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Øvlisen, Andreas Kiesbye

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BY
ANDREAS KIESBYE ØVLISEN

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AALBORG UNIVERSITY
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Andreas Kiesbye Øvlisen

AALBORG UNIVERSITY
DENMARK

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PhD supervisor: Professor Tarec C. El-Galaly, MD, DMSc
Department of Clinical Medicine, Aalborg University
Department of Hematology, Aalborg University Hospital

Assistant PhD supervisors: Professor Marianne T. Severinsen, MD, PhD
Department of Clinical Medicine, Aalborg University
Department of Hematology, Aalborg University Hospital

Associate Prof. Lasse H. Jakobsen, PhD
Department of Clinical Medicine, Aalborg University
Department of Hematology, Aalborg University Hospital

Associate Prof. Kristian H. Kragholm, MD, PhD
Department of Cardiology, Aalborg University Hospital

Professor Martin Bøgsted, PhD
Department of Clinical Medicine. Aalborg University
Department of Hematology, Aalborg University Hospital

PhD committee: Associate Clinical Professor Salome Kristensen
Aalborg University

Professor Christen Bertel Lykkegaard Andersen
University of Copenhagen

Consultant Haematologist Graham P Collins
Oxford University Hospitals NHS Trust Oxford

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

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PREFACE

This PhD thesis presents the work performed during my PhD from October 2018 to September 2021 at the Department of Hematology, Aalborg University Hospital, and the Department of Clinical Medicine, Aalborg University. The thesis consists of three scientific papers. The content of the thesis is primarily intended for epidemiologists and clinicians.

The PhD thesis would not have been possible without the support and guidance from people I would like to acknowledge here. First and foremost, I would like to thank my main supervisor, Tarec El-Galaly, for the opportunity to work as a PhD student at the Department of Hematology. Your encouragement, guidance, and faith in me throughout the years as well as pushing me beyond limits have made sure, that I advanced my skills as a researcher. You have always found time to help and guide me day or night and sharing your network with me, for which I'm grateful.

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I would also like to thank my family (Mor, Far, Therese, and Thomas) and friends (Dennis, Nanna, Ian, Sabrina, Julie, Ditte, Sille, and Line) for their support and

understanding throughout the years and for listening to my enthusiastic talks on recent results. Last but not least, a heartfelt thanks to my beloved Michelle. Without your love, support, and understanding throughout the years this would not have been possible.

Andreas Kiesbye Øvlisen, October 2021

ENGLISH SUMMARY

Hematological malignancies cover a wide range of cancers with different natural histories in terms of severity, curability, treatment strategies, and outcomes. Better treatment strategies, including more therapeutic options, have led to an increase in the number of long-term survivors. The fact that more patients are expected to survive for years, in some cases with a normal life expectancy, has spurred a relevant and growing interest in late toxicities and the psychosocial consequences of cancer treatment, ultimately aiming to improve survivorship care. However, limited research has focused on late toxicities and socioeconomic consequences following modern treatment of hematological malignancies on a population level. The aim of this PhD thesis was to provide hematologists with data that identify focal points for improving survivorship, including identifying patients who may benefit from more social support with focus on mental health problems and fertility in lymphoma patients.

This PhD thesis consists of three epidemiological, population-based, matched cohort studies. Study I showed that Hodgkin lymphoma (HL) patients have a higher risk of psychotropic drug (PD – antidepressants, antipsychotics, and anxiolytics) use compared to matched comparators. The higher risk is transient, as the risk for HL patients was normalized to that of the background population 5 years into survivorship. Study II revealed that parenthood rates in young relapse-free HL survivors are comparable to the rates of matched comparators. Moreover, no adverse effects on the born children were identified. The use of assisted reproduction techniques in higher in HL survivors, especially male HL survivors treated with BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone]. Study III showed that non-Hodgkin lymphoma (NHL) patients have a higher risk of PD use compared to matched comparators. More aggressive subtypes of NHL have the highest risk. For all patients except those with indolent NHL, the risk is transient and normalized 5 years after NHL diagnosis. Risk of intentional self-harm and suicide is also higher in NHL patients.

In conclusion, the three studies included in this thesis provide clinically relevant information regarding the risk of mental health problems after diagnosis of HL and NHL, as well as parenthood rates and birth outcomes for younger HL survivors. The results from these three studies underline the importance of research that not only aims to improve survival, but also increases awareness of socioeconomic consequences and late treatment complications that lymphoma survivors may experience.

DANSK RESUME

Hæmatologiske kræftsygdomme, herunder lymfom, leukæmi og myelomatose, er en heterogen gruppe af kræftsygdomme, hvad angår sygdomspræsentation, sværhedsgrad, behandlingsmuligheder og respons på behandling. Behandlingen af hæmatologiske kræftsygdomme har gennemgået en gennemgribende udvikling over de seneste årtier, hvor flere og bedre behandlingsmuligheder er kommet til. Dette har medført bedre respons på behandlinger generelt, hvilket betyder, at flere i dag bliver langtidsoverlevere, og at flere vil opnå en forventet restlevetid, der er på højde med resten af befolkningen. Det er derfor relevant og vigtigt at undersøge sene konsekvenser af behandlingerne, herunder sene bivirkninger og psykosociale konsekvenser, da dette ville kunne have en stor effekt på patienternes liv efter hæmatologisk kræft. Derudover vil viden om sene bivirkninger og socioøkonomiske konsekvenser også kunne bidrage til at forbedre og optimere forløbsprogrammer for rehabilitering efter kræft. På trods af vigtigheden heraf, sene bivirkninger og socioøkonomiske konsekvenser efter behandling for hæmatologisk kræftsygdom fortsat sparsomt belyst i større populationsbaserede studier. Formålet med dette ph.d.-projekt er derfor at identificere og undersøge sene bivirkninger og socioøkonomiske konsekvenser efter at være blevet diagnosticeret med en hæmatologisk kræftsygdom, hvor fokus mentale problemer og fertilitet blandt lymfom patienter. Denne viden vil medvirke til, at hæmatologer kan forbedre og optimere forløbsprogrammer for rehabilitering af patienter efter lymfom.

Dette ph.d.-projekt består af tre forskellige epidemiologiske populationsbaserede studier. Alle tre studier er udført som matchede kohorte studier, hvor patienterne gennemgående er matchet på blandt andet alder og køn med 5 tilfældige kontroller fra den danske baggrundsbefolkning. Studie I undersøgte forekomsten af mentale problemer, herunder angst og depression, blandt alle danske Hodgkin lymfom (HL) patienter, hvor psykotropika (PD – antidepressiva, antipsykotika og anxiolytika) blev brugt som et estimat herfor. Sammenlignet med den matchede kohorte, havde HL patienter en signifikant højere risiko for at få brug for behandling med PD. Den forhøjede risiko var dog forbigående, idet risikoen for at modtage PD var normaliseret til den matchede kohorte efter 5 års overlevelse. Studie II undersøgte, hvorvidt at patienter med HL kunne få børn efter endt behandling med kemoterapi, hvis de havde overlevet 9 måneder efter diagnosedatoen uden at få relaps af HL. Resultatet var, at raten for at blive forældre ikke var forskellig ved sammenligning med den matchede kohorte. HL patienternes børn var desuden født til tiden, havde normalt vægt og havde ikke øget risiko for misdannelser. Assisteret reproduktion (ART) blev i højere grad brugt af patienter med HL sammenlignet med den matchede kohorte. Her var det især mandlige patienter med HL behandlet med BEACOPP [bleomycin, etoposid, doxorubicin, cyklofosfamid, vincristin, procarbazin og prednisolon], der havde et hørt forbrug af ART i forbindelse med at få et barn. Studie III undersøgte risikoen for at modtage PD behandling blandt patienter med non-Hodgkin lymfom (NHL). Dette

viste at patienter med NHL havde en signifikant højere risiko for at modtage PD behandling sammenlignet med den matchede kohorte. NHL består af flere undertyper, og resultaterne viste, at patienter med de aggressive undertyper havde den største risiko. For alle undertyper af NHL, på nær patienter med indolent NHL, normaliserede risikoen sig til den matchede kohorte efter 5 års overlevelse. Ydermere var risikoen for selvskade og selvmord var ligeledes forhøjet blandt patienter med NHL.

De tre studier inkluderet i dette ph.d.-projekt har bidraget med klinisk relevant information omhandlende risiko for mentale problemer efter at være diagnosticeret med lymfom samt muligheden for HL patienter at kunne få et barn efter endt behandling. Resultaterne fra de tre studier understreger vigtigheden i at fortsætte og udbygge forskning indenfor socioøkonomiske konsekvenser og sene bivirkninger efter behandling for lymfom.

LIST OF PAPERS IN THE THESIS

The thesis is based on the following three papers:

I: **Depression and anxiety in Hodgkin lymphoma patients: A Danish nationwide cohort study of 945 patients**
Andreas K Øvlisen, Lasse H Jakobsen, Kristian H Kragholm, René E Nielsen, Martin Hutchings, Rasmus B Dahl-Sørensen, Henrik Frederiksen, Danny Stoltenberg, Martin Bøgsted, Lene S G Østgård, Marianne T Severinsen, Tarec C El-Galaly
Cancer Medicine, Vol. 9, Nr. 12, (2020) 4395-4404

II: **Parenthood Rates and Use of Assisted Reproductive Techniques in Younger Hodgkin Lymphoma Survivors: A Danish Population-Based Study**
Andreas K Øvlisen, Lasse H Jakobsen, Sandra Eloranta, Kristian H Kragholm, Martin Hutchings, Henrik Frederiksen, Peter Kamper, Rasmus Bo Dahl-Sørensen, Danny Stoltenberg, Caroline E Weibull, Joshua P Entrop, Ingrid Glimelius, Karin E Smedby, Christian Torp-Pedersen, Marianne T Severinsen, Tarec C El-Galaly
Journal of Clinical Oncology, (2021)

III: **Mental Health Among Patients with non-Hodgkin Lymphoma: A Danish Nationwide Study of Psychotropic Drug Use in 7,201 Patients and 36,005 Matched Comparators**
Andreas K Øvlisen, Lasse H Jakobsen, Kristian H Kragholm, René E Nielsen, Peter de Nully Brown, Rasmus B Dahl-Sørensen, Henrik Frederiksen, Nikolaj Mannering, Pär L Josefsson, Ahmed L Al-Mashhadi, Judit M Jørgensen, Andriette Dessau-Arp, Michael R Clausen, Robert S Pedersen, Christian Torp-Pedersen, Marianne T Severinsen, Tarec C El-Galaly
Manuscript submitted for publication October 2021

TABLES AND FIGURES

ABBREVIATIONS

ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
ART	Assisted reproduction technique
ATC	Anatomical therapeutic classification
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
CCI	Charlson Comorbidity Index
COPP	Cyclophosphamide, vincristine, procarbazine, and prednisone
CPR	Personal identification number
CR	Complete remission
CRS	Civil Registration System
CRu	Unconfirmed complete remission
DAG	Directed acyclic graph
DER	Danish Education Register
DHDA	Danish Health Data Authority
DIVF	Danish In Vitro Fertilization Register
DLBCL	Diffuse large B-cell lymphoma
DNPR	Danish National Prescription Register
DPCRR	Danish Psychiatric Central Research Register
DPR	Danish Pathology Register
EBV	Epstein-Barr virus
ECOG PS	Eastern Cooperative Oncology Group performance score
EFS	Event-free survival
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FTDB	Fertility Database
HL	Hodgkin lymphoma
ICD	International Classification of Diseases
IPI	International Prognostic Index
IQR	Interquartile range
IRR	Incidence rate ratio
ISCED	International Standard Classification of Education
IVF	In vitro fertilization
LYFO	Danish Lymphoma Registry
MFR	Medical Birth Register
MOPP	Nitrogen mustard, vincristine, procarbazine, and prednisone
NHL	Non-Hodgkin lymphoma
NPR	National Patient Register
OS	Overall survival
PCR	Polymerase chain reaction

PD	Psychotropic drug
PET-CT	Positron emission tomography and computed tomography
PFS	Progression-free survival
PR	Partial remission
R-CHOP	Rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone
RKKP	Danish Clinical Quality Program
SEP	Socioeconomic position
SMR	Standardized mortality ratio
SNOMED	Systematized Nomenclature of Medicine
WaW	Wait and watch
95% CI	95% confidence interval
/1000py	per 1000 person years

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CHAPTER 1: INTRODUCTION

1.1 LYMPHOMA

Lymphomas constitute a heterogenous group of hematological malignancies that arise from B, T, and NK cells. Lymphomas constitute approximately 5% of all new cancers, and the yearly incidence is approximately 23 and 35 per 100,000 persons for females and males, respectively (1,2). The etiology of lymphomas is complex and includes iatrogenic, herbicides, infections (e.g., *Helicobacter pylori,* Epstein Barr virus [EBV], human immune deficiency virus [HIV]), and immunodeficiency. The median patient age is 67 years, and there is a male predominance for most lymphomas (1,3,4). Lymphomas are classified as either Hodgkin (HL) or non-Hodgkin lymphoma (NHL), with the latter being the most common (~90%). Both the incidence and subsequent 1- and 5-year overall survival (OS) have been increasing steadily over the years, including the 1-year OS for lymphomas from 2004-2006 to 2016-2018 for both males (81% and 90%, respectively) and females (85% and 92%, respectively) (5). The same tendency was observed for the 5-year OS for males (62% and 76%, respectively) and females (70% and 83%, respectively) (5). However, NHLs, and to a lesser extent HLs, are characterized by a heterogenous biology and clinical presentation, which influence treatment decisions and survival. More detailed descriptions of the major lymphoma subtypes used in the papers included in this thesis are provided below.

1.1.1 HODGKIN LYMPHOMA

HL is a rare lymphoid malignancy with an incidence of 2-3 per 100,000 persons (approximately 130-140 new incidents in Denmark per year), and the incidence is higher among males (1,2). HL is characterized by a bimodal age distribution, with the first incidence peak observed in young adulthood between 18 and 30 years of age (6,7). Thus, HL is among the most frequent cancers in young adults after breast cancer, melanoma of the skin, and testicular cancer (8,9). The majority of HL patients present with lymph node involvement and extranodal disease (bone marrow, lungs, etc.) less frequently than in aggressive NHL types. At the time of diagnosis, approximately 40% of HL patients experience “B-symptoms” (night sweats, unexplained fever, and weight loss >10%). Other symptoms of HL include fatigue and itching without any skin pathology (10). The etiology of HL is not well understood, but several risk factors for the development of HL have been identified, including infections with EBV (causes mononucleosis) and HIV (10–12). Moreover, a family history of HL in parents or siblings is also associated with an increased risk of developing HL, especially if the age of the parents or siblings was < 40 years (13).

The diagnosis of HL requires a thorough anamnesis, objective investigation, and biopsies from available lymph nodes, as well as a bone marrow sample and a whole-body position emission tomography and computed tomography (PET-CT) scan for diagnosis, stage classification, and risk stratification. Based on the pathology, HL can be classified as either classical HL (~95%) or nodular lymphocyte predominant HL (~5%) (1,14). Classical HL is characterized by Reed-Sternberg cells, which are giant polynuclear cells with pale cytoplasm. The diagnosis is made based on the pathological examination of the lymph node tissue (10–12). To ensure that there is enough specimen for proper analysis, the involved lymph node should be excised. Fine needle aspirate from the lymph node is not sufficient because the architecture and Reed-Sternberg cell may not be identified from such a small specimen (10–12). Based on the diagnostic work-up, HL can be staged according to the Ann Arbor staging system developed in 1989 (1,10,14) as a limited stage (stage I and II non-bulky) or advanced stage (stage III/IV and II bulky) depending on the number and anatomical distribution of involved lymph nodes/sites. A or B can be added to the stage to indicate whether B-symptoms are absent or present, respectively (1,10,14,15).

Throughout the past four decades, the treatment of HL has changed dramatically. Treatments predominantly based on alkylating agents (MOPP regimen: nitrogen mustard, vincristine, procarbazine, and prednisone) and extensive field radiation (i.e., inverted Y field radiation) have been abandoned and newer, less toxic but highly effective therapies have been introduced (16). When the MOPP regimen was first introduced in the 1960s, the OS significantly improved; however, due to the toxicity of the agents in the regimen, the number of adverse effects and late toxicities (i.e., cardiovascular disease, infertility, secondary cancer) were high (15,16). Many of the acute and late toxicities are worsened in combination with extensive field radiation, which often included the heart, lungs, and gonads (17). Prior to implementing chemotherapy in the treatment of HL, only radiotherapy was available (18,19). At the time, the method used for radiation was extended field radiotherapy, which also involved lymph nodes in the same region as the affected lymph nodes. Radiotherapy given solely above the diaphragm was called Mantle field irradiation, whereas inverted Y field radiotherapy was used if para-aortic, iliacal, inguinal, and upper femoral lymph nodes were included in the irradiation field. This would result in delivering ≥44 Gy to the heart and other tissue without disease involvement, causing severe toxicity (18,19). With the introduction of effective chemotherapy regimens, such as MOPP and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), the concept of involved field radiotherapy was developed in which radiotherapy was only given to the fields with affected lymph nodes. The more recent concept is involved nodal radiotherapy, which was implemented in 2006 to minimize the dose of radiation received. In this approach, only the initially involved lymph nodes should be included for radiation based on pre-chemotherapy CT or PET-CT (17,18,20). However, this approach could be problematic if based on suboptimal CT or PET-CT. Consequently, involved site radiotherapy in which radiotherapy should be

administered to the sites initially involved prior to chemotherapy was developed and implemented in 2014 (17).

The two chemotherapy regimens used as first-line treatments are ABVD and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). Over the years, the number of cycles given have been reduced for both treatment modalities. Prior to current standards, treatment for patients with limited stage disease and favorable prognosis was four cycles of ABVD followed by radiotherapy. However, studies from the German Hodgkin Study Group (the HD7 and HD10 studies) showed that two cycles of ABVD followed by radiotherapy is just as effective if the interim PET-CT after the two first cycles is negative (21,22). Limited stage disease with an unfavorable prognosis was initially treated with four cycles of COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)/ABVD based on the HD8 trial, which showed that this is superior to prior standards (23). This was later changed to four cycles of ABVD without COPP to reduce toxicity. Later, the HD14 study showed that two cycles of escalated BEACOPP combined with two cycles of ABVD can increase tumor control and progression-free survival (PFS) (24). BEACOPP was initially introduced in 1998 by the German Hodgkin Study Group as a new regimen for the treatment of advanced stage disease (25,26). This was given for eight cycles, yielding a high cumulative dose. Several studies (including the HD15, HD18, and RATHL study) showed that treatment guided by interim PET-CT can reduce the number of cycles to four if PET-CT was negative (27–29). Therefore, PET-CT guidance has been implemented in the treatment of HL as the cumulative dose of BEACOPP and treatment-related toxicities have been reduced.

With current standard treatments, the cure rate of HL is high and has surpassed >80% regardless of age and disease stage (24,28–30). In 2019, the risk of relapse and loss of lifetime was investigated in a Nordic cohort of 2,585 young patients (age 18-49 years) with classic HL diagnosed between 2000 and 2013 who were treated with modern combined modality treatment (31). The 5-year OS was 95% and the corresponding 5-year risk of relapse 13.4%. HL patients who reached event-free survival (EFS) at 24 months (EFS24) had a lower risk of relapse (4.2%). Evaluating the loss of expected lifetime, during the first 5 years following diagnosis, the expected loss was 45 days compared to only 13 days if the EFS24 was reached. Due to the low rate of relapse after reaching the EFS24, follow-up for relapse should be limited (31). These results confirmed the BCCA study of 1,402 HL patients that showed the highest risk of relapse within the first 2 years following diagnosis (72% of all relapses) (32). The risk of relapse in patients reaching the EFS24 was 5.6% regardless of stage. As the prognosis is excellent and very few NHLs relapse, there is a need for improved survivorship care programs.

1.1.2 NON-HODGKIN LYMPHOMA

NHLs are the most common lymphoid malignancy in Denmark, with approximately 1,400 diagnoses per year (males, 35.2 per 100,000 persons; females, 22.7 per 100,000 persons) (2). NHLs are a very heterogenous group with highly variable incidence and disease course spanning from very acute, fast-growing, and potentially curative lymphomas to chronic, indolent lymphomas (33). The indolent NHLs are, by definition, incurable with conventional therapies unless they are present in a very localized form amendable to radiotherapy. Therapeutic options for indolent NHLs range from mild to moderate intensity immunochemotherapy regimens to single agent rituximab, or even observation without treatment (wait and watch [WaW]) for patients who present with asymptomatic disease. Treatment for aggressive NHLs include intensive and dose dense chemotherapy regimens and, in selected cases, consolidation strategies with autologous stem cell transplantation (33,34). Below, two of the most common NHL subtypes are described in more detail.

Diffuse large B-cell lymphoma
Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive lymphoma with approximately 500 new cases annually in Denmark (1). The diagnostic work-up and staging of DLBCLs is equivalent to that of HL. In 1993, the International Prognostic Index (IPI) was developed as a tool for physicians to predict the outcome prior to treatment (35). Items included in the index are tumor stage, serum lactate dehydrogenase level, number of extranodal sites, performance status, and age. A higher IPI indicates a worse prognosis.

The treatment of DLBCL has changed little in the past 20 years due to the introduction of the anthracycline-based multi-agent chemotherapy regimen used as a frontline therapy (cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone [CHOP]) combined with immunotherapy (CD20 antibody therapy, rituximab [R]). The R-CHOP regimen is usually given for 6-8 cycles and has been the first choice for treatment since the 2000s (36–39). The response rate to this regimen is high, and approximately 80% of patients will go into complete remission (CR) following therapy. Despite several attempts to improve on R-CHOP, it is still the first choice as first-line therapy because the addition of proteasome inhibitors, next generation CD20 antibodies, intensified chemotherapy regimens, and maintenance therapies have not been able to improve outcomes over and above what is achieved with standard R-CHOP (40–44). Even though the CR rate is high, the rates of relapse, progression, or failure to respond to treatment remain as high as 30-40% after evaluation of the initial response (45,46). These patients also have poorer outcomes, with only 20-30% achieving durable remission after salvage therapy (i.e., high dose chemotherapy, autologous stem cell transplant) (47). This group has been given a great amount of attention, and recent research brought hope to this group with recent concepts, such as CAR-T and bispecific antibodies (48–52).

Few studies have assessed the effect of reaching specific EFS milestones in regards to expected survival compared to the expected survival of the background population taking into account the declining survival probability of age (53–55). In one study, the different EFS milestones were investigated in 1,621 patients treated for DLBCL and in CR between 2003 and 2011 (53). In general, DLBCL patients had lower survival than the background population (78% vs. 87%, respectively; standard mortality ratio [SMR] = 1.75); however, patients reaching the EFS24 had favorable outcomes (SMR = 1.32), especially younger patients aged <50 years (SMR = 1.11). Loss of residual lifetime for all DLBCL patients was 1.07 months per year compared to the DLBCL patients reaching the EFS24, in which the loss of lifetime was minimal (0.31 months per year). In younger DLBCL patients, the survival normalized to that of the background population after reaching the EFS24, whereas mortality did not normalize for those aged ≥50 years. The results were consistent with a prior study of 767 DLBCL patients treated between 2002 and 2009, including not lonely patients who achieved CR (56). In this study, DLBCL patients who reached the EFS24 had an OS comparable to that of an age- and sex-matched general population (SMR = 1.18).

Follicular lymphoma

Follicular lymphoma (FL) is the most common type of indolent lymphoma, with a yearly incidence of approximately 3.2 per 100,0000 in Western countries, equivalent to approximately 250 new cases in Denmark per year (1,57–59). The diagnostic work-up is similar to that of HL, and staging is done using the Ann Arbor classification (60). Follicular lymphomas are graded as grade 1-3B based on histological analysis of the number of centroblasts, with grade 1-3A treated as indolent disease and grade 3B as an aggressive lymphoma. In 2004, the IPI was evaluated and adapted to follicular lymphoma as the FLIPI score (60,61). The prognostic score ranges from low to high risk based on the number of nodal sites involved, age, serum lactate dehydrogenase level, stage, and hemoglobin level. As a group, FLs are heterogenous, with initial management of the disease differing widely according to stage, grade, symptoms, and disease burden (62,63). Treatment spans from radiation therapy and single agent treatment with immunotherapy (rituximab) to immunochemotherapy (64–69). First-line therapy for asymptomatic patients with advanced disease should be WaW or rituximab monotherapy to reduce the risk of toxicity compared to the minimal beneficial effect of chemotherapy in this group. When tumor burden increases and symptoms develop, treatment with chemotherapy should be offered depending on age and fitness. Treatment modalities include rituximab in addition to lenalidomide, CHOP, bendamustine, or chlorambucil, among others. FL patients with limited stage disease and no symptoms should be offered localized radiotherapy, as CR can be achieved, and the need for treatment including chemotherapy can be postponed (60,70). The disease course for the patient is often long and consists of multiple periods in which patients are given treatment, go into remission, and then are re-treated. After the completion of immunochemotherapy, patients can be given maintenance rituximab, which has been shown to extend the PFS. However, this approach has not been shown to increase the OS (71).

Outcomes in FL patients have significantly improved over the years due to the implementation of anthracyclines, aggressive chemotherapy regimens, and rituximab (72–74). In FL patients with grade 1-2 disease, the introduction of aggressive chemotherapy regimens results in a median OS increasing from 11 years to 18.5 years (corresponding 10-year OS increase from 54% to 73%) (74). With the introduction of rituximab, the 10-year OS improved even more, to 73%. In a Swedish register study, the 10-year OS in the rituximab era was 59% when including all FL patients, and even higher in FL patients with grade 1-2 disease (~70%) (73).

FL can transform into a more aggressive type of lymphoma, most often DLBCL (75–77). The risk of transformation in the pre-rituximab era was 3% per year (continuous) compared to a transformation rate of 10.7% after 5 years of follow-up (2% per year) in the rituximab era (76,77). Outcomes of FL with transformation in the pre-rituximab era were poor (median survival 1.7 years); however, the 5-year survival was highly dependent on the extent of disease (66% in limited disease and 19% in advanced disease) (76). In the rituximab era, the median survival was 50 months with a 5-year OS of 48% (77).

The effect of a WaW strategy on survival and other outcomes was investigated in 286 FL patients with advanced disease compared to FL patients with advanced disease who received treatment and a matched cohort of 2,860 individuals (78). WaW patients had longer OS than non-WaW patients ($p = 0.02$). During the first 50 months after diagnosis, the WaW patients and the matched cohort had similar OS, but the WaW patients had worse OS after the 50-month milestone. During the first decade after diagnosis, the average loss of lifetime in WaW patients compared to the matched background population was 6.8 months, and the overall loss of lifetime calculated by a piecewise constant hazard ratio model was estimated to be 6 years.

1.2 CANCER SURVIVORSHIP CARE

1.2.1 DEVELOPMENT IN CANCER SURVIVAL

The incidence of cancer has been steadily increasing. In 2019, 45,453 new cancers (excluding basal cell skin cancer) were diagnosed in Denmark, resulting in an overall sex- and age-adjusted cancer incidence rate of 651 per 100,000 persons (2). Compared to 2018, the incidence increased by 2.7 in 2019 and by 21.8% in males and 17.8% in females over the last decade. The survival of cancer patients has also been increasing. The 1-year OS between 2016 and 2018 for all cancer types in Denmark was 82% for males and 83% for females, which is markedly higher than in the period 2004-2006, in which the 1-year survival was 71% and 73%, respectively. In addition, the long-term survival (5-year OS) increased between 2016 and 2018, 66% for males and 68% for females, whereas those diagnosed between 2004-2006 had a 5-year OS of 44%

and 48%, respectively. The combination of better survival and higher incidence has resulted in a high prevalence of both patients with cancer and cancer survivors (2). A recent report made by the Danish Health Data Authorities (DHDA) using the Danish Cancer Register found that, as of 2019, a total of 351,757 living Danish citizens had been diagnosed with at least one cancer during their lifetime. Compared to 2018, there was an absolute increase of 12,134 persons (3.6%). In 2010, the prevalence was 243,226, yielding a 10-year increase of 44.6%.

Increased cancer incidence and better survival for cancer patients with the subsequent higher prevalence of cancer patients and survivors can be explained by several factors. First, during the last few decades there has been extensive research into improving cancer therapies, which has increased the survival rates for several cancers and minimized the lethal toxic side effects of the therapies. Second, several screening programs have been introduced to diagnose early-stage cancers (79–82). Another contributing factor may be the introduction of specific cancer patient pathways in the 2000s in Denmark. The purpose of these pathways is to streamline and accelerate cancer diagnostics in Denmark to ensure equality in cancer diagnosis (83). The hope is that these policies, which must be followed by the Danish Regions, will lead to faster diagnosis and better survival when patients are diagnosed at an early stage.

1.2.2 CANCER SURVIVORSHIP CARE

Due to the increased number of cancer patients and survivors, more focus has been placed on improving survivorship. National cancer rehabilitation programs have been established to prevent loss of functioning and support full recovery (84,85). Return to normal functioning, including younger patients returning to the workforce, is of paramount importance to society to reduce the economic burden of cancer. Previous studies have shown that patients with cancers are at significant risk of prolonged sick leave, with some never returning to work (86–92).

Recognizing the uncertain value of current practice, the Danish Ministry of Health issued roadmaps for improved survivorship care in 2015, with a recent update in 2018 (84,85). This program aims to provide survivorship care that reflects the actual medical needs of individual patients in terms of risk of relapse and treatment complications. The update focused on decentralization of health-related care from the Regions to general practitioners and municipalities, and the importance of interdisciplinary cooperation. To further increase the survivorship care of cancer patients, it is now mandatory to prepare individualized rehabilitation programs for cancer patients to reduce the risk of substantial loss of function during and after cancer treatment (93,94). Rehabilitation programs should include a continuous focus on four different patient needs: physical (i.e., relapse, exercise, nutrition, late toxicities),

psychological (i.e., mental health problems), social (i.e., work, family, economy), and existential (93).

1.2.3 SURVIVORSHIP CARE FOR LYMPHOMA PATIENTS

Recent studies suggest that toxicity patterns are changing as novel therapies are introduced (17,30,95,96). Thus, the implementation of evidence-based, individualized follow-up following hematological malignancies requires extensive descriptions of health care use following contemporary treatments, including analyses of possible associations between patient characteristics, treatments, and the occurrence of specific toxicities. This is particularly relevant in this time when sophisticated methods for the detection of minimal disease using polymerase chain reaction (PCR) methods and/or circulating tumor DNA are being developed (97–100). In the future, these new technologies may become so sensitive and effective that clinical examinations and other tests for relapse could be redundant and post-treatment follow-up will focus exclusively on improving survivorship and address the specific needs of individual patients to maximize physical and social functioning after cancer (54,101–103). Though fear of relapse and disease progression are indisputable concerns among patients with hematological cancers, research consistently points to other significant health issues following cancer in general (104). Fatigue, pain, and insomnia are some of the frequently encountered health problems that may reduce quality life (105–108). As with other types of cancer, the roadmaps issued by the Danish Ministry of Health in 2018 also apply to lymphoma. Thus, lymphoma physicians are responsible for delivering personalized rehabilitation programs as needed based on clinical evaluations and discussions with the patients. To provide this, more studies are needed on late complications and the socioeconomic impact experienced by lymphoma patients after diagnosis and treatment. This includes delineating the differences between lymphoma survivors and the background population to separate the burden of lymphoma from the health issues experienced by similarly aged persons from the background population. Within the lymphoma patient group, identifying patterns of toxicity and their association with treatment selection and patient characteristics is equally important to target intervention to the patients in the most need, so-called personalized rehabilitation programs.

1.3 SOCIOECONOMIC CONSEQUENCES AND LATE TOXICITIES

1.3.1 SOCIOECONOMIC CONSEQUENCES AFTER LYMPHOMA

Socioeconomic position (SEP, also known as socioeconomic status) is a term to describe both social and economic factors that may influence the position of a person

in society. It is a widely used concept in healthcare research both for estimating inequality in healthcare access and as an adjusting factor in analyses. Despite the concept of SEP being widely used, the definition used across countries and researchers is very heterogenous. Thus, a definition of the term was established in 1997:

> *"Socioeconomic position: An aggregate concept that includes both resource-based and prestige-based measures, as linked to both childhood and adult social class position. Resource-based measures refer to material and social resources and assets, including income, wealth, educational credentials; terms used to describe inadequate resources include "poverty" and "deprivation". Prestige-based measures refer to individual's rank or status in a social hierarchy, typically evaluated with reference to people's access to and consumption of goods, services, and knowledge, as linked to their occupational prestige, income, and education level."* Cited from "Measuring Social Class in US Public Health Research: Concepts, Methodologies, and Guidelines" (109).

Based on this definition, which variables should be included to properly describe the SEP were later defined. Variables that could be included in the definition of SEP are education, housing tenure/conditions/amenities, income, occupation, wealth, social class, crowding (household size), and other proxies (i.e., number of siblings, infant/maternal mortality) (109–114).

Increasing prevalence, longer expected residual life, and high cure rates in lymphoma patients all contribute to the relevance of looking at the effect of lymphoma on SEP. Lymphoma survivors wish to return to a "normal" life after therapy, suggesting that this is also an indicator of perceived quality of life (115–117). Returning to a normal life would include being able to continue and complete an education, maintain employment and occupation, and maintaining the same income and lifestyle as prior to diagnosis. In addition, society would also benefit from more patients being able to join the workforce again, thereby reducing the economic burden (87,88,113,118).

Income is an important variable included in the definition of SEP, which is highly related to employment. This was investigated in a study including 1,094 NHL and 546 HL Norwegian patients (119). In the year following diagnosis, income declined for both NHL (males by 13.2%; females by 21.4%) and HL patients (males by 8.5%; females by 26.2%). No further analysis was conducted to investigate potential risk factors or whether the income would normalize with time.

Studies have also evaluated the chance of returning to the workforce among hematological cancer patients (87,88,113,118–120). In general, there was a high risk of not returning to the workforce (35%), especially within the first year after diagnosis (57%), whereas 36% of patients had still not returned to the workforce after 4 years. Several factors are negatively associated with maintaining employment after HL diagnosis and include late toxicity to treatment, anxiety, depression, marital status,

education level, and previous sick leave (113,118). Therefore, it is important to keep these factors in mind when analyzing return to the workforce and other SEPs.

1.3.2 MENTAL HEALTH COMPLICATIONS IN LYMPHOMA PATIENTS

Being diagnosed with cancer has a profound effect on a patient's mental health due to the distress that inevitably follows. Distress may be caused by anxiety of death, fear of relapse, fear of symptoms (losing hair, etc.), and acute and late toxicities (121–124). Therefore, there has been interest in the effect of cancer on mental health. Several studies have concluded that the risk of developing mental health problems, including depression, anxiety, and adjustment disorders, are increased in newly diagnosed cancer patients (125–133). These studies had various settings, as some described the absolute incidence of mental health disorders in cancer patients only, whereas others compared the incidence in cancer patients with matched comparators providing relative risks. Regardless of design, all concluded that a high risk of mental health problems exists. Living with depression, anxiety, and/or adjustment disorders may have a profound impact on several aspects of cancer patients' lives, including quality of life (134,135). Furthermore, SEPs may also be affected, as mental health disorders have been associated with prolonged sick leave, increased risk of disability pension, increased risk of not returning to the workforce, and increased risk of social complications, especially regarding family (136–139). Therefore, cancer-related distress and mental health problems are of high importance not only due to the direct suffering of affected patients, but also for the potentially devastating indirect effects of mental health problems on SEP.

Several factors associated with the risk of developing mental health problems, such as depression and anxiety, are shared among cancer patients and the general population. This includes higher age, females, and type of cancer (125,128,131). As for the effect of cancer type, patients with a favorable prognosis (i.e., prostate cancer, skin cancer) have a lower incidence of depression and anxiety compared to patients with an unfavorable prognosis (i.e., lung cancer, gynecological cancer, hematological cancer).

Alternative methods for studying mental health are needed because population-based studies investigating the risk of depression and anxiety using the standard approach of diagnosing depression and anxiety require prospective evaluations of patients and controls over long periods, with a high risk of incomplete follow-up and drop-out that will bias results. Psychotropic drugs (PDs; antidepressants, antipsychotics, and anxiolytics) has previously been used as a proxy for mental health problems, and results were comparable to studies using an interview-based approach (120,126,131,140). Thus, using PDs as a proxy for mental health problems is an

alternative approach to describe the incidence of depression and anxiety in cancer patients. This approach has limitations, as the grade of depression and anxiety cannot be assessed. Moreover, pharmacological treatment of depression should only be started when the severity of the depression is moderate or severe according to the Danish national guidelines on managing and treating patients with depression (141). Therefore, it will not capture subtle treatment. The indication for treatment is also unknown and prescriptions cannot differentiate between short-term stress and depression/anxiety. Finally, bias can arise due to increased surveillance of cancer patients from the multiple hospital visits. This should be considered when investigating mental health problems using this approach.

1.3.3 FERTILITY/PARENTHOOD IN LYMPHOMA PATIENTS

The parental age at first childbirth in Denmark has been steadily increasing over the years (142). The average age at first childbirth in Denmark is given in **Figure 1**. For females, the average age at first childbirth has risen from 23.1 years in 1961 to 29.6 years in 2020. In the same period, the average age at any childbirth for females increased from 27.0 years to 31.2 years. For males, the average age at first childbirth was 28.4 years in 1986 (no prior data available) and 31.5 years in 2020. The average age at any childbirth for males was 30.9 years in 1986 and 33.5 years in 2020.

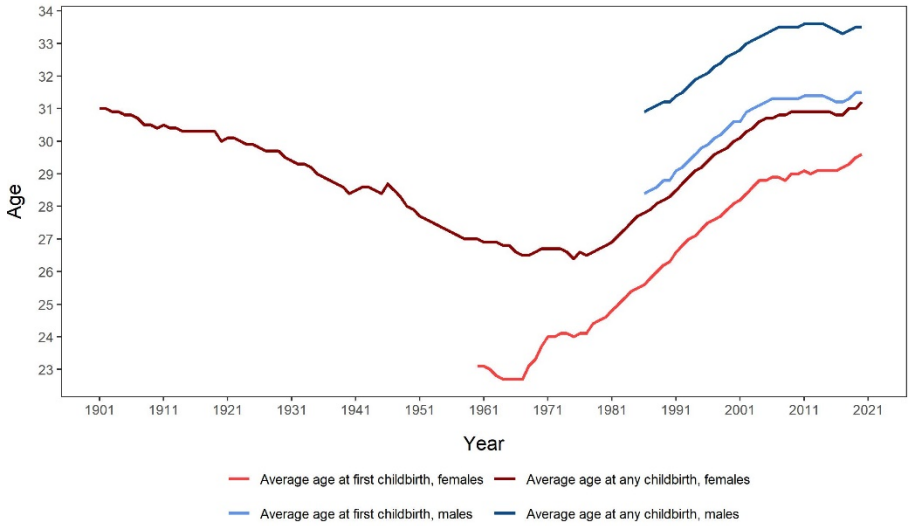

Figure 1: Average age at first or any childbirth for males and females in Denmark during the period from 1901 - 2019 (Statistics Denmark - statbank.dk).

Even though cancer is rare in young adults, the increasing age at first childbirth results in more young adults being diagnosed with cancer prior to parenthood. This is especially the case for cancers with a high incidence in young adults, such as HL. Consequently, more young adults without children need to receive therapy for cancer, including systemic chemotherapy and possibly radiotherapy. Many types of radio- and chemotherapies are associated with gonadal dysfunction and infertility. The use of alkylating agents is of particular concern, as they have been linked to a higher risk of infertility (143,144). To protect against infertility, fertility preservation, including cryopreservation of sperm, ovarian tissue, or mature oocytes, is now offered to many young cancer patients (145–147). According to Danish guidelines, young female lymphoma patients should be offered cryopreservation of ovarian tissue when HL is treated with BEACOPP, NHL is treated with CHOP, or Burkitt's lymphoma is present, regardless of treatment (145). Males should be offered sperm cryopreservation if possible (145). The cryopreserved material may then later be used in assisted reproduction techniques (ARTs) (147,148).

1.4 RATIONALE FOR RESEARCH

The substantial impact of mental health problems and infertility on the quality of life of lymphoma survivors warrants more research focused on patients diagnosed and treated in more recent time periods. Results of such studies can directly impact post-treatment follow-up programs and patient information.

CHAPTER 2: HYPOTHESIS AND AIMS

The aim of the research included in this PhD thesis was to examine whether lymphoma survivors have increased occurrence of mental health problems and infertility, which are both factors that can affect the SEP. To address this, three studies with the following objectives were included in this PhD thesis:

Study I: To investigate mental health complications after HL diagnosis using prescriptions of PDs as a proxy for depression and anxiety.

Study II: To investigate parenthood rates (rate of first child after HL diagnosis), use of ARTs, and pregnancy outcomes in young HL survivors.

Study III: To investigate mental health complications after NHL diagnosis using prescriptions of PDs as a proxy for depression and anxiety.

CHAPTER 3: METHODS

3.1 STUDY DESIGN

The three studies included in this PhD thesis were carried out as matched cohort studies based on Danish nationwide registers. Patients were chosen according to the specific inclusion criteria listed for each study below. Incidence density matching was used to identify and randomly choose five comparators for each index patient. The comparators were matched on a set of variables that varied between studies; however, year and month of birth, as well as sex, were consistent matching factors for all three studies.

3.2 SOURCES OF INFORMATION

3.2.1 DANISH REGISTER-BASED RESEARCH

In Denmark, all permanent residents are given a unique 10-digit Civil Personal Register (CPR) number at the time of birth or immigration (149–151). Since its introduction in 1968, the CPR has been used by the Danish Civil Registration System (CRS) and coupled with demographic information, such as age, sex, marital status, citizenship, and municipality of residence (152–154). The CPR number is used for several administrative procedures in Denmark, such as opening a bank account and obtaining a Danish phone number. It is also used in contacts with the health care system (general practitioner, hospitals, physiotherapist, psychologists, etc.) and educational services, among others. The Danish national registers also use the CPR number when collecting and storing individual level data. Therefore, Danish registers offer a unique possibility for linking data and conducting population-based epidemiological research. As of 2014, more than 9,000,000 persons were included in the CRS, 8.0% of whom had emigrated, 0.3% had disappeared, and 4.5% were annulled/deleted/changed CPR numbers (155).

3.2.2 THE DANISH CLINICAL REGISTRIES

The Danish Clinical Registries (RKKP) is a Danish interregional organization that governs a total of 85 quality databases in Denmark. Data for the various quality databases are retrieved continuously from other nationwide registers or registration forms completed by clinicians. Data are accessible for research projects and quality assessment through an application process (156).

In this PhD thesis, *the Danish Lymphoma Registry (LYFO)* was a key data source for information on lymphoma patients for all three studies. The LYFO is a nationwide register governed by the RKKP, in which data are retrieved primarily from registration forms completed by hematologists in Departments of Hematology in Denmark (157). This register contains information collected prospectively on all lymphoma patients diagnosed and treated at all Departments of Hematology in Denmark since 2000. Information in the register includes detailed baseline information concerning the lymphoma, risk group, treatment (i.e., first-line treatment, number of cycles, date of treatment, additional immunochemotherapy, additional radiation therapy, additional lines of treatment), and outcomes. In 2016, the coverage and validity of the LYFO was validated using the capture-recapture method (157). Both coverage (94.9%) and completeness (92-100%) were found to be high, validating the LYFO as a high-quality nationwide register. The LYFO was used in all three studies to identify the study population of HL (study I + II) or NHL patients (study III).

3.2.3 STATISTICS DENMARK

Statistics Denmark is a Danish institution that collects, compiles, and publishes statistics in Denmark with access to individual-level information (158). Information is collected and stored in several registers, and Statistics Denmark currently governs more than 300 different registers, including educational information, marriage status, yearly income, and health-specific information. The CPR number is available in most of the registers in which individual-level information is collected. To gain access to the registers at Statistics Denmark, a researcher can be given authorization to work through a secure remote online connection to a specific project folder or a hosted server at Statistics Denmark. To comply with Danish law (i.e., the data minimization principle: "*Personal information must be adequate, relevant, and limited to what is necessary for the purposes for which they are processed,"* translated and cited from Retsinformation (159)), researchers are only granted access to registers and information relevant for the studies that will be conducted. With a hosted server at Statistics Denmark, researchers also have the opportunity to upload their own datasets/registers for linkage. Only processed data can leave the server (i.e., tables and figures), as detailed individual information is not allowed to be sent out. At all times, the data on Statistics Denmark servers are pseudo-anonymized, as the CPR numbers are converted to PNR numbers with a conversion key kept by Statistics Denmark. Registers from Statistics Denmark used in the present PhD thesis were as follows.

The National Patient Register (NPR) is administered by the Danish Health Authority and contains data on all inpatient visits at Danish hospitals since 1977 and has also included outpatient visits since 1995. International Classification of Diseases (ICD)-8 codes were used until 1994, after which ICD-10 codes have been used (160). The data in the NPR is collected prospectively, and the register is updated on a daily basis.

The NPR was used in all three studies to calculate a Charlson Comorbidity Index (CCI) score (161–164). Patients in contact with a psychiatric hospital are not registered in the NPR, but in *the Danish Psychiatric Central Research Register (DPCRR)*. The DPCRR contains data regarding all psychiatric admissions since 1970 and all outpatient treatment and emergency room contacts since 1995 (165). *The Fertility Database (FTDB)* contains data on all births since 1942 with a child-parent reference in Denmark. Supplemental data regarding age at childbirth, parity, marital status, income, social benefits received, occupational status, and SEP is also included (166). *The Danish Education Registers (DERs)* are a combination of several registers first established 1910. Together, they contain information on the yearly highest achieved education level of Danish residents, as well as the name of the institution, grades, and exam results (167). Completeness has been proven to be high for 15 to 69-year-olds (96.4%); however, education level is not registered automatically at immigration, so immigrants in Denmark only have a completeness of 85-90%. *The Danish Register of Causes of Death* was established in 1875 and contains data regarding all deceased persons in Denmark. Data include date of death, manner of death, and cause of death (168). By Danish law, it is mandatory to complete a death certificate for every deceased person, from which this register collects data. Therefore, the completeness is very high.

3.2.4 THE DANISH HEALTH DATA AUTHORITY

DHDA is an institution within the Danish Ministry of Health that is responsible for several databases and registers concerning Danish health data (155,169). Similar to Statistics Denmark, data can be accessed by authorized researchers through a secure remote online connection. Moreover, researchers with access to Statistics Denmark can apply for data from the DHDA to be uploaded to a hosted server at Statistics Denmark to facilitate the linkage of registers from both institutions. Danish law regarding the data minimalization principle also applies to data from the DHDA. The registers from the DHDA used for this PhD thesis were as follows.

The Danish National Prescription Register (DNPR) contains information regarding all prescriptions redeemed at Danish pharmacies since 1994. The DNPR includes individual CPR-linked information regarding the date that redeemed prescription products were prescribed and redeemed, anatomical therapeutic chemical (ATC) codes, dose units, and indications for prescribing, among other information (170,171). The register was used as a supplement for calculating the CCI using antidiabetic drugs as a proxy of diabetes for the “Diabetes” item. *The Danish In Vitro Fertilization Register (DIVF)* contains data regarding high-technology ARTs in women in both public and private clinics, such as IVF, intracytoplasmic sperm injection, frozen embryo replacement, and egg donation, since 1994. Data concerning the cause of infertility, outcome, and whether any child was born are included (166,172). In

Denmark, it is legally required to report the use of ARTs conducted at public hospitals or private fertility clinics to the register. Thus, the completeness of the register is very high. *The Medical Birth Register (MFR)* was established in 1973 and contains data on parents; date of birth; place of birth; maternal information, such as smoking; pregnancy/delivery-related variables; and gestational age (173). For complete data regarding children born in Denmark and their parents, the MFR should be used in combination with the FTDB governed by Statistics Denmark. *The Danish Pathology Register (DPR)* was established in 1997 to introduce a common guideline for all pathology departments to ensure a common approach to reporting patient and diagnostic information (174). The register contains information on all pathology examinations, including requisition ID, type of investigation, description, and diagnosis coded by a Danish version of the Systematized Nomenclature of Medicine (SNOMED). The completeness of the register is very high because it is mandatory to report all pathology results to the register. The DPR was used in combination with the LYFO to ensure all relapses were identified.

3.3 STUDY I

3.3.1 STUDY POPULATION

The LYFO was used to identify HL patients fulfilling the following inclusion criteria (hereafter referred to as index patients): diagnosis of classical or predominant HL between 1 January 2005 and 31 December 2015, aged ≥18 years at time of diagnosis, and no prescriptions for any PDs within 10 years prior to the date of HL diagnosis (index date). Using the CRS, five random comparators were identified matched for year and month of birth, sex, no diagnosis of HL prior to index date, alive at index date, and no redeemed prescriptions for PDs within 10 years prior to the index date to ensure that only incident PD use was evaluated. An HL patient was eligible for inclusion as a comparator until the date of HL diagnosis.

3.3.2 EXPOSURE AND OUTCOME

In study I, exposure was defined as being diagnosed with HL (exposed) or being a matched comparator without HL (unexposed). Outcome was defined as any incident PD use (antidepressants [ATC - N06A], antipsychotics [ATC - N05A], and anxiolytics [ATC - N05B]), which were identified by redeemed prescriptions in the DNPR. The classic definition of PDs does not include hypnotics (ATC – N05C), which is also relevant to consider when analyzing depression and anxiety. Thus, an additional analysis was carried out to investigate the patterns of hypnotics' use. Follow-up started at the index date and stopped at the date of the first redeemed PD prescription, death, relapse, censoring due to emigration, a person becoming missing,

a matched comparator being diagnosed with HL, or end of follow-up (24 August 2018), whichever came first.

3.3.3 STATISTICS

Baseline characteristics at the index date were described as proportions for categorical variables, whereas continuous variables were described as medians with the interquartile range (IQR). Differences between HL patients (exposed) and matched comparators (unexposed) were tested using Pearson's chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables. Cumulative incidence curves were constructed to analyze the time from the index date to the date of the first redeemed PD prescription. To evaluate the difference between exposed and unexposed in the cumulative incidence plot, Gray's test was used (175) to obtain a P-value. The Aalen-Johansen estimator was used to compute the 5-year cumulative incidence, in which relapse, death, or a matched comparator being diagnosed with HL before first PD prescription was treated as a competing risk (176). To evaluate differences in the use of the various PDs, stratified analyses were conducted using the above-mentioned approach for each PD. Furthermore, the 5-year cumulative incidence of redeeming a PD prescription stratified by sex, age group, CCI, stage, and ECOG PS was determined to evaluate the effect of the various baseline characteristics. Estimates were visualized with a forest plot including the 95% confidence intervals (95% CIs). An adjusted Cox proportional hazards regression analysis was conducted to investigate the association between baseline characteristics and being prescribed PDs. Known risk factors for developing anxiety and depression, including age, sex, and history of depression and/or anxiety were considered by the inclusion criteria and the matching procedure and were not included in the Cox model. Results were presented as hazard ratios (HRs) with 95% CIs. To investigate whether a potential increased risk of PD use in HL patients would persist or normalize over time, a landmark analysis at set timepoints after inclusion (1, 2, and 5 years after index date) was performed. At each set landmark, HL patients without an event between the index date and the new landmark were rematched to five new comparators from the background population. The matching approach did not differ from the initial matching at the index date described previously. At each landmark, the 5-year cumulative incidence of incident PD use was computed for both HL patients and their matched comparators, after which the incidences were subtracted from each other to find the absolute difference. The absolute differences were then interpreted in a forest plot along with 95% CIs. For this analysis, the pseudo-observation method was used due to the amount of right-censoring (the event could occur after censoring) increasing for each new landmark investigated (177,178). For example, calculating the 5-year cumulative incidence at the latest landmark (5 years after inclusion) could require a longer follow-up than what was available (the study period ended in August 2018) if the study participant was included in 2015. In this example, the follow-up should last until 2025. Hence, the pseudo-observation method was used to permit both absolute and relative analyses.

3.4 STUDY II

3.4.1 STUDY POPULATION

The following inclusion criteria were used to identify eligible HL patients from the LYFO for inclusion in this study, hereafter referred to as the index patients: diagnosed with classical or predominant HL between 1 January 2000 and 31 December 2015, age between 18 and 40 years at time of diagnosis (both ages included), in CR/unconfirmed CR (CRu)/partial remission (PR) following first line therapy, and alive and without relapse 9 months after diagnosis (because patients are not recommended to become pregnant during the course of therapy and the aim was to investigate how therapy impacted fertility in survivors after first-line therapy). The 9-month landmark after the date of diagnosis was used as the index date. Using the CRS, five random comparators were identified and matched for year and month of birth, sex, parenthood status at inclusion (having children or not having children at time of inclusion), no diagnosis of HL prior to index date, and alive at index date. An HL patient was eligible for inclusion as a comparator until the date of HL diagnosis.

3.4.2 EXPOSURE AND OUTCOME

Exposure was defined as having survived at least 9 months after diagnosis (exposed) or being a matched comparator without HL (unexposed). Several outcomes of interest were investigated, including the first live childbirth after the index date, the total number of live childbirths after the index date, first use of ARTs, and outcomes of live births after the index date (e.g., Apgar score, gestational age at time of birth, malformations). An important secondary analysis was the effect of various chemotherapy regimens on parenthood rates. For this analysis, exposure was defined as HL patients treated with 2-4 cycles of ABVD, 6-8 cycles of ABVD, or 6-8 cycles of BEACOPP. The outcome in this analysis was the first live childbirth after the index date. The FTDB and MFR were used in combination to identify all live childbirths, outcomes at birth, and their parents. The DIVF was used to identify all uses of ARTs, reasons for using ARTs, and outcomes of ARTs. Follow-up was started at the index date (9 months after HL diagnosis of the index patient) and follow-up stopped at the date of the first live childbirth, death, relapse, censoring due to emigration, a person becoming missing, a matched comparator being diagnosed with HL, end of follow-up reached (24 August 2018), or 10 years after the index date, whichever came first. For the outcome total number of live childbirths, the follow-up time continued after the first live childbirth until one of the previously mentioned events occurred.

3.4.3 STATISTICS

All analyses were stratified by sex due to known differences in parenthood among males and females. Baseline characteristics at the index date were described as proportions for categorical variables and medians with IQRs for continuous variables. The same approach was used for the outcomes of the children born after the index date, in which differences between HL patients and matched comparators were tested using Pearson's chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables. Time from the index date to the date of first live childbirth was described by a cumulative incidence curve. To compute the 10-year cumulative incidence of first live childbirths after the index date, the Aalen-Johansen estimator was used, in which relapse, death, or a matched comparator being diagnosed with HL before first PD prescription was treated as a competing risk (176). Differences between the exposed and unexposed groups in the cumulative incidence plot were evaluated by Gray's test (175). The parenthood rate was defined as the rate of first live childbirth per 1,000 person years (/1000py). To investigate whether any differences were present between HL survivors and the matched comparators, a Poisson regression was conducted. The Poisson regression is a generalized linear model in which counted data (i.e., first live childbirth and all live childbirths) are modelled (179). The Poisson regression model was further used to evaluate the potential associations between baseline characteristics of HL survivors and first live childbirths by calculating the incidence rate ratio (IRR). The same approach was applied to analyze the total number of live births after the index date, for which the parenthood rate was defined as the total number of live childbirths after the index date /1000py. Poisson regression is a valuable tool for calculating incidence rates and to test for any difference in incidence rates using the IRR. However, Poisson regression has a significant limitation in that the calculated incidence rate is expected to be constant over time. As the parenthood rate is most likely to differ to some degree over time, a Poisson regression model with time-varying parenthood rates was obtained as described by Carstensen et al. (180). In this approach, the rates are calculated for small time intervals (every 182.64 days) and a spline with five knots is added for smoothing (max follow-up was sequenced into 0.00, 913.25, 1826.50, 2739.75, and 3653 days). The IRR was calculated for each interval. Both parenthood and the IRR were interpreted in a y-log-transformed plot for visual inspection.

3.5 STUDY III

3.5.1 STUDY POPULATION

For Study III, the LYFO was used to identify all NHL patients fulfilling the following inclusion criteria (hereafter referred to as index patients): diagnosed with NHL between 1 January 2005 and 31 December 2015, ≥18 years old at the time of

diagnosis, and had no redeemed PD prescriptions within 10 years prior to the date of diagnosis. Date of NHL diagnosis was used as the index date. The CRS was used to identify five random comparators that were matched for year and month of birth, sex, ethnicity, no diagnosis of HL prior to index date, alive at index date, and had not redeemed any PD prescriptions within 10 years prior to the index date. An NHL patient was eligible for inclusion as a comparator until the date of NHL diagnosis. Due to the heterogenicity of NHLs, the NHL patients were categorized into five subgroups according to natural history, malignity, and prognosis (**Table 1**).

Non-Hodgkin lymphoma (NHL) subgroup	Definition
Diffuse Large B-cell lymphoma (DLBCL)	Diffuse large B-cell lymphomas
Aggressive T-cell NHL	Primary cutaneous T-cell lymphoma, mature T-cell lymphoma, angioimmunoblastic lymphoma, anaplastic large T-cell lymphoma, hepatosplenic T-cell lymphoma, intestinal T-cell lymphoma, adult T-cell lymphoma
Other aggressive B-cell NHL	Burkitt Lymphoma, Precursor B-cell lymphoblastic lymphoma
Indolent NHL	Follicular lymphoma, Marginal zone lymphoma, splenic marginal zone lymphoma, lymphoplasmacytic lymphoma, small lymphocytic lymphoma
Intermediate NHL	Mantle cell lymphoma
Abbreviations: NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma;	

Table 1: Subgroup categorization of non-Hodgkin lymphomas (NHLs) according to natural history, malignity, and prognosis (181).

3.5.2 EXPOSURE AND OUTCOME

Exposure was defined as either being diagnosed with NHL (exposed) or being a matched comparator without NHL (unexposed). The following outcomes were defined: first redeemed PD prescription (antidepressants [ATC - N06A], antipsychotics [ATC - N05A], and anxiolytics [ATC - N05B]) after the index date, first redeemed hypnotics prescription (ATC – N05C), first redeemed PD prescription after the relapse date, first contact with a department of psychiatry (both in- and out-patient visits), and first incident of self-intentional harm or suicide. Information on redeemed prescriptions were retrieved from the DNPR, whereas information regarding contacts with any Danish department of psychiatry was captured using the DPCRR. Intentional self-harm and suicide were defined using the DK algorithm from Gasse et al. (

Table 2) (182,183). This algorithm was developed to be applied to health register data from the NPR and DPCRR. In 2018, the DK algorithm was validated by comparing it

to information obtained from a review of patient records. The positive predictive value was 51.5% (95% CI 46.4-56.7%).

The DK-algorithm for identifying incidents of intentional self-harm or suicide (182)
All hospital contacts with the cause of contact registered as 4 (suicide attempt or intentional self-harm)
All hospital contacts with a main diagnosis in the National Patient Register (NPR) in chapter F (mental disorders) using the 10th revision of the International Classification of Diseases (ICD-10) along with one of the following secondary poisoning ICD-10 codes: • T36-T50 (drugs and biological substances) • T52-T60 (non-medical substances)
All hospital contacts with a main diagnosis in the NPR in chapter F (mental disorders) using the 10th revision of the ICD-10 along with a one of the following secondary ICD-10 codes (cuts): • S51, S55, S59, S61, S65, and S69.
All hospital contacts with a main diagnosis in the NPR of any specific intoxications based on the ICD-10 codes: • T39, T40, T42, T43, and T58
All hospital contacts with main diagnosis in the NPR of intentional self-poisoning or intentional self-harm using the ICD-10 codes: • X60-X84

Table 2: The DK algorithm for identifying incidents of intentional self-harm and completed suicides (182).

3.5.3 STATISTICS

All analyses were stratified by NHL subgroup (**Table 1**). Baseline characteristics at the index date for all subgroups and the matched comparators were described by proportions for categorical variables and medians supplied with IQRs for continuous variables. Differences between NHL patients (exposed) and the matched comparators

(unexposed) were tested using Pearson's chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables. The statistical analyses in this study resemble those of study 1, as cumulative incidence curves for the time from the index date to the date of first redeemed PD prescription were constructed. A P-value was obtained for comparing and evaluating whether any difference exists between the plots using Gray's test (175). Two-year cumulative incidences were calculated using the Aalen-Johansen estimator, treating relapse, death, or a matched comparator being diagnosed with NHL before first redeemed PD prescription as a competing risk (176). The same approach was used for time to first redeemed hypnotics prescription, first contact with any department of psychiatry, and first incident of intentional harm or suicide. The approach was also used to analyze the risk of PD use in NHL patients with relapse, in which the index date was changed to the date of relapse, at which time the NHL patients were rematched to five new comparators from the background population. Associations between baseline characteristics and incident PD use were analyzed by a Cox proportional hazards regression model and presented as HRs with 95% CIs. Similar to study I, whether a potential increase in the risk of PD use in NHL patients was persistent or normalized over time was investigated. At set timepoints after the index date (1, 2, and 5 years after the index date), NHL patients still alive and without PD use were rematched to five new comparators from the background population using the same approach for matching. For all timepoints, a 1-year HR and 95% CI were calculated and shown in a forest plot for all subgroups of NHL patients. An additional analysis was performed to evaluate post-relapse PD use in the time up until death. This analysis included NHL patients with relapse who later died. The use of PDs was described by a cumulative incidence plot for the last 12 months prior to the date of death. This cumulative incidence plot was analyzed by visual inspection.

3.6 SOFTWARE

For all three studies, data management and analyses were carried out in the following statistical software: SAS version 9.4 (SAS Institute Inc., Gary, NC, USA), R version 3.6.1 (R foundation for Statistical Computing, Vienna, Austria), and RStudio version 1.1.447 (RStudio, Inc., Boston, MA, USA). In R, the following packages were used: survival, prodlim, Epi, pseudo, geepack, data.table, ggplot2, mgcv, and popEpi.

3.7 ETHICS

All studies in this PhD thesis were approved by the Danish Data Protection Agency (internal ID No. 2018-88), and data management and analyses were carried out on data stored at a secure server available within Statistics Denmark. Data on the server was pseudo-anonymized.

CHAPTER 4: SUMMARY OF RESULTS

4.1 STUDY I

A few studies investigating the effect of being diagnosed with HL on the risk of depression and anxiety were conducted previously, but most have pooled lymphoma patients (both HL and NHL) into one group and did not include disease-specific variables (i.e., Eastern Cooperative Oncology Group performance score [ECOG PS], disease stage) (88,125,184,185). In this nationwide prospective study, a total of 945 HL patients were matched to 4,725 comparators with a median age of 39 years and median follow-up of 7.2 years (reverse Kaplan-Meier method) (186,187).

The overall incident PD use after the index date was significantly higher for HL patients (22.8%) than the matched comparators (11.5%) as shown in the cumulative incidence plot (**Figure 2**) (186). Cumulative incidence plots stratified by type of PD prescription yielded similar results (**Figure 2**) (186). Antidepressants were the most frequent PDs, whereas antipsychotics were the least frequent PDs. A sensitivity analysis was performed in which the outcome of interest was defined as the redemption of at least two PD prescriptions. Though the incidence of PD use in this analysis was lower compared to only having redeemed one prescription, the use of PDs was still higher in HL patients than the matched comparators.

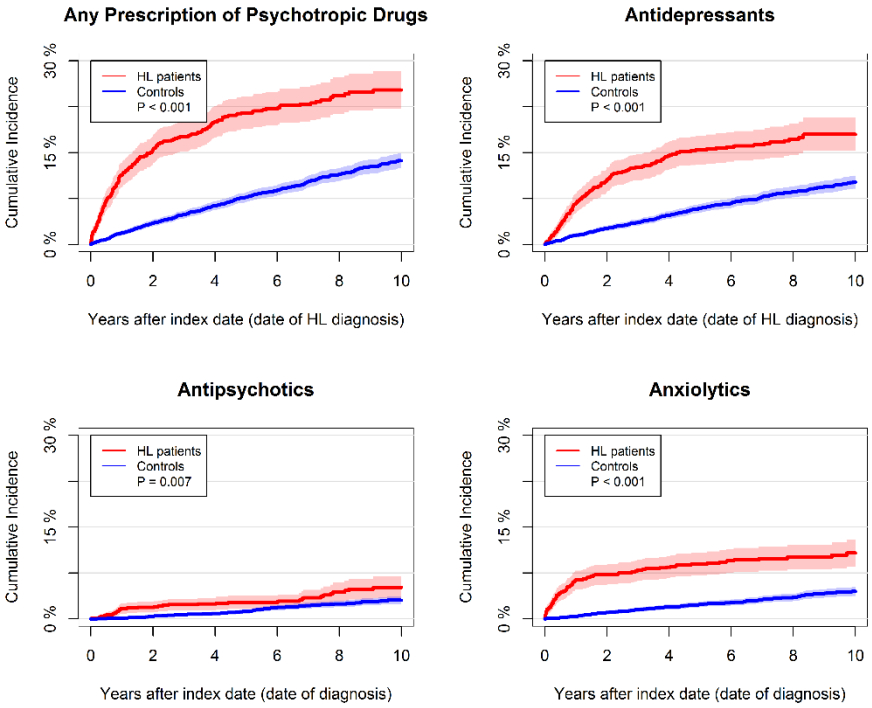

Figure 2: Cumulative incidence plot of the risk of incident psychotropic drug (PD) use for any PDs and stratified by type of PD. P-values are calculated by Gray's test and provided in the plots (186).

A similar approach was used in HL patients with relapse, in which incident use after the date of relapse was investigated. Results showed high use among the relapsed HL patients (27.1%) compared to the matched comparators (7.7%).

A Cox regression analysis to address the association between being diagnosed with HL and being prescribed PDs showed consistent results (HR 2.63, 95% CI 2.24-3.08) (186). Moreover, higher age, ECOG PS ≥1, advanced stage disease, CCI ≥1, and treatment with 6-8 cycles of ABVD were associated with higher use of PDs.

The increase in incident use of PDs after diagnosis of HL did not last, as the risk of PD use decreased over time. Five years into survivorship, the risk of PD use was normalized to that of the matched comparators (**Figure 3**) (186).

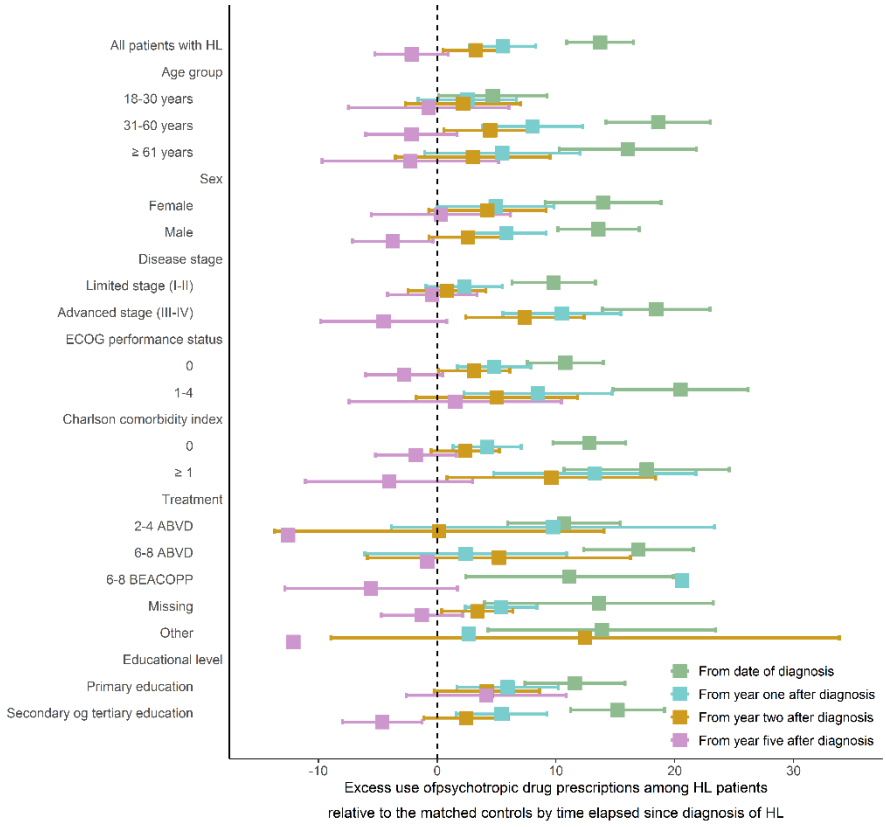

Figure 3: Forest plot of excess use of psychotropic drugs (PDs) in Hodgkin lymphoma (HL) patients compared to the matched comparators at various landmarks calculated as the difference in 5-year cumulative incidence (186).

4.2 STUDY II

Previous studies on the risk of infertility in HL patients after treatment have primarily been secondary analyses of clinical trials with limited follow-up and primarily conducted in females, or conducted during time periods in which outdated treatment regimens were used (188–193). Therefore, Study I investigated the parenthood rates in relapse-free HL survivors, including both females and males, in a modern setting.

This study included 793 young relapse-free HL survivors and 3,965 matched comparators with a median age of 29-30 years and a median follow-up of 8.7 years (194). Both females and males were included, but males were more frequent (54.7%). The sex-stratified parenthood rates and cumulative incidences of first live childbirth after the index date were comparable between HL survivors and their matched

comparators for both males and females (**Figure 4**) (194). Analyses including all live childbirths after the index date had similar results.

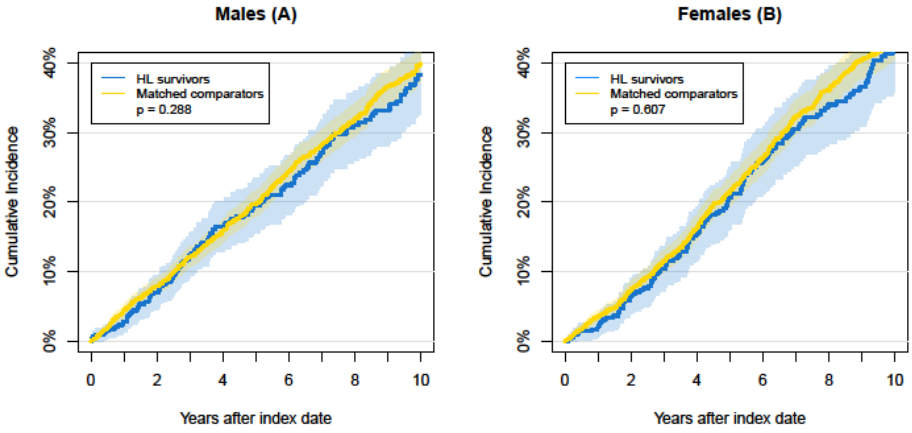

Figure 4: Cumulative incidence plots of time to first live childbirth after the index date for Hodgkin lymphoma (HL) survivors and matched comparators stratified by sex. P-values were calculated by Gray's test and provided in the plots (194).

A Poisson regression model was used to calculate parenthood rates; to account for the time-varying nature of fertility, a model with time-varying parenthood rates was made (**Figure 5**) (194). The figure showed no difference in the time-varying parenthood rates at any time point.

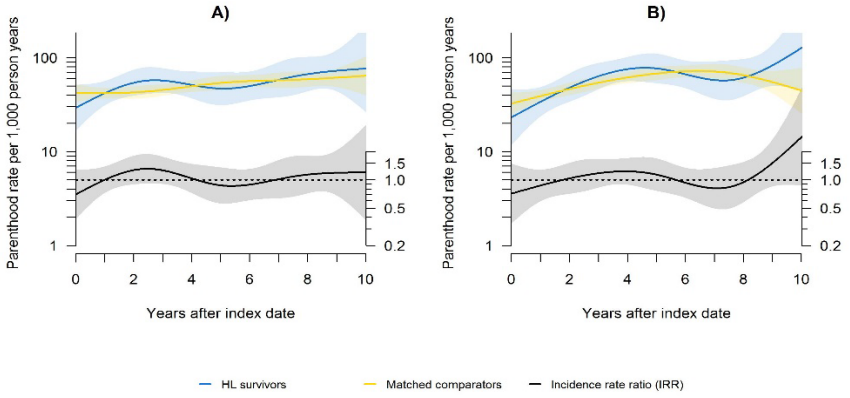

Figure 5: Time-varying parenthood rates for HL survivors (blue) and matched comparators (yellow) calculated by a Poisson model with an added spline and stratified by sex (A – males; B - Females). In addition, the plot is provided with time-varying incidence rate ratio (grey) (194).

Analyses of the association between baseline characteristics and parenthood rates in HL survivors compared to the matched comparators revealed that male HL survivors treated with 6-8 cycles of BEACOPP had lower parenthood rates (p=0.02). This was supported by an additional analysis of the IRRs for HL survivors; those treated with 6-8 cycles of BEACOPP had significantly lower parenthood rates compared to HL survivors treated with 6-8 cycles of ABVD. In addition, a lower education level was associated with decreased IRRs for the parenthood rates of both female and male HL survivors compared to those with higher education levels.

The use of ARTs for first live childbirth after the index date was also investigated in this study to gain valuable information on fertility. ARTs were used more for the first live childbirth after the date for HL survivors than by the matched comparators for both males and females.

One possible explanation for the comparative parenthood rates between HL survivors and matched comparators may be the use of ARTs, which were more common among HL survivors than the matched comparators. The use of ARTs was higher for both females and males, though males had the highest use and highest absolute difference from the matched comparators. Patterns in ART use according to the treatment received were examined, and male HL survivors treated with 6-8 cycles of BEACOPP had a higher risk of ART use than HL survivors treated with ABVD (both 2-4 and 6-8 cycles; **Figure 6**) (194). For females, no difference was found.

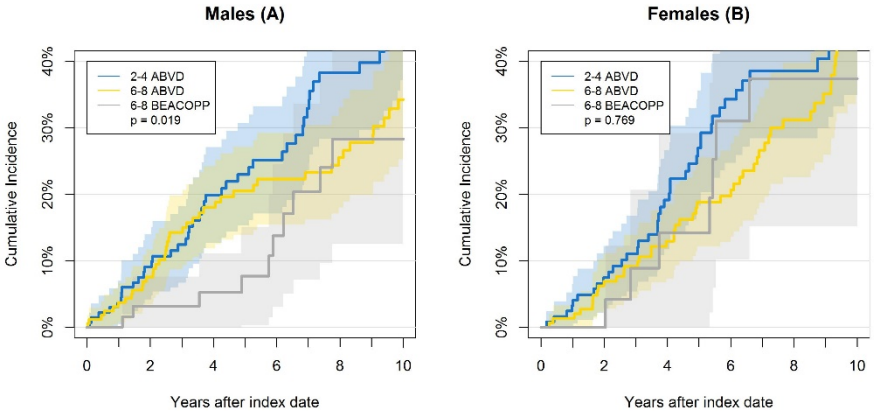

Figure 6: Cumulative incidence plot of assisted reproduction techniques (ARTs) use among Hodgkin lymphoma (HL) survivors for the various treatment regimens and stratified by sex. Treatment regimens included was ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine] and BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone] (194).

Offspring of the HL survivors were compared to the offspring of the matched comparators, and no difference was found for gestational age, Apgar score, weight, or malformation rate.

4.3 STUDY III

Previous studies describing mental health problems, including PD use, after being diagnosed with NHL are limited, and NHL and HL patients have often been pooled into one group (116,125,132,195–197). Therefore, Study III investigated the use of PDs in NHL patients compared to matched comparators, in addition to the risk of contacts with departments of psychiatry, intentional self-harm, and suicide.

This study included 7,201 NHL patients and 36,005 matched comparators. To account for the heterogenicity of NHLs, analyses were stratified by NHL subgroup (see

Diffuse Large B-cell lymphoma (DLBCL)	**Diffuse large B-cell lymphomas**
Aggressive T-cell NHL	Primary cutaneous T-cell lymphoma, mature T-cell lymphoma, angioimmunoblastic lymphoma, anaplastic large T-cell lymphoma, hepatosplenic T-cell lymphoma, intestinal T-cell lymphoma, adult T-cell lymphoma
Other aggressive B-cell NHL	Burkitt Lymphoma, Precursor B-cell lymphoblastic lymphoma
Indolent NHL	Follicular lymphoma, Marginal zone lymphoma, splenic marginal zone lymphoma, lymphoplasmacytic lymphoma, small lymphocytic lymphoma
Intermediate NHL	Mantle cell lymphoma
Abbreviations: NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma;	

Table 1) (181). The overall 5-year cumulative incidence of incident PD use was significantly higher in NHL patients than their matched comparators for all subgroups of NHL (**Figure 7**) (181). The highest 5-year incidence was found in aggressive subtypes of NHL, whereas indolent NHL had the lowest incidence. Similar to the results of Study I, antidepressants were the most frequently used PDs and antipsychotics the least frequently used. Results were consistent in the sensitivity analysis in which the outcome of interest was having at least two prescriptions of any PD.

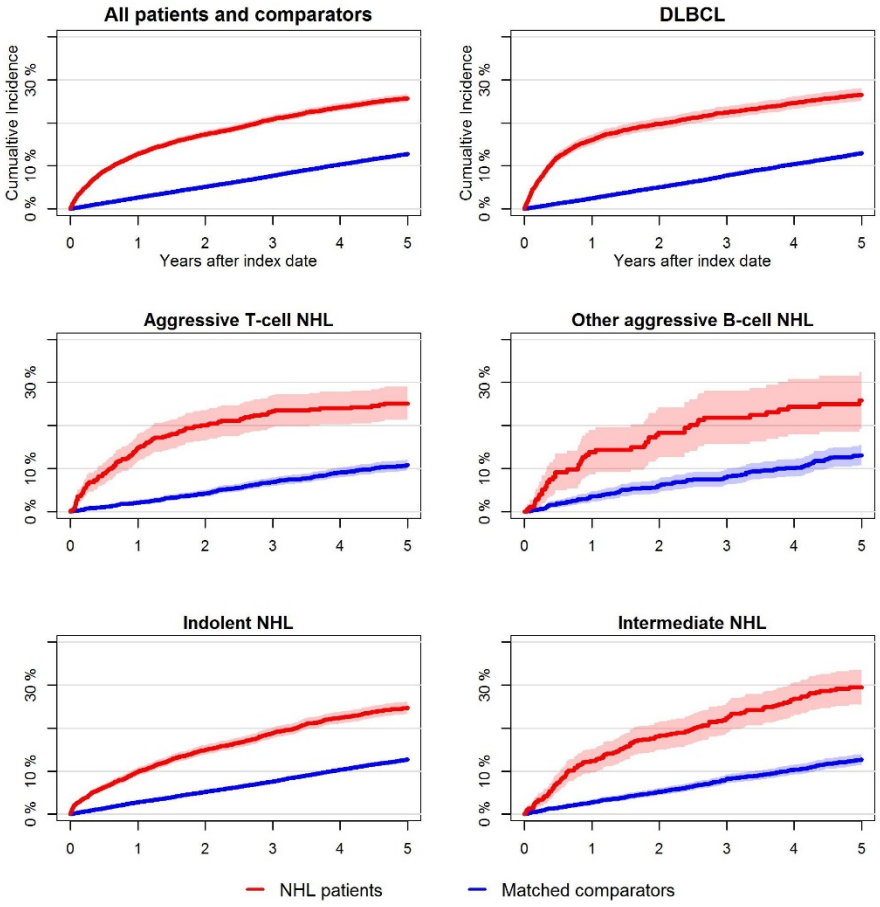

Figure 7: Cumulative incidence plots of incident psychotropic drug (PD) use among non-Hodgkin lymphoma (NHL) patients and matched comparators after the index date stratified by any PDs and by type of PDs (181).

To describe the potential effect of a severe disease course, PD use after the relapse date among NHL patients with relapse and during the last 12 months prior to death (only for relapsed NHL patients who died) was investigated. After the date of relapse the use of PDs were significantly higher as compared to the matched comparators (**Figure 8** (181)), and in the last 12 months prior to death the incidence was even higher.

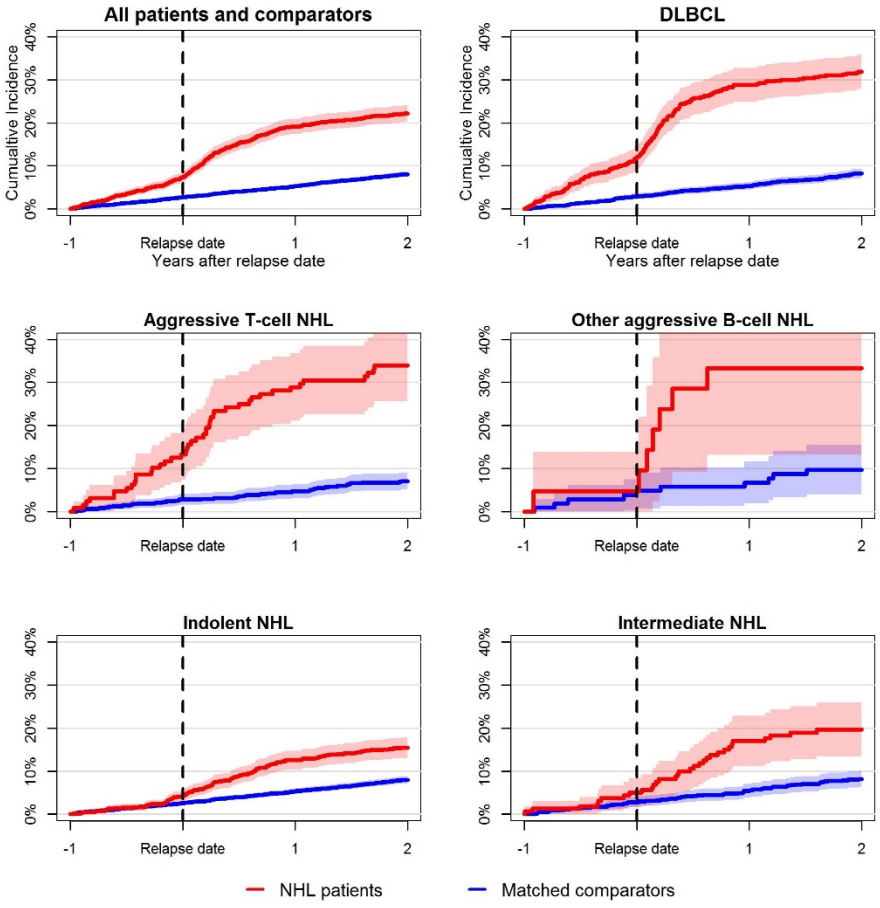

Figure 8: Cumulative incidence plots of incident psychotropic drug (PD) use among relapsed non-Hodgkin lymphoma (NHL) patients and matched comparators after the date of relapse stratified by any PDs and by type of PDs (181).

The associations between an NHL diagnosis and risk of PD use were described using a Cox proportional regression model. Higher age, higher CCI, lower education level, poorer ECOG PS, and higher IPI score were associated with increased risk of PD use.

The risk of PD use did not remain elevated but decreased over time. Except for patients with indolent NHL, the risk of PD use normalized to their matched comparators 5 years into survivorship for all subgroups of NHL patients (**Figure 9**) (181). However, for patients with indolent NHL, the risk of PD use compared to the matched comparators remained elevated 5 years into survivorship.

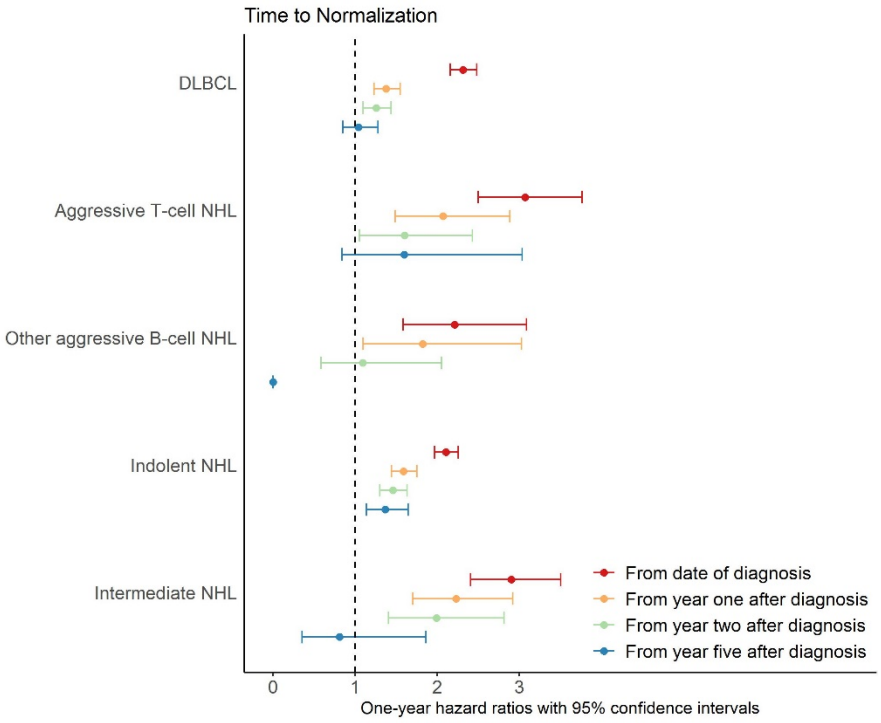

Figure 9: One-year hazard ratios of the excess psychotropic drug (PD) use in non-Hodgkin lymphoma (NHL) patients compared to matched comparators stratified by type of NHL using a proportional Cox regression analysis calculating one-year hazard ratios (181).

The high use of PDs in all subgroups of NHL patients was not reflected in greater use of the Danish departments of psychiatry, as the cumulative incidence was comparable to that of the matched comparators across all NHL subgroups. Nonetheless, the risk of intentional self-harm and suicide was higher among NHL patients compared to the matched comparators. Due to a limited number of incidents with intentional self-harm and suicide, it was not possible to stratify this analysis by NHL subgroup.

CHAPTER 5: GENERAL DISCUSSION

5.1 METHODOLOGICAL CONSIDERATIONS

5.1.1 RANDOM ERROR AND PRECISION

Random error is the chance of a variation between the observed estimates and the true estimates, which is unpredictable (i.e., random) (179,198,199). Random error directly correlates with the precision of the estimates. Precision is defined as how reproducible the same estimates are in equivalent circumstances. When random error is present, the estimates will cluster around the true estimate without a pattern reasoned by the random effect. Due to the clustering, using the average of the observed estimates will yield an estimate very close to the true estimate. The precision is reflected by the 95% CIs of the estimate. Random error and precision are highly dependent on the study sample size, as a larger study sample size will reduce the random error and increase the precision. In Studies I-III, stratified analyses were performed, which decreased the sample size in each stratum. As a result, the precision would decrease, and random errors increase. Thus, statistically significant results for true associations may have been excluded. One example of this could be in Study II, in which the number of female HL survivors treated with 6-8 cycles of BEACOPP was low (n=26) and there was not enough power to evaluate whether BEACOPP affected parenthood rates in young female HL survivors (194).

5.1.2 SYSTEMATIC ERROR AND BIAS

Systemic errors occur when the difference between the observed estimates and the true estimates is consistent and not random (179,198–200). When repeating the study, the same error will occur due to the consistency of the error. Systematic errors induce bias via three overall mechanisms: confounding, selection bias, and information bias.

Confounding happens when the estimate of the association between exposure and outcome is mixed up with the real effect of another variable (confounder) in the same outcome (179,198–200). A confounder is defined as a variable that is associated with both the outcome and the exposure but not directly affected by the exposure itself (179,198–200). Confounders that are not identified or not accounted for when analyzing the data would bias the results in a direction that depends on the association/effect on exposure and outcome. For example, in Studies I and III, age is thought to be a confounder, as higher age is a risk factor for developing depression and anxiety (outcome), and higher age is associated with a higher incidence of HL/NHL (exposure). In this case, the direction of the bias introduced by age would

be upwards if not accounted for in the analysis. To control for the effect of confounders, a valuable tool in epidemiological research is matching, whereas in clinical trials randomization can be performed. Other methods for controlling the effect of confounders includes stratification of the confounding variable or including confounding variables in regression models (179,198–200). Confounders should be identified a priori when designing the study. A method for identifying confounders is the use of directed acyclic graphs (DAGs), in which the assumptions for being a confounder can be examined based on epidemiological evidence. In all three studies in this thesis, confounding was present, which is discussed later (See 5.1.3 Matching variables).

If there is systematic deviation in a study population selected from a source population due to the selection process, this is called selection bias (179,198–200). This is present when the relationship between exposure and disease is different for selected participants and the source population of eligible participants. A well-known example is self-selection, in which participants agree to participate. Agreeing to participate in a study may be because the participant is already associated with the outcome of interest, healthier, or has more resources (i.e., SEP). Several other types of selection bias exist (i.e., healthy worker effect, non-response, differential loss-to-follow-up) (179,198–200). Studies I-III are all population-based cohort studies in which participants were chosen based on whether they have been diagnosed with HL or NHL using the high-quality LYFO. The validity of the LYFO has already been established, which is why there is no systematic error when including exposed participants (157). Moreover, unexposed participants were chosen based on multiple matching variables; five unexposed participants were randomly chosen as the matched comparators. In addition to complete recruitment of participants, there is complete follow-up for all participants.

Information bias arises when a systematic misclassification of study participants with respect to exposure status or outcome is present among participants already included in the study (179,198–200). Types of misclassifications include differential and non-differential. Non-differential misclassification occurs when the exposure/outcome does not depend on the value of other variables – the probability of misclassification is equal regardless of exposure/outcome. Examples include recording and coding errors in databases and using surrogate measures of exposure. In contrast, differential misclassification arises when the exposure/outcome is dependent on the values of other variables – the probability of misclassification is not equal in exposed/unexposed or with/without outcome. Examples of differential misclassification bias are recall bias, interviewer bias, and surveillance bias. Use of data from high-quality registers drastically reduced the risk of information bias due to most of the registers having already been validated. Furthermore, Danish legislation regarding mandatory reporting of patients and procedures to several registers (i.e., DIVF, DPR) is a contributing factor to high completeness even if a register has not been validated yet. Even though surveillance bias could be present in Studies I and

III, the risk of developing depression and anxiety was investigated using PDs as a proxy. The exposed group (HL and NHL patients) would most likely have more contacts with health care services and other facilities (i.e., hospitals, general practitioner, the Danish Cancer Society, etc.), resulting in greater surveillance of the exposed. As a result, the risk of PD use may be higher in the exposed group (HL and NHL patients) than the unexposed group (matched comparators).

5.1.3 MATCHING VARIABLES

In all three studies, matching was conducted for various variables to reduce heterogenicity, controlling for the effect of confounding. Confounding variables were identified a priori when defining the setup of each of the three studies. As age directly correlates with both exposure and outcome in all three studies, it was used as a matching criterion. In all studies, exposure was a diagnosis of lymphoma (HL in Studies I and II and NHL in Study III). The incidence of NHL is higher among older age groups, whereas the incidence of HL is bimodal with a peak in younger age and older age (1). Therefore, age is directly associated with the exposure. The outcome for Studies I and III was redeeming at least one prescription for any PD, which was a proxy for depression and anxiety. A known risk factor for developing depression or anxiety and other mental health problems is older age, which is why age is directly associated with the outcome. For Study II, the outcome was first live birth after HL diagnosis + 9 months. As previously mentioned, the mean age at first live birth in Danish citizens is 29 years for females and 30 years for males, and higher age is associated with a lower incidence of childbirth. In conclusion, age is directly associated with both outcome and exposure in all three studies, which is why it was included as a matching criterion.

Another variable considered as a confounder was the sex of the study participants. For both HL and NHL, the incidence is markedly higher in males compared to females; thus, sex is directly associated with exposure. Regarding the risk of developing depression or anxiety, it is well established that females are at higher risk of developing these conditions, as well as other mental health problems. In Study II, sex is also considered a confounder because male sex is negatively associated with having a child, as male Danes are more likely to never have a child and to have fewer children in total compared to female Danes (201). Thus, sex is directly associated with the exposure and the outcome in all three studies and is included as a matching criterion.

In Study II, another matching criterion was parenthood status (whether or not a patient/comparator had any child(ren) prior to the index date). Parenthood status is directly associated with the outcome, as having at least one child decreases the chance of having more children in the future, which is reflected in the overall average number of children per woman in Denmark being 1.7 (155). On the other hand, an association between parenthood and the exposure (lymphoma diagnosis) is speculative and has not yet been proven (202). As a result, parenthood status is not considered a

confounder in this study. Even so, parenthood status was included as a matching criterion to reduce heterogeneity between HL survivors and comparators. Moreover, as parenthood status is considered to be strongly associated with the outcome of interest, if matching was not conducted for this variable, it should have been adjusted for in the analyses. Including parenthood status as a matching criterion, even if not considered a confounder, would not introduce bias, as would have been the case if it was only associated with the exposure (179).

5.1.4 ADJUSTING FOR MULTIPLE COMPARISONS

In all three studies, multiple tests were performed to evaluate a list of various hypotheses; that is, the effect of age, sex, CCI, and more on the risk of PD use were each a separate hypothesis. Investigating several hypotheses by conducting multiple tests increases the risk of type 1 errors (false positives) (179). A common way to handle the multiple comparisons problem is to use a correction procedure to adjust the P-values for multiple comparisons (e.g., Bonferroni correction or Benjamini and Hochberg). However, decreasing the risk of type 1 errors comes with the price of increasing type 2 errors (false negatives), which have been criticized in the literature (160–162). In the context of Study II, depending on the chosen method and number of tests adjusted for, we may (erroneously) conclude that parenthood is not affected by HL treatment in a specific subgroup (e.g., BEACOPP treated), which could be disadvantageous to the patients from the aspect of fertility counseling prior to treatment. The issue of whether to adjust reported P-values for multiple comparisons has been heavily debated, dating back to the early 1990s, but there is no firm consensus on the best practice for epidemiological investigations (203–205). Given the observational nature of the data in the studies in this thesis, we favor a balanced discussion of the collection of evidence supported by our broader study context and the need for external validation studies (203).

5.2 DISCUSSION OF THE MAIN RESULTS

5.2.1 STUDY I

The results of Study I suggest that HL patients are more likely to redeem PD prescriptions compared to matched comparators, which is in accordance with previous studies on the risk of depression and anxiety in cancer patients (186). Several risk factors for PD use were identified, including increasing age, higher CCI, poor ECOG PS, and advanced stage of disease at diagnosis. Interestingly, no association between female sex or education level and PD use was identified, though they are known factors that impact the risk of depression and anxiety. This could be due to a lack of

power because of the limited number of female HL patients included in the study. The risk was markedly higher in the months following the index date, after which the risk would start to normalize to the matched comparators. As a result, 5 years into survivorship, HL patients would no longer be at increased risk of PD use. As no register of depression and anxiety in Denmark is available, a surrogate endpoint (PD use) was chosen as the outcome of interest, though using this proxy could have affected the results for several reasons. The indication of PD use was not available through the DNPR, which is why it was not possible to confirm that PDs were prescribed for depression or anxiety. Moreover, a proportion of HL patients, as well as matched comparators, only redeemed one prescription for PDs, which is not considered enough for treating depression or anxiety. The prescription may have been for short-term stress or there may have been treatment intolerability. Therefore, a sensitivity analysis was conducted with PD use defined as redeeming at least two separate PD prescriptions, which yielded similar results as the main analysis: HL patients had greater use of PDs. A reason for only receiving a few prescriptions of PDs could be misinterpretation of adjustment disorders as depression or anxiety, as the symptoms and diagnostic criteria are very similar (206). Adjustment disorders occur at a high incidence in cancer patients due to the distress following a cancer diagnosis. Other indications for PDs, more specifically antidepressants, could be for managing pain, such as neuropathic pain. However, neuropathy and neuropathic pain are not common side effects of HL treatment regimens (96,207).

5.2.2 STUDY II

In the investigation of parenthood rates in a modern era of treatment regimens, no significant differences in parenthood rates were found between HL survivors and matched comparators. Regarding the total number of live childbirths and outcomes of the newborns (e.g., Apgar score, weight, length, malformations), there was also no difference between HL survivors and matched comparators. However, male HL survivors treated with 6-8 cycles of BEACOPP had significantly lower parenthood rates compared to the matched comparators. As mentioned previously, this result was not adjusted for multiple comparisons, mainly due to the importance of this potential association. Furthermore, it is plausible that BEACOPP treatment is more gonadotoxic than ABVD (189,208,209). Therefore, additional analyses were carried out to investigate this result, showing that male HL patients treated with 6-8 cycles of BEACOPP were comparable to male HL survivors treated with ABVD (2-4 and 6-8 cycles). Moreover, the use of ARTs for first live childbirth after the index date was more common in BEACOPP-treated male HL survivors compared to ABVD-treated male HL survivors. Given that three different analyses indicated that 6-8 cycles of BEACOPP reduces parenthood rates, despite the higher use of ARTs, there is no reason to believe that this finding was a false negative. Therefore, measures such as semen cryopreservation after diagnosis to ensure that HL patients can later have a live

childbirth must remain a focus for HL survivors. Trials concluded during the last few years have investigated the outcomes (OS, PFS, etc.) in HL patients treated with PET-CT-guided therapy, in which fewer cycles of BEACOPP are used (28,29). The overall conclusion of the trials was that the response rate would not be altered if the number of cycles of BEACOPP was reduced to only four in those who had a negative interim PET-CT. A decreased dose of BEACOPP could potentially lead to an increased parenthood rate, as the toxicity of BEACOPP may be dose-dependent. This is to be investigated in an upcoming joint Nordic collaboration within the Nordic Lymphoma Group.

5.2.3 STUDY II

This is the first nationwide population-based study investigating the risk of mental health problems in all subtypes of NHL, as previous research mainly focused on DLBCL and FL (the two most common subtypes) or lymphomas as one pooled group. Results from this study were consistent with the results of Study I, as all subgroups of NHL patients were more likely to use PDs than the matched comparators. Moreover, 5 years into survivorship, all NHL patients except indolent NHL patients would have normalized to the background population. Risk factors associated with increased PD use were more aggressive subtypes of NHL, older age, high CCI, high ECOG PS, high IPI score, and low education status, many of which were similar to Study I. Moreover, female sex was found to be a risk factor in DLBCL and indolent NHL patients. Patients with indolent lymphomas had a high risk of PD use compared to the matched comparators; however, the risk was not as high as with other types of NHL. In addition, the risk normalized to that of the matched comparators 5 years into survivorship. This indicates that the chronic nature of indolent lymphomas may explain the continuous risk of PD use. NHL patients also had a higher risk of intentional self-harm and suicide; however, contacts with any department of psychiatry were not different between NHL patients and matched comparators. In NHL patients with relapse, the risk of PD use was even higher, and the risk of PD use was also high in the last 12 months prior to death. Both results indicate that a more severe course of the disease is associated with greater use of PDs. Analyses of DLBCL and indolent NHL were carried out in two very large cohorts of patients (and matched comparators) compared to the three remaining subgroups of NHL (n = 142-460), in which precision would be compromised due to the limited number of patients. Similarly, incidents of intentional self-harm and suicide could not be stratified according to the type of NHL, as too few HL patients and matched comparators experienced this event. Other factors potentially affecting the results in this study were similar to those in Study I: no indication for PD use was available (anxiety, depression, neuropathy, neuropathic pain, adjustment disorder), many NHL patients and matched comparators only received one or a few PD prescriptions, and the incidence of adjustment disorder in NHL patients was unknown. Intentional self-harm and suicides were identified using an algorithm described by Gasse et al., but the algorithm only

had a PPV of 52%, which is why results regarding intentional self-harm and suicide should be interpreted with caution (182).

CHAPTER 6: CONCLUSION

The three studies included in this PhD thesis address two important topics using high-quality registers: 1) mental health problems after being diagnosed with lymphoma (HL and NHL) and 2) the parenthood rate in HL survivors.

A higher cumulative incidence of PD prescriptions was observed in lymphoma patients (both HL and NHL patients) compared to a matched representative cohort from the Danish background population. The high risk of PD use is most likely associated with a higher incidence of mental health problems, which are possibly triggered by distress related to the newly diagnosed lymphoma. Fortunately, the risk of PD use did not seem to last; the risk diminished with time and was completely normalized for most lymphoma types 5 years into survivorship. Therefore, it is important to remain focused on mental health in lymphoma patients after diagnosis, especially during the first months/years following diagnosis, to ensure that any mental health problem that would occur is identified and properly treated.

For young relapse-free HL survivors, the parenthood rates were comparable to those of matched comparators, which is reassuring and encouraging for young HL survivors who have not yet started a family or plan to expand their family with another child. The results indicate that the dream of parenthood is still possible, either spontaneously or by using ARTs. ARTs were more likely to be used by HL survivors, mainly in males treated with BEACOPP. Therefore, a focus on fertility preservation in young newly diagnosed HL patients is still clinically relevant and fertility should be discussed before initiation of first-line treatment when possible.

Thus, the overall conclusion of this PhD thesis regarding life after lymphoma is positive. For young HL survivors, starting or expanding a family is not impossible and should be pursued if desired. In addition, all lymphoma patients who reach certain landmarks in survivorship no longer have an elevated risk of mental health problems. However, the focus on both fertility and mental health problems must not be neglected in survivorship care and focusing on these topics could potentially diminish the negative effects of lymphoma even more.

CHAPTER 7: PERSPECTIVES

The three studies included in this thesis have contributed important insights into and understanding of mental health and fertility after lymphoma for both patients and survivors. Continuous revision of the survivorship care programs for lymphoma patients during and after treatment is needed to optimize the patients' quality of life, but the requisite information on the mental health and fertility among patients with lymphoma is sparse. Thus, the results presented in this thesis can be implemented to personalize survivorship care programs and emphasize the need for further attention to and assessment of symptoms of mental health problems in the routine follow-up of lymphoma patients.

All three population-based studies conducted within this thesis were based on nationwide high-quality registers in which bias was minimized. Each study is the first nationwide study to date in their respective fields – investigating mental health in lymphoma patients and investigating both male and female fertility in lymphoma patients based on register data. The methods developed for investigating parenthood rates and aspects of fertility involve the use of high-quality registers (including the DIVF register) and can be extended to studies of fertility in other hematological cancers, such as NHL, or cancers in general.

In collaboration with the Nordic Lymphoma Group, projects investigating parenthood in both NHL and HL patients treated with escalated BEACOPP have been planned and will use the methods developed in Study II on a pooled Scandinavian cohort. These results, in addition to the results presented in this thesis, could be used to inspire more modern fertility preservation practices in lymphoma patients when relevant.

Future studies focusing on SEP and late toxicities in lymphoma patients are warranted to meet the increasing demand for high-quality survivorship care programs as the number of long-term lymphoma survivors increases.

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