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RESEARCH ARTICLE

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Sex differences in lymphoma incidence and mortality by subtype: A population-based study

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Abstract

It is well established that the male sex is associated with increased risk for, as well as poorer survival of, most cancers. A similar pattern has been described in lymphomas but has not yet been comprehensively assessed. In this nationwide population-based cohort study, we used the Swedish Lymphoma Register to investigate sex differences in lymphoma subtype incidence and excess mortality in adults (age 18–99) diagnosed in 2000–2019. Male-to-female incidence rate ratios (IRRs) and excess mortality ratios (EMRs) adjusted for age and calendar year were predicted using Poisson regression. We identified 36 795 lymphoma cases, 20 738 (56.4%) in men and 16 057 (43.6%) in women. Men were at significantly higher risk of 14 out of 16 lymphoma subtypes with IRRs ranging from 1.15 (95% confidence interval [CI] 1.09–1.22) in follicular lymphoma to 5.95 (95% CI 4.89–7.24) in hairy cell leukemia. EMRs >1 were seen in 13 out of 16 lymphoma subtypes indicating higher mortality in men, although only statistically significant for classical Hodgkin lymphoma 1.26 (95% CI 1.04–1.54), aggressive lymphoma not otherwise specified 1.29 (95% CI 1.08–1.55), and small lymphocytic lymphoma 1.52 (95% CI 1.11–2.07). A corresponding analysis using data from the Danish Lymphoma Register was performed with comparable results. In conclusion, we demonstrate a significantly higher incidence and trend toward higher mortality in men for most lymphoma subtypes. Future studies with large patient material that include detailed clinicopathological prognostic factors are warranted to further delineate and explain sex differences in lymphoma survival to enable optimal management of lymphoma patients regardless of sex.

1 | INTRODUCTION

Malignant lymphoma is one of the ten most common cancers globally[1] and constitutes a heterogenous group of diseases with more than 80 subtypes ranging from aggressive to indolent as well as curable to chronic diseases.[2,3] Similar to most other malignancies, a majority of lymphoma subtypes seem to be more common in men compared to women.[4–6] A marked male predominance has been observed in

Burkitt lymphoma (BL), hairy cell leukemia (HCL), mantle cell lymphoma (MCL), and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).[4] In contrast, primary mediastinal B-cell lymphoma (PMBL) is more common in women.[7] The underlying reasons for sex differences in lymphoma incidence remain unknown but have been suggested to reflect different exposures to environmental carcinogens and/or intrinsic disparities such as immunological and hormonal factors, body size, and tumor biology, in men and women.[5,8]

Furthermore, a survival disadvantage among men has been observed for several types of lymphoma.[9,10] Male sex is included as an adverse risk factor in the International Prognostic Score (IPS) for classic Hodgkin lymphoma (cHL),[11] which is supported by more recent studies.[12,13] A protective effect of female sex hormones has been suggested, since the female survival advantage in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) was limited to premenopausal women in some studies.[14,15] However, elderly women with DLBCL and FL have also been reported to have higher survival compared to elderly men, which may reflect sex differences in drug exposure and response to lymphoma treatment, unrelated to age.[16,17] Of note, many of the previous studies did not account for a longer female life expectancy, a potential driver of the reported sex differences in lymphoma survival, especially in elderly patients.[18]

Comprehensive studies of sex differences in lymphoma incidence and prognosis in the era of immunochemotherapy are sparse and previously reported differences may not persist. In this large, population-based Swedish cohort study, we aimed to quantify and outline sex differences in lymphoma incidence and excess mortality by subtype and corroborate results using Danish lymphoma register data. Studying sex differences in lymphoma can improve the understanding of the etiology and disease trajectories of lymphoma and aid clinicians to optimize management and outcomes in both male and female lymphoma patients.

2 | METHODS

2.1 | Data sources and study design

This is a population-based cohort study including all incident adult (age 18–99) lymphoma cases recorded in the Swedish Lymphoma Register (SLR) between 2000 and 2019. Compared to the Swedish Cancer Register, the completeness of the SLR is approximately 95%.[2] The SLR contains lymphoma-specific clinical data on patient and disease characteristics.

To avoid duplicate registrations including relapses, we only included the first record of the same lymphoma subtype. Multiple recordings of different lymphoma subtypes in the same individual were allowed ($n = 242$). The SLR does not include cases based on

TABLE 1 Number of cases (n), proportions (%) and median age, in men, women, and overall, by lymphoma subtype in the Swedish study population

	Men		Women		Total		Median age (range)	
Lymphoma subtype	*n*	%	*n*	%	*n*	%	Men	Women
Total	20 738	56.4	16 057	43.6	36 795	100	68 (18–99)	70 (18–99)
DLBCL	6262	55.8	4958	44.2	11 220	30.5	70 (18–99)	73 (18–99)
FL	2519	49.5	2568	50.5	5087	13.8	66 (18–96)	67 (19–98)
TCL	1216	61.8	752	38.2	1968	5.3	66 (18–95)	70 (18–96)
cHL	1789	54.3	1504	45.7	3293	8.9	47 (18–93)	39 (18–99)
MCL	1464	72.3	560	27.7	2024	5.5	71 (35–96)	72 (22–97)
MZL	1046	46.2	1216	53.8	2262	6.1	69 (18–99)	70 (24–98)
LPL	1364	60.9	875	39.1	2239	6.1	73 (24–96)	74 (29–94)
Aggressive NOS	593	56.3	461	43.7	1054	2.9	71 (18–97)	74 (20–96)
Indolent NOS	891	52.1	818	47.9	1709	4.6	73 (18–98)	74 (20–98)
HCL	620	83.8	120	16.2	740	2.0	62 (29–94)	66 (31–96)
PMBL	77	42.1	106	57.9	183	0.5	39 (18–85)	36 (18–83)
BL	237	73.1	87	26.9	324	0.9	56 (18–89)	63 (19–93)
PCNSL	311	51.9	288	48.1	599	1.6	65 (20–96)	69 (18–95)
NLPHL	165	73.7	59	26.3	224	0.6	45 (18–86)	59 (18–88)
SLL	798	61.7	496	38.3	1294	3.5	73 (28–97)	73 (24–96)
Cutaneous	369	59.8	248	40.2	617	1.7	68 (19–96)	67 (18–97)

Abbreviations: Aggressive NOS, aggressive not otherwise specified; BL, Burkitt lymphoma; Cutaneous, cutaneous lymphoma; cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; Indolent NOS, indolent not otherwise specified; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; PMBL, primary mediastinal B-cell lymphoma; SLL, small lymphocytic lymphoma; TCL, T-cell lymphoma.

death certificates only and patients with the date of diagnosis recorded >28 days after the date of death ($n = 17$) and patients with missing data on histology ($n = 169$) were excluded. We defined 16 clinically relevant lymphoma subtypes according to the most recent WHO classification system in use at the date of diagnosis (2001, 2008, and 2016 respectively)[3,19,20] (Table S1). PMBL was recorded as a distinct disease entity and included as a separate subtype from the year 2007. Rare lymphoma subtypes and cases with less detailed data on histology were grouped as indolent not otherwise specified (NOS) or aggressive NOS (Table S1). A subset of patients ($n = 1958$) was only recorded as lymphoma NOS and could not be further subclassified. Results for this group are not reported.

Information on the date of death was linked from the Swedish Cause of Death Register using the national registration number assigned to all Swedish residents. Publicly available, aggregated age-, sex-, and calendar year- specific population and mortality counts were retrieved from Statistics Sweden to estimate the incidence and excess mortality, respectively.

2.2 | Statistical analysis

If not otherwise stated, all analyses were stratified by lymphoma subtype. Age distribution in men and women was explored by plotting the number of cases by age group (18–44, 45–54, –64, 65–74, and 75–99 years) and sex (Figure S1). Age-standardized incidence rates (ASIRs) were computed as the number of incident lymphoma cases per 100 000 person-years and standardized to the Swedish population distribution (1-year age intervals) in 2019. Age- and calendar year-adjusted male-to-female incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were estimated using Poisson regression. Smooth incidence rates (IRs) in men and women and male-to-female IRRs by year and age were predicted from Poisson regression using restricted cubic splines with four or five degrees of freedom. Model fit was ascertained by visual comparisons of year- and age-specific estimates and the corresponding spline-derived predictions (Figure S2).

Survival time was counted from the date of diagnosis to the date of death or end of follow-up (December 31, 2020), whichever occurred first. A relative survival (RS) framework was applied to assess lymphoma-specific survival.[21] This was done by contrasting the observed all-cause survival among lymphoma patients to the expected all-cause survival in the general population matched by age, sex, and calendar year of diagnosis, using the Ederer II method. The 5-year RS in men and women was age-standardized according to the International Cancer Survival Standard (ICSS) 1, except for in young age-onset lymphomas; cHL, PMBL, BL, and NLPHL, where ICSS 3 was used.[22] The age-standardized RS in men and women was plotted over

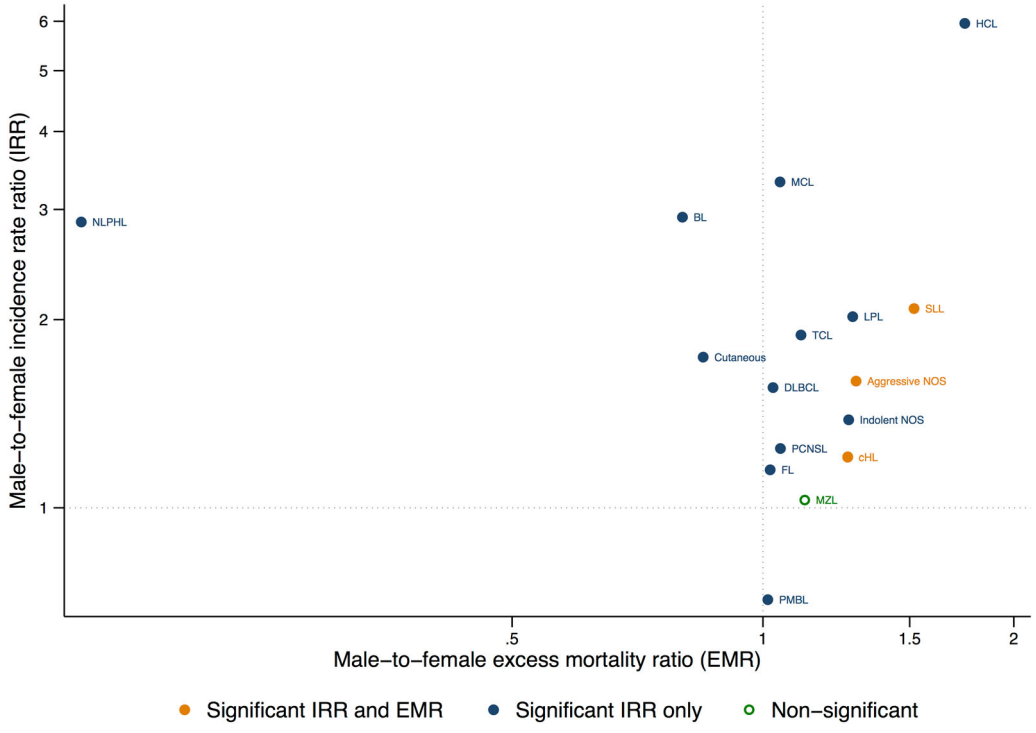

FIGURE 1 Male-to-female incidence rate ratio (IRR) by male-to-female excess mortality ratio (EMR), both adjusted for age and year of diagnosis, by lymphoma subtype in the Swedish study population. Abbreviations: Aggressive NOS, aggressive not otherwise specified; BL, Burkitt lymphoma; Cutaneous, cutaneous lymphoma; cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; Indolent NOS, indolent not otherwise specified; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; PMBL, primary mediastinal B-cell lymphoma; SLL, small lymphocytic lymphoma; TCL, T-cell lymphoma. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Age-standardized incidence rates (ASIR), adjusted male-to-female incidence rate ratios (IRR) including 95% confidence interval (CI), 5-year relative survival (RS), and adjusted male-to-female excess mortality ratios (EMR) including 95% CI, by lymphoma subtype in the Swedish study population

	ASIR[a]			5-year RS[c]		
Lymphoma subtype	Men	Women	Male-to-female IRR[b] (95% CI)	Men	Women	Male-to-female EMR[b] (95% CI)
DLBCL	9.57	6.40	1.56 (1.50–1.62)	63 (61–64)	64 (62–65)	1.03 (0.96–1.10)
FL	3.67	3.39	1.15 (1.09–1.22)	81 (79–84)	82 (80–84)	1.02 (0.85–1.23)
TCL	1.79	0.99	1.89 (1.72–2.07)	37 (34–40)	42 (38–45)	1.11 (0.98–1.26)
cHL*	2.46	2.02	1.21 (1.13–1.29)	85 (83–86)	87 (85–88)	1.26 (1.04–1.54)
MCL	2.25	0.72	3.32 (3.01–3.66)	57 (54–60)	59 (55–64)	1.05 (0.89–1.24)
MZL	1.58	1.60	1.03 (0.95–1.12)	83 (80–86)	84 (81–87)	1.12 (0.82–1.54)
LPL	2.14	1.14	2.02 (1.86–2.20)	79 (76–81)	84 (80–86)	1.28 (0.97–1.70)
Aggressive NOS	0.90	0.59	1.59 (1.41–1.80)	47 (42–51)	53 (48–58)	1.29 (1.08–1.55)
Indolent NOS	1.40	1.06	1.38 (1.26–1.52)	75 (71–79)	81 (77–84)	1.27 (0.97–1.65)
HCL	0.88	0.16	5.95 (4.89–7.24)	90 (84–93)	94 (82–98)	1.75 (0.50–6.06)
PMBL*	0.10	0.14	0.71 (0.53–0.96)	82 (73–89)	86 (73–93)	1.01 (0.37–2.81)
BL*	0.33	0.12	2.92 (2.28–3.73)	74 (68–79)	66 (53–76)	0.80 (0.54–1.19)
PCNSL	0.45	0.40	1.24 (1.06–1.46)	27 (22–32)	27 (22–33)	1.05 (0.86–1.29)
NLPHL*	0.22	0.08	2.86 (2.13–3.86)	97 (80–100)	95 (85–98)	0.15 (0.01–2.59)
SLL	1.25	0.65	2.08 (1.86–2.33)	72 (68–75)	81 (76–85)	1.52 (1.11–2.07)
Cutaneous	0.55	0.32	1.74 (1.48–2.05)	73 (67–78)	74 (66–80)	0.85 (0.57–1.27)

Abbreviations: Aggressive NOS, aggressive not otherwise specified; BL, Burkitt lymphoma; Cutaneous, cutaneous lymphoma; cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; Indolent NOS, indolent not otherwise specified; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; PMBL, primary mediastinal B-cell lymphoma; SLL, small lymphocytic lymphoma; TCL, T-cell lymphoma.
[a]Age-standardized according to the Swedish population in year 2019.
[b]Adjusted for age and calendar year at diagnosis.
[c]Age-standardized according to the International Cancer Survival Standard 1 (3 in young age-onset lymphomas marked*).

time since diagnosis. Sex differences in lymphoma-specific mortality were quantified by estimating male-to-female excess mortality ratios (EMRs) using Poisson regression, including age and calendar year in the models. The excess mortality is defined as the absolute difference between the mortality (i.e. hazard rate) in the lymphoma population and the expected mortality in a matched (sex, age, and year) general population. It is thus a measure of the excess mortality that can be attributed to lymphoma disease. The male-to-female EMR is the excess mortality in males divided by the excess mortality in female lymphoma patients. As a sensitivity analysis to explore age modification, we allowed for the effect of sex on lymphoma mortality to vary over age by including an interaction term between sex and age group (18–49, 50–69, and 70–99 years) in the adjusted Poisson regression model. The likelihood ratio test was used to assess whether the model allowing for age interaction fitted the data better than the model without.

The significance level was set to 0.05 and all tests of statistical significance were two-sided. Data management and statistical analyses were performed using Stata Statistical Software (Release 16. College Station, TX: StataCorp LLC), R (version 4.0.3), and SAS (SAS Institute Inc., Gary, NC, USA). The study was approved by the Ethical Review Board in Stockholm, Sweden (2021–02209) and the North Jutland Region (2021–255) as well as the Danish Clinical Quality Program (LYFO-2022-01-18).

2.3 | Danish data

Corresponding analyses were performed using data on adult (age 18–99) lymphoma patients recorded in the high-coverage (95%) Danish Lymphoma Register (LYFO)[23] diagnosed in 2000–2019. Efforts were made to harmonize subtype definitions but due to different coding systems and disease classifications, it was not possible to define the exact same subtypes in the Danish material. For comparability, IRs were age-standardized according to the Swedish population in 2019.

3 | RESULTS

3.1 | Swedish data

We identified 36 795 lymphoma cases in 36 553 individuals, 20 738 (56.4%) in men and 16 057 (43.6%) in women. The most common

subtypes were DLBCL, FL, and cHL, representing 30.5%, 13.8%, and 8.9% of cases respectively. Median age at diagnosis (all lymphomas combined) was 68 years in men and 70 years in women (Table 1). Except for in cHL, BL, PMBL, and NLPHL, a majority of patients were diagnosed at an advanced age (Figure S1).

Fourteen out of 16 lymphoma subtypes were significantly more common in men (male-to-female IRR >1) compared to women (Figure 1, Table 2). The largest male predominance was seen in NLPHL, BL, MCL, and HCL, with IRRs ranging from 2.86 (95% CI 2.13–3.86) in NLPHL to 5.95 (95% CI 4.89–7.24) in HCL. PMBL was significantly more common in women, IRR 0.71 (95% CI 0.53–0.96), and marginal zone lymphoma (MZL) was equally common in men and women, IRR 1.03 (95% CI 0.95–1.12) (Table 2). ASIRs in men and women and by lymphoma subtype, are presented in Table 2.

To explore incidence trends over time, we plotted the ASIRs in men and women (right y-axis) together with male-to-female IRRs (left y-axis) over calendar year (Figure 2). Incidence in men and women was roughly stable over time in most lymphoma subtypes and so was the male predominance.

With few exceptions, the incidence of most lymphoma subtypes increased with age and peaked around age 75–80 years (Figure S3). The age-incidence pattern in cHL was bimodal with a more distinct peak in young women and elderly men. PMBL was more common among young and the incidence was higher in young women compared to young men.

Excess mortality was higher in men (male-to-female EMR >1) in most lymphomas, but only statistically significant in three subtypes; cHL 1.26 (95% CI 1.04–1-54), aggressive NOS 1.29 (95% CI 1.08–1-55), and small lymphocytic lymphoma (SLL) 1.52 (95% CI 1.11–2.07) (Figure 1, Table 2). The age-standardized 5-year RS in men and women is presented in Table 2 and plotted over years since diagnosis in Figure S4.

We explored the effect modification of male sex on excess mortality by age group 18–49, 50–69, 70–99 years and saw no clear patterns suggestive of age interaction nor evidence of superior model fit compared to the model without age interaction (Figure S5).

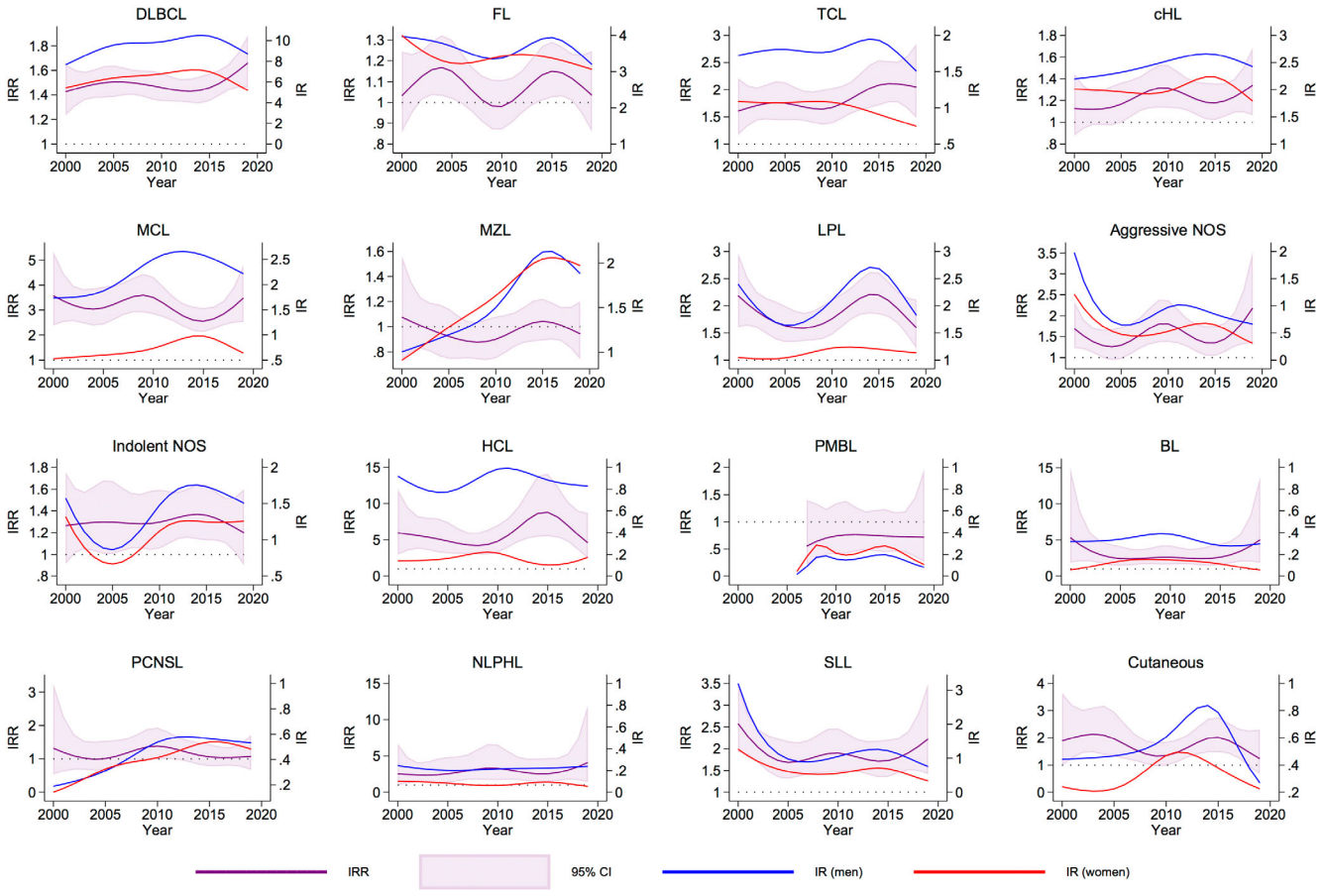

FIGURE 2 Male-to-female age-adjusted incidence rate ratios (IRR) and age-standardized incidence rates (IR) for men and women by calendar year of diagnosis for all included lymphoma subtypes in the Swedish study population. Abbreviations: Aggressive NOS, aggressive not otherwise specified; BL, Burkitt lymphoma; Cutaneous, cutaneous lymphoma; CI, confidence interval; cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; Indolent NOS, indolent not otherwise specified; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; PMBL, primary mediastinal B-cell lymphoma; SLL, small lymphocytic lymphoma; TCL, T-cell lymphoma. [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Danish data

In Denmark, 23 794 lymphoma cases in the same number of individuals were registered in LYFO during the period under study, 13 280 (55.8%) in men and 10 514 (44.2%) in women. The most common subtypes were DLBCL, FL, SLL, and cHL representing 31.9%, 16.4%, 9.9%, and 9.8% of cases, respectively (Table S2a). The sex distribution within subtypes was similar compared to the Swedish material and a statistically significantly higher incidence (male-to-female IRR >1) among men was seen in all investigated lymphoma subtypes. The excess mortality was higher in men (male-to-female EMR >1) in most lymphoma subtypes, with statistically significant differences in MZL, LPL, and SLL (Table S2b).

4 | DISCUSSION

This large Swedish population-based cohort study is, to the best of our knowledge, the first comprehensive nationwide report of sex differences in incidence and mortality of all lymphoma subtypes. We observed a significantly higher incidence in men for all lymphoma subtypes except PMBL and MZL. We also demonstrate a trend toward higher excess mortality in men in most lymphoma subtypes and significantly so in cHL, aggressive NOS, and SLL. Comparable results were found in a corresponding Danish nationwide lymphoma population. These data serve as a real-world reference for sex differences in lymphoma incidence and mortality and may aid the design of future studies on sex differences in lymphoma.

Our results support previous findings of an excess lymphoma risk in men. Similar male-to-female IRRs were reported in the white US population in a large study from 1992 to 2001.[4] In a more recent study of PMBL patients diagnosed in the US in 2001 to2012, a significantly higher incidence was seen in white women compared to men.[24] A study performed in the UK also reported most lymphoma subtypes to be more common in men, but in contrast to our results, FL was more common in women.[25] It is well known that men are at increased risk of a majority of cancer types compared to women.[5,6] In some cancers, such as lung, head, and neck, this is partly explained by a historically unequal exposure to cigarette smoking and alcohol consumption.[5] In other cancers, including hematological malignancies, underlying mechanisms remain unclear.[5] Sex differences in immunological surveillance that make men more vulnerable to proto-oncogenic mutations but also chronic, potentially carcinogenic infections, have been suggested.[26] There is evidence of an inverse relationship between the number of pregnancies and lymphoma risk, suggesting an influence of sex hormones on lymphoma development.[27] Men are in general larger than women and attained body height is associated with elevated cancer risk assumingly by increased mutational load through a higher number of stem cell divisions and/or growth hormone exposure in childhood.[28] Given that the male excess risk varies between lymphoma subtypes there is probably not one, universal explanation behind the observed sex differences.

We found MZL to be equally common in men and women. Parotid MALT lymphoma is known to be more common in women, possibly through the association with Sjogren's syndrome, an autoimmune disorder mainly affecting women.[29] Most autoimmune disorders are more common in women and some (e.g., Sjogren's syndrome and systemic lupus erythematosus) have been linked to increased risk of specific lymphoma subtypes such as MZL and DLBCL.[30] This association is believed to be related to the increased inflammatory activity in autoimmune diseases rather than the immunosuppressive treatment.[31]

Our results indicate poorer lymphoma-specific survival in males compared to females, across a majority of subtypes, in both Sweden and Denmark. The survival differences were less pronounced compared to previous studies on older material,[9,10] however there are also reports of comparable lymphoma survival in men and women.[25] We only adjusted the excess mortality estimates for age and year of diagnosis, but cancer survival is affected by multiple, interacting factors such as disease stage, tumor characteristics, treatment and ability to tolerate and comply to treatment, comorbidity burden, performance status, socioeconomic status, and more. In studies including detailed prognostic factors, male sex has remained a significant negative prognostic factor in several lymphoma subtypes.[13,14,16,17,32–41] In a large UK study that explored the effect of comorbidity and socioeconomic factors on DLBCL and FL survival, male sex was an independent, negative prognostic factor in both subtypes despite meticulous adjustments.[32] In a Swedish study on comorbidity and DLBCL survival, the male survival disadvantage persisted after adjustments for comorbidity, education, performance status, and lymphoma-related prognostic factors.[33]

Furthermore, the effect of sex on survival can differ between age groups. In recent studies, the male survival disadvantage was reported to be confined to old DLBCL and FL patients.[17,34] Proposed explanations include more effective clearance of rituximab in elderly men compared to women causing an underdosage of rituximab in men.[16] This could also explain the increased risk of early disease progression and worse survival in men reported in FL clinical trials.[36,37] Higher doses of rituximab do indeed seem to mitigate the inferior prognosis seen in elderly men with DLBCL.[42] Sex differences in pharmacokinetics have been reported for various drugs. Suggested mechanisms include differences in plasma volume, body size, plasma protein levels, gastric emptying time, liver enzyme activity, drug transporter function, and excretion.[43] Other studies have reported the female survival advantage in DLBCL and FL to be limited to patients of premenopausal age, indicating an effect of sex hormones on lymphoma survival.[14,15] Sex differences in lymphoma survival have also been described in adolescents but not prepubertal children, strengthening the hormonal hypothesis. Interestingly, male adolescents had superior survival compared to female.[44] A better understanding of the underlying mechanisms behind sex differences in survival are of importance to optimize the management of all lymphoma patients, through for example sex adapted chemoimmunotherapy dosage.

We found a significant survival disadvantage in men compared to women with cHL. Male sex is included in the IPS[11] and has remained a consistent negative prognostic factor in recent studies,[9,12,13] although some studies have suggested a weakened association over time.[38,45,46] Interestingly, cHL subclass distribution differs between men

and women,[12] suggesting sex-related differences in pathogenesis. Women with MCL are reported to have better prognosis[39] and more frequently present with indolent disease compared to men,[47] also suggesting sex differences in tumor biology. We found that men have worse SLL survival than women, both in the Swedish and Danish material. This is in line with clinical studies on chronic lymphocytic lymphoma (CLL), where male sex has been established as a poor prognostic factor.[40,41] One proposed explanation is that women with CLL less often harbor negative genetic markers such as unmutated *IGHV* and *TP53*-mutations.[41]

As in all observational studies using register data the present study has limitations mainly regarding potential information bias and unmeasured, residual confounding. However, information bias is unlikely to affect men and women differently. For example, the incomplete registration of lymphomas in 2019 in SLR is reflected in a discrete downward trend in incidence in both men and women in the Swedish material. Further, the WHO classification system has changed twice over the inclusion period, possibly affecting subtype distribution over calendar time. Differences in coding practices hamper direct comparisons between Swedish and Danish results but do not override the general pattern. Although the SLR and LYFO do not collect data on ethnicity, the Swedish and Danish populations are predominantly white. Differences in lymphoma incidence by ethnicity have been described previously,[4] and therefore our results may not be applicable to non-white populations. The lack of information on patient- and disease-related factors precludes adjustments and identification of possible explanations to the reported incidence and survival differences. Our study is however merely descriptive and hypothesis-generating and was not designed to disentangle underlying drivers. Due to low numbers of cases and deaths, the study was probably underpowered to detect small sex differences in excess mortality in rare lymphoma subtypes. To increase power, we plan to conduct detailed subtype-specific studies using pooled data from multiple countries and include variables si treatment, stage, performance status, comorbidity burden, and socioeconomic factors to provide a more detailed understanding of sex differences in lymphoma survival.

The main strengths of this study include the unique nationwide design, large data volume, and the completeness of the SLR encompassing close to all lymphoma patients diagnosed during the last two decades in Sweden. In addition to high completeness, the SLR contains high-quality clinical data enabling a detailed classification into clinically relevant lymphoma subtypes. Individual-level data-linkage to the Swedish Cause of Death Register provided an unbiased and complete follow-up of all included study participants. The population-based approach and age-adjusted estimates make our results representative and generalizable to other countries with similar ethnic composition, demographics, and health care systems. Furthermore, we were able to reproduce our findings in corresponding Danish lymphoma register data.

In summary, in this comprehensive and nation-wide population-based cohort study extending over the last two decades, we demonstrate a higher risk for a majority of lymphoma subtypes as well as a trend toward poorer lymphoma survival in men compared to women. The present work provides a generalizable real-world reference for sex differences in lymphoma. Further studies are warranted to explain sex differences in incidence and excess mortality in order to better understand disease mechanisms and optimize the management of both men and women with lymphoma.

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DATA AVAILABILITY STATEMENT

Data subject to third party restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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