Late effects after treatment for malignant lymphoma

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Abbreviations

BMI: Body Mass Index

BSFI: Brief Sexual Function Inventory

CF: chronic fatigue

ESR: erethrocyte sedimentation rate

FQ: Fatigue Questionnaire

FSH: Follicle Stimulating Hormone

GnRH: Gonadotropin Releasing Hormone

HADS: Hospital Anxiety and Depression Scale

HDT: high dose chemotherapy with autologous stem cell support

HL**:** Hodgkin lymphoma

IPS: International Prognostic Score

LH: Luteinizing Hormone

MCS: Short form 36 (SF-36) Mental Component Scale

NHL: Non-Hodgkin lymphoma

NRH: Norwegian Radium Hospital

OS: overall survival

PCS: Short form 36 (SF-36) Physical Component Scale

POF: premature ovarian failure

QoL: Quality of life

RR: relative risk

SHBG: Sex Hormone Binding Globulin

TBI: Total body irradiation

The mostly used chemotherapy regimens in the treatment of malignant lymphomas

Hodgkin's lymphoma

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine

BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

ChlVPP: chlorambucil, vinblastine, procarbazine, prednisone

EBVP: epirubicin, bleomycin, vinblastine, prednisolone

MIME: mitoguazone, ifosfamide, methotrexate, etoposide

MOPP: nitrogen mustard, vincristine, procarbazine, prednisone

MVPP: nitrogen mustard, vinblastine, procarbazine, prednisone

OPPA: vincristine, procarbazine, prednisone, doxorubicin

OEPA: vincristine, etoposide, prednisone, doxorubicin

Non-Hodgkin's lymphoma

Chlorambucil

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone

CVP: cyclophosphamide, vinblastine, prednisone

ENAP: mitoxantron, cytarabin, etoposide, prednisone

MACOP-B: methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin

MIME: mitoguazone, ifosfamide, methotrexate, etoposide

High dose therapy with autologous stem cell support

Conditioning regimens used for both Hodgkin's and Non-Hodgkin's lymphomas:

Total Body Irradiation (TBI) with high dose cyclophosphamide until 1995

BEAM: carmustine, etoposide, cytarabine, melphalan used from 1995

BEAC: carmustine, etoposide, cytarabine, cyclophosphamide in 1995

1. List of papers

Paper 1

Mortality is persistently increased in Hodgkin's lymphoma survivors and highest among the non-responders in a previous survey.

CE Kiserud, JH Loge, A Fosså, H Holte, M Cvancarova, SD Fosså

Submitted to European Journal of Cancer, November 2009

Paper 2

Gonadal function in male patients after treatment for malignant lymphomas, with emphasis on chemotherapy.

CE Kiserud, A Fosså, T Bjøro, H Holte, M Cvancarova, SD Fosså

British Journal of Cancer, 2009, 100, 455-463

Paper 3

Do male lymphoma survivors have impaired sexual function?

CE Kiserud, LR Schover, AA Dahl, A Fosså, T Bjøro, JH Loge, H Holte, Y Yuan, SD Fosså

Journal of Clinical Oncology, 2009, 27:6019-6026

Paper 4

Post-treatment parenthood in Hodgkin's lymphoma survivors.

CE Kiserud, A Fosså, H Holte, SD Fosså

British Journal of Cancer, 2007, 96, 1442-1449

2. Introduction

During the last two decades the number of cancer survivors in the Western world has been steadily increasing. Estimates from the National Cancer Institute (United States) show that the numbers of cancer survivors now exceeds 12 million people in the United States (NCI, 2009). In Norway, there are more than 180 000 people living with or after a cancer diagnosis (1). The growing numbers of cancer survivors is explained by increasing cancer incidence, improved diagnostic procedures and the use of more effective treatment modalities with improved survival rates. Currently, about 60% of cancer patients live for more than five years (1).

Cancer survivorship was first introduced as a concept in 1985 (2), and three phases of cancer survivorship was described: acute survival (from diagnosis to the completion of primary treatment), extended survival (remission of the disease, including follow-up examinations and eventual treatment for relapse) and permanent survival (evolves from extended disease-free survival when the likelihood for recurrence is low) (2;3). Usually, long-term cancer survivors are defined as those living more than five years after initial diagnosis (3).

There has been an increasing interest for the field of cancer survivorship over the last years, even though this is still regarded as a new area of research within oncology. Chemotherapy, radiotherapy and surgery, alone or in combination, may lead to long-term adverse health effects, and cancer survivors are at increased risk of various medical and psychosocial complications after treatment (4;5). Overall, the goal of cancer survivorship research is to study the health and quality of life of patients treated for cancer beyond the phase of diagnosis and primary treatment, and seek to prevent and treat adverse late effects (3).

This thesis concerns late adverse health effects after treatment for malignant lymphomas, namely Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL). According to the Norwegian Cancer Registry there lived 7961 survivors of malignant lymphoma in Norway by the end of 2007 (1). As an oncologist I have taken a particular interest in the issues of survivorship after treatment for malignant lymphoma, and this thesis consists of four studies on various aspects of late effects after both HL and NHL. First, an introduction to these diseases and their treatment will be given.

3. Background

3.1. Malignant lymphomas: incidence – prevalence – treatment

The incidence of HL in Norway has been stable the last 50 years, and in 2007, there were 114 new cases (64 males, 50 females) (1). For NHL the incidence has been steadily increasing, and in 2007 there were 797 new cases of NHL (418 males, 379 females) in Norway (1). A total of 1989 persons were alive in Norway by the end of 2007 with a previous diagnosis of HL, the comparable number for NHL being 5972 (**Table1**). Of these, 1063 persons had lived for more than 10 years after the diagnosis of HL and 1896 after the diagnosis of NHL (1). The five year relative survival for patients diagnosed with HL in 1998-2002 was 91% for males and 89% for females, with the comparable numbers for NHL being 58% for males and 61% for females (1).

Type of lymphoma	**Total**	**<1 year after diagnosis**	**1-4 years after diagnosis**	**5-9 years after diagnosis**	**10+ years after diagnosis**
	N	*n*	*n*	*n*	*n*
Hodgkin's lymphoma	1989	109	415	402	1063
Non-Hodgkin's lymphoma	5972	683	1990	1403	1896
Total	7961	792	2405	1805	2959

Table 1. Number of Norwegian survivors of HL and NHL by the end of 2007 according to the Norwegian Cancer Registry related to years after diagnosis.

HL is a disease mainly affecting young adults, and with the excellent survival rate, most of the patients treated for HL have a long life-expectancy. Therefore, long-term toxicity and psychosocial complications in HL survivors are important to investigate, and it also makes this group suitable for long-term follow up studies.

NHL is a heterogeneous group of diseases that for the purpose of this overview may be divided in indolent, aggressive and very aggressive forms. For NHL age at diagnosis is higher than in HL, and NHL comprises heterogeneous subgroups with different treatment recommendations over time. In Norway, the incidence and prevalence registrered by the Cancer Registry is usually given for the whole group of NHL, and the prognosis for the whole group is not as favorable as for HL. Therefore, among survivors after malignant lymphomas,

most studies on long-term effects after treatment have been performed in HL survivors, with a more scarce literature available on survivorship after NHL.

Treatment strategies for HL at the NRH in the period 1970 – 2007

The treatment strategies for HL at the Norwegian Radium Hospital (NRH) have followed national and international guidelines, and are summarized in **Table 2** for the period 1970-2007.

Limited disease - stage I and II

From 1970 – 1997 mantle field and inverted-Y field radiotherapy dominated in stage I/II patients given alone or after chemotherapy (6;7). If possible, the standard inverted-Y field was modified (to unilateral L-field or para-aortic field) in order to reduce the doses. Gonadal shielding was routinely used, reducing gonadal doses from 0.6 to 0.1–0.2 Gy during mantle field irradiation. Inverted-Y field resulted in testicular doses of 0.6–0.9 Gy. In the 1970's, medial transposition of the ovaries in order to protect them, was offered to young patients. In these patients, the shielded ovaries received about 3 Gy when treated with inverted-Y field (Jetne, NRH, 1972, unpublished data). Radiotherapy was fractionated as 2 Gy x 20 from 1970 and 1.8 Gy x 23 from 1982.

From 1997 the radiation fields were limited to modified involved fields (including the affected lymph node with 5 cm craniocaudal margine) and the dose was reduced to 1.75 Gy x 17-20 in order to reduce long-term adverse effects.

From 1980 two - four courses of chemotherapy were given to patients with risk factors at diagnosis before irradiation. In the period 1980-88 chemotherapy was given as MOPP/MVPP/ChlVPP (8), and as EBVP in the period 1988-1997. ABVD/ABOD has been the standard chemotherapy regimen for patients with stage I/II from 1997 and as ABVD from 1997 (without risk factors 2 courses, with risk factors 4 courses) (9-12).

Risk factors in 1980-1997 were: large mediastinal tumor, bulky disease, involment of > three lymph node sites above diaphragm, B-symptoms, infradiaphragmatic disease, lymphocyte depleted type. Risk factors from 1999 were (for supradiaphragmatic disease) at least one of the following: bulky disease, ≥ three involved sites, erethrocyte sedimentation rate (ESR) ≥ 50, involvement of two not neighbour localications. Risk factors for infradiaphragmatic disease were at least one of the following: pelvic localization, stage IIA, bulky disease, inguinal disease IA and ESR ≥ 50 (combined)(13).

Advanced disease - stage III and IV

As a general strategy from 1970, stage III and IV patients were treated with 6-8 courses of chemotherapy supplemented with radiotherapy to sites of bulky tumor or residual masses. In the period 1970 – 1980 some stage III patients received total nodal irradiation (TNI: mantle and inverted-Y field, 2Gy x 20), but TNI was abandoned from 1980. Chemotherapy was given as MVPP / ChlVPP until 1985 (8). From 1985 to 1990, primary chemotherapy with MVPP/ChlVPP was gradually replaced by ABOD or EBVP (14) and in the period 1992-98 chemotherapy has been given as 8 courses of ABVD. From 1999 chemotherapy was given as 6-8 ABVD for patients with an International Prognostic Score (IPS) 0-3, whereas the BEACOPP regimen was used if IPS score 4-7 (15). The seven parameters defining the IPS for advanced HL are: serum albumin<4g/dl, hemoglobin<10.5 g/dl, male sex, stage IV disease, age ≥ 45 years, white cell count ≥15 000/mm^3, lymphocyte count <600/mm^3 or <8 % of white cell count (16) .
The radiotherapy was fractionated as 2 Gy x 20 until 1985, as 2 Gy x 20 or 1.8 Gy x 23 until 1998, and as 1.75 Gy 17-20 from 1997.

At relapse, patients have been treated with non cross-resistant chemotherapy or from 1990 with high-dose chemotherapy with autologous stem cell support (HDT) in case of early relapse. HDT consisted of fractionated total body irradiation (TBI) combined with high-dose cyclophosphamide until 1995 and thereafter of chemotherapy only (BEAC/BEAM) (17;18).

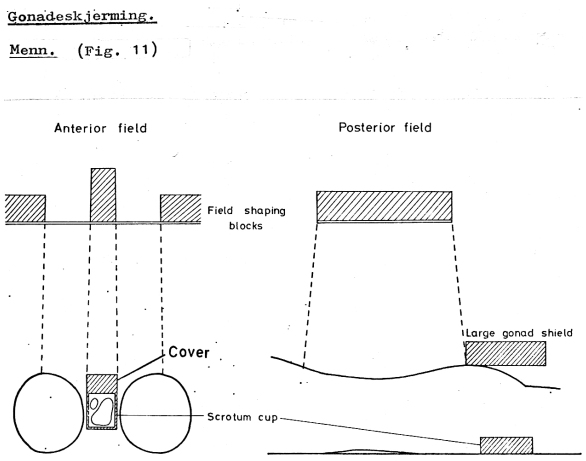


Figure showing gonadal shielding in males during inverted-Y field irradiation.
Figure copied from radiotherapy protocol for HL at the NRH 1976.

Table2.

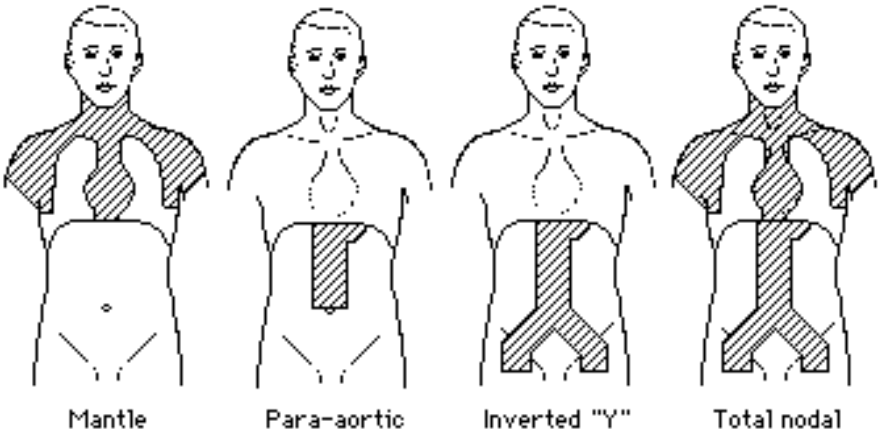
Treatment of HL at the NRH 1970-2007.

	Chemotherapy	**Radiotherapy (RT)**	**Dose and fractions of radiotherapy**
Stage I & II			
1970-80		Extended field RT (MF / Inv Y)	2 Gy x 20
1980-88	With risk factors: 4 MVPP/ChlVPP before RT	Extended field RT (MF /Inv Y)	2 Gy x 20, from 1982 1,8 Gy x 23
1988-97	With risk factors: 2-4 EBVP before RT	Extended field RT (MF/Inv Y)	1,8 Gy x 23
1997-2007	No risk factors: 2 ABVD With risk factors: 4 ABVD	Modified involved field	1,75 Gy x 17 -20
Stage III & IV			
1970-80	8 MVPP/ChlVPP	III: MF+InvY (TNI)	2 Gy x 20
1980-1985	8 MVPP/ChlVPP	To sites of initial bulky tumor or residual mass	2 Gy x 20
1985-1991	8 ChlVPP or 8 ABOD/ChlVPP (alternating)	To sites of initial bulky tumor or residual mass	2 Gy x 20 or 1,8 Gy x 23
1992-1998	8 ABVD	To sites of initial bulky tumor or residual mass	2 Gy x 20 or 1,8 Gy x 23
1999-2007	IPS[2] 0-3 6-8 ABVD IPS 4-7 2 escalated BEACOPP + 6 standard BEACOPP	To bulky tumor or residual mass	1,75 Gy x 17-20

Abbreviations:

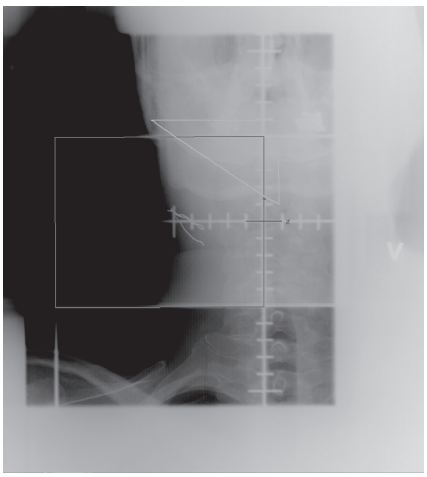
MF: Mantle field
Inv Y: Inverted Y field
TNI: Total nodal irradiation
Risk factors and IPS explained in text.

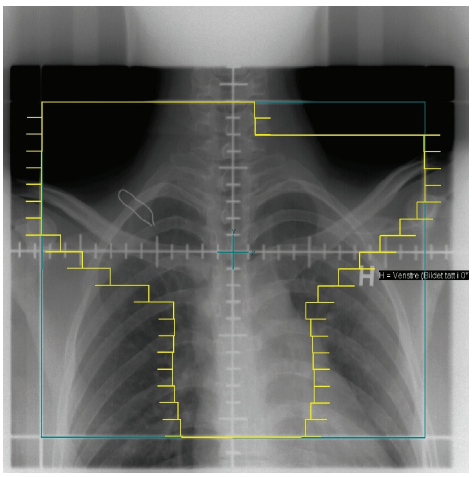
Extended radiation fields used for HL



from: www.med-ed.virginia.edu/.../wcd/hodgclinic.cfm

Example of modified involved radiation fields used for HL





Pictures provided by A. Fosså.

Treatment strategies for NHL at the NRH 1980 – 2002.

The treatment strategies for NHL at the NRH have followed national guidelines, and are summarized in **Table 3** for the period 1980-2002.

Indolent NHL localized disease (stage I, early stage II disease) has been treated with radiotherapy only (fractionated as 2 Gy x 15) as curative treatment (19).

Advanced disease has been and to a large extent still is regarded as incurable (20;21) and in asymptomatic patients initial therapy may be postponed (watchful waiting). Indolent lymphomas are sensitive to several chemotherapeutic drugs (21). Indolent NHL has traditionally been treated with Chlorambucil alone at the NRH, with repetition of this treatment in case of relapse. Other chemotherapy regimens have also been possible options, such as CHOP and CVP. From year 2000, Rituximab, either alone or combined with chemotherapy, or interferon-alpha has been used for CD20 positive lymphomas (22). Radiotherapy has mainly been used as as palliation for local symptomatic disease in patients with advanced stages (typically fractionated as 2 Gy x 15).

At early relapse or after several cycles of Chlorambucil, CVP or CHOP chemotherapy have been used. Alternatively, for younger patients MIME (23) has been used at relapse after CHOP, especially as induction chemotherapy before HDT. ENAP has been used at relapse in the elderly patients (24).

Aggressive NHL, localized disease, was until 1990 treated with radiotherapy only, from 1990 treated with CHOP based chemotherapy followed by irradiation. Radiotherapy has been given to involved fields only, typically 2Gy x 20.

Advanced disease has traditionally been treated with CHOP-based chemotherapy, combined with consolidating radiotherapy to sites of initial bulky disease or residual masses after chemotherapy. At relapse non-cross resistant chemotherapy has been given, mostly as MIME for the younger patients and ENAP for the elderly. From the beginning of the 1990's HDT has been offered in second remission using the same conditioning regimens as for HL. For aggressive T-cell lymphoma and mantle cell lymphoma in younger patients, HDT has been given as consolidation therapy in first remission from year 2000. Rituximab has been in use from about 2004 for CD-20 positive lymphomas.

Very aggressive NHL in the form of Burkitt- and Burkitt-like lymphomas were in the 1980's treated with CHOP chemotherapy combined with high dose methotrexate intravenously and intrathekal (CHOPmM). From 1987 this regimen was followed by HDT in younger patients responding to CHOP. From 1995 treatment has been given according to BFM / GMALL protocols (25). Lymphoblastic lymphomas were initially treated with

CHOPmM, with HDT offered to younger patients in first remission from 1987. From 1992 the induction treatment has been given according to leukemia-protocols (26;27). From about 2006 Rituximab has been given in combination with chemotherapy if CD20 positivity also in very aggressive lymphomas. Radiotherapy has had a minor role in the treatment of very aggressive NHL, but has to some extent been used according to the guidelines in aggressive forms of NHL.

Table3. Treatment strategies of NHL 1980-2002

NHL	Primary treatment	Relapse treatment
Indolent lymphomas	**Localized disease (stage I, early stage II) RT only (2Gy x 15)** **Advanced disease Whatcful waiting Chlorambucil CVP* CHOP* Rituximab ± Interferon-alpha**	**Watchful waiting Chlorambucil CVP* CHOP* ENAP* to elderly patients MIME* to younger patients alone or as induction before HDT HDT for chemosensitive disease at first or subsequent relapse or after transformation** **RT for local symptomatic disease (2 Gy x 15)**
Aggressive lymphomas	**Localized disease** **1980-1990 (Stage I, early stage II) RT only (2Gyx20)** **1990 - CHOP* based chemotherapy followed by RT (2Gyx20)** **Advanced disease** **CHOP* based chemotherapy** **T-cell lymphomas / Mantle cell lymphomas** **HDT in 1. remission from 2000** **RT if residual mass or initial bulky disease (2 Gy x 20)**	**Non-cross resistant chemotherapy MIME* in the younger From 1990: HDT in 2.remission ENAP* in the elderly**
Very aggressive lymphomas	**Burkitt lymphomas: Until 1995: CHOP with Mtx i.t. and high dose Mtx iv. (CHOPmM) 1987 - 1995 HDT in first remission** **1995 - BFM / GMALL protocols** **Lymphoblastic lymphomas** **until 1992: CHOPmM 1987 - HDT in first remission** **1992 – Leukemia protocols ****	

RT: Radiotherapy. HDT: High dose chemotherapy with autologous stem cell support.
*:Rituximab used in CD20 positive indolent NHL from about 2000, and in CD20 positive aggressive – and very aggressive lymphomas from 2004.
** Leukemia-protocols for lymphoblastic lymphomas: LSA2L2:1992-1997, Hammersmith: 1997-.

3.2. Long-term adverse effects after treatment for malignant lymphoma

Some of the long-term adverse effects after treatment for malignant lymphoma may be severe and even life-threatening, like second cancers and cardiovascular diseases (28-32). Other late effects, like infertility, hormonal disturbances and fatigue (33-42) need not be life-threatening, but may nevertheless have significant impact on the survivors' health and quality of life. An overview of the long-term adverse effects most relevant for this thesis will now be given.

Mortality

Previous studies have shown that patients treated for HL have increased mortality when compared to expected mortality in the general population (28;31;43;44). These studies have explored the standardized mortality ratio; the ratio between the observed deaths in the cohort and the expected number of deaths if the cohort had the same mortality rate as the general population (28;31;43;44). The mortality in HL patients later than 10 years after treatment is only explored in a few studies (28;31). The study including the largest sample of HL survivors (n= 4401) reported the standardized mortality rate to be 7.4 at a median follow-up of 7.8 years (44). A comparable figure was found in a survey of 1261 HL survivors treated before the age of 41 years in the period 1965-1987 (median follow-up time 17.8 years), with a 6.8 times higher relative risk (RR) of death from all causes other than HL compared to the general population (28). The RR of mortality from all causes has been shown to remain significantly elevated more than 20 years after treatment for stage IA - IIB HL (31). The most common causes of deaths are reported to be relapse of HL, second cancers, cardiovascular diseases and infections (28;31). Mortality after treatment for NHL has been studied in the Childhood Cancer Survivors Study, which reported elevated death rates from solid tumors, leukemia, cardiovascular diseases and pneumonia compared to US population rates (45).

Second malignancies

Second malignancies after treatment for HL may appear as leukemia, NHL or solid tumors (46). The increased risk of leukemia following treatment for HL has been related to the use of alkylating agents (47), with the highest risk for reported to be 2-10 years after primary treatment, and the prognosis is considered to be poor (31;46).

An elevated risk for development of NHL after the treatment for HL has also been observed (31;48). Such development may be treatment induced, but may also be seen as the natural course of HL (46). Another explanation may be changes in histopathological

classification. Some lymphomas earlier classified as HL, especially of the lymphocyte depleted and unclassified subtypes in the elderly (considered to be associated with poor prognosis), may at relapse have been classified as NHL (49).

Solid tumors account for almost 80% of all cases of second malignancies after HL, and they typically develop after a latency of more than 10 years after treatment, with incidence curves increasing with longer observation time (30;31;48;50-52). Breast -, lung- and gastrointestinal cancer are the most frequently observed secondary solid tumor after HL (30;31;48;50-52), and the elevated risk has been associated with radiotherapy treatment (52-54). After chemotherapy, an increased lung cancer risk has been reported after treatment with alkylating agents (50;53;55).

Also after treatment for NHL an increased risk of subsequent second malignancies has been reported (56-58).

Cardiovascular diseases

There is an elevated risk of cardiovascular complications after treatment for HL including coronary artery disease, valvular disorders, ventricular dysfunction and congestive heart failure (29;59-63). Mediastinal radiotherapy increases the risk of valvular disorders, coronary heart disease and congestive heart failure (29;61;62). Chemotherapy, especially anthracyclines, may induce cardiomyopathy and may further elevate the risk of coronary heart disease in combination with mediastinal radiotherapy (29;64;65). Increased risk of cardiac mortality after treatment with chemotherapy for HL has been reported in recent years (62;66).

After treatment of both HL and NHL, doxorubicin-associated cardiomyopathy and congestive heart failure have been shown to be dose dependent (65;67). Adult patients receiving cumulative doses of doxorubicin not exceeding 500-550 mg/m^2 of body surface are considered to have a relatively low risk for developing cardiomyopathy (65;67). However, even after treatment with doxorubicin in lower doses (median dose doxorubicin 300mg/m^2) for NHL, subclinical cardiomyopathy has been reported in almost one third of the patients more than five years after treatment (68).

Gonadal dysfunction

Gonadal dysfunction may be classified as primary and / or secondary. Primary hypogonadism is due to testicular or ovarian damage, i.e. after intensive chemotherapy or irradiation to these organs. Secondary hypogonadism is caused by damage to the pituitary gland or hypothalamus, i.e. after cranial radiotherapy. Gonadal dysfunction may result in

impaired spermatogenesis and / or dysfunction of the Leydig cells in males and premature ovarian failure in females, with infertility, hormonal disturbancies and reduced sexual function as potential consequences.

Hormonal disturbances and infertility may not be life-threatening, but may cause psychological distress and reduced quality of life (69-71). Male hypogonadism and premature menopause in females may, if not substituted, contribute to serious somatic diseases as arteriosclerosis and osteoporosis (72-76). Since studies of gonadal function in males treated for HL and NHL (paper 2) and post-treatment parenthood in both sexes after treatment for HL (paper 4) are included in this thesis, studies of gonadal function after treatment for malignant lymphomas will be considered in some detail.

Female gonadal function / dysfunction

At birth, the normal female ovary contains about 1-2 million oocytes. By the time a girl enters puberty, only about 25% of her total egg pool remains, around 300,000. After a progressive decrease, there remains 400 follicles at the time of menopause (77).

Chemotherapy and radiotherapy may result in reduced follicle count and ovarian atrophy, with premature ovarian failure (POF) as a result (78). Regular menstruation post-treatment can be assessed by asking the patients, but does not equal possibility of pregnancy due to the risk of anovulatory cycles. POF (defined as persistent amenorrhea before the age of 41) was found in 37% of female HL survivors (n=99), with increased risk after treatment with chemotherapy in addition to radiatiotherapy (79). Secondary amenorrhea has been reported to be more frequent in women older than 30 years at treatment for HL compared to younger women, and after more intensive chemotherapy (37).

Male gonadal function / dysfunction

Testicular damage caused by chemotherapy and / or irradiation may result in elevated follicle stimulating hormone (FSH) as an indication of impaired spermatogenesis, whereas permanently elevated luteinizing hormone (LH) indicates Leydig cell dysfunction. Secondary hypogonadism caused by damage to the pituitary gland or hypothalamus may lead to decreased LH and FSH followed by both exocrine and endocrine gonadal failure. Male gonadal function can be screened for by assessment of serum levels of LH, FSH, testosterone, sex-hormone binding globuline (SHBG), sperm cell count and by documentation of fatherhood.

Some studies have shown that pre-treatment spermatogenesis in HL patients is more impaired than in NHL patients (80-82), which indicates that there might be factors specific for HL that impairs spermatogenesis more than in NHL patients.

Post-treatment spermatogenesis in male malignant lymphoma survivors is dependent on the type of chemotherapy, the drugs' cumulative dose, the radiation dose to the testicles from scattered or direct irradiation, and the time since treatment (42;83). Alkylating agents (cyclophosphamide, ifosfamide, chlorambucil, nitrosureas, melphalan, busulfan and procarbazine) appear to be the most gonadotoxic cytostatic drugs. After treatment with MOPP-like chemotherapy for HL, long-lasting impaired spermatogenesis is observed in about 90% of the patients, whereas only about 10% of the males become permanently infertile after ABVD-like regimens (42;84). Elevated FSH in was found in 35% of male HL survivors at a median observation time of 32 months after treatment for early stage upper-diaphragmatic disease with radiotherapy with or without chemotherapy (n=355) (85). The probability of elevated FSH increased after treatment with alkylating agents, age above 50 years at treatment and stage II compared to stage I disease. After treatment with CHOP-like chemotherapy for NHL, recovery of spermatogenesis to normal levels can be expected in about two thirds of the patients (86).

The sperm cells are very radiosensitive, and the damage of the gonads after radiotherapy is dose-dependent. Recovery of spermatogenesis can be expected after 9-18 months after radiation doses of 1 Gy or less to the testicles, 30 months after a dose of 2-3 Gy and 5 years or more for doses of 4 Gy and above. Radiation doses of 4 Gy and above may result in permanent azoospermia (87;88).

During recent years evidence has emerged that male survivors after malignant lymphoma also may have subnormal serum levels of testosterone and / or elevated LH (40;75;89;90).

Most studies on post-treatment gonadal function in male lymphoma survivors have assessed spermatogenesis measured by sperm cell count and / or the level of serum FSH, with some reports on Leydig cell damage. Most of these previous studies have been performed in limited series of HL survivors. Studies assessing both endocrine (LH/testosterone) and exocrine (measured as FSH) gonadal function in a large sample of male survivors after treatment for both HL and NHL, treated with different chemotherapy regimens, have been lacking so far.

Sexual function in malignant lymphoma survivors

Sexual dysfunction may be a distressing late-effect after cancer treatment (71), and a survey assessing information needs in NHL survivors of both sexes showed that 28% wanted information about sexual functioning (91).

In a survey on long-term effects after treatment for HL performed at the NRH in 1994, 16% of the survivors of both sexes reported transient and 12% reported long-term sexual problems (35). Similar figures have been reported by other studies on sexual function also including both male and female HL survivors; 24% reported at least one sexual problem attributed to having had cancer (92), and sexual interest and activity had decreased in about 20% of HL survivors compared to their pre-treatment situation after a median duration of follow-up of 9 years (93).

In studies including only males, approximately 30% of survivors after malignant lymphoma and testicular cancer reported one or more sexual dysfunctions (94). This proportion is similar to that observed in the general male population (95). However, when a standardized questionnaire on erectile function was used, reduced erectile function was reported by 61% (36/59) of male lymphoma survivors aged 18-55 years (96), which is more than what is observed in the general male population. This may indicate that the prevalence of self-reported sexual problems may be higher when more extensive and detailed questionnaires are used.

Only few studies on sexual function in male lymphoma survivors have so far assessed sexual function with standardized questionnaires and none of them have included controls from the general population. When assessing sexual function in cancer survivors, the use of a comparison group from the general population is of great importance, because sexual dysfunction is prevalent also among men in the general population, with the prevalence increasing with ageing (95;97;98). We therefore are in need of more studies that fulfil these methodological requirements.

Parenthood after treatment

Most previous studies on fertility in HL survivors have examined post-treatment spermatogenesis in males and secondary amenorrhea in females (37;42;99). Although the number of achieved pregnancies and childbirths is sometimes reported in small series (90;100-103), only few reports have taken into consideration the proportion of survivors attempting parenthood (36;104). Adult childhood cancer survivors (among others treated for HL or NHL) reported less frequently birth of biological children compared to a control group,

with the controls selected among patients from the patient lists of the survivor's regular GPs (105).

To counter for the risk of reduced post-treatment spermiogenesis, Norwegian male cancer patients have had the option for pre-treatment semen cryopreservation since 1980. However, studies of male cancer survivors have shown that less than 15% of them use their pre-treatment cryopreserved semen in order to obtain post-treatment paternity (106;107). In Norway, assisted reproductive techniques have been offered and performed as intrauterine insemination (IUI) in the early 1980s, in vitro fertilization (IVF) since 1988, and Intracytoplasmatic sperm injection (ICSI) has been offered since 1995. Pretreatment cryopreservation of fertilised oocytes has been a possible option since 1988, but in such cases the female patient has to delay startup of cancer treatment for several weeks in order to obtain mature oocytes. Since 2004 pre-treatment preservation of ovarian tissue has been a legalized opportunity in Norway, but this procedure is still considered to be experimental. Until now, no child has been born in Norway with use of this method. Use of donated semen is legalized, whereas use of donated oocytes is not.

For many of the young adult survivors after malignant lymphomas the struggle for post-treatment parenthood becomes an important dimension of their quality of life (5), though the exact percentage of the Norwegian HL survivors who plan and achieve post-treatment parenthood, with or without assisted reproduction techniques, has remained unknown. It is well-known that such struggles might be a considerable stress for the couple (108).

Health related quality of life

Health related quality of life (HRQoL) is a multidimensional concept that refers to an individual' usual physical, emotional and social well-being (109). This has been self-reported by the patients by using stardardized questionnaires. Compared to a normative sample representative for the general Norwegian population HL survivors reported poorer HRQoL at a median of 12 years after diagnosis, mainly on physical health (110), and higher prevalence of anxiety (111).

Fatigue

Fatigue can be defined as "a persistent feeling and subjective sense of tiredness that interferes with usual functioning" (112). Fatigue lasting for more than six months has been defined as chronic fatigue (CF) (113). The first study on fatigue in HL survivors was published in 1986 where 37% stated that their energy level had not returned to normal at a median follow-up of 9 years after treatment (93). Later studies have shown that HL survivors

have increased levels of fatigue compared to the general population (41;114;115). A cross-sectional questionnaire survey in 1994 on late adverse effects in 557 HL survivors treated at the NRH, 26% reported CF compared to 11% in a sample of the general Norwegian population (41). There was no significant associations between CF and type of primary treatment, and the prevalence of CF seemed stable in spite of the introduction of less toxic treatment regimens (41;116). A significant association between late pulmonary sequelae and CF was observed (117), while no significant association were observed between cardiac sequelae and CF. A significant association between CF and B-symptoms (night sweats, fever of unknown cause, weight loss) has been demonstrated (41;116).

In contrast to psychological distress, sexuality and QoL, fatigue is among the more researched issues in survivors of HL with high methodological quality of most studies. However, the mechanisms underlying CF in HL survivors still remain unclear (118). One might speculate whether CF in HL survivors reflects aspects of the disease itself such as persistently altered cytokine levels or immune dysfunction both stimulating low-grade inflammatory processes which may lead to fatigue of variable durations.

It is not known whether CF in cancer survivors predicts reduced somatic health outcomes in the future, and to our knowledge, no study has investigated the possible association between CF and future significant health events such as mortality in cancer survivors.

4. Aims of this thesis

Overall, the aims of this thesis were to examine selected aspects of survivorship after treatment for malignant lymphomas in both males and females, with emphasis on mortality and causes of deaths **(Part I)**, male endocrine hypogonadism and sexual function, and fertility in both males and females **(Part II)**.

The specific aims were:

Part I

Mortality and causes of deaths among ≥ 3 years survivors after HL

(Paper1)

- To analyse mortality and causes of death in a cohort of ≥ 3 years survivors after treatment for HL compared to controls from the general population matched for age and gender.

Hypothesis: HL survivors have increased mortality compared to age and gender matched controls from the general population.

- To explore if HL survivors identified with chronic fatigue (CF) in a previous survey have increased mortality compared to HL survivors without CF

Hypothesis: CF in HL survivors is associated with increased mortality.

Part II

A: Male gonadal - and sexual function after treatment for malignant lymphoma
(Paper 2 and 3)

- To assess the prevalence of post-treatment gonadal dysfunction in male lymphoma survivors in relation to age and treatment.

Hypothesis: Endocrine gonadal dysfunction in male lymphoma survivors is associated with increasing age and treatment intensity.

- To examine sexual function in male lymphoma survivors as compared to that of age matched controls from the general population and to examine factors associated with reduced sexual function in male lymphoma survivors.

Hypothesis: Sexual function is decreased in lymphoma survivors as compared to males in the general population, and is associated with increasing age and endocrine testicular function in the lymphoma sample.

B: Fertility, as post-treatment parenthood, in male and female HL survivors
(Paper 4)

- To determine rates of attempted and achieved post-treatment parenthood in HL survivors related to age and treatment.

Hypothesis: Attempts of post-treatment parenthood in HL survivors are associated with age at diagnosis. Achievment of post-treatment parenthood, among those who have attempted to become this, is associated with treatment intensity in both genders.

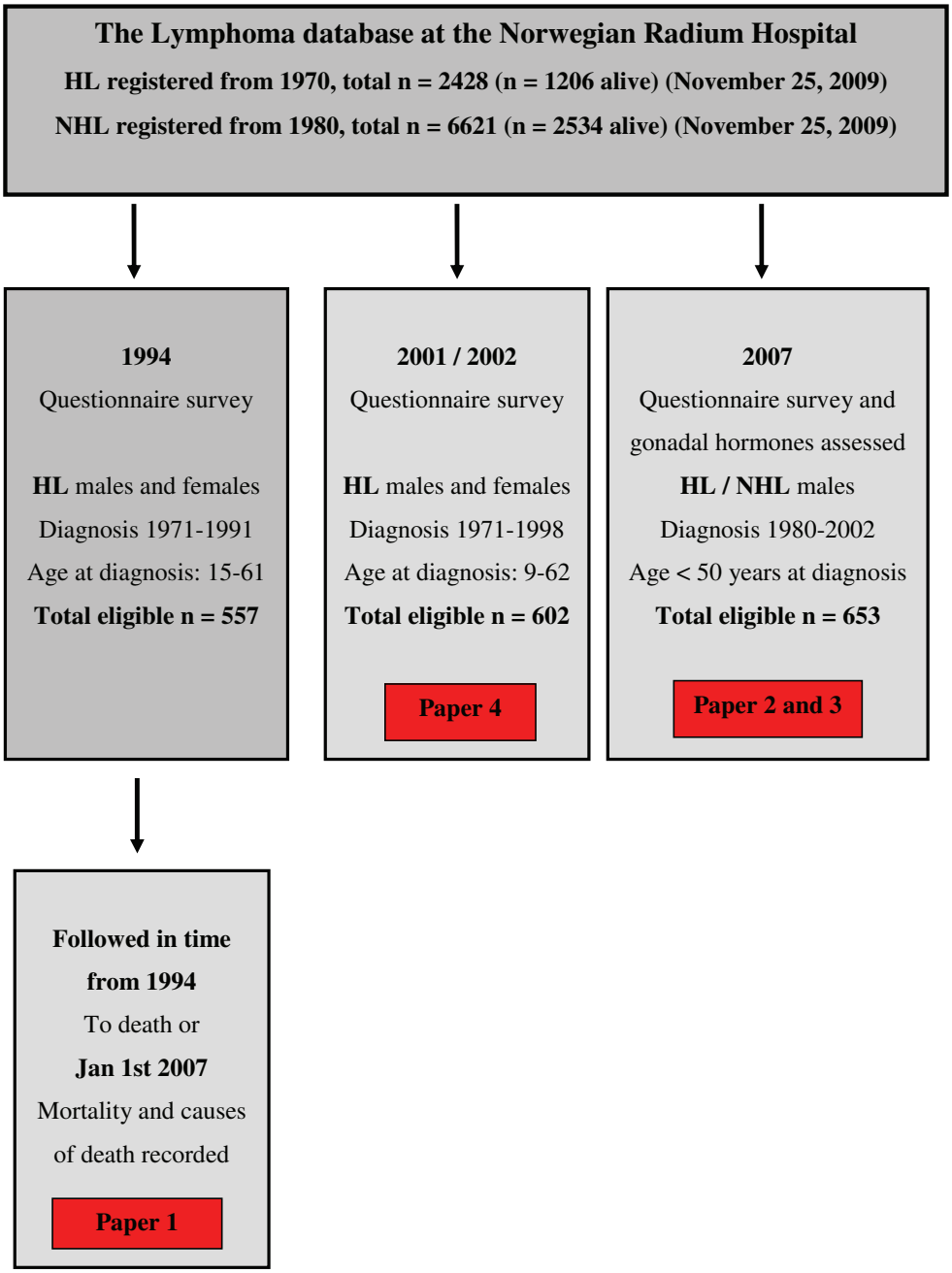
5. Patients and Methods

5.1. Study populations

Selection of patients

The Lymphoma database at the Norwegian Radium Hospital

The Lymphoma database at the NRH was established in 1980 and contains relevant data on all lymphoma patients referred to the hospital, for HL from 1970 and for NHL from 1980. For each patient, information on diagnostic parameters such as stage at diagnosis, chemotherapy and radiotherapy treatment and relapses in addition to date of eventual death is recorded. A total of 2428 HL patients (n = 1206 alive) and 6621 NHL patients (n = 2534 alive) are registered in the lymphoma database at the NRH (date for search November 25. 2009). In the studies included in this thesis, medical and treatment data on each patient was extracted from the Lymphoma database. **See figure below.**


The Lymphoma database at the Norwegian Radium Hospital
HL registered from 1970, total n = 2428 (n = 1206 alive) (November 25, 2009)
NHL registered from 1980, total n = 6621 (n = 2534 alive) (November 25, 2009)
1994
Questionnaire survey
HL males and females
Diagnosis 1971-1991
Age at diagnosis: 15-61
Total eligible n = 557
2001 / 2002
Questionnaire survey
HL males and females
Diagnosis 1971-1998
Age at diagnosis: 9-62
Total eligible n = 602
Paper 4
2007
Questionnaire survey and gonadal hormones assessed
HL / NHL males
Diagnosis 1980-2002
Age < 50 years at diagnosis
Total eligible n = 653
Paper 2 and 3
Followed in time from 1994
To death or
Jan 1st 2007
Mortality and causes of death recorded
Paper 1

Patients Paper 1

This study was a follow-up investigation of a previously described patient cohort from a survey on late-effects after treatment conducted in 1994 (41;110;111), but in the current study with mortality and causes of death as end-points. The eligibility criteria for the 1994-survey were HL survivors treated at the NRH from 1971 - 1991, aged 15 - 61 years at diagnosis and aged 19 - 74 at the time of the survey, alive and in complete remission by the end of 1993 (35). A total of 557 patients were contacted by mail, and 459 (82%) returned filled-in questionnaires.

Of the 557 HL survivors who were approached in 1994, 43% were female and almost 80% were treated with mediastinal radiotherapy with or without chemotherapy. Median age at diagnosis was 30 years (range 15-60), and median age at survey in 1994 was 43 years (range 19-74). The median time from diagnosis to the 1994-survey was 12.2 years (range 2.3-23.0 years). Fatigue, and in particular CF, was assessed by the Fatigue Questionnaire (FQ), vide infra (119).

Based on the findings in the 1994-survey the patients were categorized in three groups: 1: participants without CF (n= 329)

2: participants with CF (n=113)

3: non-participants who did not return the questionnaire (n = 98).

Patients Paper 2 and 3.

In 2007 a cross-sectional survey was performed among male lymphoma survivors, including measurements of serum gonadal hormones (testosterone, SHBG, FSH, and LH) and a questionnaire assessing various aspects of quality of life (QoL). Only male survivors were included because a study on POF in female HL survivors had recently been published by our group (79).

The eligibility criteria for the survey were: male patients ≤ 50 years at diagnosis, treated for HL or NHL, diagnosed in the period 1980 – 2002, age above 18 years at the time of the survey, alive in June 2007 and having a valid postal address. Patients treated with total brain or scrotal irradiation was excluded. A total of 653 male patients met the inclusion criteria and were contacted by mail (360 HL survivors, 293 NHL survivors). Observation time was calculated from date of diagnosis to January 1st 2007, and was further categorized in three groups: 1: 4–10 years, 2: 11–20 years, 3: 21–28 years.

Paper2: Of the 653 male lymphoma survivors, 294 (45%) had their gonadal hormone levels assessed and were included in the study of gonadal hormones.

The compliers (with assessed serum gonadal hormones) were older both at diagnosis and at survey compared to the non-compliers (without assessed hormones) and the compliers had significantly longer observation time [age at diagnosis: median 33 versus 31 years (P=0.006), age at survey: median 49 versus 45 years (P<0.001), observation time: median 15 versus 13 years (P=0.028)]. No differences were observed between the compliers and non-compliers in relation to lymphoma diagnosis and treatment groups.

Of the 294 compliers (n=165 HL survivors, n=129 NHL survivors), 64% (n=187) had received chemotherapy and radiotherapy, 21% (n=63) had had chemotherapy only and 15% (n=44) had received radiotherapy only.

In Paper 3 only males with assessed serum gonadal hormone levels were included in the study on sexual function. Three men reported current use of testosterone substitution therapy and were excluded, leaving 291 men in the sample. Of these, 246 had completed the Brief Sexual Function Inventory (BSFI) (120), which was used to assess sexual function.

Mean ages at diagnosis and at survey were significantly lower among those who had completed BSFI compared to those who had not completed the BSFI (n=45) (mean age at diagnosis: 32 years [SD = 9.4 years] versus 36 years [SD = 10.5 years] p=0.02; mean age at survey, 47 years [SD: =0.2 years] versus 51 years [SD =10.6 years], p=0.02). No significant differences were observed for follow-up time, proportion of HL versus NHL survivors or treatment group between the compliers and non-compliers of the BSFI. Seventy-nine percent of the male lymphoma survivors completing the BSFI were living in a committed relationship.

Patients Paper 4

In 2001/2002 a cross-sectional survey including a questionnaire on various late effects and quality of life aspects after treatment was performed among consecutive HL survivors. The eligibility criteria for the study were: treatment period 1971 – 1998, age 18 – 75 years at time of survey, no relapse after 1998, no secondary cancer and a valid postal address. Since the study assessed attempted and achieved post-treatment parenthood females aged > 50 years and males aged > 65 years at survey were excluded. A total of 602 HL survivors were contacted by mail. For supplementary information on fertility, the female responders from 2002 were contacted again in 2005, finally resulting in 269 male and 184 female responders.

There were no differences in observation time, initial stage, treatment group or relapse rates among responders and non-responders. In males, the responders were significantly older than the non-responders [29 versus 27 years (median)], whereas the opposite was observed in

females [26 versus 32 years (median)]. Eighty-six percent of the responders were aged < 40 years at diagnosis, and 46% had at least one child at diagnosis. The median time from last treatment to survey was 15 years (range 3–34 years).

Selection of control groups

Control group Paper 1

Five controls per HL survivor were randomly drawn from the general population matched on the patient's gender and year of birth (HL survivors, n=557, controls: n=2785). The draw was performed by Statistics Norway (SSB). The controls had to be alive on 31.12.1993, as the HL patients were at the inclusion to the survey in 1994.

All subjects were followed from the survey in 1994 until date of death or to cut-off at January 1st 2007. The information on date of death and causes of death were retrieved from the Statistics for Causes of Deaths, Statistics Norway (SSB).

Control group Paper 3

In 2004, a target population of 3500 men aged 20 - 79 years was identified using public address lists, and a questionnaire was mailed containing among other questionnaires the BSFI (121) to be completed and returned anonymously. The response rate was 34% (n = 1185). For each lymphoma survivor participant two age-matched controls were drawn from this normative sample (lymphoma survivor participants n= 246, controls n = 492).

5.2. Measures

Questionnaires

Sociodemographic Factors and Comorbidities (explanatory variables Paper3)

Men were classified as having a committed relationship if they were married or cohabiting versus those who were not. Level of education was dichotomized into ≤12 years versus >12 years of completed school years. Comorbidity was present if one of the following diseases were self-reported: myocardial infarction, angina pectoris, stroke, diabetes, asthma, or hypertension (defined by regular use of antihypertensive medication). Body mass index (BMI) defined as kg/m^2 was also recorded.

Brief Sexual Function Inventory (BSFI) (outcome variable Paper3)

Sexual function was assessed by the Brief Sexual Function Inventory (BSFI) which includes 11 items covering the following five sexual domains: sexual drive (two items), erectile function (three items), ejaculatory function (two items), problem assessment (three items), and overall satisfaction with sexual life (one item) (120;121). The response format ranges from 0 (poor function, big problem) to 4 (good function, no problem). The sexual domain scores were calculated by summing response scores of the individual items. Lower scores indicate poorer function. The BSFI domain scores were presented either as the sum score or as the average score per item. The BSFI total score was calculated by summing the scores of all items except the overall satisfaction item (BSFI items 1 to 10) as previously described (121). Cronbach's α measuring internal consistency of the BSFI total score was .93 in the lymphoma survivor sample.

To compare the prevalence of sexual problems among lymphoma survivors and controls, problems were defined as follows: drive problems: score ≤ 3, erection problems: score ≤ 7, and satisfaction problems: score ≤ 1, as described previously (122). Because of some minor differences in wording between the BSFI administered to the lymphoma survivors and to the controls on the problem assessment and one of the ejaculatory items (BSFI items 7 to 10), the comparison between the lymphoma survivors and the controls was restricted to the other BSFI items.

In Paper 3 sexual function was presented either as the BSFI total score or the mean score of each of the five sexual domains.

Fatigue Questionnaire (explanatory variable Paper1 and Paper3)

Fatigue was assessed by the Fatigue Questionnaire (FQ), which is a self-report questionnaire for assessment of fatigue severity and case detection in clinical and epidemiological studies (119). The FQ measures physical fatigue (7 items) and mental fatigue (4 items). The sum of all items is designated total fatigue. Two additional items ask about the duration and extent of fatigue. CF was defined by a sum score of ≥ 4 on the dichotomizes total fatigue score, which is indicative of clinically relevant levels of fatigue (119), and a fatigue duration of ≥ 6 months (41). Cronbach's coefficient α was 0.90 for physical fatigue, 0.76 for mental fatigue, and 0.89 for total fatigue among the male lymphoma survivors (paper 3).

Hospital Anxiety and Depression Scale (explanatory variable Paper3)

Levels of anxiety and depression were measured by The Hospital Anxiety and Depression Scale (HADS) which consists of 14 items, seven on the depression subscale and seven on the anxiety subscale (123;124). Each item is scored from 0 (minimally present) to 3 (maximally present). The depression and anxiety scores were added to a total HADS score, with higher scores indicating more distress. The total HADS score was used as a continuous variable. Cronbach's coefficient α was .89 for the total HADS score among the lymphoma survivors.

Medical Outcomes Study Short Form 36 (explanatory variable Paper3)

The Medical Outcomes Study Short Form 36 (SF-36) is a self-reported measure for assessment of quality of life and includes eight dimensions (125;126). As previously reported, summary scores for physical health (Physical Component Scale [PCS]) and mental health (Mental Component Scale [MCS]) are derived by T-transformation (125) . Both scores have a mean of 50 and standard deviation of 10 points, and these figures are relevant for the Norwegian population (127). Both the PCS and the MCS were used as continuous variables in the analyses. Among the lymphoma survivors, Cronbach's coefficient α was 0.82 for the PCS and 0.84 for the MCS.

Gonadal hormone measurements *(outcome variable Paper2 and explanatory variables Paper3)*

Participating male lymphoma survivors had their blood samples drawn before noon by their general practitioners and they were mailed to the Department of Medical Biochemistry at Oslo University Hospital. Analyses of serum gonadal hormone levels (testosterone, sex

hormone–binding globulin [SHBG], luteinizing hormone (LH), and follicle-stimulating hormone [FSH]) were performed consecutively with the E170 module for Modular Analytics (Roche Diagnostic, Berlin, Germany).

Normal ranges for the gonadal hormones were: testosterone: 9.0 - 31.0 nmol/L; SHBG: 15 - 85 nmol/L; FSH: < 12.0 U/L; and LH< 10.0 U/L at the laboratory doing the analyses. The testosterone/SHBG ratio was calculated for each patient as a surrogate for free testosterone.

The patients' gonadal hormone levels were categorized into three groups: 1: all gonadal hormones within the normal range; 2: elevated FSH but normal LH, SHBG, and testosterone (exocrine hypogonadism); and 3: low testosterone and/or elevated LH, independent of FSH (endocrine hypogonadism). This categorization was used to discriminate between patients with normal gonadal function, patients with damage only to the germinative epithelium (exocrine hypogonadism), and patients with Leydig cell dysfunction with or without damage to the germinative epithelium (endocrine hypogonadism).

Grading of gonadotoxicity of treatment *(explanatory variable Paper 2-4)*

For the purpose of the studies on gonadal- and sexual function and post-treatment parenthood (Paper 2-4) the entire treatment (primary and relapse) for each patient was combined based on the records in the Lymphoma database of the NRH.

Treatment groups paper 2 and 3

Since there is less knowledge concerning damage of the Leydig cell function by chemotherapy, the categorization of chemotherapy was performed according to the expected exocrine gonadal damage mainly based on the literature in low, medium and highly gonadotoxicity (37;42;83;104;128). In addition, in preliminary analyses, a separate group was constructed including patients who had received radiotherapy only. Analysis of this group showed no differences between patients who had received supradiaphragmatic radiotherapy only and those who had been irradiated with inverted Y / inguinal- or other infradiaphragmatic fields with respect to gonadal hormone levels. In addition, there was no difference between the group treated with radiotherapy only and the group treated with low gonadotoxic chemotherapy.

In Paper 2 the final treatment groups were defined as shown in **Table 4.**

Table 4. Grading of expected gonadotoxicity of chemotherapy in Paper 2.

Expected gonadotoxicity	Treatment
No chemotherapy / low gonadotoxic chemotherapy Both HL and NHL **No/low**	**Radiotherapy only** **Rituximab only** **ABVP / EBVP** and similar without regard to number of cycles
Medium gonadotoxic chemotherapy NHL **Med-NHL**	**CHOP / COP / CHOEP ≤ 8 courses** alone **CHOP ≤ 8 courses** combined with high dose Mtx **MACOP B** **GMALL, BFM 90** **Hammersmith** only **Chlorambucil** **MIME**
Medium gonadotoxic chemotherapy HL **Med-HL**	**LVPP ≤ 4 courses** alone or combined with ABOD / EBVP or dexa BEAM (2 courses) **BEACOPP ≤ 4 courses** **OEPA + 0-4 COPP** **MIME**
Highly gonadotoxic chemotherapy NHL **High-NHL**	**CHOP > 8 courses** **CHOP = 8 courses** combined with **MIME, ENAP or Chlorambucil** **Maxi-CHOP ≥ 6 courses** **HDT with BEAM as conditioning regimen** **HDT with cyclophosphamide and TBI as conditioning regimen**
Highly gonadotoxic chemotherapy HL **High-HL**	**LVPP > 4 courses** **LVPP = 4 courses** combined with CHOP or MIME **BEACOPP > 4 courses** **HDT with BEAM as conditioning regimen** **HDT with cyclophosphamide and TBI as conditioning regimen**

HDT: high dose chemotherapy with autologous stem cell support.
TBI : Total Body Irradiation.

In Paper 3 the five treatment groups from Paper 2 were merged into three groups:

low: radiotherapy only and/or low gonadotoxic chemotherapy (both HL and NHL)

medium: medium gonadotoxicity chemotherapy for NHL ("med-NHL") and HL ("med-HL")

high: highly gonadotoxic chemotherapy for NHL ("high-NHL") and HL ("high-HL")

Treatment groups Paper 4

Chemotherapy was grouped according to expected gonadotoxicity of the regimens used in low, medium and highly gonadotoxic chemotherapy (37;42;83;104;128).
In preliminary analyses no differences were observed between those irradiated with supradiaphragmatic radiotherapy only and those treated with infradiaphragmatic radiotherapy with or without supradiaphragmatic irradiation according to achieved post-treatment parenthood. Therefore, one treatment variable was constructed discriminating patients with radiotherapy only from those having chemotherapy with low, medium and highly gonadotoxicity (with or without radiotherapy) as shown in **Table 5.**

Table 5. Treatment groups Paper 4.

Treatment groups			
Radiotherapy only	**Chemotherapy with low gonadotoxicity**	**Chemotherapy with medium gonadotoxicity**	**Chemotherapy with high gonadotoxicity**
	ABO(V)D **EBVP**	**ChlVPP** **MVPP** Medium if ≤ 4 courses **CHOP** **MIME**	**ChlVPP** **MVPP** High if > 4 courses **High dose chemotherapy with autologous stem cell support**

5.3. Statistical considerations

All papers

Data were analyzed using SPSS software versions 13.0 to 16.0. The level of significance was set at $p<0.05$ in all studies and all tests were two-sided. Means were compared by t-tests and categorical data were compared by x^2 test. In case of skewed distributions, non-parametric tests were used.

Paper 1

Observation time was calculated from January 1st 1994 until date of death or to cut-off at January 1st 2007 for both the HL survivors and controls. Crude cumulative probabilities of overall mortality were calculated for all subjects by the Kaplan-Meier method. Cox proportional hazard regression models stratified by the matched groups were used for univariate and multivariate analyses. Variables significant in the univariate analyses were entered into the multivariate Cox regression model. The proportionality of hazards assumption was investigated using log minus log plots.

Causes of deaths were categorized into three groups: 1: malignant tumor (all malignant diagnosis), 2: cardiovascular disease, 3: other (including infections, diabetes, pulmonal diseases, gastrointestinal diseases, diseases of the urinary system, diseases in the musculo-skeletal system, traumas and mental disorders). In case of death from tumors, these were further divided in two groups: 1: malignant lymphomas and 2: other malignancies, including solid tumors, multiple myeloma and leukemias.

The risk of death was analyzed using a competing risk approach (129) with causes of death categorized in four groups: 1: malignant lymphomas, 2:other cancers, 3:cardiovascular diseases and 4: other causes of death.

Paper 2

Multivariate analyses were performed as multinomial regression analyses with the dependent variable being the three groups of gonadal hormones: 1: normal (reference), 2: exocrine hypogonadism (elevated FSH, normal LH, testosterone and SHBG), 3: endocrine hypogonadism (low testosterone and/or elevated LH). The model was adjusted for the five treatment groups (1: No chemo/low gonadotoxicity, 2: medium gonadotoxicity NHL, 3: medium gonadotoxicity HL, 4: highly gonadotoxcicity NHL, 5: highly gonadotoxicity HL),

age groups and observation time. Preliminary analyses showed that time since diagnosis was not a significant factor associated with groups of gonadal dysfunction, and this variable was thus excluded from the final model.

Paper 3

Univariate and multivariate linear regression analyses were performed with the BSFI total score as the dependent variable. Variables significant in univariate regression analyses were included as independent variables, and the strength of the associations was expressed as standardized beta-values. Statistically significant group differences were examined for clinical significance with effect sizes (ESs). For continuous variables we used Cohen's coefficient d, and for 2 x 2 contingency tables the differences between arcsine transformed proportions and ES values ≥ 0.40 were considered as clinically significant based on the recommendations of Cohen (130;131).

Paper 4

To discriminate for the introduction of ABVD chemotherapy, period of diagnosis was defined as 1: diagnosis before 1989 and 2: diagnosis in/after 1989. Factors influencing attempted post-treatment parenthood were analyzed by x^2 tests for categorical variables, and by t-test for continuous variables. Binary logistic regression analyses were carried out with attempted post-treatment parenthood regarded as the dependent variable.

Evaluation of achieved post-treatment parenthood was restricted to patients who reported attempted post-treatment parenthood. Kaplan–Meier estimates, log-rank tests and Cox regression analyses evaluated the probability of achieved post-treatment parenthood, without use of assisted reproduction techniques, with the first post-treatment childbirth as the end point. Variables significant in univariate analyses were included as covariates in multivariate analyses together with the variables of major clinical interest (age, period of diagnosis, stage, treatment group).

6. Main findings

Part I

6.1. Main findings Paper 1

Mortality in HL sample versus controls – all causes

By January1st 2007 death had occurred in 149 of the 557 HL survivors (27%) and in 197 (7%) of the controls. Compared to the controls, HL survivors had nearly five times increased mortality (HR: 4.93 [95%CI: 3.91-6.21]). The ratio of mortality rate kept being positive for the entire observation period. **Figure1a.**

Among the three groups of HL survivors 72 deaths had occurred among participants without CF (22%), 35 deaths among participants with CF (31%) and 38 deaths among the non-participants (39%). When each patient group was compared to the matched control group the participants with CF had an increased mortality with HR: 4.85 (95%CI: 3.02-7.77), the participants without CF had an increased mortality with HR: 4.35 (95%CI: 3.16-6.00). However, for the non-participants the risk of mortality was more than 9 fold increased (HR: 9.45 [95% CI: 5.44-16.41]) compared to their controls.

Variables significantly associated with mortality among the HL survivors

The participants with CF (HR: 1.54, 95%CI: 1.03-2.31) and the non-participants (HR: 2.04, 95%CI: 1.37-3.02) had increased mortality compared to the participants without CF in univariate analyses. **Figure1b.**

Multivariate analysis showed that the non-participants had a two-fold increased risk of mortality (HR: 2.05, 95%CI: 1.37-3.07) compared to participants without CF. No statistically significant difference was observed between the participants with and without CF. About three times higher mortality was observed in HL survivors treated with radiotherapy (with or without chemotherapy) compared to those treated with chemotherapy only in the multivariate analyses. HL survivors diagnosed before 1981 had increased mortality compared to those diagnosed in 1981 or thereafter.

Causes of deaths

Among the HL survivors 83 of the 149 (56%) deaths were caused by malignant diseases and 36 (24%) were caused by cardiovascular diseases. Of the HL survivors who died of malignant diseases, 33 of these deaths were caused by malignant lymphomas (of which 21 by HL) and 50 by other cancer types (pulmonary cancer: n=20, cancer in the gastrointestinal tract: n=11, breast cancer: n=3, leukemias / multiple myeloma: n=3).

Compared to the controls, the HL survivors had more than six times increased mortality of cancer (HR: 6.6, 95%CI 4.7-9.2), and almost five times increased mortality of cardiovascular disease (HR: 4.9, 95%CI: 3.1-7.9).

Figure1.

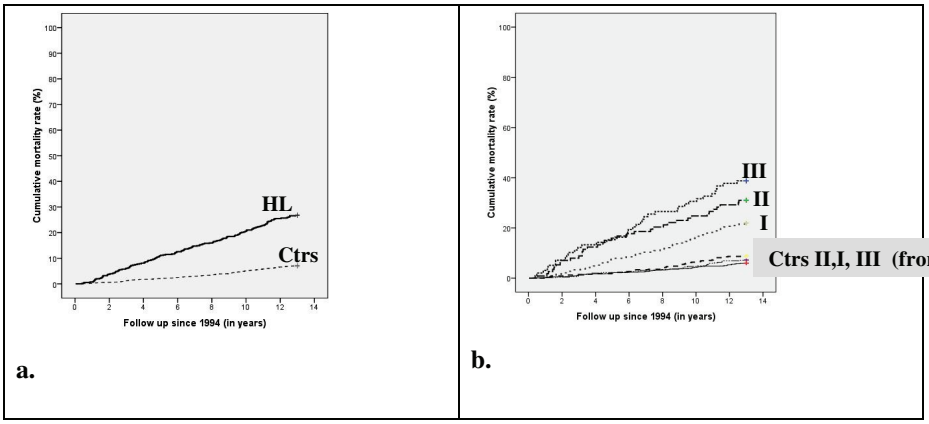


Figure1a : Cumulative overall mortality rate in HL sample (HL: n = 557) and controls (Ctrs: n = 2785)
Figure1b :
Cumulative mortality rate in HL survivors related to patient group and the matched control groups.
All patient groups displayed increased mortality compared to their controls ($p<0.001$).
HLSs: I: Participants without chronic fatigue (CF) n = 329
II: Participants with CF, n = 113
III: Non participants, n = 98
Ctrs: controls
CtrsI: controls to participants without CF, n = 1645
CtrsII: controls to participants with CF, n = 565
CtrsIII: controls to non-participants, n = 490

Part II A

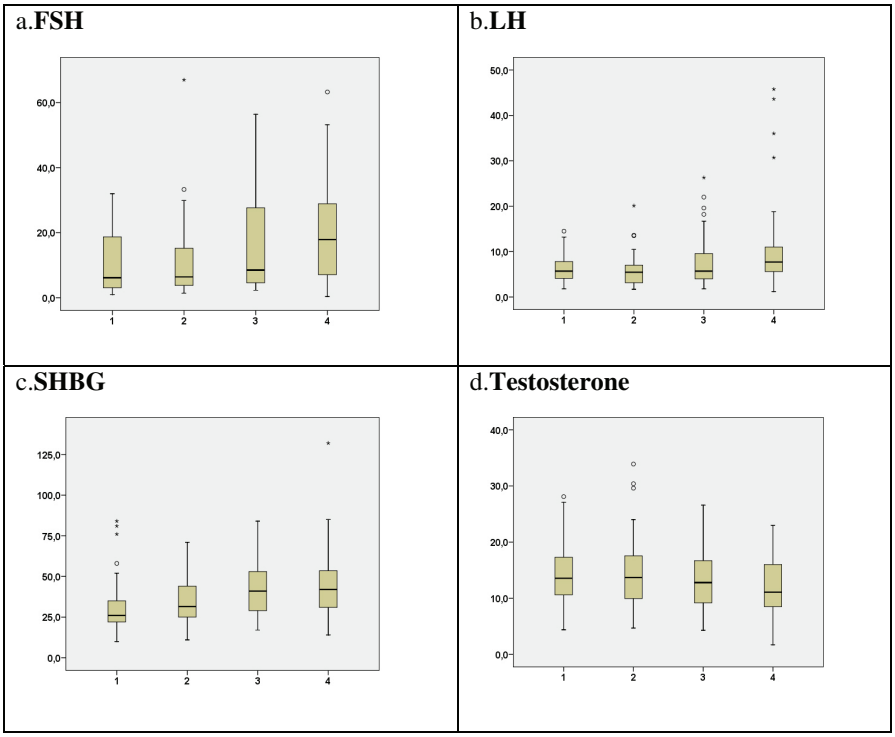
6.2. Main findings Paper 2

Levels of FSH, LH, Testosterone and SHBG

Forty-one percent of the male lymphoma survivors had FSH values above normal level (>12.0 U/L) and 16% of the survivors had elevated LH (>10.0U/L). The median testosterone value was 12.9 nmol/L (range: 1.7–33.9 nmol/L), with 20% of the survivors having testosterone value below the normal level (<9.0 nmol/L).

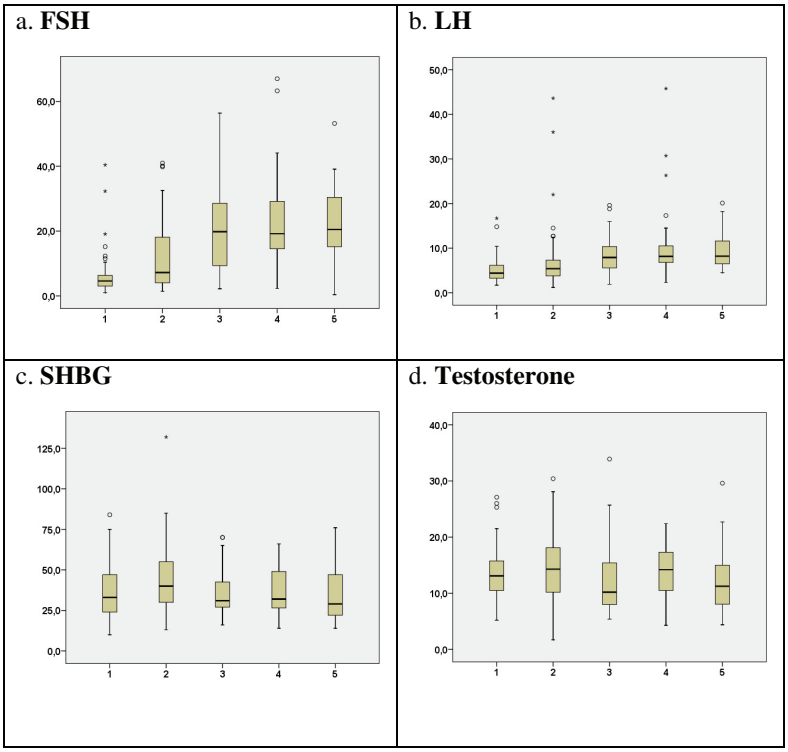
There was a significant association between age at survey and the levels of FSH, LH and SHBG ($p<0.001$), with levels increasing by age. For testosterone, no significant association with age at survey was observed. **Figure 2a**.

Figure 2a. Levels of gonadal hormones related to age groups.



Age groups: 1: 21-39, 2: 40-49, 3: 50-56, 4: 57-75 years at survey.
Boxplot showing median, upper and lower quartiles and range of values.
Datas from table 4 in Paper 2 presented as boxplot

Figure 2b. Levels of gonadal hormones related to treatment groups.



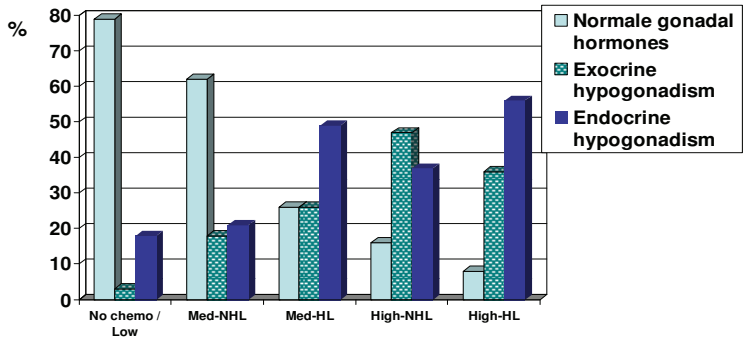
Treatment groups:
1: radiotherapy only / low gonadotoxic chemotherapy,
2: medium gonadotoxic chemotherapy NHL,
3: Medium gonadotoxic chemotherapy HL,
4: highly gonadotoxic chemotherapy NHL,
5: Highly gonadotoxic chemotherapy HL.
See table3 page 31 for explanation of treatment groups.
Data from table 4 in Paper 2 presented as Boxplot showing median, upper and lower quartiles and range of values.

There was a significant association between the levels of both FSH, LH ($p<0.001$) and SHBG ($p=0.042$) and treatment groups. The median level of FSH and LH increased significantly in all other treatment groups compared with patients treated with no/low gonadotoxic chemotherapy ($p<0.001$ – $p<0.02$). For testosterone no association with treatment groups was found, **Figure 2b**.

Groups of gonadal dysfunction

About half of the male lymphoma survivors (n=144, 49%) had all gonadal hormones within normal ranges and 20% (n=60) had isolated elevated FSH, with LH, SHBG and testosterone within normal ranges. Almost one-third of the survivors (n=90, 31%) had testosterone below and/or LH above normal range. There was a statistically significant association between treatment group and groups of gonadal dysfunction ($p<0.001$). Seventy-nine percent of those treated with no/low gonadotoxic chemotherapy had normal gonadal hormones, whereas the comparable figures were 62% after med-NHL, 26% after med-HL, 16% after high-NHL and 8% after high-HL. **Figure 2c.**

Figure 2c.



Legends Figure 2c. (same as figure 1 in paper 2)
Proportions of normal gonadal hormones, exocrine hypogonadism (elevated FSH, normal LH, testosterone and SHBG) and endocrine hypogonadism (low testosterone and/or elevated LH) in 294 male lymphoma survivors related to treatment group.
Treatment groups:
No chemo/low: radiotherapy only and low gonadotoxic chemotherapy (n=99)
Med-NHL: medium gonadotoxic chemotherapy for NHL (n=73)
Med-HL: medium gonadotoxic chemotherapy for HL (n=43)
High-NHL: highly gonadotoxic chemotherapy for NHL (n=43)
High-HL: highly gonadotoxic chemotherapy for HL (n=36)
For definitions of treatment groups, see table3 page 33.

Multinomial regression analyses

Compared to those treated with no/low gonadotoxic chemotherapy patients from all the other treatment groups had significantly elevated odds ratios (OR) for exocrine hypogonadism (elevated FSH only). Patients in the med-NHL group were 6.3 (95% CI: 1.7–23.8) times more likely to have elevated FSH compared to those treated with no/low gonadotoxic chemotherapy. The comparable ORs for the other groups were 25.7 (95% CI: 6.2–107.0) after med-HL, 73.3 (95% CI: 17.2–312.2) after high-NHL and 112.0 (95% CI: 20.1–625.2) after high-HL. Age at survey was not significantly associated with exocrine hypogonadism.

Except for those in the med-NHL group, patients from the other treatment groups had significantly elevated risk also for endocrine hypogonadism (low testosterone and/or elevated LH) compared to the group treated with no/low gonadotoxic chemotherapy. Patients in the med-HL showed OR=8.0 (95% CI: 3.2–20.4) for having endocrine hypogonadism compared to those treated with no/low gonadotoxic chemotherapy, whereas the comparable ORs for high- NHL were 10.5 (95% CI: 3.6–30.6) and 37.2 (95% CI: 9.4–147.7) for high-HL.

Patients aged above 50 years at survey were about five times more likely to have endocrine hypogonadism compared to those younger than 40 years at survey.
OR with 95%CI from table 5 in Paper 2.

6.3. Main findings Paper 3

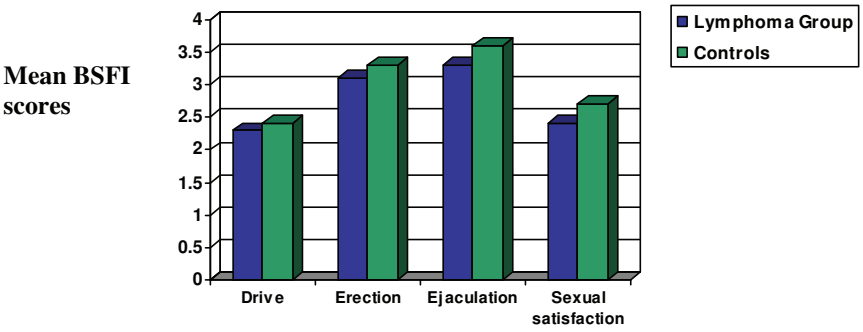
Sexual Function: HL versus NHL survivors

When adjusted for age, initial stage, and intensity of chemotherapy, there was no significant difference between HL and NHL survivors concerning the BSFI domain and total scores**.** Therefore, the whole lymphoma group taken together was compared with the controls.

Sexual function in lymphoma survivors versus normative controls

The lymphoma survivors had significantly poorer sexual function than normative controls in the BSFI erection, ejaculation, and overall sexual satisfaction domains ($p \leq 0.02$ for all) after adjusting for relationship status **Figure 3a.** There was no significant difference observed in the drive domain. The effect sizes were modest, ranging from 0.17 to 0.26.

Figure 3a. Sexual function in male lymphoma survivors compared to age-matched controls (figures from table 5 Paper 3)**.**

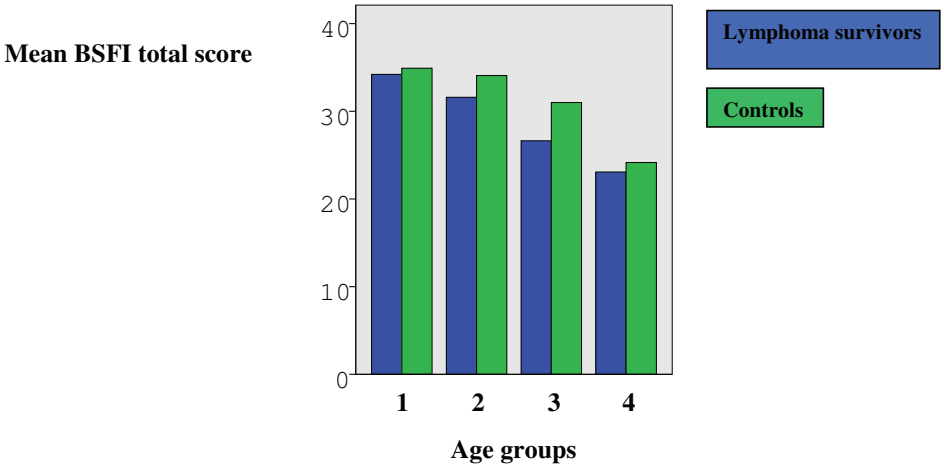


Factors associated with reduced sexual function among the lymphoma survivors

All five BSFI domains and the BSFI total scores decreased with increasing age ($p \leq 0.002$ for all) **Figure 3b**. Lymphoma survivors with normal gonadal hormone levels had the best sexual function scores, whereas the poorest scores were found in the survivors with low testosterone and/or elevated LH ($p < 0.05$) **Figure 3c**.

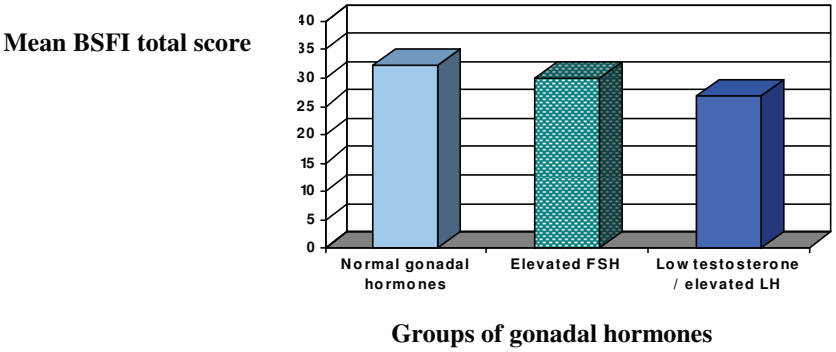
In multivariate analyses older age ($p < 0.001$), more emotional distress (total HADS score; $p < 0.001$), and poorer physical health (PCS; $p = 0.03$) were significantly associated with poorer sexual function (BSFI total score). Compared with having normal gonadal hormones, having low testosterone and/or elevated LH was also associated with poorer sexual function ($p = 0.04$).

Figure 3b. BSFI total score related to increasing age in male lymphoma survivors and controls



Age goups: 1:21-39 years, 2: 40-49 years, 3:50-59 years, 4: 60-69 years at survey.

Figure 3c. BSFI total score related to groups of gonadal hormones in male lymphoma survivors (figure from table 4 paper 3)**.**



Part II B

6.4. Main findings Paper 4

Attempted post-treatment parenthood

Attempted post-treatment parenthood was reported by 92 (50%) female and 120 (45%) male HL survivors, all aged below 40 years at diagnosis. Younger age and childlessness at diagnosis were the only variables significantly associated with attempted post-treatment parenthood in both univariate and multivariate analyses.

Achieved post-treatment parenthood

The 10-year cumulative probability of post-treatment parenthood was 59% in females and 56% in males with no significant difference between genders **Figure 4a.**

Females younger than 30 years at diagnosis had significantly higher probability of getting children post-treatment compared to older females. In males, there were no significant differences between the age groups **Figure 4b.**

Male HL survivors had a significantly higher probability of post-treatment fatherhood after radiotherapy only and after chemotherapy of low gonadotoxicity compared to those treated with chemotherapy with medium or high gonadotoxicity. The 10-year cumulative probabilities of achieving post-treatment parenthood in the various treatment groups were: 71% after radiotherapy only, 85% after chemotherapy with low gonadotoxicity, 35% after chemotherapy with medium gonadotoxicity and 18% after chemotherapy with high gonadotoxicity **Figure 4c.**

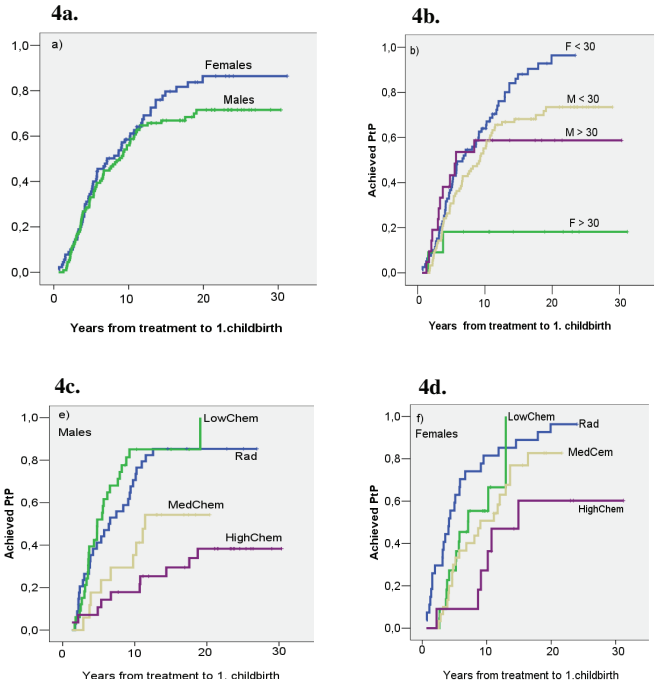
A significantly higher probability of getting children post-treatment was observed after radiotherapy only compared to chemotherapy with either medium or high gonadotoxicity also in females. A significant difference was also seen between those treated with chemotherapy with low versus high gonadotoxicity. The 10-year cumulative probabilities of post-treatment motherhood were 82% after radiotherapy only, 55% after low gonadotoxic chemotherapy, 51 % after medium gonadotoxic chemotherapy and 27% after highly gonadotoxic chemotherapy **Figure 4d.**

In the multivariate analysis post-treatment parenthood was significantly associated with treatment groups in both males and females. In males, the period of diagnosis was also a significant factor.

In addition, thirteen men had used assisted reproduction techniques with pretreatment cryopreserved semen, 10 of them successfully becoming fathers. Two women reported to have used IVF/ICSI, one of them giving birth to one child.

Finally, at the end of the observation time, 69 (76%) of the females and 85 (71%) of the males who had attempted post-treatment parenthood had become biological parents.

Figure 4 (parts similar to figure 2 in Paper 4)



7. Discussion

7.1. Methodological considerations

Response rates

High response rates among survivors after treatment for HL and NHL represent one of the strengths of this survey. For the questionnaire surveys in 1994 and 2002 (Paper 1 and 4) response rates of 82% and 75% were obtained, which is considered highly satisfactory for such studies.

For the study on gonadal hormones in 2007 (Paper 2 and 3) a response rate of 45% was achieved for the assessment of serum gonadal hormones, which is lower than what is generally obtained in questionnaire-based surveys, but should be viewed on the background of collection of blood samples and completion of a questionnaire. In addition, only male patients were included in the survey, with generally lower compliance on questionnaire studies than females. Nevertheless, serum samples from 294 male survivors could be analyzed by a single laboratory, and 246 of these survivors completed the BSFI (Paper 3). Compared to the existing literature in this field, this is a large sample size, not at least as the 2007 survey assessed sexual function since this theme often further reduces the response rates (121). Reluctance to complete the intimate questions of the BSFI is also the most probable explanation for the relative low response rate of this questionnaire among males from the general population.

Cross sectional studies

In cross-sectional studies, information is collected at one point in time. Therefore, cross-sectional studies are suited for measuring prevalence rates and detecting associations between variables. However, significant differences or associations observed do not prove causal relationships.

The cross-sectional design was considered appropriate for the objectives in Paper 2-4 because we were interested in assessing prevalence of gonadal dysfunction with associations to treatment and age in Paper2, the associations of reduced sexual function in male lymphoma survivors in Paper 3, and the rates of attempted and achieved post-treatment parenthood in Paper 4. A prospective design would probably give more information on the natural course of the late effects studied in these papers with improved knowledge of variations over time, but would require more time and labor to accomplish.

Time to event

In Paper 1 the endpoint for the survival analyses was date of death for HL survivors and controls with sensoring 13 years after the 1994-survey. This information was retrieved from the Statistics Norway (SSB), which are considered to provide accurately information.

In Paper 4 the endpoint for the survival analyses was year of the first post-treatment childbirth without considering abortions. This information was provided from the questionnaires, and it was expected that parents gave the correct year of birth for their children.

Bias

Bias can be categorized in three groups: selection bias, confounding and information bias.

Selection bias results from procedures used to select subjects of the study population, and selection bias occurs when the association between the exposure and the outcome differs systematically between those who participated and those who did not within a sample.

Paper 1 demonstrates that the characterization of non-response represent a significant problem in questionnaire based surveys. Our result indicate that significant differences between responders and non-responders remained undetected in 1994, in spite of comparability on important medical and sociodemographic parameters. As far as we know, a significant association between the willingness / ability to respond to a questionnaire survey and increased mortality has not been previously described in cancer survivors. This finding indicates that impaired physical health may explain why some HL survivors did not respond to the survey in 1994. A possible higher burden in non-responders as to having more symptoms and impaired physical health may imply that adverse effects in HL survivors might be underestimated in follow-up surveys due to selection bias.

In addition, the cross-sectional nature of the 1994-survey makes our result biased toward to higher rate of survival compared to other studies on mortality in HL survivors, since only HL survivors alive in 1994 were included in our sample.

In Paper 2 the compliers (with assessed serum gonadal hormones) were older at survey than the non-compliers (without assessed serum gonadal hormones). This may have caused a biased sample with a higher proportion of lymphoma survivors having endocrine hypogonadism (low testosterone and/or elevated LH) in our patient sample than in the total sample since the testosterone levels decrease with increasing age in the general population (132).

In Paper 3 those who had completed the BSFI (n=246) were younger at diagnosis and at survey compared to those who had not completed BSFI (n=45), which may give bias towards better sexual function in the responders than in the total sample of male lymphoma survivors approached. This may indicate that the extent of reduced sexual function in the total sample approached might be higher than suggested by our results since sexual function decreases with increasing age in the general population.

In Paper 4 we related our end point, achieved post-treatment parenthood, to the number of patients who reported attempted post-treatment parenthood. However, the number of HL survivors who reported to have attempted post-treatment parenthood may represent a response bias because only surviving patients could report their attempts of post-treatment parenthood. This could lead to an underestimation of attempts on post-treatment parenthood.

Reported rates of parenthood after treatment for cancer will depend on the selection criteria of the samples. In our study sample, 68% of those who reported to have attempted post-treatment parenthood conceived children spontaneously. As the proportion of patients who reported to have attempted parenthood may be underestimated, our reproduction rates may therefore be too favorable. This point is supported by the findings from a registry-based study from our group, showing a 20-year probability of first post-treatment childbirth of 8% in female and 28% in male lymphoma patients aged 15–45 years at diagnosis, when all patients treated at the NRH are included in the denominator without consideration of attempted post-treatment parenthood (133).

Confounding factors are variables in statistical models that correlate (positively and negatively) with both the dependent variable and the independent variable. Failure to control for such factors influencing the outcome may lead to confounding bias. In the studies included in this thesis, we have tried to avoid such bias as much as possible by adjusting for potential confounders in the analyses.

As an example, in Paper 1, the univariate analysis showed that participants with CF had significantly increased mortality compared to participants without CF. The significance of this difference disappeared in the multivariate analysis, probably reflecting confounding by age, since the chronically fatigued HL survivors were significantly older than those without CF in 1994. However, not all potentially confounders are known about this patient sample and could therefore not be adjusted for, like for instance comorbidity present in 1994.

In paper 3 a higher proportion of the controls from the general population lived in a committed relationship compared to the lymphoma survivor sample, and since relationship status is associated with sexuality, this was adjusted for when analyzing differences in the

BSFI in order to get the effect of the treatment of the disease teased out from that of the relationship status.

Internal validity

Internal validity refers to which extent the results of the studies can be generalized to the whole sample of lymphoma survivors approached in the surveys included in this thesis. In order to estimate the internal validity representativeness, possible biases and confounding factors which may affect internal validity have to be considered (134). In cross-sectional questionnaire-based surveys, there will always be some differences between the responders and the non-responders. Accounting for the limitations of the various differences between the reponders and non-responders in the samples of lymphoma survivors approached, as mentioned above, and the adjustment for confounding factors, we overall consider the internal validity of the surveys included in this thesis to be as good as possible.

External validity

External validity refers to the extent a study's results can be generalized to other populations than the study population, and for the present study this means to which degree our results can be generalized to the Norwegian lymphoma survivors in general.

In the period 1970-1980 the treatment of HL in Norway was centralized to the NRH, and 92% of the patients aged 15-39 years and 80% of the patients aged 40-59 years were admitted to the hospital. Since 1981 four other national oncological centers gradually began to treat HL following the same treatment principles as the NRH (49). From 1985 all HL patients from a defined health region constituting about 50% of the Norwegian population have been referred to the hospital. The treatment of HL at the NRH has been performed according to national and international guidelines. On this background we consider the external validity for the results on the HL patients included in this thesis to be very good and that our results may be generalized to the Norwegian HL survivors in general.

The proportion of NHL patients referred to the NRH has been somewhat lower than the proportion of HL patients, but the treatment of NHL has been performed according to national guidelines. With this background we consider the external validity of our results to be good and that our findings also can be transferable to the Norwegian population of male NHL survivors for the age groups examined in our analyses.

The use of normative controls

The use of control groups drawn from the general population allows comparison of the findings in the lymphoma survivors to that of the general population. This is of importance because health problems in cancer survivors may also be prevalent in the general population.

For Paper 1, a control group was constructed by randomly drawing five controls per patient from the general population matched for gender and year of birth, and these controls were followed similarly as the HL survivors. The use of matched controls gave the background mortality rate of the general population in order to evaluate the mortality rate in the HL survivors. Moreover, having five controls per patient compensated for random error in population sample controls.

In Paper 3 two age-matched controls were drawn from the normative sample (121) for each lymphoma survivor participant. This allowed us to compare sexual function in male lymphoma survivors compared to age matched controls, data which have been lacking in the literature so far. However, the information about the controls is limited by the lack of hormonal and other health data from men in the comparison group. The relatively low response rate (34%) in the normative sample also seen in other questionnaire studies of sexual function is another limitation because we do not know the representativity of the sample in relation to the total population.

7.2. Discussion of specific results

Part I

Mortality and causes of deaths in HL survivors compared to matched controls (Paper 1)

This study provides information on long-term mortality and causes of death in HL survivors with a longer follow-up period than previous studies (31;43;44). The median follow-up time was 12 years from diagnosis to the survey in 1994, and this study prolonged the observation time until 2007.

Compared to the controls, the HL survivors had almost five times higher risk of death due to any cause, and the mortality of HL survivors was persistently higher than the rate of their controls throughout the entire observation period. The presence of CF was not significantly associated with increased mortality, which is of clinical importance, as it indicates that CF itself is not associated with life-threatening somatic morbidity. Unexpectedly, an increased mortality among the non-participants from the 1994-suvey was observed.

At inclusion in the 1994-survey, the HL survivors were considered to be in complete remission. However, the observation time from diagnosis to inclusion in 1994 had a wide time span ranging from 2 – 23 years, with those with the shortest observation time from diagnosis to the 1994-survey having the highest risk for relapse.

Patients diagnosed in the period 1971 – 1980 had increased mortality compared to those diagnosed in the period 1981 – 1991, which is comparable to earlier findings (43). The difference in mortality over time periods may be due to more toxic treatment in the first period, particularly caused by the use of larger radiation fields, whereas less toxic treatment options were available in the latter period. Another explanation is change in the histopathological diagnosis; some lymphomas classified as HL in the earliest period, especially of the lymphocyte depleted and unclassified subtypes in the elderly (considered to be associated with poor prognosis), probably have been classified as NHL during the second period (49).

Malignant diseases and cardiovascular disorders were the most frequent causes of deaths among the HL survivors, which is similar to previous reports (28;31). Mortality of cancer was more than six times higher in HL survivors compared to the control group, and almost five times higher for mortality due to cardiovascular disorders. These results are comparable to those observed in 1261 patients treated for HL before the age 41 where the relative risk (RR) of deaths resulting from solid tumors was 6.6 and for cardiovascular diseases 6.3 (28). In comparison, Ng et al reported the RR of excess mortality from second

tumors to be 11.2 and 3.2 from cardiovascular diseases in their cohort of 1080 HL survivors (31).

Over the last decades, treatment for HL has been modified in order to reduce long-term adverse effects without changing the very good survival rates. Extended radiation fields, such as Mantle and inverted-Y field, is no longer used as standard radiotherapy, and for chemotherapy, MOPP-like regimens have to a large extent been abandoned. Nevertheless, it is of importance to study the morbidity and mortality after treatment with these regimens because a large number of survivors after such treatment are still alive, and for these is it of importance that medical complications can be prevented if possible, detected and eventually treated. In addition, today's patients still receive radiotherapy, albeit to smaller volumes and with lower doses, and chemotherapy regimens used today, such as ABVD and BEACOPP, still contain many of the same compounds as did earlier regimens. In a recently published study comparing overall survival (OS) after treatment for advanced stage HL with COPP/ABVD, BEACOPP or escalated-dose BEACOPP (median follow-up 111 months), OS was reported to be significantly improved after treatment with escalated-dose BEACOPP compared to the two other treatment regimens (135). However, a higher number of acute myeloid leukemia and myelodysplastic syndrome was observed in the dose-escalated BEACOPP arm, whereas no differences were observed in the total number of secondary malignancies between the treatment arms (135). This report emphasizes the importance of clinicians being aware of the possibility of long-term complications even after today's treatment for HL, warranting optimal follow-up care of the patients. A question is whether the total long-term mortality is a better estimate of successful treatment of HL, than HL specific mortality.

Part II A

Gonadal function in male lymphoma survivors (Paper 2)

Almost 50% of the 294 male lymphoma survivors had all gonadal hormones within normal ranges, 20% had isolated elevated FSH (exocrine hypogonadism), and almost one-third had low testosterone and/or elevated LH (endocrine hypogonadism). Patients from all the other treatment groups had significantly elevated risk for having elevated FSH compared to those treated with radiotherapy only / chemotherapy with low gonadotoxicity. Except for the patients in the med-NHL group, patients from the other treatment groups had a significantly elevated risk also for endocrine hypogonadism compared to the group treated with radiotherapy only / chemotherapy with low gonadotoxicity. Patients aged above 50 years at survey were about five times more likely to have endocrine hypogonadism compared to those younger than 40 years at survey.

In the present lymphoma sample, 41% had elevated FSH, which is comparable to 35% reported after at a median follow-up of 32 months after treatment for stage I/II supradiaphragmatic HL in the period of 1982 to 2004 (n=355) (85). However, this has to be considered in the light of major differences between the two patient samples. Our sample included survivors after both HL and NHL, men with initially advanced disease and treated for relapse, and thereby those who had received more intensive chemotherapy than usually given in stage I/II disease. Finally, our median observation time was 15 years and thereby much longer than that of van der Kaaij et al (85). We consider our proportion of FSH elevation as definite, whereas one still can expect some recovery of spermatogenesis with longer follow up in early stage lymphoma patients with limited treatment, based on the experience in testicular cancer patients (136).

The results of our study supported findings of low risk of elevated FSH in HL survivors after treatment with ABVD-like regimens or radiotherapy only compared to chemotherapy combinations incorporating alkylating agents (42;85;90). A recent report on fertility in males treated for advanced stage HL with BEACOPP regimens (n=38) showed that the majority of patients had elevated FSH levels and were azoospermic after treatment (137).

The risk of elevated FSH increased with chemotherapy intensity also in male survivors after treatment for NHL. To our knowledge, this has not been shown in such a large patient sample earlier, but is comparable to the findings of Pryzant et al showing that cumulative doses of cyclophosphamide higher than 9.5 g/m^2 resulted in significanlty lower probability of recovered spermatogenesis compared to cumulative doses of cyclophosphamide less than 9.5 g/m^2 (86).

Except for male NHL survivors treated mainly with CHOP-based chemotherapy (med-NHL group), the risk of endocrine hypogonadism (low testosterone and/or elevated LH) increased for all treatment groups compared to the group treated with radiotherapy only or low gonadoxic chemotherapy. Intensification of chemotherapy increased the risk of endocrine gonadal failure more in HL survivors than in NHL survivors. This result may reflect that chemotherapy regimens used for HL generally are more gonadotoxic than those used for NHL. This difference may also be explained by the differences in the pre-treatment gonadal function between HL and NHL patients as previously reported (80). Also for testicular cancer survivors an increasing risk of endocrine hypogonadism along with chemotherapy intensification has been reported (138).

We have followed the definition of endocrine hypogonadism based on elevated LH and normal testosterone (compensated hypogonadism) or low testosterone with or without elevated LH (40). Our data indicated that the duration of follow-up time might be associated with development of an uncompensated hypogonadism (elevated LH, low testosterone). In addition, our patient sample showed a more diverse picture regarding the endocrine dysfunction, with 27 of 57 patients with low testosterone having normal LH. Similar results has been reported earlier by Greeenfield et al, with only one third (8/24) of male cancer survivors with low testosterone value having elevated LH (75). This finding may reflect that the causes of endocrine hypogonadism in male lymphoma survivors may be more complex than previously described. Chemotherapy and/or radiation-induced damage may develop either in the gonads, the hypothalamus-pituitary axis or as a combination of these two. Further, except for the pathway through the hypothalamus–pituitary axis and the release of Gonadothropin-releasing hormone (GnRH), the mechanisms related to Leydig cell dysfunctions after cancer treatment are not well known. In addition, it has been noted that lower testosterone levels in elderly males may not be fully accompanied by rising FSH and LH levels (139).

The blood samples for assessment of the gonadal hormones were generally taken during the morning, since testosterone levels have a diurnal variation with highest levels in the mornings. The normal range for serum levels of testosterone (9-31 nmol/l) was not age adjusted in the laboratory at the NRH which analyzed all the gonadal hormones, which may have lead to a comparatively broad allocation of older men to the group of endocrine hypogonadism. However, a recent report on reference intervals for serum testosterone, SHBG, FSH and LH, with analyses performed at the same laboratory as our samples, the normal range for age 70 years was 8.6-30.7 nmol/l which is quite similar to the normal range

used in the present study (139). For the age group 40-50 the normal range for testosterone was found to be 9.7-31.8 nmol/l (139), which in retrospect indicates that our estimates of endocrine hypogonadism in the younger male lymphoma survivors have been an underestimation.

Testosterone deficiency in adult males has been associated with negative health effects such as declining bone mass, increasing BMI, reduced muscle strength and energy levels in addition to altered sexual function both in cancer survivors and in the general population (75;76;140;141). It is therefore of clinical importance to identify male cancer survivors with endocrine hypogonadism, and in this context, it is surprising that only three of the male patients included in this study reported testosterone substitution therapy at the time of the survey, when endocrine hypogonadism was found in one-third of the patients. This is probably because levels of gonadal hormones have not been measured regurlarly in male lymphoma survivors.

Sexual function in male lymphoma survivors (Paper 3)

Lymphoma survivors reported statistically significant poorer sexual function in the domains of erection, ejaculation, and overall sexual satisfaction compared with age-matched controls. Among the lymphoma survivors the most important variables associated with reduced sexual function were older age, more emotional distress and poorer self-reported physical health. Lymphoma survivors having low testosterone and/or elevated LH displayed impaired sexual function compared to those with normal gonadal hormones.

The gradual reduction of sexual function with increasing age in the lymphoma sample is similar to reports from the general population (98;121). A previous survey of male lymphoma survivors did not find an association between age and reduced erectile function, but only men under age 55 were studied and the sample size (n=59) was much smaller than ours (96), which may explain the differerences between their findings and ours.

The finding of an association between sexual function and Leydig cell or pituitary dysfunction in our study is similar to the results of studies of men from the general population and observations from a group of men treated for hematological malignancies (132;142-144). However, in both the study by Howell et al (144) and our sample, the hormonal abnormalities only accounted for a small part of the decline in sexual function. In the multivariate analysis, emotional distress and report of poor physical health remained associated with reduced sexual function at a much higher degree, which is similar to findings in studies of testicular cancer survivors (122) and in aging men in the general population (95;97). The association between low testosterone levels and reduced sexual function may be explained in different ways. First,

low testosterone levels may directly decrease physical health and impair sexual function as a consequence of the gonadal dysfunction. Second, systemic illness may result in reduced testosterone levels and may direct impact on sexual function.

It is generally assumed that if a man's testosterone levels are below the normal range, testosterone supplementation will improve sexual function. However, it is difficult to assess the effects of testosterone substitution on sexual function because most studies are methodologically flawed (143;145). A conservative approach would be to treat cancer survivors with sexual dysfunction initially by encouraging a healthy lifestyle, particularly in terms of increasing physical exercise and eventual weight reduction (143;145). Such an approach may improve hypertension, diabetic control, and other cardiac risk factors. Men who might not be motivated to make lifestyle changes to prevent future health problems might be receptive to such a program if it could improve sexual function.

Although impaired sexual function may be a distressing late effect for men after lymphoma treatment, many do not receive information about the impact of cancer treatment on sexuality. In a survey assessing information needs in survivors of NHL, 28% wanted information about sexual functioning (91). Sexual counseling is not routinely available even in comprehensive cancer centers in the United States (146). A survey from a large cancer center reported that 51% of responding male cancer survivors stated that they most probably would make an appointment at a reproductive health clinic in the next year if the cancer center offered such a service (147).

Part II B

Post-treatment parenthood in HL survivors (Paper 4)

Approximately half of the HL survivors reported attempted post-treatment parenthood, and among these, two thirds (68 %) were successful in becoming parents without use of assisted reproduction techniques. Multivariate analyses revealed that type of treatment was significantly associated with post-treatment parenthood in both genders, with highest probabilities after radiotherapy only and low gonadotoxic chemotherapy. In addition, a significantly higher success rate was observed in males diagnosed after 1988 compared to before 1989.

Most studies on post-treatment gonadal function in HL survivors have assessed secondary amenorrhea and /or spermatogenesis measured by sperm cell count and the level of serum FSH (37;42;89;99). For females, regular menstruation post-treatment does not equal ovulation and the possibility of pregnancy. For males, however, sperm count analyses and

serum levels of FSH are relatively valid indicators of fertility. Some studies on fertility in HL survivors have reported the number of childbirths, but often in small series (100-103), and rarely with those attempting post-treatment parenthood as a denominator (36;104).

Achievement of post-treatment parenthood was associated with treatment groups in both males and females. Our results correspond to earlier reports on male fertility after treatment for HL, with higher rates of preserved fertility after treatment with ABVD-like regimens compared to MOPP-like regimens (42;89;99;100). In our patient sample, two male patients spontaneously fathered children after HDT. Earlier studies have reported that fertility may be restored in a few patients after treatment with HDT for HL and NHL (148;149). Only a small proportion of the male HL survivors had used their pretreatment cryopreserved semen, which has also been shown for other cancer survivors (106;107).

The improved chance of post-treatment parenthood in males diagnosed after 1989 compared to before 1989 is probably due to changes in the treatment of HL in late 1980s with introduction less gonadotoxic chemotherapy, such as ABVD, and less extensive radiation fields. In the females, our findings support earlier studies which have shown that female post-treatment fertility depends both on the gonadotoxicity of chemotherapy and age at diagnosis (37;101-104).

In preliminary analyses no differences were found in post-treatment parenthood after supradiaphragmatic radiotherapy only compared to infradiaphragmatic irradiation. However, the majority of the irradiated patients had received supradiaphragmatic radiotherapy only (almost 80%), and the group of HL survivors who had attempted post-treatment parenthood after infradiaphragmatic radiotherapy was too small for valid statistical comparison. As earlier reported, successful pregnancies are possible after pelvic irradiation if oophoropexy has been performed before inverted-Y field irradiation (150) or the radiation field did not include both ovaries.

This study has some limitations: neither the fertility status of the HL survivors' partners is known, nor the couples struggle for achieving children, with the exception of the use of assisted reproductive techniques. Concerning reports of attempted post-treatment parenthood, there may be some degree of memory bias of the patients. In addition, a response shift from "have attempted" to "have not attempted" post-treatment parenthood as part of a coping strategy in some patients that did not succeed in having children post-treatment can not be excluded. It is also unknown to us at what time after treatment the HL survivors started attempting parenthood. In addition, we assume that male HL survivors who reported spontaneous post-treatment fatherhood are the biological fathers of the born children.

Information on fertility issues is important in clinical oncological practice, and fertility-saving tasks and the risk of post-treatment infertility should be discussed with patients the patients at risk before treatment is initiated. Females should be informed that both the treatment and their age at treatment influence their fertility potential. Females aged above 30 years at diagnosis are at high risk of becoming infertile. They constitute a subgroup for which cryopreservation of ovarian tissue should be considered. Since males have the opportunity for pretreatment cryopreservation of semen, and as spermatogenesis usually recovers, their risk of potential infertility after treatment is less and easier to deal with.

8. Conclusions

Part I

- HL survivors had almost five-fold increased mortality compared to controls from the general population matched for age and gender.
- The presence of chronic fatigue in the 1994-survey was not associated with increased mortality.
- The highest mortality among the HL survivors was observed in the non-participants in the 1994-survey, which was unexpected.

Part II

- Almost one third of the male lymphoma survivors had endocrine hypogonadism defined as elevated LH and / or low testosterone, independent of FSH value.
- Lymphoma survivors aged above 50 years at survey were about five times more likely to have endocrine hypogonadism compared to those aged less than 40 years at survey.
- Except for the lymphoma survivors in the Med-NHL treatment group (mainly treated with eight or less courses CHOP-based chemotherapy), those from the other treatment groups had higher risk for endocrine hypogonadism compared to those treated with radiotherapy only or low gonadotoxic chemotherapy.

- Compared to age matched controls from the general population, male lymphoma survivors reported reduced sexual function in the domain scores of erection, ejaculation and overall sexual satisfaction.
- Among the male lymphoma survivors reduced sexual function was associated with increasing age, more emotional distress and reduced perception of physical health.
- Male lymphoma survivors with low testosterone and / or elevated LH had impaired sexual function than those with normal gonadal hormones.

- About half of the HL survivors reported to have attempted post-treatment parenthood, with young age and childlessness at diagnosis being significantly associated with attempts of post-treatment parenthood.
- Of those who had attempted post-treatment parenthood, about two thirds became parents spontaneously.
- Type of treatment was significantly associated with achievement of post-treatment parenthood in both genders, with highest probabilities of achieveing children post-treatment after radiotherapy only and low gonadotoxic chemotherapy.

9. Clinical implications and future perspectives

The finding of increased mortality in the non-responders compared to the responding HL survivors in the 1994-survey needs to be confirmed and explored by further examinations, also in other groups of cancer survivors. In addition, in our study the underlying cause of death was recorded, whereas comorbidities which may have contributed to death were not taken into account, which may give further information on the development of comorbidities in lymphoma survivors in future studies.

Few studies have been performed on mortality and causes of death after treatment for NHL, and such studies could be interesting to perform with the basis in the Lymphoma database at the NRH. In the future, one of the main questions is whether late adverse health affects and overall long-term survival after treatment for malignant lymphomas has been improved after the introduction of newer treatment strategies, such as the reduction of the radiotherapy fields in the treatment of HL in 1997.

The results of the study on gonadal hormones in male lymphoma survivors imply that these should be assessed regularly in male lymphoma survivors, especially after treatment with high-dose alkylating agents and HDT and in males 50 years and older, because low levels of testosterone may give symptoms as sexual problems, reduced energy and impaired vitality. If gonadal hormones indicate hypogonadism, further analyses and clinical evaluations should examine the need for testosterone substitution in order to avoid serious health problems in the future. To evaluate the effect of testosterone substitution in hypogonadal male lymphoma survivors more studies are needed.

The mechanisms underlying reduced sexual function in lymphoma survivors should be explored in more details. Based on our findings in male lymphoma survivors, it would it be of clinical relevance to analyse factors related to impaired sexual function also in female lymphoma survivors. In order to offer malignant lymphoma survivors optimal follow-up care, further research on the effects of sexual counseling, hormonal treatments and lifestyle-changes are needed.

Studies on late-effects after treatment for malignant lymphoma should include prospective studies to a larger degree, with assessment of survivor outcomes pre- and post treatment. Longitudinal studies will provide data on the natural history / development of specific long-term effects after cancer treatment. As an example, to follow the natural course of both gonadal and sexual function in cancer survivors over time from diagnosis to post-treatment would gather new information. In the aspects of fertility, longitudinal studies would

give information on for instance at what time point after treatment cancer survivors start to plan parenthood.

Studies including genetic analyses could provide improved knowledge about the diseases itself but also about long-term effects after treatment for HL and NHL. Translational research may in addition to the usual “bench to bed”-view refer to the incorporation of new knowledge into the community (151), for instance on cancer survivorship issues . The best follow-up care of long-term lymphoma survivors for detection and eventual prevention of long-term effects is an issue of debate in today’s health care system. For the majority of the lymphoma survivors, regular controls by a general practioner may probably provide the best follow-up care, while subgroups of lymphoma survivors may need follow-up by oncologists or other medical specialists.

Reference List

(1) Cancer Registry of Norway. Cancer in Norway 2007. 2009.

(2) Mullan F. Seasons of survival: reflections of a physician with cancer. N Engl J Med 1985 Jul 25;313(4):270-3.

(3) Aziz NM. Cancer survivorship research: state of knowledge, challenges and opportunities. Acta Oncol 2007;46(4):417-32.

(4) Fossa SD, Loge JH, Dahl AA. Long-term survivorship after cancer: how far have we come? Ann Oncol 2008 Jul 1;19(suppl_5):v25-v29.

(5) Fosså S, Vassilopoulou-Sellin R, Dahl A. Long term physical sequelae after adult-onset cancer. Journal of Cancer Survivorship 2008 Mar 19;2(1):3-11.

(6) Abrahamsen AF, Host H. Mantle field irradiation for stages IA and IIA Hodgkin's disease. Scandinavian Journal of Haematology 1981;26(4):306-10.

(7) Abrahamsen AF, Hannisdal E, Nome O, Holte H, Hager B, Langholm R, et al. Clinical stage I and II Hodgkin's disease: long-term results of therapy without laparotomy. Experience at one institution. Ann Oncol 1996;7(2):145-50.

(8) DeVita VT, Jr., Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 1970 Dec;73(6):881-95.

(9) Bonadonna G, Santoro A. ABVD chemotherapy in the treatment of Hodgkin's disease. Cancer Treat Rev 1982 Mar;9(1):21-35.

(10) Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD Plus Subtotal Nodal Versus Involved-Field Radiotherapy in Early-Stage Hodgkin's Disease: Long-Term Results. J Clin Oncol 2004 Jul 15;22(14):2835-41.

(11) Evens AM, Hutchings M, Diehl V. Treatment of Hodgkin lymphoma: the past, present, and future. Nat Clin Prac Oncol 2008 Sep;5(9):543-56.

(12) Press OW, LeBlanc M, Lichter AS, Grogan TM, Unger JM, Wasserman TH, et al. Phase III Randomized Intergroup Trial of Subtotal Lymphoid Irradiation Versus Doxorubicin, Vinblastine, and Subtotal Lymphoid Irradiation for Stage IA to IIA Hodgkin's Disease. J Clin Oncol 2001 Nov 15;19(22):4238-44.

(13) Norsk lymfomgruppe. Norsk handlingsprogram for diagnostikk og behandling av maligne lymfomer (Norwegian). 2003.

(14) Holte H, Mella O, Wist E, Telhaug R, Hannisdal E, Abrahamsen AF. ChlVPP is as effective as alternating ChlVPP/ABOD in advanced stage Hodgkin's disease. Acta Oncologica 1996;35:Suppl-80.

(15) Diehl V, Franklin J, Hasenclever D, Tesch H, Pfreundschuh M, Lathan B, et al. BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 1998 Dec;16(12):3810-21.

(16) Hasenclever D, Diehl V, Armitage JO, Assouline D, Bjorkholm M, Brusamolino E, et al. A Prognostic Score for Advanced Hodgkin's Disease. N Engl J Med 1998 Nov 19;339(21):1506-14.

(17) Blystad AK, Holte H, Kvaloy S, Smeland E, Delabie J, Kvalheim G. High-dose therapy in patients with Hodgkin's disease: the use of selected CD34(+) cells is as safe as unmanipulated peripheral blood progenitor cells. Bone Marrow Transplantation 2001;28(9):849-57.

(18) Blystad AK, Torlakovic E, Holte H, Kvaloy S, Lenschow E, Kvalheim G. CD34(+) cell enrichment depletes atypical CD30(+) cells from PBPC grafts in patients with HD. Cytotherapy 2001;3(4):295-305.

(19) Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 1996 Apr 1;14(4):1282-90.

(20) Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. Semin Oncol 1993 Oct;20(5 Suppl 5):75-88.

(21) Tan D, Horning SJ. Follicular Lymphoma: Clinical Features and Treatment. Hematology/Oncology Clinics of North America 2008 Oct;22(5):863-82.

(22) Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994 Jan 15;83(2):435-45.

(23) Hagemeister FB, Tannir N, McLaughlin P, Salvador P, Riggs S, Velasquez WS, et al. MIME chemotherapy (methyl-GAG, ifosfamide, methotrexate, etoposide) as treatment for recurrent Hodgkin's disease. J Clin Oncol 1987 Apr 1;5(4):556-61.

(24) Merk K, Idestrom K, Johansson B, Kimby E, Lindemalm C, Osby E, et al. Mitoxantrone, etoposide, cytarabine and prednisone as salvage therapy for refractory non-Hodgkin lymphoma (NHL) and alternated with CHOP in previously untreated patients with NHL. European Journal of Haematology.

(25) Smeland S, Blystad AK, Kvaloy SO, Ikonomou IM, Delabie J, Kvalheim G, et al. Treatment of Burkitt's/Burkitt-like lymphoma in adolescents and adults: a 20-year experience from the Norwegian Radium Hospital with the use of three successive regimens. Ann Oncol 2004 Jul 1;15(7):1072-8.

(26) Evensen S, Brinch L, Tjønnfjord G, Stavem P, Wisloff F. Estimated 8-year survival of more than 40% in a population-based study of 79 adult patients with acute lymphoblastic leukaemia. British Journal of Haematology 1994;88:88-93.

(27) Sweetenham JW, Santini G, Qian W, Guelfi M, Schmitz N, Simnett S, et al. High-Dose Therapy and Autologous Stem-Cell Transplantation Versus Conventional-Dose Consolidation/Maintenance Therapy as Postremission Therapy for Adult Patients With Lymphoblastic Lymphoma: Results of a Randomized Trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group. J Clin Oncol 2001 Jun 1;19(11):2927-36.

(28) Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21(18):3431-9.

(29) Aleman BMP, van den Belt-Dusebout A, De Bruin ML, van 't Veer MB, Baaijens MHA, Boer JPd, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007 Mar 1;109(5):1878-86.

(30) Hodgson DC, Gilbert ES, Dores GM, Schonfeld SJ, Lynch CF, Storm H, et al. Long-Term Solid Cancer Risk Among 5-Year Survivors of Hodgkin's Lymphoma. J Clin Oncol 2007 Apr 20;25(12):1489-97.

(31) Ng AK, Bernardo MP, Weller E, Backstrand KH, Silver B, Marcus KC, et al. Long-Term Survival and Competing Causes of Death in Patients With Early-Stage Hodgkin's Disease Treated at Age 50 or Younger. J Clin Oncol 2002 Apr 15;20(8):2101-8.

(32) Toda K, Shibuya H, Hayashi K, Ayukawa F. Radiation-induced cancer after radiotherapy for non-Hodgkin's lymphoma of the head and neck: a retrospective study. Radiation Oncology 2009;4(1):21.

(33) Abrahamsen AF, Loge JH, Hannisdal E, Nome O, Lund MB, Holte H, et al. Late medical sequelae after therapy for supradiaphragmatic Hodgkin's disease. Acta Oncologica 1999;38(4):511-5.

(34) Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991;325:599-605.

(35) Abrahamsen AF, Loge JH, Hannisdal E, Holte H, Kvaloy S. Socio-medical situation for long-term survivors of Hodgkin's disease: a survey of 459 patients treated at one institution. European Journal of Cancer 1998;34(12):1865-70.

(36) Aisner J, Wiernik PH, Pearl P. Pregnancy outcome in patients treated for Hodgkin's disease. J Clin Oncol 1993;11(3):507-12.

(37) Behringer K, Breuer K, Reineke T, May M, Nogova L, Klimm B, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol 2005;23(30):7555-64.

(38) Blackhall FH, Atkinson AD, Maaya MB, Ryder WD, Horne G, Brison DR, et al. Semen cryopreservation, utilisation and reproductive outcome in men treated for Hodgkin's disease. British Journal of Cancer 2002;87(4):381-4.

(39) Bokemeyer C, Schmoll HJ, van RJ, Kuczyk M, Schuppert F, Poliwoda H. Long-term gonadal toxicity after therapy for Hodgkin's and non-Hodgkin's lymphoma. Annals of Hematology 1994;68(3):105-10.

(40) Howell SJ, Radford JA, Ryder WD, Shalet SM. Testicular function after cytotoxic chemotherapy: evidence of Leydig cell insufficiency. J Clin Oncol 1999;17(5):1493-8.

(41) Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. J Clin Oncol 1999;17(1):253-61.

(42) Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. European Journal of Cancer & Clinical Oncology 1985;21(5):601-5.

(43) Provencio M, Millan I, Espana P, Sanchez AC, Sanchez JJ, Cantos B, et al. Analysis of Competing Risks of Causes of Death and their Variation Over Different Time Periods in Hodgkin's Disease. Clin Cancer Res 2008 Aug 15;14(16):5300-5.

(44) Favier O, Heutte N, Stamatoullas-Bastard A, Carde P, Van't Veer MB, Aleman BM, et al. Survival after Hodgkin lymphoma: causes of death and excess mortality in patients treated in 8 consecutive trials. Cancer 2009 Feb 10.

(45) Bluhm EC, Ronckers C, Hayashi RJ, Neglia JP, Mertens AC, Stovall M, et al. Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. Blood 2008 Apr 15;111(8):4014-21.

(46) Ng AKM, Mauch PMM. Late Effects of Hodgkin's Disease and Its Treatment. Cancer Journal 2009 Mar;15(2):164-8.

(47) van Leeuwen FE, Chorus AM, van den Belt-Dusebout A, Hagenbeek A, Noyon R, van Kerkhoff EH, et al. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. J Clin Oncol 1994 May 1;12(5):1063-73.

(48) van Leeuwen FE, Klokman WJ, Veer MB, Hagenbeek A, Krol ADG, Vetter UAO, et al. Long-Term Risk of Second Malignancy in Survivors of HodgkinÆs Disease Treated During Adolescence or Young Adulthood. J Clin Oncol 2000 Feb 1;18(3):487.

(49) Abrahamsen A.F., Egeland T, Hansen S, Langholm R, Holte H, Kvaloy S. Hodgkin's disease in a national and hospital population: trends over 20 years. European Journal of Cancer 1997;33(14):2380-3.

(50) Swerdlow AJ, Barder JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, et al. Risk of Second Malignancy After Hodgkin's Disease in a Collaborative British Cohort: The Relation to Age at Treatment. J Clin Oncol 2000;18:498-509.

(51) Behringer K, Josting A, Schiller P, Eich HT, Bredenfeld H, Diehl V, et al. Solid tumors in patients treated for Hodgkin's disease: a report from the German Hodgkin Lymphoma Study Group. Ann Oncol 2004 Jul 1;15(7):1079-85.

(52) Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Breast Cancer Following Radiotherapy and Chemotherapy Among Young Women With Hodgkin Disease. JAMA 2003 Jul 23;290(4):465-75.

(53) Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Andersson M, Glimelius B, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002 Feb 6;94(3):182-92.

(54) van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, Van't Veer MB, Noordijk EM, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003 Jul 2;95(13):971-80.

(55) Swerdlow AJ, Schoemaker MJ, Allerton R, Horwich A, Barber JA, Cunningham D, et al. Lung cancer after Hodgkin's disease: a nested case-control study of the relation to treatment. J Clin Oncol 2001 Mar 15;19(6):1610-8.

(56) Brennan P, Scelo G, Hemminki K, Mellemkjaer L, Tracey E, Andersen A, et al. Second primary cancers among 109[thinsp]000 cases of non-Hodgkin's lymphoma. Br J Cancer 2005 Jun 21;93(1):159-66.

(57) Mudie NY, Swerdlow AJ, Higgins CD, Smith P, Qiao Z, Hancock BW, et al. Risk of second malignancy after non-Hodgkin's lympnoma: a british cohort study. J Clin Oncol 2006;24:1568-74.

(58) Tward JD, Wendland MM, Shrleve DC, Szabo A, Gaffney DK. The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin's lymphoma. Cancer 2006;107:108-15.

(59) Hudson MM, Poquette CA, Lee J, Greenwald CA, Shah A, Luo X, et al. Increased mortality after successful treatment for Hodgkin's disease. J Clin Oncol 1998 Nov 1;16(11):3592-600.

(60) Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular Dysfunction and Carotid, Subclavian, and Coronary Artery Disease in Survivors of Hodgkin Lymphoma Treated With Radiation Therapy. JAMA 2003 Dec 3;290(21):2831-7.

(61) Lund MB, Ihlen H, Voss BM, Abrahamsen AF, Nome O, Kongerud J, et al. Increased risk of heart valve regurgitation after mediastinal radiation for Hodgkin's disease: an echocardiographic study. Heart 1996;75(6):591-5.

(62) Swerdlow AJ, Higgins CD, Smith P, Cunningham D, Hancock BW, Horwich A, et al. Myocardial Infarction Mortality Risk After Treatment for Hodgkin Disease: A Collaborative British Cohort Study. J Natl Cancer Inst 2007 Feb 7;99(3):206-14.

(63) Wethal T, Lund MB, Edvardsen T, Fossa SD, Pripp AH, Holte H, et al. Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. Br J Cancer 2009 Jul 21.

(64) Meinardi MT, Gietema JA, Van Veldhuisen DJ, van der Graaf WT, De Vries EG, Sleijfer DT. Long-term chemotherapy-related cardiovascular morbidity. Cancer Treat Rev 2000 Dec;26(6):429-47.

(65) Singal PK, Iliskovic N. Doxorubicin-Induced Cardiomyopathy. N Engl J Med 1998 Sep 24;339(13):900-5.

(66) Aviles A, Neri N, Nambo JM, Huerta-Guzman J, Talavera A, Cleto S. Late cardiac toxicity secondary to treatment in Hodgkin's disease. A study comparing doxorubicin, epirubicin and mitoxantrone in combined therapy. Leuk Lymphoma 2005 Jul;46(7):1023-8.

(67) Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973 Aug;32(2):302-14.

(68) Hequet O, Le QH, Moullet I, Pauli E, Salles G, Espinouse D, et al. Subclinical Late Cardiomyopathy After Doxorubicin Therapy for Lymphoma in Adults. J Clin Oncol 2004 May 15;22(10):1864-71.

(69) Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer. A pilot survey of survivors' attitudes and experiences. Cancer 1999;86(4):697-709.

(70) Schover LR. Psychosocial aspects of infertility and decisions about reproduction in young cancer survivors: a review. Medical & Pediatric Oncology 1999;33(1):53-9.

(71) Schover LR. Sexuality and fertility after cancer. Hematology Am Soc Hematol Educ Program 2005;523-7.

(72) Ratcliffe MA, Lanham SA, Reid DM, Dawson AA. Bone mineral density (BMD) in patients with lymphoma: the effects of chemotherapy, intermittent corticosteroids and premature menopause. Hematol Oncol 1992 May;10(3-4):181-7.

(73) Redman JR, Bajorunas DR, Wong G, McDermott K, Gnecco C, Schneider R, et al. Bone mineralization in women following successful treatment of Hodgkin's disease. Am J Med 1988 Jul;85(1):65-72.

(74) Finkelstein JS, Klibanski A, Neer RM, Greenspan SL, Rosenthal DI, Crowley WF, Jr. Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. Ann Intern Med 1987;106(3):354-61.

(75) Greenfield DM, Walters SJ, Coleman RE, Hancock BW, Eastell R, Davies HA, et al. Prevalence and Consequences of Androgen Deficiency in Young Male Cancer Survivors in a Controlled Cross-Sectional Study. J Clin Endocrinol Metab 2007 Jun 19;jc.

(76) Howell SJ, Radford JA, Adams JE, Shalet SM. The impact of mild Leydig cell dysfunction following cytotoxic chemotherapy on bone mineral density (BMD) and body composition. Clinical Endocrinology 2000;52:609-16.

(77) Gurgan T, Salman C, Demirol A. Pregnancy and assisted reproduction techniques in men and women after cancer treatment. Placenta 2008 Oct;29 Suppl B:152-9.

(78) Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001 Nov;7(6):535-43.

(79) Haukvik UK, Dieset I, Bjoro T, Holte H, Fossa SD. Treatment-related premature ovarian failure as a long-term complication after Hodgkin's lymphoma. Ann Oncol 2006 Sep;17(9):1428-33.

(80) Botchan A, Hauser R, Gamzu R, Yogev L, Lessing JB, Paz G, et al. Sperm quality in Hodgkin's disease versus non-Hodgkin's lymphoma. Human Reproduction 1997 Jan 1;12(1):73-6.

(81) Fitoussi, Eghbali H, Tchen N, Berjon JP, Soubeyran P, Hoerni B. Semen analysis and cryoconservation before treatment in Hodgkin's disease. Ann Oncol 2000;11(6):679-84.

(82) Rueffer U, Breuer K, Josting A, Lathan B, Sieber M, Manzke O, et al. Male gonadal dysfunction in patients with Hodgkin's disease prior to treatment. Ann Oncol 2001;12(9):1307-11.

(83) Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006;24(18):2917-31.

(84) Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM. Gonadal function following chemotherapy for Hodgkin's disease: a comparative study of MVPP and a seven-drug hybrid regimen. J Clin Oncol 1995;13(1):134-9.

(85) van der Kaaij MAE, Heutte N, Le Stang N, Raemaekers JMM, Simons AHM, Carde P, et al. Gonadal Function in Males After Chemotherapy for Early-Stage Hodgkin's Lymphoma Treated in Four Subsequent Trials by the European Organisation for Research and Treatment of Cancer: EORTC Lymphoma Group and the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2007 Jul 1;25(19):2825-32.

(86) Pryzant RM, Meistrich ML, Wilson G, Brown B, McLaughlin P. Long-term reduction in sperm count after chemotherapy with and without radiation therapy for non-Hodgkin's lymphomas. J Clin Oncol 1993 Feb;11(2):239-47.

(87) Howell SJ, Shalet SM. Effect of cancer therapy on pituitary-testicular axis. International Journal of Andrology 2002;25(5):269-76.

(88) Rowley MJ, Leach DR, Warner GA, Heller CG. Effect of graded doses of ionizing radiation on the human testis. Radiat Res 1974 Sep;59(3):665-78.

(89) Viviani S, Ragni G, Santoro A, Perotti L, Caccamo E, Negretti E, et al. Testicular dysfunction in Hodgkin's disease before and after treatment. European Journal of Cancer 1991;27(11):1389-92.

(90) Whitehead E. The effects of Hodgkin`s Disease and combination chemotherapy on gonadal function in the adult male. Cancer 1982;49:418-22.

(91) Hammond CT, Beckjord EB, Arora NK, Bellizzi KM, Jeffery DD, Aziz NM. Non-Hodgkin's lymphoma survivors' fertility and sexual function-related information needs. Fertil Steril 2008 Oct;90(4):1256-8.

(92) Kornblith AB, Anderson J, Cella DF, Tross S, Zuckerman E, Cherin E, et al. Comparison of psychosocial adaptation and sexual function of survivors of advanced Hodgkin disease treated by MOPP, ABVD, or MOPP alternating with ABVD. Cancer 1992 Nov 15;70(10):2508-16.

(93) Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Spiegel D. Psychosocial problems among survivors of Hodgkin's disease. J Clin Oncol 1986 May;4(5):805-14.

(94) Jonker-Pool G, Hoekstra HJ, van Imhoff GW, Sonneveld DJ, Sleijfer DT, van Driel MF, et al. Male sexuality after cancer treatment--needs for information and support: testicular cancer compared to malignant lymphoma. Patient Educ Couns 2004 Feb;52(2):143-50.

(95) Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999 Feb 10;281(6):537-44.

(96) Aksoy S, Harputluoglu H, Kilickap S, Dincer M, Dizdar O, Akdogan B, et al. Erectile dysfunction in successfully treated lymphoma patients. Support Care Cancer 2008 Mar;16(3):291-7.

(97) Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med 2007 Aug 23;357(8):762-74.

(98) O'Leary MP, Rhodes T, Girman CJ, Jacobson DJ, Roberts RO, Lieber MM, et al. Distribution of the Brief Male Sexual Inventory in community men. Int J Impot Res 2003 Jun;15(3):185-91.

(99) Hill M, Milan S, Cunningham D, Mansi J, Smith I, Catovsky D, et al. Evaluation of the efficacy of the VEEP regimen in adult Hodgkin's disease with assessment of gonadal and cardiac toxicity. J Clin Oncol 1995;13(2):387-95.

(100) Anselmo AP, Cartoni C, Bellantuono P, Maurizi-Enrici R, Aboulkair N, Ermini M. Risk of infertility in patients with Hodgkin's disease treated with ABVD vs MOPP vs ABVD/MOPP. Haematologica 1990;75(2):155-8.

(101) Bonadonna G, Santoro A, Viviani S, Lombardi C, Ragni G. Gonadal damage in Hodgkin's disease from cancer chemotherapeutic regimens. Archives of Toxicology 1984;7:140-5.

(102) Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, DeVita VT. Long-term follow up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. American Journal of Medicine 1981;71(4):552-6.

(103) Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG. The effect of combination chemotherapy on ovarian function in women treated for Hodgkin's disease. Cancer 1983;52(6):988-93.

(104) Hodgson DC, Pintilie M, Gitterman L, Dewitt B, Buckley CA, Ahmed S, et al. Fertility among female hodgkin lymphoma survivors attempting pregnancy following ABVD chemotherapy. Hematol Oncol 2006 Oct 12;25:11-5.

(105) Langeveld NE, Ubbink MC, Last BF, Grootenhuis MA, Voute PA, de Haan RJ. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psychooncology 2003 Apr;12(3):213-25.

(106) Magelssen H, Haugen TB, von D, V, Melve KK, Sandstad B, Fossa SD. Twenty years experience with semen cryopreservation in testicular cancer patients: who needs it? European Urology 2005;48(5):779-85.

(107) Ragni G, Somigliana E, Restelli L, Salvi R, Arnoldi M, Paffoni A. Sperm banking and rate of assisted reproduction treatment: insights from a 15-year cryopreservation program for male cancer patients. Cancer 2003 Apr 1;97(7):1624-9.

(108) Cousineau TM, Domar AD. Psychological impact of infertility. Best Pract Res Clin Obstet Gynaecol 2007 Apr;21(2):293-308.

(109) Cella DF, Bonomi AE. Measuring quality of life: 1995 update. Oncology (Williston Park) 1995 Nov;9(11 Suppl):47-60.

(110) Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Reduced health-related quality of life among Hodgkin's disease survivors: a comparative study with general population norms. Ann Oncol 1999;10(1):71-7.

(111) Loge JH, Abrahamsen AF, Ekeberg O, Hannisdal E, Kaasa S. Psychological distress after cancer cure: a survey of 459 Hodgkin's disease survivors. British Journal of Cancer 1997;76(6):791-6.

(112) Ganz PA, Bower JE. Cancer related fatigue: a focus on breast cancer and Hodgkin's disease survivors. Acta Oncol 2007;46(4):474-9.

(113) Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. J Epidemiol Community Health 1992 Apr;46(2):92-7.

(114) Kornblith AB, Herndon JE, Zuckerman E, Cella DF, Cherin E, Wolchok S, et al. Comparison of psychosocial adaptation of advanced stage Hodgkin's disease and acute leukemia survivors. Cancer and Leukemia Group B. Ann Oncol 1998 Mar;9(3):297-306.

(115) Ruffer JU, Flechtner H, Tralls P, Josting A, Sieber M, Lathan B, et al. Fatigue in long-term survivors of Hodgkin`s lymphoma; a report from the German Hodgkin Lymphoma Study Group (GHSG). European Journal of Cancer 2003 Oct;39(15):2179-86.

(116) Hjermstad MJ, Fossa SD, Oldervoll L, Holte H, Jacobsen AB, Loge JH. Fatigue in long-term Hodgkin's Disease survivors: a follow-up study. J Clin Oncol 2005;23(27):6587-95.

(117) Knobel H, Loge JH, Lund MB, Forfang K, Nome O, Kaasa S. Late Medical Complications and Fatigue in Hodgkin's Disease Survivors. J Clin Oncol 2001 Jul 1;19(13):3226-33.

(118) Loge JH, Abrahamsen AF, Ekeberg, Kaasa S. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. Journal of Pain & Symptom Management 2000;19(2):91-9.

(119) Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. Journal of Psychosomatic Research 1993;37:147-53.

(120) O'Leary MP, Fowler FJ, Lenderking WR, Barber B, Sagnier PP, Guess HA, et al. A brief male sexual function inventory for urology. Urology 1995 Nov;46(5):697-706.

(121) Mykletun A, Dahl AA, O'Leary MP, Fossa SD. Assessment of male sexual function by the Brief Sexual Function Inventory. BJU Int 2006 Feb;97(2):316-23.

(122) Dahl AA, Bremnes R, Dahl O, Klepp O, Wist E, Fossa SD. Is the sexual function compromised in long-term testicular cancer survivors? Eur Urol 2007 Nov;52(5):1438-47.

(123) Mykletun A, Stordal E, Dahl AA. Hospital Anxiety and Depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. The British Journal of Psychiatry 2001 Dec 1;179(6):540-4.

(124) Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-70.

(125) Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol 1998 Nov;51(11):903-12.

(126) Ware JE, Jr. SF-36 health survey update. Spine (Phila Pa 1976) 2000 Dec 15;25(24):3130-9.

(127) Ware JE., Gandek B, Kosinski M, Aaronson NK, Apolone G, Brazier J, et al. The Equivalence of SF-36 Summary Health Scores Estimated Using Standard and Country-Specific Algorithms in 10 Countries: Results from the IQOLA Project. Journal of Clinical Epidemiology 1998 Nov;51(11):1167-70.

(128) Howell SJ, Shalet SM. Testicular function following chemotherapy. Human Reproduction Update 2001;7(4):363-9.

(129) Pintilie M. Competing Risks: A Practical Perspective. Wiley; 2006.

(130) Cohen J. Statistical power Analysis for the Behavioral Sciences. New Jersey: Lawrence erlbaum Associates Inc, Publishers; 1988.

(131) Lipsey MW. Practical meta-analysis. Thousand Oakes, CA: SAGE; 2001.

(132) Svartberg J, Midtby M, Bonaa KH, Sundsfjord J, Joakimsen RM, Jorde R. The associations of age, lifestyle factors and chronic disease with testosterone in men: the Tromso Study. Eur J Endocrinol 2003 Aug 1;149(2):145-52.

(133) Fossa SD, Magelssen H. Fertility and reproduction after chemotherapy of adult cancer patients: malignant lymphoma and testicular cancer. Ann Oncol 2004;15:Suppl-65.

(134) Benestad HB, Laake P. Forskningsmetode i medisin og biofag (Norwegian). 1 ed. 2004.

(135) Engert A, Diehl V, Franklin J, Lohri A, Dorken B, Ludwig WD, et al. Escalated-Dose BEACOPP in the Treatment of Patients With Advanced-Stage Hodgkin's Lymphoma: 10 Years of Follow-Up of the GHSG HD9 Study. J Clin Oncol 2009 Aug 24;JCO.

(136) Lampe H, Horwich A, Norman A, Nicholls J, Dearnaley DP. Fertility after chemotherapy for testicular germ cell cancers. J Clin Oncol 1997 Jan 1;15(1):239-45.

(137) Sieniawski M, Reineke T, Nogova L, Josting A, Pfistner B, Diehl V, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG). Blood 2008 Jan 1;111(1):71-6.

(138) Nord C, Bjoro T, Ellingsen D, Mykletun A, Dahl O, Klepp O, et al. Gonadal Hormones in Long-Term Survivors 10 Years after Treatment for Unilateral Testicular Cancer. European Urology 2003 Sep;44(3):322-8.

(139) Bjerner J, Biernat D, Foss+Ñ SD, Bj+©ro T. Reference intervals for serum testosterone, SHBG, LH and FSH in males from the NORIP project. Scandinavian Journal of Clinical & Laboratory Investigation 2009;0(0):1-7.

(140) Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, et al. Prevalence of symptomatic androgen deficiency in men. Journal of Clinical Endocrinology and Metabolism 2007;92(11):4241-7.

(141) Huddart RA, Norman A. Changes in BMI after treatment of testicular cancer are due to age and hormonal function and not chemotherapy. British Journal of Cancer 2003.

(142) Ahn HS, Park CM, Lee SW. The clinical relevance of sex hormone levels and sexual activity in the ageing male. BJU Int 2002 Apr;89(6):526-30.

(143) Yeap BB. Are declining testosterone levels a major risk factor for ill-health in aging men? Int J Impot Res 2009 Jan;21(1):24-36.

(144) Howell SJ, Radford JA, Smets EM, Shalet SM. Fatigue, sexual function and mood following treatment for haematological malignancy: the impact of mild Leydig cell dysfunction. British Journal of Cancer 2000.

(145) Buvat J, Bou JG. Significance of hypogonadism in erectile dysfunction. World J Urol 2006 Dec;24(6):657-67.

(146) Tesauro GM, Rowland JH, Lustig C. Survivorship resources for post-treatment cancer survivors. Cancer Pract 2002 Nov;10(6):277-83.

(147) Huyghe E, Sui D, Odensky E, Schover LR. Needs assessment survey to justify establishing a reproductive health clinic at a comprehensive cancer center. J Sex Med 2009 Jan;6(1):149-63.

(148) Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 1996;87(7):3045-52.

(149) Carter A, Robison LL, Francisco L, Smith D, Grant M, Baker KS, et al. Prevalence of conception and pregnancy outcomes after hematopoietic cell transplantation: report from the Bone Marrow Transplant Survivor Study. Bone Marrow Transplantation 2006;37(11):1023-9.

(150) Le FO, Donaldson SS, Kaplan HS. Pregnancy following oophoropexy and total nodal irradiation in women with Hodgkin's disease. Cancer 1976;38(6):2263-8.

(151) Woolf SH. The Meaning of Translational Research and Why It Matters. JAMA 2008 Jan 9;299(2):211-3.

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Mortality is persistently increased in Hodgkin's lymphoma survivors and highest among the non-responders in a previous survey.

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Abstract

Background

Negative health outcomes of chronic fatigue (CF) in disease-free cancer survivors are mainly unexplored. Aims of this study were to examine mortality and causes of death in Hodgkin's lymphoma survivors (HLSs) compared to controls from the general population, and to explore if CF was associated with increased mortality.

Methods

HLSs (n=557) invited to participate in a survey on late effects in 1994 were divided into three groups: participants without CF (n=329), participants with CF (n=113), non-participants (n=98). Controls matched for gender and age were drawn from the general population (five per HLSs, n=2785). Observation time was calculated from January 1st 1994 until date of death or cut-off at January 1st 2007. Kaplan-Meier plots were used for univariate analyses and Cox models for multiple covariates.

Results

Compared to controls HLSs had nearly five times higher mortality (HR=4.93; 95%CI:3.91-6.21) and the mortality rate of HLSs was higher than the rate of their controls for the entire observation period. Mortality was increased in all groups: participants with CF: HR= 4.85 (95%CI:3.02-7.77), participants without CF: HR=4.35 (95%CI: 3.16-6.00), non-participants: HR= 9.45 (95%CI:5.44-16.41).

Compared to the controls HLSs had over six times increased mortality of cancer (HR: 6.6, 95%CI: 4.7-9.2) and almost five times increased mortality of cardiovascular diseases (HR: 4.9, 95%CI: 3.1-7.9).

Conclusions

HLSs had almost five-time increased mortality compared to controls. CF was not associated with increased mortality rate. The high mortality among the non-participating HLSs indicates that serious health problems are underestimated in this group. This has implications for the interpretation of surveys in cancer survivors.

Keywords: Hodgkin's lymphoma, mortality, causes of death, matched controls, fatigue

Introduction

Long-term survivors after Hodgkin's lymphoma (HL) are at increased risk of different morbidities after treatment, such as second cancers, cardiovascular diseases, hormonal dysfunction and infertility (1-9). Previous studies have shown that Hodgkin's lymphoma survivors (HLSs) also have increased mortality when compared to expected death rates in the general population (2, 10-12). Few studies have examined mortality in HLSs observed for more than 12 years (2). Patients treated for HL before the age of 41 years in the period 1965-1987 (median follow-up 17.8 years, n=1261) were reported to have a 6.8 times higher relative risk (RR) of death from all causes other than HL compared to the general population (2). Another survey reported that the RR of mortality from all causes remained significantly elevated more than 20 years after treatment for stage IA-IIB HL (n=1080) (10). The most common causes of deaths are reported to be relapse of HL, second cancers, cardiovascular diseases and infections (2, 10). In addition, HLSs have been shown to have increased levels of fatigue persisting several years after treatment (13, 14).

The present study is based on a cohort of 557 HLSs included in a survey in 1994 on long-term effects including the presence of chronic fatigue (CF) (15, 16). The HLSs were treated at the Norwegian Radium Hospital (NRH) from 1971-1991 and were considered to be in complete remission when included in the survey in 1994. The main finding among the responding HLSs was that 26% had CF after a median observation time of 12 years, compared to 11% of controls representative of the general Norwegian population (16). Uncertainty exists as to the causes of CF in HLSs, and one might speculate whether it reflects aspects of the disease itself such as altered cytokine levels or immune dysfunction which can exert long-term negative health effects. Knowledge about possible negative impact of CF upon somatic health outcomes is lacking, and no study has investigated the association between CF and future significant health events such as mortality in cancer survivors. In addition, to our knowledge, no studies in cancer survivors have investigated mortality in participants versus non-participants in questionnaire surveys.

Thus, the main objectives of this study were as follows:

1. To examine mortality and causes of death in a defined cohort of HLSs who were considered to be disease-free when surveyed in 1994 (15, 16) and compare the mortality to a control group from the general population matched for age and gender.
2. To examine whether HLSs with CF in 1994 display increased mortality compared to HLSs without CF and the non-participants from the same survey (16).

Patients and Methods

Subjects

The eligibility criteria for the cross-sectional survey in 1994 were HLSs treated at the NRH from 1971-1991, aged 15-61 years at diagnosis and aged 19-74 at the time of the survey, alive and in complete remission by the end of 1993, with only a small percentage of the patients treated for relapse (15, 16). In the period 1970-1980 the treatment of HL in Norway was centralized to the NRH, and 92% of patients aged 15-39 years and 80% of patients aged 40-59 years were admitted to the hospital. Since 1981 four other national oncological centers gradually began to treat HL (17). After 1985 all HL patients from a defined region constituting about 50% of the Norwegian population have been referred to the hospital. The treatment of HL at the NRH in the period 1971-1991 followed international guidelines and have been described previously (1, 15, 16, 18). Stage I/II were treated with extended radiation fields (Mantle/Inverted-Y field) alone or after chemotherapy. Stage III/IV was treated with eight chemotherapy courses, with radiation to sites of initial bulky tumor or residual masses from 1980. Chemotherapy was given as MVPP/ChlVPP, gradually replaced by ABVD from 1985.

In 1994, 557 patients were contacted by mail and 459 returned the completed questionnaire. The main outcome was self-reported health status including fatigue (16, 19, 20). Fatigue was assessed by Fatigue Questionnaire (FQ) (21) which measures physical fatigue (7 items) and mental fatigue (4 items). The sum of all items is designated total fatigue. Two additional items cover the duration and extent of fatigue. The prevalence of CF was assessed as described and required substantial fatigue for 6 months or more at time of assessment (16).

Based on findings from the 1994 survey the HLSs were categorized in three groups: participants without CF (No-CFgroup,n=329), participants with CF (CFgroup,n=113), and non-participants who did not return the questionnaire (Non-Partgroup,n=98), 17 patients had invalid FQ and were not categorized. Medical information on the HLSs was retrieved from the lymphoma database of the NRH. Age at diagnosis was divided into four groups: 15-21 years, 22-30 years, 31-40 years, 41-60 years.

Controls

A control group was constructed by randomly drawing five controls per patient from the general population matched for gender and age. The draw was performed by Statistics Norway (SSB). The controls had to be alive on 31.12.1993, as were the HLSs at inclusion in the 1994-survey. For both the HLSs and the controls date of death and causes of death were

retrieved from the Statistics for Causes of Deaths, Statistics Norway (SSB). Causes of deaths were categorized into three groups: 1: tumor (all malignant diagnosis), 2: cardiovascular disease, 3: other (including infections, diabetes, pulmonal diseases, gastrointestinal diseases, traumas, diseases in the urinary system, diseases in the musculo-skeletal system, psychiatric diseases. In case of deaths from tumors, these were subdivided in two: 1: malignant lymphomas and 2: other malignancies, including solid tumors, multiple myeloma and leukemias.

Statistics

Continuous variables were described using median and range, whereas categorical data were described with proportions. Crude differences in categorical variables were assessed with Chi-square tests, whereas continuous variables were analyzed with Mann-Whitney-Wilcoxon tests. Observation time for survival analyses was calculated from January 1st 1994 until date of death or to cut-off at January 1st 2007. Crude cumulative probability of survival was calculated using the Kaplan-Meier method and the groups compared with log-rank tests. Cox proportional hazard regression models stratified by the matched group were used for univariate and multivariate analyses. The proportionality of hazards assumption was investigated using log minus log plots.

The three groups of HLSs were compared to the matched control groups in separate analyses. Considering the HLSs only, possible predictors of death were first investigated in univariate analyses. Secondly, statistically significant variables (age at diagnosis, period of treatment, treatment and patient group (No-CFgroup, CFgroup, Non-Partgroup)) were entered into a multiple model.

The cumulative probability of dying was computed using a competing risk approach (22) with death causes divided into four categories:1: malignant lymphomas; 2:other cancers; 3:cardiovascular diseases and 4: other causes of death.

A p-value$\leq$ 0.05 (two-sided) was considered statistically significant. All analyses were performed with SPSS 16 and Stata version 10.

Ethical considerations

The Regional Committee for Medical Research Ethics, Health Region South, Norway approved the study.

Results

Patients' characteristics

Of the 557 HLSs who were approached in 1994, 43% were female. Median age at diagnosis was 30 years (range 15-60) and median age at survey in 1994 was 43 years (range 19-74) (**Table 1**). The median observation time from diagnosis to the survey in 1994 was 12.2 years (range 2.3-23.0 years). Seventy-eight percent were treated with mantle field or mediastinal radiotherapy with or without chemotherapy. The CFgroup had a higher median age at diagnosis than the two other subgroups ($p<0.01$), whereas there were no statistically significant differences in gender, period of diagnosis, primary stage or treatment among the three groups of HLSs. For further details on the patient cohort, see previous publications (15, 16).

All cause mortality in HLSs versus controls

By January1st 2007 death had occurred in 149 of the 557 HLSs (27%), 72 deaths in the No-CFgroup (22%), 35 deaths in the CFgroup (31%) and 38 deaths in the Non-Partgroup (39%). In comparison, 197 (7%) deaths had occurred among the controls (**Table 1**). Mortality among all HLSs was significantly increased compared to the controls, the HLSs were almost five-times more likely to die (HR: 4.93 [95% CI: 3.91-6.21]). The mortality rate of patients was higher than the rate of their controls throughout the entire observation period **Table 2 and Figure 1a**.

When comparing each patient group to its matched control group, the CFgroup had an increased mortality rate of 4.85 [95%CI: 3.02-7.77], whereas the No-CFgroup had an increased mortality rate of 4.35 [95%CI: 3.16-6.00]. The comparable figures for the Non-Partgroup were 9.45 [95% CI: 5.44-16.41] (**Table 2 and Figure 1b**).

Factors associated with mortality within the HLSs

In univariate analyses both the CFgroup (HR: 1.54, [95%CI: 1.03-2.31]) and the Non-Partgroup (HR: 2.04, [95%CI: 1.37-3.02]) had increased mortality rate compared to No-CFgroup (**Table 3**). When comparing overall mortality ratio in the Non-Partgroup to all participants (with and without CF) the HR for the Non-Partgroup was almost doublet (HR: 1.8 [95%CI: 1.24-2.60]).

Patients treated with mantle field or mediastinal radiotherapy had a two-fold increased mortality rate compared to patients treated with chemotherapy only (HR: 2.02, [95%CI: 1.09-

3.74]). Compared to those diagnosed in the period 1981-1990, patients diagnosed in 1971-1980 had increased mortality rate (HR: 2.46, [95% CI: 1.76-3.44]).

Multivariate analysis revealed that the Non-Partgroup had a two-fold increased risk of mortality (HR: 2.05, [95%CI: 1.37-3.07]) compared to the No-CFgroup. No statistically significant difference was observed between the participants with and without CF. Treatment group remained significant with patients treated with radiotherapy with or without chemotherapy having about three times higher mortality risk than those treated with chemotherapy only. Patients diagnosed before 1981 had increased risk of mortality compared to those diagnosed from 1981 onwards (HR: 1.56, [95%CI: 1.10-2.27]).

Causes of deaths

Among the HLSs 83 of the 149 (56%) deaths were caused by malignant disease and 36 (24%) were caused by cardiovascular diseases. Among the controls 41% (81/197) of the deaths were caused by malignant diseases and 25% (50/197) by cardiovascular diseases **(Table 4a).** Overall, the risk of dying of cancer or all other causes was always higher for HLSs compared to their controls, as depicted in **Figure 2**. Compared to the controls, the HLSs had more than six times increased mortality of cancer (HR: 6.6, 95%CI 4.7-9.2) and almost five times increased mortality of cardiovascular disease (HR: 4.9, 95%CI: 3.1-7.9) **(Table4b)**. No differences between the predefined patient groups in regard to causes of deaths were observed (data not shown).

Among the HLSs who died of malignant diseases, 33 of these deaths were caused by malignant lymphomas (of which 21 by HL) and 50 by other cancer types (pulmonary cancer: n=20, cancer in the gastrointestinal tract: n=11, breast cancer: n = 3, leukemia / multiple myoloma: n=3). Deaths due to malignant lymphomas occurred significantly earlier than deaths by secondary solid tumors (data not shown).

Discussion

In the present study mortality and causes of death were examined in an unselected cohort of disease-free HLSs included in a previous questionnaire survey (16). The present study provides new information on mortality and causes of death in HLSs due to a substantially longer follow-up period than previous studies (10-12), with a median observation time of 12 years from diagnosis to the survey in 1994, and thereafter observation until 2007. Compared to the controls, the HLSs had almost five times higher mortality, and the mortality rate of patients was higher than the rate of their controls throughout the entire observation period. In the multivariate analysis, the presence of CF was not significantly associated with increased mortality among the HLSs who participated in the 1994-survey, but the Non-Partgroup displayed a two-fold increased mortality compared to the No-CFgroup.

The cross-sectional nature of the 1994-survey makes the patient group biased with regard to survival compared to other studies on mortality in HLSs, because only HLSs alive in 1994 were included. Nevertheless, the survival in the 1994 cohort after 13 years of additional observation time was 73%, which is comparable to figures reported from other studies (2, 11). A ten year overall survival of 75% was reported when investigating 1261 patients treated for HL in the period 1965-1987 (2). However, that patient cohort included only patients treated at age less than 41 years at diagnosis, whereas our sample included patients up to 60 years at diagnosis (2). Ng et al found a somewhat higher 15-year survival rate of 84% in their patients treated for early-stage HL at age 50 or younger (10).

There was almost a five-fold increase in mortality risk among the HLSs compared to the control group from the general population. This number is slightly lower than the increased RR of mortality of 6.4 and 6.8 found in other studies (2, 10). In comparison, Provencio et al reported the mortality rate among patients treated for HL to be >10-fold higher than mortality rates from the general population (11). Methodologically, these earlier studies explored the standardized mortality ratio; the ratio between the observed deaths in the cohort and the expected number of deaths if the cohort had the same mortality rate as the general population (2, 10, 11). In contrast, our control group was constructed by drawing five persons per HLSs from the general population matched for age and gender, and both the HLSs and controls were followed to either death or time for cut-off. The use of matched controls selected from the general population provides an intuitively understandable interpretation of the results. Moreover, having 5 controls per patient ensured a high level of efficiency and precision of our estimates (23).

At inclusion in the 1994-survey, the patients were considered to be in complete remission. However, the observation time from diagnosis to inclusion in 1994 had a wide time span from 2-23 years (median 12 years) and makes the patient group heterogeneous, with patients with the shortest observation time from diagnosis to the 1994-survey having higher risk for relapse than patients with longer observation time.

Of particular interest, a two-fold increased risk of mortality among the Non-Partgroup compared to the No-CFgroup was observed. To our knowledge, such an association between the willingness/ability to respond to a questionnaire survey and a central health outcome has not been described in cancer survivors earlier. However, epidemiological studies have indicated impaired health status and higher mortality in groups of non-responders (24, 25). The observation of increased mortality among the Non-Partgroup indicates that impaired health may explain why some HLSs did not respond to the questionnaire survey in 1994. A possible burden in the Non-Partgroup as to having more symptoms and impaired physical health may imply that adverse health effects in HLSs might be underestimated in follow-up surveys. This finding needs to be confirmed and explored by further examinations, also in other groups of cancer survivors.

In univariate analysis, increased mortality in the CFgroup compared to the No-CFgroup was observed. However; this difference disappeared in the multivariate analysis, probably reflecting confounding by age, since, in 1994, the CFgroup were significantly older than the No-CFgroup. The finding of similar mortality in HLSs with and without CF is of clinical importance, as it indicates that CF itself is not associated with life-threatening somatic morbidity. Theoretically, HLSs with CF might have had more intense follow-up due to their condition than the HLSs without CF with possible beneficial effects upon morbidity and mortality. However, no special programs for HLSs with CF have been running during the observation period, and in our opinion a possible bias related to this can therefore be excluded.

Patients diagnosed in the period 1971-1980 had increased mortality rate compared to those diagnosed in the period 1981-1991 both in univariate and multivariate analyses, which is comparable to earlier findings (11). This observation may be due to more toxic treatment in the first period, particularly caused by the use of larger radiation fields, and/or better treatment options in the latter period. Another explanation is improved histopathological diagnosis; some lymphomas classified as HL in the earliest period, especially of the lymphocyte depleted and unclassified subtypes in the elderly (considered to be associated with poor prognosis), probably have been classified as NHL during the second period (17).

Malignant diseases and cardiovascular diseases were the most frequent causes of deaths among the HLSs, which is similar to earlier reports (2, 10). Mortality of cancer was more than six times higher in HLSs compared to the control group, and almost five times higher for cardiovascular diseases. This is comparable to the RR of deaths resulting from solid tumors reported to be 6.6 and cardiovascular disease reported to be 6.3 in 1261 patients treated for HL before age 41 (2). In comparison, Ng et al reported the RR of excess mortality from second tumors to be 11.2 and 3.2 from cardiovascular diseases in their cohort of 1080 HLSs (10).

The treatment of the patients in the described cohort is no longer standard therapy, as the treatment for HL has been modified in order to avoid long-term effects without reducing the very good survival rates. Mantle field irradiation is no longer used as standard therapy, and for chemotherapy, MOPP-like regimens have to a large extent been abandoned. Nevertheless, it is of importance to study the morbidity and mortality after treatment with these regimens because a large number of survivors after such treatment are still alive. In addition, patients today still receive radiotherapy, albeit to smaller volumes and with lower doses, and chemotherapy regimens used today, such as ABVD and BEACOPP, still contain many of the same compounds as did earlier regimens. In a recently published study comparing overall survival (OS) after treatment for advanced stage HL (median follow-up 111 months), OS was significantly improved after treatment with escalated-dose BEACOPP compared to COPP/ABVD and standard BEACOPP (26). However, a higher number of acute myeloid leukemia and myelodysplastic syndrome in the dose-escalated BEACOPP arm was observed, whereas there were no differences in the total number of secondary malignancies between the treatment arms (26). This emphasizes the importance of clinicians being aware of possible long-term complications after curative treatment for HL and provides the best follow-up care as possible.

Overall, we showed that in this cohort of HLSs, assumed to be in complete remission in 1994, the overall mortality risk was almost five times higher than for matched controls from the general population. This raises the question whether the total long-term mortality is a better estimate of successful treatment of HL, than specific mortality of HL.

Table 1.
Patients characteristics, Hodgkin lymphoma sample n=557, Control sample n=2785.

	All HLSs	No-CFgroup*	CFgroup*	Non-partgroup*	Controls
	N=557	N=329	N=113	N=98	N=2785
Age at diagnosis (years)[1]					
Median (range)	30 (15-60)	28 (15-60)	**33** (15-60)	28 (15-60)	
Age at survey 1994 (years) [2]					
Median (range)	43 (19-74)	41 (19-74)	46 (21-74)	41 (20-72)	
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gender					
Male	320 (57)	187 (57)	60 (53)	65 (66)	
Female	237 (43)	142 (43)	53 (47)	33 (34)	
Period of diagnosis					
1971 - 1980	242 (43)	132 (40)	50 (44)	50 (51)	
1981 – 1991	315 (57)	197 (60)	63 (56)	48 (49)	
Treatment group					
1. Chemotherapy only	73 (13)	40 (12)	15 (13)	16 (17)	
2. Radiotherapy including mediastinum ± chemotherapy	429 (78)	256 (80)	88 (79)	73 (76)	
3. Radiotherapy not including mediastinum ± chemotherapy	45 (8)	26 (8)	9 (8)	7 (7)	
Primary stage					
I / IIA	269 (48)	165 (50)	50 (44)	45 (46)	
I / IIB	67 (12)	32 (10)	21 (19)	13 (13)	
III / IV A	104 (19)	61 (19)	24 (21)	16 (16)	
III / IV B	117 (21)	71 (22)	18 (16)	24 (25)	
Mortality[3]					
Alive	408 (73)	257 (78)	78 (69)	60 (61)	2588 (93)
Dead	149 (27)	72 (22)	35 (31)	38 (39)	197 (7)

CF:chronic fatigue
No-CF group: Participants without CF
CF group: Participants with CF
Non-Partgroup: Non-participants
[1]participants with CF higher median age at diagnosis than the two other subgroups of HLSs ($p<0.01$).
[2] participants with CF higher median age at survey 1994 than participants without fatigue ($p<0.001$)
[3] Mortality at cut-off January 1st 2007

Table 2.
All cause mortality in Hodgkin lymphoma sample versus controls.

Hodgkin lymphoma sample versus controls	HR	95% CI
Controls (n=2785)	reference	
HLSs (n=557)	4.93	3.91-6.21
Each patient group versus the equivalent control group	**HR**	**95% CI**
Non-Partgroup (n=98)	9.45	5.44-16.41
CF group (n=113)	4.85	3.02-7.77
No-CF group (n=329)	4.35	3.16-6.00

Non-Partgroup: Non-participants
CFgroup: Participants with CF
No-CF group: Participants without CF
CF:chronic fatigue

Table 3.
Uni- and Multivariate analyses of predictors for deaths among HLSs (n=540)

Within the cohort of HLSs (n=540)				
	Univariate Cox model		Multivariate Cox model	
Variable	**HR univariate COX**	**95% CI**	**HR multivariate Cox**	**95%CI**
Patient groups				
No-CFgroup	reference		reference	
CFgroup	1.54	1.03-2.31	1.31	0.87-1.97
Non-Partgroup	2.04	1.37-3.02	2.05	1.37-3.07
Treatment groups				
Chemotherapy only	reference		reference	
Radiotherapy including mediast	2.02	1.09-3.74	2.94	1.29-6.97
Radiotherapy not including mediast	1.88	0.81-4.33	3.00	1.56-5.53
Period of diagnosis				
1971 – 1980	2.46	1.76-3.44	1.56	1.10-2.27
1981 - 1991	reference		reference	
Age at diagnosis				
15-21 years	reference		reference	
22-30 years	2.78	1.37-5.62	2.44	1.15-5.20
31-40 years	4.71	2.37-9.36	3.87	1.83-8.20
41-60 years	11.19	5.71-21.94	11.55	5.54-24.09

Non-Partgroup: Non-participants
CFgroup: Participants with CF
No-CF group: Participants without CF
CF:chronic fatigue
HLSs:Hodgkin's lymphoma survivors

Table4a. Causes of deaths in HLSs (n=557) and controls (n=2785).

Group	Malignant disease		Cardiovascular disease	Other
Controls (N=2785) Dead by Jan 1st 2007 n=197 (7%)	**81 (3%)**		**50 (2%)**	**66 (2%)**
% of this group				
All HLSs (N=557)	**83 (15%)**		**36 (6%)**	**30 (5%)**
Dead by Jan 1st 2007 n=149 (27%)	**Malignant Lymphoma**	**Other cancers**		
% of this group	**33 21 HL / 12 NHL**	**50**		
No-CFgroup N=329 Dead by Jan 1st 2007 n=72 (22%)	**46 (14%)**		**16 (5%)**	**10 (3%)**
% of this group	**Malignant Lymphoma**	**Other cancers**		
	19	**27**		
CFgroup N=113 Dead by Jan 1st 2007 n=35 (31%)	**15 (13%)**		**11 (10%)**	**9 (8%)**
% of this group	**Malignant Lymphoma**	**Other cancers**		
	3	**12**		
Non-Partgroup N=98 Dead by Jan 1st 2007 n=38 (39%)	**20 (20%)**		**7 (7%)**	**11 (11%)**
% of this group	**Malignant Lymphoma**	**Other cancers**		
	10	**10**		

Non-Partgroup: Non-participants
CF group: Participants with CF
No-CF group: Participants without CF
CF: chronic fatigue
HLSs: Hodgkin's lymphoma survivors

Table4b
HR and 95%CI for the various causes of deaths comparing all HLSs (n=557) to controls (n=2785).

Hodgkin lymphoma sample versus controls	HR	95% CI	p-value
Cancer	**6.6**	**4.7-9.2**	**<0.001**
Cardiovascular disease	**4.9**	**3.1-7.9**	**<0.001**
Other	**2.9**	**1.9-4.7**	**<0.001**

HLSs: Hodgkin's lymphoma survivors

Figure 1a

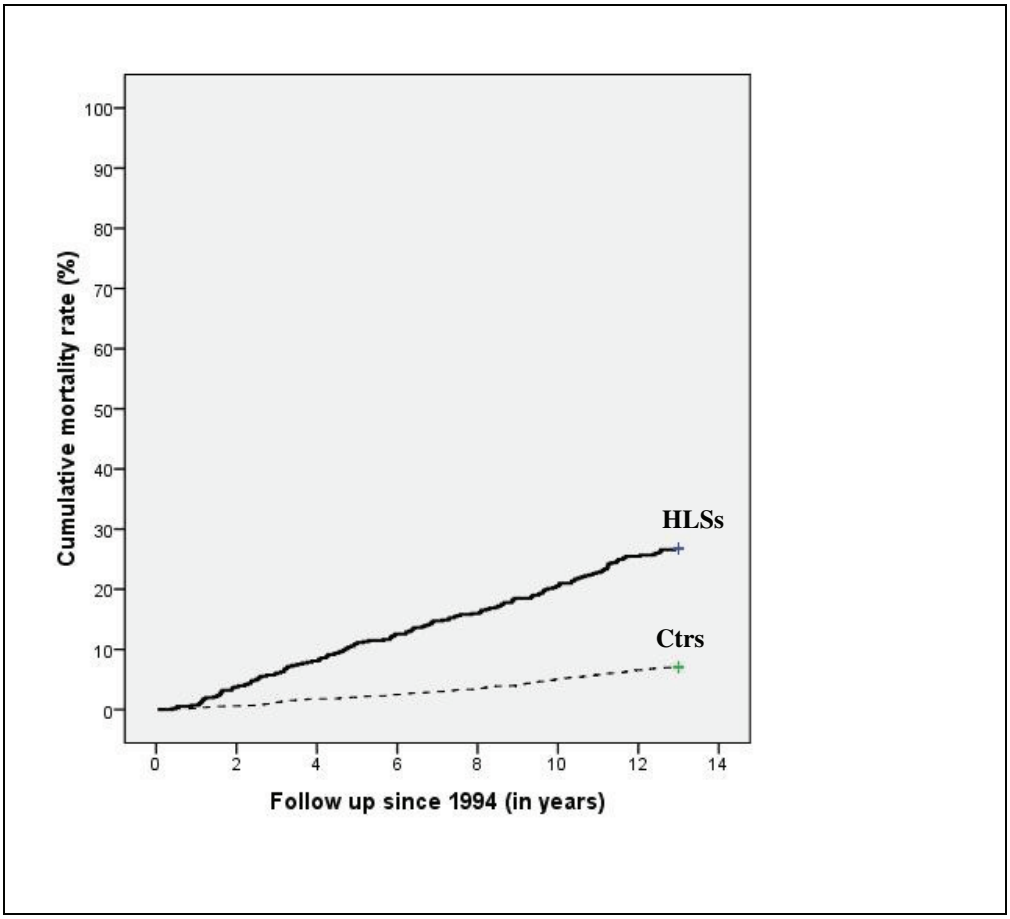
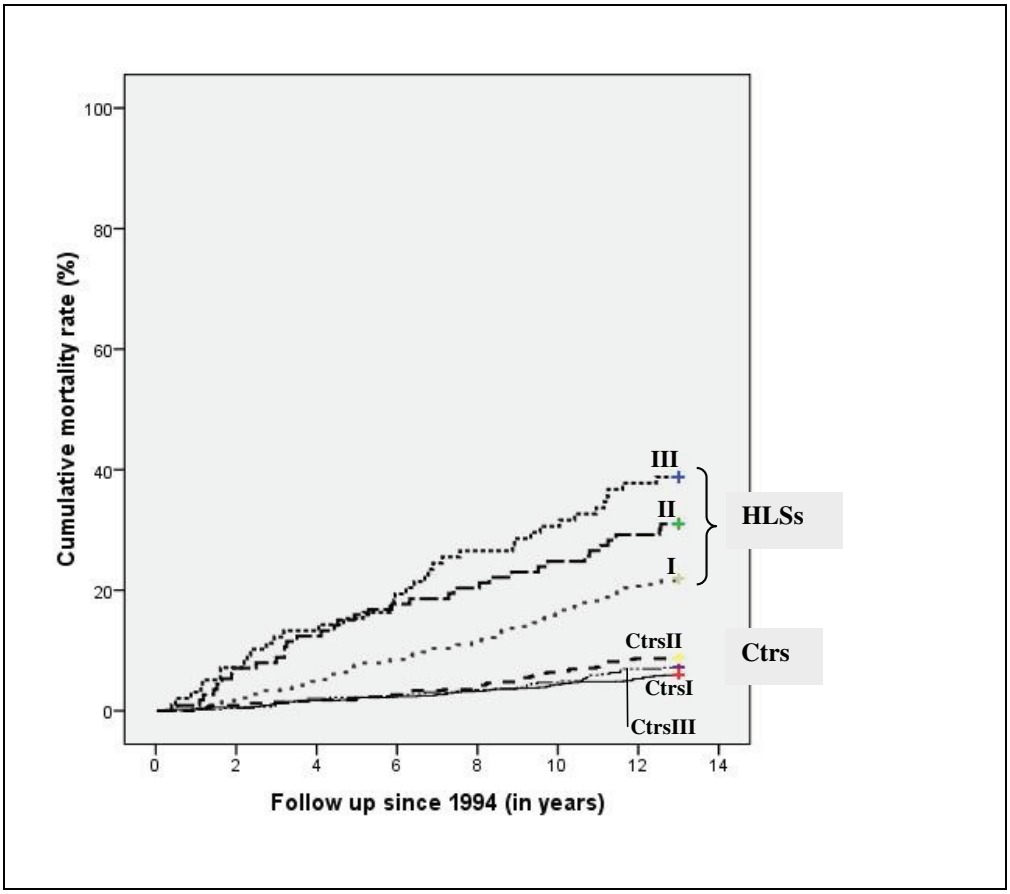


Figure1a
Cumulative overall mortality rate in Hodgkin lymphoma sample (HLSs, n=557) and controls (n=2785)

Figure1b



Legends Figure 1b.
Cumulative mortality rate in HLSs related to patient group and the relevant control groups.
All patient groups displayed increased mortality compared to their controls ($p<0.001$).
HLSs: I: Participants without chronic fatigue (CF) n=329
II: Participants with CF, n =113
III: Non participants, n=98
Ctrs: controls
CtrsI: controls to participants without CF, n=1645
CtrsII: controls to participants with CF, n=565
CtrsIII: controls to non-participants, n=490

Figure2

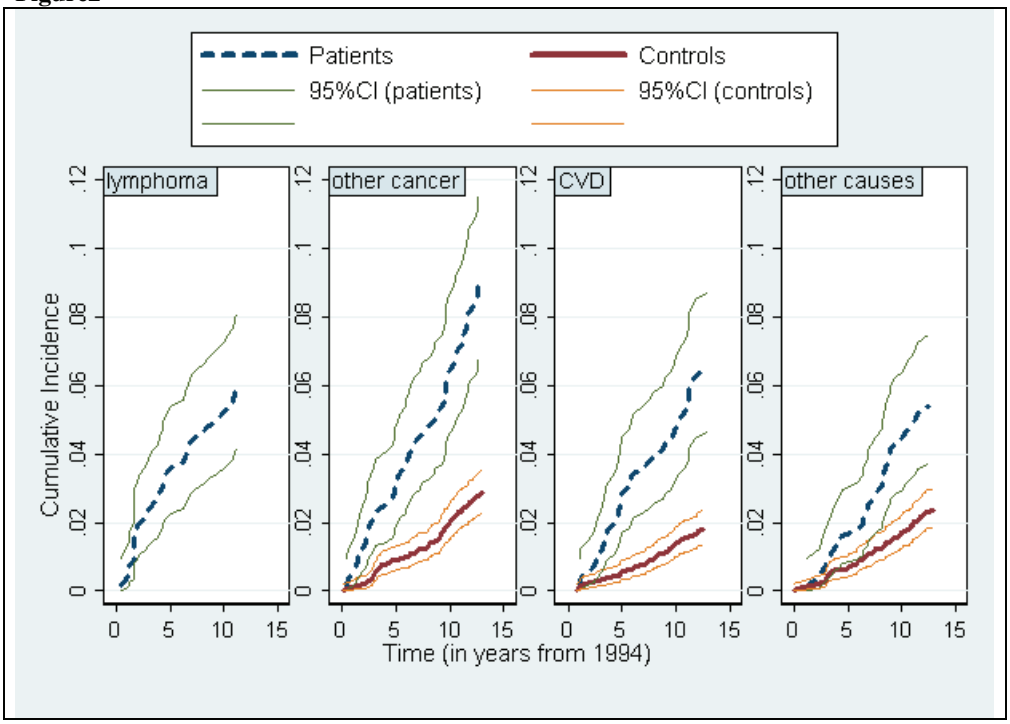


Figure2.
Plot of competing causes of deaths among HLSs and controls.

Reference List

(1) Abrahamsen AF, Loge JH, Hannisdal E, et al. Late medical sequelae after therapy for supradiaphragmatic Hodgkin's disease. *Acta Oncologica* 1999,38(4), 511-515.

(2) Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 2003,21(18), 3431-3439.

(3) Aleman BMP, van den Belt-Dusebout A, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007 Mar 1,109(5), 1878-1886.

(4) Behringer K, Breuer K, Reineke T, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2005,23(30), 7555-7564.

(5) Hodgson DC, Gilbert ES, Dores GM, et al. Long-Term Solid Cancer Risk Among 5-Year Survivors of Hodgkin's Lymphoma. *J Clin Oncol* 2007 Apr 20,25(12), 1489-1497.

(6) Howell SJ, Radford JA, Ryder WD, Shalet SM. Testicular function after cytotoxic chemotherapy: evidence of Leydig cell insufficiency. *J Clin Oncol* 1999,17(5), 1493-1498.

(7) Howell SJ, Radford JA, Adams JE, Shalet SM. The impact of mild Leydig cell dysfunction following cytotoxic chemotherapy on bone mineral density (BMD) and body composition. *Clinical Endocrinology* 2000,52, 609-616.

(8) Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular Dysfunction and Carotid, Subclavian, and Coronary Artery Disease in Survivors of Hodgkin Lymphoma Treated With Radiation Therapy. *JAMA* 2003 Dec 3,290(21), 2831-2837.

(9) Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. *European Journal of Cancer & Clinical Oncology* 1985,21(5), 601-605.

(10) Ng AK, Bernardo MP, Weller E, et al. Long-Term Survival and Competing Causes of Death in Patients With Early-Stage Hodgkin's Disease Treated at Age 50 or Younger. *J Clin Oncol* 2002 Apr 15,20(8), 2101-2108.

(11) Provencio M, Millan I, Espana P, et al. Analysis of Competing Risks of Causes of Death and their Variation Over Different Time Periods in Hodgkin's Disease. *Clin Cancer Res* 2008 Aug 15,14(16), 5300-5305.

(12) Favier O, Heutte N, Stamatoullas-Bastard A, et al. Survival after Hodgkin lymphoma: causes of death and excess mortality in patients treated in 8 consecutive trials. *Cancer* 2009 Feb 10.

(13) Kornblith AB, Herndon JE, Zuckerman E, et al. Comparison of psychosocial adaptation of advanced stage Hodgkin's disease and acute leukemia survivors. Cancer and Leukemia Group B. *Ann Oncol* 1998 Mar,9(3), 297-306.

(14) Ruffer JU, Flechtner H, Tralls P, et al. Fatigue in long-term survivors of Hodgkin`s lymphoma; a report from the German Hodgkin Lymphoma Study Group (GHSG). *European Journal of Cancer* 2003 Oct,39(15), 2179-2186.

(15) Abrahamsen AF, Loge JH, Hannisdal E, Holte H, Kvaloy S. Socio-medical situation for long-term survivors of Hodgkin's disease: a survey of 459 patients treated at one institution. *European Journal of Cancer* 1998,34(12), 1865-1870.

(16) Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol* 1999,17(1), 253-261.

(17) Abrahamsen A.F., Egeland T, Hansen S, Langholm R, Holte H, Kvaloy S. Hodgkin's disease in a national and hospital population: trends over 20 years. *European Journal of Cancer* 1997,33(14), 2380-2383.

(18) Holte H, Mella O, Wist E, Telhaug R, Hannisdal E, Abrahamsen AF. ChlVPP is as effective as alternating ChlVPP/ABOD in advanced stage Hodgkin's disease. *Acta Oncologica* 1996,35, Suppl-80.

(19) Loge JH, Abrahamsen AF, Ekeberg O, Hannisdal E, Kaasa S. Psychological distress after cancer cure: a survey of 459 Hodgkin's disease survivors. *British Journal of Cancer* 1997,76(6), 791-796.

(20) Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Reduced health-related quality of life among Hodgkin's disease survivors: a comparative study with general population norms. *Ann Oncol* 1999,10(1), 71-77.

(21) Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. *Journal of Psychosomatic Research* 1993,37, 147-153.

(22) Pintilie M. Competing Risks: A Practical Perspective. Wiley, 2006.

(23) Raboud J, Breslow NE. Efficiency gains from the addition of controls to matched sets in cohort studies. *Stat Med* 1989 Aug,8(8), 977-985.

(24) Barchielli A, Balzi D. Nine-year follow-up of a survey on smoking habits in Florence (Italy): higher mortality among non-responders. *Int J Epidemiol* 2002 Oct 1,31(5), 1038-1042.

(25) HEILBRUN LK, NOMURA ABRA, STEMMERMANN GN. The Effects of Non-Response in a Prospective Study of Cancer: 15-Year Follow-Up. *Int J Epidemiol* 1991 Jun 1,20(2), 328-338.

(26) Engert A, Diehl V, Franklin J, et al. Escalated-Dose BEACOPP in the Treatment of Patients With Advanced-Stage Hodgkin's Lymphoma: 10 Years of Follow-Up of the GHSG HD9 Study. *J Clin Oncol* 2009 Aug 24, JCO.

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