uncover clonal hematopoiesis in DLBCL could hold promise for early detection [162]. In the meantime, ascertaining personal and medical histories will remain important for disease prevention and early detection; prevention of and monitoring individuals with many of these risk factors, such as young adult obesity and infections, will be pertinent for multiple health outcomes, including DLBCL.

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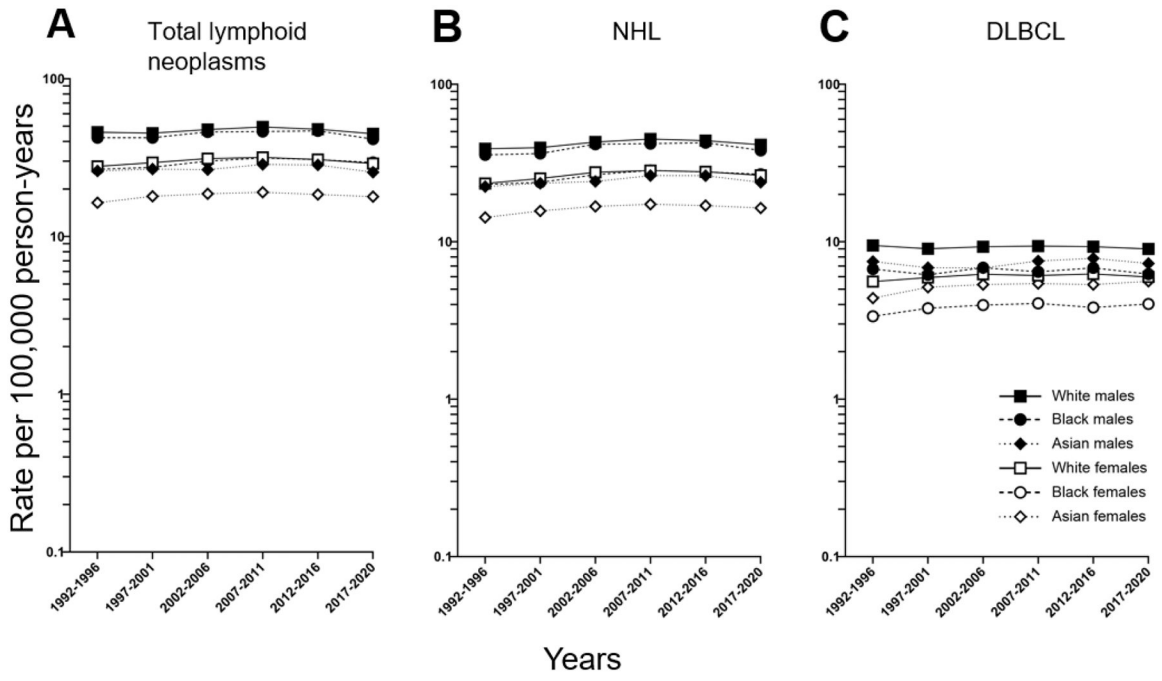

Fligure 1.

Trends in DLBCL incidence by race and sex, 12 SEER registries, 1992–2020.

Presented for 6 fixed time periods (1992–1996, 1997–2001, 2002–2006, 2007–2011, 2012–2016, 2017–2020)

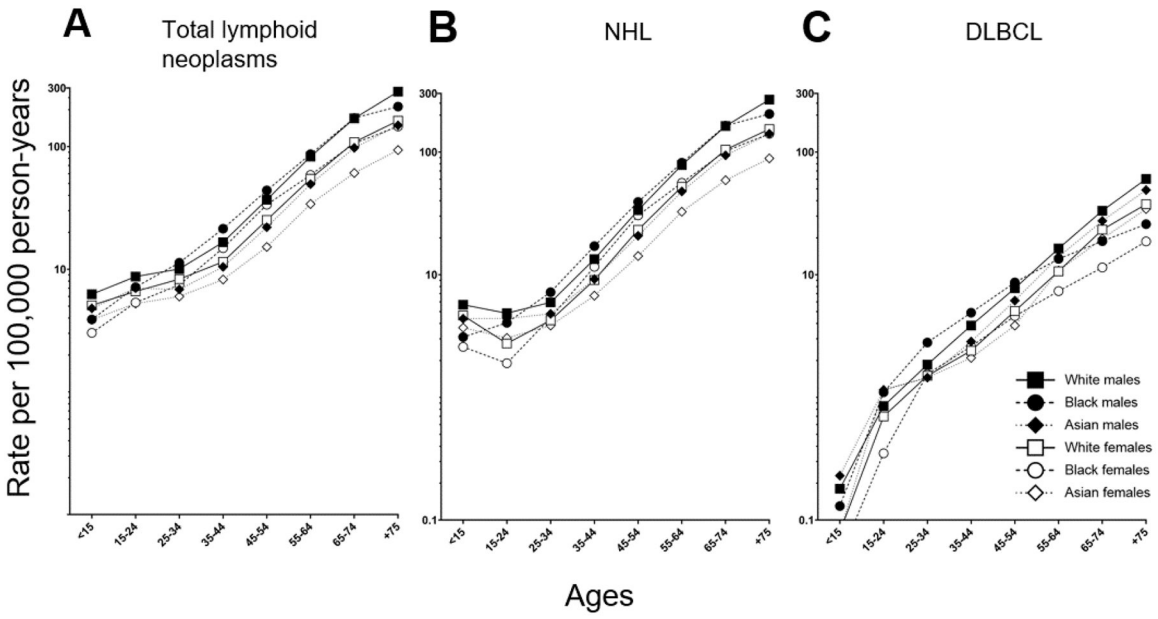

FIGURE 2.

DLBCL incidence by age, race and sex, 12 SEER registries, 2011–2020. All incidence rates are age-adjusted to the 2000 United States population.

Table 1.

Incidence of hematopoietic neoplasms and DLBCL (defined by ICD-O-3 codes), 12 SEER registries, 2010–2020.

	ICD-O-3 codes[#]	No.	Rate[*]
Lymphoid neoplasms, total	-	165 364	35.7
B-cell lymphoid neoplasms, total	9591, 9597, 9670, 9671, 9673, 9675, 9678, 9679(B), 9680(B), 9684(B), 9687, 9688(B), 9687–9691, 9695, 9698, 9699, 9712(B), 9731–9735(B), 9737(B), 9738(B), 9760–9762, 9764, 9823, 9826, 9833(B), 9940	125 575	26.8
Diffuse large B-cell lymphoma	9678, 9679(B), 9680 (B), 9684(B), 9688(B), 9712(B), 9735(B), 9737(B), 9738(B),	33 359	7.2
T-NK-cell lymphoid neoplasms, total	9700–9702, 9705, 9708, 9709, 9714, 9716–9719(T/NK), 9726, 9727, 9827, 9831, 9832, 9834, 9948(T/NK)	9 866	2.1
Hodgkin lymphoma	9650–55, 9659, 9661–9667	10 726	2.4
Unknown type lymphoid neoplasm	9727 (unknown), 9832 (unknown)	212	0.0

ICD-O: International classification of diseases for oncology; SEER: Surveillance, Epidemiology, and End Results

[#]Codes followed by parentheses indicate that immunophenotyping data (B-cell, T/NK-cell, or unknown) were used to assign cases to that lymphoid neoplasm subtype

[*]All incidence rates are age-adjusted to the 2000 US population and expressed per 100,000 person-years

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER

Research Data, 12 Registries, Nov 2022 Sub (1992–2020) - Linked To County Attributes - Time Dependent (1990–2021)

Income/Rurality, 1969–2021 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission.

Table 2.

DLBCL Incidence by Race and Sex, 12 SEER Registries, 2011–2020

		Lymphoid neoplasms, total		B-cell lymphoid neoplasms, total		DLBCL	
		No.	Rate*	No.	Rate*	No.	Rate*
Male	White	68 907	46.5	58 950	39.7	13 565	9.2
	Black	7 101	44.2	5 677	36.3	1 082	6.5
	Asian	7 805	27.2	6 481	22.6	2 162	7.6
	AI/AN	696	23.4	574	19.9	128	4.8
Female	White	50 894	30.0	43 704	25.4	10 450	6.1
	Black	6 130	30.3	4 940	24.6	771	3.8
	Asian	6 543	18.3	5 516	15.3	1 996	5.5
	AI/AN	640	18.6	526	15.4	137	4.3

AI/AN: American Indian or Alaska Native; DLBCL: diffuse large B-cell lymphoma

*All incidence rates are age-adjusted to the 2000 US population and expressed per 100,000 person-years

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER

Research Data, 12 Registries, Nov 2022 Sub (1992–2020) - Linked To County Attributes - Time Dependent (1990–2021)

Income/Rurality, 1969–2021 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission.

TABLE 3.

Incidence Rate Ratios (IRR) by Race and Sex, 12 SEER Registries, 2011–2020

		Lymphoid neoplasms, total	B-cell lymphoid neoplasms, total	DLBCL
		IRR*	IRR*	IRR*
Male:Female IRR	White	1.6	1.6	1.5
	Black	1.5	1.5	1.7
	Asian	1.2	1.5	1.4
White:Black IRR	Males	1.1	1.1	1.4
	Females	1.0	1.0	1.6
White:Asian IRR	Males	1.7	1.8	1.2
	Females	1.6	1.7	1.1

DLBCL: diffuse large B-cell lymphoma

*All incidence rates are age-adjusted to the 2000 US population and expressed per 100,000 person-years

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER

Research Data, 12 Registries, Nov 2022 Sub (1992–2020) - Linked To County Attributes - Time Dependent (1990–2021)

Income/Rurality, 1969–2021 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission.

Table 4.

Summary of risk associations of established risk factors for diffuse large B-cell lymphoma

Established risk factors for DLBCL	
Risk factors	**Risk association * = OR <2.0 *** = OR >2.0**
Family and person history	
Family history for any heme malignancy	*
Family history of DLBCL	***
Personal history of cancer	*
Genetic susceptibility	*
Inherited immunodeficiency syndrome	***
Organ transplants	***
Autoimmune conditions	*
Sjogren's syndrome	***
Systemic lupus erythematosus	***
Rheumatoid arthritis	*
Infections	
HIV	***
KSHV/HHV8	*
HCV	*
HBV	*
Anthropometric measures	
Adult BMI	*
Young adult BMI	*

Table 5.

Genetic susceptibility loci associated with DLBCL risk.

SNP	Locus	Nearest Gene	RAF* (controls)	OR	Reference
GWAS of European Ancestry					
rs79480871	2p23.3	NCOA1	0.076	1.34	[43]
rs6773363	3p24.1	EOMES	0.45	1.2	[44]
rs9831894	3q13.33		0.40	0.83	[44]
rs2523607	6p21.33	HLA-B	0.12 0.0003	1.32 3.05	[43] [45]
rs116446171	6p25.3	EXOC2	0.019 0.06	2.20 2.04	[43] [45]
rs13255292	8q24.21	PVT1	0.32 0.20	1.22 1.34	[43] [45]
rs4733601	8q24.21	PVT1	0.48	1.18	[43]
rs10484561	6p21.32	HLA Class II		1.36 9, p=1.4×10–7	[47]
GWAS of Asian Ancestry					
rs6773854	3q27	BCL6/LPP	0.22	1.47	[52]
rs2523607	6p21.33	HLA-B	0.0003	3.05	[45]
rs116446171	6p25.3	EXOC2	0.06	2.04	[45]
rs13255292	8q24.21	PVT1	0.20	1.34	[45]
Candidate SNPs					
rs1800629	6p21	TNF −308A	0.28	1.29	[51]
rs3132453		PRRC2A, BAG6/BAT3	0.066	0.68 (B cell lymphomas)	[50]
rs3789068	2q13	BCL1L11	0.46	1.21 (B cell lymphomas)	[50]
AH 8.1	6p21.3	HLA A*0101-B*0801-DR*0301-TNF-A	0.13	1.65	[46]

*Risk allele frequenc