Cardiovascular Risk Factors and Pulmonary Function in Long-term Survivors of Testicular Cancer

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LIST OF PAPERS

I. **Sagstuen H**, Aass N, Fosså SD, Dahl O, Klepp O, Wist EA, Wilsgaard T, Bremnes RM. Blood pressure and body mass index in long-term survivors of testicular cancer. *Journal of Clinical Oncology* 23:4980-4990, 2005

II. **Haugnes HS**, Aass N, Fosså SD, Dahl O, Klepp O, Wist EA, Svartberg J, Wilsgaard T, Bremnes RM. Components of the metabolic syndrome in long-term survivors of testicular cancer. *Annals of Oncology* 18:241-248, 2007

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ABBREVIATIONS

BMI	Body mass index
BPT	Bleomycin pulmonary toxicity
CI	Confidence interval
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EORTC	European Organisation for Research and Treatment of Cancer
FEV1	Forced expiratory volume in 1 second
FVC	Functional vital capacity
Mg	Magnesium
MRC	British Medical Research Council
NCEP	National Cholesterol Education Program
NRH	Norwegian Radium Hospital
OR	Odds ratio
RPLND	Retroperitoneal lymph node dissection
RT	Radiotherapy
SBP	Systolic blood pressure
SHBG	Sex hormone-binding globulin
SMR	Standardized mortality rate
TC	Testicular cancer
TCS	Testicular cancer survivors
UNN	University Hospital of North Norway
WHO	The World Health Organization

1. INTRODUCTION AND HISTORICAL PERSPECTIVE

Germ cell testicular cancer (TC) is a relatively uncommon disease, accounting for approximately 2% of all incident cancer cases in Norway in 2006.[1] However, it is an important disease as it represents a highly curable cancer, and primarily affects young men (Figure 1) at their peak of family life, reproduction, education and career.

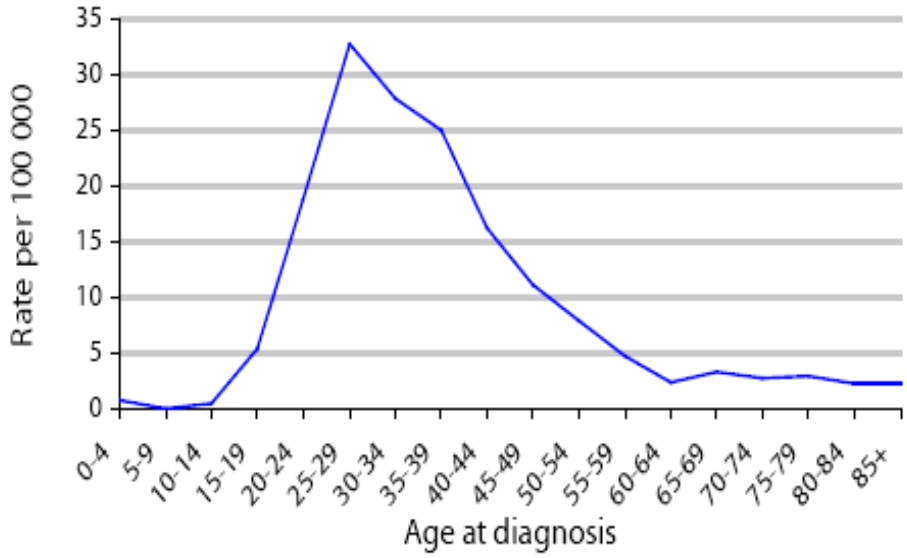

Figure 1. Age-specific incidence rates of TC 2000-2004. The Norwegian Cancer Registry 2004.

The prognosis of metastatic TC was poor less than half a century ago. Based on the understanding of the pattern of lymphatic spread, retroperitoneal lymph node dissection (RPLND) was developed as a treatment option for patients with limited retroperitoneal disease. This technique yielded 5-year survival rates for selected patients at 46% already in the 1950s.[2] The original surgical technique involved bilateral, non-nerve sparing operations with considerable morbidity, mainly retrograde ejaculation. In the early 1980s, modified unilateral and nerve sparing techniques were introduced, aiming at reducing the side-effects.[3]

Today, the RPLND procedure is primarily used as treatment post chemotherapy for non-seminoma patients with initial retroperitoneal disease.[4] Additionally, it is a diagnostic procedure for clinical stage I non-seminoma patients internationally.[5]

Radiotherapy (RT) is a treatment modality which evolved during the 20th century. Traditionally, patients with localized disease or retroperitoneal lymph node metastases were treated with high-voltage RT since the 1950/60s.[6,7] This treatment yielded excellent long-term results for pure seminoma patients, while those with lymphatic spread from non-seminoma had a worse prognosis.[7] Irradiation is today a treatment option primarily for seminoma patients with localized disease or small retroperitoneal metastases.[4,5]

A broad spectrum of chemotherapy agents was tested in disseminated germ cell TC during the 1960s and 1970s. Vinblastine and bleomycin were reported to have significant antitumor activity, and the combination of these two led to an overall response rate at 75% including complete remission in 32% of the patients, some of which were durable responses.[8] A major advance was the discovery of *cis*-diammine-dichloroplatinum (cisplatin) activity in germ cell TC.[9] In the first study combining cisplatin, vinblastine and bleomycin (CVB) in patients with metastatic TC, 74% achieved a complete remission,[10] and the 5-year survival was 64%.[11] Proving that patients with metastatic cancer could be cured with chemotherapy, the study by Einhorn et al[10] is still a landmark study in modern oncology.

Today, germ cell TC is a highly curable disease (Figure 2). Since most TC patients are relatively young at diagnosis, they can expect to live for another 30-50 years after being successfully treated for TC. The growing number of testicular cancer survivors (TCS) combined with their long life expectancy has lead to an increased attention towards treatment-

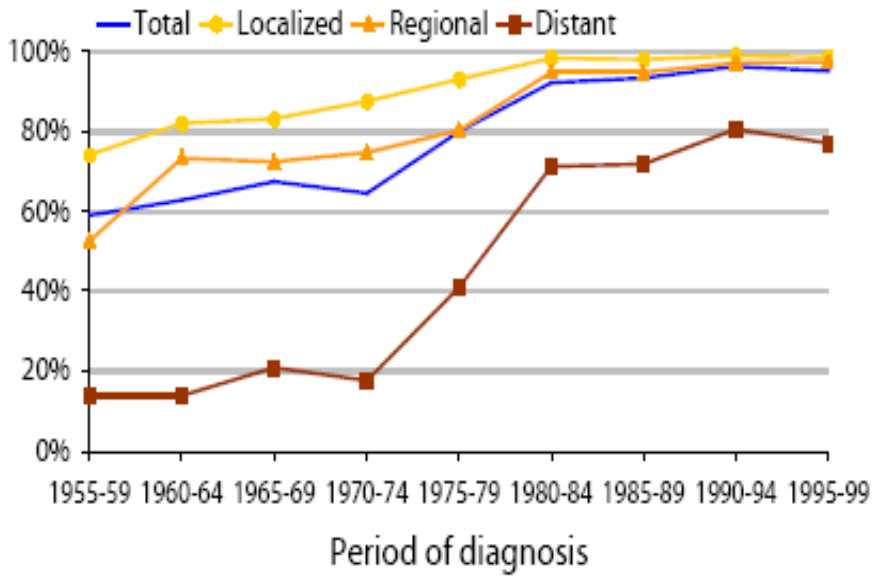

Figure 2. 5-year relative survival by period and stage of TC 1955-1999. The Norwegian Cancer Registry 2004.

related long-term morbidity. Already in early 1980, Raynaud's phenomenon was described as a common toxicity after combination chemotherapy for TC.[12] Several studies published around 1990 further indentified ototoxicity, decreased renal function, peripheral neuropathy, sexual dysfunction, hypertension, obesity and hypercholesterolemia as possible late effects after cisplatin-based chemotherapy.[13-18] However, most of these studies included small patient series and many of them included only chemotherapy-treated patients.

The need for more knowledge regarding long-term treatment-related toxicity stimulated the initiation of a large, national, unselected follow-up survey which focused on several aspects of somatic and psychosocial health in long-term TCS. This survey was conducted as a Norwegian Urological Study Group (NUCG) study and involved all five regional university clinics in Norway. This thesis is based on the results of the cardiovascular and pulmonary examinations of this follow-up survey.

2. BACKGROUND

2.1 Epidemiology

Worldwide, the incidence of TC is highest in Northern Europe and North America, while Asia and Africa have the lowest incidence rates.[19] Norway has one of the highest incidence rates of germ cell TC in the world.[20] In total, 255 men were diagnosed with TC in Norway in 2006, corresponding to an age-adjusted incidence rate at 10.4 per 100 000.[1] Although TC is a relatively rare disease compared with other malignancies, TC is the most common malignancy among 15-44 year old males.[1] Only 15% of Norwegian men diagnosed with TC in 2006 were older than 50 years. The incidence rates are increasing in most European countries, including Norway (Figure 3), while mortality rates are declining.[20]

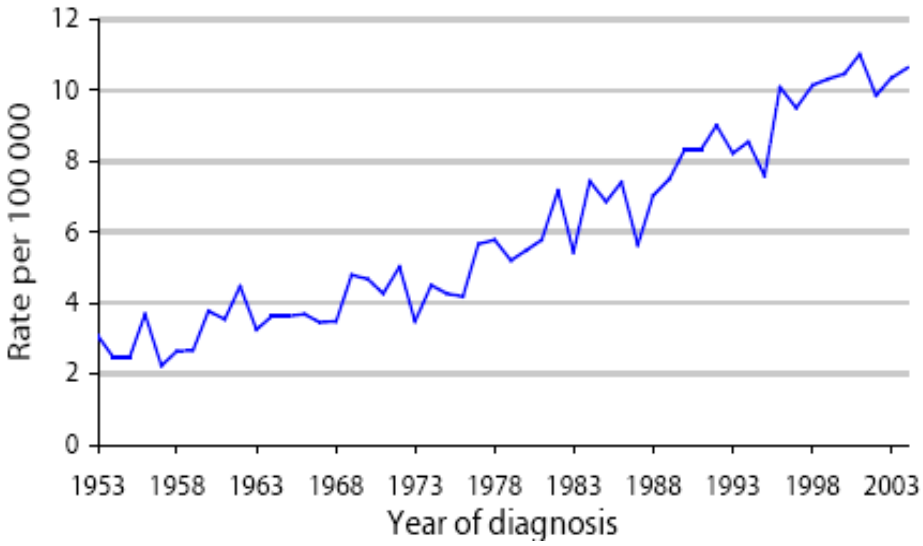

Figure 3. Age-adjusted incidence rates of TC 1953-2004. Norwegian Cancer Registry 2004.

The overall 5-year cancer specific survival in Norway is currently 96%, while approximately 80% of patients with advanced disease are cured.[1] This cure rate is the highest of any solid tumor and is the result of the chemotherapeutic agent cisplatin,[10,21] better diagnostic tools and a multimodal treatment strategy where surgery and either chemotherapy or RT are combined.[4]

The combination of increasing incidence and high TC cure rates has lead to an increasing number of TCS. In 2006 there were 5253 Norwegian males alive with a prior TC diagnosis, representing a 56% increased prevalence during a 10-year period.[1] This constitutes 3% of all Norwegian individuals with a previous cancer diagnosis. On the other hand, TC deaths accounted for only 0.1% of all cancer deaths in Norway in 2004. Although there are indications for higher mortality rates among long-term TCS,[22,23] these cancer survivors have a life expectancy which is almost comparable to healthy age-matched men.

2.2 Risk factors for testicular cancer

The increasing incidence rate of TC during the last 50 years may be related to an increased exposure to different environmental carcinogens. However, the etiology of TC is not well understood.[24] Since TC primarily occurs in early adult life, it is likely that the carcinogenetic process is initiated already *in utero* or in early childhood. The increasing incidence rate follows a birth cohort pattern, indicating that the lifetime risk of having TC is highly dependent on year of birth.[20,25,26] The birth cohort effect implies that the risk factors for TC exert their effect *in utero* or early in life.

Family studies have demonstrated that TC may have an inherited susceptibility, with a 3-10 fold increased risk of having TC for first degree family members of TC patients.[27,28] Familial risks may be due to shared genes and/or shared childhood environment. Immigrant studies have shown that the TC risk among first-generation immigrants reflected the risk in the country of origin, while second-generation immigrants had a risk similar to that of natives in the country of immigration.[29,30] These studies have indicated that environmental influence early in life contributes to the TC risk.

It is well established that cryptorchidism (undescendend testes) is associated with an increased risk of TC, with an odds ratio (OR) at 4.8 in a large meta-analysis.[28] Subfertility and genital malformations are also associated with increased risks of developing TC.[24,28,31] It is, however, unclear whether cryptorchidism, subfertility and genital malformations are risk factors for TC. These conditions may instead possibly share common etiological factors with TC, in what is called the testicular dysgenesis syndrome (TDS).[32] It has been hypothesized that the testicular dysgenesis origins *in utero*, and that TDS is initiated by environmental factors such as hormone-disrupting compounds acting on both the mother and the fetus.[32,33] The precursor of invasive TC, carcinoma in situ, has features of transformed gonocytes and is also probably a part of the TDS.[33]

2.3 Histopathology and tumor markers

About 95% of all malignant tumors in the testicles originate from the primordial germ cells, the cells predestined to become spermatozoa. Lymphomas, sarcomas and other malignant tumors constitute the remaining 5%.[34] Germ cell testicular tumors are broadly divided into two groups, seminomas and non-seminomas, comprising about 50% of cases each. According to the World Health Organization (WHO) classification, the non-seminomas consist of one or several histological elements (embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma), while seminomas only consist of seminoma elements.[35]

Non-seminomas arise in the late teens/early adult life and are highly aggressive tumors, with approximately 50% of patients displaying metastatic disease at the time of diagnosis. Seminomas are less aggressive tumors and generally affect men in their third to fourth decade of life; sometimes, however, older men are affected. Germ cell tumors may also arise outside of the testicles (extragonadal germ cell tumors), mainly in the mediastinum or

retroperitoneum. These tumors have a less favorable prognosis, require specialized treatment and are not further described in this thesis.

Human chorionic gonadotropin (HCG) is produced by syncytiotrophoblastic components (choriocarcinoma), while α-fetoprotein (AFP) is a glycoprotein produced by embryonal carcinoma elements of germ cell cancers. These tumor markers are essential in the diagnosis, prognosis and treatment of patients with germ-cell TC, and should be determined both before and after orchiectomy, and during and after further treatment. Tumor marker decline less than the half-life during chemotherapy may indicate treatment resistance, and warrants treatment intensification or second line chemotherapy.

Serum HCG and/or AFP is elevated in 85% of patients with disseminated non-seminoma TC, while around 10% of seminoma patients have elevated HCG.[34] The degree of tumor marker elevation is a prognostic factor together with the number and site of visceral metastases.[21]

2.4 Treatment principles 1980-1994

Treatment of Norwegian TC patients during the last decades have been according to the Swenoteca collaboration[36-38] or EORTC and MRC protocols.[39-44] All patients were initially orchiectomized. After histological verification of the germ cell TC diagnosis, all patients underwent X-ray or computed tomography (CT) of thorax and CT of abdomen and pelvis. If necessary, supplemental imaging was performed. Clinical staging was performed according to the Royal Marsden Staging System (Table 1).[45]

Table 1. The Royal Marsden Staging System.[45]

Stage	Description
I	Tumor confined to the testicle. No evidence of metastases.
IMk/II	No radiological evidence of metastases, but positive markers after orchiectomy (IMk) or involvement of retroperitoneal lymph nodes (II).
A	Maximum diameter of metastases < 2 cm
B	Maximum diameter of metastases 2-5 cm
C	Maximum diameter of metastases >5 cm
III	Involvement of supradiaphragmatic lymph nodes. A, B and C as for stage II.
IV	Hematological metastases. Involvement of lungs, liver, skeleton and/or brain.

2.4.1 Seminomas

Within this period, most patients with early stages (≤ IIA) of seminoma were treated with infra-diaphragmatic RT. The dog-leg technique involving radiation to the para-aortic and ipsilateral iliac nodes was generally used (Figure 4), but some patients received radiation to the para-aortic area only, as this technique was introduced at one institution in 1989.[43] A very small number of patients received additional mediastinal irradiation (stage II and III) as this treatment option was abandoned as late as the early 1980s.[13] From early 1980s to mid 1990s the standard RT dose was gradually reduced from 36-40 Gy to 25.2-30 Gy. The majority of patients with more advanced disease (≥ IIB) received cisplatin-based chemotherapy followed in some cases by retroperitoneal surgery or radiation.

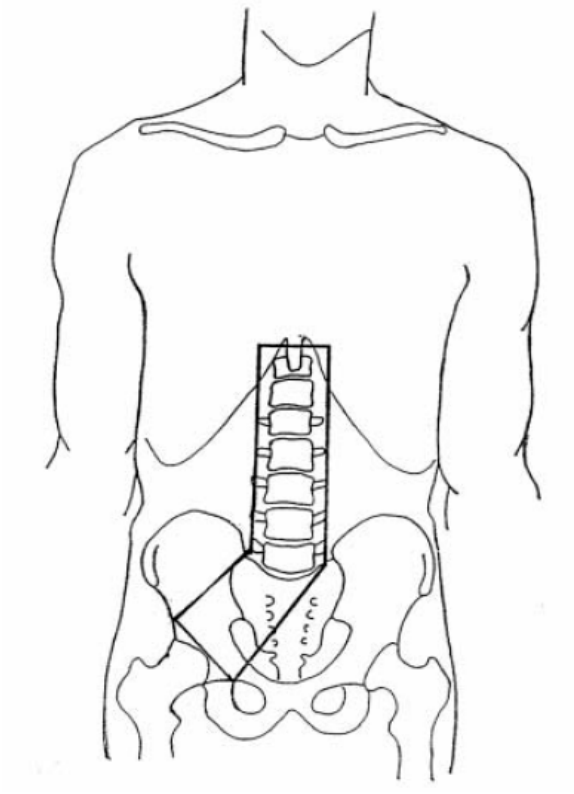

Figure 4. Dog-leg radiotherapy field. From Swenoteca V.

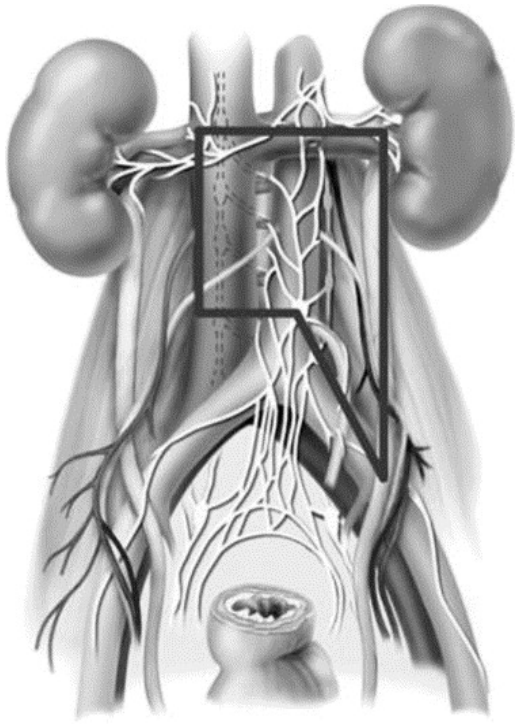

Figure 5. An example of left modified retro-peritoneal lymph node dissection template.[46]

2.4.2 Non-seminomas

Patients with early stages (≤ IIA) of non-seminomas were until late 1980s routinely treated with primary RPLND (Figure 5), followed by cisplatin-based chemotherapy if metastases was detected. Later, the diagnostic RPLND was replaced by surveillance or adjuvant chemotherapy for clinical stage I patients, dependent on risk-factor assessments.[38] Patients with stages ≥ II received 3-4 courses of cisplatin-based combination chemotherapy[37,42] followed by RPLND and further chemotherapy was administered in case of malignant cells in the biopsy specimen. Residual tumors in the lungs and other organs after chemotherapy treatment were resected whenever possible.

2.4.3 Chemotherapy regimens and the most frequently used agents

Table 2. Chemotherapy regimens.

Chemotherapy regimen/drugs	Dose	Administration
CVB regimen[37]		
Cisplatin	20 mg/m^2	iv infusion day 1-5 each cycle
Vinblastine	0.12mg/kg	iv bolus day 1 and 2 each cycle
Bleomycin	30 mg in total	iv bolus day 2, 9 and 16 each cycle
BEP regimen[47]		
Cisplatin	20 mg/m^2	iv infusion day 1-5 each cycle
Etoposide	100 mg/m^2	iv infusion day 1-5 each cycle
Bleomycin	30 mg in total	iv bolus day 1, 5 and 15 each cycle

All patients participating in this follow-up study were treated after the introduction of cisplatin in late 1970s.[10] The majority of chemotherapy-treated patients received cisplatin in combination with bleomycin and either vinblastine (CVB) or etoposide (BEP, Table 2). The original CVB regimen included maintenance therapy with vinblastine. The maintenance treatment was omitted in 1981 due to the lack of effect.[48] After 1987, vinblastine was replaced by etoposide due to improved survival for those with advanced disease and less toxic effects.[47] Standard treatment for the patients included in the present survey consisted of three to four cycles of CVB or BEP given at three-week intervals. Some patients received high-dose cisplatin regimens as primary treatment,[37,49] and/or more than four cycles[44] of cisplatin-based chemotherapy due to poor prognosis, inadequate response, progressive disease or relapse. Also, some patients received other cisplatin-based combinations or carboplatin instead of cisplatin[41,42] due to inclusion in research protocols.

Cisplatin is a platinum compound which forms cross-links with DNA[19] and ultimately induces apoptosis. This chemotherapy agent is excreted renally, but the secretion is often incomplete

and cisplatin has been detected in plasma up to 20 years after administration of cisplatin-based chemotherapy.[50] The major dose-limiting toxicity of cisplatin is renal, which in some cases are manifested as acute interstitial nephritis. High fluid intake and forced diuresis during treatment is a routine prophylactic measure which reduces the incidence of renal toxicity. Other acute side-effects include severe nausea and vomiting, ototoxicity, Raynaud's phenomenon and neurotoxicity.

Bleomycin is an antibiotic agent which exerts its antitumor effect by induction of free radicals,[19] ultimately leading to tumor cell death. This drug is eliminated renally. Bleomycin can be deactivated by bleomycin hydrolase, an enzyme which is found in normal and malignant cells. Due to the lack of this enzyme in the skin and lungs, bleomycin toxicity occurs primarily in these organs.[51] The most serious side-effect is pneumonitis, which occasionally progresses to pulmonary fibrosis during or shortly after treatment.

Vinblastine is a vinca alkaloid which mainly interacts with tubulin and disturbs the microtubule function, leading to metaphase arrest.[19] It is metabolized and excreted primarily by the hepatobiliary system. Neutropenia is the major dose-limiting toxicity. Neurotoxicity is also a common side-effect, including peripheral polyneuropathy.[47]

Etoposide is an epipodophyllotoxin with topoisomerase as its target of action.[19] This drug is primarily excreted renally. Myelosuppression is the major dose-limiting toxicity.

2.5 Cardiovascular risk factors and the metabolic syndrome

Atherosclerotic cardiovascular disease (CVD) results in high mortality rates and is considered a major health problem. Although CVD mortality rates are declining in Western Europe,[52]

CVD is the leading cause of death in Norway, accounting for 35% of all deaths in 2006.[53] CVD comprises a group of chronic diseases including coronary heart disease (CHD), stroke and peripheral arterial disease. These conditions cause serious disabilities for a large number of individuals, and the medical treatment involves considerable expenses for the society.

Non-modifiable atherosclerotic cardiovascular (CV) risk factors include age, sex and a family history of CVD.[54-56] In particular, CHD tends to cluster in families, and a positive family history of premature CHD is an independent risk factor.[55] At any given age, men are at a greater risk for CV mortality than women.[56] The sex difference is partially explained by a higher prevalence of modifiable CV risk factors in men.[57] The most important modifiable atherosclerotic CV risk factors include hypertension, obesity, an unfavorable lipid profile, diabetes, smoking, an unhealthy diet and lack of physical activity.[58-60] Identification of individuals with any or several of these risk factors is important in order to initiate lifestyle interventions and, if necessary, primary prophylaxis to prevent the development of CVD.

The metabolic syndrome is a constellation of metabolic abnormalities which was first characterized by Reaven as "syndrome X" in 1988.[61] Later, WHO,[62] National Cholesterol Education Program (NCEP) expert panel[63] and the International Diabetes Federation[64] have published definitions of the metabolic syndrome. These definitions differ in several aspects as outlined in Table 3. The most widely accepted metabolic risk factors included in the metabolic syndrome are dyslipidemia, hypertension, abdominal obesity and insulin resistance. The metabolic syndrome is important due to its association with diabetes, CV morbidity, CV mortality and overall mortality.[65-69] Thus, this syndrome is important in identifying individuals at an increased CVD risk.

Table 3. Definitions of the metabolic syndrome.

WHO definition[62]	**NCEP definition**[63]	**IDF definition**[64]
1. Diabetes, impaired glucose tolerance or insulin resistance	At least three of the following:	1. Central obesity, waist girth ≥ 94 cm for men, ≥ 80 cm for women (Europe)
2. Plus two or more of the following components:	A. Blood pressure ≥ 130/85 mmHg or med	2. Plus two or more of the following components:
A. High blood pressure ≥ 160/90 mmHg	B. Serum HDL-C < 1.0 mmol/l in men, < 1.3 mmol/l in women	A. Blood pressure ≥ 130/85 mmHg or med
B. Serum TG ≥1.7 mmol/l and/or serum HDL-C < 0.9 mmol/l in men, 1.0 mmol/l in women	C. Serum TG ≥1.7 mmol/l	B. Serum HDL-C < 1.0 mmol/l in men, < 1.3 mmol/l in women
C. Central obesity (males: waist-to-hip ratio >0.90, females >0.85) and/or BMI ≥ 30 kg/m^2	D. Waist girth: > 102 cm in men, > 88 cm in women	C. Serum TG ≥ 1.7 mmol/l and /or specific treatment of lipid abnormalities
D. Microalbuminuria	E. Fasting blood glucose ≥ 5.6 mmol/l (includes diabetes)*	D. Fasting blood glucose ≥ 5.6 mmol/l (includes diabetes)

Abbreviations: WHO, World Health Organization; NCEP, National Cholesterol Education Program; IDF, International Diabetes Federation; TG, triglycerides; med, medication; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index.

* The 2002 definition identified fasting blood glucose ≥ 6.1 mmol/l as elevated. This was modified in 2004 to be ≥ 5.6 mmol/l.[70]

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It has been debated whether the metabolic syndrome is merely a clustering of unrelated risk factors, or a constellation of risk factors linked through a common underlying mechanism.[65] Criticism has been raised against the term "metabolic syndrome", as the risk associated with the syndrome is not greater than the sum of its parts.[71] It is, however, beyond the scope of this thesis to further discuss possible limitations regarding the metabolic syndrome.

2.6 Treatment-related long-term toxicity in testicular cancer survivors

2.6.1 General aspects

During the early 1980s, the overall 5-year germ cell TC survival was rising to rates >90%.[1] As overall survival today has surpassed 95%, clinical studies increasingly focus long-term toxicity in TCS. The research of late effects from germ cell TC treatment is in general retrospective, and has identified toxicities related to obsolete treatment strategies such as the identification of increased risk for cardiac disease after mediastinal irradiation in seminoma patients.[6,72,73] However, cisplatin-based chemotherapy is still a cornerstone in the treatment of disseminated TC. Except for etoposide substituting vinblastine in 1987,[47] the first line chemotherapy schedule have been basically unchanged since the introduction of cisplatin-based chemotherapy in 1977.[10]

The acute renal toxicity observed during cisplatin-based chemotherapy may in up to 30% of the patients result in persisting subclinical impaired renal function,[74] primarily after high cumulative cisplatin doses or when chemotherapy and irradiation is combined.[74,75] Persisting hypomagnesemia is a frequent finding after cisplatin-based chemotherapy,[76] and is probably the result of tubular dysfunction. Raynaud's phenomenon, characterized by transient vasoconstriction of digital arteries, is a common acute side-effect related to chemotherapy and

persists in 30-40% of the patients.[16,76,77] Chemotherapy-induced endothelial damage is a possible mechanism responsible for the development of Raynaud's phenomenon.

Other long-term somatic adverse effects after multimodality TC treatment include ototoxicity, peripheral neuropathy, infertility, Leydig cell impairment and an increased risk of secondary cancers.[15,76,78-82] Most of these side-effects are related to cisplatin-based chemotherapy. The increased risk for secondary cancer is also attributable to infradiaphragmatic irradiation, either alone or in combination with chemotherapy.[80-82]

2.6.2 Cardiovascular risk factors and morbidity

During the second half of the 1980s there were case reports describing acute CVD during or shortly after cisplatin-based combination chemotherapy.[83,84] Several later papers have focused on CV risk factors and CVD as possible late effects following chemotherapy for TC.[14-16,18,76,77,85,86] These studies have identified hypertension, obesity, and hypercholesterolemia as possible late side-effects due to chemotherapy. They reported rates of cardiac events between 1% and 6% several years after treatment.

The study by Meinardi et al[86] was the first to make comparisons of cardiac event rates with the normal population, and found an observed/expected ratio for cardiac disease at 7.1 (95% CI 1.9-18.3), accompanied by an unfavorable CV risk profile. This study was published in 2000, while our follow-up survey was being conducted. All these prior reports had, however, limited power due to small patient series (<100 patients included), inclusion of chemotherapy treated patients only, and generally the lack of control groups.

In 2003 the first large report describing CVD in a large cohort of TCS (n=992) was published by Huddart et al.[87] They found a more than 2-fold increased risk for CVD after chemotherapy alone, irradiation alone or both modalities combined in comparison to surveillance cases, with a median follow-up of 10.2 years. The authors did not observe any differences between the treatment groups with regard to blood pressure, BMI and cholesterol levels, but their data were not age adjusted.

Another large study published by Zagars et al in 2004 described cardiac mortality in 453 men previously treated with RT for stage I/ II seminoma with a median follow-up of 13.3 years.[6] The majority of patients had been treated with infradiaphragmatic irradiation only, while 71 (16%) had received additional prophylactic mediastinal irradiation (PMI). The authors observed a significantly elevated cardiac mortality risk among patients receiving PMI with a standardized mortality rate (SMR) at 2.04, with the highest risk for those followed beyond 15 years. The Zagars study also noted excess cardiac deaths among those not receiving PMI, but only in those with ≥ 15 years of follow-up (SMR 1.80). The study described only cardiac mortality, and did not report the prevalence of cardiovascular risk factors.

The first study describing the prevalence of metabolic syndrome in TCS was presented in 2005.[88] In this Dutch study, Nuver et al reported a higher prevalence of metabolic syndrome in both cisplatin-treated (26%) and surveillance patients (36%) compared with healthy controls (9%). Surprisingly, they found the highest prevalence in stage I patients, although not significantly different from cisplatin-treated patients (p=.23). Thus, based on previously published studies, several questions regarding the development of CV risk factors in long-term TCS remained unanswered.

2.6.3 Pulmonary toxicity

Pulmonary toxicity was early identified as the major dose-limiting side-effect of bleomycin treatment.[89,90] Bleomycin may cause pneumonitis, occasionally progressing to pulmonary fibrosis during or shortly after treatment.[51,77,91,92] Patients with bleomycin pulmonary toxicity (BPT) present with non-productive cough, exertional dyspnoea and sometimes fever, and the radiological findings are bilateral infiltrates.[51,93] As there are no agreed criteria to define BPT, the prevalence of patients with non-fatal BPT varies in different studies. Fatal BPT has been reported to occur in 1-3% of patients treated with bleomycin.[92,94]

It is essential to detect pulmonary toxicity prior to the onset of severe pulmonary symptoms during or after TC treatment. Pulmonary function assessments seem to be the most proper tool.[51] A decrease in the lung transfer capacity for carbon monoxide (TLCO) measured during or shortly after chemotherapy treatment has been indicative of subclinical BPT in several studies,[90,91,95-97] but these reductions in TLCO were generally normalized years after treatment. Spirometry assessments have also been performed during and after chemotherapy treatment to identify subclinical pulmonary disease. A decreased vital capacity (VC) and/or functional vital capacity (FVC) was observed during chemotherapy in the majority of previous studies. However, all were normalized at follow-up.[90,93,96,97] In two small clinical studies, spirometry changes during or after treatment were not observed.[95,98]

The majority of previously published studies on pulmonary function in TC patients have 1) focused on treatment with bleomycin, 2) included small numbers of individuals and/or 3) had a limited follow-up period. With the exception of BPT, no conclusions regarding long-term effects of TC treatment on the pulmonary function in an unselected TCS population can be drawn from these previous publications.

3. AIMS OF THE THESIS

Based on the existing knowledge as described in chapter 2, the purpose of this thesis is to examine any associations between TC treatment and CV risk factors, the metabolic syndrome and pulmonary function in a large, unselected national cohort of long-term TCS. More specifically, the aims are to address the following questions:

1. Are there any associations between blood pressure, BMI, hypertension and obesity and the different treatment modalities (surgery, RT and chemotherapy)? (Paper I)
2. Do TCS differ from controls representing the general population with respect to any of these CV risk factors? (Paper I)
3. Does the prevalence of the metabolic syndrome by using a modified NCEP definition differ according to previously administered treatment? (Paper II)
4. Do TCS differ from controls with respect to the metabolic syndrome? (Paper II)
5. Are there any associations between pulmonary function assessed by spirometry and a questionnaire and the different treatment modalities (surgery, RT and chemotherapy)? (Paper III)

4. SUBJECTS AND METHODS

4.1 Testicular cancer survivors survey

4.1.1 Study population

During the period 1998 to 2002, the five academic oncology departments in Norway conducted a follow-up survey focusing on several aspects of somatic and psychosocial health in long-term TCS. All Norwegian survivors of unilateral germ cell TC who had been treated in the period 1980 to 1994 and aged between 18 and 75 years were identified through the Cancer registry of Norway and the five regional university hospitals. They were invited to participate in this cross-sectional national multicenter survey (Appendix I), which consisted of a comprehensive mailed 219-item questionnaire and an outpatient visit including laboratory tests, clinical examination, audiometry, spirometry at three of the centers and an optional semen analysis. Patients with extragonadal germ cell tumors, bilateral orchiectomy for any reason, secondary malignancy except skin cancer, or mental retardation were excluded. The study was approved by the Committee for Medical Research Ethics, Region South.

In total 1814 patients met the eligibility criteria and were invited to participate in the study. Overall 1463 (81%) signed the informed consent form and participated in the study by either completing the questionnaire (n=1438) and /or participating in the clinical examination including laboratory tests (n=1289). There were overall 351 non-responders (Figure 6). Data on responders vs. non-responders are presented in Table 4. Additionally, one patient has later withdrawn from the database after paper II was prepared.

All patients with clinical examination data (n=1289) formed the study population in paper I (Figure 6). In paper II, we used data from the clinical examination, laboratory tests and the

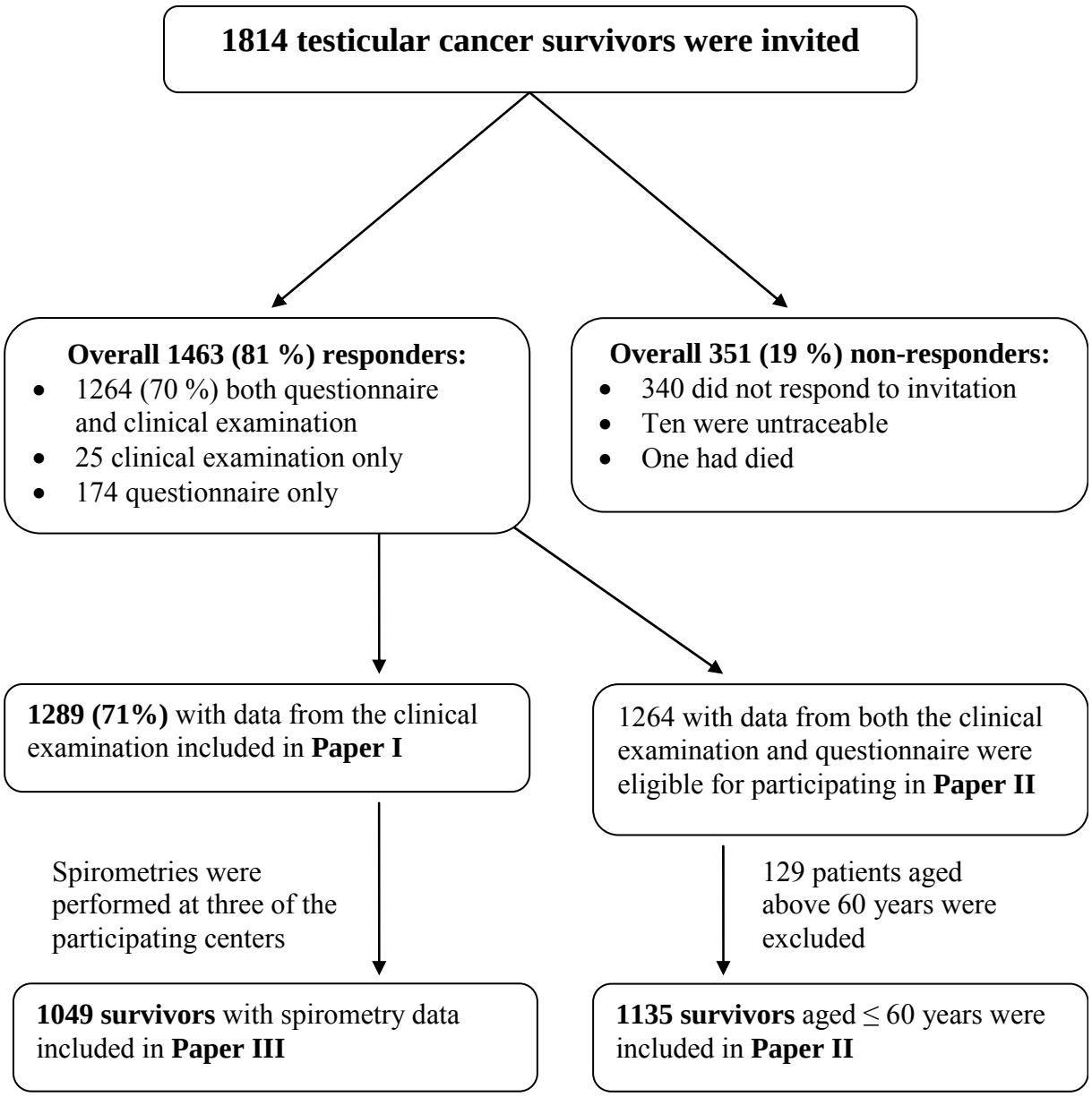

Figure 6. Study populations.

Table 4. Characteristics of responders versus non-responders.

	Responders N=1463	Non-responders N=351	P value
Age at diagnosis, years			
Median (range)	32 (15-64)	30 (16-65)	0.03
Age at follow-up, years			
Median (range)	44 (23-75)	44 (24-74)	0.94
Royal Marsden stage, n (%)			
Stage I	1022 (70)	238 (68)	0.90
Stage IM/II	295 (20)	75 (21)	
Stage III	32 (2)	8 (2)	
Stage IV	114 (8)	30 (9)	
Histology, n (%)			
Non-seminoma	728 (50)	180 (51)	0.61
Seminoma	735 (50)	171 (49)	
Treatment group, n (%)			
Surgery	275 (19)	77 (22)	0.22
Radiotherapy	624 (43)	142 (41)	
Chemotherapy cis ≤ 850	453 (31)	114 (32)	
Chemotherapy cis > 850	111 (8)	18 (5)	

questionnaire. Since the metabolic syndrome is highly prevalent among the elderly,[99] 129 men aged above 60 years were excluded from the 1264 study patients with both questionnaire and clinical examination data, leaving 1135 TCS in the study population. Only three of the five participating hospitals (the Norwegian Radium Hospital [NRH, n=711], Haukeland University Hospital [Haukeland, n=232] and the University Hospital of North Norway [UNN, n= 106]) investigated the participants with spirometries as part of their outpatient visit. These 1049 TCS formed the study population in paper III.

Data regarding histology, initial staging and treatment as well as blood pressure, weight and height at the time of diagnosis were obtained from medical records. The cumulative cisplatin doses, not the number of courses or doses for other agents, were initially reported (paper I). During 2006, it was possible to retrieve complete details regarding regimes, doses and relapse treatment from the hospital records for all chemotherapy treated patients (paper II and III).

4.1.2 Treatment groups

Principles for treatment of TC in Norway in the period 1980 to 1994 are described in chapter 2. To evaluate the impact of specific treatment on the different outcome variables, the TCS were categorized into treatment groups according to initial and eventual relapse treatment:

(1) Surgery only, including orchiectomy and possibly RPLND;

(2) Radiotherapy (RT) only;

(3) Chemotherapy with a cumulative dose of cisplatin≤850 mg (cis≤850);

(4) Chemotherapy with a cumulative dose of cisplatin>850 mg (cis>850).

This categorization was applied in paper I and II. In paper III, we additionally allocated chemotherapy treated patients (any dose) who underwent pulmonary surgery, into a separate group (cis/pulmsurg) as it is well known that thoracic surgery may influence the pulmonary function.[100]

The cut-off point for the two chemotherapy groups was set at 850 mg cisplatin to roughly differentiate between 1) patients who received standard four courses or less and 2) those who received more than four courses or "higher dose" chemotherapy regimens due to a poor prognosis, inadequate response, progression or relapse. The cut-off at 850 mg was chosen to include men treated with maximum four cycles in the lower dose group, including those with a body surface area of 2.1 m^2, which is rather common in Norway. Doses higher than corresponding to 2.1m^2 (840 mg) are seldom prescribed. This cut-off also allocates those who were treated with "high-dose" cisplatin-based chemotherapy (BEP40 and BEP60) into the higher dose group even if they received maximum four courses.

4.1.3 Assessments

Clinical examination, laboratory tests and spirometries

Resting blood pressure was measured manually or with an automatic device. Weight was measured with the individual in light clothing and without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Blood samples were drawn non-fasting by venipuncture at each hospital laboratory primarily between 0800 and 1200 hours. In this thesis, levels of serum cholesterol, serum magnesium (Mg) and serum testosterone have been reported. Serum total cholesterol was measured enzymatically, and serum Mg was measured by a colorimetric endpoint method. Levels of serum total testosterone were determined using a commercial immunoassay, expressed as nanomol per liter (nmol/l). The reference ranges were similar at each hospital laboratory. Sex hormone-binding globulin (SHBG) was also measured for the majority of patients, but with different immunoassays with different reference ranges at each hospital laboratory. Thus, analyses of SHBG or the calculation of free testosterone based on total testosterone and SHBG[101] were not included in the publications.

The spirometries were carried out using Welch Allyn Pneumocheck 61000 at NRH, Vitalograph at Haukeland and Sensormedics VMAX227 at UNN. Spirometric variables included FVC and forced expiratory volume in 1 second (FEV1). The largest FVC and FEV1 from at least three maneuvers were reported for patients at Haukeland and UNN, according to recommendations for spirometry maneuvers.[102] At NRH, only one maneuver was performed and reported accordingly.

Questionnaire

Information regarding family status, educational level, smoking habits and physical activity were obtained from the questionnaire (Appendix II). The questionnaire also contained data on medication (antihypertensive, antidiabetic, asthmatic and/or lipid lowering medication), the prevalence of diabetes, pulmonary disease and dyspnea. Respondents with missing questionnaire data on antihypertensive treatment, lipid-lowering medication, asthma medication, diabetes or pulmonary disease were categorized as being without such treatment or disease, respectively. Study patients reporting that they had diabetes and/or received treatment with antidiabetic medication were classified as having diabetes, while those reporting having asthma and/or regularly used asthma medication were classified as having asthma. Dyspnea was assessed by one question where the participants were asked to state if they suffered "much", "some" or "not at all" from dyspnea during the last 12 months. All patients reporting some or much were classified as having dyspnea.

Data for family status and educational level were dichotomized according to living alone vs. married/cohabitant and college/university vs. lower education (paper I and II). Physical activity (paper II and III) was assessed by two questionnaire items, one assessing a low physical activity level (such as walking) and the other a high level (leading to sweating and breathlessness). Based on the responses, physical activity was divided into three categories (no, moderate and high activity) as described in a previous publication.[103] Cigarette smoking was assessed by pack-years, calculated as number of cigarette packs smoked per day multiplied by the number of years smoked. Accordingly, the patients were categorized into four groups: never smokers, 0.1-9.9 pack-years, 10-19.9 pack-years and ≥ 20 pack-years (paper II and III).

4.2 The Tromsø Study (paper I and II)

The control group was recruited from the Tromsø Study, a longitudinal population-based epidemiological study in Tromsø, Northern Norway. This study was initiated in 1974, primarily to identify possible risk factors for CVD. Large parts of the population have gone through repeated health examinations. Five surveys have been performed: Tromsø 1 (1974), Tromsø 2 (1979/1980), Tromsø 3 (1986/1987), Tromsø 4 (1994/1995), and Tromsø 5 (2001), which was conducted during the same time period as our follow-up survey. The sixth survey is being conducted now. Methods and attendance rates are previously published.[104] Men treated with testosterone substitution were excluded before matching to our TCS study population.

Tromsø covers a relatively large geographical area with both urban and rural population. The Tromsø study control group is representative for Norwegian males with regard to CV risk factors such as obesity and hypertension.[104-107] Thus, this is a suitable control group even though the controls are recruited within a limited geographical region.

In paper I, the control group consisted of 2847 males (born after 1925) who attended the Tromsø 5 survey, and had participated in at least one earlier survey. The median age was 63 years (range 30-76 years). Systolic blood pressure (SBP), diastolic blood pressure (DBP) and BMI from Tromsø 5 were compared to the patients' values at follow-up. SBP, DBP and BMI from either Tromsø 2, 3 or 4 were compared with the patients' values at diagnosis. In paper II, the control group consisted of men who participated in Tromsø 5. After excluding those who were older than 60 years, 1150 males with a median age of 48 years (range 30-60) constituted the control group.

4.3 Definitions of outcome variables

Paper I:

Paper I is both a longitudinal and a cross-sectional study. Blood pressure and BMI was evaluated both at diagnosis and at follow-up, and for BMI the 10-year change was calculated. SBP, DBP and BMI at time of diagnosis were characterized as pre SBP, pre DBP and pre BMI, respectively. The same variables at follow-up were characterized as post SBP, post DBP and post BMI. Hypertension and obesity was evaluated at follow-up only. Hypertension was defined as SBP ≥140 mmHg, and/or DBP ≥90 mmHg, and/or anti-hypertensive treatment,[108] according to the WHO guidelines. The applied 10-year BMI-change was calculated as the difference between post and pre BMI, divided by the observation time in years, multiplied by 10 [(post BMI-pre BMI)*10/ observation time]. Obesity at follow-up was defined as BMI ≥30,[109] in agreement with the WHO guidelines.

Paper II:

Paper II is a cross-sectional study, reporting the prevalence of the metabolic syndrome at follow-up. Our study was planned and partially conducted before the WHO and NCEP definitions of the metabolic syndrome were published. Due to the lack of necessary data for applying these definitions of the metabolic syndrome, a modified NCEP definition was used. Hypertension and obesity was defined according to the WHO publications as indicated in paper I. Hypercholesterolemia was defined as total cholesterol ≥ 5.2 mmol/l[63] and/or the use of lipid lowering drugs. Since blood glucose was measured non-fasting and only in a subgroup of patients, we instead applied patient-reported prevalence of diabetes and/or use of antidiabetic medication. According to our definition, metabolic syndrome was present if two or more of the following four components were present:

(1) Hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or medication)

(2) Obesity (BMI ≥ 30 kg/m^2)

(3) Self-reported prevalence of diabetes

(4) Hypercholesterolemia (serum total cholesterol ≥ 5.2 mmol/l and/or medication)

Additionally, we performed analyses using a more restrictive definition of metabolic syndrome, defined as three or more components present.

Paper III:

Paper III is a cross-sectional study based on spirometries and questionnaire data from a subset of the study patients. The spirometry variables were expressed in absolute values (FVC and FEV1) and in percentages of predicted normal values (FVC%pred and FEV1%pred). Predicted normal values were calculated on the basis of sex, age and height, according to internationally approved equations.[110] Restrictive lung disease was defined as FEV1/FVC ≥ 70% and FVC%pred < 80%.[111,112]

4.4 Statistical analyses

The data were analyzed using SPSS versions 11.0 to 15.0 (SPSS Inc., Chicago, IL). All p-values are two-tailed, with statistical significance set at $p<0.05$. The matching of cases and controls were performed at a group level, not an individual level, due to an inadequate number of young controls. Analyses with controls as reference group were included in paper I and II. The surgery group was used as reference when comparing the impact of different treatment modalities (paper I, II and III).

Mean doses of cytotoxic drugs in the two chemotherapy groups were compared using Student's t-test. Differences between treatment groups or between cases and controls with

respect to continuous variables were analyzed using multiple linear regression. All the continuous dependent variables analyzed in the papers were considered normally distributed. The regression coefficient, β, is used to indicate the mean difference in the dependent variable, when comparing different treatment groups.

Dichotomous variables were analyzed using multiple logistic regression. Metabolic syndrome was also analyzed using ordinal logit regression, with the variable divided into quintiles (0, 1, 2, 3, or all 4 components). The model calculated the probability for having a larger number of metabolic syndrome components. A test of parallel lines confirmed that the proportional odds assumption was met.

All regression analyses were adjusted for age. Analyses of DBP and SBP were additionally adjusted for testosterone and BMI, and analyses of BMI were adjusted for testosterone. Analyses with metabolic syndrome as the outcome variable were additionally adjusted for total testosterone, smoking (pack years), physical activity, educational level and family status. Analyses of FVC%pred and FEV1%pred were additionally adjusted for total testosterone, BMI, pack years and physical activity. The statistical methods are described in detail in the individual papers.

5. RESULTS

Paper I

Blood pressure and body mass index in long-term survivors of testicular cancer.

This paper describes blood pressure, hypertension, BMI, obesity and change in BMI in a large group of unselected TCS with comparisons to controls from the general population.

The study patients were categorized into four treatment groups: Surgery (n=242), RT (n=547), and two chemotherapy groups: cis≤850 mg (n=402) and cis>850 mg (n=98). A large part of the chemotherapy treated patients underwent retroperitoneal surgery (n=321, 64%) and 53 (11%) received additional RT, primarily abdominal. The overall median follow-up was 11.2 years (range 5-22). The RT group was significantly older than the surgery group at diagnosis (36 vs. 29 years, $p<0.001$) and at follow-up (48 vs. 41 years, $p<0.001$), whereas the cis>850 group was significantly younger than the surgery group at follow-up (37 vs. 41 years, $p=.005$).

At diagnosis, there were no differences between the treatment groups with respect to BMI, DBP or SBP in age-adjusted analyses. At follow-up, age-adjusted blood pressure values were significantly higher for the cis≤850 mg group (SBP: 4.1 mmHg, $p=.005$; DBP: 1.9 mmHg, $p=.04$) and the cis>850 group (SBP: 5.0 mmHg, $p=.02$; DBP: 3.4 mmHg, $p=.01$) compared with the surgery group. These differences were basically unchanged after adjusting for BMI and testosterone. BMI did not differ significantly between the treatment groups.

The percentage of persons with hypertension at follow-up was 39% in the surgery group, 54% in the RT group, 50% in the cis≤850 group and 53% in the cis>850 group. Chemotherapy-

treated patients had increased odds for hypertension at follow-up compared to the surgery group, highest for the cis>850 group (odds ratio [OR] =2.4, 95% confidence interval [CI] 1.4-4.0). The cis>850 group had a significantly higher 10-year BMI-increase, and a higher prevalence of obesity at follow-up than the surgery group.

Compared with healthy controls, chemotherapy-treated patients had, at follow-up, increased SBP, DBP, excessive BMI-increase and a higher prevalence of hypertension. SBP, DBP and 10-year BMI-increase in surgery/RT treated patients did not differ from healthy controls. Though, patients treated with RT had increased hypertension rates.

In conclusion, hypertension and augmented weight gain were identified as potential long-term side-effects after treatment with cisplatin-based chemotherapy, in particular after cumulative cisplatin doses above 850 mg.

Paper II

Components of the metabolic syndrome in long-term survivors of testicular cancer.

This paper describes the prevalence of the metabolic syndrome according to a modified NCEP definition in a large group of unselected TCS with comparisons to controls from the general population.

The study participants were categorized into the following four groups: Surgery (n=225), RT (n=446), cis≤850 (n=376) and cis>850 (n=88). Median follow-up was 11.1 years (range 5-22). Compared with the surgery group, the RT group was older at diagnosis and at follow-up ($p<0.001$, both), while the Cis>850 group was younger at diagnosis ($p=.016$) and at follow-up ($p<0.001$), and had a shorter observation time ($p=.001$).

The metabolic syndrome was observed in 33% of patients in the surgery group, 42% in the RT group, 40% in the cis≤850 group and 48% in the cis>850 group. Both chemotherapy groups had increased odds for metabolic syndrome compared with the surgery group, highest for the Cis>850 group (OR 2.8, 95% CI 1.6-4.7). Also, the Cis>850 group had increased odds for metabolic syndrome compared with the control group (OR 2.1, 95% CI 1.3-3.4). The association between metabolic syndrome and the Cis>850 group was strengthened after adjusting for testosterone, smoking, physical activity, education and family status.

On the basis of our more restrictive definition of the metabolic syndrome (≥3 components included), the syndrome was observed in overall 8% of the study patients. Compared with the surgery group, only the Cis>850 group had increased odds for metabolic syndrome, with an OR of 2.6 (95% CI 1.1-6.0). When using ordinal logit regression, both chemotherapy groups had increased probability for having a larger number of metabolic syndrome components compared with the surgery group, with highest odds for the cis>850 group (OR=3.1, 95% CI 2.0-5.0). Compared with controls, the surgery and RT groups had lower odds, while the cis>850 group had higher odds for having a larger number of metabolic syndrome components (OR 2.1, 95% CI 1.4-3.3).

Metabolic syndrome was positively associated with cumulative cisplatin (p=.001), bleomycin (p=.001) and etoposide doses (p=.002) in age-adjusted analyses. Cumulative vinblastine dose was not associated with metabolic syndrome (p=.27). Logistic regression using a backward stepwise model with all four chemotherapy agents and age included, left only age and cumulative cisplatin dose as significant variables.

In conclusion, TCS treated with high cumulative cisplatin doses had an increased risk of developing the metabolic syndrome in comparison to surgery treated patients or to controls.

Paper III

Pulmonary function in long-term testicular cancer survivors.

This paper describes the pulmonary function assessed by spirometries and a questionnaire in a large group of unselected TCS.

The participants were categorized into the following five groups: Surgery (n=202), RT (n=449), cis≤850 (n=306), cis>850 (n=62) and cis/pulmsurg (n=30). Only two patients in the RT group and three chemotherapy-treated patients received mediastinal irradiation. Only two patients received more than 360 mg bleomycin. Median observation time was 11.2 years (range 5-21). The RT group was significantly older than the surgery group at diagnosis ($p<.001$) and follow-up ($p<.001$), while the cis>850 group was younger than the surgery group at follow-up ($p=.002$).

Compared with the surgery group, the cis>850 and cis/pulmsurg groups had considerably lower age-adjusted FVC (cis>850: $\beta=-0.37$, $p=.001$; cis/pulmsurg: $\beta=-0.58$, $p<.001$), FEV1 (cis>850 $\beta=-0.24$, $p=.014$; cis/pulmsurg $\beta=-0.55$, $p<.001$), FVC%pred (cis>850 $\beta=-8.3$; cis/pulmsurg $\beta=-10.5$, both $p<.001$) and FEV1%pred (cis>850 $\beta=-6.8$, $p=.003$; cis/pulmsurg $\beta=-12.4$, $p<.001$). Adjustment for total testosterone, BMI, smoking and physical activity did not change these associations.

In a multiple model including age and the chemotherapy variables (bleomycin, cisplatin, etoposide and vinblastine), the cumulative bleomycin dose ($p=.034$), cisplatin dose ($p<.001$) and age ($p<.001$) were significantly associated with FVC%pred. Only cisplatin and age ($p<.001$, both) were significantly associated with FEV1%pred. FVC%pred tended to be lower for men with initially stage IV disease in comparison to men with stage I-III (88.6% vs. 94.2%, $p=.07$). FEV1%pred did not differ between these two groups (89.9% vs. 91.9%,

p=.44), and the risk for restrictive lung disease was comparable (18.2% vs. 17.5%, OR=1.01, 95% CI 0.94-1.07).

Overall, 101 (10%) patients reported having dyspnea and 27 (2.6%) were classified as having asthma. The cis>850 group had the highest percentage of both dyspnea and prevalent asthma, but their odds did not differ significantly from the surgery group. Eight percent of all patients had restrictive lung disease, with the highest prevalence in the cis>850 (17.7%) and cis/pulmsurg group (16.7%). Compared with the surgery group, the cis>850 and cis/pulmsurg groups had ORs for restrictive disease at 3.1 (95% CI 1.3-7.3) and 2.5 (95% CI 0.8-7.6), respectively.

In conclusion, reduced pulmonary function was identified as a possible long-term side-effect after cisplatin-based chemotherapy.

6. DISCUSSION

6.1 Methodological considerations

6.1.1 General aspects

The findings in this thesis are based on data from a follow-up study where information on treatment (exposure) and the outcome variables were collected simultaneously, although the treatment had been administered at an earlier point in time. Cross-sectional studies are well suited for detecting differences between samples. However, they are based on prevalence and not incidence of the outcome variable. Thus, cross-sectional studies do not necessarily yield information on causal relationships, but can indicate whether there are associations between exposure and outcome.[113]

It has been speculated whether TC itself is associated with an increased CVD risk, irrespective of administered treatment.[86,88] Thus, it is important to compare results on CV risk factors and the metabolic syndrome with controls representing the general population. Due to the relatively young age of our study patients and the limited follow-up, we do not have sufficient data on CV events.[114] CV risk factors and the metabolic syndrome are therefore surrogate endpoints for CVD.

In epidemiological and clinical studies, the conclusion is based on an estimated association between the exposure and the outcome variable. The estimate should be a valid measure for the association. It is important to ensure both the internal validity (the degree to which the observed associations are representative for the study population) and the external validity (the degree to which the results also are applicable for other study populations).[113] The internal validity depends on to what degree systematic errors (bias) occur. Systematic errors can be divided into selection bias, information bias and confounding, which may all cause

incorrect estimates.[115] The internal validity is a prerequisite for the external validity, and will thus be discussed in more detail in the following pages.

6.1.2 Selection bias

The recruitment of study subjects and factors influencing study participation may lead to selection bias. This type of systematic error occurs when the association between exposure and outcome differs from those who participate (responders) and those who do not participate in the study (non-responders).[115]

Our study recruited unselected survivors of unilateral germ cell TC. All Norwegian men who were eligible (chapter 4) were invited to participate, and overall 81% participated in this study. This high participation rate makes it unlikely that our findings are influenced by selection bias. Additionally, based on the information we have on non-responders, they did not differ from the responders with regard to age at follow-up, stage, histology or treatment as described in section 4.1.1.

6.1.3 Information bias

Information bias can occur when measurement or classification of information obtained from or about the study participants is incorrect. Information is being misclassified if the actual variable is measured on a categorical scale and the misclassification leads to an individual being classified into an erroneous category.[115]

Misclassification of lifestyle indicators, such as smoking and physical activity, may place the subjects in more "healthy" categories than what is the true instance.[113] Self-reporting of

medical conditions and treatment may lead to both under-reporting and over-reporting, while reporting of familiar conditions such as asthma and diabetes is often accurate.[116] Nevertheless, it is unlikely that possible misclassifications of the questionnaire variables depend on the administered treatment.

Blood pressure is characterized by large spontaneous variations and several measurements are required to diagnose hypertension according to the guidelines.[108] Our blood pressure measurements were not in agreement with these guidelines. However, our observed differences between the treatment groups with regard to SBP, DBP and hypertension was probably unaffected by this lack of adherence to the guidelines since all study participants had their blood pressure measured only once. Controls from the Tromsø study had their blood pressure measured three times at each survey, and we chose to use their first measurement to achieve as similar conditions for study patients and controls as possible.

The reproducibility of height and weight measurements is excellent and these are among the most precise biological measurements.[117] The calculation of BMI in this thesis is based on measurements of weight and height, not self-reported values. Thus, it is unlikely that the estimation of BMI was biased.

Blood samples should be collected at the same time of the day for all participants due to the diurnal variation of testosterone. Most of our study patients had their blood samples drawn before 1200 in the morning, when the testosterone levels are highest.[118] While there may exist variability between different laboratories with respect to measurements of sex steroids in general, total testosterone variability is within acceptable limits.[119]

Spirometry variables often show large intra individual variability, and it is recommended that each person performs at least three spirometry maneuvers.[102] The spirometry values for patients at NRH, having performed only one spirometry each, could possibly be biased. However, no interaction[113] was observed between institution and treatment group (categorical variables) for any of the outcome variables described in paper III.

6.1.4 Confounding

A simple definition of confounding would be the confusion, or mixing, of effects.[115] Thus, confounding occurs when the estimated association between the outcome variable and the exposure variable is distorted by one or several other variables. Confounding can be controlled by either adjustments in multivariate analyses or stratification.

The prevalence of CV morbidity, CV risk factors, and the metabolic syndrome increase substantially with increasing age,[99] while the pulmonary function decreases with increasing age.[110,120] Since there are significant differences in age at follow-up between our treatment groups and between patients and controls, age is a possible confounder of our results. Thus, it was essential to adjust for age in all the analyses of outcome variables.

Another possible confounder is serum testosterone. Our estimated associations between the cis>850 group and the outcome variables could be due to low serum testosterone values, and not the chemotherapy treatment itself. Consequently, additional adjustments for serum testosterone were performed to potentially clarify the effect of testosterone. This was also the case for other life-style factors.

6.2 Discussion of results

6.2.1 Cardiovascular risk factors and the metabolic syndrome

In paper I and II, we found that previous cisplatin-based treatment to TCS was associated with increased age-adjusted SBP and DBP and a higher prevalence of hypertension, obesity and the metabolic syndrome in comparison to TCS treated with surgery only. The risk factor levels were highest after cumulative cisplatin doses above 850 mg. This heavily treated group also had increased CVD risk compared with the control group.

Our blood pressure data are in accordance with Meinardi and co-workers,[86] who reported higher SBP and DBP in cisplatin-treated patients compared with orchiectomized patients observed in a surveillance program. Our results do not, however, support the findings by Huddart and co-workers who did not observe any differences in blood pressure levels between the treatment groups.[87] Several investigators have reported hypertension as a possible long-term complication in TCS after cisplatin-based chemotherapy,[14-16,18,76,85,86] with reported hypertension rates between 13% and 39%. Our hypertension rates in chemotherapy treated patients were higher, probably due to the inclusion of patients receiving antihypertensive medication and the application of a more liberal hypertension definition.[108]

BMI measured as a continuous variable did not differ between the treatment groups, corroborating other studies.[86,87,121,122] We found that the cis>850 group had a higher prevalence of obesity at follow-up compared with the surgery group, and also an excessive weight gain compared with both the surgery group and healthy controls, supporting previous studies describing overweight (BMI>25 kg/m^2) as a possible complication after cisplatin-based chemotherapy.[76,77]

Hypertension, obesity and hypercholesterolemia all seem to be involved in the increased risk for metabolic syndrome in our heavily cisplatin-treated patients. Our hypercholesterolemia rates of 67% and 73% after standard and high cumulative cisplatin doses, respectively, are in line with other studies reporting rates at 67% to 84%.[18,77,85,86]

As we observed that only chemotherapy treated patients had an increased risk for the metabolic syndrome, our data are inconsistent with the Dutch study by Nuver et al.[88] They found a higher prevalence of the metabolic syndrome in Stage I patients treated with surgery alone than in chemotherapy treated patients, although both groups had a significantly increased prevalence of the metabolic syndrome in comparison to controls. A subset of our study patients was recently described with regard to inflammatory markers and the metabolic syndrome, after further laboratory analyses in blood samples.[123] Wethal and co-workers found that chemotherapy treated patients, irrespective of cisplatin dose, had the highest risk for metabolic syndrome in comparison to surgery only patients (OR 3.7). In addition, they noticed that also RT treated patients had a significantly increased risk for the metabolic syndrome (OR 3.3). The most probable explanation for the discrepancy between our and the Nuver and Wethal results is the different criteria applied in the definition of the metabolic syndrome.

While mediastinal irradiation has been associated with increased risk for CVD,[6,72,73] there are conflicting data regarding the association between infradiaphragmatic RT and CVD risk.[6,87,124] SBP, DBP, BMI, hypertension, obesity and metabolic syndrome rates for RT treated patients were not significantly different from the surgery group in our study, which is in line with the only other publication reporting CV risk factors after infradiaphragmatic RT.[87] On the other hand, this British study did find an increased risk for CV events following RT alone or in combination with chemotherapy. It is, however, possible that the increased risk for

CVD after RT in the British study is mediated via other mechanisms such as elevation of inflammation markers.[123] Assuming that an increased CVD risk in TCS is mediated via the classical CV risk factors, our results are in line with a relatively recent Dutch study indicating that patients treated with infradiaphragmatic RT alone did not have any increased CVD risk.[124] In this study, cisplatin-based treatment was associated with a 1.5 to 1.9-fold increased risk for CVD in comparison to surgery.

Paper I had both a longitudinal and a cross-sectional design. Although blood pressure measurements prior to treatment probably were biased leading to temporarily increased values, an important finding is that blood pressure measurements did not differ between treatment groups at diagnosis. Thus, our observed differences in blood pressure develop later probably as a result of cisplatin-based treatment. This is the first study comparing blood pressure measurements between TCS and controls from the general population, in which the surgery/RT treated patients did not differ from the controls. Hence, it is unlikely that an increased risk for CVD is related to the TC diagnosis itself.

Cisplatin-based chemotherapy may lead to Leydig cell insufficiency.[79] Low endogenous testosterone levels are associated with increased levels of cardiovascular risk factors,[125-127] the metabolic syndrome[128,129] and an increased risk of CVD mortality.[130,131] However, cisplatin-based treatment was associated with increased levels of CV risk factors and the metabolic syndrome even after adjusting for serum total testosterone, indicating other causative mechanisms.

Hypomagnesemia, a potential consequence of cisplatin-induced nephrotoxicity,[132] is associated with the metabolic syndrome[133,134] and may be a possible link between cisplatin-based chemotherapy and the components of the metabolic syndrome. Mean serum Mg levels

in our study did not differ between the Cis>850 and the surgery group, and serum Mg was not associated with the metabolic syndrome. However, it is particularly the intracellular levels of Mg which are reduced following cisplatin administration,[135] and the intracellular levels are also probably more important in the metabolic and vascular regulation.[133]

Another possible explanation for our findings in paper I and II is a chemotherapy-dependent induction of endothelial dysfunction.[122,136] The endothelium is involved in the regulation of vascular tone, metabolism of lipoproteins and in immune response.[137] There is evidence for a cisplatin-induced endothelial activation from *in vitro* studies,[138,139] and it has been shown that the level of von Willebrand factor, a marker of endothelial activation, increases during cisplatin-based chemotherapy.[140]

6.2.2 Pulmonary function

In paper III, we found that patients treated with large cumulative cisplatin doses, or with chemotherapy combined with pulmonary surgery, had a significantly reduced pulmonary function compared with patients treated with surgery alone. The heavily chemotherapy-treated patients also had a higher risk for restrictive lung disease.

Prior studies evaluating pulmonary function after treatment for TC have focused on BPT and thus included chemotherapy treated patients only. In the majority of these studies, the conclusion is that possible reductions in the pulmonary function during or shortly after treatment are normalized at follow-up.[90,93,95-97] Hence, this is the first study indicating that large cumulative chemotherapy doses are associated with reduced pulmonary function several years after treatment. Previous studies did not detect any associations between cumulative bleomycin dose and spirometry values,[90,95,98] except in one study which showed an

association between bleomycin dose and VC.[96] Although we found bleomycin to be significantly associated with FVC%pred, our results indicate a stronger association between the cumulative cisplatin dose and both FVC%pred and FEV1%pred. These results are supported by Stuart et al as they found VC to correlate with number of chemotherapy courses, but not with the cumulative bleomycin dose.[141] Since the maximum cumulative bleomycin doses have been set at 300-360 mg, the cumulative cisplatin rather than bleomycin dose emerge as the pivotal factor influencing long-term pulmonary function negatively in TC survivors.

Low serum testosterone levels have been associated with decreased spirometric variables[142] and an increased risk for respiratory disease mortality in epidemiological studies.[131,143] Thus, part of our findings could be explained by low serum testosterone levels. After controlling for testosterone as a potential confounder, the cumulative cisplatin dose still had a highly significant influence on the pulmonary function. Cisplatin-based chemotherapy has several long-term organ toxicities,[78] and it is not unlikely that this treatment also affects the lungs.

The reduced pulmonary function among men in the cis>850 group may be caused by other factors than the cytotoxic treatment alone. High tumor burden in the lungs and/or recurrent disease may affect the pulmonary status. Our results indicate that men in the cis>850 subgroup with stage IV disease tended to have a lower FVC%pred, but FEV1%pred and the risk for restrictive lung disease did not differ from those with stage I-III disease.

Although the majority of our study patients had subclinically reduced pulmonary function, it may possibly further develop into clinical pulmonary disease. In fact, the effect on the pulmonary function by large cumulative cisplatin doses equals 2-4-fold the effect of smoking. In a large international study, TCS previously treated with chemotherapy were reported to

have increased respiratory disease mortality with a SMR at 2.53.[23] Further, population-based epidemiological studies have shown an association between pulmonary function and all-cause mortality, and suggest that pulmonary function could be used as a predictor for overall survival.[111,144]

7. CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

In this thesis we have identified hypertension, obesity and an increased risk for the metabolic syndrome as possible long-term side-effects after high doses of cisplatin-based chemotherapy in an unselected group of TCS. Treatment with infradiaphragmatic RT was not associated with any increased CV risk factor levels. In paper III we identified reduced pulmonary function as a long-term side-effect following treatment with high cumulative cisplatin doses or with chemotherapy combined with pulmonary surgery. Our findings regarding the pulmonary function in TCS are novel and due to the cross-sectional study design, our results are only hypothesis-generating.

In summary, our results indicate that treatment with large doses of cisplatin-based chemotherapy affects both CV risk factors and the pulmonary function in a manner which displays similarities with premature aging. Our findings need to be confirmed by large prospective studies. Future studies should include patients with a longer follow-up to obtain sufficient data on CV events, and if possible, the evaluation of CV risk profile and pulmonary function before treatment is administered. Basic research in this field is also required to clarify the mechanisms behind various chemotherapy-related toxicity effects.

Our data suggest that TCS treated with cisplatin-based chemotherapy should be followed regularly beyond the standard 10-year follow-up period, with regard to both CV risk factors and the pulmonary function. There is a great need for national follow-up guidelines for these cancer survivors. All physicians involved in the treatment and follow-up of these men should be aware of the possible side-effects related to treatment and offer information about potential benefits of life-style factors including smoking cessation, weight control and regular exercise.

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Forespørsel om å delta i etterundersøkelse av pasienter behandlet for testikkelkreft

Takket være medisinske framskritt helbreder vi stadig flere kreftpasienter. Dette gjelder spesielt pasienter med testikkelkreft. Etter 1980 har behandlingen av testikkelkreft gjort store framskritt, noe som også norske pasienter har hatt nytte av. Vi vet at det i Norge i dag lever ca. 6.000 menn som har fått behandling for testikkelkreft.

De fleste kreftsentra i verden kontrollerer sine testikkelkreftpasienter årlig i 10 år eller hele livet ut, først og fremst for å kartlegge og behandle eventuelle senbivirkninger etter at nye behandlingsmetoder ble innført på slutten av 70-tallet.

Av kapasitetsmessige grunner er vi ved Kreftavdelingen nødt til å avslutte rutinekontrollene etter 5 – 10 år. Vi vet at ca. 95% av pasienter behandlet for testikkelkreft kureres. Siden de fleste behandles i ung alder er det viktig at behandlingen ikke medfører uakseptable seneffekter. Av denne grunn er det nødvendig at man fra tid til annen utfører etterkontroller mht evt legemlige og psykiske senbivirkninger hos våre pasienter.

Som ledd i en nasjonal etterundersøkelse av pasienter som har vært behandlet for testikkelkreft planlegger vi ved Kreftavdelingen, Regionsykehuset i Tromsø en større oppfølging av alle nordnorske pasienter som er helbredet for testikkelkreft i tiden 1980–1994.

Du forespørres herved om å delta i undersøkelsens to deler:

1. **Spørreskjemaundersøkelsen.**
   Hvis du samtykker i det, vil du få tilsendt et spørreskjema med 219 spørsmål som vurderer din legemlige og psykiske helsetilstand og din sosiale situasjon (arbeid, familie). Det vil ta ca. 1 time å fylle ut dette skjema.

2. **Poliklinisk undersøkelse.**
   Dette er en poliklinisk undersøkelse ved Kreftavdelingen, Regionsykehuset i Tromsø hvor vi vil foreta en klinisk undersøkelse, blodprøver, lungetest, hørselsundersøkelse, og for dem som samtykker i det, en sædanalyse.
   På sykehuset vil du også bli bedt om å fylle ut et spørreskjema på knapt 200 spørsmål (ca. en ½ time å fylle ut). Det vil bli avsatt tid for dette og du vil få hjelp ved behov.
   Noen vil også få en samtale om forholdet til din egen sykdom. Denne samtalen vil ta utgangspunkt i det første spørreskjemaet.

   For de pasientene som allerede har avsluttet sine faste kontroller ved Regionsykehuset i Tromsø vil vi ordne med henvisning fra privatlege/sykehuslege, slik at reiseutgifter refunderes av trygdekontoret som ved en vanlig poliklinisk kontroll ved RiTø (som regel bruk av offentlige transportmidler).

Din deltakelse i denne spørreundersøkelsen er frivillig. Du kan når som helst trekke deg fra undersøkelsen uten at dette får konsekvenser for din videre oppfølging. De innsamlede opplysninger kan i så tilfelle kreves slettet.

Alle undersøkelsesdata vil bli behandlet konfidensielt, og ved behandling av resultatene vil data bli anonymiserte. Det vil si at dataene ved offentliggjøring ikke kan knyttes til personer. Alle data vil bli samlet i en database ved Radiumhospitalet i Oslo.

Om du er villig til å delta i denne etterundersøkelsen vil vi be om at du signerer dette informasjonsskrivet (kopien skal du beholde). For å kunne planlegge de videre undersøkelser, vil vi be deg svare på spørsmålene på vedlagte grønne skjema. Både underskrevet informasjonsskriv (dette) og utfylt grønt skjema returneres snarest i vedlagte frankerte konvolutt.

Kontaktperson for studien ved Regionsykehuset i Tromsø er
overlege dr. med. Roy M. Bremnes
Kreftavdelingen
Regionsykehuset i Tromsø
9038 Tromsø
Tel. 77 62 67 80. Faks 77 62 67 79.

Jeg bekrefter at jeg er blitt informert om undersøkelsen, samt fått en kopi av dette informasjonsskrivet. Jeg samtykker i å delta i studien. Jeg er opplyst om at min deltakelse i studien er frivillig, samt at jeg når som helst, og uten nærmere forklaring, kan trekke meg fra spørre-undersøkelsen.

_____ _____

Signatur Dato

Navn: _____

Blokkbokstaver

For at avdelingen lettere skal kunne planlegge den polikliniske undersøkelsen, ber vi deg svare på følgende spørsmål:

1. Er du villig til å delta i spørreskjemaundersøkelsen om pasienter behandlet for testikkelkreft? Nei …… Ja ……..

2. Er du villig til å komme til en poliklinisk kontroll ved Kreftavdelingen, Regionsykehuset i Tromsø med refusjon av utlegg (etter vanlige retningslinjer for trygdekontoret)? Nei …… Ja ……..

3. Kan du tenke deg å avlevere en sædprøve under den polikliniske undersøkelsen, enten fordi du selv er interessert i resultatet eller fordi du kunne tenke deg å bistå oss i vår forskning? Nei …… Ja ……..

4. Går du fremdeles til rutinekontroll ved RiTø? Nei …… Ja ……..

5. Har du noen spesielle ønsker med henblikk på poliklinikkontrollen?

Navn: _____ _____
Sign.

Fødselsdato: _____

Adresse: _____

Tlf. arbeid: _____ Tlf privat: _____

Legen som eventuelt skal få opplysninger om deg som følge av undersøkelsen (din faste lege):

Navn: ……

Adresse: ……

Etterundersøkelse av pasienter behandlet for testikkelkreft

REGIONSYKEHUSET I TROMSØ

Vi ber deg om å fylle ut dette spørreskjemaet så godt du kan, enten ved å krysse av eller sette ring rundt det svaret som passer, eller ved å skrive ned dine kommentarer. Alle svar behandles konfidensielt.

Dato for utfylling: _____

Navn: _____

Født: _____

Høyde: _____ cm Vekt: _____ kg

Blodtrykk (hvis kjent): _____

Sosial og økonomisk situasjon

SIVIL STATUS

1. Hva er din nåværende sivilstatus? (Sett ring rundt det svaret som passer.)

a.	Aldri vært gift		1
b.	Gift	Antall år _____	2
c.	Samboene	Antall år _____	3
d.	Enkemann	Antall år _____	4
e.	Separert	Antall år _____	5
f.	Skilt	Antall år _____	6

2. Har ditt partnerforhold forandret seg etter at du ble behandlet for testikkelkreft? (Sett kryss ved det svaret som passer. Flere svaralternativer er mulig.)

Jeg er blitt gift	☐ Ja 1	☐ Nei 2
Jeg er blitt separert	☐ Ja 1	☐ Nei 2
Jeg er blitt skilt	☐ Ja 1	☐ Nei 2
Jeg er blitt enkemann	☐ Ja 1	☐ Nei 2
Jeg har startet en nytt fast forhold	☐ Ja 1	☐ Nei 2
Jeg har avsluttet et fast forhold	☐ Ja 1	☐ Nei 2
Ingen forandring av partnerforholdet	☐ Ja 1	☐ Nei 2

3. Tror du at diagnosen og behandlingen for testikkelkreft har hatt innflytelse på ditt nåværende forhold til partneren din? ☐ Ja 1 ☐ Nei 2

Hvis «ja», på hvilken måte? _____

_____

_____

BOFORHOLD

4. Hvem bor du sammen med? (Sett ett kryss for hver linje, og oppgi hvor mange du bor sammen med.)

	Ja	Nei	Antall
Ektefelle/samboer	☐ 1	☐ 2	
Andre personer over 18 år	☐ 1	☐ 2	_____
Personer under 18 år	☐ 1	☐ 2	_____

ARBEID/UTDANNING

5. Hvilken utdanning er den høyeste du har fullført?

- ☐ Grunnskole 7-10 år, framhaldskole, folkehøgskole 1
- ☐ Realskole, middelskole, yrkesskole, 1-2 årig videregående skole 2
- ☐ Artium, økonomisk gymnas, allmennfaglig retning i videregående skole 3
- ☐ Høgskole/universitet, mindre enn 4 år 4
- ☐ Høgskole/universitet, 4 år eller mer 5

6. Hva er din nåværende arbeidssituasjon? (Sett ring rundt det svaret som passer.)

1.	Arbeidsledig/permittert	1
2.	Ikke i stand til å arbeide	
	a) sykemeldt	2
	b) attføring	3
	c) uføretrygdet	4
3.	Delvis i arbeid	5
4.	I fullt arbeid	6
5.	Alderspensjonist	7
6.	Student/skoleelev	8

<u>Hvis du for tiden ikke har inntektsgivende arbeid eller du ikke har heltids husarbeid: Gå til spørsmål nr. 11.</u>

7. Har du i løpet av de siste 12 månedene hatt sykefravær:

	Ja	Nei
med egenmelding?	☐ 1	☐ 2
med sykemelding fra lege?	☐ 2	☐ 2

8. Hvis «ja»; hvor lenge til sammen?

☐ 2 uker 1 ☐ 2 - 8 uker 2 ☐ Mer enn 8 uker 3 eller mindre

9. Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag?

☐ Ja, nesten alltid 4 ☐ Ganske sjelden 2
☐ Ganske ofte 3 ☐ Aldri, eller nesten aldri 1

10. Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag?

☐ Ja, nesten alltid 4 ☐ Ganske sjelden 2
☐ Ganske ofte 3 ☐ Aldri, eller nesten aldri 1

11. Tror du diagnosen og behandlingen av testikkelkreft har hatt negativ innflytelse på din nåværende arbeidssituasjon/utdanningssituasjon?

☐ Ja 1 ☐ Nei 2

Hvis «ja», på hvilken måte? _____

_____

_____

_____

12. Har du hatt noen vanskeligheter vedrørende arbeid, forsikring og/eller lån, eller innenfor andre praktiske områder av ditt liv, etter behandlingen for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

Vennligst angi de organisasjoner/institusjoner som har vært involvert i vanskelighetene, og beskriv hva problemene bestod i:

a) Arbeid: _____

_____

_____

b) Forsikring: _____

_____

_____

c) Lån: _____

_____

_____

d) Andre forhold: _____

_____

_____

ØKONOMI

13. Mottar du noen av følgende offentlige ytelser?

Sykepenger/sykelønn/ rehabiliteringspenger	☐ Ja [1]	☐ Nei [2]
Ytelser under yrkesrettet attføring	☐ Ja [1]	☐ Nei [2]
Uførepensjon	☐ Ja [1]	☐ Nei [2]
Alderspensjon	☐ Ja [1]	☐ Nei [2]
Sosialstøtte	☐ Ja [1]	☐ Nei [2]
Arbeidsledighetstrygd	☐ Ja [1]	☐ Nei [2]
Overgangsstønad	☐ Ja [1]	☐ Nei [2]
Etterlattepensjon	☐ Ja [1]	☐ Nei [2]
Andre ytelser	☐ Ja [1]	☐ Nei [2]

14. Har det i løpet av det siste året hendt at husholdningen har hatt vansker med å klare de løpende utgifter til mat, transport, bolig og liknende?

☐ Ja, ofte [4] ☐ Ja, en sjelden gang [2]
☐ Ja, av og til [3] ☐ Nei, aldri [1]

VENNER

15. Hvor mange gode venner har du?
(Regn med de du kan snakke fortrolig med og som kan gi deg god hjelp når du trenger det. Tell ikke med de du bor sammen med, men regn med andre slektninger.)

Antall:_____

16. Føler du at du har mange nok gode venner?
☐ Ja [1] ☐ Nei [2]

17. Hvor ofte tar du vanligvis del i foreningsvirksomhet, som f.eks. idrettslag, politiske lag, religiøse møter eller andre foreninger?

☐ Aldri, eller noen få ganger i året [4]
☐ 1-2 ganger i måneden [3]
☐ Omtrent en gang i uken [2]
☐ Mer enn en gang i uken [1]

Generell helsetilstand/livsstil

KREFT/ALVORLIG SYKDOM

18. Har du fått en annen kreftdiagnose etter din testikkelkreft-behandling? (Kryss av for det svaret som passer og angi mnd./år for diagnose.)
☐ Ja [1] ☐ Nei [2]
Hvis «ja», angi type og tidspunkt: _____

_____

_____

19. Har du hatt noen andre alvorlige sykdommer/ operasjoner? ☐ Ja [1] ☐ Nei [2]
Hvis «ja», angi type og tidspunkt: _____

_____

_____

20. Har noen i din familie fått testikkelkreft eller en annen form for kreft? ☐ Ja [1] ☐ Nei [2]
Hvis «ja», angi type, slektsforhold, eventuelt navn, krefttype og sykehus (f.eks.: Morbror Peder Ås, magekreftoperert i 1997 på Aker Sykehus.)

_____

_____

FØR/ETTER BEHANDLING FOR TESTIKKELKREFT

21. Brukte du noen ganger nervemedisiner før du fikk behandling for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

22. Har du noen gang brukt nervemedisiner etter behandlingen for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

23. Brukte du noen gang narkotika før du fikk behandling for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

24. Har du noen gang brukt narkotika etter behandlingen for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

25. Oppsøkte du noen gang en psykolog/psykiater før du fikk behandling for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

26. Har du noen gang oppsøkt en psykolog/psykiater etter behandlingen for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

27. Har du noen gang tenkt på/ forsøkt selvmord? ☐ Ja [1] ☐ Nei [2]

ALKOHOLBRUK

28. Hvor ofte er du beruset flere dager i strekk på grunn av alkohol? (Sett ring rundt det svaret som passer best.)

Aldri	1
Sjeldnere enn månedlig	2
Noen ganger i måneden	3
Noen ganger i uken	4
Daglig eller nesten daglig	5

29. Hvor ofte hopper du over måltider på grunn av alkohol?

Aldri	1
Sjeldnere enn månedlig	2
Noen ganger i måneden	3
Noen ganger i uken	4
Daglig eller nesten daglig	5

30. Hvor ofte har du blitt mer vennlig og omgjengelig etter å ha drukket siste år?

Aldri	1
Sjeldnere enn månedlig	2
Noen ganger i måneden	3
Noen ganger i uken	4
Daglig eller nesten daglig	5

31. Hvor ofte trenger du en drink om morgenen etter å ha drukket kvelden før?

Aldri	1
Sjeldnere enn månedlig	2
Noen ganger i måneden	3
Noen ganger i uken	4
Daglig eller nesten daglig	5

RØYKING

32. Røyker du	Ja	Nei
- sigaretter til daglig?	☐ 1	☐ 2
- sigarer/sigarillos til daglig?	☐ 1	☐ 2
- pipe til daglig?	☐ 1	☐ 2
- kun til fest?	☐ 1	☐ 2

Aldri røykt daglig (Sett kryss) ☐

33. Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? Antall år: _____

34. Hvis du røyker daglig nå eller har røykt tidligere; hvor mange sigaretter røyker eller røykte du vanligvis daglig? Antall sigaretter: _____

35. Hvor gammel var du da du begynte å røyke daglig? Alder: _____ år

36. Hvor mange år til sammen har du røykt daglig?
Antall år: _____

SYKDOM/PLAGER

I noen av de følgende spørsmål ber vi deg oppgi alderen din da eventuell sykdom inntrådte. Hvis du ikke husker nøyaktig hvor gammel du var, skriver du et tall som er nærmest det du antar er korrekt. Kryss av for det svaret som passer, og sett kun ett kryss.

37. Har du, eller har du hatt:

	Ja	Nei	Alder første gang
Hjerteinfarkt	☐ 1	☐ 2	_____ år
Angina pectoris (hjertekrampe)	☐ 1	☐ 2	_____ år
Hjerneslag/hjerneblødning	☐ 1	☐ 2	_____ år
Diabetes (sukkersyke)	☐ 1	☐ 2	_____ år

38. Hva ble resultatet siste gang du målte blodtrykket ditt?

- ☐ Begynne med/fortsette med blodtrykksmedisin 4
- ☐ Komme til kontroll, men ikke ta blodtrykksmedisin 3
- ☐ Ingen kontroll og ingen medisin nødvendig 2
- ☐ Har aldri fått målt blodtrykket 1

39. Har legen din noen gang sagt at du har/har hatt noen av disse sykdommene?

	Ja	Nei
Beinskjørhet (osteoporose)	☐ 1	☐ 2
Fibromyalgi (fibrositt/kronisk smertesyndrom)	☐ 1	☐ 2
Leddgikt (reumatoid artritt)	☐ 1	☐ 2
Slitasjegikt (artrose)	☐ 1	☐ 2
Bechterews sykdom	☐ 1	☐ 2
Andre langvarige skjelett- eller muskelsykdommer	☐ 1	☐ 2

40. Har du eller har du hatt smerter eller kramper i bena som begrenser deg når du går eller som gjør at du våkner om natten?
☐ Ja 1 ☐ Nei 2
Hvis «ja», angi når smertene/krampene begynte:
_____

41. I hvilken grad har du hatt disse plagene det siste året?

	Ikke plaget	Litt plaget	Mye plaget
Kvalme	☐ 1	☐ 2	☐ 3
Brystbrann/ sure oppstøt	☐ 1	☐ 2	☐ 3
Diaré	☐ 1	☐ 2	☐ 3
Treg mage	☐ 1	☐ 2	☐ 3
Hjertebank	☐ 1	☐ 2	☐ 3
Åndenød	☐ 1	☐ 2	☐ 3

42. Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?
☐ Ja 1 ☐ Nei 2

Hvis «nei», gå videre til spørsmål nr. 45. Hvis «ja», svar på følgende:

43. Hvor har du hatt disse plagene?

	Ja	Nei
Nakke	☐ 1	☐ 2
Skuldre (aksler)	☐ 1	☐ 2
Albuer	☐ 1	☐ 2
Håndledd, hender	☐ 1	☐ 2
Bryst/mage	☐ 1	☐ 2
Øvre del av rygg	☐ 1	☐ 2
Korsrygg	☐ 1	☐ 2
Hofter	☐ 1	☐ 2
Knær	☐ 1	☐ 2
Ankler, føtter	☐ 1	☐ 2

(Hvis du har hatt plager i flere områder i minst 3 måneder det siste året, sett ring rundt det ja-krysset hvor plagene har vart lengst.)

44. Har plagene redusert din arbeidsevne det siste året? (Gjelder også hjemmearbeidende.)

☐ Nei/ubetydelig [1] ☐ I betydelig grad [3]
☐ I noen grad [2] ☐ Vet ikke [4]

45. Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? ☐ Ja [1] ☐ Nei [2]
(Langvarig = Minst ett år)

Hvis «nei», gå til spørsmål nr. 47.

46. Hvis «ja»; hvor mye vil du si at dine funksjoner er nedsatt?

	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet	☐ [1]	☐ [2]	☐ [3]
Har nedsatt syn	☐ [1]	☐ [2]	☐ [3]
Har nedsatt hørsel	☐ [1]	☐ [2]	☐ [3]
Hemmet pga. kroppslig sykdom	☐ [1]	☐ [2]	☐ [3]
Hemmet pga. psykiske plager	☐ [1]	☐ [2]	☐ [3]
Andre plager, beskriv: _____	☐ [1]	☐ [2]	☐ [3]

MEDISINBRUK

47. Har du i deler av det siste året brukt noen medisiner daglig eller nesten daglig?

☐ Ja [1] ☐ Nei [2]

48. Hvis «ja»; angi hvor mange måneder du brukte følgende medisiner/kosttilskudd. (Sett 0 hvis du ikke har brukt medisinene.)

	Antall måneder
Smertestillende	_____ mnd.
Sovemedisin	_____ mnd.
Beroligende medisin	_____ mnd.
Medisin mot depresjon	_____ mnd.
Allergimedisin	_____ mnd.
Astmamedisin	_____ mnd.
Hjertemedisin	_____ mnd.
Blodtrykksmedisin	_____ mnd.
Jerntabletter	_____ mnd.
Vitamintilskudd	_____ mnd.
Tran/fiskeoljer	_____ mnd.
Annen medisin, spesifiser navn og antall mnd.: _____	_____ mnd.

49. Hvor ofte har du brukt avslappende/beroligende medisiner eller sovemedisiner den siste måneden?

☐ Daglig [4] ☐ Sjeldnere enn hver uke [2]
☐ Hver uke, men ikke hver dag [3] ☐ Aldri [1]

BRUK AV HELSETJENESTER

50. Har du i løpet av de siste 12 månedene vært hos:

(Sett ett kryss for hver linje.)	Ja	Nei
Allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat)	☐ [1]	☐ [2]
Bedriftslege	☐ [1]	☐ [2]
Lege ved sykehus (uten innleggelse)	☐ [1]	☐ [2]
Annen lege	☐ [1]	☐ [2]
Fysioterapeut	☐ [1]	☐ [2]
Kiropraktor	☐ [1]	☐ [2]
Homøopat	☐ [1]	☐ [2]
Annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, «healer», «synsk» e.l.)	☐ [1]	☐ [2]

51. Har du vært innlagt på sykehus de siste 5 årene?

☐ Ja [1] ☐ Nei [2]

Hvis «ja», vennligst spesifiser hvilke sykehus (utenom RiTø) og hvorfor du var innlagt? _____

FRITID

52. Hvordan har din fysiske aktivitet i fritida vært det siste året? (Tenk deg et ukentlig gjennomsnitt for året. Arbeidsvei regnes som fritid.)

	Ingen	Timer pr uke: Under 1	1-2	3 og mer
Lett aktivitet (ikke svett/andpusten)	☐ [4]	☐ [3]	☐ [2]	☐ [1]
Hard fysisk aktivitet (svett/andpusten)	☐ [4]	☐ [3]	☐ [2]	☐ [1]

HVORDAN DU FØLER DEG

Under følger noen flere spørsmål om hvordan du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uken. Ikke tenk for lenge på svaret - de spontane svarene er best.

53. Jeg er nervøs eller anspent.

☐ For det meste [4] ☐ Noen ganger [2]
☐ Ofte [3] ☐ Ikke i det hele tatt [1]

54. Jeg gleder meg fortsatt over ting slik jeg pleide før.

☐ Avgjort like mye [1] ☐ Bare lite grann [3]
☐ Ikke fullt så mye [2] ☐ Ikke i det hele tatt [4]

55. Jeg har en urofølelse som om noe forferdelig vil skje.

☐ Ja, og noe svært ille [4] ☐ Litt, bekymrer meg lite [2]
☐ Ja, ikke så veldig ille [3] ☐ Ikke i det hele tatt [1]

56. Jeg kan le og se det morsomme i situasjoner.

☐ Like mye nå som før [1] ☐ Avgjort ikke som før [3]
☐ Ikke like mye nå som før [2] ☐ Ikke i det hele tatt [4]

57. Jeg har hodet fullt av bekymringer.
- ☐ Veldig ofte 4
- ☐ Ganske ofte 3
- ☐ Av og til 2
- ☐ En gang i blant 1

58. Jeg er i godt humør.
- ☐ Aldri 4
- ☐ Noen ganger 3
- ☐ Ganske ofte 2
- ☐ For det meste 1

59. Jeg kan sitte i fred og ro og kjenne meg avslappet.
- ☐ Ja, helt klart 1
- ☐ Vanligvis 2
- ☐ Ikke så ofte 3
- ☐ Ikke i det hele tatt 4

60. Jeg føler meg som om alt går langsommere.
- ☐ Nesten hele tiden 4
- ☐ Svært ofte 3
- ☐ Fra tid til annen 2
- ☐ Ikke i det hele tatt 1

61. Jeg føler meg urolig som om jeg har sommerfugler i magen.
- ☐ Ikke i det hele tatt 1
- ☐ Fra tid til annen 2
- ☐ Ganske ofte 3
- ☐ Svært ofte 4

62. Jeg bryr meg ikke lenger om hvordan jeg ser ut.
- ☐ Ja, jeg har sluttet å bry meg 4
- ☐ Ikke som jeg burde 3
- ☐ Kan hende ikke nok 2
- ☐ Bryr meg som før 1

63. Jeg er rastløs som om jeg stadig må være aktiv.
- ☐ Uten tvil svært mye 4
- ☐ Ganske mye 3
- ☐ Ikke så veldig mye 2
- ☐ Ikke i det hele tatt 1

64. Jeg ser med glede fram til hendelser og ting.
- ☐ Like mye som før 1
- ☐ Heller mindre enn før 2
- ☐ Avgjort mindre enn før 3
- ☐ Nesten ikke i det hele tatt 4

65. Jeg kan plutselig få en følelse av panikk.
- ☐ Uten tvil svært ofte 4
- ☐ Ganske ofte 3
- ☐ Ikke så veldig ofte 2
- ☐ Ikke i det hele tatt 1

66. Jeg kan glede meg over gode bøker, radio og TV.
- ☐ Ofte 1
- ☐ Fra tid til annen 2
- ☐ Ikke så ofte 3
- ☐ Svært sjelden 4

HVORDAN DU SER PÅ DEG SELV

Folk ser på seg selv på ulike måter. Vennligst kryss av for hvert utsagn hvor enig eller uenig du er.

	Svært enig	Enig	Uenig	Svært uenig
67. Jeg har en positiv holdning til meg selv.	☐ 1	☐ 2	☐ 3	☐ 4
68. Jeg føler meg virkelig ubrukelig til tider.	☐ 4	☐ 3	☐ 2	☐ 1
69. Jeg føler at jeg ikke har mye å være stolt av.	☐ 4	☐ 3	☐ 2	☐ 1
70. Jeg føler at jeg er en verdifull person, i alle fall på lik linje med andre.	☐ 1	☐ 2	☐ 3	☐ 4

HVORDAN DU FØLER DEG NÅ

Vennligst kryss av for det svaret som best beskriver dine følelser i den siste uken. Sett bare ett kryss.

71. Er du vanligvis glad eller nedstemt?
- ☐ Svært nedstemt 7
- ☐ Nedstemt 6
- ☐ Nokså nedstemt 5
- ☐ Både - og 4
- ☐ Nokså glad 3
- ☐ Glad 2
- ☐ Svært glad 1

72. Føler du deg stort sett sterk og opplagt, eller trøtt og sliten?
- ☐ Meget sterk og opplagt 1
- ☐ Sterk og opplagt 2
- ☐ Ganske sterk og opplagt 3
- ☐ Både - og 4
- ☐ Ganske trøtt og sliten 5
- ☐ Trøtt og sliten 6
- ☐ Svært trøtt og sliten 7

73. Når du tenker på hvordan du har det for tiden, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
- ☐ Svært fornøyd 1
- ☐ Meget fornøyd 2
- ☐ Ganske fornøyd 3
- ☐ Både/og 4
- ☐ Nokså misfornøyd 5
- ☐ Meget misfornøyd 6
- ☐ Svært misfornøyd 7

Fertilitet, sex og samliv

FERTILITET (FRUKTBARHET)

74. a. Ble du født med begge testikler i pungen? ☐ Ja 1 ☐ Nei 2

b. Hvis «nei», er du blitt operert? ☐ Ja 1 ☐ Nei 2

Årstall for operasjon: _____

75. Har du hatt kusma med hevelse av en eller begge testiklene? ☐ Ja 1 ☐ Nei 2

FØR diagnosen for testikkelkreft:

76. Prøvde du å bli far? ☐ Ja 1 ☐ Nei 2

77. Hadde du egne barn? ☐ Ja 1 ☐ Nei 2

Antall barn: _____

Barnas fødselsår: _____

78. Oppsøkte du eller din partner en lege på grunn av problemer med å få barn? ☐ Ja 1 ☐ Nei 2

79. Frosset du ned sæd før du ble behandlet for testikkelkreft? ☐ Ja 1 ☐ Nei 2

ETTER behandling for testikkelkreft:

80. Har du prøvd å bli far? ❑ Ja [1] ❑ Nei [2]

81. Har du fått egne barn? ❑ Ja [1] ❑ Nei [2]
Antall barn: _____
Barnas fødselsår: _____

82. Har din partner hatt aborter etter at hun ble gravid med deg? ❑ Ja [1] ❑ Nei [2]

83. Trengte dere hjelp av en medisinsk spesialist for at partneren din skulle bli gravid? ❑ Ja [1] ❑ Nei [2]

a. Hvis «ja», ble din partner gravid med sæd som du selv produserte etter behandlingen? ❑ Ja [1] ❑ Nei [2]

b. Hvis «ja», ble nedfrosset sæd fra før behandlingen benyttet? ❑ Ja [1] ❑ Nei [2]

84. Ble noen av dine barn født med alvorlige sykdommer? ❑ Ja [1] ❑ Nei [2]
Hvis «ja», spesifiser hvilke sykdommer:
_____
_____

85. Har du adoptert barn? ❑ Ja [1] ❑ Nei [2]
Hvis «ja», angi årstall for adopsjon:_____

86. Eventuelt andre opplysninger angående svangerskap, barn, etc.
_____
_____
_____

SEKSUALDRIFT

La oss definere seksualdrift som en følelse som kan omfatte ønske om seksuell aktivitet (onani eller samleie), tanken på å ha sex eller frustrasjon som følge av mangel på sex.

87. Hvor mange dager har du følt seksualdrift de siste 30 dagene? (Sett ring rundt det svaret som passer.)

Ingen dager	Bare noen få dager	Noen dager	De fleste dagene	Nesten hver dag
1	2	3	4	5

88. Hvordan vurderer du nivået på seksualdriften din de siste 30 dagene?

Ingen drift	Lav drift	Middels drift	Middels sterk drift	Sterk drift
1	2	3	4	5

REISNING

89. Hvis du er blitt seksuelt stimulert på noen måte de siste 30 dagene; hvor ofte har du hatt delvis eller full reisning?

Aldri	Noen få ganger	Ganske ofte	Vanligvis	Alltid
1	2	3	4	5

90. Hvis du har hatt reisning de siste 30 dagene; hvor ofte var penis stiv nok til at du kunne ha samleie?

Aldri	Noen få ganger	Ganske ofte	Vanligvis	Alltid
1	2	3	4	5

91. Hvor store vansker har du hatt med å få reisning de siste 30 dagene?

Har ikke fått reisning	Store vansker	Noen vansker	Få vansker	Ingen vansker
1	2	3	4	5

SÆDUTTØMMING

92. Hvor store vansker har du hatt med å få sæduttømming når du er blitt seksuelt stimulert de siste 30 dagene?

Har ikke hatt noen seksuell stimulering de siste 30 dagene	Store vansker	Noen vansker	Få vansker	Ingen vansker
1	2	3	4	5

93. I hvilken grad har du over de siste 30 dagene sett på mengden sæd ved uttømming som et problem for deg?

Stort problem	Middels problem	Lite problem	Ganske lite problem	Ikke noe problem
1	2	3	4	5

94. Har sæduttømmingen blitt helt borte etter behandlingen for testikkelkreft? ❑ Ja [1] ❑ Nei [2]

PROBLEMVURDERING

95. I hvilken grad har du over de siste 30 dagene sett på manglende seksualdrift som et problem?

Stort problem	Middels problem	Lite problem	Ganske lite problem	Ikke noe problem
1	2	3	4	5

96. I hvilken grad har du over de 30 siste dagene vurdert din evne til å få og beholde reisning som et problem?

Stort problem	Middels problem	Lite problem	Ganske lite problem	Ikke noe problem
1	2	3	4	5

97. I hvilken grad har du over de 30 siste dagene sett på din sæduttømming som et problem?

Stort problem	Middels problem	Lite problem	Ganske lite problem	Ikke noe problem
1	2	3	4	5

98. Hvor tilfreds har du samlet sett vært med ditt seksualliv de siste 30 dagene?

Veldig utilfreds	For det meste utilfreds	Omtrent like tilfreds som utilfreds	For det meste tilfreds	Svært tilfreds
1	2	3	4	5

Livshendelser

Vennligst kryss av for det svaralternativet som passer best, og angi med et tall fra 0-100 hvor stor påkjenning/ belastning du syntes ulike hendelser eventuelt har medført for deg. 0 betyr ingen belastning, mens 100 betyr stor belastning. Har du krysset av for «ja» under ett eller flere av spørsmålene, pass på at du også har skrevet ned et tall fra 0-100 som best beskriver hvor stor påkjenning/ belastning hendelsen førte til.

Har du i løpet av de siste 12 månedene opplevd noe av det følgende:			Angi grad av belastning fra 0-100
99. Egen alvorlig sykdom/ ulykke/sykehusinnleggelse?	❑ Nei [2]	❑ Ja [1]	_____
100. Skilsmisse/separasjon/ brudd med samboer?	❑ Nei [2]	❑ Ja [1]	_____
101. Giftet deg/flyttet sammen med samboer?	❑ Nei [2]	❑ Ja [1]	_____
102. Fått barn?	❑ Nei [2]	❑ Ja [1]	_____
103. Opplevd dødsfall i familie/nære venner?	❑ Nei [2]	❑ Ja [1]	_____
104. Alvorlig sykdom/ ulykke/sykehusinnleggelse hos familie eller nære venner?	❑ Nei [2]	❑ Ja [1]	_____
105. Andre vansker hos nær familie (skilsmisse, alkoholproblemer, nerveproblemer osv.)?	❑ Nei [2]	❑ Ja [1]	_____
106. Vært arbeidsløs/ permittert?	❑ Nei [2]	❑ Ja [1]	_____
107. Ektefelle/samboer har vært arbeidsløs/ permittert?	❑ Nei [2]	❑ Ja [1]	_____
108. Alvorlige økonomiske problemer?	❑ Nei [2]	❑ Ja [1]	_____
109. Alvorlige bomessige problemer?	❑ Nei [2]	❑ Ja [1]	_____
110. Har du selv eller noen i din nære familie vært utsatt for eller innblandet i alvorlig lovbrudd?	❑ Nei [2]	❑ Ja [1]	_____

Livskvalitet

HELSE

Spørsmålene under dreier seg om hvordan du ser på din egen helse. Sett en ring rundt det tallet som best beskriver din tilstand.

111. Stort sett, vil du si at din helse er:

Utmerket	Meget god	God	Nokså god	Dårlig
1	2	3	4	5

112. Sammenlignet med for ett år siden; hvordan vil du si at din helse stort sett er nå?

Mye bedre nå enn for ett år siden	1
Litt bedre nå enn for ett år siden	2
Omtrent den samme som for ett år siden	3
Litt dårligere nå enn for ett år siden	4
Mye dårligere nå enn for ett år siden	5

AKTIVITETER

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå, og eventuelt i hvor stor grad? (Sett ring rundt ett tall på hver linje.)

	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
113. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett.	1	2	3
114. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid.	1	2	3
115. Løfte eller bære en handlekurv.	1	2	3
116. Gå opp trappen flere etasjer.	1	2	3
117. Gå opp trappen en etasje.	1	2	3
118. Bøye deg eller sitte på huk.	1	2	3
119. Gå mer enn to kilometer.	1	2	3
120. Gå noen hundre meter.	1	2	3

	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
121. Gå hundre meter.	1	2	3
122. Vaske deg eller kle på deg.	1	2	3

FYSISKE PROBLEMER

I løpet av de siste fire ukene; har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse? (Sett ring rundt ett tall.)

	Ja	Nei
123. Har du redusert tiden du har brukt på arbeidet ditt eller på andre aktiviteter pga. din fysiske helse?	1	2
124. Har du utrettet mindre enn du hadde ønsket pga. din fysiske helse?	1	2
125. Har du vært hindret i visse typer arbeid eller andre aktiviteter pga. din fysiske helse?	1	2
126. Har du hatt vanskeligheter med å utføre arbeidet ditt eller andre aktiviteter (f.eks. fordi det krevde ekstra anstrengelser)?	1	2

FØLELSESMESSIGE PROBLEMER

I løpet av de siste fire ukene; har du hatt følelsesmessige problemer som har ført til vanskeligheter i arbeidet ditt eller i andre av dine daglige gjøremål, f.eks. fordi du har følt deg deprimert eller engstelig? (Sett ring rundt ett tall.)

	Ja	Nei
127. Har du redusert tiden du har brukt på arbeidet ditt eller på andre aktiviteter pga. følelsesmessige problemer?	1	2
128. Har du utrettet mindre enn du hadde ønsket pga. følelsesmessige problemer?	1	2
129. Har du ikke arbeidet eller utført andre aktiviteter like nøye som vanlig pga. følelsesmessige problemer?	1	2

130. I løpet av de siste fire ukene; i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger? (Sett ring rundt ett tall.)

Ikke i det hele tatt	Litt	Endel	Mye	Svært mye
1	2	3	4	5

131. Hvor sterke kroppslige smerter har du hatt i løpet av de siste fire ukene? (Sett ring rundt ett tall.)

Ingen	Meget svake	Svake	Moderate	Sterke	Meget sterke
1	2	3		5	6

132. I løpet av de siste fire ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)? (Sett ring rundt ett tall.)

Ikke i det hele tatt	Litt	Endel	Mye	Svært mye
1	2	3	4	5

De neste spørsmålene dreier seg om hvordan du har følt deg og hvordan du har hatt det de siste fire ukene. For hvert spørsmål, vennligst sett ring rundt det tallet som best beskriver hvordan du har hatt det.

Hvor ofte i løpet av de siste fire ukene har du:

133. - følt deg full av tiltakslyst?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

134. - følt deg veldig nervøs?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

135. - vært så langt nede at ingenting har kunnet muntre deg opp?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

136. - følt deg rolig og harmonisk?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

137. - hatt mye overskudd?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

138. - følt deg nedfor og trist?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

139. - følt deg sliten?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

140. - følt deg glad?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

141. - følt deg trett?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

142. I løpet av de siste fire ukene; hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)? (Sett ring rundt ett tall.)

Hele tiden	Nesten hele tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5

Hvor riktig eller gal er hver av de følgende påstander for deg? (Sett ring rundt det tallet som passer.)

143. Det virker som om jeg blir lettere syk enn andre.

Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
1	2	3	4	5

144. Jeg er like frisk som de fleste jeg kjenner.

Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
1	2	3	4	5

145. Jeg forventer at min helse vil bli dårligere.

Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
1	2	3	4	5

146. Min helse er utmerket.

Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
1	2	3	4	5

ALT I ALT

Som svar på de neste spørsmålene, sett en ring rundt det tallet fra 1 til 7 som best beskriver din tilstand.

147. Hvordan har din helse vært i løpet av den siste uken?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

148. Hvordan har livskvaliteten din vært i løpet av den siste uken?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

SMERTER/PLAGER

Sett ring rundt det tallet som best beskriver din tilstand.

	Ikke i det hele tatt	Litt	Endel	Svært mye
149. Er du plaget av smerter, stikninger eller nummenhet i hendene/ fingrene?	1	2	3	4
150. Er du plaget av smerter, stikninger eller nummenhet i føttene/tærne?	1	2	3	4
151. Er du plaget av hvite/ kalde hender/fingre når det er kaldt?	1	2	3	4
152. Er du plaget av hvite/ kalde føtter/tær når det er kaldt?	1	2	3	4
153. Er du plaget av øresus?	1	2	3	4
154. Er du plaget av nedsatt hørsel?	1	2	3	4

BEKYMRINGER

155. Har du lite hår i forhold til jevnaldrende?

❑ Ja [1] ❑ Nei [2] ❑ Vet ikke [3]

Hvis «ja», tror du dette er en følge av din behandling?

❑ Ja [1] ❑ Nei [2]

156. Hvis du mener du har lite hår i forhold til jevnaldrende; har du vært bekymret for dette? (Sett ring rundt det tallet som best beskriver din tilstand.)

Ikke i det hele tatt	Litt	Endel	Svært mye
1	2	3	4

I løpet av den siste uken:

Sett ring rundt det tallet som best beskriver din tilstand.

	Ikke i det hele tatt	Litt	Endel	Svært mye
157. Har ditt egenbilde som mann vært nedsatt som følge av din sykdom eller behandling?	1	2	3	4

	Ikke i det hele tatt	Litt	Endel	Svært mye
158. Har du vært plaget av bekymringer for ikke å kunne få barn?	1	2	3	4
159. Har du vært redd for tilbakefall av din sykdom?	1	2	3	4
160. Har du vært fornøyd med måten sykehus(ene) har foretatt undersøkelsene/ kontrollene av deg?	1	2	3	4
161. Har du følt at de avgjørelser som er foretatt med henblikk på din behandling har vært riktig for deg?	1	2	3	4

Mestring av plager/problemer

Utsagnene nedenfor handler om hvordan du opplever og mestrer de plagene/problemene du har. Utsagnene er skrevet i jeg-form og du setter kun ett kryss i den ruten som passer best i forhold til hvordan du opplever deg selv.

	Helt enig	Nokså enig	Både og	Nokså uenig	Svært uenig
162. Jeg sier fra når jeg er sint eller trist.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
163. Jeg snakker gjerne med noen utvalgte mennesker når det røyner på.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
164. Å gjøre nye ting er ofte vanskelig for meg.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
165. Jeg går aktivt inn for å finne en løsning på problemene mine.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
166. Fysisk aktivitet er viktig for meg.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
167. Jeg prøver å glemme plagene mine.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
168. Jeg legger problemene mine bak meg ved å konsentrere meg om noe annet.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
169. Jeg tror det kan komme noe positivt ut av plagene/ problemene mine.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
170. Jeg har god tro på at plagene mine vil bli bedre.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
171. Jeg graver meg ned i arbeid for å holde plagene/ problemene på avstand.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
172. Jeg føler langt på vei at jeg har gitt opp.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
173. Jeg trekker meg tilbake fra andre når jeg har det vanskelig.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

FØLELSER

Vennligst beskriv hvordan du har hatt det de siste syv dagene ved å sette en ring rundt det tallet som best beskriver din tilstand.

174. Jeg har hatt perioder med sterke følelser omkring sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

175. Ting jeg har sett og hørt minnet meg plutselig om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

176. Tanker om sykdommen har trengt seg på også når jeg ikke har villet.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

177. Bilder fra sykdommen har plutselig dukket opp i tankene mine.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

178. Enhver påminnelse har gjenopplivet følelser knyttet til sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

179. Jeg har hatt vanskelig for å sove på grunn av tanker og bilder om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

180. Jeg har hatt vonde drømmer om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

181. Jeg vet mange uforløste følelser er der, men jeg har skjøvet dem bort.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

182. Jeg har ikke tillatt meg å bli følelsesmessig berørt når jeg tenker på sykdommen eller blir minnet om den.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

183. Jeg har ønsket å bli kvitt minner om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

184. Jeg har forsøkt å la være å snakke om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

185. Jeg har opplevd det uvirkelig, som om sykdommen ikke var hendt eller ikke var virkelig.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

186. Jeg har holdt meg unna ting eller situasjoner som kan minne meg om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

187. Mine følelser rundt sykdommen er nærmest lammet.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

188. Jeg har ikke tillatt meg selv å ha tanker om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

Tretthet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste tiden. Vi spør om hvordan du har følt deg i det siste, dvs. de tre siste månedene, og ikke hvordan du følte deg for lenge siden. Hvis du har følt deg sliten lenge, ber vi om at du sammenligner deg med hvordan du følte deg sist du var bra. Sett kun ett kryss for hvert spørsmål.

189. Har du problemer med at du føler deg sliten?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

190. Trenger du mye hvile?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

191. Føler du deg søvnig eller døsig?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

192. Har du problemer med å komme i gang med ting?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

193. Mangler du overskudd?

❑ Ikke i [1] det hele tatt	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

194. Har du redusert styrke i musklene dine?

❑ Ikke i [1] det hele tatt	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

195. Føler du deg svak?

❑ Mindre [1] enn vanlig	❑ Som [2] vanlig.	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

196. Har du vansker med å konsentrere deg?

❑ Mindre [1] enn vanlig	❑ Som [2] vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

197. Forsnakker du deg i samtaler?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

198. Er det vanskelig å finne de rette ordene?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

199. Hvordan er hukommelsen din?

❑ Bedre [1] enn vanlig	❑ Ikke verre [2] enn vanlig	❑ Verre [3] enn vanlig	❑ Mye verre [4] enn vanlig

200. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Sett kun ett kryss.)

- ❑ Mindre enn en uke 1
- ❑ Mindre enn tre måneder 2
- ❑ Mellom tre og seks måneder 3
- ❑ Seks måneder eller mer 4

201. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det?

- ❑ 25 % av tiden 1
- ❑ 50 % av tiden 2
- ❑ 75 % av tiden 3
- ❑ Hele tiden 4

Personlighet

Spørsmålene nedenfor dreier seg om hvordan du vanligvis opptrer, føler og handler. Vennligst kryss av for enten «ja» eller «nei» for hvert spørsmål. Svar hurtig og ikke tenk for lenge over den nøyaktige meningen med hvert spørsmål.

202. Er du forholdsvis livlig?	❑ Ja 1	❑ Nei 2
203. Ville du bli oppskaket av å se et barn eller et dyr lide?	❑ Ja 1	❑ Nei 2
204. Liker du å treffe nye mennesker?	❑ Ja 1	❑ Nei 2
205. Blir dine følelser lett såret?	❑ Ja 1	❑ Nei 2
206. Hender det ofte at du "går trøtt"?	❑ Ja 1	❑ Nei 2
207. Liker du å spille andre et puss som av og til kan såre dem?	❑ Ja 1	❑ Nei 2
208. Er du ofte bekymret?	❑ Ja 1	❑ Nei 2
209. Er gode manerer og renslighet viktig for deg?	❑ Ja 1	❑ Nei 2
210. Bekymrer du deg for at fryktelige ting kan skje?	❑ Ja 1	❑ Nei 2
211. Tar du vanligvis selv det første skrittet for å få nye venner?	❑ Ja 1	❑ Nei 2
212. Er du for det meste stille når du er sammen med andre?	❑ Ja 1	❑ Nei 2
213. Liker du å komme til avtaler i god tid?	❑ Ja 1	❑ Nei 2
214. Har du ofte følt deg trøtt og giddeløs uten grunn?	❑ Ja 1	❑ Nei 2
215. Er det mange mennesker som forsøker å unngå deg?	❑ Ja 1	❑ Nei 2
216. Klarer du holde fart i et selskap?	❑ Ja 1	❑ Nei 2
217. Bekymrer du deg lenge etter en pinlig opplevelse?	❑ Ja 1	❑ Nei 2
218. Liker du å ha masse liv og røre rundt deg?	❑ Ja 1	❑ Nei 2
219. Forteller folk deg en masse løgner?	❑ Ja 1	❑ Nei 2

Vennligst legg det ferdig utfylte spørreskjemaet i vedlagte svarkonvolutt.
Porto er allerede betalt av oss.

Tusen takk for hjelpen!

RiTø

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