Changes in sex-specific incidence of lymphoid neoplasms across the lifespan

While male predominance for most subtypes of lymphoid neoplasms (LN) has been described,[1] the underlying reasons for this observation are not well understood. Certain established LN risk factors (e.g., autoimmune diseases, infections, or occupational exposures) differ by sex but generally are rare and thus unlikely to explain the observed sex differences in LN incidence, and previous studies assessing hormonal factors have been inconclusive.[2] Notably, however, there is substantial age variation in the prevalence of some lymphoma risk factors (e.g., viral infections), with certain risk factors and immune function known to vary substantially by age and sex.[3] To date, the understanding of male predominance across age groups remains limited.[3-5] To contribute novel epidemiologic insights, we explore sex-specific incidence rates and male-to-female incidence rate ratios (IRR) according to finely categorized age groups across the lifespan for common and rare LN subtypes by leveraging US population-based cancer registry data.

We identified all first primary incident LN diagnosed during 2001-2017 in 16 Surveillance, Epidemiology, and End Results (SEER-16) registry areas. Cases with unknown age (N=21), unknown race and ethnicity (N=4,385), or those diagnosed through autopsy/death certificate only (N=4,775) were excluded. We also excluded human immunodeficiency virus (HIV)-positive cases (N=7,562) because of the known age- and sex-specific incidence patterns of HIV infection, which would potentially obscure other incidence patterns. Analysis was limited to cases diagnosed after the 2001 World Health Organization classification introduction (*Online Supplementary Table S1*) through 2017, the last available HIV status date. Three registries (Iowa, Hawaii, and Connecticut) lacking HIV data were included, assuming low HIV prevalence as previously described.[6,7]

We estimated age-adjusted incidence rates by sex and fitted multivariable Poisson regression models to estimate male-to-female IRR and 95% confidence intervals (CI) in each of the 18 5-year age groups (0-4, 5-9, ..., and ≥85 years [yrs]). Age groups with <16 cases for males or females were combined with the next oldest group. Models were adjusted for race and ethnicity, and population size was used as an offset. Using joinpoint models, we estimated the average percent change (APC) in the sex-specific incidence rates and the male-to-female IRR to evaluate the significance of trends across age groups. Additionally, we performed a sensitivity analysis by comparing the IRR from the main analysis (restricted to cases without known HIV) with those based on all cases regardless of HIV status at diagnosis using a Z-score.[8] Analyses were performed using SEER*Stat (v8.4.1.2), Joinpoint (v4.9.0), and R (v4.1.1). This study is not considered human subjects research and thus did not require review by an Institutional Review Board.

We analyzed 492,948 incident LN (273,620 males and 219,328 females) (Table 1). For all ages combined, males had a significantly higher incidence than females for most subtypes, with >2-fold IRR for hairy cell leukemia, mantle cell lymphoma (MCL), T-cell precursor leukemia/lymphoma (T-ALL), Burkitt leukemia/lymphoma (BL), and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). In contrast, no male predominance was observed for nodular sclerosis Hodgkin lymphoma (NSCHL); primary mediastinal large B-cell lymphoma (PMBCL); marginal zone lymphoma (MZL), including nodal, extranodal, and splenic MZL; and adult T-cell leukemia/lymphoma.

Male-to-female IRR increased considerably with age for lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM; IRR [age group], from 0.81 [0-39 yrs] to 2.47 [≥85 yrs]), T-cell large granular lymphocytic leukemia (LGLL, from 0.76 [0-49 yrs] to 2.83 [≥85 yrs]), and primary cutaneous anaplastic large cell lymphoma (PCALCL, from 0.86 [<30 yrs] to 3.91 [≥85 yrs]) (Figure 1; *Online Supplementary Table S1*). Sex-specific APC analyses illustrate that the increasing male predominance with age for these lymphomas resulted from a steeper incidence increase among males than females (*Online Supplementary Figure S1; Online Supplementary Table S2*). Modest IRR increases with age were noted for multiple myeloma (MM), chronic lymphocytic leukemia/small lymphocytic lymphoma, cutaneous T-cell lymphoma, NOS (CTCL), splenic MZL, and mycosis fungoides/Sézary syndrome (MF/SS). Conversely, steeper increases in the incidence by age in females *versus* males resulted in a decrease in the IRR with advancing age for NLPHL (from 3.94 [15-19 yrs] to 1.89 [≥80 yrs]), BL (from peak of 3.75 [10-14 yrs] to 1.70 [≥85 yrs]), and lymphocyte-rich Hodgkin lymphoma (LRHL, from 2.81 [<25 yrs] to 0.81 [75-79 yrs]).

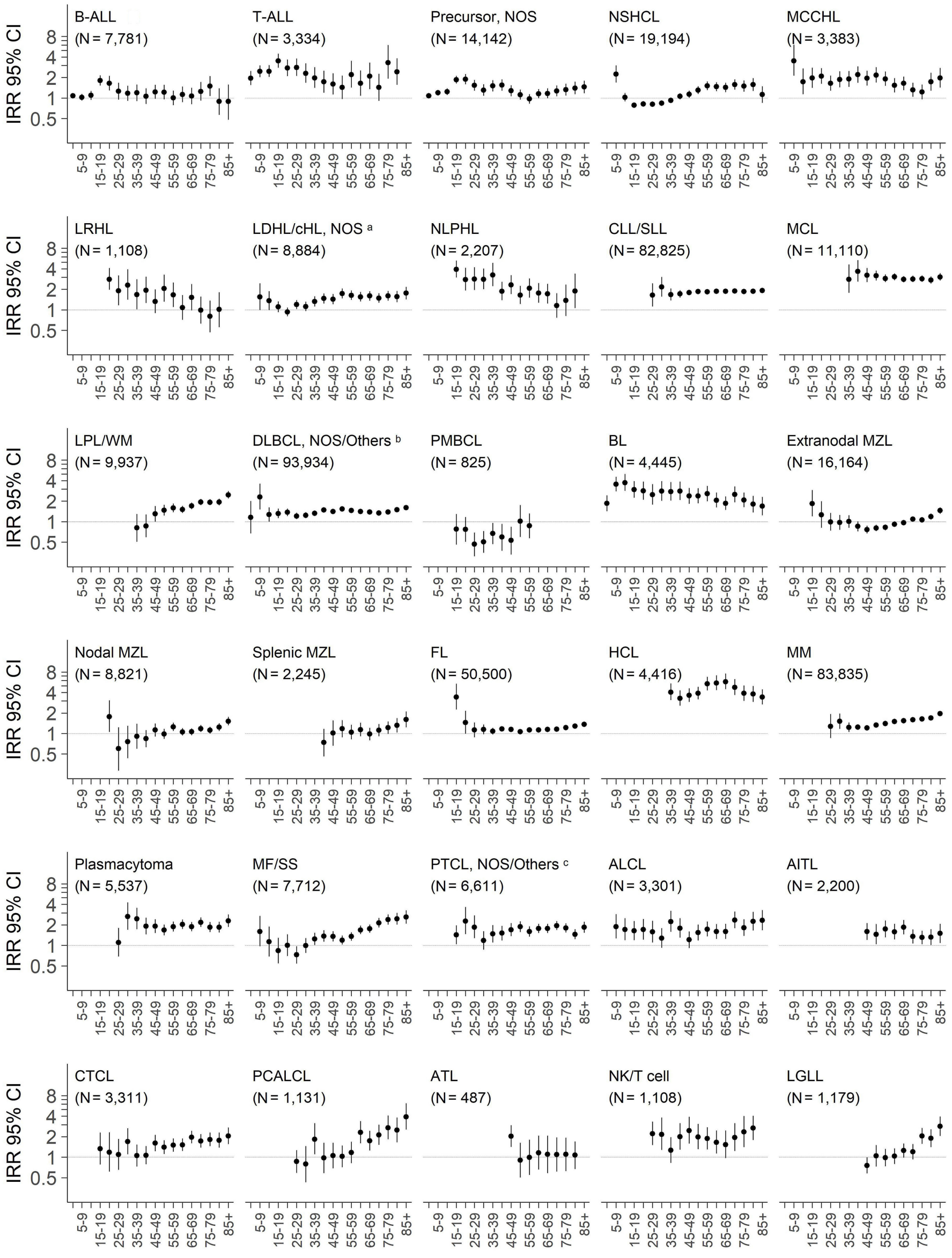
Notably, female predominance was observed for selected LN in specific age groups. Incidence was significantly higher among females (i.e., IRR<1) for NSCHL (IRR=0.78-0.84 [15-34 yrs]), extranodal MZL (IRR=0.76-0.82 [45-59 yrs]), and PMBCL (IRR=0.47-0.67 [25-49 yrs]).

Male predominance was substantially pronounced in the youngest and oldest age groups for T-ALL, NSCHL, mixed cellularity Hodgkin lymphoma, extranodal and nodal MZL, follicular lymphoma (FL), and diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). Joinpoint analyses suggested a constant male predominance across age groups for MCL, NK/T-cell lymphoma, and B-cell precursor

Table 1. Incidence rates by sex and male-to-female incidence rate ratios of lymphoid neoplasms subtypes among all ages, cases diagnosed between 2001 and 2017 from 16 registries of the Surveillance, Epidemiology, and End Results Program.

Lymphoid neoplasm subtypes	Males N=273,620		Females N=219,328		Male-to-female IRR (95% CI)[a]
	N	IR per 100,000	N	IR per 100,000	
Precursor lymphoid neoplasms					
B-ALL	4,200	0.62	3,619	0.54	1.17 (1.12-1.23)
T-ALL	2,339	0.34	1,007	0.15	2.38 (2.22-2.57)
Precursor, NOS	7,881	1.17	6,391	0.92	1.25 (1.21-1.29)
Hodgkin lymphomas					
cHL	17,632	2.6	15,602	2.21	1.16 (1.13-1.18)
NSCHL	9,642	1.40	9,833	1.41	1.00 (0.98-1.03)
MCCHL	2,387	0.36	1,447	0.2	1.69 (1.58-1.80)
LRHL	649	0.10	435	0.06	1.53 (1.36-1.73)
LDHL/cHL, NOS[b]	4,954	0.75	3,887	0.54	1.31 (1.25-1.36)
NLPHL	1,417	0.21	659	0.09	2.22 (2.03-2.44)
Mature B-cell lymphomas					
CLL/SLL	49,381	7.95	33,129	4.22	1.53 (1.51-1.55)
MCL	7,787	1.24	3,287	0.42	2.43 (2.33-2.53)
LPL/WM	5,505	0.91	3,873	0.5	1.46 (1.40-1.52)
DLBCL, NOS/Others[c]	50,443	8.08	42,967	5.59	1.20 (1.19-1.22)
PMBCL	322	0.05	503	0.07	0.66 (0.57-0.76)
BL	3,089	0.46	1,365	0.19	2.32 (2.17-2.47)
MZL	12,594	2.00	14,501	1.88	0.89 (0.87-0.91)
Extranodal MZL	7,438	1.18	8,986	1.17	0.85 (0.83-0.88)
Nodal MZL	3,966	0.63	4,252	0.55	0.96 (0.92-1.00)
Splenic MZL	1,190	0.19	1,263	0.16	0.97 (0.89-1.05)
FL	25,075	3.86	25,019	3.26	1.03 (1.01-1.04)
HCL	3,282	0.5	880	0.12	3.82 (3.55-4.12)
PCN	49,531	7.91	39,381	5.08	1.30 (1.28-1.32)
MM	46,199	7.40	37,338	4.81	1.28 (1.26-1.29)
Plasmacytoma	3,332	0.52	2,043	0.27	1.68 (1.59-1.77)
Mature T-cell lymphomas					
MF/SS	4,133	0.63	2,994	0.4	1.42 (1.36-1.49)
PTCL	9,103	1.41	6,469	0.86	1.45 (1.40-1.50)
PTCL, NOS/Others[d]	3,594	0.56	2,517	0.33	1.47 (1.40-1.55)
ALCL	1,842	0.28	1,175	0.16	1.61 (1.50-1.73)
AITL	1,107	0.17	899	0.12	1.27 (1.16-1.38)
CTCL	1,796	0.28	1,323	0.18	1.40 (1.30-1.50)
PCALCL	764	0.12	555	0.07	1.42 (1.27-1.58)
ATL	252	0.04	235	0.03	1.11 (0.93-1.32)
NK/T cell	696	0.11	393	0.05	1.81 (1.60-2.05)
LGLL	931	0.15	861	0.11	1.11 (1.01-1.22)
Others/lymphoid, NOS[e]	18,027	2.98	16,193	2.07	1.14 (1.12-1.17)

*Denotes statistically significant APC changes at *P* value <0.05. [a]Incidence rate ratios (IRR) adjusted for race and ethnicity (Hispanic, non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, and non-Hispanic White). [b]LDHL cases were combined with cHL, NOS because of limited case counts across age groups. [c]Others include intravascular large B-cell lymphoma (N=145), primary effusion lymphoma (N=72), and plasmablastic lymphoma (N=314, since 2010). [d]Others include subcutaneous panniculitis-like T-cell lymphoma (N=200); enteropathy-type T-cell lymphoma (N=188); hepatosplenic T-cell lymphoma (N=135). [e]Others include prolymphocytic B- or T-cell leukemia (N=792), heavy chain disease (N=53), and composite Hodgkin lymphoma and non-Hodgkin lymphoma (N=712). Lymphoid, NOS (N=32,663). AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; APC: average percent change; ATL: adult T-cell leukemia/lymphoma; B-ALL: B-cell lymphoblastic leukemia/lymphoma; BL: Burkitt leukemia/lymphoma; cHL: classical Hodgkin lymphoma; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; CI: confidence interval; CTCL: cutaneous T-cell lymphoma, NOS; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HCL: hairy cell leukemia; IR: incidence rate; LDHL: lymphocyte-depleted Hodgkin lymphoma; LGLL: T-cell large granular lymphocytic leukemia; LPL/WM: lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; LRHL: lymphocyte-rich Hodgkin lymphoma; MCCHL: mixed cellularity Hodgkin lymphoma; MCL: mantle cell lymphoma; MF/SS: mycosis fungoides/Sézary syndrome; MM: multiple myeloma; MZL: marginal zone lymphoma; NK/T cell: NK/T cell lymphoma; NLPHL: nodular lymphocyte predominant Hodgkin lymphoma; NOS: not otherwise specified; NSCHL: nodular sclerosis Hodgkin lymphoma; PCALCL: primary cutaneous anaplastic large cell lymphoma; PCN: plasma cell neoplasms; PMBCL, primary mediastinal large B-cell lymphoma; PTCL: peripheral T-cell lymphoma; SEER-16: 16 cancer registry areas of the Surveillance, Epidemiology, and End Results Program, which include Connecticut, Atlanta (Metropolitan), Greater Georgia, Rural Georgia, Los Angeles, San Francisco - Oakland SMSA, San Jose - Monterey, Hawaii, Iowa, Kentucky, Louisiana, New Mexico, New Jersey, Seattle (Puget Sound), and Utah; T-ALL: T-cell lymphoblastic leukemia/lymphoma.



Continued on following page.

Figure 1. Male-to-female incidence rate ratios across the lifespan for lymphoid neoplasms. Incidence rate ratios (IRR) (95% confidence intervals [CI]) were adjusted for race and ethnicity (Hispanic, non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, and non-Hispanic White) and stratified by 5-year age groups (unless otherwise specified). Cases diagnosed between 2001 and 2017 from 16 registries of the Surveillance, Epidemiology, and End Results. [a]LDHL cases were combined with cHL, NOS because of limited case counts across age groups. [b]Others include intravascular large B-cell lymphoma, primary effusion lymphoma, and plasmablastic lymphoma. Cases were combined because of low counts across age groups. [c]Others include subcutaneous panniculitis-like T-cell lymphoma, enteropathy-type T-cell lymphoma, and hepatosplenic T-cell lymphoma. Cases were combined because of low counts across age groups. AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; ATL: adult T-cell leukemia/lymphoma; B-ALL: B-cell lymphoblastic leukemia/lymphoma; BL: Burkitt leukemia/lymphoma; cHL: classical Hodgkin lymphoma; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; CTCL: cutaneous T-cell lymphoma, NOS; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HCL: hairy cell leukemia; LDHL: Lymphocyte-depleted Hodgkin lymphoma; LGLL: T-cell large granular lymphocytic leukemia; LPL/WM: lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; LRHL: lymphocyte-rich Hodgkin lymphoma; MCCHL: mixed cellularity Hodgkin lymphoma; MCL: mantle cell lymphoma; MF/SS: mycosis fungoides/Sézary syndrome; MM: multiple myeloma; MZL: marginal zone lymphoma; NK/T cell: NK/T cell lymphoma; NLPHL: nodular lymphocyte predominant Hodgkin lymphoma; NOS: not otherwise specified; NSCHL: nodular sclerosis Hodgkin lymphoma; PCALCL: primary cutaneous anaplastic large cell lymphoma; PCN: plasma cell neoplasms; PMBCL: primary mediastinal large B-cell lymphoma; PTCL: peripheral T-cell lymphoma; T-ALL: T-cell lymphoblastic leukemia/lymphoma.

leukemia/lymphoma. The sensitivity analyses indicated that the male predominance was higher when all cases (regardless of HIV status) were included for DLBCL in ages 30-54 ($IRRs_{All\text{-}cases}$ =1.57-1.89 *vs*. $IRRs_{HIV\text{-}excluded}$ =1.34-1.54; $P<0.05$) and for BL in ages 40-49 ($IRRs_{All\text{-}cases}$ =3.56-4.64 *vs*. $IRRs_{HIV\text{-}excluded}$ =2.38-2.81; $P<0.05$). No difference in IRR was found for other subtypes.

This population-based study revealed age-related variations in the male-to-female IRR for several LN subtypes across the lifespan. Although previous studies have described a male predominance across age groups, these reports primarily focused on broad LN (e.g., non-Hodgkin lymphoma or acute leukemias) and age categories, masking sex-based variations within recognized subtypes.[3] Our study uncovers nuanced patterns of sex-specific incidence rates and male-to-female IRR with advancing age across LN. While IRR remained stable across age groups for certain LN, others exhibited notable fluctuations, such as increasing and decreasing IRR or a combination of both patterns. These findings support the heterogeneous nature of lymphoid neoplasms and may reflect the possible contributions of multiple etiologic factors within subtypes, as well as support subtype-specific differences in risk factors.[9]

The female predominance during ages 15-34 for NSCHL contrasts with previous reports of an IRR of 1 for all ages combined.[1] Findings for PMBCL expand previous data[10] and suggest female predominance between ages 25-49. Similar incidence rate peaks in both sexes for NSCHL and PMBCL during early adulthood suggest a possible epidemiological link between these two morphologically distinct entities, supporting molecular evidence that these subtypes arise from a common precursor cell.[11] The female predominance in extranodal MZL at ages 45-59 aligns with the peak incidence of autoimmune diseases and differs from incidence patterns for nodal and splenic MZL.[12] This observation provides epidemiologic evidence lending support for the role of autoimmune conditions, particularly those affecting extranodal sites (e.g., thyroid gland), in the etiology of MZL.

The disproportionate age-related decline in male immune function, compared to females,[13] may have contributed to the observed increase in LN incidence rates and male predominance at older ages for specific subtypes, including cutaneous lymphomas (i.e., CTCL, PCALCL, MF/SS), LGLL, LPL/WM, and MM. For instance, epigenetic dysregulation significantly influences the pathogenesis of cutaneous T-cell lymphomas,[14] and thus, factors associated with epigenetic modulation may be related to the observed sex difference for only some subtypes. In contrast, the attenuation of male predominance with advancing age in BL, NLPHL, and LRHL appeared to be driven by a steeper increase in the incidence rates of females. The reasons behind this pattern require further investigation.

Although incidence rates increased with age in both sexes for most LN, the IRR were relatively constant across the lifespan for several subtypes (e.g., B-ALL; chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL; DLBCL, NOS; plasmacytoma; peripheral T-cell lymphoma, NOS; anaplastic large cell lymphoma; angioimmunoblastic T-cell lymphoma; NK/T-cell lymphoma; and adult T-cell leukemia/lymphoma). This suggests that age-related variations in immune function (e.g., increased senescence of T and B cells among males), steroid hormone production,[2,13] or other sex-specific risk factors between males and females are unlikely to drive the observed sex differences.

A strength of this study was the large number of incident cases diagnosed in the SEER data, particularly relevant for rare subtypes for which previous international studies have had a limited sample size. The large population size allowed the examination of sex differences across age groups, even for rarer subtypes, although the sample size was generally too small to evaluate differences by race and ethnicity. Limitations of our study include the lack of a central expert hematopathology review. Although misclassification of LN may have occurred, we do not

expect misclassification to differ by sex. The absence of dedicated ICD-O-3 codes for recognized subtypes such as Epstein-Barr virus-positive DLBCL) precluded their distinction in our study. The lack of individual LN risk factors (e.g., autoimmune disease) and their timing in SEER precludes the analysis of their contribution to the observed estimates and the impact of latencies of exposures on LN risks during aging.

In conclusion, examining sex-specific incidence rates and male-to-female IRR across ages revealed previously undocumented incidence patterns for some LN that were not evident when age groups or subtypes were combined in previous studies. This observed variability reflects the heterogeneity of LN and emphasizes the need for stratifying by sex and age in future etiologic studies. Identifying sex- and age-related risk factors associated with subtype-specific differences in LN development between males and females could improve our understanding of LN etiology. Future research may evaluate the role of sex-dependent changes in immune function during aging, genetic susceptibility, the potential impact of latencies of LN risk factors exposure, and the interaction between these factors on LN development.

Authors

Bryan Valcarcel,[1] Sara J. Schonfeld,[1] Sarah S. Jackson,[2] Graça M. Dores,[1,3] Martha S. Linet[1] and Lindsay M. Morton[1]

[1]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD and [3]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

Correspondence:
B. VALCARCEL - bryan.valcarcel@nih.gov

https://doi.org/10.3324/haematol.2024.285281

Received: February 15, 2024.
Accepted: June 7, 2024.
Early view: June 13, 2024.

©2024 NIH (National Institutes of Health)

Disclosures

No conflicts of interest to disclose.

Contributions

BV, SJS, SSJ, GMD, MSL, and LMM conceptualized and designed the study. BV performed the analysis. BV, SJS and LMM drafted the manuscript. SJS and LMM contributed to data acquisition and acquired funding. LMM supervised and administered the study. SJS, SSJ, GMD, MSL and LMM provided valuable edits to the manuscript and approved the final version of the manuscript.

Funding

This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute, National Institutes of Health, Bethesda, MD. The opinions and information in this article are those of the authors and do not represent the views and/or policies of the U.S. Food and Drug Administration.

Data-sharing statement

De-identified data are available at https://seer.cancer.gov/.

References

1. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006;107(1):265-276.
2. Costas L, de Sanjosé S, Infante-Rivard C. Reproductive factors and non-Hodgkin lymphoma: a systematic review. Crit Rev Oncol Hematol. 2014;92(3):181-193.
3. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer. 2011;105(11):1684-1692.
4. Lamb M, Painter D, Howell D, et al. Lymphoid blood cancers, incidence and survival 2005-2023: a report from the UK's Haematological Malignancy Research Network. Cancer Epidemiol. 2024;88:102513.
5. Radkiewicz C, Bruchfeld JB, Weibull CE, et al. Sex differences in lymphoma incidence and mortality by subtype: A population-based study. Am J Hematol. 2023;98(1):23-30.
6. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2015-2019. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html Accessed February 02, 2021.
7. Shiels MS, Engels EA, Linet MS, et al. The epidemic of non-Hodgkin lymphoma in the United States: disentangling the effect of HIV, 1992-2009. Cancer Epidemiol Biomarkers Prev. 2013;22(6):1069-1078.
8. Paternoster R, Brame R, Mazerolle P, Piquero A. Using the correct statistical test for the equality of regression coefficients. Criminology. 1998;36(4):859-866.
9. Chihara D, Nastoupil LJ, Williams JN, Lee P, Koff JL, Flowers CR. New insights into the epidemiology of non-Hodgkin lymphoma and implications for therapy. Expert Rev Anticancer Ther. 2015;15(5):531-544.
10. Liu P-P, Wang K-F, Xia Y, et al. Racial patterns of patients with primary mediastinal large B-cell lymphoma: SEER analysis.

Medicine (Baltimore). 2016;95(27):e4054.
11. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood. 2003;102(12):3871-3879.
12. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev. 2003;2(3):119-125.
13. Gubbels Bupp MR, Potluri T, Fink AL, Klein SL. The confluence of sex hormones and aging on immunity. Front Immunol. 2018;9:1269.
14. Marchi E, O'Connor OA. The rapidly changing landscape in mature T-cell lymphoma (MTCL) biology and management. CA Cancer J Clin. 2020;70(1):47-70.