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**Sexual function and lifestyle behavior among lymphoma survivors after high dose chemotherapy with autologous stem-cell transplantation**

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## **ABSTRACT**

Background/Aims: Lymphoma is one of the most prevalent malignancies among young persons. The survival rate is high, though comes with a risk of late effects including secondary cancer, cardiovascular disease (CVD) and chronic fatigue (CF). Some lymphoma patients require especially intensive treatment, high dose chemotherapy with autologous stem-cell transplantation (auto-SCT), to achieve curation or prolonged survival. This thesis aimed to investigate sexual function and lifestyle factors among auto-SCT survivors and to compare the results to controls. Methods: A national cross-sectional survey was conducted, inviting 399 survivors who were >18 years at auto-SCT, treated during 1987-2008 and without ongoing cancer treatment. Participants responded anonymously on a mailed multi-item questionnaire. Independent t-test and  $X^2$ -test were performed for comparison of mean and prevalence, respectively, between groups. Age-adjusted and multivariable logistic and linear regression models were used to assess associations between explanatory variables and categorical and linear outcome variables, respectively. Effect size was estimated to assess clinical significance of differences. Controls were randomly drawn from three normative cohorts, using frequency matching. Results: In total, the response rate was 78%, 60% was men and median follow-up time was 8.5 years. In **paper I**, male survivors had lower sexual functioning and satisfaction than controls. In multivariable models, lower sexual functioning was related to increasing age, less physical activity and CF. Reduced erectile function was related to CVD. In **paper II**, female survivors more frequently reported personal-issues as cause of sexual inactivity than controls. Sexual activity was related to younger age, being in a relationship and hormone replacement therapy among the postmenopausal women. Sexually active survivors had more sexual discomfort (vaginal dryness and coital pain) and were more often too tired to have sex compared with controls. Reduced sexual functioning was related to younger age, total body irradiation, mental distress and CF. In **paper III**, 55% was sedentary and overweight while 18% smoked. Compared to controls, more survivors were adhering to lifestyle recommendations. Among survivors, an unhealthier lifestyle was related to male gender, less chemotherapy prior to auto-SCT, a higher burden of somatic disease and CF. Conclusions: Sexual function was lower among survivors than controls and there was a potential for improvement of healthy lifestyle factors among survivors.

## SAMMENDRAG

Mange lymfompasienter er unge på diagnosetidspunktet og kurasjonsraten er høy. Høydosebehandling med autolog stamcellestøtte (HMAS) tilbys enkelte subgrupper og de uten tilstrekkelig effekt av 1.linjes behandling. I etterkant av HMAS har overleverne økt risiko for seneffekter som ny kreftsykdom, kardiovaskulær sykdom og kronisk fatigue. Målsetningene med dette arbeidet var å kartlegge seksualfunksjon og livsstils faktorer blant overlevne etter HMAS for lymfom.

Studien er del av en nasjonal tverrsnittsundersøkelse. Inklusjonskriterier: >18 år ved tidspunkt for HMAS for lymfom, behandlet fra 1987 til 2008 og ingen pågående kreftbehandling. Totalt 399 overlevne ble invitert, og 78% besvarte et omfattende spørreskjema. Totalt blant responderne var 60% menn, median alder 55 år og median tid siden HMAS var 8.5 år. Alders- og kjønnsmatchede kontroller ble randomisert trukket fra 3 ulike norm materialer. Ved bruk av t-test, effektstørrelser og logistisk regresjonsmodeller fant vi at mannlige overlevne hadde dårligere seksualfunksjon enn kontrollene, i justerte modeller var dette knyttet til økende alder, mindre fysisk aktivitet og kronisk fatigue. Kardiovaskulær sykdom var relatert til redusert ereksjonsevne. Blant kvinnelige overlevne, fant vi ved bruk av  $\chi^2$ -kvadrat at overleverne hyppigere rapporterte «personlige-forhold» som årsak til seksuell inaktivitet enn kontroller. Seksuell aktivitet var relatert til yngre alder, å være i et forhold samt at de som brukte hormon substitusjonsbehandling oftere var seksuelt aktiv enn de postmenopausale uten slik behandling (aldersjustert logistisk regresjonsmodell). De seksuelt aktive overleverne hadde oftere ubehag ved samleie (tørr vagina og smerter) og de var for trøtt til å ha sex, sammenlignet med kontrollene (uavhengig t-test og effektstørrelser). Redusert seksualfunksjon var relatert til yngre alder, helkroppsbestråling, angst, depresjon og kronisk fatigue (aldersjusterte lineære regresjonsmodeller). I artikkel III overholdt ikke 55% anbefalinger om fysisk aktivitet, 55% var overvektig og 18% røykte. Dog, sammenlignet med kontroller imøtekom flere overlevne disse livsstilsrådene (logistisk regresjonsmodeller). Økende grad av usunn livsstil var relatert til å være mann, færre linjer kjemoterapi før HMAS, flere somatiske sykdommer og kronisk fatigue (multivariat ordinal logistisk regresjonsmodell).

Redusert seksualfunksjon ser ut til å være en seneffekt etter HMAS og det er grunn til å øke fokus på livsstilsendring hos lymfomoverlevne etter HMAS.



## LIST OF PAPERS

### Paper I

**“Sexual function in long-term male lymphoma survivors after high-dose therapy with autologous stem-cell transplantation”**

Hanne Skjerven Bersvendsen, Hege Sagstuen Haugnes, Alv A. Dahl, Unn-Merete Fagerli, Øystein Fluge, Harald Holte, Mette Seland, Tom Wilsgaard, Knut Bjøro Smeland, Cecilie Esholt Kiserud

*Bone Marrow Transplantation* 2019 November. doi:10.1038/s41409-019-0745-4

### Paper II

**“Sexual function in long-term female lymphoma survivors after high-dose therapy with autologous stem-cell transplantation “**

Hanne Skjerven Bersvendsen, Hege Sagstuen Haugnes, Alv A. Dahl, Unn-Merete Fagerli, Øystein Fluge, Harald Holte, Tom Wilsgaard, Knut Bjøro Smeland, Cecilie Esholt Kiserud

*Bone Marrow Transplantation*, submitted 2019 December.

### Paper III

**“Lifestyle behavior among lymphoma survivors after high dose therapy with autologous hematopoietic stem-cell transplantation”**

Hanne Skjerven Bersvendsen, Hege Sagstuen Haugnes, Unn-Merete Fagerli, Øystein Fluge, Harald Holte, Knut Bjøro Smeland, Tom Wilsgaard, Cecilie Esholt Kiserud

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## ABBREVIATIONS

ABVD	Adriamycin, bleomycin, vinblastine and pro/dacarbazine
ALL	Acute lymphoblastic leukemia
Allo-SCT	Allogeneic stem-cell transplantation
Auto-SCT	High dose chemotherapy with autologous stem-cell transplantation
BEACOPP	Bleomycin, cyclophosphamide, doxorubicin, etoposide, prednisone, procarbazine, vincristine
BEAM	BCNU®/carmustine, etoposide, cytarabine and melphalan.
GMALL	German Multicenter Group for adult ALL protocol
BMI	Body mass index
BSFI	Brief Sexual Function Inventory
CD	Cluster of differentiation
CF	Chronic fatigue
ChlVPP	Chlorambucil, vincristine, procarbazine, and prednisone (MVPP-like regimen)
CHOP	Doxorubicin, cyclophosphamide, vincristine and prednisone
CI	Confidence interval
CVD	Cardiovascular disease
CT	Computerized tomography
EBVP	Epirubicin, bleomycin, vinblastine and prednisone. ABVD-like regimen
ED	Erectile dysfunction
FAI	Free androgen index
FSH	Follicle stimulating hormone
HL	Hodgkin lymphoma
HRT	Hormone replacement therapy
iNHL	Indolent non-Hodgkin lymphoma
IPI-score	International Prognostic Index score
LH	Luteinizing hormone
MVPP	Mechlorethamine, vincristine, procarbazine, and prednisone
NK cell	Natural killer cell
NLPHL	Nodular lymphocyte-predominant Hodgkin lymphoma
NHL	Non-Hodgkin lymphoma
PET	Positron emission tomography
POI	Premature ovarian insufficiency
PROMs	Patient-reported outcome measures
QoL	Quality of life
SAQ	Sexual Activity Questionnaire
SD	Standard deviation
SHBG	Sex hormone-binding globulin
SMD	Standardized mean difference
WHO	World Health Organization

## **1 Chapter: INTRODUCTION**

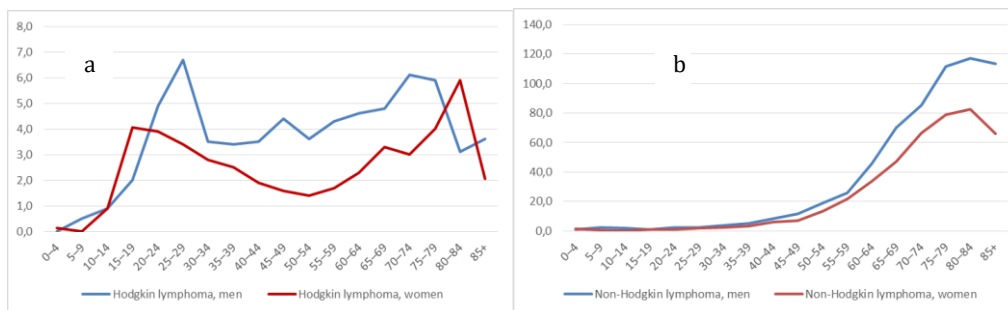
The population of cancer survivors is rapidly growing and survivorship care is an emerging field within oncology. In line with improved survival of cancer, the knowledge of treatment consequences in the long-term (>5 years) has evolved. This knowledge has become a part of the judgment of patients' therapeutic benefit [1], and raised the awareness of survivors need for information, follow-up, support and intervention in order to mitigate risk of late effects and improve mastering of life beyond cancer.

Many lymphoma patients treated with high dose chemotherapy with autologous stem-cell transplantation (auto-SCT) are young or middle-aged adults [2], with presumably expectations of a normal sexual function, however sexual function among survivors after auto-SCT in the long term is largely unstudied. Lifestyle behavior may influence on risk of late effects, yet knowledge of auto-SCT survivors health-promoting behavior is lacking. These areas of interest will be investigated in this thesis.

## 1.1 Lymphoma

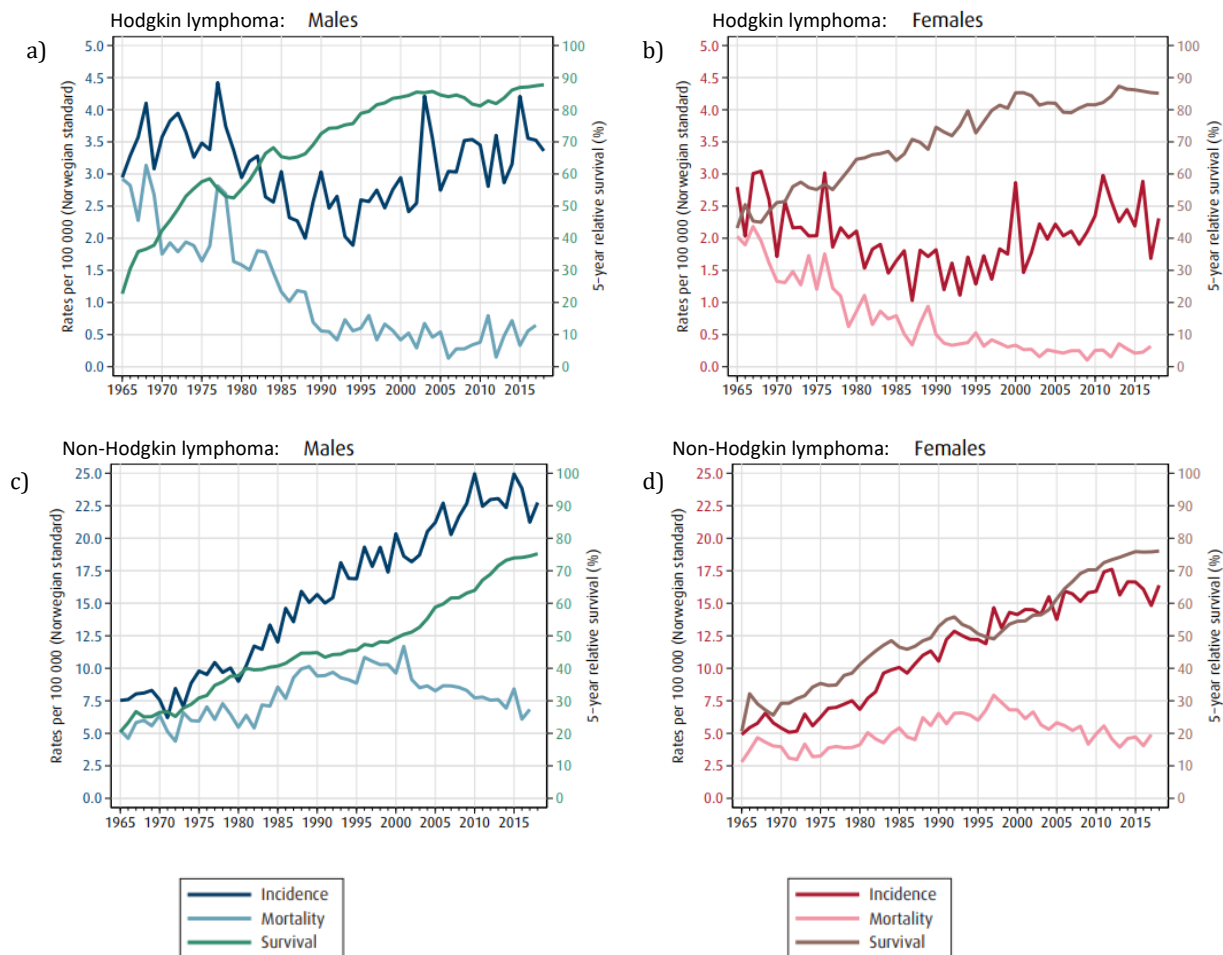
### 1.1.1 *Epidemiology*

The incidence of lymphoma, especially non-Hodgkin lymphoma (NHL) has increased over the last five decades. In 2018, 144 adults were diagnosed with HL in Norway, and 1053 were diagnosed with NHL [3]. Lymphoma affects people of all ages; the incidence of HL is highest among young adults age 20-35 years and older people >60 years with median age at diagnosis of 44 years. The incidence of NHL increase with older age and median age at diagnosis is 69 years (Figure 1a and b) [3].



**Figure 1 a and b.** Age specific incidence rates per 100 000 person-years and five-year age group, 2013-2017 for Hodgkin lymphoma and non-Hodgkin lymphoma, respectively. Based on data from Cancer in Norway 2018, Cancer Registry of Norway [3].

During these last decades, the 5-year survival rates have increased due to improvements in diagnosis and treatment. In 1983-87, the 5-year relative survival for patients diagnosed with HL was about 67%, increasing to 86% in 2018 (Figure 2a and b), corresponding numbers for NHL was 45%, increasing to 76% in 2018 (Figure 2c and d) [3]. Consequently, the prevalence of lymphoma survivors increased with 60% from about 8000 in 2007 to almost 13000 persons in 2017, (2868 HL and 9989 NHL). Sixty-five percent of these persons were alive >5 years after diagnosis, thus defined as long-term survivors (total 8418, HL 2201, NHL 6217)[4].



**Figure 2 a-d.** Trends in incidence and mortality rates and 5-year relative survival proportions of Hodgkin (a and b) and Non-Hodgkin lymphoma (c and d). Reprinted with permission from Cancer Registry of Norway. Cancer in Norway 2018 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2019 [3].

### 1.1.2 *Etiology and classification*

The lymphoma classification used in this thesis is according to the World Health Organization (WHO) report on classification of hematopoietic and lymphoid tumors [5]. A revised 4<sup>th</sup> edition has been published in 2017 [6]. Correct classification depends on clinical and morphological features, immunophenotype (expression of proteins named cluster of differentiation (CD)) and genetic alterations. These features are provided using histopathology, immune-histochemistry, flowcytometry, fluorescence in-situ hybridization (FISH) and cytogenetic analyses.

There are two major types of lymphoma, HL and NHL, which both arises from a malignant transformation of lymphocytes. HL is subdivided into classical HL (cHL) and

nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL); the latter makes up only 5% of all HL. The Hodgkin and Reed-Sternberg cells and lymphocyte predominant cells represents cHL and NLPHL, respectively, and both originate from a germinal center B-cell.

NHL is a larger and much more heterogenic group of lymphomas; constitutes more than 60 subentities and 85% of all lymphomas [5]. The major distinctions are between very aggressive/aggressive (lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, T-cell lymphoma and transformed lymphoma) and indolent NHL (follicular lymphoma, marginal zone lymphoma, small cell lymphocytic lymphoma). The WHO classifications divide lymphoma into B-, T-/NK cell neoplasia of either precursor or mature cell type and Hodgkin lymphoma. For the purpose of this thesis, the lymphomas were categorized into three groups; HL, indolent NHL (mainly follicular lymphomas) and aggressive NHL (lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, T-cell lymphoma and transformed lymphoma).

### *1.1.3 Clinical features, staging, prognostic factors*

Lymphomas most often affect lymphatic glands and patients present with a “lump”. The presentation may however show great diversity as the lymphoma can affect all parts of the human body. Advanced disease (stage  $\geq$ IIB) is less common in HL (49%) than NHL patients (65%), as is extranodal involvement [3, 7]. Clinically significant lymphoma progression may occur during few weeks to years, depending on the growth rate of the lymphoma.

Of note, a correct classification of the lymphoma, staging and determination of prognostic factors are essential as treatment recommendations are based on these factors [8].

Staging of lymphoma is referred in table 1. The B-symptoms of lymphoma disease are: Persistent or residual body temperature  $>38^{\circ}$  C last month, weight loss  $>10\%$  during last six months and persistent profuse night sweats the last month.

**Table 1.** Staging of lymphoma.

<b>Ann Arbor staging of nodal lymphoma [9]:</b>	
Stage I	One lymph node region
Stage II	Two lymph node regions (suffix 1 or 2 if the disease is includable in one radiation field or not)
Stage III	Two non-neighboring lymph node regions on the same side of diaphragm
Stage IV	Lymph node regions on both side of diaphragm or involvement of extranodal tissue or bone marrow.
Suffixes added in case of:	
A/B	B-symptoms present or not
X	Bulky disease defined by tumor mass $\geq 7$ cm but varies according to entity
E	Extranodal disease
<b>Musshof's staging of extranodal lymphoma [10]:</b>	
PeI	Extranodal organ/tissue
PeII 1	Extranodal organ/tissue with regional lymph node involvement
PeII2	Extranodal organ/tissue with involvement beyond regional lymph nodes, but on the same side of diaphragm
Suffix added in case of:	
E	Growth per continuitatem on another extranodal organ/tissue, used from $\geq$ stage PeII

**Prognostic indices** are available for diffuse large B-cell lymphoma [11], follicular lymphoma [12], mantle cell lymphoma [13] and risk factors associated with HL have been identified [14, 15]. It is beyond the scope of this thesis to describe these in detail. A common feature is that the risk factors generally mirror clinical or para-clinical disease burden of the patient, in addition to age. E.g. risk factors for diffuse large B-cell lymphoma (The revised International Prognostic Index score) includes age  $>60$  years,  $\geq$  stage III-IV disease, performance status  $\geq 2$ , lactate dehydrogenases  $>$  reference level and extranodal involvement [11].

#### *1.1.4 Treatment strategies for lymphoma during 1970-2008*

Survivors in the study cohort were diagnosed during 1973-2008, and treatment was performed according to national and international guidelines. Lymphomas are generally sensitive to both chemo- and radiotherapy and combined modality treatment are often used. The most commonly used chemotherapeutic agents for lymphoma has been the alkylating

agents (cyclophosphamide, ifosfamide, mechlorethamine, chlorambucil, melphalan, busulfan, BCNU<sup>®</sup>/carmustine and procarbazine), anthracyclines (doxorubicin, epirubicin), vinca alkaloids (vinblastine, vincristine), anti-metabolites (methotrexate, cytarabine) in addition to bleomycin, etoposide and carmustine. Combinations of these agents were used in multi-agent chemotherapy regimens.

Immunotherapy was introduced in the late 1990s and was a game changer for treatment of B-cell NHL. The first agent was rituximab, a monoclonal antibody directed to the B-cell specific cell surface protein CD20 [16]. The adding of rituximab to CHOP<sup>1</sup> based chemotherapy increased 6-year event-free survival from 56% to 74% among young patients with good prognosis diffuse large B-cell lymphoma [16, 17].

### **Primary treatment of Hodgkin lymphoma**

Early stage HL (stage I-IIA): 1970-80: The first curative treatment for HL was extended field radiation (mantle field irradiation, inverted Y/ L, dog-leg) to 40 Gy in 2 Gy fractions [18]. Later, chemotherapy was introduced prior to radiotherapy for patients with risk factors (1980-88, four courses MVPP<sup>2</sup> [19]/ChIVPP<sup>3</sup>; 1988-97, two-four courses EBVP<sup>4</sup>) and from 1998 all patients with early stage HL received combined modality treatment (no risk factors, two courses ABVD<sup>5</sup> [20]; risk factors, four courses ABVD) [21, 22]. The radiotherapy changed during these years with dose and fractioning: 1982-97, 1.8 Gy x 23; 1997-2007, 1.75 Gy x17-20 and from 1997 the fields were reduced from extended to involved fields (Figure 4) [18, 23].

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<sup>1</sup> CHOP: doxorubicin, cyclophosphamide, vincristine and prednisone.

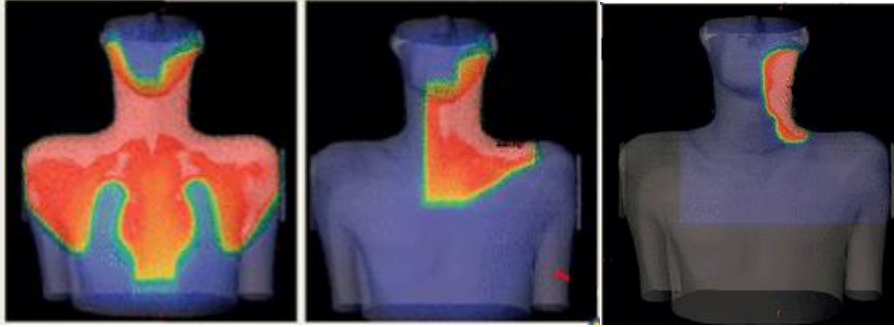
<sup>2</sup> MVPP: mechlorethamine, vincristine, procarbazine, and prednisone.

<sup>3</sup> ChIVPP: chlorambucil, vincristine, procarbazine, and prednisone. MVPP-like regimen.

<sup>4</sup> EBVP: epirubicin, bleomycin, vinblastine and prednisone. ABVD-like regimen.

<sup>5</sup> ABVD: adriamycin, bleomycin, vinblastine and pro/dacarbazine.





**Figure 4.** Illustrations of extended (left) and involved field (middle) radiation therapy, and involved node (right) radiation therapy. Reprinted with permission from Specht et al. *Int Journ Clin Oncol*, 2015 [23].

Advanced disease HL (stage IIB-IV): MVPP was the first chemotherapy regimen with a curative potential for patients with advanced stage HL [19]. Eight courses of this regimen (or the MVPP-like, ChlVPP) was used in Norway from 1970-85 for these patients. During 1985-1991, 8 courses of ChlVPP or a combination with alternating ABVD [20] for a total of 8 courses were used. In 1992, 6-8 courses of AVBD replaced CvLPP as standard chemotherapy for HL due to increased efficacy and considerably less gonado- and bone marrow toxicity, including secondary myeloid malignancies. The ABVD regimen has been the backbone of HL treatment ever since [22, 24]. During 1999-2007, a more intense regimen BEACOPP<sup>6</sup> (2 courses of escalated BEACOPP + 6 courses BEACOPP) was used on a subgroup of patients with at least four out of seven risk factors [25].

The chemotherapy was consolidated with radiotherapy, during 1970-80 all stage III patients received total nodal irradiation (mantle field + inverted Y). Stage IV patients received radiotherapy to areas of initial bulky mass or residual mass post-chemotherapy and the fractioning regime was 2 Gy x 20. From 1980, indications for consolidative radiotherapy to stage III patients were restricted according to indications for stage IV patients. During 1985-1991, the dosage and fractioning was either 2 Gy x 20 or 1.8 Gy x 23, and from 1997-2007, 1.75 Gy x 17-20 was used.

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<sup>6</sup> BEACOPP: bleomycin, cyclophosphamide, doxorubicin, etoposide, prednisone, procarbazine, vincristine.

### **Primary treatment of aggressive non-Hodgkin lymphoma**

Limited stage disease (I-II): During 1980-90 these patients were treated with radiotherapy only, 2 Gy x 20. From 1990, combined modality treatment with CHOP prior to radiation was used.

Advanced stage disease (III-IV): These patients have been treated with CHOP regimen (6-8 courses) for almost five decades [26]. Consolidation with radiotherapy to involved field was used in case of initial bulky disease, skeletal or testicular involvement or a residual mass post-chemotherapy, 2 Gy x 18-20 [8].

Slight adjustments have been made to subgroups of patients with diffuse large B-cell lymphoma such as: intensification from three to two week intervals for those with age-adjusted IPI-score  $\geq 2$ ; addition of etoposide for younger patients, in particular those with mediastinal large B-cell lymphomas; addition of high dose methotrexate and cytarabine (intravenous or intrathecal or both) for patients with risk of central nervous system disease [8].

Systemic peripheral T-cell lymphomas had a poor prognosis with conventional chemotherapy, thus patients were included in a clinical trial (2000-2008) investigating the efficacy of auto-SCT in first remission [27].

### **Primary treatment of very aggressive non-Hodgkin lymphoma**

Lymphoblastic lymphoma and Burkitt lymphoma patients have a dismal prognosis with CHOP based chemotherapy. Introduction of ALL-like treatment, Hammersmith regimen (1992) and GM ALL (1995) for lymphoblastic and Burkitt lymphoma, respectively, improved survival. From 1999, patients with lymphoblastic lymphoma received auto-SCT as consolidation in first remission instead of maintenance chemotherapy and additionally mediastinal radiation in cases of a mediastinal mass [28].

### **Primary treatment of indolent Non-Hodgkin lymphoma**

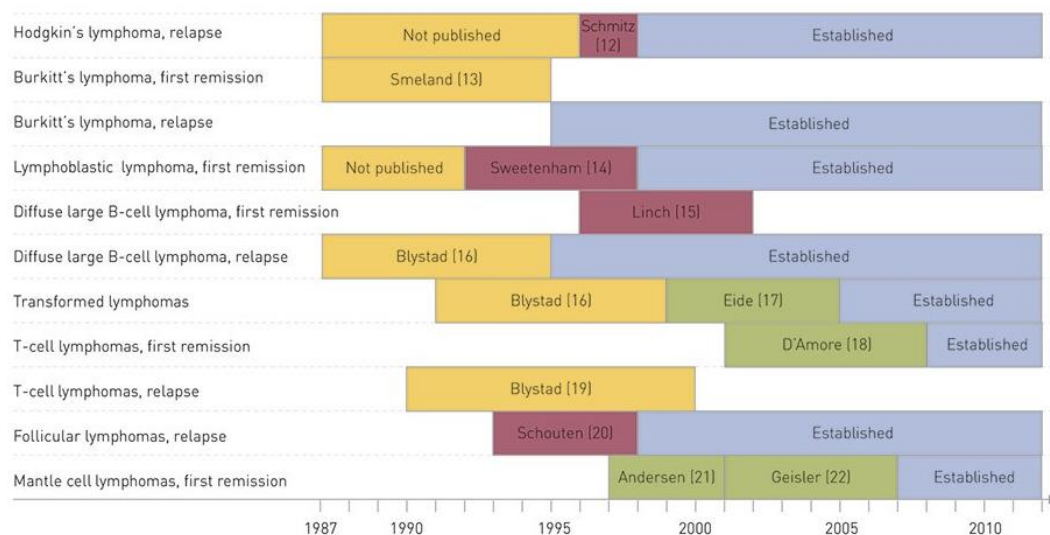
Limited stage disease (I-IIA): Radiotherapy to involved area including the draining lymph node region 2 Gy x 15 was used with curative intent [8].

Advanced stage disease (IIB-IV): Patients in need of systemic treatment, received per oral chlorambucil or the CHOP regimen either with or without doxorubicin as first line treatment,

later rituximab-monotherapy was introduced as a non-chemo containing regimen [29]. In cases of an aggressive clinical presentation and advanced disease, rituximab-chemotherapy (usually CHOP) was the preferred therapy to achieve a rapid response [8].

### 1.1.5 High dose chemotherapy with autologous stem-cell transplantation

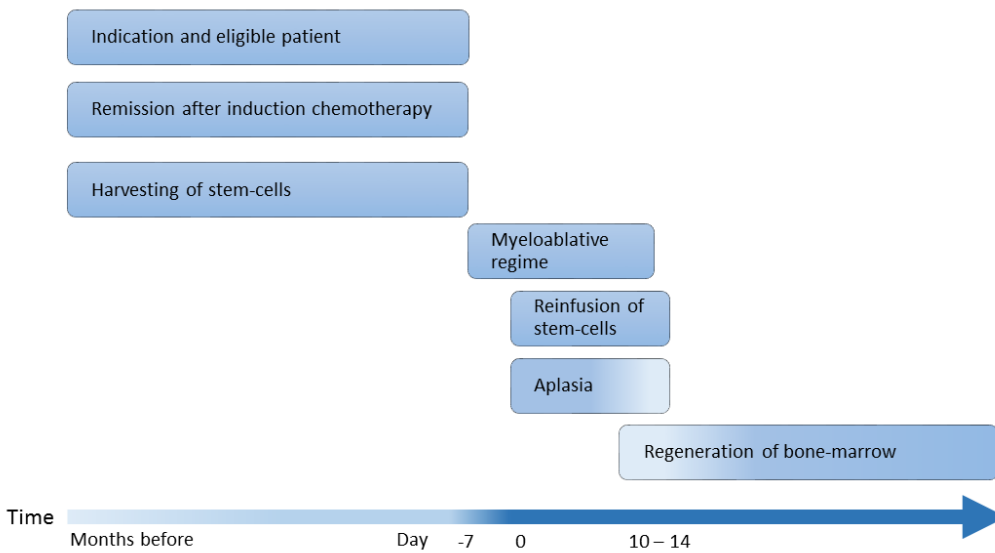
Auto-SCT was initially introduced in Norway as part of clinical trials, and the selection of patients was strictly specified both when it came to indication and suitability of the patient [30, 31]. During 1987-1995, median age at auto-SCT was 11 years lower than in 1996-2008 [31]. Based on results from clinical trials, auto-SCT was implemented as standard treatment for relapsed/refractory diffuse large B-cell lymphoma and Burkitt lymphoma, followed by relapsed/refractory Hodgkin lymphoma and other lymphoma entities (Figure 5), hence the number of treated patients increased until 2004 [30]. Later on, reports on improved overall survival for mantle cell and follicular lymphoma patients, paved the way for auto-SCT as an indication not only for curative intent but also as a recommendation for extending disease free and overall survival [32-34].



**Figure 5.** Illustration of clinical studies giving rise to established indications for high-dose therapy with autologous stem cell support for lymphomas in Norway. Yellow, single-centre phase 2 study; green, multicenter phase 2 study; red, randomized phase 3 study; blue, established indication/treatment. Reprinted with permission from Smeland et al. 2013 Tidsskr Nor Legeforen [30]. References in figure presented in footnote<sup>7</sup>.

<sup>7</sup> 12) Schmitz 2002, 13) Smeland 2004, 14) Sweetenham 2001, 15) Linch 2010, 16) Blystad 1999, 17) Eide 2011, 18) d'Amore 2012, 19) Blystad 2001, 20) Schouten 2003, 21) Andersen 2003, 22) Geisler 2008.

The process leading up to the auto-SCT is illustrated in figure 6. The eligible and fit patient in remission after induction (immuno-)chemotherapy is admitted to the hospital on day -7 and receives the myeloablative treatment (1987-1996, total body irradiation and high dose cyclophosphamide; 1996 – today, high dose chemotherapy, usually BEAM<sup>8</sup>). The acute side effects of the high dose chemotherapy present at the time of aplasia with febrile neutropenia and symptoms of gastro-intestinal toxicity during which the patient is under careful observation. After regeneration of stem cells and normalization of peripheral blood cell levels, the patient slowly recovers and is discharged from the hospital.



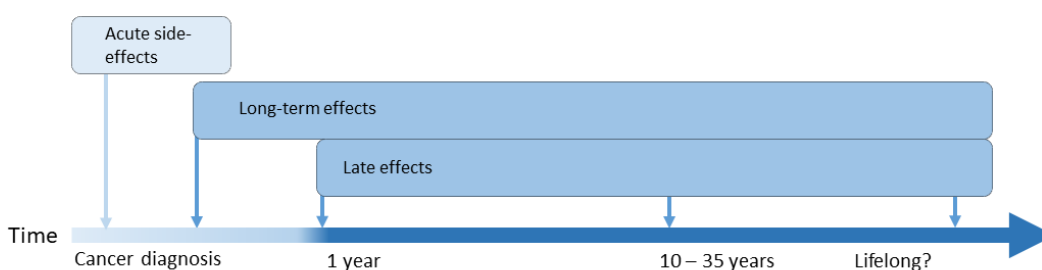
**Figure 6.** Illustration of the process leading up to auto-SCT.

Auto-SCT lymphoma survivors are a heterogeneous group according to lymphoma entities and treatment prior to auto-SCT. First line treatment depends on year of diagnosis, lymphoma subgroup, classification, prognostic factors in addition to age and fitness of the patient. Additionally, the treatment necessary to achieve a second remission (induction treatment) may differ. Hence, the patient cohort providing data for this thesis have received various treatments, even though they all received auto-SCT for lymphoma.

<sup>8</sup> BEAM: BCNU®/carmustine, etoposide, cytarabine and melphalan.

## 1.2 Late effects

Complications after cancer treatment are referred to as long-term or late effects and are adverse effects occurring during cancer treatment and lasting >1 year, or presenting >1 year after end of treatment (Figure 1) [35]. Examples are treatment induced premature ovarian insufficiency (POI) presenting as amenorrhea shortly after chemotherapy treatment and persisting throughout life, and secondary malignancy, which usually occurs many years after treatment. In this thesis, I will use the term late effects including both long-term and late effects.



**Figure 1.** Adverse effects according to time of cancer treatment.

Childhood cancer and Hodgkin lymphoma (HL) in young adults represents cancer trajectories in which long-term consequences of treatment (late effects), first became apparent [36]. These cancer survivors have a long life expectancy, and the risk of many late effects in lymphoma survivors is documented [37]. Auto-SCT is an especially intensive lymphoma treatment with a high risk of late effects [38-40].

When the work on this thesis began, knowledge on the following late effects in this study cohort were published; secondary cancer, cardio-pulmonary toxicity and negative consequences for working ability [2, 41-46]. Later, a report on chronic fatigue (CF), bone mineral density and knowledge of late effects after auto-SCT has been published [47-49]. In the following, I will give a description of the late effects most relevant for my thesis.

### *1.2.1 Life threatening late effects: second cancer and cardiovascular disease*

Excess mortality among lymphoma survivors compared with the general population has been reported in previous studies [36, 50, 51]. During the first 12-15 years post treatment,

lymphoma is the main cause of death, later surpassed by secondary cancer and cardiovascular disease (CVD) as reported in survivors of early stage HL [36, 50] and auto-SCT survivors [38]. In a former study on the cohort of survivors included in this thesis, life expectancy approximated that of the general population for those who were alive 10 years after auto-SCT, (conditioning on 10-years survival), however this may not occur with longer follow up time due to late-onset secondary cancer and CVD [2].

Second cancer is a well-known late effect after lymphoma treatment with hematological secondary malignancies occurring 2-10 years after treatment while solid malignancies usually occur decades after treatment [52, 53]. In a large cohort of HL survivors, they found a 4.6-fold increased risk of second cancers compared with the general population persisting >35 years after treatment (median follow-up time 19 years) [54]. The relative risk of secondary cancer was lower after chemotherapy-only for HL than after combined modality treatment, relative risk 2.0 and 3.9, respectively [53]. Breast- (among females), lung-, gastrointestinal cancer and NHL were the malignancies who contributed most to overall absolute excess risk [54].

In lymphoma patients risk factors for a second primary cancer are younger age (after combined modality treatment), alkylating chemotherapy, radiation and shared risk factors [52-55]. It has previously been shown that among the study cohort of this thesis, the risk of secondary cancer was increased 2-fold compared to the general population, with a median follow-up time of five years [56]. In line with an earlier report, with a 2.6-fold increased risk of secondary cancer after seven years. In the study by Tarella et al, older age, radiotherapy post-transplant and rituximab were independent risk factors of secondary solid tumors [57]. Of note, the incidence of secondary cancers in both these cohorts is expected to increase with longer follow up time.

CVD include disorders affecting the heart and blood vessels and include; hypertension, thromboembolism, disease of peripheral and coronary arteries in addition to disease of heart valves and the myocardium. Risk factors for stroke and coronary heart disease are tobacco use, physical inactivity, obesity, alcohol misuse, diabetes type I/II, hypertension and hyperlipidemia [58, 59]. In lymphoma survivors, late effects on coronary structures (arteries, valves, myo- and pericardia) are documented, and related to both radio- and chemotherapy [60]. Anthracyclines are known to cause cardiac failure in a dose-

dependent pattern and has been related to oxidative stress, cardiomyocyte death and remodeling from these injuries [61, 62]. Mediastinal irradiation induces cardiac damage largely due to fibrosis and endothelial damage and is related to dose, fractioning and heart-volume irradiated [62, 63].

The risk of CVD was increased 3-5 fold in HL survivors compared with the general population [64], confirmed in a 20 years up-date of these data [65]. The risk of CVD seems to persist even 20-35 years after treatment [65-67]. CVD-related mortality was increased 7- and 5-fold among HL and NHL treated patients, respectively, compared with the general population (median follow-up time 13.8 years) [68]. After auto-SCT for hematological malignancies, the risk of heart failure was increased 4.5-fold compared to the general population, with a cumulative incidence increasing from 5 to 15 years after auto-SCT. Risk factors for heart failure were older age at transplantation, female gender, anthracycline dose and comorbidity (hypertension and diabetes), pre-transplantation radiotherapy was not significantly related possibly due to lack of power [69]. In a study on the same cohort as used in this thesis, increased risk of left ventricular systolic dysfunction was related to anthracycline dose  $>300 \text{ mg/m}^2$  and mediastinal irradiation  $>30\text{Gy}$ , with greatest risk among survivors with both these risk factors [42].

### *1.2.2 Gonadal endocrinopathy after lymphoma treatment*

The gonads are responsible for adequate levels of sex hormones and maturation of germ cells. The focus in this thesis will be on sex hormones, and the production of these may be affected by both radio- and chemotherapy. Risk of chemotherapy induced gonadal endocrinopathy are related to high doses, especially of alkylating agents, in addition to age at diagnosis for both gender [70-72]. Alkylating agents (cyclophosphamide, ifosfamide, mechlorethamine, chlorambucil, melphalan, busulfan, BCNU<sup>®</sup>/carmustine and procarbazine) are present in MOPP, ChlVPP, BEACOPP, CHOP and BEAM but not included in the ABVD regimen.

Males: The testicular Leydig cells responsible for testosterone production are relatively robust to radio- and chemotherapy in contrast to the sperm producing Sertoli cells [73]. In testicular cancer patients, hypogonadism occurred in 30% after irradiation of testis with total dose 18-20Gy [74]. However, increased levels of gonadotropins are regularly

reported after lymphoma treatment [71, 75]. In male HL, testosterone levels have been reported to be reduced after conventional chemotherapy, but not below reference values, not even after six courses of BEACOPP [71]. Kiserud et al. reported that chemotherapy of  $\geq$ medium-risk of gonadotoxicity in HL survivors and high-risk in NHL survivors, were related to an increased risk of lower testosterone levels compared with men treated with low-risk chemotherapy [72]. Auto-SCT treatment was included in the high-risk gonadotoxic chemotherapy group and 20/41 of these men had endocrine hypogonadism related to older age at diagnosis and at survey [72].

Females: The toxic effect of chemotherapy on ovarian function is not fully understood, however possibly related to: 1) Induced apoptosis of maturing primordial follicles causing loss of menstrual bleeding shortly after chemotherapy. 2) Ovarian cortical fibrosis and vascular damage injuring the primordial follicles and a compensatory increased recruitment of primordial follicles into maturing follicles, called the follicular “burn-out hypothesis”. This “burn-out” causes depletion of the primordial follicle reserve and POI [70].

In female HL survivors treated with conventional chemotherapy, irregular menstrual cycles were reported in 10-55% at a median follow-up of 46 months, the prevalence was highly dependent of age at diagnosis and accumulated doses of alkylating agents [71]. Another study reported POI in 56% and 23% of HL survivors treated with or without alkylating chemotherapy, respectively, confirming the negative impact of conventional chemotherapy on ovarian function [76]. Risk of radiation induced ovarian failure are strongly related to age at treatment and radiation dose. Hence, ovarian failure may occur after 6 Gy in 40-50-year-old women, and after 20 Gy in women <40 years [77]. After auto-SCT treatment, POI has been reported in 64-100% of women [78, 79] and related to both total body irradiation and high doses of alkylating chemotherapy [70].

### 1.2.3 *Chronic fatigue*

Fatigue after cancer treatment is defined as “*a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that significantly interferes with usual functioning*” [80]. Duration of fatigue  $\geq$ 6 months defines chronic fatigue (CF) [81]. CF is a multifactorial phenomenon influenced by demographic, physiological and psychosocial



factors and may have debilitating consequences for daily-life and functioning in cancer survivors [82]. However, the underlying mechanisms of CF are largely unknown. Pro-inflammatory markers, has been associated with prevalence of CF in the current study population [47], still researchers are calling out for more research on the biological origin of CF [1].

The first reports on energy-loss in HL survivors were published in 1986. About a third of the survivors reported problems median 9 years after treatment [83]. In later reports on CF in cancer survivors, including studies among lymphoma survivors, a prevalence of 25-35% has been found [84]. In a recent study, severe CF was present in 37% of NHL survivors (additionally 27% had moderate CF) with a median follow up of 11 years [1]. Treatment intensity, including auto-SCT, does not seem to influence on the prevalence of CF [1, 85]. However, a relationship between fatigue at end of therapy and later has been reported in HL survivors [86]. Recently, the level of CF in long-term HL and NHL survivors was reported to increase with follow-up time [87].

In lymphoma survivors, CF has been associated with increasing age, anxiety, depression, obesity, impaired pulmonary diffusing capacity and general health disorders [1, 87-90]. CF might influence multiple aspects of life after lymphoma treatment, including working ability, economic status [91] and health-related QoL [89]. To what extent CF is related to healthy behavior remains to be investigated in lymphoma survivors after auto-SCT. Among lymphoma survivors, CF is associated with lower sexual function [92, 93], whether this association is relevant among auto-SCT survivors is largely not studied [94].

#### *1.2.4 Anxiety and depression*

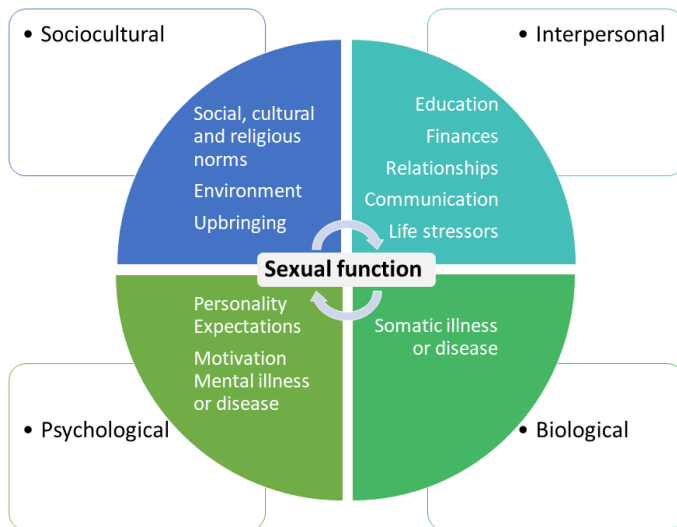
A longitudinal study reported anxiety and depression rates between 17-24% among HL (n=180) and NHL survivors (n=309) which was higher than the general population [95], and in line with previous reports [96, 97]. Among SCT survivors of hematological malignancies (29% lymphomas) 15% reported moderate to severe depression, compared to 9% in the general population [98]. Depression was less prevalent among auto-SCT survivors compared with allogeneic-SCT (allo-SCT). These findings were in contrast to an earlier report, where no difference in anxiety or depression was found between allo- and auto-SCT treated survivors or between auto-SCT survivors and the general population [99].

### 1.3 Sexual function

WHO defines sexual health as “a state of physical, emotional, mental and social well-being in relation to sexuality”, and sexuality is “the result of a dynamic interaction between physiological, psychological and social dimensions which in a positive manner enriches and enhances personality, communication and love” [100] (full text in footnote<sup>9</sup>).

The sexual health of an individual is influenced by multiple factors of which sexual function is an important part [101]. The sexual response cycle is a model of sexual function (see below in paragraph 1.3.1). Factors influencing on sexual function might be explained using a biopsychosocial model, where multiple factors influence on, relate to and probably overlap the other (figure 7) [102, 103].

Sexual function was important for health-related QoL among HL survivors [92, 104] and after SCT for hematological malignancies [105].

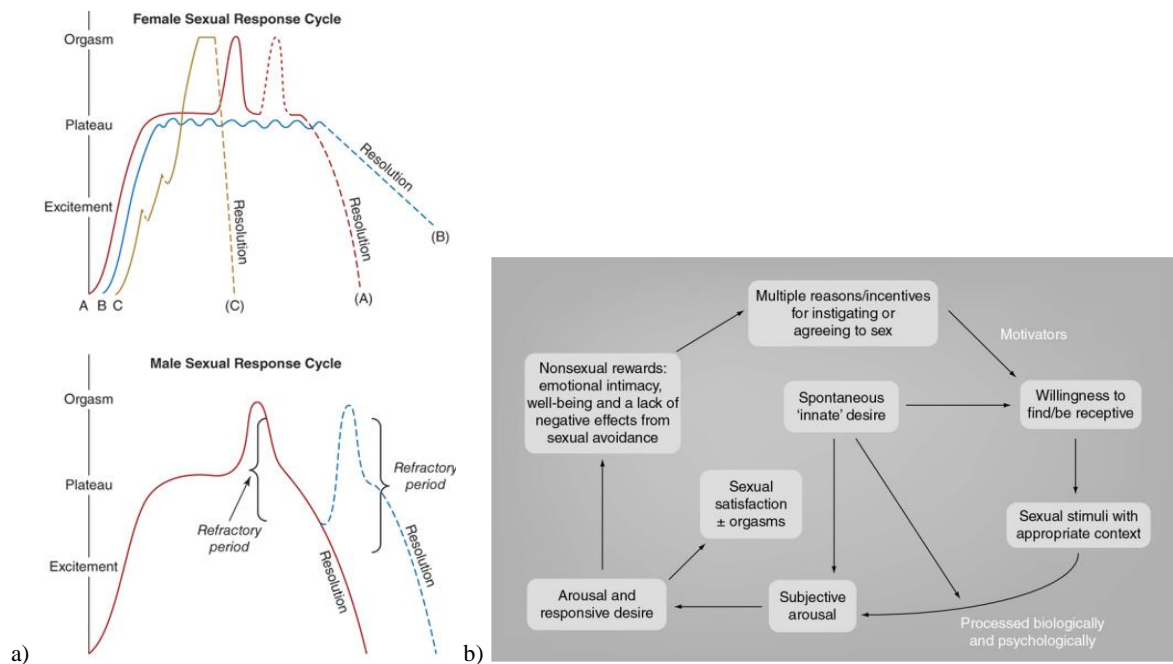


**Figure 7.** Illustration of factors influencing sexual function. Adapted from Thomas and Thurston, Maturitas 2016 [102].

<sup>9</sup> Sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled. WHO, 2006a

### 1.3.1 The sexual response cycle

The sexual response cycle describes the physiological processes that occur during sexual activity and was first described by Masters and Johnson in 1966 [106]. Their original model had four phases and is called linear as the entry to sexual activity was excitement (arousal) leading to a plateau (advanced arousal) followed by orgasm and finally resolution.



**Figure 8a og b.** Models of the sexual response cycle, a) Linear model. Reprinted with permission from McGrawHill Education [106, 107] b) Circular model. Reprinted with permission from Basson, *Women's Health* 2010 [108].

Later Kaplan added desire to this model, a phase preceding arousal [109]. Further modifications have been proposed, yet the basic elements of this model are still relevant [110]. In 2000, Basson proposed a circular model for female sexual response taking into account other entries to sexual activity in addition to innate desire [111]. She described emotional or relational benefits as motivation to be receptive of sexual stimuli causing responsive desire, arousal and engagement in sexual activity. The linear models have been endorsed by the vast majority of males and about half of females, however the circular model has shown increased relevance among women with sexual dysfunctions [112, 113]. The biopsychosocial model and sexual response cycles identify areas which might be related to sexual difficulties and relevant for sexual dysfunctions, sexual therapy and research [101].

### 1.3.2 Sexual dysfunction in the general population and in lymphoma survivors

There is a significant difference between sexual dysfunction and a sexual problem, as sexual dysfunction not necessarily imply a problem for the individual. A sexual problem is present only if the individual defines it as such [100].

General population: Sexual dysfunction are common in the general population (age 16-80 years), and more prevalent among women (43-51%) than men (30-42%) [114-116]. Of note, only 10% of both genders reported distress related to the sexual dysfunction [115]. Women report on lack of sexual interest, difficulties reaching orgasm, vaginal dryness and lack of sexual enjoyment, while the most prevalent problems among men were lack of interest and erectile problems [115]. The most important risk factors for a lower sexual functioning were increasing age, depression, self-reported poor health status, lower frequency of sexual activity and sexual factors in relationships, additionally among women; postmenopausal status probably due to loss of estrogen stimulation of the vaginal mucosa causing vulvovaginal atrophy and dryness in addition to reduced sexual responsiveness (arousal, sexual pleasure and orgasm) and among men; vascular disease [115-117].

In a cohort of younger cancer patients, aged 15-39 years at diagnosis and 52% with a lymphoma diagnosis, 43% experienced a negative influence on sexual life by their cancer diagnosis at two years follow-up [93]. In lymphoma survivors after conventional chemotherapy, 24-36% reported that the lymphoma experience had negatively influenced their sexual life (mean follow-up time of 20 years) [118]. In NHL lymphoma survivors with follow-up time of 2-5 years, 24-29% usually or always had sexual dysfunctions, while 31-46% of the survivors reported sexual dysfunctions to occur sometimes, no comparison to the general population was reported [104]. In a study on HL survivors, median 18 years follow-up time, the prevalence of sexual problems was high (54% decreased sexual interest and 41% decreased sexual activity). However, this did not differ from sibling controls [119] and illustrates the importance of a control group in studies on sexual function. In a longitudinal study of HL patients, sexual dysfunction at time of diagnosis improved with time in younger persons with early stage disease, while those >50 years with advanced stage disease experienced longer lasting sexual difficulties [92]. In that study, Behringer and colleagues found a strong association between sexual functioning at time of diagnosis and later during follow up, in addition to a negative association between CF and sexual functioning.

Among SCT survivors, sexual function was one of the most frequently reported transplant-related concerns; reported by 28-31%, 1-3 years after treatment [98]. In a longitudinal study on sexual function in auto- or allo-SCT treated men and women with hematological malignancies with 3 years follow-up, the survivors had lower sexual functioning than normative controls, and female survivor had inferior sexual functioning compared with males [120]. The difference in sexual functioning between gender was in line with a report on SCT-survivors of hematological cancer from 1999 [94]. Still, data on sexual function in long-term lymphoma survivors after auto-SCT are sparse. In a cross-sectional study on 50 lymphoma survivors after auto-SCT with a median follow-up of 30 months, 33% had reduced sexual desire and 40% reduced sexual function, while 12/31 men had erectile dysfunction (ED) [121].

Previously reported risk factors for sexual dysfunctions in lymphoma survivors were older age, female gender, shorter time since diagnosis, advanced stage disease, altered body image, mental distress, CF, lower physical health, and lower social functioning [92, 93, 104, 118, 122] in addition to low testosterone level among males [122]. Among SCT-survivors, risk factors for sexual dysfunctions were older age, female gender, lower education and income, fatigue, decreased emotional functioning, global QoL and graft vs. host disease [94, 120] and among males and female leukemia survivors; total body irradiation [120, 123]. However, knowledge on sexual function and associated risk factors among long-term auto-SCT lymphoma survivors is limited and one of the reasons for including this in my thesis.

#### **1.4 Lifestyle behavior**

It is expected that noncommunicable diseases<sup>10</sup> will continue to be the main cause of years of life lost in high-income communities also in the future [58, 124]. The major noncommunicable diseases contributing to morbidity and mortality are; CVD, cancer, chronic respiratory disease and diabetes [125]. CVD and secondary cancer are conditions more frequent among auto-SCT lymphoma survivors compared with the general population

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<sup>10</sup> "Noncommunicable diseases, also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behaviors factors. The main types of noncommunicable diseases are CVD, cancers, chronic respiratory diseases and diabetes". WHO

as described earlier. However, reducing the burden of noncommunicable diseases is possible with a shift towards a healthier lifestyle; non-smoking, weight control, physical activity and avoiding alcohol misuse [126]. Additionally, a healthy lifestyle may improve health-related QoL in survivors of non-hematological malignancies [127] and lymphoma survivors [128].

#### *1.4.1 Physical activity*

It is widely accepted that physical activity has positive implications for CVD and type 2 diabetes and mental health in the general population [58, 59, 129]. In addition, studies have reported on positive effects of physical activity on the risk of primary cancer [130], cancer recurrence [131] and survival [132, 133]. Health institutions unanimously recommend physical activity in order to improve health outcomes in the general population [58, 134] and these recommendations also apply to cancer patients and survivors [135, 136]. The potential health benefits may be due to the physical activity per se, or indirectly due to a healthy energy balance and weight control. In a small study on lymphoma patients (n=29), 61% met recommendations for physical activity at time of diagnosis [137]. In previous studies on lymphoma survivors, physical activity has been related to better QoL [138] and an intervention study documented positive effect of physical exercise on psychological and physical fitness [139].

Despite recommendations on physical activity, studies indicate that cancer survivors are less physically active than cancer free controls [140]. Previous reports from Canadian and North-American cohorts found that 27%-33% of cancer survivors were physically active [127, 141], while 45% of Norwegian cancer survivors has been reported to be physically active [142]. Based on clinical experience, most lymphoma patients experience a significant reduction of physical functioning after auto-SCT treatment.

#### *1.4.2 Overweight*

Body mass index (BMI) is by definition not a human behavior, however often the result of the balance between diet and energy consumption through physical activity. In the following I will refer to BMI as a lifestyle factor. The prevalence of overweight is rapidly increasing in high-income countries and is a risk factor for noncommunicable diseases like CVD and type 2 diabetes [58, 124]. Additionally, there is a growing body of evidence for a positive

association between overweight and risk of several malignancies, including HL [143, 144]. Additionally, reduced survival has been reported in overweight persons with ovarian, endometrial, pancreatic, colorectal and prostate cancer and recurrence of breast cancer might be more frequent in overweight females than those with a normal weight [145]. As a consequence of the global epidemic of overweight and associations to negative health outcomes, obesity is ranked as the fifth cause of death worldwide [125]. In order to improve public health, health authorities recommend a BMI<25 for the adult population (table 2) [58, 126].

Weight gain after treatment has been reported in lymphoma patients both with and without B-symptoms at diagnosis [146], however data on prevalence of overweight in auto-SCT lymphoma survivors, is sparse.

**Table 2** The classification of body mass index into different levels.

<b>Body mass index classes</b>	
<b>Class</b>	<b>Body mass index (kg/m<sup>2</sup>)</b>
Underweight	≤18.5
Normal weight	18.6 – 24.9
Overweight	25.0 – 29.9
Obesity	≥ 30.0

### 1.4.3 *Smoking*

Smoking tobacco is currently one of the main risk factors for noncommunicable disease-related morbidity and mortality worldwide [58]. Smoking causes an increased risk of CVD and several malignancies of which lung cancer is the most frequent [147]. Preventable mortality due to lifestyle-changes is mainly related to CVD, chronic obstructive pulmonary disease and lung cancer [148]. Smoking cessation has been recommended for more than five decades [149], and the smoking prevalence has declined in Norway during this time. However, 19% of the population was smoking in 2017 (11% daily and 8% occasionally), with no difference between genders [150].

In addition to the increased risk of CVD among lymphoma survivors, an increased risk of lung cancer among HL survivors treated with radiotherapy has been observed [54], and smoking had an additive effect on the risk [55]. Hence, smoking cessation is of great importance in auto-SCT survivors and even more so for those treated with radiotherapy.

#### 1.4.4 *Diet*

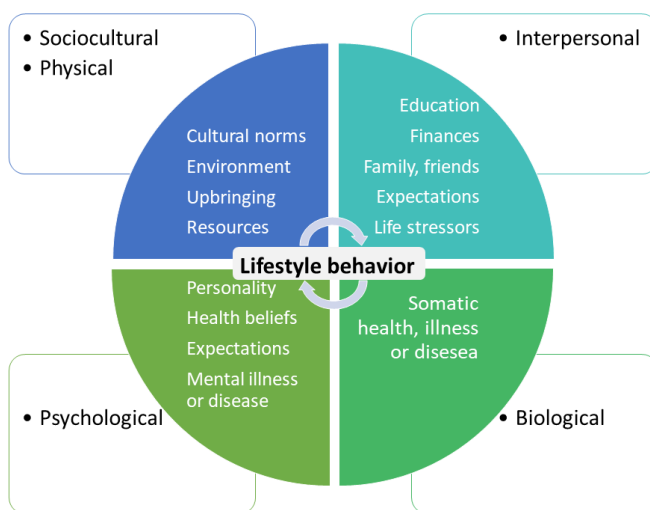
Diet is an important factor for maintenance of a healthy energy balance. On the other hand, certain nutrients have been associated with risk of cancer. The health authorities recommendations for a healthy diet incorporates these findings [58]. In spite of acknowledging the importance of a healthy dietary intake, this will not be the main focus in this thesis due to a high level of methodological uncertainty.

#### 1.4.5 *Alcohol*

Alcohol misuse is associated with a more risky health behavior and relates to increased risk of both CVD and cancer as well as psychological illness [58]. Accordingly, it is of great importance to limit alcohol consumption after auto-SCT. In survivors of hematological malignancies treated with SCT, risky alcohol consumption was less frequent among survivors compared to sibling controls [151]. This issue will be briefly examined within this thesis.

#### 1.4.6 *Risk factors of an unhealthy lifestyle*

The biopsychosocial model is also applicable to lifestyle behavior, as it is influenced by multiple factors which relate to and probably overlap the other [103]. Figure 9 illustrates the main influences on lifestyle behavior and the conceptual framework this thesis is based on.



**Figure 9.** Illustration of factors influencing lifestyle behavior.



Facing the need of auto-SCT treatment might motivate for lifestyle change in order to avoid future illness, hence be a “teachable moment” [152, 153]. However, information on lifestyle behavior among auto-SCT lymphoma survivors is sparse [151, 154], and will be investigated within this thesis.

## **2 Chapter: AIMS OF THESIS**

**Aim 1:** Investigate sexual activity and sexual functioning in male and female long-term lymphoma survivors treated with auto-SCT, and to compare the results to those of gender and age-matched normative controls (paper I and II).

**Aim 2:** Investigate the associations between relevant characteristics of the survivors and sexual activity and sexual functioning, with a special emphasis on the relationship between CVD in the male sample and menstrual status and hormone therapy in the female sample and sexual outcomes (paper I and II).

**Aim 3:** Acquire information regarding lifestyle behavior in long-term lymphoma survivors treated with auto-SCT, and to compare the results to those of gender and age-matched normative controls (paper III).

**Aim 4:** Investigate associations between adherence to recommendations for a healthy lifestyle and relevant characteristics of the survivors, especially CF (paper III).

### **3 Chapter: MATERIAL AND METHODS**

#### **3.1 Study design, setting and participants**

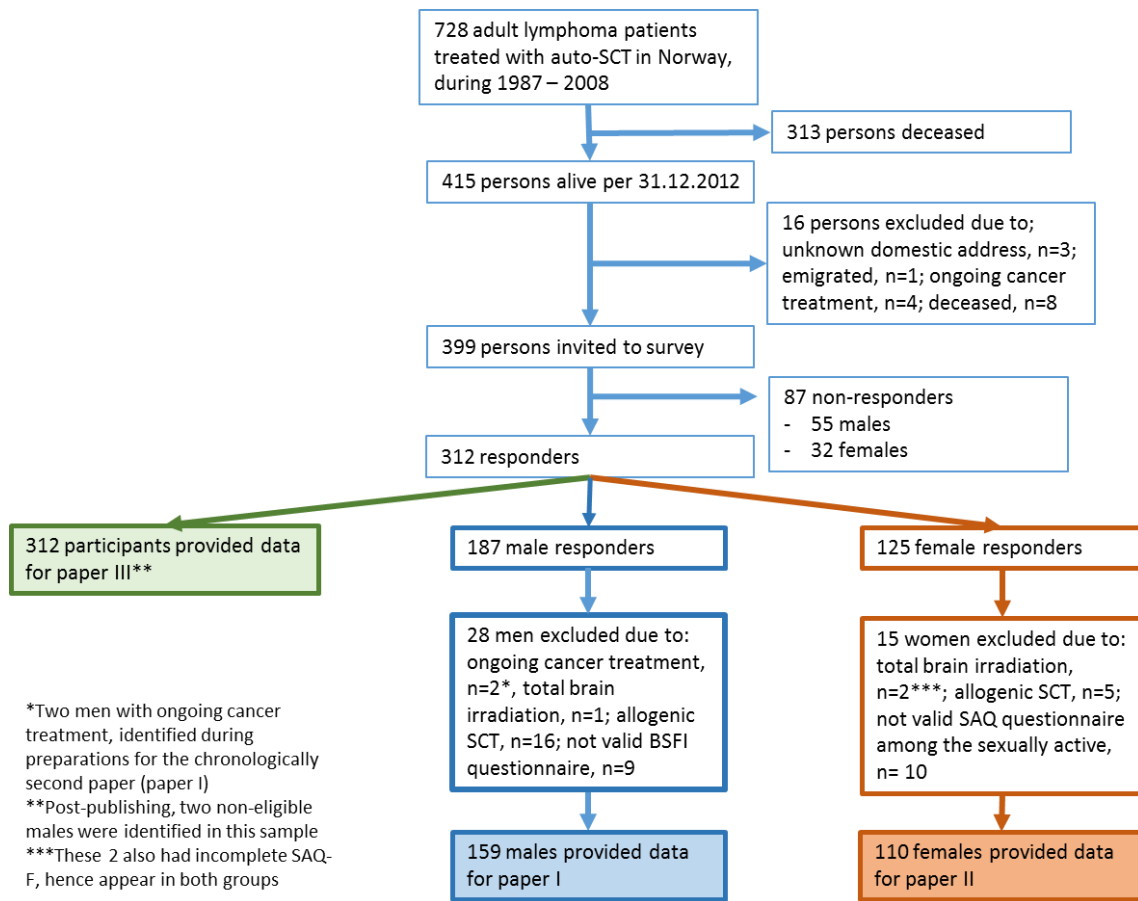
A cross-sectional study on auto-SCT lymphoma survivors in Norway was conducted during 2012-2014 by the four university hospitals responsible for such treatment. The main purpose was to investigate long-term adverse effects in this group of heavily treated cancer survivors. This thesis is part of this comprehensive national study. The lymphoma patients treated with auto-SCT were identified through the Oslo Lymphoma Registry and records from multidisciplinary meetings at the Norwegian Radiumhospital and through separate treatment records at the other university hospitals. Eligibility criteria were; age  $\geq 18$  years at auto-SCT; auto-SCT treatment during 1987-2008 for lymphoma; alive per 31.12.2012. Exclusion criteria were ongoing cancer treatment and no or unknown domestic address. Eligible participants received postal invitation including a questionnaire with a reminder 6 weeks later, and 78% (n=312) of them returned the questionnaire (Figure 10). Overall 274 (69%) of the eligible auto-SCT lymphoma survivors participated in an outpatient clinical examination.

During preparations for the chronologically second article, paper I, two men with active cancer treatment were identified, and excluded from further analyses (remaining study sample, n=310). Regarding the published article, paper III, the exclusion of these two participants was considered unlikely to alter the conclusions. Reasons for the lack of identification of these non-eligible survivors at an earlier time point has been evaluated and will be improved upon in future projects. Additional exclusion criteria for paper I and II were; total brain irradiation; treatment with allo-SCT; and incomplete assessment of sexual outcomes in respective questionnaires. Figure 10 details the eligibility process and participants providing data for paper I-III.

Information on diagnosis and treatment were retrieved retrospectively from medical and radiation records at the respective hospitals and the Oslo Lymphoma Registry (Norwegian Radium Hospital). The respondents completed a multi-item questionnaire (men 125-items, women 133-items), including socio-demographic, psychological and somatic factors in addition to information on sexual functioning and lifestyle behavior (physical activity, height and weight, smoking, alcohol consumption and diet) (Appendix A-C).

Overall 274 (69%) of the eligible auto-SCT lymphoma survivors participated in an outpatient clinical examination.

The attrition analysis did not identify any difference between respondents and non-respondents regarding gender, lymphoma- or treatment-related factors. The mean age at survey was higher in respondents (55 years) than in non-respondents (52 years).



**Figure 10.** Flowchart of lymphoma survivors after high dose chemotherapy with autologous stem-cell transplantation, detailing eligible and non-eligible survivors and among eligible survivors detailing samples providing data for respective papers.

## 3.2 Controls

In order to compare the findings in lymphoma auto-SCT survivors to controls, age- and gender matched controls were drawn from three different samples.

**Paper I:** Normative data came from a sample of Norwegian males (age 20-79 years) were 3494 men had received a postal invitation. A valid Brief Sexual Function Inventory (BSFI) questionnaire was obtained from 31% (n=1092) of these men. Response rate according to age was; 20-29 years, 19%; 30-39 years, 27%, 40-49 years, 32%, 50-59 years-old, 37%; 60-69 years, 30% and >70 years, 29% [155].

**Paper II:** Normative data came from a sample of Norwegian females (age 20-69 years). Overall, 2800 women received a postal invitation including the Sexual Activity Questionnaire (SAQ). A valid SAQ questionnaire was obtained from 42% (n=1165) of these women. Response rate according to age was; 20-34 years, 32%; 35-44 years, 47%; 45-55 years, 50%; 56-69 years 41% [156].

**Paper III:** The Tromsø study is a population-based cohort, considered representative of the Norwegian population. The sixth wave of this survey (Tromsø 6, n=12,984) was conducted in 2007 – 2008 and included persons 30-87 years of age, the response rate was 63% and 68% for men and women, respectively. All participants had measurements of height and weight. Items regarding physical activity and smoking were identical to items in our questionnaire, while items on food habits were similar [157].

## 3.3 Main outcomes

### 3.3.1 *Male sexual functioning*

The main outcome in paper I was sexual function in male auto-SCT lymphoma survivors, assessed by the BSFI (Appendix B). The BSFI is a validated short instrument assessing current sexual experiences among men. It was developed in men (median age 41 and 60 years), attending either a urology clinic due to sexual problems or the general practitioner due to any cause. The BSFI has been used and validated in general population cohorts [158, 159], and normative data from a sample of Norwegian men was available [156].

The instrument (total 11 items) assess three functional subscales; drive (two items), erection (three items), ejaculation (two items), perception of problem related to drive,

erectile and ejaculatory function (one item on drive, erection and ejaculation, respectively), and overall sexual satisfaction (one item)[158]. Responses were rated 0-4, with zero presenting the poorest function, biggest problem and least satisfaction, and four the best function, no problem and greatest satisfaction. Subscale scores were calculated by adding values for corresponding items divided by number of items (possible range 0-4), and a total BSFI score (adding all values except sexual satisfaction, possible range 0-40). The total BSFI score was considered an assessment of overall sexual functioning. The response alternatives on item 7 was slightly different between survivors and controls, hence score 2 and 3 were merged for controls. In order to compare sexual problems between survivors and controls, a subscale caseness was defined. This operationalization was not part of the original BSFI, but has been described as a method to compare sexual problems between different cohorts [160]. Total sum score for each subscale was calculated, and the cut-off values for caseness (problem) were; drive  $\leq 3$ , erection  $\leq 7$ , ejaculation  $\leq 5$ , DEE (a combined sum score for drive, erection and ejaculation)  $\leq 10$ ; satisfaction  $\leq 1$ . A problem with overall sexuality was defined as either satisfaction or DEE caseness.

Three men had missing values on one of the three items concerning erection. We performed a single imputation by adding the mean value of the two known item responses to the third unknown. Cronbach's alpha coefficient for the BSFI within the study cohort was 0.94.

### 3.3.2 *Female sexual functioning*

The main outcome in paper II was female sexual functioning assessed by the SAQ (Appendix C). This instrument was developed for breast cancer patients in order to assess sexual activity and sexual functioning among women with and without hormonal therapy [161]. The SAQ has been validated and used in several cancer populations, and shows good psychometric properties, response rates and acceptability among cancer patients [162, 163].

The SAQ consist of three parts; 1) information on marriage or intimate relation and sexual activity or not; 2) reasons for sexual inactivity, and 3) sexual functioning last month, addressing four subscales (domains): pleasure (six items on desire, enjoyment and satisfaction), discomfort (one item on vaginal dryness and dyspareunia each), habit (one item on frequency of sexual activity compared to normal) and too tired for sex (one item) [161]. In

current study, two items (one on orgasm and one on arousal) were included and added to the pleasure subscale according to a previous study [163].

Reasons for sexual inactivity were categorized into: no partner, partner issues and personal issues (items included in the two latter categories were: “too tired”, “physical problem” or “not interested in sex”).

Responses to the four functional subscales; pleasure, discomfort, frequency of sexual behavior, and sexual tiredness were rated 0-3, (not at all/not as much/never- very much/ $\geq 5$  times/much more/ always). Low value representing low degree of pleasure, discomfort, frequency of sexual behavior and sexual tiredness. The sexual function subscales were made by summing up scores from respective items. Possible ranges were: pleasure (range 0-18 (0-24 when items on arousal and orgasm were added)); discomfort (range 0-6), habit and tiredness (range 0-3 for both). Of note, values indicating sexual dysfunction were low values for pleasure and frequency of sexual behavior and high values for discomfort and sexual tiredness.

Participants who were sexually inactive last month did not respond to items on sexual functioning, while those sexually active did not respond to items on reasons for sexual inactivity. Cronbach’s alpha coefficients for sexual functioning among the sexually active survivors was 0.83.

### *3.3.3 Adherence to healthy lifestyle recommendations*

The main outcome of paper III was adherence to recommendations for a healthy lifestyle. The items on physical activity, smoking, alcohol consumption and diet were adopted from the Nord-Trøndelag Health Study [164] (Appendix A). Definitions of the recommendations for a healthy lifestyle investigated in this thesis were [134]:

- 1) Moderate physical activity for  $\geq 150$  min per week or strenuous physical activity for  $\geq 75$  min per week
- 2) Normal weight (body mass index  $< 25$ )
- 3) Non-smoking
- 4) Alcohol consumption less than 10g/day and 20g/day for women and men, respectively
- 5) 5-a-day, of fruit and vegetables.

### **Assessment and operationalization of the outcome variables**

Physical activity: Respondents reported frequency (never, <once a week, once a week, 2-3/week, about every day), intensity (no sweating or heavy breathing, sweat and heavy breathing, get exhausted) and duration (<15 min, 15-29 min, 30 min-1 hour, >1hour) with one item each. Physically active time per week was computed by multiplying frequency and duration. The maximum of the computed time-interval was registered. Physically active was defined as a proper intensity of physical activity for the required duration of time, as described above. The variable was dichotomized into adherence or no adherence (sedentary).

Body mass index: see paragraph 3.3.2.

Smoking: Respondents reported on whether they smoked currently, occasionally, prior or never had been smoking. The variable was dichotomized into adherence (prior or never) and no adherence (current or occasionally).

Unhealthy alcohol consumption: Respondents reported on mean alcohol intake the last two weeks in number of glasses of beer, wine and spirit, respectively. One alcohol unit was estimated to be 12g alcohol. Adherence to recommendations was defined as >6 units or >12 units/week for women and men, respectively, and the variable was dichotomized into adherence and no adherence.

Diet: Respondents reported on intake of fruit and vegetables separately: “How often do you usually eat these foodstuffs?” (1/day,  $\geq 2$ /day, 1-3/week, 4-6/week or 0-3/month). Consumption of juice or nectar was reported in a similar way, (one glass = one fruit). Five-a-day was defined as  $\geq 3$  vegetables and  $\geq 2$  fruits. The variable was dichotomized into adherence and no adherence.

Degree of adherence to lifestyle recommendations: An ordinal variable computed by sum score of the variables: physical activity, BMI <25, non-smoking and adherence to alcohol consumption recommendations was made. The possible range was 0-4 (lowest degree of adherence – highest degree of adherence).



**Table 3.** Explanatory and outcome variables according to paper I, II and III. Of note, a sedentary lifestyle was an explanatory variable in paper I and an outcome variable in paper III.

	Paper I	Paper II	Paper III
<b>EXPLANATORY VARIABLES</b>			
Age at auto-SCT	x		
Age at survey	x	x	x
Time auto-SCT - survey in years	x	x	
Gender			x
In a paired relationship	x	x	x
Education	x	x	x
Household income			x
Lymphoma entity	x	x	x
Stage at diagnosis	x	x	x
N <sup>o</sup> of chemotherapy regimens prior to auto-SCT	x	x	x
Total body irradiation part of myeloablative regime	x		
Radiotherapy			x
Radiotherapy in sub-groups	x	x	
Relapse after auto-SCT			x
Type D personality	x	x	x
Chronic fatigue	x	x	x
Anxiety	x	x	
Depression		x	
Mental burden			x
Cardiovascular risk and comorbidity	x		
Medication interfering with sexual function	x		
Hormonal status and among women; replacement therapy	x	x	
Somatic burden			x
Somatic illness, interference on activity of daily living			x
Sedentary lifestyle	x		

**Table 3 Continued. Explanatory and outcome variables according to paper I, II and III**

	Paper I	Paper II	Paper III
OUTCOME VARIABLES			
Male sexual function	x		
Male sexual problem caseness	x		
Female sexual activity		x	
Female sexual function		x	
Sedentary lifestyle			x
Overweight			x
Smoking			x
Alcohol consumption			x
Degree of adherence to lifestyle recommendations			x

### 3.4 Socio-demographics and lymphoma-related factors

#### 3.4.1 *Socio-demographic information*

Data related to age were obtained from medical records, while the remaining data were self-reported and used in all three papers (Appendix A).

Age: Age at survey was analyzed according to four age-groups; 26-40 years, 41-55 years, 56-65 years and >65 years in paper I. Age at diagnosis, age at auto-SCT and age at survey were analyzed as continuous variables in paper II and III.

Household income: dichotomized with cut-off >600.000 nkr/year ( $\approx$  63.900 €) or not.

Education: dichotomized with cut-off >12 years of education or not.

Being in a relationship: dichotomized into being married or cohabitant or not.

#### 3.4.2 *Lymphoma-related factors*

These data were obtained from medical and radiation records and the Oslo Lymphoma Registry.

Lymphoma diagnosis: Participants were sub-grouped according to HL (cHL and NLPHL), indolent NHL (follicular lymphoma and other indolent lymphomas) and aggressive NHL (lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, T-cell lymphoma, transformed lymphoma) (paper I-III).

Lymphoma stage: Dichotomized with cut-off  $\geq$  stage III (paper I-III).

N<sup>o</sup> of chemotherapy regimens prior to auto-SCT: Sub grouped into one, two and  $\geq 3$  chemotherapy regimens prior to SCT (paper I-III).

Radiotherapy: Dichotomized between prior treatment with irradiation or not in paper III. In paper I and II the following sub-groups were defined: supradiaphragmal, subdiaphragmal, total body irradiation and other (irradiation not specified).

TBI myeloablative regime: Dichotomized between a myeloablative regime containing total body irradiation or not (paper I-III).

Relapse after auto-SCT: Dichotomized between lymphoma relapse after auto-SCT or not (paper III).

### **3.5 Measurements**

In survivors attending the clinical examination the following measurements were performed at the respective hospitals: blood pressure (three consecutive measures with mean of the last two reported), height and weight, and collection of fasting blood samples by venipuncture (before 10.00 AM). Frozen samples were sent to The Department of Medical biochemistry, Oslo University hospital, The Norwegian Radium Hospital for assessment of low-density lipoprotein, hemoglobin A1c, glucose, testosterone, sex hormone-binding globulin (SHBG), estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH), (Roche E-platform). The equation for estimation of free androgen index (FAI) was: testosterone\*10/SHBG.

#### *3.5.1 Psychological factors*

The Type D personality score (DS14) assesses two personality traits; negative affectivity (seven items) and social inhibition (seven items) [165]. Responses were given according to a Likert scale 0-4, possible range of responses 0-28 with cut-off  $\geq 10$  for negative affectivity and social inhibition. Presence of both these traits was consistent with a Type D personality. Cronbach's alpha coefficients for negative affectivity/social inhibition were: 0.90/0.88 (paper I), 0.90/0.84 (paper II), 0.90/0.87 (paper III).

Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale with seven items on both anxiety and depression [166]. Responses were rated 0-3, (not present-

highly present). Possible range 0-21 for both anxiety and depression, with cut-off  $\geq 8$  for caseness of both these two conditions. Cronbach's alpha coefficients for anxiety/depression were: 0.83/- (paper I), 0.89/0.85 (paper II), 0.86/0.82 (paper III).

Symptoms of post-traumatic stress was assessed by the Impact of Event Scale with seven items on intrusion and eight items on avoidance [167]. Scoring of responses were: 0, not at all; 1, rarely; 2, once in a while; 3, sometimes; 4, quite often; 5, often. The responses were summarized into a total score with possible range 0-75. We considered a cut-off  $\geq 35$  to be consistent with a probability of post-traumatic stress syndrome. Cronbach's alpha coefficients were: intrusion 0.92, avoidance 0.90 (paper III).

Mental burden: We constructed a categorical variable on mental burden by adding caseness of anxiety and depression and post-traumatic stress symptoms with cut-off  $\geq 2$  for presence of mental burden (paper III).

Chronic Fatigue is a condition with both psychological and somatic factors, however included in this paragraph.

Chronic fatigue was assessed by the Fatigue Questionnaire with four items on mental fatigue and seven items on physical fatigue [81, 82]. Severity of symptoms the last four weeks are compared to similar symptoms the last time the respondent was well-being. Responses were rated 0-3, (as before-very much more). Summarizing respective item scores gave the following possible scores; mental fatigue 0-12, physical fatigue 0-21 and total fatigue summarizing all items 0-33. In this thesis, we used a dichotomized variable with CF considered present if  $\geq 4$  symptoms were graded  $\geq 2$  and the duration of symptoms was  $\geq 6$  months. Cronbach's alpha coefficients were: total fatigue 0.93 (paper I), total fatigue 0.92 (paper II), total fatigue 0.92, physical fatigue 0.93, mental fatigue 0.80 (paper III).

### 3.5.2 *Somatic factors*

All participants reported on height, weight, prior or present somatic illness (secondary malignancy, heart-, lung-, kidney-, liver-, thyroidal- or hematological disease, stroke, high blood pressure, diabetes, gastric ulcer, arthritis, osteoarthritis, back pain or other diseases), medication and whether the somatic disease interfered on activity of daily living or not. Participants attending the clinical examination (n=274, men n=168, women n=104) had

additional information: measured blood pressure, height and weight; blood samples and a physicians' report regarding transient ischemic attack, stroke, angina pectoris and myocardial infarction. Measured parameters were used when available and self-reported measures for the remaining participants. The following somatic factors were defined:

Body mass index (BMI): calculated as weight (kg) divided by squared height (m<sup>2</sup>) and categorized into; normal weight BMI <25; overweight BMI ≥25; and obesity BMI ≥30.

Hypertension: Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication or self-report of high blood pressure (paper I). Self-report only (paper III).

Hypercholesterolemia: Low-density lipoprotein ≥4.1 mmol/L (160 mg/dL) or cholesterol-lowering medication (paper I).

Diabetes: Hemoglobin A1c ≥6.5% or fasting glucose ≥7.0 mmol/L or anti-diabetic medication or self-report of diabetes (paper I).

Cardiovascular comorbidity was based on risk factors for CVD (smoking, obesity, hypertension and hypercholesterolemia), diabetes mellitus and CVD (angina pectoris, myocardial infarction, transient ischemic attack or stroke). We divided this variable into four sub-groups: 1) neither cardiovascular risk factors, diabetes nor CVD, 2) ≥1 cardiovascular risk factor, but no diabetes or CVD, 3) prevalent diabetes and 4) prevalent CVD (paper I).

Somatic burden: was based on self-report of the somatic diseases listed at the beginning of this paragraph and we constructed a summary score, with cut-off ≥4 for somatic burden (paper III).

Interference of somatic disease on activity of daily living: Dichotomized between participants reporting somatic disease interfering on activity of daily living and not (paper III).

### 3.5.3 Gonadal hormonal status and hormonal replacement therapy

#### **Male sample**

Age-specific reference values of free androgen index (FAI) and LH were used to define low, normal and elevated serum levels of male gonadal hormones and the FAI [168]. In order to distinguish between males with an adequate testosterone production and those with low levels of free testosterone despite hypophyseal stimulation, we computed a categorical

variable with three subgroups: 1) Normal FAI + normal LH, 2) normal FAI + elevated LH and 3) low FAI + any level of LH. Additionally, the male sample was dichotomized according to ongoing testosterone replacement therapy or not, hence analyses excluding men on replacement therapy could be performed (paper I).

### **Female sample**

A categorical variable for gonadal hormonal status with three subgroups was defined: 1) Premenopausal status with regular bleedings and cyclic ovarian function (any level of estradiol, FSH <20 IU/l and LH<15 IU/l), 2) postmenopausal status with persistent amenorrhea, estradiol <0.10 nmol/l, FSH >20 IU/l and LH >15 IU/l) [169], 3) hormone replacement therapy (HRT) (estrogen supplemental therapy n=25, oral contraceptives n=1) and we assumed these women to be postmenopausal. An individual consideration was performed in five cases with an inconsistency among reported menstrual bleeding and blood samples. Perimenopausal women (irregular bleeding or amenorrhea in addition to estradiol >0.10 - <0.30 nmol/l, FSH>20 IU/l and LH>15 IU/l, n=3) were categorized in the postmenopausal group. POI was defined by postmenopausal status or initiation of HRT before the age of 40 years, and dichotomized into POI or not (paper II).

## **3.6 Statistics**

### *3.6.1 All papers*

Categorical variables were presented as number (percent), age and time as median (range) and the sexual function scores as mean (standard deviation (SD)). Independent sample t-test was used to compare means (normally distributed data) between survivors and controls and among sub-groups of survivors (equal variances not assumed, paper I).

Age-adjusted binary logistic regression models were used to assess risk of dichotomic outcomes among survivors and controls (paper I, BSFI problem; paper II, sexual activity; paper III, physical activity, overweight and smoking) and to assess associations between explanatory variables and dichotomic outcome variables among the survivors (paper II, sexual activity; paper III, physical activity, overweight and smoking). Effect estimates were presented as odds ratios (OR) [95% Confidence Intervals (CI)]. Multivariable regression models using a backward selection process was performed (paper I and III), and included

explanatory variables with a p-value  $\leq 0.25$  in age-adjusted regression models. Additionally, covariates relevant for each model were included in order to adjust for possible confounding. A two-sided p-value  $\leq 0.05$  was considered statistically significant. SPSS version 24 (paper III) and 25 (paper I and II) was used as statistical software (IBM Corporation, New York, USA).

Controls were drawn by frequency matching with three (paper I) and five (Paper I and III) times as many controls as survivors randomly drawn within each ten-years age-interval [170]. Internal consistency reliability of the instruments in the study sample was measured by Cronbach's coefficient alpha and 0.7-0.9 was considered acceptable [171].

### 3.6.2 *Paper I and II*

Analyses on sexual functioning (items and domains) among the total sample of male survivors and the sexually active sub-group of female survivors were performed and compared to respective controls. Additionally, differences between survivors' and controls' domain scores were analyzed according to age groups (males: 20-40 years, 41-55 years, 56-65 years, >65 years and females: 20-44 years, 45-54 years and  $\geq 55$  years of age.)

Age-adjusted linear regression models were used to assess associations between explanatory variables and continuous outcome variables (sexual functioning) among respective male and female cohorts of survivors (the sexually active sub-group). Effect estimates were presented as unstandardized regression coefficients [95% CI]. A second-degree polynomial was added for age and observation time to assess non-linearity. Accordingly, in paper I, age at survey was included in the models as a categorical variable with four age-groups (20-40 years, 41-55 years, 56-65 years, >65 years).

Standardized mean difference (SMD) was calculated as effect size and clinical significance was considered to be none (SMD 0-0.20), small (SMD 0.21-0.49), moderate (SMD 0.50-0.79) or large (SMD  $\geq 0.80$ ) [172, 173].

Sensitivity analysis with non-parametric methods were performed and revealed few qualitative differences from the results reported, (data not shown).

### 3.6.3 Paper I

Agreement on obesity (BMI  $\geq 30$ ) based on measured and self-reported height and weight was considered to be good (kappa 0.86). In multivariable linear regression models, age at survey, relationship status, education and medication with possible interference on sexual function were added as covariates. In the estimation of SMD, SD of controls was used as denominator due to heteroskedasticity [173, 174].

Equation (Glass delta): 
$$SMD = \frac{mean_{survivors} - mean_{controls}}{SD_{controls}}$$

### 3.6.4 Paper II

Pearson Chi-square test was used to compare proportion of sexually inactive survivors to the proportion among controls, and to compare differences in reasons for sexual inactivity between the same groups. In the estimation of SMD, the denominator was computed based on SD and sample size from both controls and survivors. Additionally, a correction factor for small sample size was added to the equation (not shown) [175, 176].

Equation ( $g_{Hedges}$ ): 
$$SMD = \frac{mean_{survivors} - mean_{controls}}{\sqrt{\frac{(n_{survivors} - 1)SD_{survivors}^2 + (n_{controls} - 1)SD_{controls}^2}{n_{survivors} + n_{controls} - 2}}}$$

### 3.6.5 Paper III

The agreement on overweight (BMI  $\geq 25$ ) based on measured and self-reported height and weight was good (kappa 0.80). Ordinal logistic regression models were used to assess associations between explanatory variables and degree of unhealthy lifestyle in survivors. In multivariable analyses age, education and income were added as covariates.

## 3.7 **Ethics**

All procedures performed in this thesis involving the participants were in accordance with the ethical standards of Regional Ethics Committee South East (no #2011/1353) who approved the study. Informed consent was obtained from all individual participants included in the study cohort of this thesis.

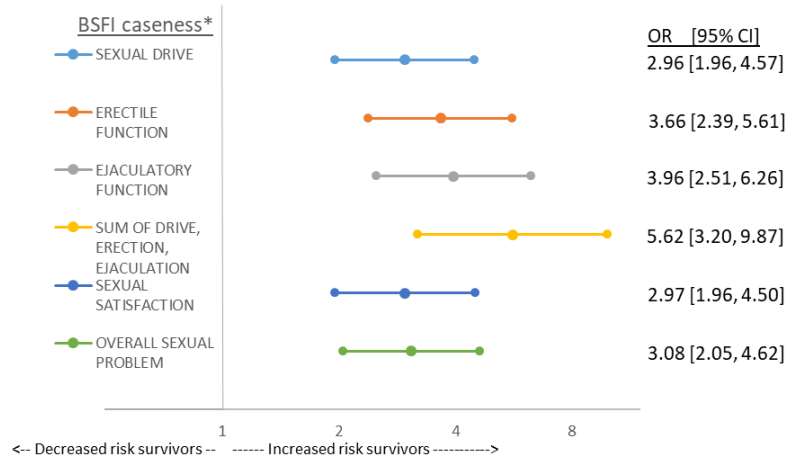


## 4 Chapter: SUMMARY OF MAIN RESULTS

### 4.1 Paper I

*“Sexual function in long-term male lymphoma survivors after high-dose therapy with autologous stem-cell transplantation”*

This paper reports on a total of 159 male survivors median age 55 years at survey of whom 75% were in a partnered relationship at a median of 8.2 years after auto-SCT. Low FAI and LH was found in 15% and 5% used testosterone replacement therapy while 27%, 14% and 12% reported CF, anxiety and CVD, respectively. A total of, 55% had a sedentary lifestyle. Forty-three percent of survivors had problems with sexual drive and 54% had erectile problems, corresponding proportions among controls were 24% and 31%. Odds ratio [95% confidence intervals] of sexual problems among survivors compared with controls are presented in figure 11 (figure 4 in the paper).



**Figure 11** (figure 4 in paper I). Odds Ratio (OR) and 95% confidence interval for BSFI caseness (problem).

In multivariable models, the following statistically significant relations were found between characteristics of the male survivors and sexual outcomes:

- Lower sexual drive: Age >55 years at survey, higher education, medication with possible adverse effect on sexual function, sedentary lifestyle.
- Lower erectile functioning: Age >55 years at survey, CF, CVD, medication with possible adverse effect on sexual function.

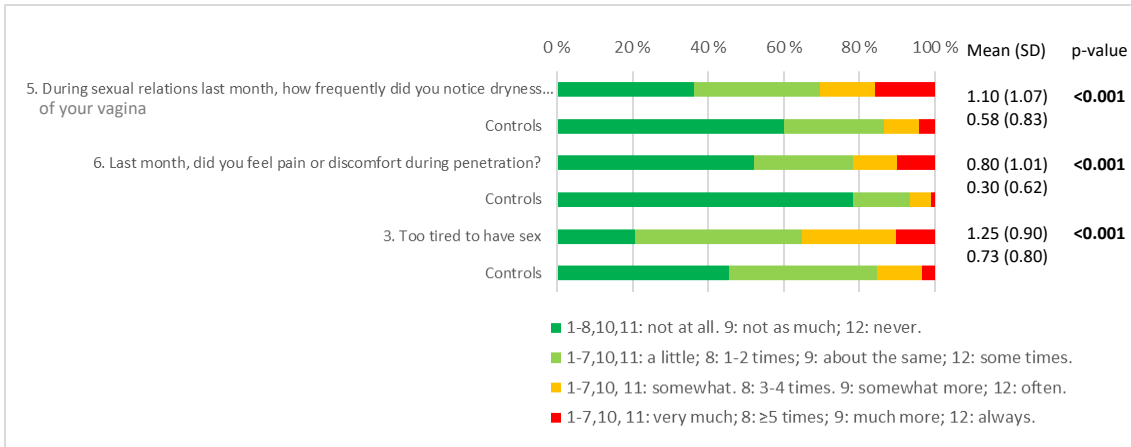
- Lower ejaculatory functioning: Age >55 years at survey, medication with possible adverse effect on sexual function, sedentary lifestyle.
- Perception of sexual functioning as problematic: Testosterone replacement therapy, sedentary lifestyle.
- Lower overall sexual functioning: Age >55 years at survey, CF, medication with possible adverse effect on sexual function, testosterone replacement therapy, sedentary lifestyle.
- Lower overall sexual satisfaction: CF.

To conclude, this paper showed that the risk of sexual problems was significantly higher in male lymphoma auto-SCT survivors than controls. Older age, higher education, CF, CVD, medication interfering with sexual function and a sedentary lifestyle were associated with lower sexual outcomes.

## **4.2 Paper II**

*“Sexual function in long-term female lymphoma survivors after high-dose therapy with autologous stem-cell transplantation “*

This paper report on a total of 110 female auto-SCT survivors median age 53 years and with a median follow-up time from auto-SCT of nine years. Thirty-seven percent of the survivors was sexually inactive, a prevalence which did not significantly differ from that of controls. However, female survivors were more likely to report personal issues as cause of sexual inactivity, than controls. In the sexually active survivors, vaginal dryness, pain during intercourse and sexual tiredness was reported by 30%, 22% and 35%, respectively while corresponding proportions among controls were 14%, 7% and 15% as shown in figure 12 (figure 2b in the paper).

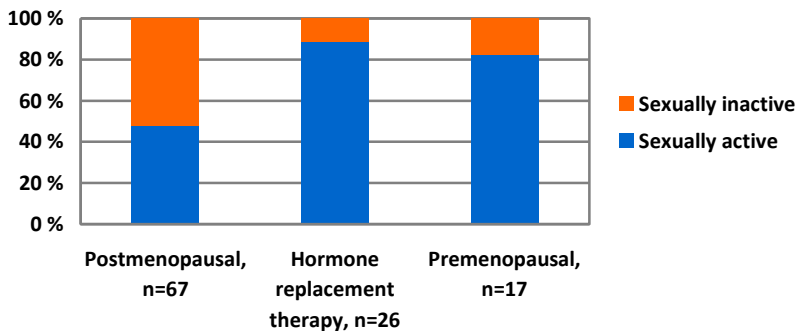


**Figure 12** (figure 2b in paper II). Sexual Activity Questionnaire item response regarding sexual discomfort and sexual tiredness in sexually active survivors and controls.

The sexual function domains; discomfort, habit and sexual tiredness were significantly worse in survivors compared with controls (p-values <0.001, 0.03 and <0.001, respectively). The differences in sexual discomfort and sexual tiredness were considered to be moderate as effect sizes were above 0.50. In age-adjusted models, the following statistically significant relations were found between characteristics of the female survivors and sexual outcomes:

- Lower sexual pleasure: Total body irradiation, a distressed personality.
- Too tired to have sex (sexual tiredness): Younger age, a distressed personality, anxiety, depression and CF.

Sexual activity was related to younger age, being in a relationship and use of HRT, the latter compared to postmenopausal survivors (illustrated in figure 13).



**Figure 13.** Proportion of sexually active and inactive female auto-SCT survivors according to hormonal group.

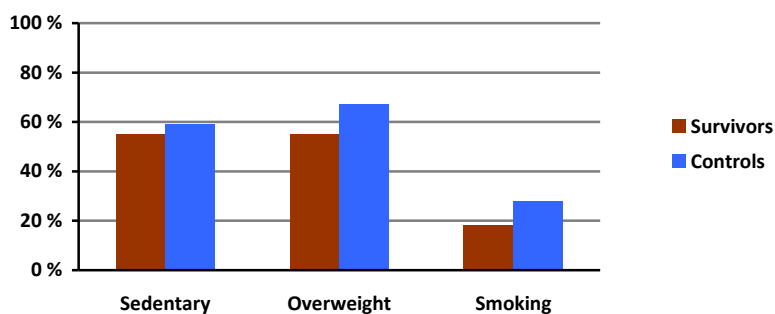
In the total sample, 32 women had POI, 10 women before and 22 women after auto-SCT. As 42 women were premenopausal and <40 years at time of auto-SCT, the proportion of women developing POI post-SCT was 52%.

To conclude, female survivors were more likely to report personal-issues as cause of sexual inactivity, while the sexually active experienced more sexual discomfort than controls. Among the survivors, younger age, having a partner and HRT-use was related to sexual activity. Total body irradiation and a distressed personality was associated with less sexual pleasure, whereas younger age, mental distress and CF was associated with sexual tiredness.

### 4.3 Paper III

*“Lifestyle behavior among lymphoma survivors after high dose therapy with autologous hematopoietic stem-cell transplantation”*

This paper reports on the total cohort of 312 auto-SCT survivors, median age 55 years at survey and the majority, 60%, were males. Proportion of survivors and controls not adhering to lifestyle recommendations is illustrated in figure 14. The survivors had lower risk of not meeting recommendations compared with controls. The risk was reduced by 23%, 39% and 45% for a sedentary lifestyle, overweight and smoking, respectively. An unhealthy alcohol consumption was reported by 5% of survivors and 3.7% of controls, however these numbers were not directly comparable.

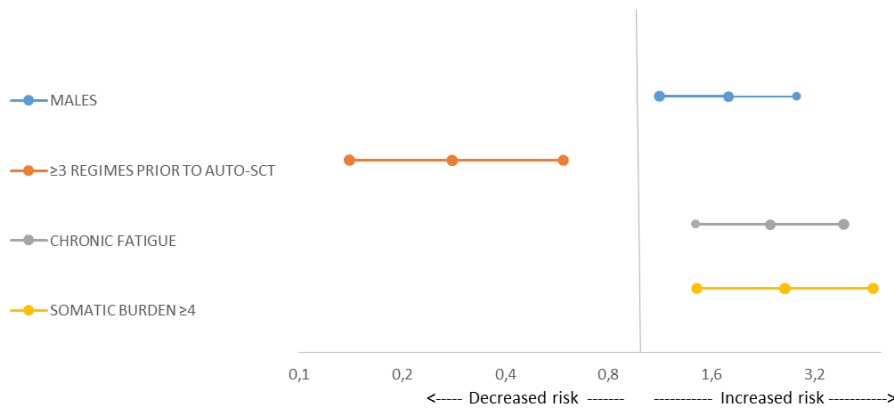


**Figure 14** Proportion of non-adherence to lifestyle recommendations among survivors and controls.

In multivariable models, the following statistically significant relations were found between characteristics of the survivors and unhealthy lifestyle factors:

- Sedentary lifestyle: Older age, low income, CF and a higher burden of somatic disease.
- Overweight: Male gender, fewer chemotherapy regimens prior to auto-SCT.
- Smoking: Younger age, not in a paired relationship, CF.

In multivariable ordinal regression models an unhealthier lifestyle was related to male gender, more chemotherapeutic regimens prior to auto-SCT, CF and a higher burden of somatic diseases (figure 15).



**Figure 15.** Odds ratio and 95% confidence interval for an unhealthier lifestyle according to explanatory variables. Adjusted for age, education and income. Reference group was the opposite subgroup and for chemotherapeutic regimens prior to auto-SCT, the reference was one regimen.

To conclude, despite adhering to more lifestyle recommendations than controls, the majority of survivors were sedentary and overweight and every fourth survivor <40 years at survey was smoking. Male survivors, those with CF and a higher burden of somatic diseases had a 1.8-2.6-fold increased risk for an unhealthier lifestyle than the opposite subgroup, while those with  $\geq 3$  chemotherapy lines prior to auto-SCT (vs. one regimen) had a 72% reduced risk of an unhealthier lifestyle.

## 5 Chapter: GENERAL DISCUSSION

### 5.1 Methodological considerations

#### 5.1.1 *Validity*

Validity refers to “*the degree to which an observation or measurement can be shown to be true and accurate*” [177]. Validity of results depends on quality in all parts of the study process from establishment of the research questions to the final presentation of the data.

**Internal validity** refers to how well the study measures what it claims to measure in the study population. This depends on the degree of systematic error and bias in the study [178]. This is determined by the quality and appropriateness of the study design, the selection process, the collection of information (instrument validity, systemic measurement errors, information bias, misclassifications), non-response bias, confounding as well as analytical methods, type I and II errors and the interpretation of results [177, 178].

**External validity** refers to the generalizability of the results, or to which degree the results apply to populations or groups that did not participate in the study [178]. High internal validity is a prerequisite for external validity, moreover it depends on how much the study population differs from the group or population in question.

#### 5.1.2 *Study design*

A cross-sectional study is an observational epidemiologic study investigating the prevalence of health outcomes and relationships between explanatory factors and outcomes of interest, in a specified population in a narrowly defined time period [178]. Based on an interest of prevalence and risk factors for late effects after cancer, the cross-sectional design was appropriate and allowed for recruitment of survivors with a long follow-up time. Hence, the survivors’ long-term sexual function after auto-SCT was established, even though new late adverse-effects may occur with a possible influence on sexual function. Comparisons to samples from the general population made it possible to assess differences in prevalence of outcomes between the survivors and controls without the cancer and auto-SCT experience, thus this thesis is based on a comparative cross-sectional study.

This study design had limitations: the survey provided “snapshot” information about the participants, hence there is a possibility of a different response at a later point of time;

due to lack of baseline data it was not possible to explore the dynamics of the outcomes over time; and finally, no interpretations of causality could be made.

### 5.1.3 *Bias*

*“Bias is a systematic deviation of results or inferences from truth”* [178]. In this thesis, bias might result from error which applies unequally to the compared groups [177]. There are three main types of bias; selection, information and confounding bias which all might influence on the validity of the study.

#### **Selection bias**

Selection bias arises if there are systematic errors in the procedure of selecting participants to the study or analyses, which affects the estimation of prevalence of outcomes and associations between explanatory factors and outcomes. If selection bias occurs, the estimates will differ between the study sample and the population it was drawn from [170, 178]. In this thesis, the sampling frame was well known, all eligible survivors nationwide were invited and the response rate was high. Additionally, the respondents only differed from non-respondents with regard to age at survey (55 vs 52 years respectively) and not regarding lymphoma-related factors. Hence, the sample is considered representative of Norwegian auto-SCT lymphoma survivors. The control groups were chosen based on comparability to the study samples regarding outcomes of interest and representativeness of the general population [155-157]. The latter is a weakness of the control group in paper I as the response rate was low, a trend reported in other population-based surveys on sexuality [179]. In paper III, the Tromsø-6 study was not the contemporaneous wave of the Tromsø-study, however it included age groups comparable to those of the study sample.

Non-response bias may occur if characteristics differ between responders and non-responders. In general population surveys, non-response is related to lower education, a less healthy lifestyle and more health issues [180]. However, among the study cohort, it is possible that those with more health issues had an increased motivation to participate owing to perceived self-interest [181]. Altogether; it is difficult to assess the direction of non-response/response bias within this thesis. The responding survivors were older than the non-responders, which might cause an overestimation of lower sexual function, physical

inactivity and overweight while smoking was less prevalent in older age groups, which could cause an underestimation of smoking survivors.

The motives for completion and response to questionnaires may differ between the study and control samples. The survivors might have an increased interest in the study questions due to high prevalence of problems at issue or they may have a strong wish to help future cancer patients and survivors. Whereas controls may respond due to loneliness, boredom, or perhaps non-respond due to lack of interest or because they were more easily intimidated by the sensitive aspect of the questionnaire [182]. There was an especially low response rate in the control group in paper I but they had a remarkably higher educational rate than survivors. It is possible that healthy men with greater sexual confidence are more likely to respond compared with healthy men with sexual problems. On the other side, sexual problems could be a motivating factor for response among survivors. Altogether, this would bias the comparison between survivors and controls towards a greater difference. A lower proportion of survivors were in a paired relation and a lower proportion had a higher level of education (males) compared with controls, factors which also could overestimate the difference in sexual function as not being in a relationship and less education (males) is related to more sexual dysfunctions [115, 116].

### **Information bias**

*“Information bias arises in case of inaccurate measurement of independent, covariate and outcome variables”* [178]. The inaccuracy may arise between participants of the study sample or between compared groups.

The outcomes in this thesis were based on patient-reported outcome measures (PROMs) which have the inherent possibility of recall and social desirability bias factors that must be taken into consideration [183, 184]. Among the survivors, sexual expectations may differ according to age, and influence on reporting of sexual function [171]. The lymphoma survivors might be more likely to report on a symptom if they believe it to be caused by the cancer treatment [184]. Additionally, the survivors might have a greater wish of “good behavior” (social desirability) hence a tendency to report a healthier living than controls without a cancer experience. Such biases would influence on the differences between survivors and controls. In paper I and II, survivors and controls reported on the same



instrument and non-cancer related parts of the recall bias might be more similar, hence the comparison less affected by recall bias. Sexual activity and functioning can be assessed using other methods with less recall bias, or other PROMs, however compatibility with current study design and availability of normative controls were prioritized.

Erroneous classification of participants' characteristics is another possible source of information bias [178]. A systematic misclassification of outcomes may cause inaccurate prevalence estimates, while non-systematically occurring misclassifications of participants' characteristics or outcomes may influence on estimates of associations between these variables [177].

Self-reported measures are generally more prone to errors than measurements performed by objective personnel [177]. Hence the latter was used for assessment when available and in case of more than one source of data these were combined in order to reduce the chance of misclassification. I acknowledge that classification of explanatory variables and covariates based on different data sources could introduce bias.

In paper II, based on mismatch between blood samples and self-report of menstrual bleeding in five women, one might suspect that women's reporting of medication like intra-uterine device was inadequate. Additionally, there was an ambiguity in the questioning of menstrual bleeding, as they did not report cause of non-bleeding, hence this could be either physiological or iatrogenic. In paper III, the agreement between self-reported and measured BMI was evaluated by estimation of kappa and a Bland-Altman plot [170] and the agreement was good, additionally no qualitative differences was found in sensitivity analyses (data not shown).

In paper III, shortness of breath was an indication of adherence to recommendations for physical activity. However, an alternative cause of dyspnea could be cardiorespiratory disease, hence survivors might fulfill criteria of intensity of physical activity not because of health-gain related to level of activity, but due to disease. This type of misclassification would cause an underestimation of physical inactivity in people with cardiorespiratory disease and an underestimation of the association between somatic comorbidity and a sedentary lifestyle. The operationalization of physical activity was liberal and might have underestimated the prevalence of sedentary living. This misclassification would be systematic and not interfere with the comparison between the two groups. Regarding diet, the

survey questionnaire was less capable than the Tromsø 6 questionnaire to differentiate between intake of 5-a-day and not. In both samples the computing of adherence to diet was strict, and might explain the very low number of survivors eating 5-a-day.

In the interest of avoiding diurnal and inter-laboratory measurement differences, blood samples were collected before 10.00 AM, frozen, shipped and finally assessed at one laboratory (the Norwegian Radium Hospital).

### **Confounding**

Confounding is the distortion of the direction and magnitude of the association between the explanatory and outcome variable, by a third variable (the confounder). The confounder is causally or non-causally related to the explanatory variable and causally related to the outcome of interest, however not as an intermediate between the explanatory and outcome variable [170]. Confounding bias may lessen validity, reliability and transferability of the results. In a cross-sectional study, confounding bias can be reduced by either stratification according to the confounder or by adding the confounders as covariates in the regression models, assuming the confounders have been identified and measured.

Medication, age and education might interfere with sexual function and comorbidity; hence the multivariable models were adjusted for these variables in paper I [185]. Age and education are both related to comorbidity and lifestyle behavior and were added as covariates in the multivariable regression models in paper III [59]. Gender and income were also included as covariates in adjusted models in paper III, as lifestyle behavior differ between women and men and by different levels of income [59].

The risk of residual confounding is still considerable as both psychological and somatic health, lifestyle behavior and sexual function are matters of great complexity and unidentified confounders are likely to be present. This has to be considered while interpreting the results.

#### 5.1.4 *Statistical considerations*

##### **Collinearity**

Collinearity is the presence of a very strong linear relationship between two or more explanatory variables or covariates in a regression model [178]. The inclusion of such variables may cause unreliable or biased estimates of the relationship between these variables and the outcome, and one of the variables should be excluded. Of note, the removed explanatory variable or covariate might also be a confounder, and removal might cause confounding bias.

In paper I, medication was included in the multivariable models to avoid confounding, however it is possible that this introduced collinearity to other variables like CVD and anxiety and influenced on their relationship to the outcomes. Multicollinearity was assessed by variance inflation factor (VIF) and was considered not to represent a problem as VIF were mostly below 3.

##### **Missing data**

Respondents with missing outcome data in paper I and II, 5.4% and 8.3%, respectively, were excluded from analyses. The latter proportion was higher than the acceptable 5% and might cause selection bias, which must be considered while interpreting the results in paper II. Missing data on main explanatory or covariate factors were <6%. With the exception described above, missing data was considered a minor problem in analyses of the work included in this thesis.

##### **Null hypothesis testing, type I and II errors**

The null hypothesis states that there is no effect and is the reverse of the research question. The statistical analysis examines the probability of the estimated effect truly being different from zero. The level of confidence is usually set to 5% (p-value  $\leq 0.05$ ), which relates to a max 5% probability of detecting a difference if the null hypothesis is true or a minimum of 95% probability that a difference between two groups are in fact different and not present by chance [186]. A statistical significance does not inform on the magnitude of the detected effect.

Two errors can be made according to null hypothesis testing: **Type I error**, to conclude that there is a difference, when in fact there is not. **Type II error**, to conclude that there is no difference, when in fact there is. **Statistical power** relates to the probability of detecting an effect when an effect exists. An adequate level of statistical power is usually set to 80% and is influenced by effect size, sample size and level of significance. It is possible to calculate the required sample size for an 80% power to detect an effect (quantified) with a 95% probability of a true difference. Overpowering by including many participants may lead to detection of statistical differences which have no clinical relevance. Underpowering by including too few participants may lead to a type II error.

In paper II, the female sample was probably too small for statistically significant differences to be detected (type II error).

### **Clinical relevance**

In order to investigate the magnitude of an effect, an effect size should be estimated. A small effect may be statistically detected if the sample size is big, however this effect may have no clinical relevance. Additionally, a sample size may be too small to detect a statistical difference, even though the difference exists and the magnitude is of clinical relevance. An effect size is less influenced by sample size and may provide information on the clinical relevance of an effect.

In paper I-II, SMD was the reported effect size [173, 186]. The SMD indicates how many standard deviations the mean of the cases is from the mean of the general population; in this thesis survivors vs. controls: see paragraph 3.5.2 for interpretation of SMD. The SMD estimate becomes uncertain in small groups (<10-20), despite use of a correction factor [187], hence estimates of SMD in young male survivors were uncertain (paper I).

### **Statistical assumptions**

In all papers, there was independence between observations in the compared groups, essential for the use of t-test and regression analyses. Linear models used in paper I-II assume a linear relationship between explanatory and outcome variables a normal distribution of the

residuals and homoskedasticity [186]. The latter two assumptions were evaluated by residual analyses, which confirmed model assumptions.

In paper I, non-linearity was present in the association between age at survey and the outcomes of interest, accordingly age at survey was treated as a categorical variable. The reported outcome scores in paper I-II could be considered skewed, with an argument for use of non-parametric methods. However, these methods are more likely to make a type II error than parametric methods [171] and the linear regression models are robust models against violation of the assumption of normality [171, 188]. Additionally, a normal distribution of the means was assumed in variables with a sample size  $>30$ , according to the central limit theorem [186]. Another strong incentive for the use of regression models, was the concern about confounding bias, and current choice of methods allowed for adjustment to reduce confounding of the results.

In paper I-II, the lowest possible number of values for the outcome variables was four, however these were assumed to be approximations of an underlying continuous scale and moderate variations in scoring systems infrequently produce marked changes in conclusions [171]. Additionally, linear regression models have been reported to perform well with ordinal outcomes, which further supports the use of this model [171, 189].

Sensitivity analyses with non-parametric methods was performed and showed that most of the main outcomes in paper I-II remained qualitatively unchanged and gave support to appropriateness of the selected methods (data not shown).

#### *5.1.5 Considerations regarding the validity of this project*

The internal validity was considered good with high representativeness, internal consistency and limited bias. Major confounders were adjusted for in statistical models.

The generalizability to today's patients is affected by changes in primary treatment and auto-SCT between the study cohort and the lymphoma patients of today. The change with strongest impact on risk of late effects is probably the abortion of total body irradiation as part of the conditioning regime for auto-SCT. In addition, reduced radiotherapy dose and improvements in radiotherapy with reduced field size and improved tumor/normal tissue irradiation will most likely reduce long-term side effects. The latter is caused by use of three-

dimensional based CT dose planning and respiratory-gating techniques and use of PET/CT to better select patients with residual viable tumor tissue. These factors decrease number of irradiated patients, and reduce the amount of tissue irradiated with high doses.

Nevertheless, the health system in Norway assures equal treatment to all inhabitants regardless of ethnicity, religion, socioeconomic status or domestic address. The results are therefore transferable to other populations of auto-SCT lymphoma survivors treated within the same time period, with the same eligibility criteria for auto-SCT, in countries with a similar health system and probably also restricted to developed Western countries. Altogether, external validity seems satisfactory.

## 5.2 Discussion of main results

### 5.2.1 *Sexual function in males treated with auto-SCT for lymphoma (Paper I)*

In this paper, 43% and 54% of male survivors had problems with sexual drive and erectile function, respectively. The risk of sexual problems was higher among survivors than controls. Reduced erectile function was related to CVD, while age above 55 years and a sedentary lifestyle were related to lower sexual functioning overall. Additionally, CF was related to both lower sexual functioning overall and lower sexual satisfaction.

Sexual problems are common in the general population where 31-42% of men report some difficulties [114, 115], as well as among male lymphoma survivors not treated with auto-SCT with 22-50% reporting sexual dysfunctions [92, 104, 118]. A recent study on auto-SCT treated lymphoma survivors, found sexual problems to be the most frequently reported late effect, reported by 62% (men and women) [190]. In this thesis, the mean level of sexual function was 0.5-0.9 SDs lower in the cohort of long-term male auto-SCT survivors compared with controls indicating a clinically significant reduction in sexual functioning.

Increasing **age** was a risk factor for sexual dysfunction in the general male population and among cohorts of lymphoma survivors treated with and without auto-SCT, [92, 94, 115, 122]. Corroborating results from the current study cohort. Additionally, considering differences between survivors compared to their peers, within different age groups, we found the difference in erectile function and sexual satisfaction to increase with increasing age groups, (estimated by effect size). Importantly however, survivors  $\leq 55$  years, perceived their

sexual function as considerably more problematic compared to their peers, than survivors >55 years. This might be explained by either the younger survivors being more concerned by a smaller degree of sexual dysfunction, or the older survivors had greater acceptance for the sexual dysfunction, possibly due to a response shift [171]. Nonetheless, the difference in sexual satisfaction was lower in younger survivors compared with controls which might indicate a greater tolerance for sexual dysfunctions as long as it did not affect satisfaction.

Previous studies have reported an association between worse physical health, and lower sexual function in the general population, especially among men, [115, 116, 191]. In line with reports on male NHL survivors, where worse physical health was related to decreased sexual activity [104, 122]. In this thesis, there was a trend for lower erectile function with increasing severity of CVD risk factors/morbidity and a statistically significant relationship between current **CVD** and ED. This finding was in line with ED being a predecessor of CVD events in the general population [192]. Male auto-SCT survivors have increased risk of CVD, possibly due to accelerated atherosclerosis [193] and endothelial dysfunction, factors known to increase the risk of ED [116, 194]. Identification of ED may disclose CVD risk or disease which could elicit risk reducing interventions [40, 68]. Additionally, CVD related interventions may also improve ED [195]. Lately, a theory of accelerated aging after cancer treatment has been proposed, which might be an explanation for premature onset of age-related sexual dysfunction [196, 197]; this will be further discussed later. The results in this paper might be hypothesis generating for future clinical studies exploring the importance of cardiovascular etiology vs. other causal factors for ED in male auto-SCT survivors.

**CF** was strongly associated with poorer sexual function in a previous report on HL patients not treated with auto-SCT [92] and related to lower sexual pleasure and a decreased ability to have sex in SCT-survivors [94]. In the cohort of male auto-SCT survivors, CF was the only explanatory factor with a negative association to both sexual function and satisfaction and I will return to this relationship later in the discussion.

**Mental distress** (anxiety, depression and poorer mental function) has been associated with reduced sexual function and satisfaction in male lymphoma survivors after conventional chemotherapy [104, 122] and in survivors after SCT for hematological malignancies [198]. In this thesis, medication with a possible adverse effect on sexual function was related to

lower sexual functioning overall. Antidepressant or anxiolytic medication were included in this variable which might indirectly be a measure of the relationship between mental distress and sexual function in this cohort.

A **sedentary lifestyle** was related to lower sexual functioning overall in the study cohort, in line with results in a previous meta-analysis on lifestyle and erectile function [195]. Physical activity has been proposed to cause changes in systemic vascular inflammation and thereby influence ED [195]. In this cohort, physical activity might be an indirect measure of the importance of good health for maintenance of a sexually active life as described in the general population [191].

In the study cohort, we found an association between low free-androgen index and lower sexual outcomes. In general, a certain level of **testosterone** is necessary for adequate sexual function. In addition, low testosterone level is related to increased risk of CVD [199]. Hence, low testosterone level might influence sexual function through more than one mechanism among auto-SCT survivors. It is however, unclear how testosterone replacement therapy influences CVD risk in younger cancer survivors [200]. Altogether; one has to include an evaluation of hypogonadal symptoms in addition to possible adverse effects on CVD when considering initiation of testosterone replacement therapy in males with low testosterone levels [201].

The proportion of male survivors reporting use of pro-erectile medication was only 2%, which is surprisingly low considering that half of this cohort reported erectile problems. This may be due to underreporting, but may also illustrate a lack of attention on sexual problems among auto-SCT lymphoma survivors and health care personnel.

### *5.2.2 Sexual function in females treated with auto-SCT for lymphoma (Paper II)*

In this paper, we found no difference in percentage of sexually active women in auto-SCT lymphoma survivors compared with age-matched controls. However, the survivors more frequently reported personal issues as a cause for sexual inactivity. Among the sexually active, the risk of sexual discomfort was higher among survivors than controls.

In the general female population, having a partner was strongly related to sexual activity [191]. This resembles findings in the study cohort, as being in a paired relationship was the strongest explanatory factor of being sexually active.



The auto-SCT survivors in our study more frequently reported **personal issues** (too tired, no interest in sex or had a physical problem) as reasons for sexual inactivity, compared with controls, which might represent indirect measures of the relationship between burden of late effects [40] and sexual inactivity [108]. In both the general population and among female NHL survivors, worse physical health has been related to reduced sexual function [104, 115, 185].

There was a significant difference in sexual activity between **postmenopausal** survivors and survivors using HRT, with the latter being more sexually active. Hormonal status and HRT was not available for the control group. However, these factors were reported in the cohort of the initial SAQ validation study [161] and indicates that the postmenopausal auto-SCT female survivors might be less sexually active, while survivors on HRT might not differ from the general population. Hence, the reference group chosen for the statistical models might be the one deviating from the norm, which needs to be considered when interpreting the result.

Reduced sexual function has been related to **older age** in the general female population [115] and in samples of lymphoma survivors [92, 94]. Contrasting these results, younger age among auto-SCT survivors was related to lower sexual functioning with regard to sexual tiredness. Possible explanations could be that tiredness has a greater influence among those of younger age due to higher expectations of sexual functioning, or the reporting of sexual tiredness might be lower among older survivors due to lower expectations regarding sexual functioning, which might be considered an age-related response shift [171].

Survivors more often reported sexual discomfort than controls. Among survivors, 22% had dyspareunia always or often, while this was reported by 6.5% of controls. In the general population, the etiology of dyspareunia is complex and related to menopause, an increasing number of chronic health conditions, depression, other sexual problems and sexual aspects of relationships [117, 185, 202]. Ovarian insufficiency is frequent after auto-SCT [70] and theoretically, this might represent one of the main biological causes for sexual discomfort in the subgroup of women with POI or in elder women where auto-SCT might have caused a shortened time to menopause [117]. However, the cross-sectional design and small sample size might have prevented us from detecting these associations in this thesis. Nonetheless, regardless of cause, sexual discomfort could be treatable for many women [203]

and the high prevalence has implications for follow-up. In a previous report, early initiation of HRT among women experiencing menopause shortly after SCT was related to better sexual function later [204]. Transition into menopause and sexual function, should be addressed at consultations with recommendations for HRT in women experiencing undesirable symptoms of menopause and especially among women with POI. Additionally, vaginal moisturizers and lubricants or referral to a specialist on sexual health should be considered.

In the general female population various chronic somatic diseases and an increasing number of chronic conditions has been related to sexual dysfunction [185]. In this thesis, **CF** was associated with sexual tiredness and greater problems achieving orgasm. These relationships are possibly due to energy depletion and mental fatigue, which negatively influences the sexual experience in line with previous reports on the general population [185] and NHL survivors [104].

**Mental distress** was also related to sexual tiredness in age-adjusted analyses. This result could be confounded by CF, which is known to be associated with both mental distress [47] and sexual tiredness within this study cohort. Nevertheless, sexual dysfunctions in women are often multifactorial and an evaluation of mental health in women with sexual dysfunction is advisable [185, 203].

### *5.2.3 Concerns regarding sexual function in both gender*

Previous reports have described an increased prevalence of sexual dysfunction compared to the general population among survivors of HL with advanced disease treated with conventional chemotherapy [92], among male NLH survivors were the majority had received conventional chemotherapy [122] and recently sexual problems was reported among 62% of auto-SCT lymphoma survivors [190]. To the best of my knowledge, this thesis represents the largest detailed studies to date on sexual function in long-term lymphoma survivors after auto-SCT, showing significantly lower functioning among both males and females compared with age-matched controls.

In the study cohort, no lymphoma or treatment related factors, except total body irradiation among women, were associated with sexual outcomes. Our results contrast findings in a large cohort of HL survivors after conventional treatment where advanced stage

disease was related to lower sexual functioning [92]. There are two plausible explanations for the lack of relationship between lymphoma related factors and outcomes in this thesis; either the heterogeneity within the study cohort was too large, hence the power to detect differences between defined subgroups were too small, or the intensity of the auto-SCT treatment overcame previous treatment burden.

In age-adjusted models, **total body irradiation** was related to less drive and lower ejaculatory function among males and less sexual pleasure (importance of sex, enjoyment, drive, arousal, satisfaction) among female survivors. In previous reports in SCT treated survivors after hematological malignancies, total body irradiation was associated with sexual dysfunction in men [120] and mucosal damage and vaginal dryness in women [123]. Neuropathy, vascular damage and fibrosis interfering on sexual function including ejaculation, might result from radiotherapy [205]. There were a limited number of survivors treated with total body irradiation in our study, hence lack of an association to sexual discomfort among females might be a type II error. Theoretically and based on previous data such an association is likely.

**Infertility** is a concern likely to influence sexual function among young cancer patients and survivors [206]. A recent paper examined knowledge of late effects within the current study cohort [49]. Simensen and colleagues observed that infertility was the late effect that most survivors recalled after auto-SCT. In the study cohort, fertility-related issues might have caused mental distress and secondarily lower sexual functioning, especially among the female survivors.

#### *5.2.4 Lifestyle behavior in lymphoma auto-SCT survivors (paper III)*

In this paper, the majority of auto-SCT survivors had a sedentary lifestyle and were overweight, while one of five were smoking and a minority had unhealthy alcohol consumption. Adherence to lifestyle recommendations for physical activity, BMI and non-smoking was significantly more frequent among survivors compared with age-matched controls. In the study cohort, an unhealthier lifestyle was related to male gender, less chemotherapy regimens prior to auto-SCT a higher somatic burden and CF and I will focus on these factors in the following.

The prevalence of physically inactive and overweight/obese persons is increasing worldwide. In 2015-16, in the Norwegian population (median age 39 years) 34% were physically inactive, 39% of females and 56% of males overweight while 19% were smoking [58, 207]. Previous studies on cancer survivors have reported an increased risk of a sedentary lifestyle and overweight/obesity compared with the general population [129, 140, 208, 209]. In a previous study on NHL survivors and SCT survivors of diverse malignancies survivors were less physically active than the general population [138, 154]. Contrasting these reports, survivors were more likely to practice healthy habits than controls (physical activity, diet and smoking) in a study on a large number of survivors after SCT for hematological malignancies [210]. Corroborating results in this thesis, where survivors were more likely to meet recommendations for physical activity, normal weight and smoking.

There is consistent reports on a lower prevalence of smoking among cancer survivors in general [140, 208], survivors after SCT (20-30% lymphoma) [151] and among auto-SCT survivors in this thesis.

Several possible explanations for the apparently healthier lifestyle among auto-SCT survivors exist: They might always have had a healthy lifestyle and good health, disregarding the lymphoma. Hence, they are positively selected during the cancer trajectory by staying alive (selection by survival). The majority were treated with auto-SCT due to progressive or relapsing disease which is an even more serious threat to life than the initial cancer diagnosis. Hence, the effect of a “teachable moment” might have been stronger in this study cohort than in other cohorts of survivors. Other possibilities were a stronger social desirability bias in reporting of lifestyle behavior with the same psychological mechanisms as for the teachable moment, and a liberal definition of physical activity causing an overestimation of healthy lifestyle.

Regardless of a healthier lifestyle than the general population, there was still many survivors who presumably could benefit from lifestyle change. A population-based survey found that younger cancer survivors were more likely to be smoking compared with those of older age [211] and in a report on older NHL survivors only 6% were smoking [128]. In line with this finding, in the current study cohort, younger age was a risk factor for smoking and every fourth survivor under 40 years was smoking. This finding is supported by a previous study on SCT-survivors, where a tendency for increased risk of smoking was found among

younger survivors [151]. Smoking cessation is of special importance, due to the increased risk of smoke-related diseases like CVD and second cancers among lymphoma survivors [54, 65] and in auto-SCT survivors as reported in this study cohort [2, 45, 56].

**Males** had a 2-fold increased risk of being overweight and a 79% increased risk of an unhealthier lifestyle compared to female auto-SCT survivors. The difference between men and women might have been present before auto-SCT, as overweight and obesity is more common in males than females in the general population [207]. In addition, it might be a result of male cancer survivors being less likely to adopt health-promoting behaviors [128, 152], also found among SCT-survivors [212].

Survivors with **more chemotherapy prior to auto-SCT** had a 72% lower risk of an unhealthier lifestyle compared with survivors with auto-SCT as first line treatment. This lifestyle factor contributing most to this finding was probably BMI. Theoretically, higher cumulative doses of chemotherapy might cause physiological changes and a lower weight. This theory is in line with a lower percentage of overweight survivors in this study cohort compared with lymphoma survivors after conventional chemotherapy [128]. In the general population, BMI increases until the age of 65 years and decreases thereafter [207]. Theoretically BMI could be influenced by accelerated aging after chemotherapy among auto-SCT survivors [196]. Of note, regarding BMI and health risk, it would probably have been more interesting to examine obesity [126], however adherence to recommendations were the aim of this thesis.

**A higher burden of somatic diseases** was associated with an unhealthier lifestyle in the study cohort, which corroborates the well-known relationship between lifestyle and general health in the general population [124, 126] and among NHL lymphoma survivors [128], however in contrast to earlier findings among SCT-survivors [151].

#### 5.2.5 *Chronic fatigue*

In this thesis, we examined several explanatory factors related to sexual and lifestyle outcomes. Of these, **CF** was repeatedly related to worse outcomes among auto-SCT survivors; sexual function and satisfaction among males, sexual tiredness in females and a sedentary lifestyle and higher probability of smoking in both genders.

Despite knowledge of the positive impact of physical activity on CF, auto-SCT survivors with CF were less physically active. These conditions possibly have mutual effect on each other, which probably increase the sustainability of both conditions and cause a vicious circle difficult to break out of [137]. A certain intensity of physical activity seems to be required for CF improvement to occur [213].

Prior studies have described the relationship between CF and more health disorders [1, 88]. This relationship was not directly examined in this thesis; however, the results are suggestive of a constellation of survivors with an unhealthier lifestyle, a higher somatic burden and CF. This information is valuable in the follow-up of auto-SCT survivors and helps to identify vulnerable survivors in need of support for lifestyle changes and early detection of risk factors for disease or prevalent health disorders including CF.

Physical activity and cognitive behavioral therapy should be offered to survivors with CF, and probably at an early time point [80, 214]. Additionally, understanding, acceptance, adjustment of expectations and prioritizing in daily life are probably reasonable recommendations for survivors to improve coping with CF [215]. Considering the results within this thesis, an improvement of CF and fatigue level could perhaps secondarily improve sexual function among auto-SCT survivors. This needs to be investigated in future clinical trials.

#### *5.2.6 The burden of survival; the concept of accelerated aging*

In a cohort of auto/allo-SCT survivors of hematological malignancies, increased frailty was found compared with siblings, and frailty was related to subsequent mortality [216]. Among auto-SCT survivors in this thesis, one in five had  $\geq 4$  somatic diseases, one of three had CF, and sexual functioning were lower than among controls despite having a healthier lifestyle compared with controls, which intuitively should be related to better health outcomes. Could there be a universal factor influencing risk of late effects after chemotherapy?

In 2006, a hypothesis on a possible cause for the increased frailty in cancer survivors was published, namely accelerated aging due to chemotherapy [197]. McCormick described how chemotherapy possibly could influence four mechanisms related to aging; free radical damage, DNA damage, telomere shortening and neuroendocrine/immunologic dysfunction.

A permanent shortening of myeloid stem-cells has been reported in auto-SCT lymphoma survivors [217]. However, a recent review found inconsistent results regarding telomere length after chemotherapy for solid and hematological malignancies, possibly owing to methodological diversity, and further research is warranted [218].

Sexual function is known to decrease with ageing, and perhaps accelerated aging among auto-SCT survivors could be a player in the complex interactions of sexual functioning causing more sexual difficulties in this group of cancer survivors.

## 6 Chapter: CONCLUSIONS

This thesis provides new knowledge about pattern of sexual function and lifestyle behavior in long-term lymphoma survivors treated with auto-SCT, the generalizability to similar groups of survivors is the main scientific value of this thesis and the findings should inform on information and follow-up of auto-SCT survivors.

**Aim 1:** The proportion of sexually active female survivors did not differ from controls. However, personal issues were a more frequent reason for sexual inactivity among the female survivors than controls. Sexual functioning was reduced in male (overall sexual functioning and sexual satisfaction) and female (sexual discomfort, lower frequency of sexual activity compared with usual, sexual tiredness) auto-SCT survivors compared with controls (paper I and II).

**Aim 2:** Among male auto-SCT survivors, cardiovascular disease was related to erectile dysfunction while older age and a sedentary lifestyle were associated with lower overall sexual functioning. Older age and chronic fatigue were related to lower sexual satisfaction (paper I).

Among female auto-SCT survivors, those of younger age and in a relationship were more likely to be sexually active compared with the opposites. Additionally, users of hormone substitution therapy were more sexually active compared with postmenopausal women. A distressed personality and treatment with total body irradiation were related to reduced sexual pleasure while younger age at survey, chronic fatigue, anxiety and depression were related to more sexual tiredness (paper II).

**Aim 3:** The majority of auto-SCT survivors had a sedentary lifestyle (55%) and were overweight (55%), while 18% were smoking and 5% had an unhealthy alcohol consumption. The survivors had a lower risk of being sedentary, overweight and smoking compared with controls (paper III).

**Aim 4:** Older age, chronic fatigue and a higher somatic burden was related to a sedentary lifestyle. Male gender and less chemotherapy regimens prior to auto-SCT was related to



overweight. Younger age, not in a paired relationship and chronic fatigue was related to smoking. Older age, more chemotherapy regimens prior to auto-SCT, chronic fatigue and a higher somatic burden were related to an increasingly unhealthy lifestyle (paper III).

## **7 Chapter: IMPLICATIONS FOR THE FUTURE**

### **7.1 Sexual dysfunctions, profound yet neglected**

In the general population, persons above 50 years seldom discuss sexual problems with their doctors [219], and despite 43% of cancer survivors in general reported concerns about sexual dysfunctions, only 25% of them received care for their sexual concerns [220]. This is possibly due to health personnel's barriers and cancer patients reluctance to address sexual problems [221]. Accordingly, sexuality has been a neglected issue during cancer survivorship care.

Of note, transplanted NHL survivors reported a greater need for information on sexual function than NHL survivors after conventional chemotherapy 50% vs. 28%, respectively [222]. Among SCT-survivors, a discussion of possible adverse effects on sexual function post-treatment was related to a lower level of sexual problems at 3 years of follow-up [223]. These observations along with the finding of reduced sexual functioning among auto-SCT survivors in this thesis encourage the integration of sexual function as a theme in the cancer care trajectory of auto-SCT survivors.

Health care providers are encouraged to use models for communication about sexual problems [221] and to follow guidelines on interventions for sexual problems among cancer patients [203]. Sexuality is a complex phenomenon and a holistic approach is usually warranted [224]. Unfortunately, there is a lack of specialists within sexology in Norway. Referral to available expertise based on the probable cause of the survivor's sexual dysfunction is nevertheless recommended [203].

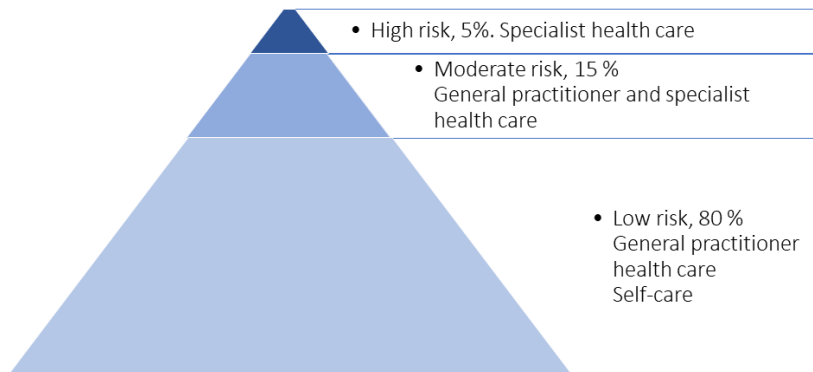
### **7.2 The importance of a healthy lifestyle**

Auto-SCT survivors have increased risk of life-threatening late effects like cardiovascular disease and secondary cancer as well as CF, and according to the results herein; sexual dysfunctions. However, the risk and occurrence of these conditions and other late effects may be modifiable by a healthy lifestyle, as indicated in relation to CVD [210] and ischemic heart disease post-SCT in particular [225]. The prevalence of unhealthy behavior reported in the study cohort inform on the need to include lifestyle behavior into cancer survivorship care of auto-SCT survivors [40, 226].

An evaluation of health-risk based on prior disease, lymphoma treatment and lifestyle behavior should be performed in auto-SCT survivors and lead to individualized recommendations and support for lifestyle change. However, weight reduction is difficult, and a focus on physical activity and a healthy diet may be more useful (E. Giovannucci, oral presentation, Onkologisk Forum 2019). Moreover, a respectful approach focusing on the individual's preferences are mandatory.

### 7.3 Cancer survivorship care

Cancer survivorship care is an evolving area within oncology. The British National Cancer Survivorship Initiative has proposed a risk-based follow-up at different levels in the health care system (figure 15), and most auto-SCT survivors probably belong to the high-risk group. It is worth mentioning that specialized care delivery during follow-up has been related to an insufficient level of preventive health care [227]. Hence, a follow-up including both specialist health-care and the general practitioner could perhaps be the best alternative for both high- and moderate-risk survivors.



**Figure 25.** Survivorship health care delivery according to risk of late effects. Adapted from Kiserud, Dahl, Fosså. *Kreftoverlevende*, 2019 [215].

The British group has also proposed a shift towards personalized advice and information from health personnel according to the individuals need and preferences instead of their diagnosis, aiming to increase self-management and empowerment of the survivors [228]. The personalized approach has also been acknowledged in follow-up of SCT survivors [40]. Attention on the importance of the health care support and the individuals' responsibility for

a behavioral change into a healthier lifestyle among cancer survivors [227], is in line with the British proposal.

A consideration on how and when to reveal information on late effects is in place. There is agreement that attention on late effects prior to treatment and during follow-up is required. Most likely, receiving a treatment summary and survivorship care plan describing future risk and appropriate assessments at end of therapy are meaningful [229]. In a randomized clinical trial among SCT treated patients, receiving a survivorship care plan reduced mental distress [226] and written information was related to higher levels of knowledge on late effects among survivors within this thesis [49]. The use of digital based information platforms is emerging and a smartphone application on survivorship among allo-SCT treated patients was perceived informative, however more relevant >one year after treatment [230]. Still, the most appropriate model for survivor care is under debate [215, 227, 231].

#### **7.4 Future research**

Cross-sectional studies have provided urgently needed information on prevalence of late-effects and risk factors among cancer survivors. Most late effects are diseases common in the general population; hence an estimate of excess risk among cancer survivors is warranted. In Norway, there are two major surveys on the general population, the HUNT and the Tromsø study [232, 233]. In a future process of developing study questionnaires, it would be of importance to use instruments comparable to those used in these large, well-defined populations. In the last wave of the HUNT study, PROMs on sexual function is included. In recent years, a National Quality Registry for lymphoid malignancies have been established within the Cancer Registry [234]. An inclusion of relevant and validated PROMs for later use in longitudinal studies could be of interest.

The dynamics, causality, and effect of interventions to improve on 1) sexuality and 2) lifestyle behavior among auto-SCT survivors should be explored in future prospective

longitudinal trials and interventional studies. Areas of great interest within the fields of this thesis:

- Is reduced sexual activity and functioning related to POI, and is POI preventable by gonadotropin releasing hormone agonists?
- Is it possible to mitigate sexual dysfunctions among auto-SCT survivors by informational and consultative interventions, and will this influence health-related QoL?
- Which interventions are most efficient for durable lifestyle change to occur among auto-SCT survivors, and is lifestyle behavior important for health-related QoL in this group of cancer survivors?
- Does accelerated aging occur after auto-SCT treatment, and is this related to risk of late effects among these survivors?

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## **APPENDIX A**

Study questionnaire, including male specific items

















































Ikke med

## **APPENDIX B**

### Female specific study questionnaire items









Ikke med

## **ERRATA**

### **Paper I**

#### **Abstract**

Original text: Chronic fatigue and anxiety were related to lower sexual satisfaction.

Correct text: Chronic fatigue were related to lower sexual satisfaction.

#### **Statistics**

Original text: The multivariable models were adjusted for age, relationship status, and level of education.

Correct text: The multivariable models were adjusted for age, relationship status, level of education and medication interfering with sexual function.

### **Paper III**

#### **Comorbidity characteristics**

Original text: Internal consistency (Cronbach's alpha) in our study was: type D personality, 0.90 for negative affectivity and 0.44 for social inhibition; CF, 0.92, 0.93 and 0.80 for total, physical and mental fatigue and HADS, 0.82 for depression and 0.86 for anxiety.

Correct text: Internal consistency (Cronbach's alpha) in our study was: type D personality, 0.90 for negative affectivity and 0.84 for social inhibition; CF, 0.92, 0.93 and 0.80 for total, physical and mental fatigue and HADS, 0.82 for depression and 0.86 for anxiety.

Original text: Assessment for PTSD was performed using IES, which combines seven questions on intrusion and eight questions on avoidance to produce a sum score (0–77).

Correct text: Assessment for PTSD was performed using IES, which combines seven questions on intrusion and eight questions on avoidance to produce a sum score (0–75).

