Lifestyle and Adverse Effects in Selected Norwegian Cancer Patients and Survivors

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Synne-Kristin Hoffart Bøhn

In this thesis I have used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the author, and has not been endorsed by the Cancer Registry of Norway.

Abbreviations

ADT: androgen deprivation therapy

AEs: adverse effects

ALL: acute lymphoblastic leukemia

AYA: adolescent and young adult

BC: breast cancer

BMI: body mass index

CF: chronic fatigue

CRC: colorectal cancer

CRN: Cancer Registry of Norway

EPIC-CP: Expanded Prostate Cancer Index Composite for Clinical Practice

FQ: Chalder Fatigue Questionnaire

HADS-A: The Hospital Anxiety and Depression Scale, anxiety subscale

HUNT: The Nord-Trøndelag Health survey

NHL: non-Hodgkin lymphoma

NOR-CAYACS: Norwegian childhood, adolescent and young adult cancer survivors

MM: malignant melanoma

PA: physical activity

PC: prostate cancer

PHQ-9: The Patient Health Questionnaire

PROFO: the Norwegian Prostate Cancer Association

PROM: patient-reported outcome measure

PSA: prostate specific antigen

QoL: quality of life

RP: radical prostatectomy

RT: radiation therapy

YACSs: young adult cancer survivors

Definitions and concepts

Cancer survivor: as defined by the National Coalition for Cancer Survivorship, an individual is considered as a cancer survivor from the moment of diagnosis, and through the rest of his or her life (1). This definition is widely used in the United States (U.S.). In general, the term *long-term cancer survivors* is applied to individuals with at least 5 years of tumor-free survival after a cancer diagnosis (2).

In this thesis, the study population in Paper I is referred to as cancer patients because some participants still received active cancer treatment at the time of survey, and the majority were less than 5 years from diagnosis. The study population in Paper II and III is referred to as long-term cancer survivors, as these individuals were 5 years or more from diagnosis at survey, and had completed cancer treatment.

Cancer-related adverse effects are physical and psychosocial complications and conditions related to cancer or cancer treatment (3). *Acute adverse effects* begin during treatment and lasts for up to 1 year after completed treatment, while *late effects* appear at least 1 year after completed treatment (3). In this thesis, late effects also comprise long-term effects; adverse effects that persist more than 1 year after completed treatment (2).

Physical activity is defined as "any bodily movement produced by the skeletal muscles that results in energy expenditure" (4).

Physical exercise is defined as "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective of improvement or maintenance of physical fitness" (4). In this thesis, both the terms physical activity and exercise are used.

Lifestyle guidelines: As outlined by the American Cancer Society, cancer survivors are recommended to undertake at least 150 minutes of moderate intensity, 75 minutes high intensity, or an equivalent combination of moderate and high intensity *physical activity* every week, as well as to include strength training at least twice per week (5, 6). In this thesis, strength training is not considered in the categorization of participants meeting or not meeting physical activity recommendations, because the measurements used did not evaluate type of physical activity. Further, the American Cancer Society recommends to achieve and maintain *a healthy body weight* (defined as a body mass index (BMI) between 18.5 and 24.9 kg/m^2), *avoid smoking* and to consume a healthy diet, with emphasis on plant food (7). In this thesis, consumption of at least *five daily servings of vegetables and fruits* (5-a-day) is used as an indicator of a healthy diet. These lifestyle guidelines are consistent with the public lifestyle guidelines published by the Norwegian Directorate of Health (8).

Summary of the thesis

With the growing population of individuals surviving cancer, more attention has been directed towards maintaining and improving their long-term health. Cancer and its treatments may put survivors at risk of a broad spectrum of acute and late adverse effects, which may have a large negative impact on health and function throughout survivorship. In this regard, a healthy lifestyle, including physical activity (PA), a healthy body-weight and diet, and non-smoking, is highlighted as a relevant self-management strategy for cancer survivors. In order to help cancer survivors maintain and obtain a healthy lifestyle, support and counselling must be targeted towards the specific needs and challenges existing across the broad spectrum of cancer survivors. However, for many subpopulations of cancer survivors, knowledge about their lifestyle, characteristics of those with an unhealthy lifestyle and cancer-related adverse effects are scarce. The overall aim of this thesis was therefore to provide new knowledge about lifestyle and cancer-related adverse effects in selected groups of Norwegian cancer patients and survivors. This was investigated through two sub-studies, resulting in three separate papers:

In *sub-study I* (*Paper I)*, we compared the level of PA among prostate cancer (PC) patients across treatment modalities and explored the association between level of PA and treatment-induced adverse effects. A total of 696 PC patients treated with radical prostatectomy, radiation therapy (RT) + androgen deprivation therapy (ADT) or lifelong ADT completed a questionnaire assessing PA and treatment-induced adverse effects. Overall, there was no statistically difference in level of PA across treatment groups. Results from multivariable logistic regression analyses showed that patients with increasing bowel symptoms related to RT, age ≥ 70 years, participating in the work force and body mass index (BMI) ≥ 25 kg/m^2 were less likely to exercise ≥ 2 times per week. Among patients undergoing lifelong ADT, being ≥ 5 years since diagnosis was inversely associated with exercising ≥ 2 times per week.

Sub-study II included long-term young adult cancer survivors (YACSs) diagnosed with breast cancer (BC), colorectal cancer (CRC), non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL) or localized malignant melanoma (MM) at the age of 19-39 years. Survivors of localized MM treated with skin surgery served as a comparison group. A total of 1488 YACSs responded to a mailed questionnaire.

In *Paper II* adherence to public lifestyle guidelines on PA, BMI, smoking and intake of fruits and vegetables among long-term YACSs was investigated. Further, factors associated with not meeting a single or an increasing number of lifestyle guidelines (PA, BMI and/or smoking) were explored. A total of 1056 survivors were included. Forty-three per cent did not meet the PA guidelines, 49 % reported a BMI ≥ 25 kg/m^2, 20 % smoked and 92 % did not consume at least five daily servings of fruits and vegetables. Only one of four met the combination of PA, BMI and smoking guidelines. The

adherence to lifestyle guidelines did not differ between YACSs treated for BC, CRC, NHL or ALL and the comparison group (MM). Results from multivariable analyses showed that male gender, not living with a partner, education ≤ 13 years, comorbidities, lymphedema, pain, depressive symptoms and/or chronic fatigue (CF) were associated with an elevated risk of not meeting single and/or an increasing number of lifestyle guidelines.

In *Paper III* we examined the prevalence and associated factors of CF among long-term YACSs. Also, the retrospective change of fatigue with time among participants with CF was explored. Among the 1088 included YACSs, the prevalence of CF was 25 %. CF was significantly more common among survivors of BC, CRC and NHL than among survivors of MM (15%). Multimodal treatment, comorbidities, pain, numbness in hands/feet and depressive symptoms were associated with an increased risk of CF in multivariable analyses. The majority (60 %) of survivors with CF had been tired since cancer treatment, and 65 % of these reported worsening or no change of fatigue with time.

In conclusion, the results in this thesis indicate a high need to improve the lifestyle of selected Norwegian cancer patients and survivors. The associations between lifestyle and adverse effects suggest a need to inform cancer survivors about the potential benefits of a healthy lifestyle in relation to adverse effects. Further, health personnel working with YACSs should be aware of the high prevalence of CF among long-term YACSs, and of strategies to improve fatigue.

List of papers

Paper I:
Physical activity and associations with treatment-induced adverse effects among prostate cancer patients
Synne-Kristin Hoffart Bøhn, Sophie Dorothea Fosså, Torbjørn Wisløff, Lene Thorsen.
Supportive Care in Cancer, 2019 Mar;27(3):1001-1011. DOI: 10.1007/s00520-018-4389-5.Epub 2018 Aug 9

Paper II:
Lifestyle among long-term survivors of cancers in young adulthood
Synne-Kristin Hoffart Bøhn, Hanne Cathrine Lie, Kristin Valborg Reinertsen, Sophie Dorothea Fosså, Hege Sagstuen Haugnes, Cecilie Essholt Kiserud, Jon Håvard Loge, Torbjørn Wisløff, Lene Thorsen.

Submitted to Journal of Adolescent and Young Adult Oncology, August 2019.

Paper III:
Chronic fatigue and associated factors among long-term survivors of cancers in young adulthood
Synne-Kristin Hoffart Bøhn, Lene Thorsen, Cecilie Essholt Kiserud, Sophie Dorothea Fosså, Hanne Cathrine Lie, Jon Håvard Loge, Torbjørn Wisløff, Hege Sagstuen Haugnes, Kristin Valborg Reinertsen.
Acta Oncologica, 2019 May;58(5):753-762. DOI: 10.1080/0284186X.2018.1557344

1.0 Introduction

Due to improved cancer diagnostics and more effective treatments, the number of people living longer with or beyond a cancer diagnosis is large and growing (9). In Norway, approximately 273 000 individuals were living with a history of cancer by the end of 2017. More than 60 % of this population were long-term survivors (9). However, cancer and its treatments also put patients and survivors at risk of a range of acute and late adverse effects (AEs), such as urinary incontinence, sexual dysfunction, fatigue, lymphedema, second cancer and cardiac morbidity (2) .

With the increasing population of cancer survivors, impaired health and AEs after cancer compose a public health concern (10). Consequently, increased attention has been directed towards optimizing the health and quality of life (QoL) in individuals with a history of cancer. Self-management behaviors, such as maintaining a healthy lifestyle, is an area that has been suggested beneficial and has received increased focus the last decades (2).

Physical activity (PA), a healthy body weight and diet, and non-smoking, are associated with lower risks for overall morbidity and mortality in cancer survivors (11). Despite this knowledge, research indicates that most adult cancer survivors are not adhering to the guidelines for PA, weight and nutrition, and some also continue smoking (12). While these lifestyle behaviors in cancer survivors seem comparable to the general population (13, 14), cancer survivors may have a higher need of the health benefits from a healthy lifestyle given their increased risk of poor health and late effects (15). However, cancer and its treatment, as well as being affected by AEs, can reduce the ability to obtain or maintain a healthy lifestyle (5, 16). Thus, tailored interventions aimed at improving the lifestyle in cancer survivors are highly needed. There is a growing recognition that the AEs and barriers towards a healthy lifestyle that cancer survivors and patients meet are unique, and vary across diagnostic groups, stages and treatments (15). For many subgroups of cancer survivors, we lack empirical knowledge on their lifestyle, characteristics of those with an unhealthy lifestyle and AEs. In order to create and implement effective lifestyle interventions for the broad spectrum of cancer survivors, there is a need to identify subgroups that might need particular support to obtain a healthy lifestyle (15, 16).

This thesis focuses on Norwegian prostate cancer (PC) patients and selected groups of long-term young adult cancer survivors (YACSs) diagnosed at the age of 19-39 years with BC, colorectal cancer (CRC), non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL) or localized malignant melanoma (MM), the latter serving as a comparison group. All these populations have overall high long-term survival rates (9, 17), but also face substantial risks of AEs (18, 19), which can possibly be prevented or alleviated by a healthy lifestyle. The overall aim of the current thesis is to contribute with new knowledge on lifestyle and AEs in these populations, which is relevant for providing these cancer survivors with targeted support, education and interventions towards obtaining a healthier lifestyle.

2.0 Background

2.1 Cancer epidemiology and cancer treatment

Cancer is a group of diseases, characterized by DNA damage and unrestricted cell proliferation (20). The overall number of individuals diagnosed with cancer in Norway increases every year, mainly due to an aging and growing population, as well as implementation of screening and improved diagnostics (9). In 2017, 33 564 individuals were diagnosed with cancer in Norway, of which approximately 50% had prostate, female breast, lung or colon cancer (9).

From 1965-2017, the 5-year relative survival rate for all new cancers in Norway has increased from less than 40% to more than 70% (9). This may be attributed to a combination of the effects of screening, more effective treatments and improved disease management (9). Cancer treatment for the individual patient is based on consideration of several cancer-related and individual factors, such as age, risk group, risk of AEs, life-expectancy, general health and the patient's own preferences (21). The major cancer treatment modalities are surgery, radiation therapy (RT) and systemic therapies, including chemotherapy and hormone therapy, which are often combined into multimodal treatment regimens (21, 22).

2.1.1 Prostate cancer

PC is the most common cancer in Norway, with approximately 5000 new cancer cases each year (9). Median age at diagnosis is 69 years. The incidence of PC in Norway has increased steeply during the recent decades (Figure 1), which is largely attributed to an aging population and introduction of prostate specific antigen (PSA) blood testing in the 1990's (9, 23).

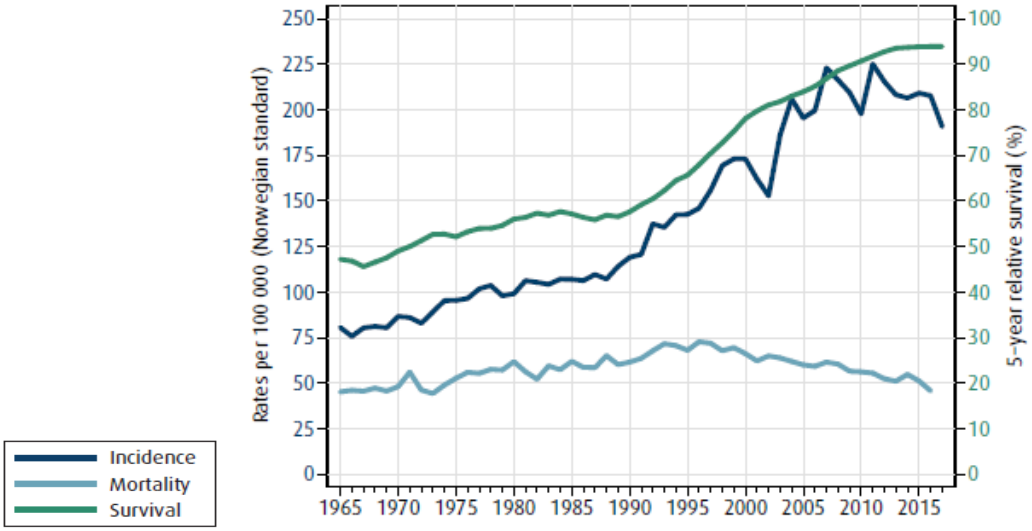

Figure 1: Trends in prostate cancer incidence, mortality and survival in Norway, 1965-2017. Reprinted with permission from the Cancer Registry of Norway.

PC may be suspected based on elevated PSA level, findings on a digital rectal exam and/or urinary problems (24). The diagnosis is confirmed through a biopsy. Staging and risk profile of PC is based on

PSA level, the Tumor, Node, Metastasis system and Gleason grading. While the Tumor, Node, Metastasis system describes the anatomical extent of the cancer, Gleason grading determines the aggressiveness of the cancer based on the growth pattern of the tumor cells (24, 25). Corresponding to the European Association of Urology guidelines 2017 (26), the risk for recurrence of localized or locally advanced PC can be classified as low-, intermediate- or high-risk. Of all new PC cases diagnosed today, the majority is at an early stage, and associated with a high relative survival rate. The 5-year relative survival for PC in Norway is currently 94% (Figure 1) (9).

Curative treatment for localized and locally advanced prostate cancer

In Norway, curative treatment options for localized and locally advanced PC include radical prostatectomy (RP), RT with or without temporary androgen deprivation therapy (ADT) or active surveillance (24).

RP involves surgical removal of the prostate gland and seminal vesicles, and sometimes additional lymph node dissection (24). The procedure is performed as open, laparoscopic or robot-assisted laparoscopic surgery. RT is given as high-dose external beam therapy and/or by radioactive sources within the prostate gland (brachytherapy) (24). RP and RT are considered equally effective for treatment of localized PC (27). In Norway, RP is mainly used in younger patients with low- or intermediate-risk PC with a life expectancy of at least 10 years, whereas RT is more common among high-risk patients and older men (23) .

Most PC cells are dependent on androgen stimulation for growth and proliferation, and ADT is therefore an effective strategy to counteract progression of PC (28). ADT comprises treatments resulting in suppression of androgen activity to castrate level (28). ADT can be performed as bilateral orchiectomy, but is more often achieved through injections of luteinizing hormone-releasing hormone agonists because of the potential of reversibility (29). RT combined with ADT has shown to improve survival in patients with intermediate- or high-risk PC compared to RT alone (30, 31). For patients receiving adjuvant ADT, the treatment period has usually been at least 6 months, sometimes extended to 2-3 years, dependent on risk group and stage of the disease (24).

Active surveillance aims to avoid or delay curative treatment and AEs associated with RT and RP, without reducing the chance of cure (26). Active surveillance is applied on patients with low-risk PC only, and includes close follow-up with PSA-testing, biopsies and magnetic resonance imaging. Curative treatment is initiated if tests reveal signs of disease progression (24).

Treatment of metastatic prostate cancer

Lifelong ADT is applied for patients with metastatic PC (24). The combination of ADT and chemotherapy has shown to result in longer survival than ADT alone for men with metastatic PC (32), and is today first-line treatment for patients with metastatic PC at first presentation and patients with castration-resistant PC (24, 29).

Watchful waiting is a conservative management for patients who are too frail to undergo radical treatment (29). Symptomatic treatment is initiated in the case of clinical progression. The treatment intent of watchful waiting is palliative, and in contrast to active surveillance, it is applied to PC patients at all stages (29).

2.1.2 Cancer in young adulthood

Cancer in young adulthood is not defined by a definitive age range. Often, adolescent and young adult (AYA) cancer survivors are included in the same cohorts, commonly with a lower age limit of 15 years, and with upper age limits varying from 24-39 years (33-36). In Europe and U.S., the field of young adult oncology typically includes individuals in the age range of 20-39 years, which is also commonly used for statistical purposes (35-38). In the Norwegian childhood, adolescent and young adult cancer survivors (NOR-CAYACS) study (39), which Paper II and III in this thesis are based upon, YACSs were defined as individuals diagnosed with cancer at age 19-39 years.

Each year, approximately one million people worldwide are diagnosed with cancer at the age between 20 and 39 years (35). In Norway, 1294 individuals aged 20-39 years (742 women and 552 men) were diagnosed with cancer in 2017, accounting for about 4% of the total number of new cancers (9). Figure 2 shows the most frequent cancers diagnosed in 2017 in Norwegian young adults (9).

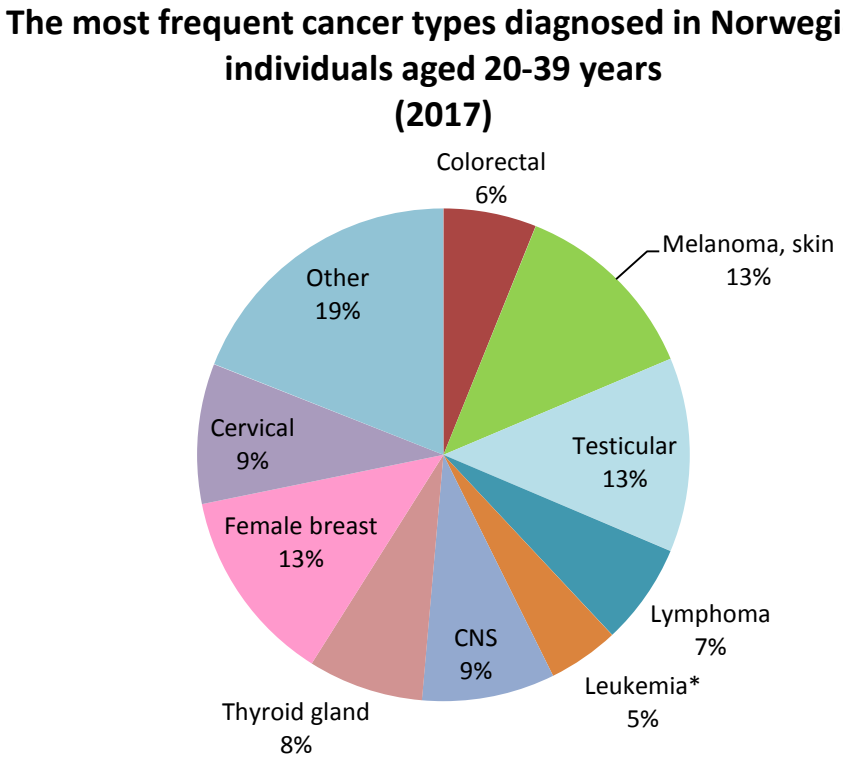

Figure 2: The most frequent cancer types diagnosed in Norwegian males and females aged 20-39 years in 2017, based on numbers from the Cancer Registry of Norway (40). Leukemia: all types, including unspecified tumors in lymphatic or hematopoietic tissue. Lymphoma: non-Hodgkin and Hodgkin lymphoma. CNS = central nervous system.

The spectrum of cancers in young adults differs from that observed in younger and older populations and varies by age among the affected (37). Young adults in the lower age range are most commonly affected by ALL, lymphoma and central nervous system tumors, whereas BC, CRC, MM and testicular cancer become more common as age increases (19). Globally, BC, cervical cancer, thyroid cancer, leukemia and CRC are the most frequent cancers in young adults (35).

The 5-year relative survival rate after cancer diagnosed in adolescence and young adulthood has now exceeded 80% in high-income countries (17). Due to better general health and higher tolerance of intensive cancer treatment, the overall survival of cancer is higher among young adults than among older individuals (41). However, for some cancers, such as BC, CRC and leukemia, the prognoses are poorer among those diagnosed in young adulthood than at other ages (41), which may be due to distinct genetic and biological disease characteristics (42). Epidemiology and treatment strategies of the cancer types relevant for this thesis are briefly presented below.

Breast cancer

In Norway, about 3400 women are diagnosed with BC each year (2013-2017), with a median age of 62 years at diagnosis (9). Approximately 5% of all women diagnosed with BC in Norway are aged 20-39 years. The current 5-year relative survival rate of BC in Norway has now exceeded 90% (9).

The Norwegian treatment recommendations for BC are issued by the Norwegian Breast Cancer Group (43). From the 1980s, surgery has involved modified radical mastectomy or breast-conserving surgery followed by RT of the remaining breast tissue (43, 44). RT is also recommended to those with axillary lymph node metastases. At present, breast-conserving surgery is typically preferred over modified radical mastectomy due to similar survival rates and less AEs (43, 44). After surgery, adjuvant systemic treatment is recommended based on tumor and patient characteristics to reduce the risk of recurrence and improve long-term survival (43). In women younger than 50 years diagnosed with early-stage BC, adjuvant chemotherapy reduces the absolute risk of recurrence by 12% and of BC mortality by 10% 15 years after (45). Anthracycline-based regimens are superior to the chemotherapy used in the past, and adjunction of taxanes to anthracyclines improved outcomes in women with more aggressive BC (46). Further, addition of trastuzumab to chemotherapy increased survival in women with human epidermal growth factor receptor 2 positive BC (47). For women with estrogen receptor-positive disease, 5 years of adjuvant endocrine treatment reduces BC mortality and recurrence (45). In premenopausal women, continuing tamoxifen for 10 years has shown to produce further benefits in BC survival (48).

Colorectal cancer

In Norway, colon cancer is the third most common cancer in men, and the second most common in women (9). Rectal cancer accounts for approximately 30% of all CRC cases. Median age at diagnosis is 73 years for colon and 69 years for rectal cancer. Annually, about 4300 individuals are diagnosed

with CRC (2013-2017), of whom about 2% are in the age range of 20-39 years (9). Although the overall incidence of colorectal cancer is decreasing in many high-income countries, the incidence of CRC in young adults has increased the last decades (49, 50). The total 5-year survival rates for colon cancer are 64% in men and 68% in women and for rectal cancer approximately 69% for both sexes (9).

Treatment of CRC is multimodal, although surgery is still the mainstay in curative treatment of CRC (51). To improve survival in patients with stage III or high risk-stage II colon cancer, surgery is often followed by adjuvant chemotherapy (51). Oxaliplatin in addition to the combination of fluorouracil and leucovorin has led to improved survival (51-53). In patients with locally advanced rectal cancer, RT alone or in combination with chemotherapy is given preoperatively to reduce the risk of local recurrence (51).

Non-Hodgkin lymphoma

Lymphomas are categorized into Hodgkin lymphoma (accounting for 10% of all lymphomas) and NHL (54). About 1000 new cases of NHL are diagnosed each year in Norway (2013-2017), with a median age of 69 years at diagnosis (9). Approximately 4% of these cases are diagnosed in individuals between the ages of 20-39 years. The 5-year relative survival rate of patients diagnosed with NHL is 73% for men and 77% for women (9).

Treatment of NHL is principally based on various chemotherapy regimens sometimes combined with RT and/or antibody-treatment (rituximab) (55). For indolent NHL, localized disease can be cured with RT alone (55).

High-dose therapy with autologous stem cell support has been offered in Norway since 1987 for selected lymphoma patients with poor prognosis, as consolidation after one or more lines of conventional chemotherapy (56). This treatment consists of highly intensive chemotherapy and/or total body irradiation, followed by reinfusion of previously harvested stem cells from blood or bone marrow to prevent permanent loss of bone marrow function (56). In Norway, high-dose therapy with autologous stem cell support consisted of total body irradiation in combination with chemotherapy until 1995, and as chemotherapy only thereafter (56).

Acute lymphoblastic leukemia

Approximately 70 individuals are diagnosed with ALL each year in Norway, of whom about 10 individuals are aged 20-39 years (2013-2017) (9, 57). The 5-year relative survival rate for ALL in Norway is 59 % for women and 75 % for men among individuals diagnosed between the ages of 20-39 years (9)

Treatment of ALL is largely based on intensive chemotherapy regimens, with a treatment duration of 2.5 years (58). In 1992, the Nordic Society of Pediatric and Hematological Oncology (NOPHO) launched a common Nordic ALL protocol (59). Today, treatment according to the NOPHO-ALL 2008

protocol is recommended first-line treatment for Norwegian patients with ALL aged 18-45 years, with different treatment intensity for defined risk groups (58, 59). Allogeneic stem cell transplantation is considered for patients with relapse or high-risk disease (58).

Malignant melanoma

Globally, Norway is one of the countries with the highest rates of MM (9). About 2050 individuals are diagnosed with melanoma each year in Norway (2013-2017), with a median age of 65 years at diagnosis. Of these, about 7% are diagnosed in between the ages of 20-39 years. In Norway, 87% of melanoma patients have localized disease at diagnosis, with relative 5-year survival rate of 94% for females and 91% for males. For patients with distant metastases at diagnosis, the 5-year relative survival rate is 39% for females and 23% for men (9).

Surgery is the definitive curative treatment of localized MM (60). Adjuvant medical treatment is given to patients with MM stage ≥ II, to reduce the risk of recurrence (60).

2.2 Cancer survivorship and adverse effects

The concept of cancer survivorship was introduced in 1985, when Dr. Fitzhugh Mullan described his own experience with cancer and the survival challenges through three seasons or phases; acute survival (from diagnosis to completion of initial treatment), extended survival (from completion of initial treatment) and permanent survival (extended disease-free survival with low risk of recurrence) (61). Emerging data on health complications among long-term childhood cancer survivors brought attention to the late effects after cancer and cancer treatment, and consequently, more focus and research were directed towards the long-term health of cancer survivors (2).

Even though many cancer survivors regain their health and functions after treatment (62), most cancer treatments are associated with a wide spectrum of acute and late physical and psycho-social AEs (2). Any organ system can be affected, dependent on the diagnosis, type and intensity of cancer therapy. Some AEs, such as urinary incontinence, bowel problems and fatigue, may influence heavily on daily functioning and QoL (2). Long-term cancer survivors may also be at risk of serious and life-threatening late effects, such as second cancer and cardiovascular diseases (18, 22). An overview of AEs most relevant for this thesis is given below.

2.2.1 Adverse effects during and after treatment for prostate cancer

Estimated prevalence rates of AEs vary across the studies described below, due to different definitions of AEs and measures, and uneven baseline characteristics of the populations studied, such as age and pre-treatment status of erectile function and incontinence (63, 64).

Radical prostatectomy

Urinary incontinence after RP mainly results from damage to the structures regulating micturition (65). In a review, Ficarra et al. found that the prevalence of urinary incontinence (defined as any use of

pads) ranged from 4-31%, 12 months post-RP (64). In the Prostate Testing for Cancer and Treatment (ProtecT) trial, 1% used urinary pads at baseline, while 45% used pads 6 months post-RP. After 6 years, 17 % used one or more urinary pads per day (66). Among Norwegian patients treated with RP, 60% had regained their pre-treatment urinary function after 2 years (67).

According to a systematic review and meta-analysis, erectile dysfunction was present among 10-46% of PC patients 1 year post-RP, and among 6-37% 2 years after treatment (63). In the ProtecT-trial, 33% had erectile dysfunction at baseline, 88% at 6 months, and 79% 1 year post-RP (66). In a study investigating the prevalence of erectile dysfunction in American, Norwegian and Spanish PC patients, 73% had erectile dysfunction 2-3 years after RP compared to 23% before RP (68). Two years after RP, Stensvold et al. reported that 30% of the patients had at least returned to their pre-treatment level of sexual bother (67).

Radiation therapy

RT for PC may result in bowel problems, urinary irritation/obstruction symptoms and sexual dysfunction (66). Despite improvement of RT planning and techniques during the past decades, occurrence of AEs, particularly bowel symptoms, represent the main dose escalation limitation in curative RT for PC (69) .

Incidence and severity of bowel symptoms following RT are dose- and volume dependent (69). Examples of acute AEs following RT are diarrhea, abdominal pain, frequent or urgent bowel movements and rectal bleeding, usually resolving within 6 months. However, these symptoms may also persist or occur as late effects, up to 2 years after completed RT (69). In a prospective study, Sanda et al. found that 9% experienced distress related to bowel symptoms 12 months after RT, compared to 2-3% at baseline (18). In the ProtecT-trial, bowel symptoms were worse for patients treated with RT than for patients treated with RP or active surveillance, particularly after 6 months, but then mostly recovered and remained stable, except for increasing incidence of rectal bleeding up to 6 years (66).

Acute urinary irritation symptoms are common the first few months after RT, but then usually recover and remain stable (18, 66). Similar observations have been made for erectile dysfunction after RT, with older age and ADT associated with poorer sexual function (18, 66). PC patients treated with RT are also at a slightly increased risk of being diagnosed with second cancers of the rectum and bladder (70, 71).

Androgen deprivation therapy

Androgens are involved in several normal bodily processes, and men undergoing ADT are therefore at risk of a range of major long-lasting AEs (72) . Loss of sexual function appears in most men receiving ADT (72). Moreover, ADT may be followed by fatigue, loss of bone mineral density and elevated risk

of fractures, increased fat mass and decreased muscle mass and reduced physical function (28, 72, 73). ADT-induced changes in lipid profile, insulin sensitivity, and body composition may result in metabolic syndrome, increasing the risk of diabetes and cardiovascular diseases (28, 72). Evidence on the link between ADT and cardiovascular mortality is, however, inconsistent (72).

2.2.2 Survivorship challenges and late effects relevant for young adult cancer survivors

Experiencing a life-threatening disease during young adulthood can have a large negative effect on adherence, participation and coping of areas typical in that stage of life, such as education, employment, social network and family establishment, which may also follow the patients into survivorship (74). Many YACSs also experience poor health in the years after finalized cancer treatment, which is not only affecting the individual, but also their families and the society as a whole in terms of elevated health care expenditures and lost productivity (75). Thus, young adults living beyond cancer have distinct physiological, psychological and social characteristics, which can provide survivorship challenges different from those experienced by individuals diagnosed with cancer at other ages (19).

Still, the understanding of survivorship in long-term YACSs is limited, and recognized as understudied compared to other age groups of cancer survivors (19). Knowledge on late effects among YACSs is largely based on studies among long-term childhood cancer survivors, and on single studies on survivors of Hodgkin lymphoma and testicular cancer (76). Late effects that are relevant for YACSs and the cancer types included in this thesis irrespective of age at diagnosis are briefly described below.

Mortality and morbidity

Studies assessing mortality among survivors of cancers diagnosed in childhood and up to age 24 describe mortality rates 6-10 times higher than the population in general, lasting for up to 25 years after the primary cancer diagnosis (77-80). The excess mortality in these studies was mainly due to cancer recurrence, second cancer and cardiovascular diseases.

Second cancer

In addition to genetic predispositions and other individual risk factors such as aging and lifestyle, the etiology of second cancers includes factors related to the treatment of the first cancer, particularly RT and certain chemotherapy regimens, such as alkylating agents and anthracyclines (80). In a U.S. study describing the incidence and characteristics of second cancers in long-term AYA survivors, the 30 years cumulative incidence of developing a second cancer was 13.9% (81). The absolute risk of second cancer was higher for AYA survivors compared to survivors diagnosed at younger and older ages, and the risk of cancer in the general population. Survivors originally diagnosed with NHL or BC were among those with the highest risk of second cancer, as well as AYAs treated with RT (81). Similar findings were recently reported in a large British population-based study (82).

Cardiovascular diseases

Long-term cancer survivors may develop cardiovascular diseases such as left ventricle dysfunction, heart failure, coronary atherosclerosis, arrhythmia and myocardial infarction (83). The risk for these conditions is largely attributed to cardiac injury from cancer therapies such as anthracyclines, and RT involving the chest (83). As in the general population, further risk factors for cardiovascular diseases in cancer survivors are smoking, hypertension and diabetes (83).

An elevated risk of cardiovascular diseases is also documented in populations diagnosed with cancer before the age of 40, mainly based on research on survivors of childhood cancer, testicular cancer and Hodgkin lymphoma (76). A large Finnish study found that long-term survivors of cancers diagnosed between the age of 20-34 years had significantly higher risks for cardiovascular diseases compared to healthy siblings (84). Survivors of NHL and ALL were among the YACSs with the highest risk of cardiovascular diseases (84). A recent study investigating cardiac mortality in more than 200 000 long-term AYA cancer survivors reported that survivors of NHL, leukemia and BC experienced a higher number of cardiac deaths compared to the general population (85).

Overweight and obesity

An analysis of the U.S. National Health Interview Survey demonstrated that the annual prevalence of obesity from 1997-2014 increased more rapidly in cancer survivors than in the general population (86). The reason why cancer survivors are at higher risk of overweight and obesity is largely unknown, but might be partly explained by that certain treatments are associated with increased risk of overweight and obesity, such as chemotherapy and endocrine cancer treatment (87, 88). Further, as several cancer types, such as post-menopausal BC and CRC are linked to obesity, a large number of cancer survivors are also overweight/obese at the time of diagnosis (86).

Pain

Pain in relation to cancer treatment is common, but usually diminishes over time as the affected tissue heals and regenerates (89). It is estimated that 5-10% of long-term cancer survivors experience pain interfering with daily functioning, with higher prevalence in certain subpopulations, such as BC survivors (89). A Danish study reported that 42% of BC survivors experienced chronic pain (at least 6 months duration) 5 years or more after surgery. Chronic pain was more common among BC survivors treated with RT and those who were less than 10 years from surgery (90). Median 4 years after surgery, Nesvold et al. found a higher prevalence of shoulder pain among BC patients treated with radical modified mastectomy (32%) than among patients treated with breast conserving therapy followed by RT (12%) (91).

Lymphedema

Lymphedema is most commonly reported after BC treatment, but can also affect survivors of other cancer types as a consequence of surgery and/or RT (92). A review estimated that approximately one

of five BC survivors develops arm lymphedema, with increasing risks among those treated with more extensive surgery and with overweight/obesity (93). In the study by Nesvold et al. the prevalence of arm lymphedema was 8% in those treated with breast conserving therapy compared to 20% among those treated with radical modified mastectomy (91).

Numbness in hands and feet

Several chemotherapeutic drugs, including platinum compounds, vinca alkaloids and taxanes, can result in neuropathic symptoms such as numbness in hands or feet, which may endure after completed treatment (94). Among BC survivors treated with taxanes, 28% reported moderate to severe symptoms of numbness in hands/feet, mean 6 years after diagnosis (95). In a study comparing neurotoxicity among long-term CRC survivors treated with or without oxaliplatin, a significantly higher level of numbness in hands and feet was found among patients treated with than without oxaliplatin after 6 years (96).

Psychological health and sleep problems

Symptoms of depression and anxiety are common during the cancer trajectory, but decrease with time (22). A large meta-analysis found that while the risk of depression among cancer survivors was high initially, no difference in prevalence of depression was found between cancer survivors (12%) and healthy controls (10%) after 2 years or more (97). However, the prevalence of anxiety was higher in cancer survivors (18%) than in the controls (14%), and the elevated risk of anxiety disorders among cancer survivors seemed to last for 10 years or more (97).

Trouble sleeping/insomnia includes difficulties initiating or maintaining sleep and/or early-morning-awakenings (98). In a recent study, 35-39% of long-term cancer survivors reported trouble sleeping compared to 23% among healthy controls (99).

Regarding the psychological health of long-term YACSs, evidence is limited, but higher levels of mental distress in this population compared to controls have been shown (100, 101).

Fatigue

As one of the main aims of this thesis was to explore fatigue among YACSs, this symptom is described in detail below.

According to the National Comprehensive Cancer Network, fatigue in cancer patients and survivors is defined as a “distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (102). The majority of cancer patients experience increased level of fatigue during therapy (103, 104). Usually the level of fatigue decreases during the first year post-treatment (105), but in a significant proportion of cancer survivors, fatigue persists or appears several years after treatment (106). Substantial fatigue lasting for 6 months or longer can be defined as chronic

fatigue (CF) (107). Fatigue persisting for years may have a substantial negative impact on physical and psychological function and may also limit the ability to participate in daily activities (103, 108).

Given the subjective nature and lack of consensus on objective, diagnostic criteria for fatigue, several questionnaires are developed to measure fatigue or similar constructs (109). Using the Short Form Survey-36 vitality subscale (110), Bower et al. found that 35% of BC survivors had fatigue 5-10 years after diagnosis (111). Thong et al. (112) classified 39% of CRC survivors as fatigued up to 10 years from diagnosis using the Fatigue Assessment Scale (113). In a sample of Hodgkin lymphoma survivors examined 5 years from treatment, Daniëls et al. reported that 43% were fatigued (114), using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ C30) fatigue subscale (115). Although all these studies demonstrate high prevalence rates of fatigue several years after cancer diagnosis, different definitions and measures of fatigue hinders direct comparison across studies. Further, as these questionnaires assess fatigue during the past few weeks, the proportion of individuals with more long-lasting symptoms is not identified. In Norway, the Chalder Fatigue Questionnaire (FQ) (107) is widely used to measure severity and duration of fatigue, and to identify the prevalence of CF in both the general population and in different cancer populations (116-134) (Table 1). While the prevalence of CF assessed by the FQ in cancer survivors mostly ranges from 15-35 %, Loge et al. (134) found that 11 % of the Norwegian general population reported CF (Table 1).

Table 1: Norwegian studies assessing chronic fatigue (CF) with the Fatigue Questionnaire

Authors	Study sample: cancer type, n, age, observation time.	Prevalence of CF	Factors associated with CF/other results
	General population		
Loge et al. 1998 (134)	The general Norwegian population, n=2323.	11%	Higher prevalence of CF in those with disease /health problems
	Cancer survivors		
Loge et al. 1999 (123)	HL, n=459. Mean age 32 years at diagnosis, 12 years from treatment.	26%	Increasing age and higher disease stage
Fosså et al. 2003 (124)	TC, n=791. Median 44 years at survey, 12 years from treatment.	16%	Comorbidity, anxiety, depression, increasing age.
Hjermstad et al. 2005 (125)	HL, n=476. Median 46 years at survey, 16 years since diagnosis.	30%	Presence of B-symptoms and treatment period
Aksnes et al. 2007 (135)	Extremity bone tumors (EBT), HL and TC, n=208. Mean 16 -25 years at diagnosis, 10-14 years since diagnosis.	EBT: 14%, HL 21%, TC 16%. Controls: 10%.	No significant difference in prevalence of CF among survivors of EBT compared to controls.
Vistad et al. 2007 (126)	Cervical cancer, n=79. Mean 62 years at survey, 8 years since treatment.	30%	Depressive symptoms
Orre et al. 2008 (127)	TC, n=1431. Mean 33 years at treatment, 11 years since treatment.	17 %	Somatic complaints, poor quality of life, neuroticism.
Reinertsen et al. 2010 (128)	BC, n=249. Median 52 years at diagnosis, 4 years since diagnosis	33% 3-7 years post-treatment, 39% 3 years after. 23% at both points	11-12 years of education, BMI ≥ 30, pain, depression, anxiety, increasing leukocyte count.
Kyrdalen et al. 2010 (118)	PC survivors treated with RP or RT (n=521). Median 63 years at diagnosis, ≤ 3 years since treatment.	RP: 13%, RT: 26%	High neuroticism, comorbidity, pain, urinary and intestinal dysfunction.
Kyrdalen et al. 2010 (121)	PC survivors post-RT, n=239. Median 65 years at diagnosis, 0-2 years since RT.	Ongoing ADT: 39%, discontinued ADT: 22%	Lower age, high neuroticism, pain, urinary and intestinal dysfunction, lower sexual function
Jóhannsdóttir et al. 2012 (122)	Childhood cancer survivors, n=398. 10-16 years since diagnosis.	11%	Survivors ≥19 years with CF had poorer physical health, but better mental health than controls with CF.
Hamre et al. 2013 (116)	ALL, NHL, HL diagnosed at age ≤18 years, n=290. Median 21 years since diagnosis.	Total 28% (ALL 23%, NHL 30%, HL: 35%).	Depression and anxiety. ALL-survivors: increasing age at survey. HL/NHL-survivors: B-symptoms
Zeller et al. 2014 (117)	Lymphoma and ALL diagnosed ≤18 years, n=102, mean 23 years since diagnosis.	31%	Depressive symptoms
Seland et al. 2015 (130)	NHL, n=98. Median 44 years at diagnosis, 16 years observation time.	29%	Hormonal dysfunction and mental stress.
Sprauten et al. 2015 (119)	TC, n=812. Median 32 years at diagnosis, 12-19 years from diagnosis.	15% median 12 years after diagnosis, 27% 7 years thereafter.	Neuropathy, Raynaud-like phenomena, low testosterone levels, anxiety and depression. Physical activity had a protective effect.
Kiserud et al. 2015 (129)	Male lymphoma survivors, n=233.Median 48 years at diagnosis, 15 years from treatment.	27 %	Depressive and anxiety symptoms and age ≥ 60 years. Survivors with CF had increased risk for not working.
Lilleby et al. 2016 (131)	PC survivors, n=206, receiving RT +ADT or RT only, mean 66 years.	Baseline: 11-18%. 36 month after RT: 36-39%.	Reduced physical and mental quality of life. No difference in prevalence of CF between treatment groups.
Steen et al. 2017 (120)	Cervical cancer, n=382. Median 41 years at diagnosis, 11 years follow-up time.	23%.	Increased level of depression and poorer global quality of life
Reinertsen et al. 2017(132)	BC, n=84. Median 50 years at diagnosis.	8% before chemotherapy, 36% at 2 years after	Psychological distress
Smeland et al. 2018 (133)	Lymphoma survivors,, n=311. Median 42 years at diagnosis, 13 years from diagnosis.	31%	Neuroticism, obesity, poor cardiorespiratory fitness, detectable serum IL-6.

CF=chronic fatigue, NHL=non-Hodgkin lymphoma, HL=Hodgkin lymphoma, TC=testicular cancer, PC=prostate cancer, AML=acute myeloid leukemia, ALL=acute lymphoblastic leukemia, BC=breast cancer, ADT=androgen deprivation therapy, IL-6= interleukin-6. QoL: quality of life. RT: radiation therapy. RP: radical prostatectomy. BMI: body mass index (kg/m^2).

The etiology of fatigue is considered multifactorial, involving both physiological and psycho-social factors (106). A recent meta-analysis including 12 327 BC survivors found that the risk of severe fatigue increased after treatment with surgery, RT and chemotherapy, and survivors with this combination plus hormone therapy, compared to other treatment combinations (136). Still, a relation between cancer-related fatigue and treatment-related factors, such as type and intensity of cancer treatment, is not consistently demonstrated (106, 108, 137). Various biological mechanisms have been studied as potential causes of fatigue, including immune activation and inflammatory processes following cancer and cancer treatment (106). Elevated levels of pro-inflammatory cytokines have been observed before, during and after treatment, primarily in BC patients and survivors. However, evidence on the association between biological mechanisms and fatigue is inconsistent and not documented in all patient groups (106). Further, endocrine, cardiac and pulmonary dysfunction, pain, obesity, psychological distress and sleep disturbances have been reported to be associated with fatigue in cancer survivors (106, 132, 138-140). Importantly, fatigue can be a symptom of depression, and the strong relationship between fatigue and depressive symptoms is documented in several studies (114, 141, 142).

Why fatigue persists and becomes chronic in some cancer survivors is not known, but several factors are associated with CF, including hormonal dysfunction, elevated level of pro-inflammatory cytokines, comorbidity, pain, neuropathy, obesity, neuroticism and psychological distress (119, 124, 128, 130, 132, 133) (Table 1).

Fatigue in young adult cancer survivors

When the work with this thesis was initiated, fatigue was studied predominantly in populations diagnosed with cancer after the age of 39 years or in childhood (143). Data from the few existing studies including YACSs suggest that these individuals have a higher level of fatigue than age-matched controls and individuals diagnosed with cancer further into adulthood (144-150) (Table 2). However, the age span at diagnosis varied considerably across these studies; from as low as 13 years (150) to as high as 45 years (147, 148). Further, the majority of these studies did not have fatigue as the primary outcome, and used subscales of health-related QoL instruments to measure fatigue severity (144, 146-149). Only two small studies conducted on survivors of mixed cancer types during or shortly after treatment reported on the prevalence of fatigue (145, 150) (Table 2), but as the instruments used in these studies did not capture fatigue lasting for more than the last month, the proportion of individuals with long-lasting fatigue could not be identified.

Table 2: cross-sectional studies investigating fatigue in young adult cancer survivors

Authors	Population	Age	Time from diagnosis/ treatment	Fatigue measure	Prevalence of fatigue	Associated factors/other results
Bifulco et al. (148)	Breast- and gynecological cancer patients, n=263.	Divided into 18-45 and 46-65 years at survey.	Within 4 years from cancer treatment	EORTC QLQ-C30 (115)	Not reported	Worse fatigue among survivors aged 18-45 years than survivors aged 45-65 years
Smith et al. (2013) (146)	Survivors mixed cancer types, n=523	Aged 15-39 years at diagnosis, median age 30 years.	6-14 months post-diagnosis	PedsQL, fatigue subscale (151)	Not reported	Older age, non-insurance, RT, current treatment, symptom burden. Worse fatigue in survivors than controls.
Champion et al. (2014) (147)	Breast cancer survivors, n=1127. N=505 diagnosed at age 45 or younger.	Divided into age groups ≤45 years and 55-70 years at diagnosis	3-8 years from diagnosis	FACT-F (152)	Not reported	Survivors diagnosed ≤45 years reported more fatigue than age-matched controls and survivors >55 years at diagnosis
Geue et al. (2014) (144)	Survivors of mixed cancer types, n=117	Aged 18-39 years at survey	Median 2 years from diagnosis	EORTC QLQ-C30 (115)	Not reported	Worse fatigue in survivors than controls, and in female than male survivors.
Poort et al. (2017) (145)	Survivors of mixed cancer types, n=83	Mean 29 years at survey	Mean 2 years from diagnosis.	CIS-fatigue (153)	48% of cancer patients with severe fatigue compared to 20% of controls.	Female gender, not employed, late cancer stage, active treatment, palliative treatment, RT, depression, anxiety and fear of recurrence.
Husson et al. (2017) (149)	Lymphoma survivors, n=198	Mean 35 years at survey	Mean 4 years since diagnosis	EORTC QLQ-C30 (115)	Not reported	Worse fatigue among survivors than controls.
Spathis et al. (2017) (150)	Survivors of mixed cancer types, n=80	Mean 18.2 years at diagnosis	Median 31 months from diagnosis	PedsQL fatigue subscale (151)	85% had experienced fatigue the last month.	Anorexia and low mood.

HL=Hodgkin lymphoma, NHL=non-Hodgkin lymphoma, EORTC QLQ-C30= the European Organization for Research and Treatment of Cancer core quality of life questionnaire, PedsQL= Pediatric Quality of Life Inventory study, FACT-F Functional Assessment of Cancer Therapy fatigue subscale, CIS-fatigue= Checklist Individual Strength, subscale fatigue severity AYA= adolescent and young adult

Thus, the prevalence of CF in YACSs was largely unknown when the work with Paper III started, with the exception of studies in survivors of lymphoma, bone cancer and testicular cancer, where parts of the study populations were diagnosed during young adulthood (119, 129, 130, 135) (Table 1). In these studies, approximately one of four reported CF. A systematic review on fatigue in individuals diagnosed with cancer at the age between 15-39 years concluded that there is a significant gap in knowledge of prevalence, severity and risk factors of fatigue in this population (143). Further, understanding how fatigue changes over time is important for the clinical care of YACSs with fatigue (143), but to our knowledge, this has not been investigated previously in long-term YACSs.

2.3 Lifestyle in relation to cancer-related adverse effects

The risk of AEs during and after cancer may be influenced, positively or negatively, by several factors, including individual characteristics (age, gender and genetics), type of cancer and its treatment, as well as lifestyle (154). In contrast to fixed individual- and cancer-related characteristics, cancer patients and survivors can often control and modify their lifestyle. A healthy lifestyle, including sufficient PA, a healthy diet and BMI, and non-smoking, is therefore suggested as a self-management strategy to prevent and/or reduce the risk of AEs during and after cancer treatment (15).

2.3.1 Physical activity

Cancer patients and survivors are at risk of impaired physical function, loss of muscle strength and reduced cardiorespiratory fitness, as a direct result of the cancer, its treatment and/or inactivity, as well as normal aging (155, 156). Previously, cancer patients were recommended to rest and avoid exercise, but during the last few decades, significant progress has been made in the field of exercise oncology. PA is now established as a safe strategy to mitigate cancer-related AEs during and after treatment (157). Several meta-analyses of interventional studies have identified significant effects of PA on physical functioning, cardiorespiratory fitness, muscle strength, fatigue, anxiety, depressive symptoms, self-esteem, fatigue and health-related QoL during and after cancer treatment (158-164).

Growing observational evidence also indicate that PA may extend survival among patients with BC (165), CRC (166) and PC (167, 168). Friedenreich et al. conducted a pooled analysis of 26 observational studies and found a 37% lower risk of death from the cancer among the most versus the least physically active cancer patients (169).

Physical activity and fatigue

Several studies have demonstrated an association between fatigue and physical inactivity in cancer patients and survivors; individuals with fatigue typically have poor cardiorespiratory fitness and/or low level of PA (170-172). Furthermore, an association between CF and physical inactivity has been documented in long-term survivors of lymphoma and testicular cancer (119, 133, 139, 173). However, the direction of this relationship has not been established. Physical inactivity may result in higher demands of work capacity in daily activities, and potentially development and worsening of fatigue during and after cancer treatment (106, 174). Longitudinal studies in BC survivors suggest that low level of PA before treatment predicts higher levels of fatigue up to 2 years afterwards (175, 176). On the other hand, cancer survivors affected by fatigue may avoid PA in order to reduce their symptoms because normal tiredness related to PA improves after rest (174). Another study in BC survivors found that women who reported higher levels of fatigue shortly after treatment were less likely to remain sufficiently physically active over time (172). Irrespective of the causality, PA seems to play a role in the development and worsening of fatigue among cancer survivors, and may be an important strategy to mitigate or avoid this symptom (106). No previous studies had explored the association between CF and PA exclusively in long-term YACSs when the work with this thesis started.

2.3.2 Other lifestyle aspects

Overweight and obesity

Obesity places individuals diagnosed with cancer with an elevated risk of cancer recurrence, second cancer and mortality (11). Large meta-analyses have demonstrated that overweight and obesity measured as BMI increases the risk of cancer specific and overall mortality in survivors of BC, PC and CRC (177-179). Obesity is also a strong risk factor for severe comorbid conditions such as heart disease and diabetes in cancer survivors, as well as lymphedema and other complications from cancer treatment (11).

Smoking

Smoking accounts for approximately 30% of all cancer deaths (180). Smoking cessation after getting cancer is associated with a better prognosis (181), better treatment response (182, 183), and reduced risk of second cancer and mortality (184) .

Intake of fruits and vegetables

Observational studies on BC survivors have found that dietary patterns including a high consumption of fruits and vegetables are associated with lower mortality from other causes than BC (185), overall mortality (186, 187) and BC recurrence (187). In a recent meta-analysis including more than 200 000 cancer survivors, a high intake of vegetables was linked to lower risk of overall mortality in cancer survivors (188).

Combination of lifestyle behaviors

Healthy lifestyle behaviors (or conversely, unhealthy behaviors), are likely to cluster within individuals, e.g. those who are physically active are likely to not smoke (189). Meeting several lifestyle guidelines probably provides superior health benefits compared to meeting only a single guideline (15). Smith et al. found that childhood cancer survivors at least 10 years from diagnosis (n=1598) were more than twice as likely of having metabolic syndrome if they met less than four guidelines on PA, BMI, and nutrition (intake of fruits and vegetables, complex carbohydrates, alcohol and sodium) than if they met at least four guidelines (190). In BC survivors diagnosed within the previous 5 years, Bruno et al. found that meeting a combination of PA and nutrition recommendations was associated with a 57% reduction in prevalence of metabolic syndrome, compared to those who met none or only one of the recommendations (191).

2.3.3 Lifestyle among cancer survivors in general

Despite the benefits associated with a healthy lifestyle, several cross-sectional studies have described that physical inactivity, overweight/obesity and unhealthy diets are common among cancer survivors (13, 189, 192, 193). Including more than 9000 survivors of BC, CRC, bladder, uterine and melanoma skin cancer, Blanchard et al. found that only 30-47% met PA guidelines and 15-19% met 5-a-day, while the majority refrained from smoking (83-92%) (189). Only 5% met the combination of PA, 5-a-day and smoking guidelines. Another large U.S. study on health behaviors of BC, PC and CRC

survivors reported that 30-47% met PA guidelines, 20-34% met 5-a-day and 25-40% had a healthy BMI (13). Similar results are demonstrated in Canadian (192) and Scottish (193) surveys.

These findings of low adherence to lifestyle guidelines among cancer survivors were recently confirmed in a systematic review including more than 2 500 000 cancer survivors (12). Pooled estimate rates showed that most cancer survivors were physically inactive (57 %), overweight (60%) and not meeting 5-a-day (66%), while a minor proportion were current smokers (13%). Few met the combination of two or more lifestyle guidelines (23%, range 7-40% across studies).

Although lifestyle among cancer survivors in general may seem well described, most of this information stems from U.S. populations aged 50 years or older at survey, within 5 years from a diagnosis of BC or CRC (12). These populations were also highly prominent in a systematic review reporting treatment-related AEs as key barriers of exercise among cancer survivors (16). To efficiently improve lifestyle of cancer survivors, tailored evidence-based interventions for the broad spectrum of cancer survivor populations are warranted (15). In this regard, knowledge about lifestyle and characteristics of survivors with an unhealthy lifestyle are needed for less studied subpopulations of cancer survivors. Current knowledge gaps regarding PA, lifestyle and AEs among men treated for PC and long-term YACSs at the time this thesis was initiated are described below.

2.3.4 Physical activity in prostate cancer patients

Physical activity level across treatment modalities and barriers of physical activity

Only a minority of PC patients and survivors meet the PA guidelines (+/- 40%) (189, 194-196). At the onset of the work with this thesis, little was known on whether treatment and AEs influence PA participation among PC patients. To our knowledge, only two prior studies had explored the association between treatment received and PA in PC patients (196, 197). These studies suggest that patients undergoing ADT are less physically active than patients treated with RT only (197), and other treatments without ADT (196). No prior study had compared the level of PA specifically across PC patients who had completed RP or RT +ADT, or were undergoing ADT.

Two qualitative studies have reported urinary incontinence (198, 199) and bowel symptoms (198) as PA barriers (Table 3). Further, two longitudinal studies have reported that urinary incontinence influence negatively on level of PA (200, 201).

Table 3: Studies exploring how adverse effects after treatment for prostate cancer influence physical activity level

Authors	Population	Results
Craike et al. 2011 (199)	PC patients who had completed treatment 6 months prior, n = 18	Barriers to PA were older age, lack of time, incontinence, fatigue, comorbidities.
Ottenbacher et al .2013 (201)	PC survivors, n = 193, BC survivors, n = 259	PC patients with urinary incontinence were less physically active
Geraerts et al. 2014 (200)	PC patients treated with RP, n = 240	Urinary incontinence was associated with less PA at 6 weeks, 3, 6 and 12 months after RP
Henriksson et al. 2016 (198)	PC patients undergoing treatment, n = 8	Bowel symptoms, urinary incontinence and lack of time were reported as PA barriers.

PC = prostate cancer, BC = breast cancer, PA = physical activity, RP = radical prostatectomy

2.3.5 Lifestyle among young adult cancer survivors: prevalence and associated factors

At the time Paper II was initiated, knowledge on lifestyle in long-term YACSs was limited. The few existing studies exclusively on long-term survivors were mainly on U.S AYA cancer survivors (14, 202, 203) for which the results do not necessarily apply to European long-term YACSs due to cultural and health care system differences. Other studies investigating lifestyle among cancer survivors within the age range of YACSs were based on small sample sizes and/or included individuals less than 5 years from diagnosis (101, 148, 204-208) (Table 4). While most of these studies report a high proportion of physically inactive and overweight, the prevalence rates of smoking vary between studies (14, 101, 202, 203) (Table 4).

Table 4: Studies exploring lifestyle aspects among young adult cancer survivors

Authors	Population (cancer type, n, age, time from diagnosis/treatment)	Results
Coups & Ostroff 2005 (202)	Mixed cancer types, n=1646, 12 % aged 18-39 years at survey. Mean 10 years from diagnosis.	Subpopulation aged 18-39 years at survey: 59% physically inactive, 52% overweight, 38% current smokers, 45% not meeting 5-a-day.
Love et al. 2010 (204)	Mixed cancer types, n=64. Mean age 28 years, 50 % 1-2 years since treatment.	39% met recommended guidelines for PA.
Shinn et al 2010 (209)	Testicular cancer, n=162. Median age 37 years, mean 4.5 years since diagnosis.	85% did not exercise for at least 20 minutes of moderate-vigorous intensity 3 times per week, 18% reported current smoking, 89% did not meet 5-a-day.
Rabin & Politi, 2010 (205)	Mixed cancer types, n=60. Aged 20-39 years, diagnosed on average 5 years prior.	42% met PA guidelines. 35% were overweight/obese, 25% meeting recommendations for vegetable consumption, 13% were smoking.
Bélanger et al. 2011 (208)	Mixed cancer types, n=588. Age 20-44. Mean 6 years from diagnosis.	49% were physically inactive, 53% overweight, 13% current smokers.
Tai et al. 2012 (101)	Mixed cancer types,n= 4054. Diagnosed at age 15-29 years, 0->20 years ago.	30% of cancer survivors reported no leisure-time PA in the past month, 31% were obese, 26% were smoking, 79 % did not meet 5-a-day.
Hall et al. 2012 (206)	Mixed cancer types, n=58. Age 18-40 years at diagnosis, 6-7 months post-diagnosis.	27% engaged in sufficient PA levels, 16% were current smokers.
Bifulco et al. 2012 (148)	BC and gynecological cancer patients, n=263,,≤4 years from cancer treatment.	Compared to survivors aged > 45 years, younger patients reported a higher daily intake of fruits and vegetables, had a lower alcohol consumption, and were more physically active
Murnane et al. 2015 (207)	Mixed cancer types, n=74. 15-25 years at diagnosis. Mean 3 years since diagnosis.	49% met PA guidelines.
Warner et al. 2016 (14)	Mixed cancer types, n=7619 Diagnosed at age 15-39 years, ≥5 years from diagnosis.	56-65 % reported low PA (less than 30 min/5 days per week), 29% were smoking, 72-89% did not meet 5-a-day.
Kaul et al. 2016 (203)	Mixed cancer types, n=1019. Diagnosed at age of 15-39, ≥5 years from diagnosis.	33% of AYA survivors were current smokers versus 22% in the comparison group. Current smokers among survivors had more comorbidity and poorer general health.

AYA: adolescent and young adult. U.S.: United States. YACSs: young adult cancer survivors. BC=breast cancer. BMI: body mass index. PA: physical activity. 5-a-day: eating at least five daily servings of fruits and vegetables.

Interventions aimed at making positive lifestyle changes are recognized as highly relevant to improve the negative effects of cancer and its treatment among YACSs (76). However, in a systematic review of health behavior interventions targeting teenage and YACSs, Pugh et al. found that only half of the interventions were successful in improving lifestyle behavior (210). Results from U.S. studies suggest that factors such as male gender, longer time since diagnosis and poor health are associated with an unhealthy lifestyle among survivors of cancers diagnosed at a young age (14, 203). However,

associations between lifestyle and cancer-related factors such as treatment and specific AEs had not been studied among long-term YACSs at the onset of the work with this thesis. Overall, a better understanding of current lifestyle behavior and factors associated with an unhealthy lifestyle among YACSs was judged as needed in order to develop targeted lifestyle interventions that can be implemented successfully in this population (210).

3.0 Aims of this thesis

Based on this background, the overall aim of this thesis was to provide new knowledge about lifestyle and AEs in selected groups of Norwegian cancer patients and survivors.

3.1 Sub-study I (Paper I)

The aims of Paper I were to:

- Compare the level of PA across PC patients treated by RP, RT +ADT or undergoing ADT.
- Explore associations between PA and treatment-induced AEs

We hypothesized that patients who had completed RP or RT +ADT would have a higher level of PA than patients undergoing ADT for metastatic disease, and that higher level of treatment-induced AEs, such as urinary incontinence and bowel problems, would be negatively associated with PA.

3.2 Sub-study II (Paper II and III)

The overall aims of sub-study II were to investigate lifestyle (Paper II) and CF (Paper III) in long-term YACSs. The specific aims were to:

Paper II

- Investigate and compare the adherence to lifestyle guidelines between long-term YACSs treated for BC, CRC, NHL or ALL, and survivors of localized MM treated with skin surgery (comparison group).
- Explore demographic and cancer-related factors associated with not meeting the guidelines for PA, BMI and smoking separately, and factors associated with not meeting an increasing number of these guidelines.

We hypothesized that many YACSs would not meet PA guidelines and/or be overweight, and that a minority would be smoking. Moreover, we hypothesized that low level of education and comorbid conditions/late effects would be associated with not meeting lifestyle guidelines.

Paper III

- Examine the prevalence of CF and the level of fatigue in long-term YACSs diagnosed with BC, CRC, ALL, NHL or MM.
- Investigate associations between CF and socio-demographic, cancer-related, somatic health/lifestyle and psychological factors.
- Describe the change of fatigue with time among YACSs with CF, based on retrospective self-report.

We hypothesized that CF would be more prevalent among cancer survivors treated with more intense therapy, compared to surgery for localized MM. Further, we hypothesized that CF would be associated with late effects and comorbid conditions.

4.0 Materials and methods

4.1 Design and study populations

The present thesis is based on data from two cross-sectional studies, one conducted in PC patients (sub-study I) and one in long-term YACSs (sub-study II) (Figure 3).

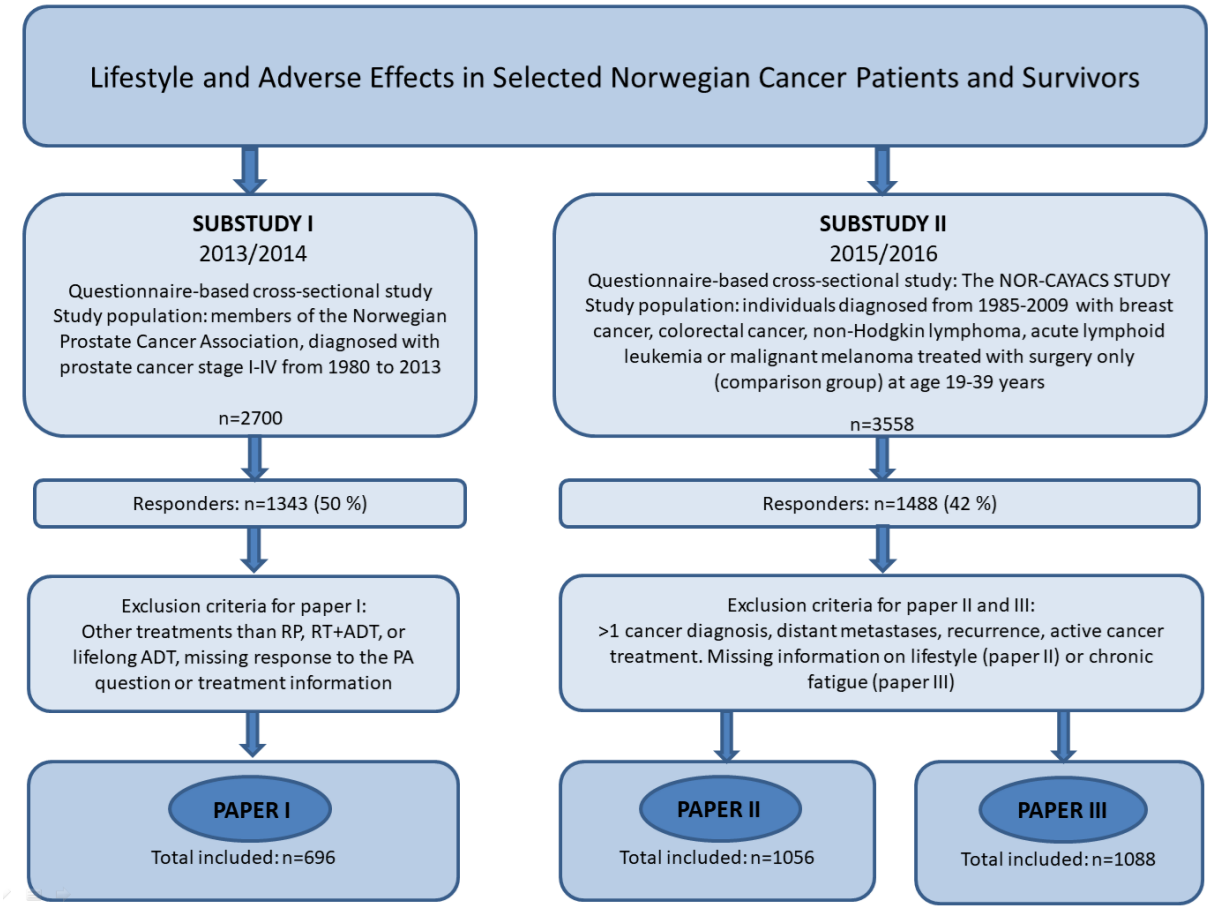

Figure 3: Overview of design and participants in the present thesis. NOR-CAYACS study: the Norwegian childhood, adolescent and young adult cancer survivors study. RP = radical prostatectomy. RT = radiation therapy. ADT = androgen deprivation therapy. PA = physical activity

4.1.1 Sub-study I (Paper I)

In 2013/2014, the Norwegian Prostate Cancer Association (PROFO) invited their members (n=2700) to participate in a cross-sectional survey assessing global QoL, treatment-induced AEs and PA (211) . These men had been diagnosed with stage I-IV PC between 1980 and 2013. An information letter, a postage paid return envelope and a questionnaire were sent out by mail in May 2013. In April 2014, a follow-up e-mail was sent by PROFO to all members with a registered e-mail address, requesting those who had not responded the first time to complete an electronic version of the questionnaire.

A total of 1343 responded to the survey. For Paper I, patients were eligible if treated with either: 1) open, robotic or other type of RP surgery who confirmed not to have received new/other treatment for PC, 2) RT with (neo)-adjuvant ADT who confirmed not to have received new/other PC treatment, or

3) undergoing life-long ADT without previous RP or RT. A total of 696 patients were included in Paper I. The remaining responders were excluded from the present study due to non-eligible treatment-regimens or missing information about PA or treatment, as shown in Figure 4.

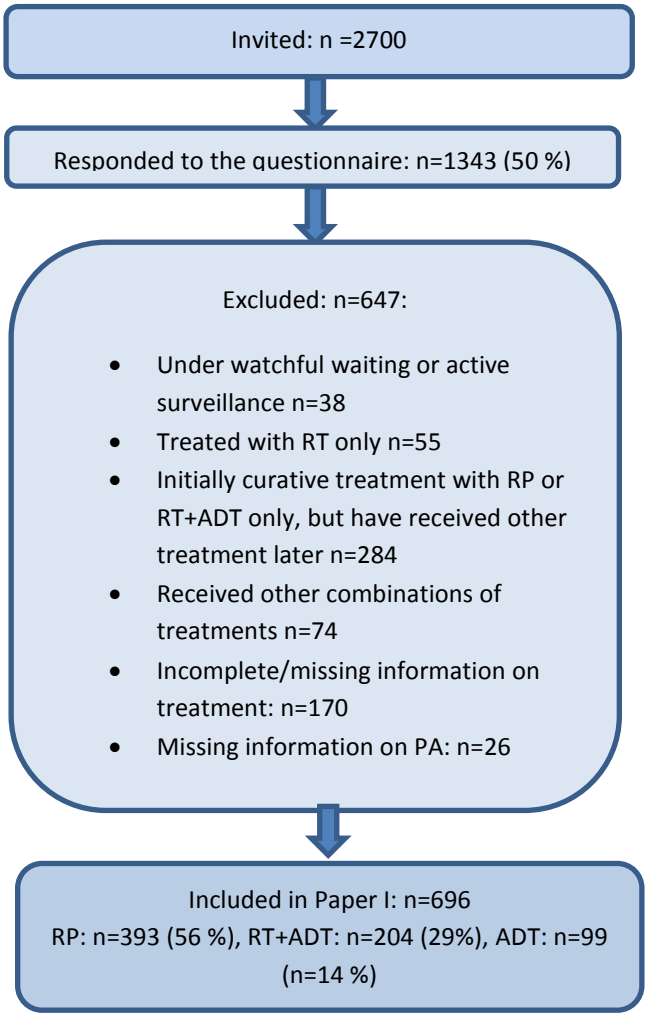

Figure 4: Flow-chart of participants in Paper I. RP = radical prostatectomy. RT = radiation therapy. ADT = androgen deprivation therapy. PA = physical activity.

Among the participants included in Paper I, the median age at survey was 69.8 years (range 47.0-105.0 years) and the median time since diagnosis was 4.7 years (range 0-23.0 years).

4.1.2 Sub-study II (Paper II and III)

The YACSs included in Paper II and III is an unselected cohort extracted from the NOR-CAYACS study (39). The NOR-CAYACS study is a national cross-sectional survey conducted in 2015/2016, focusing primarily on needs of information and health care services related to late effects after cancer treatment at a young age. The Cancer Registry of Norway (CRN) identified eligible participants. All individuals diagnosed with cancer at ages 0-18 years (except central nervous system cancer) and either BC stage I-III, CRC stage I-III, NHL, ALL and localized MM at ages 19-39 years from 1985 to 2009 and treated in Norway, were invited to participate from September 2015 to January 2016 (n=5361). For the studies in this thesis, only the YACSs were eligible (n=3558). Initially, this study population

included 1257 BC survivors, 380 CRC survivors, 623 NHL survivors, 338 ALL survivors and 2902 MM survivors. Due to the large number of MM survivors, a random sub-sample of 33% was drawn from the cohort (n=960). MM survivors were treated with surgery only, and served as a comparison group.

Except for the MM group, the cancer types among the YACSs were selected because affected individuals have good survival rates and a relatively high risk of late effects. Survivors of other relevant cancer types, such as Hodgkin lymphoma, testicular cancer and cervical cancer were not included because these groups were involved in other on-going studies at our research unit (the National Advisory Unit on Late Effects after Cancer Treatment).

Eligible survivors received the invitation by mail, including study information, informed consent form, the questionnaire and a pre-addressed pre-paid return envelope. Those who had not responded within 5 months received a mailed reminder.

Of the 3558 invited, 1488 YACSs responded to the survey (42%) (Figure 5). For the papers in this thesis, YACSs were eligible if registered in CRN with no distant metastases, no new cancer or recurrence since diagnosis, and reporting absence of active cancer treatment at the time of survey. BC survivors receiving endocrine cancer treatment were not excluded (n=23). MM survivors reporting oncological treatment other than surgery were excluded (n=6). An additional exclusion criterion was missing response to the dependent variables (PA, BMI and smoking in Paper II, the FQ in Paper III). The given exclusion criteria resulted in exclusion of 432 participants in Paper II and 400 participants in Paper III (Figure 5).

For both populations included in Paper II and III, median age was 34.0 years (range 19.0-39.0) at diagnosis and 48.6 years (range 26.6-64.9) at survey. Median time since diagnosis was 14.0 years (range 5.0-30.0). Seventy-four per cent of the participants were women.

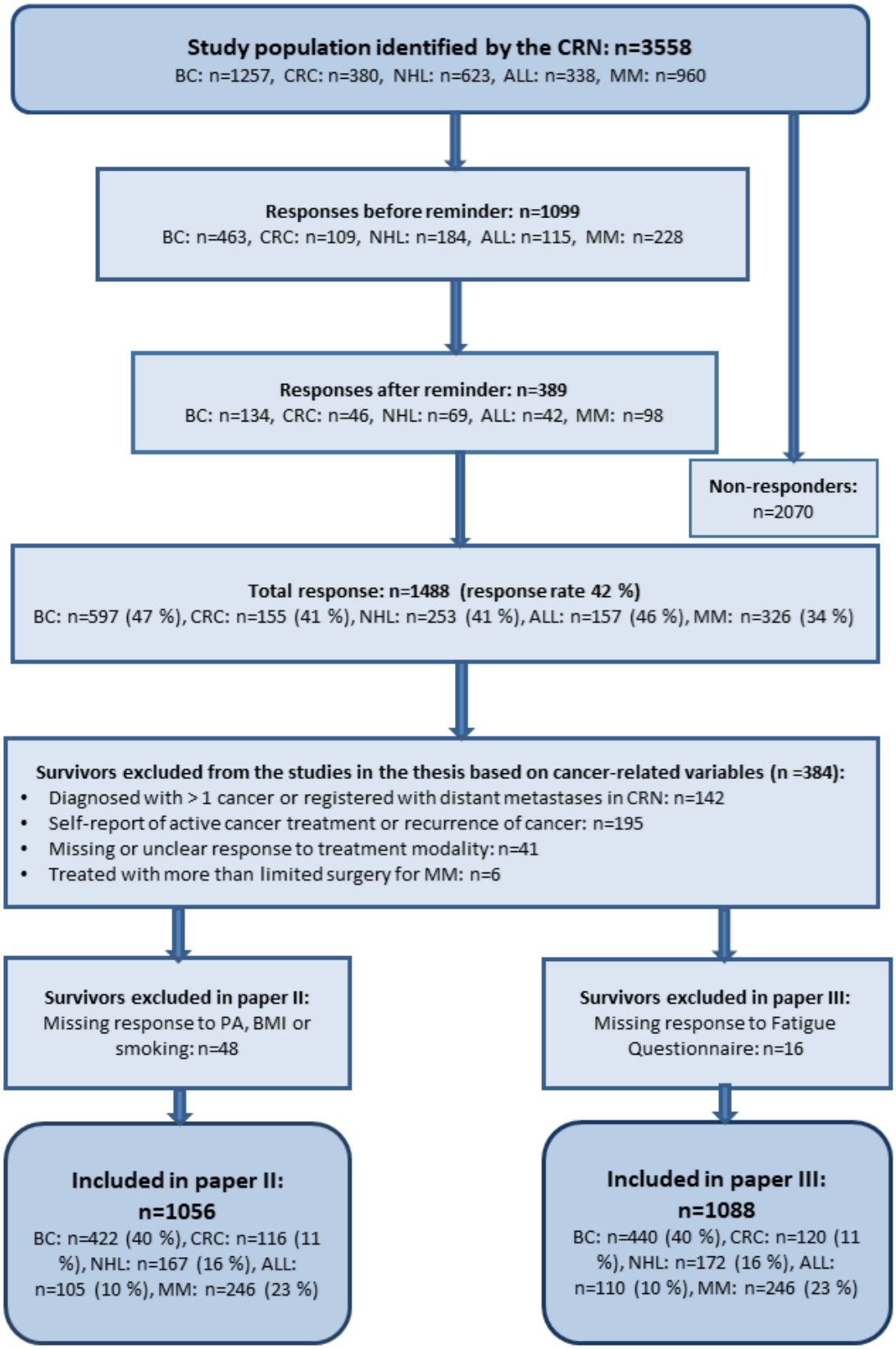

Figure 5: Flow chart of participants included in Paper II and III. CRN = Cancer Registry of Norway. BC = breast cancer. CRC = colorectal cancer. NHL = non-Hodgkin lymphoma. ALL = acute lymphoblastic leukemia. MM = malignant melanoma. PA = physical activity. BMI = body mass index.

4.2 Variables and measures

Information on how dependent and independent variables were assessed in this thesis is displayed in Table 5.

Table 5: dependent variables, independent variables and measurements included in this thesis.

Dependent variables	Paper I	Paper II	Paper III	Source of information/measurements
Lifestyle (Paper I and II)				
PA	X			HUNT
		X		GLTEQ
BMI		X		Calculated from self-reported height/weight
Smoking		X		HUNT
5-a-day		X		HUNT
Adverse effects (Paper III)				
Chronic fatigue			X	FQ
Independent variables				
Age	X			Self-reported
		X	X	Obtained from CRN
Sex		X	X	Obtained from CRN
Living as a couple/with children		X	X	Self-reported
Education level	X	X	X	Self-reported
Work-force participation	X			Self-reported
Time since diagnosis	X			Self-reported
		X	X	Obtained from CRN
Treatment modality	X	X	X	Self-reported
Comorbidity	X			Self-reported
		X	X	CCI (modified)
Treatment-related AEs after PC treatment	X			EPIC-CP
Trouble sleeping		X	X	HUNT
Pain		X	X	SF-12
Numbness in hands/feet		X	X	Self-reported
Lymphedema		X		Self-reported
Chronic fatigue		X		FQ
PA			X	GLTEQ
BMI	X	X	X	Calculated from self-reported height/weight
Binge drinking			X	HUNT
Smoking		X	X	HUNT
Anxiety symptoms		X	X	HADS-A
Depressive symptoms		X	X	PHQ-9

PA = physical activity, 5-a-day: consuming at least 5 daily servings of fruits and vegetables, BMI = body mass index (kg/m^2), AEs = adverse effects, HUNT = The Nord-Trøndelag Health survey (212, 213), GLTEQ = The Godin Leisure Time Exercise Questionnaire (214, 215), FQ = the Fatigue Questionnaire (107), PC = prostate cancer. EPIC-CP = Expanded Prostate Cancer Index Composite for Clinical Practice (216) , CCI = the Charlson Comorbidity Index (217), SF-12 =12-Item Short Form Survey (218), HADS-A = The Hospital Anxiety and Depression Scale, anxiety subscale (219). PHQ-9 = The Patient Health Questionnaire (220)

4.2.1 Sub-study I (Paper I)

All data in sub-study I were self-reported. The questionnaire included 87 items, assessing various factors related to the PC (such as cancer stage, type of treatment, AEs and experiences with health care services), health- and lifestyle (including general health, comorbidity, PA, BMI and smoking) and health-related QoL. For Paper I, 27 items of the questionnaire were included; PA (1 item), treatment specific AEs (11 items extracted from the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) (216)), socio-demographic factors (3 items), treatment information (7 items), health- and lifestyle (5 items). Selected items from the questionnaire relevant for this thesis are shown in Appendix A.

Frequency of physical activity (dependent variable)

Level of PA was measured by an item extracted from the PA questionnaire in the Nord-Trøndelag Health Study: HUNT1 (212). This item sounds as follows: "By exercise we mean, for example, skiing, swimming or training/sports leading to breathlessness or sweating. How frequently do you exercise?" The response categories were "never", "less than once per week", "once per week", "2-3 times per week" and "almost every day". Responses were categorized into exercising < 2 times and ≥ 2 times per week. This cut-off point resulted in equally sized groups, allowing sub-analyses of PA and treatment-induced AEs within the treatment groups.

Treatment-induced adverse effects (independent variables)

In Paper I, treatment-induced AEs were assessed by EPIC-CP, a questionnaire quantifying self-reported treatment-induced AEs in PC patients (216) (Appendix A). The questionnaire consists of 16 items, of which 4 cover function and 12 consider the patient's experienced problems. Five domains of PC treatment-induced AEs are covered (urinary incontinence, urinary irritation/obstruction, bowel symptoms, sexual symptoms and vitality/hormonal symptoms), with three items per domain. The questionnaire also includes a stand-alone item assessing overall urinary bother. Each item is scored from 0-4. Summarized scores for each domain range from 0-12, with increasing values reflecting worse symptoms/bother.

Complete scores of urinary incontinence, urinary irritation/obstruction, bowel symptoms and sexual symptoms were included in Paper I. The item assessing lack of energy ("How big a problem, if any has the following been for you?") was extracted from the vitality/hormonal domain, and dichotomized into no (no problem/very small problem/small problem) versus yes (moderate problem/big problem).

When one out of three items in the EPIC-CP domains was missing, substitution was done by imputing the individual's average score of the two answered items. If two items were missing, the score of the answered item was imputed. If all items in one EPIC-CP domain were missing, but the other domains had valid responses, 0 was imputed. Noteworthy, we did the analyses with and without substitution of missing, and obtained equal results.

For the study sample in Paper I, Cronbach's α was 0.84 for the urinary incontinence domain, 0.88 for the bowel domain, 0.70 for the urinary irritation/obstruction domain and 0.66 for the sexual domain.

Treatment

Data on treatment was collected by asking; "What was the initial treatment you received?" Response alternatives were: 1) open prostatectomy surgery, 2) robotic prostatectomy, 3) other type of prostatectomy surgery, 4) RT without hormone therapy, 5) RT with hormone therapy, 6) hormone therapy alone taken as pills or injections, 7) orchiectomy, 8) watchful waiting with follow-up by specialist and, 9) watchful waiting with follow-up by general practitioner. Further the patients were

asked “Has it been necessary with new/other treatment after completion of initial treatment?” Response categories were “yes” and “no”.

Background variables
Demographic variables included age (dichotomized into < 70 versus ≥ 70 years), basic education level (≤ 12 years versus >12 years) and work force participation (dichotomized into no (retired, sick-leave, work assessment allowance or disability benefits) versus yes (working fulltime or part-time)). Medical variables were year of diagnosis, time since diagnosis, time since start of treatment and presence of comorbidity affecting general health (no versus yes). Lifestyle-/health variables included BMI (based on self-reported height and weight and categorized into < 25 versus ≥ 25 kg/m^2), daily smoking (no versus yes) and perceived general health (dichotomized into poor (not so good/poor) versus good (good/excellent).

4.2.2 Sub-study II (Paper II and III)
The NOR-CAYACSs questionnaire included a total of 302 items, of which 162 were to be filled out by all participants (39). The items addressed sociodemographic background, cancer treatment, experienced late effects, health care use and needs, information needs, work ability, financial issues, physical and mental health, fatigue, lifestyle, QoL and health literacy (39). For Paper I and II, 100 items covering socio-demographic information, cancer treatment, late effects, physical and mental health, fatigue and lifestyle were included. Selected items from the questionnaire relevant for this thesis are shown in Appendix B.

The Godin Leisure-Time Exercise Questionnaire (dependent variable Paper II, independent variable in Paper III)
A modified version of the Godin Leisure Time Exercise Questionnaire (GLTEQ) (214, 215) was used to assess PA. The GLTEQ assesses the average frequency and number of minutes of mild, moderate and vigorous leisure-time PA during a typical week. The number of minutes within the different intensity levels of PA were calculated for each participant, and used to classify individuals as physically active (≥ 150 minutes of moderate intensity or ≥75 minutes of vigorous intensity per week) or inactive according to the PA guidelines (6).

Lifestyle variables (dependent variables in Paper II and independent variables in Paper III)
Smoking was assessed by the question “Do you smoke?”, from the HUNT study (213). Responses were dichotomized into yes (smoking daily or smoking now and then) versus no (discontinued smoking/never smoked).

BMI (kg/m^2) was calculated from self-reported height and body weight, and categorized according to The World Health Organization’s categorization of BMI in adults; underweight (< 18.5 kg/m^2), healthy weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (≥ 30 kg/m^2) (221). In Paper II, the proportion of participants within each of these BMI categories was described, and then

dichotomized into < 25 and ≥ 25 kg/m^2 to compare the proportion not meeting the BMI lifestyle guidelines (5), and explore associated factors. In Paper III, BMI was applied as an independent variable in logistic regression analyses, dichotomized into < 30 and ≥ 30 kg/m^2.

5-a-day was assessed by a question modified from the HUNT study (213), asking the participants how often they consume at least five daily servings of vegetables, fruits and berries. Responses were categorized into meeting (every day) and not meeting (4-6 days per week/1-3 days per week/less than one day per week) 5-a-day.

Binge drinking (independent variable in paper III) was assessed by the question: "How often do you drink five glasses or more of beer, wine or spirits at the same occasion?" extracted from the HUNT study (213). Responses were dichotomized into no (never/monthly) versus yes (weekly/ daily).

The Fatigue Questionnaire (dependent variable Paper III)

The dependent variable in Paper III was CF measured by the FQ (107). The FQ includes 11 items distributed on two subscales; physical fatigue (7 items) and mental fatigue (4 items). Each item has four response alternatives scored from 0-3 with higher scores implying more fatigue. A total fatigue score ranging from 0-33 is calculated by summing all items. An additional question assesses the duration (< 1 week/< 3 months/3-6 months/≥ 6 months) of fatigue. For case definition of CF, a dichotomized scoring system (0 = 0, 1 = 0, 2 = 1, 3 = 1) of the response alternatives can be used. Respondents reporting a dichotomized total fatigue score of ≥ 4 and a fatigue duration of 6 months or longer is defined as having CF (107).

Missing items in the FQ were substituted with the average score of answered items within the same subscale for each individual, given a response to at least 50% of the items.

In the NOR-CAYACS study, additional response alternatives were added to the question assessing duration of fatigue (6 -12 months, 1-5 years or ≥ 5 years). Participants were also asked if they had been tired since cancer treatment, and if yes, how the level of fatigue had changed over time. Cronbach's α was 0.91 for the physical scale, 0.84 for the mental scale and 0.92 for the total scale for both study samples in Paper II and III.

The Hospital Anxiety and Depression Scale, Anxiety subscale (independent variable Paper II and III)

The Hospital Anxiety and Depression Scale (HADS) questionnaire (219) consists of 14 items, equally distributed on one anxiety subscale (HADS-A) and one depression subscale (HADS-D). In Paper II and III, HADS-A was used to assess level of anxiety symptoms. Each item has four response categories ranging from 0 (not present) to 3 (highly present), providing a sum score ranging from 0 (low) to 21 (high). Missing items were replaced with the individual's mean of the answered items in HADS-A, if at least half of the seven items had been answered.

For both study samples in Paper II and III, Cronbach's α for HADS-A was 0.83.

The Patient Health Questionnaire-9 (independent variable Paper II and III)

The Patient Health Questionnaire (PHQ-9) (220) was used to measure level of depressive symptoms. The PHQ-9 contains nine items corresponding to the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria for major depressive disorders (98). The frequency of experienced depressive symptoms during the last 2 weeks with response categories ranging from 0 (not at all) to 3 (nearly every day) is assessed. If no more than two items were missing in the total scale, they were substituted with the mean score of the remaining items.

In Paper III, a modified version of the PHQ-9 was used, excluding the four somatic symptoms (sleep problems, fatigue, poor appetite/overeating and psychomotor retardation/agitation) to avoid overlap with items in the FQ. A sum score (0-15) of the 5 remaining items (anhedonia, depressed mood, feelings of worthlessness/guilt, poor concentration and thoughts of self-harm/suicidal ideations) was used to indicate level of depressive symptoms. This modified version of PHQ-9 has also been used for assessment of depression among patients with advanced cancer (222).

For the study samples in Paper II and III, Cronbach's α was 0.87 for the original version (Paper II) and 0.84 for the modified version (Paper III).

Socio-demographic variables

Gender and age at survey were extracted from CRN. The remaining socio-demographic variables were self-reported: living as a couple (yes versus no), living with children below 18 years of age (no versus yes) and education level (dichotomized into ≤ 13 years (primary school/high school) versus > 13 years (college/university)).

Cancer-related information

Information on cancer type, stage and age at diagnosis was obtained from the CRN.

Treatment information was self-reported by the following response alternatives; a) chemotherapy, b) RT, c) cancer treatment with hormones/anti-hormones, d) surgery, e) high-dose treatment with stem cell support/bone marrow transplant, f) antibody treatment and g) other treatment. Combined with information on cancer type and stage obtained from CRN, the participants were categorized into four treatment groups: 1) limited surgery (survivors after localized MM), 2) surgery and/or RT, 3) systemic treatment only and, 4) systemic treatment combined with RT and/or surgery. Systemic treatment included chemotherapy, hormone/anti-hormone treatment, antibody treatment, and high-dose treatment with stem cell support/bone marrow transplant.

Health variables

Comorbidity was assessed by a modified version of the Charlson Comorbidity Index (217), using the question: "Have you ever had any of these diseases/complaints?". The following response alternatives were given: coronary heart disease (such as myocardial infarction, angina pectoris), hypertension, chronic pulmonary disease (such as asthma, chronic bronchitis, chronic obstructive pulmonary disease), diabetes, kidney disease, liver disease, gastric ulcer or intestine disease (such as Crohn's disease or ulcerative colitis), rheumatic disease, arthrosis, other muscle/joint pain, epilepsy, stroke, depression leading to help-seeking, other mental health conditions leading to help-seeking, anemia, hypothyreosis, hyperthyreosis. Number of somatic comorbid conditions (not including depression symptoms or other mental health conditions) were defined by adding up the reported diseases/complaints for each participant, and categorized into no comorbidity, 1-2 comorbid conditions and >2 comorbid conditions. If comorbidity was reported, subsequent missing answers on comorbidity was counted as "no".

Pain was assessed by an item from 12-Item Short Form Survey (218) asking if pain had interfered with normal work the last 4 weeks (dichotomized into no (not at all/a little bit/moderately) and yes (quite a bit/extremely)).

Trouble sleeping was assessed by the question: "How often during the last 3 months has it occurred that you: a) Had difficulties falling asleep at night?, b) Woke up repeatedly during the night? c) Woke up too early and could not get back to sleep?" Response options were: "Seldom/never", "Sometimes" and "Several times a week". Trouble sleeping was defined with the answer "Several times a week" to either of the questions. The questions were extracted from the HUNT study (213) and are based on the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria for primary insomnia (98).

Other late effects: Survivors with numbness in hands/feet (Paper II and III) and lymphedema (Paper II) were identified by an answer of "Yes -have experienced it myself" to the question "Are you aware that certain cancer treatments can result in late effects?" followed by list of several late-effects including numbness in hands/feet and lymphedema.

4.3 Ethics

4.3.1 Sub-study I (Paper I)

The study in Paper I was based on an anonymous survey through PROFO. The authors were provided with anonymous data, and therefore the study did not require approval from the regulatory ethics in Norway.

4.3.2 Sub-study II (Paper II and III)

The Norwegian Data Protection Authority (15/00395-2/CGN), the Regional Committee for Medical Research Ethics (2015/232 REK sør-øst B), the Data Protection Officer at Oslo University approved

the NOR-CAYACS study. All participants signed an informed consent form for study participation and permission of linkage to information in the CRN. For non-responders, basic clinical information from CRN was de-identified.

4.4 Statistical analyses

4.4.1 All papers

All statistical analyses were performed in IBM SPSS version 21 and 25. P-values < .05 were considered statistically significant, and all tests were two-sided. Descriptive statistics included means and standard deviations, or medians and ranges. Group comparisons were carried out by t-tests or one-way ANOVA for continuous variables and chi-square tests for categorical variables. Internal consistencies of instruments were examined with Cronbach's α.

4.4.2 Sub-study I (Paper I)

Logistic regression analyses were used to identify factors associated with level of PA, dichotomized into exercising < 2 times or ≥ 2 times per week (dependent variable). Independent variables included treatment-induced AEs and background variables (age, education, work force participation, time since diagnosis, comorbidity and BMI).

In multivariable logistic regression analyses, variables associated with the dependent variable in unadjusted analyses ($p < .05$) or considered clinically relevant with p-value ≈0.1 in unadjusted analyses were included. Variables were excluded from the multivariable analyses until only statistically significant variables remained. The strengths of associations were presented as crude and adjusted odds ratios (cOR and aOR) with 95% confidence intervals (95% CI).

4.4.3 Sub-study II

Responders and non-responders

To compare responders to non-responders, de-identified information on non-responders' sex, age at survey, age at diagnosis and diagnostic group provided from the CRN was used.

Paper II

Factors associated with the three different dependent variables 1) not meeting PA guidelines, 2) BMI ≥ 25 kg/m^2 and 3) current smoking were identified through uni- and multivariable logistic regression analyses. For the multivariable analyses, variables associated with the dependent variable in unadjusted analyses ($p < .05$) were included as independent variables. Odds ratios were presented as crude odds ratio (cOR) and adjusted odds ratio (aOR) with 95% CI.

Ordinal logistic regression was used to identify factors associated with a more unhealthy lifestyle (not meeting an increasing number of lifestyle recommendations in terms of PA, BMI and smoking). The test of parallel lines confirmed the proportional odds assumption. The multivariable analyses included

variables significantly associated with the dependent variable in unadjusted analyses ($p < .05$). Odds ratios were expressed as cOR and aOR with 95% CI.

Paper III

Uni- and multivariable logistic regression analyses were performed to identify factors associated with CF (dependent variable). The independent variables were included in separate blocks in multivariable analyses, by the following order: socio-demographic, cancer-related, somatic health-/lifestyle and psychological variables. Odds ratios were expressed as OR with 95% CI.

5.0 Summary of main results

5.1 Sub-study I (Paper I)

In Paper I, we aimed to compare the level of PA across PC patients treated with RP, RT +ADT, or currently undergoing ADT. Further, we explored associations between PA and treatment-induced AEs.

Level of physical activity

Overall, the level of PA did not differ across treatment groups (p = 0.131) (Figure 6).

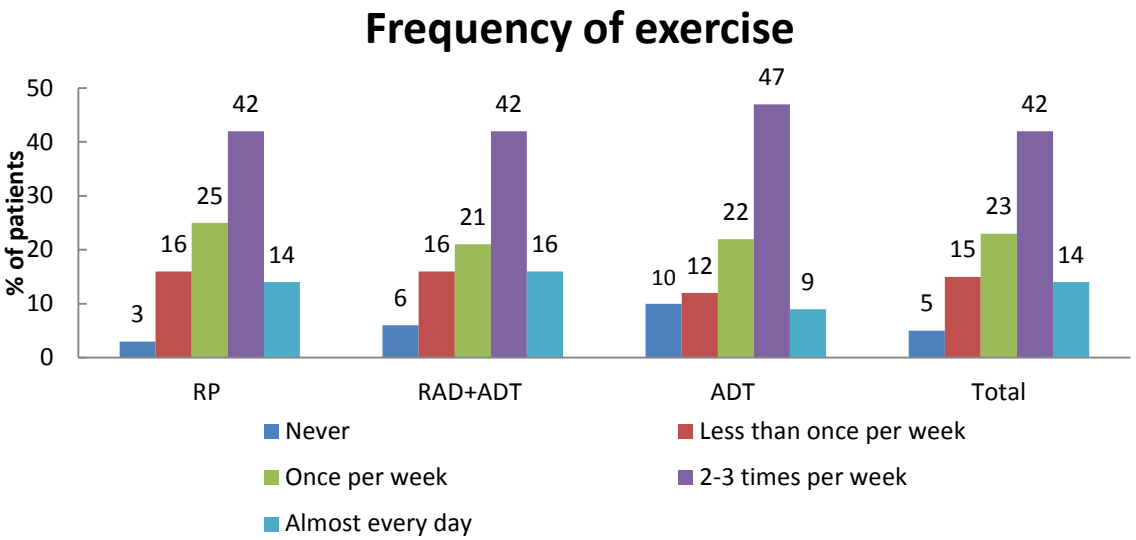

Figure 6: (Identical to Figure I in Paper I, reprinted with permission from Supportive Care in Cancer) Exercise frequency in prostate cancer patients treated with radical prostatectomy (RP), radiation therapy + androgen deprivation therapy (RAD+ADT) and ADT.

Factors associated with physical activity in multivariable analyses

In multivariable analyses for the total sample and among patients treated with RT + ADT, increasing level of bowel symptoms was the only treatment-induced AE that was negatively associated with exercising ≥ 2 times per week. All factors associated with exercising ≥ 2 times per week in multivariable analyses are listed in Table 6.

Table 6: factors associated with exercising ≥2 times per week in multivariable analyses

Dependent variable	Associated factors	aOR, 95% CI
	All patients	
Exercising ≥2 times per week*	Bowel symptoms	aOR 0.91, 95% CI 0.85-0.97
	Age ≥ 70 years	aOR 0.56, 95% CI 0.39-0.82
	Work force participation	aOR 0.52, 95% CI 0.35-0.79
	BMI ≥ 25 kg/m^2	aOR 0.66, 95 % CI 0.47-0.93
	Patients treated with radical prostatectomy	
Exercising ≥2 times per week**	Age ≥ 70 years	aOR 0.51, 95% CI 0.33-0.81
	BMI ≥ 25 kg/m^2	aOR 0.60, 95% CI 0.39-0.94
	Patients treated with RT +ADT	
Exercising ≥2 times per week***	Bowel symptoms	aOR 0.84, 95% CI 0.76-0.92
	Patients undergoing ADT	
Exercising ≥2 times per week****	≥ 5 years since diagnosis	aOR 0.41, 95% CI 0.18-0.96

aOR = adjusted odds ratio, CI = confidence interval. BMI = body mass index. RT = radiation therapy. ADT = androgen deprivation therapy. *Adjusted for sexual symptoms and lack of energy. **Adjusted for time since diagnosis ***Adjusted for sexual symptoms, lack of energy and comorbidity. ****Adjusted for lack of energy.

5.2 Sub-study II

5.2.1 Paper II

In Paper II, we investigated the adherence to lifestyle guidelines (PA, BMI, smoking, 5-a-day) among long-term YACSs, and explored factors associated with not meeting PA guidelines, being overweight and current smoking, as well as not meeting an increasing number of these guidelines (a more unhealthy lifestyle).

Adherence to lifestyle guidelines

In the total population of YACSs, (excluding the comparison group (MM)) 43% did not meet the PA guidelines, 49% were overweight or obese (33% and 16% respectively), 20% were current smokers and 92% did not meet 5-a-day guidelines. Lifestyle behavior did not differ between MM survivors and the remaining YACSs.

Overall, 26% reported to meet the combination of PA, BMI and smoking guidelines, 68% met 1 or 2, while 6% did not meet any of these guidelines (Figure 7).

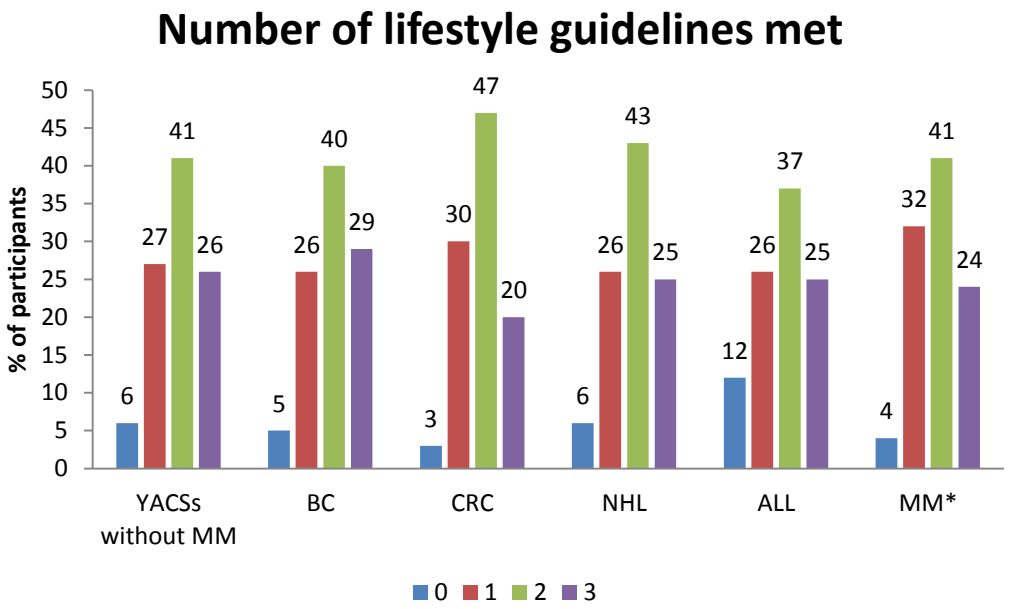

Figure 7: (Identical to Figure 2, Paper II.) Proportions of participants meeting 0, 1, 2 or 3 guidelines in terms of physical activity, body mass index < 25 kg/m^2 and smoking. YACSs = young adult cancer survivors. MM = malignant melanoma. BC = breast cancer. CRC = Colorectal cancer. NHL= non-Hodgkin lymphoma. ALL= acute lymphoblastic leukemia. *Comparison group

Factors associated with not meeting lifestyle guidelines in multivariable analyses

Several demographic, cancer-related and health variables were associated with not meeting single lifestyle guidelines and a more unhealthy lifestyle in multivariable analyses. These are listed in Table 7.

Table 7: factors associated with not meeting single lifestyle guidelines in multivariable analyses

Dependent variable	Associated factors	aOR, 95% CI
Physical inactivity*	Chronic fatigue	aOR 1.50, 95% CI 1.11-2.03
Overweight**	Male gender	aOR 2.50, 95% CI 1.80-3.45
	Multimodal treatment	aOR 0.62, 95% CI 0.44-0.89
	> 2 comorbid conditions	aOR 1.99, 95% CI 1.31-3.04
	Lymphedema	aOR 1.77, 95% CI 1.25-2.50
	Increasing level of depressive symptoms	aOR 1.03, 95% CI 1.01-1.06
Smoking***	Not living with a partner	aOR 1.50, 95% CI 1.02-2.21
	Education ≤ 13 years	aOR 1.63, 95% CI 1.18-2.27
	Lymphedema	aOR 1.67, 95% CI 1.15-2.41
A more unhealthy lifestyle****	Male gender	aOR 1.80, 95% CI 1.37-2.37
	Education ≤ 13 years	aOR 1.44, 95% CI 1.13-1.84
	>2 comorbid conditions	aOR 1.57, 95% CI 1.08-2.29
	Lymphedema	aOR1.37, 95% CI 1.02-1.84
	Pain	aOR 1.54, 95% CI 1.0-2.35

aOR = adjusted odds ratio, CI = confidence interval. Multimodal treatment: systemic treatment combined with surgery and/or radiation therapy. *Adjusted for education, comorbidity, pain and trouble sleeping ** Adjusted for education and pain. ***Adjusted for living with children, depression and anxiety. ****Adjusted for living with children, trouble sleeping, anxiety and chronic fatigue.

5.2.2 Paper III

In Paper III, we investigated the prevalence and associated factors of CF among long-term YACSs, and described the change of fatigue with time among YACSs with CF.

Prevalence of chronic fatigue

Of the 1088 YACSs included in Paper III, 25% reported CF (n = 268). When separating the YACSs by diagnostic groups, CF was more prevalent among survivors of BC ($p < .001$), CRC ($p = 0.001$) and NHL ($p = 0.003$) than among survivors of MM (Figure 8).

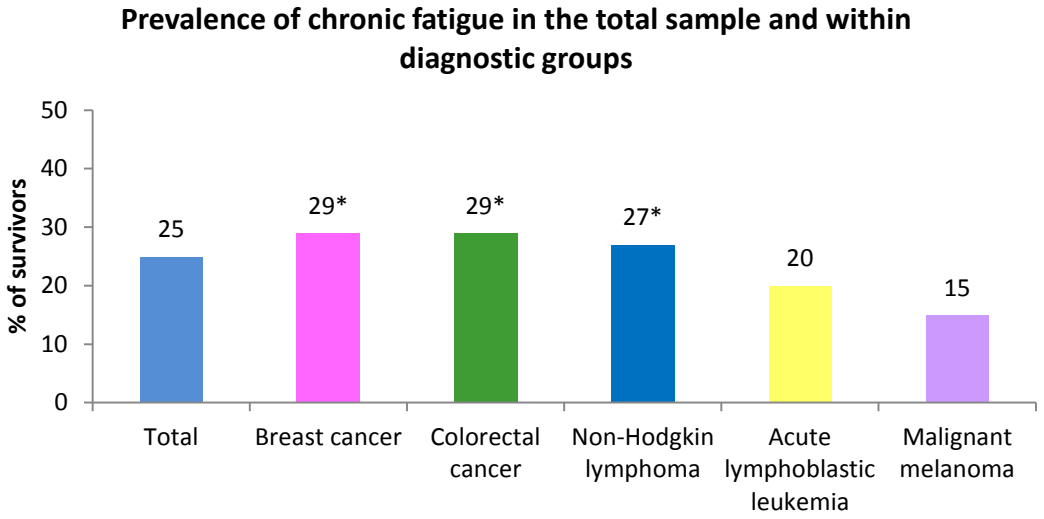

Figure 8: (Identical to Figure 2a Paper III. Reprinted with permission from Acta Oncologica). Prevalence of chronic fatigue among survivors of cancer diagnosed in young adulthood. *Statistically significant higher prevalence of chronic fatigue compared to survivors of malignant melanoma.

Factors associated with chronic fatigue in multivariable analyses

Being affected by CF was associated with treatment intensity, comorbidity and late effects/symptoms, as listed in Table 8.

Table 8: Factors associated with chronic fatigue in multivariable analyses

Dependent variable	Associated factors	OR, 95% CI
Chronic fatigue*	Multimodal treatment	OR 1.88, 95% CI 1.11-3.18
	1-2 comorbidities	OR 1.63, 95% CI 1.03-2.60
	Pain	OR 2.39, 95% CI 1.36-4.19
	Numbness in hands/feet	OR 1.60, 95% CI 1.01-2.52
	Increasing depressive symptoms	OR 1.46, 95% CI 1.32-1.61

OR= odds ratio, CI= confidence interval. Multimodal treatment: systemic treatment combined with surgery and/or radiation therapy. *Adjusted for socio-demographic variables, time since diagnosis, trouble sleeping, body mass index, physical activity, binge drinking, smoking and anxiety.

Duration and development of chronic fatigue

The participants reported duration and development of fatigue with time. Among the YACSs with CF, the results are shown in the Figure 9a-c below. The majority of YACSs with CF had been tired for ≥ 5 years (55%) (Figure 9a) and since cancer treatment (60%) (Figure 9b). Among survivors with CF who

had been tired since cancer treatment, 65% reported no change or worsening of fatigue with time (Figure 9c).

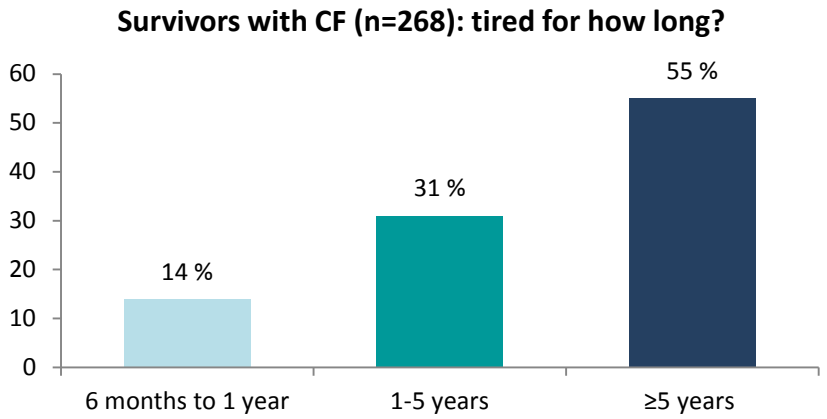

Figure 9a: (Identical to Figure 3a in Paper III, reprinted with permission from Acta Oncologica). Duration of fatigue among survivors with chronic fatigue (CF).

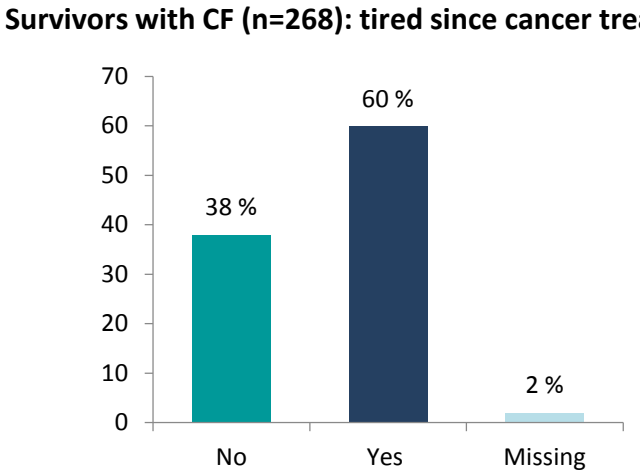

Figure 9b: (Identical to Figure 3b in Paper III, reprinted with permission from Acta Oncologica). Proportion of survivors with chronic fatigue (CF) who have or have not been tired since cancer treatment

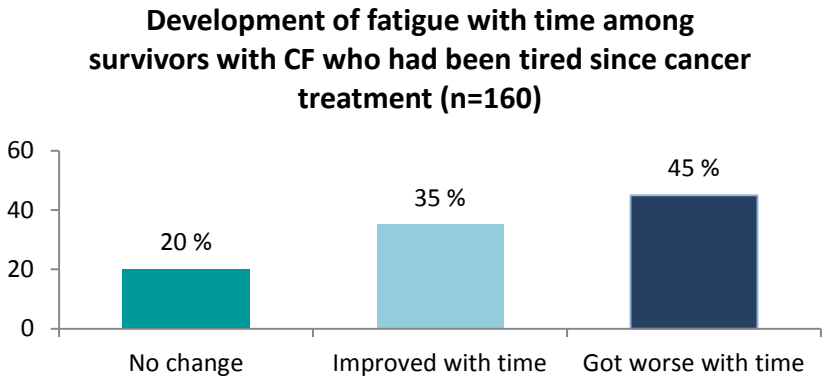

Figure 9c: (Identical to Figure 3c in Paper III, reprinted with permission from Acta Oncologica). Development of fatigue with time among survivors with chronic fatigue (CF).

6.0 Discussion

6.1 Methodological considerations

6.1.1 Internal validity

Internal validity concerns whether data are collected, analyzed and interpreted without bias (223). Threats to internal validity comprise incorrect choice of study design and statistical methods, as well as bias, commonly categorized as selection bias, confounding and information bias (223).

Study design

Both sub-studies in this thesis had a cross-sectional design, i.e. all information was collected at the same time point. A cross-sectional design is appropriate to determine prevalence rates and associations between variables (223). Hence, a cross-sectional was considered suitable according to the overall aims of the surveys on which this thesis was based on; exploring QoL and AEs in PC patients (211) and obtain information on needs of information and health care services related to late effects (39), as well as the specific aims for this thesis. Advantages of the cross-sectional design are the ability to study a large number of variables, and the efficiency regarding time and cost (223). Given the lack of a sequence of the exposure and outcome, cross-sectional studies cannot address causation, but generate hypotheses to be explored in further research (223). In this thesis, we found significant associations between the dependent and independent variables, but no conclusion on the direction of these relationships can be drawn. As an example, we found a statistically significant association between CF and physical inactivity in Paper II, but whether physical inactivity may cause CF or the other way around remain unknown. A prospective design could have provided a deeper understanding of these associations and the change of lifestyle or AEs with time (223).

Statistical considerations

Type I error

A type I error occurs when a true null hypothesis is rejected (224). The risk of a type I error is referred to as the significance level (p-value). In this thesis, the significance level was set to the generally accepted $p < .05$ (223). The risk of a type I error increases with use of repeated statistical tests, for instance with multiple comparisons (225). In this thesis, we cannot exclude the possibility that type I errors might have occurred, for example with the use of multiple chi-square tests to compare characteristics and AEs across PC treatment groups in Paper I. Seen in retrospect, a $p < .01$ could have been more appropriate for these analyses.

Type II error

A type II error occurs when a false null hypothesis is not rejected (224). The risk of a type II error is related to the power of the test, and is reduced by increasing the sample size. It is important to consider the sample size in observational studies, although the upper sample size might be limited by the source of information, e.g. the number of individuals in a health registry (224). In this thesis, the

number of members in PROFO and YACSs registered in CRN limited the upper sample sizes of sub-study I and II.

Both sub-studies in this thesis included total sample sizes of more than 600 participants, which were considered appropriate to conduct the planned statistical analyses by the project groups for the surveys on which this thesis is based upon. In Paper I, however, the sub-group analyses within each treatment group were based on lower sample sizes, which might have increased the likelihood of type II errors. As an example, this might be an explanation to why "lack of energy" was found to be only borderline statistically significant negatively associated with exercising ≥ 2 times per week among the 99 PC patients undergoing ADT ($p = 0.053$ in multivariable analyses).

Dichotomization of variables

In this thesis, multivariable logistic regression analyses were applied to analyze associations of dichotomized dependent variables, e.g. level of PA in Paper I, meeting or not meeting lifestyle guidelines in Paper II, and CF in Paper III. Also, several independent variables were dichotomized or categorized into groups, such as age in Paper I and BMI in Paper III. By dichotomizing continuous variables, information might be lost, and the statistical power to detect significant associations between variables might consequently be reduced (226). On the other hand, dichotomized variables are easier to interpret in clinical practice (226), and we therefore preferred dichotomized variables as described.

Selection bias

Selection bias occurs when the study participants are systematically different from the population of interest, and can result from selection procedures or other factors influencing study participation (223).

In this thesis, response rates were 50% in sub-study I and 42% in sub-study II. Although moderate, these response rates are in accordance with the expected response rates for health surveys (40-50%) (227). A high level of non-response might reduce the generalization of the results (228). This does not, however, necessarily equals biased response, which depends on to what degree responders and non-responders differ on factors related to the study outcomes (228).

In sub-study I the topic was QoL and AEs following PC treatment, and sub-study II concerned late effects and information needs. For both studies, it could be that the surveys were more relevant for individuals with more AEs, leading to study samples with higher prevalence rates of AEs, e.g. CF, than in the approached study populations. On the other hand, a study investigating mortality among responders and non-responders 13 years after a survey on CF among Hodgkin lymphoma survivors found an increased risk of mortality among non-responders, indicating that impaired health may have prevented survivors from responding (229). Thus, it might be that individuals with poor health refrained from participating in the surveys in this thesis, resulting in study samples with better general

health and less AEs than the approached study populations. A consequence of this could be an overestimation of the prevalence rates of PA in Paper I and II, as well as an underestimation of CF in Paper III. Further, there is evidence suggesting that even though the topic of a mailed survey is relevant, people are less likely to respond to a survey if it generates negative thoughts and memories (230). In summary, it is possible that both the most and least healthy cancer patients and survivors, as well as those with psychological reluctance, have rejected participation in sub-study I and II,.

Unfortunately, no information on non-responders in sub-study I was available, due to the anonymity of the PROFO survey. In sub-study II, basic de-identified information on non-responders was available from CRN. The assumption that YACSs suffering from late effects might have perceived the survey as more relevant than those with few late effects is supported by the lower response rate among MM survivors (34%), who were at low risk of developing late effects due to treatment of skin surgery only.

The potential of non-response bias for the entire NOR-CAYACS study has been investigated by Lie et al. (39). Despite the modest response rate, the risk of non-response bias in the survey outcomes (including lifestyle and late effects) was found to be low, suggesting a low risk of under- or overestimation of the study outcomes in Paper II and III in this thesis (39).

Confounding

A confounder is an independent variable that obscures the actual association between a potential exposure and outcome due to its association with both the dependent variable and one or more independent variables (223). In observational studies, multivariable statistical methods can be used to adjust for confounding variables if these are known (223). In this thesis, multivariable logistic regression analyses were used to adjust for possible confounders.

Information bias

Information bias occurs from errors related to collecting and/or measuring data (223). Common types of information bias in observational research are measurement error bias and self-reporting bias (231).

This thesis largely depends on data obtained by self-report trough questionnaires, using established patient-reported outcome measures (PROMs) where possible. Through PROMs, patients report directly on their health condition, including symptoms, functional status, needs, well-being, health-related QoL and satisfaction with treatment or care (232). In order to draw valid conclusions from PROMs, the scales must demonstrate good measurement properties, i.e. reliability and validity (232). *Reliability* is commonly evaluated through internal consistency (i.e. whether all items in a scale measure the same underlying construct) and test-retest reliability (232). Internal consistency is often measured by Cronbach's α, of which values exceeding 0.70 are accepted as satisfactory. For the PROMs used in this thesis, Cronbach's α in the study samples ranged from 0.66 to >0.90, indicating satisfactory/good internal consistency. *Validity* concerns whether an instrument truly measures what it intends to measure. The most relevant types of validity in relation to the PROMs included in this thesis

are content and construct validity (232). Content validity is the degree to which the PROM adequately reflects the construct to be measured by including the most relevant and important aspects. Construct validity is to which extent the scores on the PROM are expected to be associated with other measures, and comprises convergent validity (measures expected to be highly correlated) and discriminative validity (measures expected to be unrelated) (232). Whether the measurement properties of a PROM are sufficient is dependent on the context and population being studied (233).

Self-report is beneficial in epidemiological research due to benefits such as practicality in large populations, low burden on the participants and low cost (231). On the other hand, self-report is also subject to many errors; questions can be misunderstood, information related to the past can be hard to recall, and answers can be influenced by social desirability (231).

Issues with information obtained by self-report and selected measurement properties of PROMs relevant for this thesis are described below.

Self-report of physical activity

In this thesis, all PA data was collected by self-report.

In sub-study I, a single question was used to assess the frequency of PA during a typical week. This question was extracted from a PA questionnaire used in the HUNT-study, which includes two additional items assessing intensity and duration of PA (212). As we only used the single question on PA frequency, information on intensity and duration of PA were missing. Hence, the participants included in Paper I could not be categorized as physically active or inactive according to the PA guidelines, nor could the PA level in our study be directly compared to results of studies using more comprehensive measures of PA. Given that exercise was defined as "activities leading to breathlessness or sweating", it is possible that individuals with reduced general health have misclassified their PA level as high, due to experiencing breathlessness or sweating during daily activities not usually defined as exercise. However, studies have demonstrated that simple, single PA questions can provide valid information about PA levels (234, 235).

In sub-study II, a modified version of GLTEQ (214, 215) was used to classify participants as physically active or inactive according to the PA guidelines (6). The original version of GLTEQ provides a leisure-score index including both mild, moderate and vigorous PA. The modified version of GLTEQ used in this thesis is frequently used in oncology research to classify cancer survivors as active and insufficiently active (236). However, validity evidence is not fully documented, as studies estimating the agreement between this modified version and objective PA measures are lacking in cancer survivors (236). Another limitation with the modified version is loss of information on low intensity PA. Thus, people classified as physically inactive in sub-study II might still have conducted a high amount of low intensity PA although they were not classified as meeting PA guidelines.

The level of PA in this thesis may be overestimated, as people tend to over report PA and underreport sedate habits (237). Social desirability bias is a systematic error occurring from self-reported measures when the respondents give responses they believe are more socially approved (231). Social desirability bias is most frequent if the questions address private or sensitive topics (231), and has been shown to influence self-report of PA (238). Thus, social desirability might have influenced the responses of the participants in this thesis, with results indicating a higher level of PA, than reality. The risk of social desirability bias may increase if the respondents are in doubt of the anonymity and confidentiality of the data collected (231). As the participants in this thesis provided anonymous (sub-study I) or de-identified information (sub-study II) through questionnaires, one might assume the risk of social desirability bias in this thesis to be lower than studies assessing PA through telephone interviews or face-to-face.

Self-reported measures of PA are in general limited in reliability and validity (237). In a Norwegian general population survey, the proportion meeting PA guidelines varied from 20% measured by accelerometer to 67% assessed by self-report (239). Direct measures of PA, such as accelerometers, are without issues of recall, misclassification and social desirability, and are therefore considered more precise than self-reported measures (240). However, disadvantages with direct measures include higher requirements of time and cost, and difficulty to apply in large populations. Moreover, direct measures of PA also have limitations in capturing all aspects of PA. For instance, accelerometers tend to underestimate PA from activities such as cycling, climbing stairs and weight lifting (240). Importantly, PA is a behavior with multiple dimensions, and no single PA measure can fully capture information on all aspects of PA (such as intensity, frequency, duration, mode and context), and at the same time be valid, reliable and practical (241). In the studies in this thesis, self-report of PA was considered most convenient due to the large sample sizes and study context.

Body mass index

In this thesis, BMI calculated based on self-report was used as a measure of overweight/obesity. BMI is a simple and low-cost indirect parameter of body adiposity, and is widely used in epidemiological studies (242). Greater adiposity measured by BMI has shown to strongly increase the risk of premature mortality (243). However, the lack of information on body composition can lead to misclassification of adiposity and subsequent bias in studies estimating effects of body fat on for example health outcomes (244). A meta-analysis found that BMI has high specificity, but low sensitivity to detect high adiposity compared to direct body composition techniques, such as dual energy X-ray absorptiometry (242). Further, errors related to self-report, such as social desirability, may also lead to biased results, compared to objective measures (244).

Cancer-related information

As sub-study I was anonymous, all cancer-related information was self-reported. In sub-study II, information on cancer type, time since diagnosis and stage were obtained from CRN. This information is considered highly reliable, as reporting information on cancer cases to CRN is required by law, ensuring a high degree of completeness with high accuracy (245).

As the CRN does not yet have information on treatment data (9), treatment information was also based on self-report in sub-study II. In general, studies report high agreement between self-reported treatment and medical records in terms of treatments such as surgery, RT and chemotherapy (246-248). Further, Norwegian studies on long-term lymphoma survivors have demonstrated that > 90% correctly recalled their treatment (249, 250). However, less accurate data is found for more detailed treatment information such as type of self-reported hormone therapy and chemotherapy among PC patients (246) and young female cancer survivors and BC survivors (247, 248). Due to the broad categorization of treatments in the questionnaires used in both sub-studies in this thesis, we consider random errors more likely than systematic misclassification of treatments.

Adverse effects from treatment for prostate cancer

EPIC-CP was used to assess PC specific symptoms in Paper I. EPIC-CP is developed from previous versions of EPIC; the original EPIC-50 questionnaire (251), and the EPIC-26 (252). EPIC-50 and -26 were primarily designed for research, and are viewed as time-consuming to administer (253). To better comply with the clinical setting, Chang, Szymanski, Dunn et al. (216) reformatted and reduced EPIC-26 into EPIC-CP in 2011. All questions in EPIC-CP fit one page and takes 2-5 minutes to complete. Moreover, in contrast to EPIC-50 and -26, EPIC-CP does not require transformation of responses to a 0 to 100 scale, and can therefore be both completed and scored at the same time point (216). EPIC-CP correlates highly with EPIC-26/-50, has good internal consistency and discriminant validity, and is responsive to detect changes in symptoms during follow-up after PC treatment (216, 253). While the clinical feasibility has improved with EPIC-CP, however, it may lack breadth and the ability to detect all AEs following PC treatment, including rectal bleeding (254).

Fatigue

In sub-study II, the FQ (107) was used to measure the level of fatigue and to identify survivors with CF. FQ is the most common measure used in studies of cancer-related fatigue in Norway, and is one of few fatigue measures that specifically asks about the duration of fatigue, enabling identification of CF. Originally, the FQ was developed for and validated in general practice (107). A two-dimensional structure was identified (physical and mental fatigue), and FQ was concluded to have satisfactory ability to discriminate between cases and non-cases with fatigue. Later, Loge et al. translated FQ and used it in a Norwegian national representative sample to estimate the prevalence of CF and obtain population norms (134). That study confirmed the two-dimensional structure identified in the original

validation study, and found support of the discriminative ability of FQ by identifying differences in total fatigue score across subgroups with different health status.

In a systematic review of scales used for measurement of fatigue in cancer survivors and patients, the FQ was concluded to have good psychometric properties in terms of internal consistency, convergent and discriminant validity, and was recommended when multidimensional fatigue needs to be evaluated (109). However, evaluation of test-retest reliability and responsiveness to change, as well as a definition of the minimal important difference, are lacking in cancer populations (109).

Anxiety and depressive symptoms

HADS-A was used to measure anxiety symptoms in Paper II and III (219). HADS was originally developed to identify patients with probable or possible depression and anxiety disorders outside psychiatric clinical settings (219). In a systematic review of the validity of HADS in somatic (including cancer), psychiatric and primary care patients, HADS was found to have good psychometric properties to assess symptom severity and identify cases of anxiety and depression (255). In a report from the Norwegian Institute of Public Health, The Norwegian version of HADS is concluded to have good internal consistency and sufficient validity to measure level of psychological distress (256).

Depressive symptoms in Paper II and III were assessed with PHQ-9. PHQ-9 is a valid and reliable measure of depression severity (220). In cancer patients, PHQ-9 has shown to perform well in identifying major depressive disorder (257).

6.1.2 External validity

External validity is dependent on internal validity, and concerns whether the results of a study can be generalized to other subjects than those included in the study sample (223). For this thesis, external validity refers to whether the results can be generalized to all Norwegian PC patients and YACSs in general.

In sub-study I, participants were identified and invited to the study through the patient organization PROFO. The relatively low proportion reporting moderate/big problems with urinary and bowel AEs (≤ 13%) and poor general health (22%) in our study sample may imply that the participants had better general health than the overall population of PC patients. Also, 55% of the participants in Paper I had more than 12 years of education, which is higher than in the general Norwegian population of men aged >50 years (45%) (258). As individuals with high education perform more high-intensity PA than individuals with low education (239), the frequency of exercise found in Paper I may be overestimated compared to the overall population of PC patients. Consequently, our results do probably not apply to all PC patients, and particularly not those with poor health and a high degree of AEs.

Participants in sub-study II were identified by the CRN, which has a high degree of completeness (245). Further, the population-based, nation-wide selection aimed to ensure a nationally representative sample. The distribution of cancer diagnoses included in our sample was, however, different from that of the Norwegian population aged 19 to 39 years, particularly since survivors of cervical and testicular cancer were not included. In addition, BC survivors were overrepresented in the study population and among the responders. Because of the inclusion criteria, our results are only representative of Norwegian cancer survivors diagnosed with BC, CRC, NHL, ALL and localized MM at age 19 to 39 years, without recurrence, second cancer and/or distant metastasis. As all invited participants were ≥ 5 years from diagnosis, the study population might have been overrepresented by survivors with cancers that are at early stages and/or are more responsive to treatment. Further, our results may not apply to cancer survivors diagnosed and treated at present, nor YACSs in other countries, due to differences in culture and health care systems.

6.1.3 Ethical considerations

The current thesis is based on surveys with anonymous (sub-study I) or de-identified participation (sub-study II). For the NOR-CAYACS study, all required approvals were collected, the participants signed informed consent documents, and were informed that they could withdraw from the studies at any time.

Even though the surveys included in this thesis do not place the participants at any direct risk or harm, it is likely that receiving a questionnaire about a current or finalized cancer trajectory might have induced discomfort for some of the recipients. The participants in this Ph.D.-project were diagnosed with cancer up to 30 years ago, and the surveys in this thesis could potentially bring back painful memories or create new concerns.

To address these potential consequences, the participants in the NOR-CAYACS study were informed that only a minority develop late effects after cancer treatment, and that examples of AEs that were mentioned in the questionnaire are not relevant for all participants. Participants were also encouraged to contact health personnel if they became aware of health problems through the surveys.

Recognizing that the surveys in this thesis might have led to some discomfort for the participants, we believe that the surveys were highly relevant, and that the new knowledge provided will benefit both cancer patients/survivors and the health personnel involved in their follow-up care.

6.2 Discussion of main results

6.2.1 Lifestyle and adverse effects among cancer survivors: general aspects

Given their increased risk of poor health and late effects compared to individuals without a history of cancer, a healthy lifestyle is considered particularly important for cancer survivors (15). In spite of this, several studies suggest that cancer survivors in general do not live a more healthy life than the general population (13, 14, 192, 202, 259, 260). On the other hand, evidence is inconsistent, as better lifestyle behaviors have also been described among cancer survivors compared to the general population (173, 193, 261, 262) .

In this thesis, we found a high proportion of PC survivors exercising less than twice per week (44%) and long-term YACSs not meeting all assessed lifestyle guidelines (74%), and that such unhealthy lifestyle behaviors were associated with AEs. These findings indicate a need to focus on improving lifestyle and AEs in these groups of cancer survivor populations.

Traditionally, the main focus of oncological follow-up after cancer treatment has been management of acute AEs and to monitor cancer recurrence. Research on the positive effects of a healthy lifestyle on late effects and long-term health in cancer survivors have grown substantially during the recent years, and imply that the follow-up of cancer survivors should not only focus on disease control and acute care, but also on promoting healthy lifestyle behaviors (15). Importantly, the survivors included in this thesis were diagnosed with cancer up to 30 years ago, and hospital follow-up in Norway is usually limited beyond 5 years after diagnosis. Consequently, many of the participants in this thesis and other long-term survivors have probably not been informed about the particular importance of a healthy lifestyle in relation to their long-term health. As some type of late effects appear several years after treatment, cancer survivors might not be motivated for a better lifestyle before potential health problems occur. Long-term cancer survivors experiencing health problems are usually followed by their general practitioner, who might have limited knowledge about late effects (263). Hence, to reach long-term survivors with this information, general practitioners and other health personnel involved in the follow-up of cancer survivors must have knowledge and focus on late effects and healthy lifestyle behaviors.

6.2.2 Paper I

In Paper I, 57% of the included participants reported to exercise at least twice per week. The level of PA did not differ across treatment modalities (RP, RT +ADT or ongoing ADT). Bowel symptoms after RT was the only AE negatively associated with exercising at least twice per week.

Several systematic reviews conclude that PA during and after PC treatment has positive effects on muscular strength (159, 195, 264-266), physical functioning (159, 195), cardiorespiratory fitness (159, 264, 265), body composition (159, 264, 266), fatigue (159, 195, 265) and health-related QoL (195, 265). Given that most PC patients are diagnosed after the age of 65 (9), these men are also vulnerable

to age-related muscle atrophy as part of normal aging. Muscle mass tends to decrease at a rate of 1-2% per year after the age of 50, and after the age of 60, muscle strength declines by an average of 3% per year (267). Thus, being physically active is highly important to preserve and improve physical function and overall health in PC patients and survivors (159). However, our finding that 43% of PC patients exercise only once or less per week supports previous studies reporting that a large proportion of PC patients are not meeting PA guidelines (189, 195, 268), indicating a high need for interventions that aim to increase the PA level among PC patients and survivors.

As undergoing ADT is associated with treatment-induced AEs, older age and more advanced cancer, we hypothesized that the patients undergoing life-long ADT would exercise less frequently than PC patients who had completed RP or RT +ADT. In contrast to our hypothesis, we found that the level of PA was similar across treatment groups. This finding is also contrary to previous results (196, 197). Chipperfield et al. found that PC patients treated with ADT in addition to RT were significantly less physically active than patients treated with RT only (197). Forbes et al. reported that PA guidelines were met by a significantly lower proportion of PC patients treated with ADT (30%) compared to patients not treated with ADT (46%) (196). However, our results are not directly comparable with these studies, due to different categorization of treatments groups, and use of different PA measures.

One explanation to why the patients undergoing ADT were as active as those who had completed curative treatment might be that they were aware of the detrimental consequences of inactivity on body composition and physical function. As previously stated, it is also possible that patients with poor health and deconditioning could have misclassified their level of PA, due to rapid sweating and/or breathlessness from low-intensity activities not usually classified as exercise.

Factors associated with low level of physical activity

Our findings that patients with increasing bowel symptoms, age 70 years or older and overweight were less likely to exercise at least twice per week are in agreement with qualitative studies that have identified these factors as barriers to PA among PC patients (198, 199, 269). Lack of time is also a frequently reported barrier to exercise among cancer survivors (16), which might explain why patients in the work force were less likely of exercising ≥ 2 times per week.

Cross-sectional studies exploring PA barriers among PC patients have also reported lack of energy/fatigue, other health problems (270, 271), time constraints and no willpower (272) as common barriers to PA. However, few cross-sectional or longitudinal studies have focused on local AEs. Ottenbacher et al. found that PC survivors with urinary incontinence were less likely to increase their PA level in response to a PA intervention (201).A prospective study including 1917 PC survivors treated with different modalities investigated associations between PA and several local AEs related to PC treatment, but only better vitality/hormonal functioning was associated with higher level of PA (273).

In the RP group separately, we found that patients 70 years or older and with overweight (BMI ≥ 25 kg/m^2) were less likely to exercise ≥2 times per week compared to patients younger than 70 years and with healthy weight. However, worth to note, no association with common AEs related to RP was found. Geraerts et al. found that patients with worse first day urinary incontinence and urine loss were less physically active up to 12 months post-RP (200). The lack of association between exercise frequency and urinary incontinence in our study could be due to the low symptom burden of long-term urinary incontinence; most of the patients treated with RP were more than 1 year from diagnosis, and only 17% reported a moderate or big problem with urinary leakage.

Among patients treated with RT +ADT, bowel symptoms were negatively associated with exercising ≥ 2 times per week. In accordance with Henriksson et al.'s qualitative study of PA barriers among PC patients (198), this may imply that RT -induced bowel symptoms is a barrier to PA among PC patients. Health care personnel should be aware that PC patients with bowel problems after RT are at risk of a low level of PA. Follow-up of these patients should include a focus on treating/alleviating bowel symptoms, as well as providing information and support in relation to PA.

In patients undergoing ADT, a smaller proportion of those who were ≥ 5 years or more since diagnosis exercised at least twice weekly compared to patients closer to diagnosis. This finding is in agreement with results in a review reporting that long-term adult cancer survivors were less likely to meet lifestyle recommendations than survivors less than 5 years from diagnosis (12). It might be that recently diagnosed PC patients are more motivated to have a healthy lifestyle (e.g. by being physically active), but that the adherence to healthy behaviors diminishes over time. Another explanation might be that the long duration of ADT with AEs such as lack of energy and loss of muscle mass and physical function, reduce the ability to be physically active. However, in a study exploring PA predictors in 84 PC patients undergoing ADT, no relationship between PA and time on ADT was detected (270). Nevertheless, our findings indicate a need to inform patients undergoing life-long ADT about the benefits of exercise. The importance of strength training should be emphasized due to the detrimental effects of ADT on muscle mass. Patients not familiar with exercise/strength training should receive individual guidance.

Lack of energy/fatigue has previously been reported as a PA barrier specifically among PC patients undergoing ADT (269, 270). Among those undergoing ADT in our study, lack of energy was, however, only borderline statistically significant associated with PA.

6.2.3 Paper II

In Paper II, we found that most YACSs were not meeting all the guidelines on PA, BMI and smoking. Survivors with comorbidities, CF, lymphedema, pain and/or depressive symptoms, as well as men, those living without a partner and/or with low education, were less likely to meet single or an increasing number of lifestyle guidelines.

Adherence to lifestyle guidelines

The adherence to lifestyle guidelines found among the YACSs in our study was higher or similar to reports from U.S studies including subpopulations of YACSs and smaller studies including survivors less than 5 years from diagnosis, in which 50-70% were not meeting PA guidelines and more than half were overweight or obese (14, 101, 202, 204-208). The prevalence of smokers in our study (20%)is lower than the reported among YACSs in U.S. studies (≈30%) (14, 101, 202, 203), but higher than found in other populations of YACSs (13-16%) (205, 206, 208).

To meet several lifestyle guidelines is more likely to improve survival and QoL than adhering to a single recommendation only (15). Limited evidence exists on the prevalence of meeting multiple lifestyle recommendations in cancer survivors. To our knowledge, our study is the first to investigate adherence to a combination of lifestyle guidelines exclusively among long-term YACSs. Only 26% of the YACSs in our study met the combination of PA, BMI and smoking guidelines. This is somewhat higher than the findings of Spector et al. that 20% of long-term NHL survivors met the combination of PA, BMI and smoking guidelines (274). Blanchard et al. found that the proportion of BC, PC, CRC, bladder, uterine and skin melanoma survivors meeting neither PA nor smoking guidelines ranged from 8% to 14% (189). This is in agreement with findings in our study, in which 11% were physically inactive and current smokers.

Reported prevalence rates of adherence to lifestyle recommendations in cancer survivors vary greatly. A recent review on lifestyle among cancer survivors mainly aged 50 years or older identified prevalence rates ranging from 12-78% for physical inactivity, 35-74% for BMI $\geq$ 25 kg/m^2 and 3-40% for smoking (12). Because a wide range of different measures, mostly questionnaires, are used, comparing results across studies is challenging. For example, the questionnaires' complexity and type and dose of PA measured, is of great importance for classification of meeting PA guidelines or not. Further, distinctive population characteristics, such as age at diagnosis and survey, cancer type, time since diagnosis, type of treatment and burden of AEs, as well as cultural differences, might also be of significant importance and explain possible differences in adherence to lifestyle recommendations. To date, evidence on lifestyle in cancer survivors is mainly based on populations diagnosed with BC or CRC at age 50 years or older, and/or individuals less than 5 years from diagnosis (12). Due to the long survival time and specific age range at diagnosis among the YACSs in our study, we are not aware of other studies with populations that are directly comparable.

Survivors of localized MM who had undergone limited surgery only were considered as a reasonable comparison group in the NOR-CAYACS study, given their history of low treatment burden and their presumed low risk of AEs. Our finding that lifestyle did not differ between the comparison group and YACSs who had received more intensive treatment may indicate that YACSs are not more likely to have a healthy lifestyle than the general population. This is in line with previous research indicating

that YACSs and controls are in general non-adherent to lifestyle guidelines (14, 101, 202). However, better lifestyle behaviors among survivors diagnosed with cancer at a young age compared to the general population have also been identified. A systematic review on health behavior among cancer survivors aged 18-45 at the time of study (mainly childhood cancer survivors) concluded that survivors were less likely to smoke and drink alcohol cancer free controls (275). Moreover, studies on survivors of testicular cancer and Hodgkin lymphoma, which are mainly diagnosed in young adults, have found that these survivors are significantly more physically active than the general population (209, 261, 262). A possible explanation to why cancer survivors have a healthier lifestyle than controls may be the concept of a teachable moment; being diagnosed with cancer may motivate individuals to live a more healthy life (10).

Factors associated with not meeting single and an increasing number of lifestyle guidelines
We found several associations between unhealthy lifestyle and comorbidity, late effects and symptoms. CF was associated with increased risk of physical inactivity. Higher level of depressive symptoms and lymphedema were more common among overweight individuals, while >2 comorbid conditions, pain and lymphedema were associated with not meeting an increasing number of lifestyle guidelines. These associations represent new findings among YACSs, but are in line with previous findings among other groups of cancer survivors. A lower level of PA and/or cardiorespiratory fitness have previously been found in cancer survivors with higher levels of fatigue (133, 139, 172), and obesity is a risk factor for lymphedema and comorbidity (11). Also in line with our findings, Spector et al. found less comorbidities, pain and psychological distress in long-term NHL survivors meeting several lifestyle guidelines than in survivors not meeting guidelines (274).

Due to the cross-sectional design of our study, we cannot draw any conclusions on whether these conditions worsen because of an unhealthy lifestyle, lead to an unhealthy lifestyle, or if the relationship is bidirectional. However, interventional studies have demonstrated that a healthy lifestyle has a beneficial effect on several of these late effects and symptoms (15). PA improves fatigue, pain, depressive symptoms and risk factors for cardiovascular morbidity (158, 163, 164, 276), and may also reduce lymphedema in BC survivors (277). Research also indicates that weight loss interventions including dietary modifications and PA can provide clinically relevant weight loss in cancer survivors, reducing cardiovascular risk factors (278, 279). Hence, the results of our study imply a need to focus on obtaining and maintaining a healthy lifestyle in relation to comorbidity and late effects in YACSs.

As previously shown among cancer survivors diagnosed during childhood or at an older age (13, 274, 275, 280), we found that males were more likely to be overweight and have a more unhealthy lifestyle, YACSs not living with a partner were more likely of smoking, and low education was associated with smoking and a more unhealthy lifestyle. Thus, YACSs with these characteristics might need special attention to achieve and maintain a healthy lifestyle.

6.2.4 Paper III

In Paper III, one of four long-term YACSs reported CF. The prevalence of CF within each diagnostic group was 29% for BC and CRC, 27% for NHL, 20% for ALL and 15% for MM. Survivors of BC, CRC and NHL had a significantly higher prevalence of CF and level of fatigue than survivors of localized MM. Multimodal therapy, comorbidity, pain, numbness in hands/feet and depressive symptoms were associated with an increased risk of CF.

Prevalence and level of fatigue

The overall prevalence of CF found in our study is within the ranges of previous findings in studies performed at the National Advisory Unit on Late Effects after Cancer Treatment using FQ in survivors of cancer types occurring frequently in young adulthood, such as Hodgkin lymphoma and testicular cancer, as well as in cancer survivors diagnosed with BC or lymphoma further into adulthood (15-35%) (119, 128-130, 132, 133). The level of fatigue found in the present study is also in accordance with what is previously reported among survivors of BC (132) and NHL (130) diagnosed at an older age. This indicates that YACSs are not more affected by fatigue than survivors of cancers diagnosed further into adulthood, which is in contrast to previous studies reporting that YACSs experience worse fatigue than survivors diagnosed at an older age (147, 148).

Currently, there is no established consensus on how fatigue should be defined in cancer populations, and various self-reported instruments are used across studies (109). The lack of agreement on how fatigue should be measured limits the ability to compare prevalence rates of fatigue across studies. Two recent studies including YACSs < 5 years from diagnosis found considerably higher prevalence rates of fatigue compared to our findings (145, 150). Among 83 cancer patients diagnosed at age 18 to 35 years, Poort et al. found that 48% had severe fatigue, compared to 20% in a population-based control group (145). Another study including 80 survivors of mixed cancer types aged 13-24 years at diagnosis found that 85% had been affected by fatigue the last month (150). In these studies, assessment of duration of fatigue was limited to the past month, whereas the prevalence of CF in our study refers to fatigue of at least 6 months duration. Furthermore, as a large proportion of the populations were still undergoing or had recently completed cancer treatment, they might still experience acute fatigue that is likely to diminish with time. Thus, we cannot compare the prevalence of CF in our sample of long-term YACSs directly with the prevalence of fatigue in these studies.

In sub-study II, participants treated with limited surgery for MM were defined as a comparison group. In agreement with our hypothesis, survivors of MM had a significantly lower prevalence of CF than survivors of BC, NHL and CRC. The prevalence of CF (15%) and level of fatigue (mean FQ total score 12.2, SD 4.1) found among the MM survivors are comparable to Loge et al.'s findings of 11% with CF and a mean FQ total score 12.2 (SD 4.0) in the general Norwegian population using FQ (134), thus supporting the rationale for using MM as a comparison group. One should, however, note that the

prevalence of CF in the Norwegian general population may have changed since Loge et al published their results in 1998 (134). Nevertheless, our findings suggest that long-term YACSs of BC, NHL and CRC are considerably more affected by fatigue compared to the general population, confirming previous studies on fatigue in YACSs (144-146, 149) .

Factors associated with chronic fatigue

Systemic treatment combined with surgery and/or RT was associated with an increased risk of CF among the YACSs in our study. Previous evidence on the relation between fatigue and cancer treatment in YACSs is inconsistent. Two studies reported more severe fatigue among survivors treated with RT (145, 146), while a more recent study found no associations between fatigue and type of treatment among YACSs assessed within 4 years from diagnosis (281). Overall, the relation between fatigue after completed treatment and treatment-related factors such as type and intensity is inconsistent (106). In agreement with our findings, a meta-analysis on course of fatigue after BC treatment found that receiving the combination of chemotherapy, surgery, RT and hormone therapy increased the risk of severe fatigue compared to surgery+/-RT alone (136). However, in an earlier systematic review, most of the included studies found no association between fatigue and treatment-related variables (137).

Comorbidities, pain and numbness in hands or feet were associated with an increased risk CF in our study. These results are in agreement with prior studies on CF in long-term survivors of BC, PC and testicular cancer (118, 119, 124, 128). To our best knowledge, these factors have not previously been explored in relation to fatigue among long-term YACSs. Increasing levels of depressive symptoms were also strongly associated with CF. The correlation between fatigue and depression in cancer survivors is well established (282), both among YACSs (145, 150) and cancer survivors diagnosed at other ages (116, 119, 128). The relation between depression and fatigue is however complex, as fatigue may be a symptom of depression, but fatigue may also lead to depressive symptoms due to restrictions in social, work and leisure activities.

The cross-sectional design of our study prevents drawing conclusions on the directionality between CF and the associated conditions. One might hypothesize that the stress of coping with comorbidities and late effects such as neuropathy may induce or worsen fatigue. On the other hand, survivors with CF may have less capacity to handle distressing symptoms such as pain or neuropathy, or prevent/mitigate comorbid conditions e.g. through a healthy lifestyle. Rather than focusing on causality, Bower et al. suggest that factors associated with fatigue can be used to identify vulnerable patients and to induce preventive strategies at an early time point (106).

The multiple factors associated with CF confirms the multifactorial origin of fatigue following cancer treatment (106). However, given that the YACSs in our study were median 14 years from treatment, other factors than those identified in our study might have influenced CF.

Duration and development of chronic fatigue

Based on our study, it is not possible to determine whether CF was present before diagnosis or treatment. However, the majority of YACSs with CF had been tired since they were treated for cancer, suggesting that fatigue occurring during treatment continued for years after ended treatment. Of those who had been tired since treatment, 65% reported no change or worsening of fatigue with time.

In summary, our findings imply a need for health care personnel to be attentive to the high prevalence of CF among long-term YACSs, and strategies on how to improve this symptom. Interventions aimed at improving fatigue should include a focus on treatable factors associated with CF. Furthermore, the finding that the majority of YACSs with CF had been tired since cancer treatment illuminates the need to intervene early with strategies to prevent and alleviate fatigue among YACSs.

7.0 Conclusions

Overall, unhealthy lifestyle behaviors were common among the cancer patients and survivors included in this thesis. In both PC patients and long-term YACS, AEs were associated with an increased risk of unhealthy lifestyle behaviors.

Paper I

- Close to half of PC patients during and after treatment exercised less than two times per week. The level of PA did not differ across treatment groups.
- Bowel symptoms were associated with a low level of PA in the total sample and among patients treated with RT + ADT.
- Age ≥ 70 years, work force participation and BMI ≥25 kg/m^2 were also associated with a low level of PA among all patients.
- For patients undergoing ADT, being ≥ 5 years since diagnosis was associated with a low level of PA

Paper II

- A large proportion of long-term YACSs did not meet the public lifestyle guidelines for PA, BMI, smoking and 5-a-day.
- One of four met all three guidelines for PA, BMI and smoking
- Lifestyle did not differ between YACSs treated for BC, CRC, NHL or ALL, and a comparison group treated with skin surgery for localized MM.
- Chronic fatigue was associated with being physically inactive.
- Male gender, > 2 comorbid conditions, lymphedema and depressive symptoms were associated with being overweight, while multimodal treatment was associated with a lower risk of being overweight.
- Not living with a partner, education ≤ 13 years and lymphedema were associated with smoking.
- Male gender, education ≤ 13 years, > 2 comorbid conditions, lymphedema and pain were associated with not meeting an increasing number of lifestyle guidelines.

Paper III

- One fourth of long-term YACSs reported CF, and this prevalence was significantly higher among survivors of BC, CRC and NHL compared to survivors of localized MM treated with skin surgery, of which 15% reported CF.
- Multimodal treatment, 1-2 comorbidities, pain, numbness in hands/feet and increasing depressive symptoms were associated with CF.
- Among YACSs with CF, 60% had been tired since cancer treatment. Of these, 65% reported no change or worsening of fatigue with time.

8.0 Clinical implications

- Adding to the available knowledge that a high proportion of PC patients are not meeting PA guidelines (194-196), the findings in thesis can be used to identify inactive patients after curative treatment and during lifelong ADT for metastatic disease.
- Health personnel, including doctors, nurses and physiotherapists, involved in the follow-up of PC patients after RT should inform these patients that bowel symptoms may affect their ability to be physically active, and offer information and support on how to regain or maintain their level of PA. Moreover, PC patients who are in the work force, overweight or undergoing life-long ADT should receive motivational support to increase the level of PA.
- Long-term YACSs and young adults recently diagnosed with cancer should be informed about the risk of AEs and health problems and the possible impact of a healthy lifestyle. Thus, health personnel involved in the follow-up after cancer treatment should have knowledge about lifestyle and late effects.
- Given the lack of successful interventions aiming to improve the lifestyle among YACSs (210), knowledge provided from this thesis about the characteristics of YACSs with an unhealthy lifestyle can be used to develop lifestyle interventions targeted towards subgroups of YACSs in particular need of such interventions.
- The high prevalence of CF, and strategies on how to reduce or manage to live with fatigue, should be communicated to general practitioners and other health personnel involved in the follow-up of YACSs.
- YACSs and young adult cancer patients who might be at particular risk of CF, such as those who receive multimodal cancer treatment, with comorbidity and/or late effects, should be identified and informed about the risk of CF, enabling them to take preventive actions, i.e. through being physically active.

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Paper I

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ORIGINAL ARTICLE

Physical activity and associations with treatment-induced adverse effects among prostate cancer patients

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Abstract

Purpose The present study aimed to determine the level of physical activity (PA) among prostate cancer (PCa) patients across treatment modalities and explore the association between PA and treatment-induced adverse effects (AEs).

Methods The present study was based on a cross-sectional postal survey among members of the Norwegian Prostate Cancer Association. Patients were eligible for the present study if they had either (1) completed radical prostatectomy, (2) completed radiotherapy and (neo)-adjuvant androgen deprivation therapy (ADT), or (3) were undergoing lifelong ADT. Adverse effects were measured by the Expanded Prostate Cancer Index Composite for Clinical Practice.

Results In total, 696 patients were included. There was no statistically significant difference in level of PA across treatment modalities. Bowel symptoms mainly related to radiotherapy decreased the odds of exercising ≥ 2 times per week, along with age ≥ 70 years, participation in the workforce, and BMI ≥ 25 kg/m^2. Among patients who were undergoing ADT, 5 years or more since diagnosis reduced the odds of exercising ≥ 2 times per week by almost 60%.

Conclusion The level of PA did not differ across PCa patients treated with different modalities. Increasing bowel symptoms reduced the likelihood of exercising ≥ 2 times per week. PCa patients should be educated about possible treatment-induced AEs affecting PA level, enabling them to counteract the development of physical inactivity.

Keywords Prostate cancer · Physical activity · Treatment-induced adverse effects · Radiotherapy · Androgen deprivation therapy · Prostatectomy

Introduction

Prostate cancer (PCa) is the most common cancer among men in Western countries [1]. In Norway, more than 5000 men are diagnosed with PCa each year, and the relative 5-year survival rate has exceeded 90% [2]. The standard curative treatment for patients with localized PCa and a life expectancy of at least 10 years involve either radical prostatectomy (RP) or radiation therapy (RAD) with or without (neo)-adjuvant androgen deprivation therapy (ADT). Among patients with metastatic PCa, life-long ADT is the primary treatment [3]. All these treatments are associated with specific treatment-induced adverse effects (AEs). Typical AEs after RP are urinary incontinence and erectile dysfunction [4, 5], while RAD also may be followed by bowel symptoms and urinary irritation [4, 6]. During long-lasting ADT, patients often experience several systemic AEs, such as sexual dysfunction, fatigue, increased fat mass and decline in physical function, muscle mass, and bone density [7–9], as well as increased risk of diabetes and cardiovascular morbidity [10]. Lack of energy and sexual problems may persist for several months and even years after discontinuation of ADT [6].

Physical activity (PA) has beneficial effects on several health aspects during and after cancer treatment [11].

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Therefore, adult cancer survivors should avoid physical inactivity, and as far as possible follow the oncology exercise guidelines, including 150 min of moderate intensity or 75 min of vigorous intensity (or an equivalent combination) aerobic exercise per week, and resistance training on 2 days or more per week [12].

PCa patients, particularly when undergoing ADT, are likely to benefit from PA by preserving and even improving physical performance and lean body mass and reducing fatigue [13]. Despite the potential to achieve these health benefits, the majority of PCa patients are not meeting the PA recommendations mentioned above [14–18]. There is evidence indicating that PCa patients treated with ADT are less physically active compared to men who have received other types of PCa treatments [18, 19]. However, more research regarding level of PA and treatment-related factors is needed to identify PCa patients in particular need of attention aiming to increase their activity level [18].

In order to assist PCa patients to increase their PA participation, health professionals have to understand the barriers these men meet. A limited number of qualitative and quantitative studies have reported local AEs such as urinary incontinence and bowel problems following PCa treatment as barriers to PA [20–23]. However, large-scale studies in relatively unselected populations of PCa patients documenting the statistical relationship between local and systemic treatment-induced AEs and level of PA are lacking.

Therefore, the aims of the present study were to compare the level of PA among PCa patients across different treatment modalities and explore the association between PA and treatment-induced AEs. We hypothesized that (1) the level of PA would be higher among those who had completed RP or RAD + ADT than patients undergoing ADT for metastatic disease and (2) treatment-induced AEs would be negatively associated with PA.

Material and methods

The Norwegian Prostate Cancer Patients Association (PROFO) is a patient organization founded in 2003, including PCa patients at all stages of the disease. In May 2013, all PCa patients who were members of PROFO were invited to participate in a questionnaire-based cross-sectional survey including assessment of PA, treatment-induced AEs, and global quality of life [24]. Members received an information letter, a questionnaire, and a postage-paid return envelope by mail. In April 2014, a follow-up e-mail was sent out, asking members who had not responded to the mailed version to complete the questionnaire electronically.

Questionnaire variables

Physical activity

Level of PA was assessed by asking how frequently they were exercising each week. The question used was a PA item (frequency) extracted from the 3 PA items (frequency, intensity, and duration) included in the Nord-Trøndelag Health Study: HUNT 1 [25]. The wording of this item was as follows: "By exercise we mean, for example, skiing, swimming, or training/sports leading to breathlessness or sweating. How frequently do you exercise?" The response categories were "never," "less than once per week," "once per week," "2–3 times per week," and "almost every day."

Treatment-induced adverse effects

Treatment-induced AEs were assessed by the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) [26]. EPIC-CP is a 16-item questionnaire for self-rating of urinary incontinence, urinary irritation/obstruction, bowel-related symptoms, sexual dysfunction, and vitality/hormonal symptoms in men with PCa. Each of the 5 EPIC-CP domains contains 3 items with 4 or 5 response alternatives scored on a Likert scale ranging from 0 to 4, with increasing score reflecting worse symptom severity/bother [26]. Studies have shown that EPIC-CP correlates highly with previous EPIC versions [27], has good internal consistency, reliability, and discriminative validity, and is responsive to changes in treatment-induced AEs after PCa treatment [26, 28]. For the present study, complete EPIC-CP domains of urinary incontinence, urinary irritation/obstruction, bowel-related symptoms, and sexual dysfunction were included. We extracted the "Lack of energy" item from the vitality/hormonal domain and used it as a stand-alone item dichotomized into no problem/very small problem/small problem versus moderate problem/big problem (no/yes), based on Sanda et al. [6].

Treatment groups

Patients were categorized into 3 groups based on self-reported treatment modalities: (1) completed open or robotic RP and denial of new/other cancer treatment (RP-group), (2) completed RAD and (neo)-adjuvant hormone treatment (ADT) and denial of new/other cancer treatment (RAD+ADT-group), or (3) undergoing ADT or completed orchiectomy, without RP or RAD (ADT-group). Patients not eligible for one of these groups were excluded.

Background variables

Demographic variables were age (< 70/≥ 70 years), basic education level (≤ 12 years/> 12 years), and work force participation, which was dichotomized into retired, sick-leave, work assessment allowance, or disability benefits versus working fulltime or part-time (no/yes). Medical variables included year of diagnosis, time since diagnosis, time since start of treatment, treatment modality (as described previously), and presence of comorbidity affecting general health (no/yes). Lifestyle−/health variables were BMI (calculated into < 25 kg/m^2/≥ 25 kg/m^2 from reported height and weight), daily smoking (no/yes), and perceived general health, which was dichotomized into not so good/poor versus good/excellent (poor/good).

Statistics

Data were analyzed using IBM SPSS Statistics version 21.0 for Windows (SPSS Inc. Chicago, IL, USA).

Continuous variables were displayed by medians and ranges or means and standard deviations (SDs), and categorical variables by frequencies and proportions. To assess differences in level of PA, AEs and background variables between treatment groups, chi-square tests were applied on categorical variables and one-way ANOVA with Tukey post hoc test on continuous variables. Two-tailed p values of less than 0.05 were considered statisti-cally significant.

Logistic regression analyses were applied to identify factors associated with level of PA (dependent variable). For these analyses, the level of PA variable was dichotomized into "< 2 times per week" and "≥ 2 times per week". Treatment-induced AEs and background variables (age, education, work-force participation, time since diagnosis, comorbidity, and BMI) represented the independent variables.

Statistically significant variables and variables considered clinically relevant with p values ≈ 0.1 from the univariable logistic regression analyses were included in the multivariable logistic regression analyses. The variables were reduced until only statistically significant variables remained. The strengths of associations were expressed as crude and adjusted odds ratios (cOR and aOR) with 95% confidence intervals (95% CI).

Ethics

The present study was based on an anonymous survey through PROFO, providing the authors with completely anonymous data. Therefore, the present study did not require approval from the regulatory ethics in Norway.

Results

Among 2700 invited patients in PROFO, 1343 returned the questionnaire (response rate ≈ 50%). Of these, 696 patients were eligible for the present study as they reported their primary treatment as completed RP or RAD + ADT, or ongoing ADT.

Characteristics of patients

At the time of survey, the median age was 69.8 years (range from 47 to 105 years) and the median time since diagnosis was 4.7 years (range from < 1 to 23 years) (Table 1). Median time since start of treatment was 45 months (range from < 1 to 241 months). The majority of the included patients were treated with RP (56%, $n = 393$), followed by RAD+ADT (29%, $n = 204$) and ADT alone (14%, $n = 99$) (Table 1).

Treatment-induced AEs

The mean EPIC-CP domain scores are shown in Table 2. Patients treated with RP had significantly higher symptoms of urinary incontinence than patients in the RAD+ADT and ADT-group ($p < .001$). Bowel symptoms were statistically significant higher among patients treated with RAD+ADT than patients in the RP and ADT group ($p < .001$), while those undergoing ADT had the highest sexual symptoms ($p < .001$). Lack of energy was statistically significant less prevalent among patients who had undergone RP (15%) than among those who had completed RAD+ADT (29%) or were undergoing ADT (34%) ($p < .001$).

Distribution of responses to all items in the EPIC-CP urinary incontinence score, urinary irritation/obstruction score, bowel symptom score, sexual symptom score, and lack of energy are given in Online Resource, Fig. 1a-5.

Level of PA

The overall level of PA did not differ between treatment groups ($p = .131$) (Fig. 1). The proportion of men who reported to exercise ≥ 2 times per week was 57% with a minimal non-significant intergroup difference (RP 56%, RAD+ADT 58%, and ADT alone 56%, $p = .892$). Due to the large difference in never exercisers between ADT (10%) and RP (3%), we performed a post-hoc chi-square test which gave a p value of 0.004 (data not shown).

Association between PA and treatment-induced AEs

Among all patients, multivariable logistic regression analyses showed that exercising ≥ 2 times per week was inversely

Table 1 Demographic and medical characteristics of prostate cancer patients treated with radical prostatectomy (RP), radiation therapy with (neo)-adjuvant androgen deprivation therapy (RAD+ADT), and androgen deprivation therapy alone (ADT)

	RP ($n = 393$)	RAD+ADT ($n = 204$)	ADT ($n = 99$)	P	Total ($n = 696$)
Demographic variables					
Age in years, median (min.-max.)	66.8 (47.0–82.8)	73.0 (55.0–105.0)	78.0 (52.1–88.0)		69.8 (47.0–105.0)
< 70 years, *n* (%)	286 (73)	58 (28)	23 (23)	< .001* [ac]	367 (53)
≥ 70 years, *n* (%)	107 (27)	146 (72)	76 (77)		329 (47)
Basic education, *n* (%)					
≤ 12 years	177 (45)	113 (56)	48 (49)	.044* [a]	338 (49)
> 12 years	213 (55)	88 (44)	51 (52)		352 (51)
Missing (*n*)	3	3	0		6
Workforce participation [1] , *n* (%)					
No	224 (59)	169 (87)	85 (89)	< .001* [ac]	478 (72)
Yes	154 (41)	25 (13)	11 (12)		190 (28)
Missing (*n*)	15	10	3		28
Medical variables					
Year of diagnosis, *n (%)*					
Before 2010	192 (49)	129 (63)	61 (62)	.001* [ac]	382 (55)
2010 or later	201 (51)	75 (37)	38 (38)		314 (45)
Years since diagnosis, median (min.-max)	4.0 (< 1–23)	5.4 (< 1–15)	5.9 (< 1–16)		4.7 (< 1–23)
< 5 years, *n* (%)	268 (68)	98 (48)	46 (47)	< .001*[ac]	412 (59)
≥ 5 years, *n* (%)	125 (32)	106 (52)	53 (54)		284 (41)
Time since treatment start in months, median (min-max)	38 (< 1–241)	52 (< 1–171)	55 (1–188)	.010*[c]	45 (< 1–241)
Comorbidity affecting health, *n* (%)					
No	230 (60)	122 (60)	52 (54)	.564	404 (59)
Yes	156 (40)	80 (40)	44 (46)		280 (41)
Missing (*n*)	7	2	3		12
Lifestyle−/health variables					
BMI, *n* (%)					
< 25 kg/m^2	128 (33)	57 (28)	35 (35)	.354	220 (32)
≥ 25 kg/m^2	265 (67)	147 (72)	64 (65)		476 (68)
Daily smoker, *n* (%)					
No	357 (93)	188 (94)	87 (91)	.573	632 (93)
Yes	28 (7)	12 (6)	9 (9)		49 (7)
Missing (*n*)	8	4	3		15
General health, *n* (%)					
Poor	63 (16)	50 (25)	36 (37)	< .001* [abc]	149 (22)
Good	326 (84)	151 (75)	61 (63)		538 (78)
Missing (*n*)	4	3	2		9

SD standard deviation, *Min* minimum, *Max* maximum, *BMI* body mass index.*$p < 0.05$ [a] RP vs RAD+ADT; [b] RAD+ADT vs ADT; [c] RP vs ADT. Percentage may not add up to 100% because of rounding. [1] Retired: $n = 433$. Disability benefits: $n = 30$. Sick-leave: $n = 4$. Work assessment allowance: $n = 7$. Other: $n = 433$. *P* values obtained by chi-square-test and one-way ANOVA

associated with worsening (increasing score) of bowel symptoms (aOR .91, 95% CI .85–.97, $p = .003$) (Table 3). In addition, patients aged ≥ 70 years, participating in the workforce and reporting a BMI ≥ 25 kg/m^2 were statistically significant less likely to exercise ≥ 2 times per week than patients aged < 70 years, not participating in the workforce and reporting a BMI < 25 kg/m^2 (Table 3).

In the RP-group, patients aged ≥ 70 years and with a BMI ≥ 25 kg/m^2 were statistically significant less likely to exercise ≥ 2 times per week compared to patients aged < 70 years and with BMI < 25 kg/m^2 (Table 4). In the RAD+ADT-group, worse bowel symptoms decreased the likelihood of exercising ≥ 2 times per week (Table 5). In the ADT-group, time since diagnosis ≥ 5 years reduced the odds of exercising ≥ 2 times per week by approximately 60% (Table 6).

Discussion

Main findings

In the present study, there was no statistically significant difference in overall level of PA between the treatment groups. Worsening of bowel symptoms related to radiotherapy was inversely associated with exercising ≥ 2 times per week. Moreover, patients aged ≥ 70 years, those who participated in the workforce and men who were overweight, were less likely to exercise ≥ 2 times per week.

Level of PA

We hypothesized that patients undergoing ADT would report a lower level of PA than patients treated with RP and RAD+

Table 2 EPIC-CP scores and presence of lack of energy among prostate cancer patients treated with radical prostatectomy (RP), radiation therapy with (neo)-adjuvant androgen deprivation therapy (RAD+ADT), and androgen deprivation therapy alone (ADT)

	RP ($n = 393$)	RAD+ADT ($n = 204$)	ADT ($n = 99$)	*P*	Total ($n = 696$)
EPIC-CP domain score, mean (SD) (score out of 12^)					
Urinary Incontinence	3.1 (2.8)	1.4 (1.9)	1.4 (1.9)	< .001* ac	2.4 (2.6)
Urinary irritation/obstruction	1.9 (1.9)	3.0 (2.5)	2.9 (2.5)	< .001* ac	2.4 (2.2)
Bowel symptoms	1.0 (1.9)	2.7 (3.1)	1.6 (2.4)	< .001* ab	1.6 (2.5)
Sexual symptoms	7.1 (3.1)	7.3 (2.9)	9.1 (2.5)	< .001* bc	7.4 (3.0)
Lack of energy, *n* (%)					
No	335 (85)	145 (71)	65 (66)	< .001* ac	545 (78)
Yes	58 (15)	59 (29)	34 (34)		151 (22)

^Higher score = worse symptoms. *SD* standard deviation. *$p < 0.05$. [a] RP vs RAD+ADT; [b] RAD+ADT vs ADT; [c] RP vs ADT. *P* values obtained by chi-square-test and one-way ANOVA

ADT, due to the systemic AEs from ADT (e.g., fatigue and decreased muscle mass). Chipperfield et al. [19] found that patients treated with ADT were less physically active than patients treated with RAD only, and Forbes et al. [18] reported that patients who had undergone prostatectomy were more active than those who had received other PCa treatments. In contrast to our hypothesis and findings from previous studies, the overall level of PA in the present study was similar across treatment modalities. A possible explanation for this finding might be that patients in the ADT-group primarily have been more encouraged by health professionals to be physically active when starting ADT than patients treated with RP, due to the known benefits of PA on ADT-induced AEs. Also, patients in the ADT-group might have allocated more of their time to be physically active, as only 12% were active in the workforce (versus 41% in the RP-group). However, a post-hoc chi-square test comparing the prevalence of those reporting to never exercise indicated a significant difference between ADT and RP. This indicates that AEs associated with ADT, advanced cancer, and lower general health [9] can limit the ability to conduct PA leading to breathlessness and sweating, and that special attention should be paid towards PCa patients undergoing ADT to maintain or increase level of PA.

Interestingly, patients who had completed RAD+ADT were not more physically active than patients undergoing ADT. This might in part be explained by delayed recovery of testosterone production after discontinuation of adjuvant ADT, which is particularly frequent among older patients [29]. Consequently, these patients continue to suffer from AEs usually associated with undergoing ADT such as fatigue [6], a common exercise barrier among cancer survivors [30, 31].

Studies have reported that approximately 45% of PCa patients are meeting exercise guidelines of at least 150 min moderate or 75 min vigorous PA weekly [15, 17–19]. Among Norwegian men in the general population aged above 60 years,

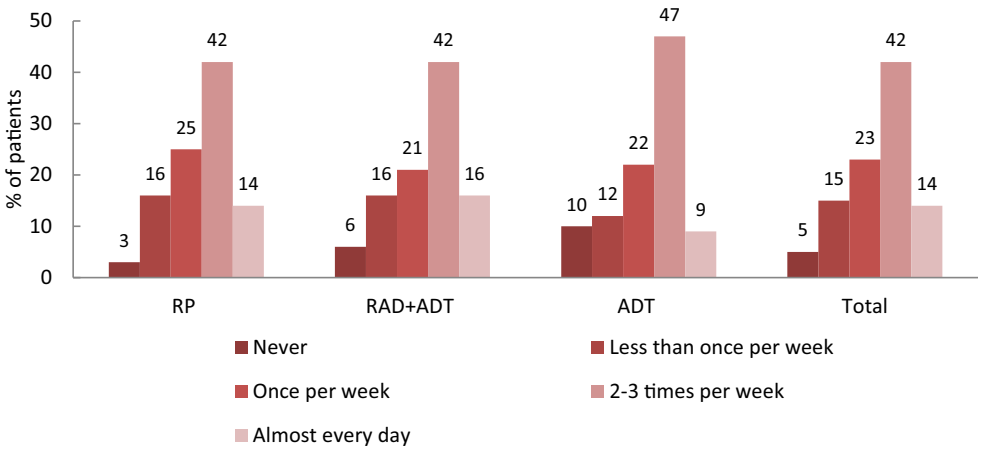

Fig. 1 Reported exercise frequency in per cent among prostate cancer patients treated with radical prostatectomy (RP), radiotherapy + androgen deprivation therapy (RAD+ADT) and ADT. There was no difference in overall exercise frequency between treatment groups ($p = .131$, obtained by chi-square test)

Table 3 All patients ($n = 696$): factors associated with exercising ≥ 2 times per week versus less

	Exercise frequency		Unadjusted analyses			Adjusted analyses		
	< 2 times/ week	≥ 2 times/ week	cOR	95% CI	*P*	aOR	95% CI	*P*
EPIC-CP domain score, mean (SD)(score out of 12[1])								
Urinary incontinence	2.5 (2.6)	2.3 (2.6)	.97	.92–1.03	.283			
Urinary irritation/obstruction	2.3 (2.2)	2.4 (2.2)	1.02	.96–1.09	.545			
Bowel symptoms	1.9 (2.6)	1.4 (2.3)	.91	.86–.97	*.003**	.91	.85–.97	.003*
Sexual symptoms	7.7 (3.0)	7.2 (3.1)	.95	.90–.99	*.027**			
Lack of energy, *n* (%)								
No (reference)	227 (42)	318 (58)	1.0					
Yes	76 (50)	75 (50)	.70	.49–1.01	*.058*			
Demographic variables								
Age, *n* (%)								
< 70 years (reference)	148 (40)	219 (60)	1.0			1.0		
≥ 70 years	155 (47)	174 (53)	.76	.56–1.03	*.072*	.56	.39–.82	.002*
Basic education, *n* (%)								
≤ 12 years (reference)	154 (46)	184 (54)	1.0					
> 12 years	144 (41)	208 (59)	1.21	.89–1.64	.218			
Work force participation, *n* (%)								
No (reference)	198 (41)	280 (59)	1.0			1.0		
Yes	91 (48)	99 (52)	.77	.55–1.08	*.128*	.52	.35–.79	.002*
Medical variables								
Time since diagnosis, *n* (%)								
< 5 years (reference)	170 (41)	242 (59)	1.0					
≥ 5 years	133 (47)	151 (53)	.80	.59–1.08	.146			
Comorbidity affecting health, *n* (%)								
No (reference)	170 (42)	234 (58)	1.0					
Yes	126 (45)	154 (55)	.89	.65–1.21	.448			
Health variables								
BMI, *n* (%)								
< 25 kg/m^2 (reference)	81 (37)	139 (63)	1.0			1.0		
≥ 25 kg/m^2	222 (47)	254 (53)	.67	.48–.93	*.015**	.66	.47–.93	.016*

[1] Higher score = worse symptoms. *SD* standard deviation, *cOR* crude odds ratio, *aOR* adjusted odds ratio, *95% CI* 95% confidence interval.*$p < 0.05$. *BMI* body mass index (kg/m^2). Numbers may not add up to 696 because of missing values. Percentage may not add up to 100% because of rounding. In adjusted analyses, bowel symptoms, sexual symptoms, lack of energy, age, work force participation and BMI were included (italic). [2] Number included in adjusted analyses: $n = 668$. Variables were reduced until only statistically significant variables were remaining

less than 40% meet these exercise guidelines, measured by accelerometer [32]. It is not possible to directly compare our findings with other studies, nor state whether the patients meet the exercise guidelines or not, as the PA question in the present study did not take into account duration or more detailed intensity. Still, our findings indicate that a considerable proportion of PCa patients are exercising once per week or less. Galvão et al. [14] found that only 12.3% of PCa survivors met the exercise guidelines of both aerobic and strength training; however, ≈ 53% reported to be physically active in some way. This finding is comparable with the prevalence of 57% reporting to exercise 2–3 times or more per week in the present study.

Level of PA and associated factors

Treatment-induced AEs

In agreement with our hypothesis, PCa patients who reported increasing bowel symptoms related to radiotherapy were less likely to exercise ≥ 2 times per week. Our finding is in line with Henriksson et al. [20], who conducted focus-group interviews with PCa patients and reported bowel symptoms after radiotherapy as a barrier to exercise. To our knowledge, this is the first cross-sectional study demonstrating that bowel symptoms may decrease the likelihood of exercising ≥ 2 times per week among irradiated PCa patients.

Table 4 Patients treated with radical prostatectomy (RP) ($n = 393$): factors associated with exercising ≥ 2 times per week versus less

	Exercise frequency		Unadjusted analyses			Adjusted analyses[2]		
	< 2 times/ week	≥ 2 times/ week	cOR	95% CI	P	aOR	95% CI	*P*
EPIC-CP domain score, mean (SD)(score out of 12[1])								
Urinary incontinence	3.2 (2.8)	3.0 (2.8)	.98	.91–1.05	.494			
Urinary irritation/obstruction	1.8 (2.0)	1.9 (1.8)	1.02	.92–1.13	.719			
Bowel symptoms	1.1 (1.9)	1.0 (1.9)	.96	.87–1.07	.471			
Sexual symptoms	7.3 (3.0)	6.9 (3.2)	.96	.90–1.02	.160			
Lack of energy, *n* (%)								
No (reference)	147 (44)	188 (56)	1.0					
Yes	26 (45)	32 (55)	.96	.55–1.69	.893			
Demographic variables								
Age, *n* (%)								
< 70 years (reference)	114 (40)	172 (60)	1.0			1.0		
≥ 70 years	59 (55)	48 (45)	.54	.34–.84	*.007**	.51	.33–.81	.004*
Basic education, *n* (%)								
≤ 12 years (reference)	84 (48)	93 (53)	1.0					
> 12 years	87 (41)	126 (59)	1.31	.88–1.96	.190			
Work force participation, *n* (%)								
No (reference)	94 (42)	130 (58)	1.0					
Yes	71 (46)	83 (54)	.85	.56–1.28	.425			
Medical variables								
Time since diagnosis, *n* (%)								
< 5 years (reference)	110 (41)	158 (59)	1.0					
≥ 5 years	63 (50)	62 (50)	.69	.45–1.05	*.083*			
Comorbidity affecting health, *n* (%)								
No (reference)	100 (44)	130 (57)	1.0					
Yes	67 (43)	89 (57)	1.02	.68–1.54	.918			
Health variables								
BMI, *n* (%)								
< 25 kg/m^2 (reference)	47 (37)	81 (63)	1.0			1.0		
≥ 25 kg/m^2	126 (48)	139 (53)	.64	.42–.99	*.043**	.60	.39–.94	.025*

[1] Higher score = worse symptoms. *cOR* crude odds ratio, *aOR* adjusted odds ratio, *95% CI* 95% confidence interval, *SD* standard deviation. *$p < 0.05$. *BM* body mass index (kg/m^2). Numbers may not add up to 393 because of missing values. Percentage may not add up to 100% because of rounding. [2] Numbers included in adjusted analyses: $n = 393$. Variables included in multivariable analyses were age, time from diagnosis to survey, and BMI (italic). Variables were reduced until only statistically significant variables were remaining

Contrary to our hypothesis, urinary incontinence did not influence PA in our study, which we expected to be particularly frequent among patients in the RP-group. According to Craike et al. [21], urinary incontinence is a barrier to PA the first weeks after surgery. Ottenbacher et al. [23] reported that recently diagnosed PCa patients who stated "problems with urination limit my activities," were less physically active in a PA intervention compared to those without urinary problems. Further, Geraerts et al. [22] found that the PA level among patients treated with RP was significantly lower 6 weeks after surgery, but returned to baseline levels shortly from that time. Most of the patients in our study only experienced urinary incontinence symptoms at a minor degree. Therefore, a reasonable explanation for our finding might be that long-term low-grade urinary incontinence is not a relevant PA barrier for most patients treated with prostatectomy.

In contrast to previous studies reporting lack of energy and fatigue as a PA barrier among PCa survivors [20, 31, 33], multivariable analyses among all patients showed no statistically significant association between PA level and lack of energy in the present study. However, patients in the ADT-group were significantly less likely of exercising ≥ 2 times per week if time since diagnosis was ≥ 5 years. In addition, lack of energy was borderline statistically significant negatively associated with exercising ≥ 2 times per week. This indicates that several factors associated with long-term ADT and aging might affect PA level, such as loss of muscle mass [34] and fatigue, which can worsen with time after initiation of ADT [35].

Table 5 Patients treated with radiotherapy and (neo)-adjuvant androgen deprivation therapy ($n = 204$): factors associated with exercising ≥ 2 times per week versus less

	Exercise frequency		Unadjusted analyses			Adjusted analyses[2]		
	< 2 times/ week	≥ 2 times/ week	cOR	95% CI	*P*	aOR	95% CI	*P*
EPIC-CP domain score, mean (SD)(score out of 12[1])								
Urinary incontinence	1.4 (2.0)	1.4 (1.9)	.99	.86–1.14	.853			
Urinary irritation/obstruction	3.0 (2.3)	3.1 (2.6)	1.02	.91–1.14	.762			
Bowel symptoms	3.6 (3.2)	2.0 (2.8)	.84	.76–.92	*< .001**	.84	.76–.92	< .001*
Sexual symptoms	7.7 (2.9)	7.1 (2.8)	.92	.83–1.02	*.101*			
Lack of energy, *n* (%)								
No (reference)	55 (38)	90 (62)	1.0					
Yes	31 (53)	28 (48)	.55	.30–1.02	*.057*			
Demographic variables								
Age, *n* (%)								
< 70 years (reference)	26 (45)	32 (55)	1.0					
≥ 70 years	60 (41)	86 (59)	1.17	.63–2.15	.626			
Basic education, *n* (%)								
≤ 12 years (reference)	51 (45)	62 (55)	1.0					
> 12 years	32 (36)	56 (64)	1.44	.81–2.55	.211			
Work force participation, *n* (%)								
No (reference)	69 (41)	100 (59)	1.0					
Yes	13 (52)	12 (48)	.64	.27–1.48	.294			
Medical variables								
Time since diagnosis, *n* (%)								
< 5 years (reference)	44 (45)	54 (55)	1.0					
≥ 5 years	42 (40)	64 (60)	1.24	.71–2.17	.446			
Comorbidity affecting health, *n* (%)								
No (reference)	46 (38)	76 (62)	1.0			1.0		
Yes	40 (50)	40 (40)	.61	.34–1.07	*.085*	.68	.37–1.21	.180
Health variables								
BMI, *n* (%)								
< 25 kg/m^2 (reference)	21 (37)	36 (63)	1.0					
≥ 25 kg/m^2	65 (44)	82 (56)	.74	.39–1.38	.339			

[1] Higher score = worse symptoms. *cOR* crude odds ratio, *aOR* adjusted odds ratio, *95% CI* 95% confidence interval, *SD* standard deviation. *$p < 0.05$. *BMI* body mass index (kg/m^2). Numbers may not add up to 204 because of missing values. Percentage may not add up to 100% because of rounding. [2] Numbers included in adjusted analyses: $n = 202$. In adjusted analyses, bowel symptoms, sexual symptoms, lack of energy, and comorbidity affecting health were included (italic). Variables were reduced until only statistically significant variables were remaining

Demographic and health variables

In the total sample and among patients treated with RP, we found that patients aged 70 years and older had nearly 50% lower odds of exercising ≥ 2 times per week compared to those younger than 70 years. It is well established that participation in PA declines with increasing age [36]. The inverse association between PA and advancing age is in line with previous studies both in healthy older adults and cancer patients [21, 30, 37].

Interestingly, workforce participation decreased the odds of exercising ≥ 2 times per week by almost 50%. This might be attributed to lack of time and energy for PA due to prioritizing being active in the workforce. Lack of time has been reported as a common PA barrier, both among PCa patients [21, 38], and among community dwelling older adults [39].

Among all patients and also in the subgroup of patients treated with RP, BMI ≥ 25 kg/m^2 was associated with lower odds of exercising ≥ 2 times per week. This is in line with previous findings among cancer patients [40, 41] and in the general population [37].

Limitations

Causal inferences between treatment-induced AEs and level of PA cannot be determined, due to the cross-sectional design of the present study.

Table 6 Patients treated with androgen deprivation therapy (ADT) ($n = 99$): factors associated with exercising ≥ 2 times per week versus less

	Exercise frequency		Unadjusted analyses			Adjusted analyses[2]		
	< 2 times/ week	≥ 2 times/ week	cOR	95% CI	*P*	aOR	95% CI	*P*
EPIC-CP domain score, mean (SD)(score out of 12[1])								
Urinary incontinence	1.7 (1.9)	1.2 (2.0)	.88	.71–1.08	.221			
Urinary irritation/obstruction	2.8 (2.5)	3.0 (2.4)	1.02	.87–1.21	.776			
Bowel symptoms	1.8 (2.6)	1.5 (2.3)	.95	.81–1.12	.560			
Sexual symptoms	9.3 (2.1)	8.9 (2.7)	.93	.79–1.10	.382			
Lack of energy, *n* (%)								
No (reference)	25 (39)	40 (62)	1.0			1.0		
Yes	19 (56)	15 (44)	.49	.21–1.15	*.100*	.42	.17–1.01	.053
Demographic variables								
Age, *n* (%)								
< 70 years (reference)	8 (35)	15 (65)	1.0					
≥ 70 years	36 (47)	40 (53)	.59	.23–1.56	.290			
Basic education, *n* (%)								
≤ 12 years (reference)	19 (40)	29 (60)	1.0					
> 12 years	25 (49)	26 (51)	.68	.31–1.51	.346			
Work force participation, *n* (%)								
No (reference)	35 (41)	50 (59)	1.0					
Yes	7 (64)	4 (36)	.40	.11–1.47	.168			
Medical variables								
Time since diagnosis, *n* (%)								
< 5 years (reference)	16 (35)	30 (65)	1.0					
≥ 5 years	28 (53)	25 (47)	.48	.21–1.07	*.073*	.41	.18–.96	.040*
Comorbidity affecting health, *n* (%)								
No (reference)	24 (46)	28 (54)	1.0					
Yes	19 (43)	25 (57)	1.13	.50–2.53	.770			
Health variables								
BMI, *n* (%)								
< 25 kg/m^2 (reference)	13 (37)	22 (63)	1.0					
≥ 25 kg/m^2	31 (48)	33 (52)	.63	.27–1.46	.281			

[1] Higher score = worse symptoms. *cOR* crude odds ratio, *95% CI* 95% confidence interval, *SD* standard deviation. *$p < 0.05$. *BMI* body mass index (kg/m^2). Numbers may not add up to 99 because of missing values. [2] Numbers included in adjusted analyses: $n = 99$. In adjusted analyses, lack of energy and time from diagnosis to survey were included (italic). Variables were reduced until only statistically significant variables were remaining

We acknowledge the shortcomings of our PA measure, not taking into account more details in terms of the reported exercise. In general, self-reported measures of PA are less accurate than objective measures of PA, such as accelerometers. By using self-report, there is a chance that the patients in the present study might have overestimated their level of PA [42]. In addition, as the patients in the present study might experience fatigue and reduced physical capacity due to their PCa trajectory resulting in more rapid breathlessness and sweating in daily activities not usually classified as "exercise," misclassification of a high PA level may have occurred. This may particularly apply for those undergoing or who recently completed ADT as these men can suffer from hot flashes causing spontaneous sweating due to hormonal changes [9]. Moreover, significantly worse physical performance among men undergoing ADT has been demonstrated compared to age-matched men from the general population [7]. However, there is also evidence that measuring PA with a single question can provide valid information about exercise participation [43]. For the present study, we believe our PA measure provide sufficient insight in PA for the aims of comparing engagement in PA across treatment groups, and explore the associations between PA and treatment-induced AEs.

As the response rate in the present study was 50% and only members of PROFO were invited to participate, our study might be limited by selection bias favoring PCa patients with relatively good general health and high education level. High education level has shown to influence level of PA positively [44]; thus, there is also chance that the patients in the present study represent PCa patients that are more likely to be physically active than PCa patients in general. Finally, as patients in the RAD+ADT-group were treated up to 14 years ago, these

patients might have experienced bowel problems at a larger scale due to outdated radiotherapy technologies compared to patients treated more recently.

Conclusion

In conclusion, the present study showed that more than 40% of PCa patients had a low level of PA after local curative treatment or during lifelong ADT. Bowel symptoms were inversely associated with exercising ≥ 2 times per week, and may represent a barrier to physical activity among irradiated PCa patients. In addition, PCa patients were less likely to exercise ≥ 2 times per week if aged 70 years or older, participating in the workforce or overweight. Health care professionals should educate patients undergoing treatment about possible treatment-induced AEs affecting PA level, enabling them to counteract the development of physical inactivity. PCa patients at risk of physical inactivity should be identified and offered support to engage in PA, e.g. by being motivated to allocate time for PA and guided in preserving or achieving a healthy body weight.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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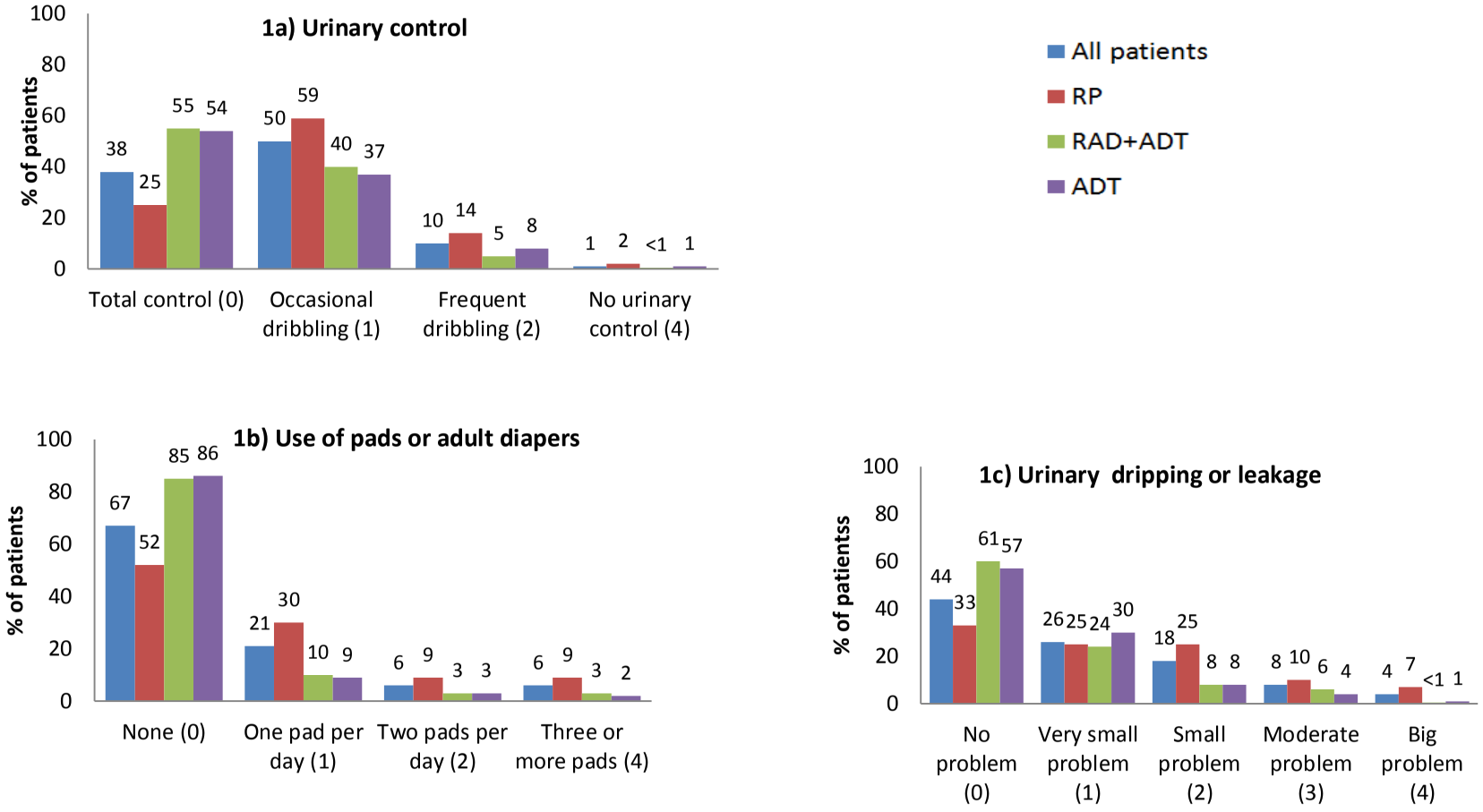
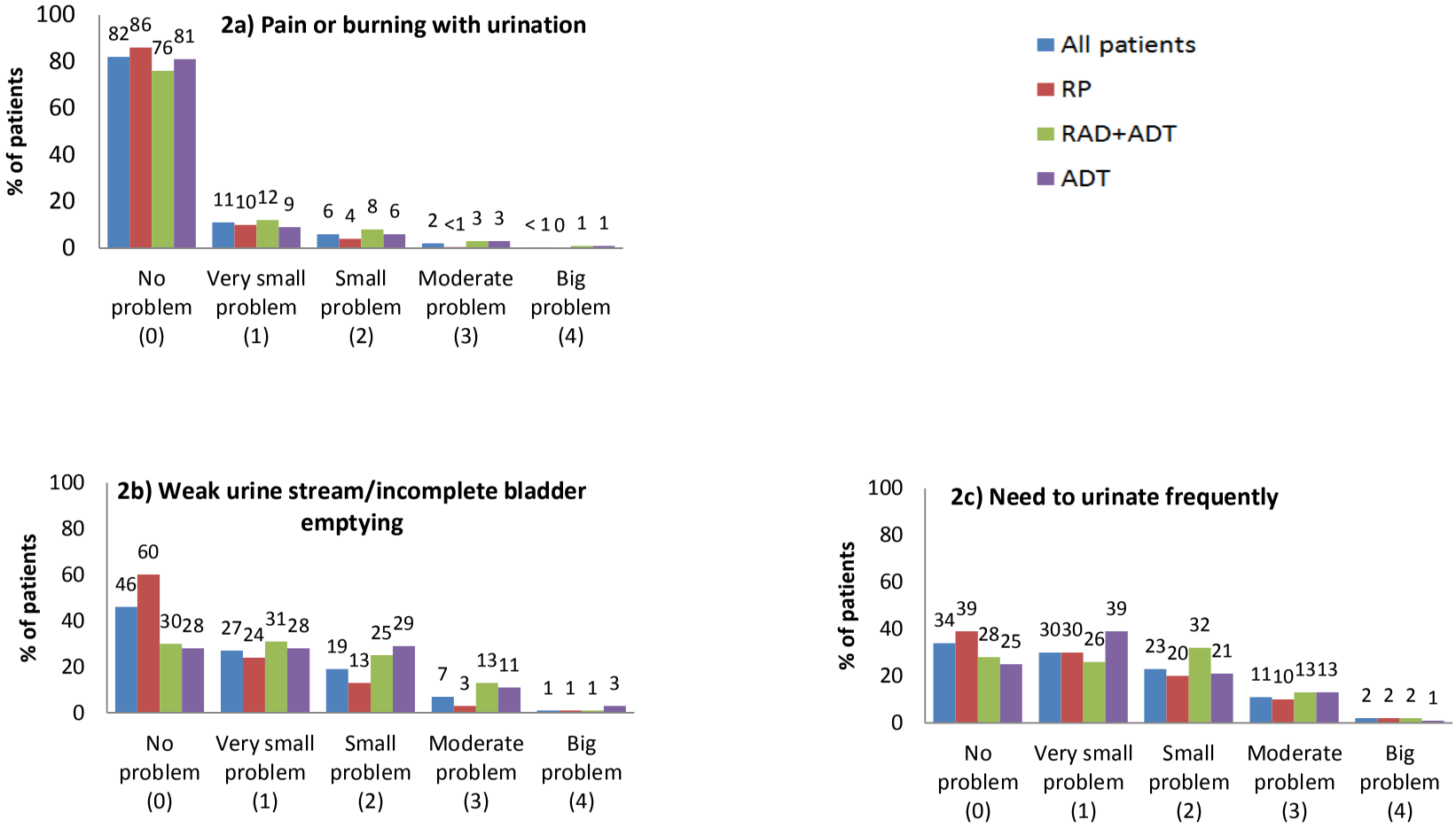
Fig. 1a-1c: Responses to the items in EPIC-CP urinary incontinence score (%)



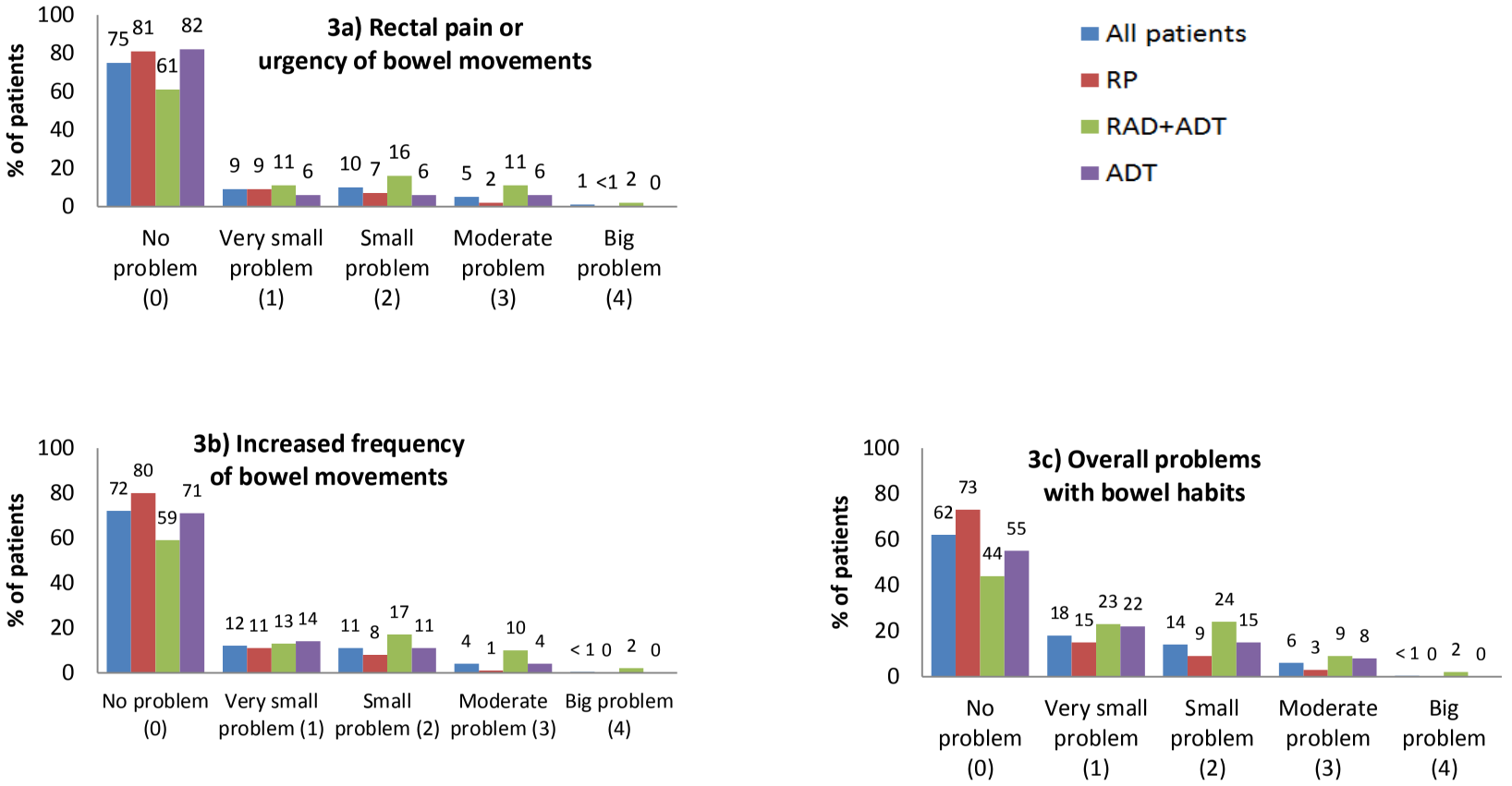
RP=radical prostatectomy. RAD+ADT=radiotherapy+(neo)-adjuvant androgen deprivation therapy. ADT=androgen deprivation therapy. Item score range from 0 to 4.
Percentages may not add up to 100 because of rounding.

Fig. 2a-2c: Responses to the items in EPIC-CP urinary irritation/obstruction score (%)



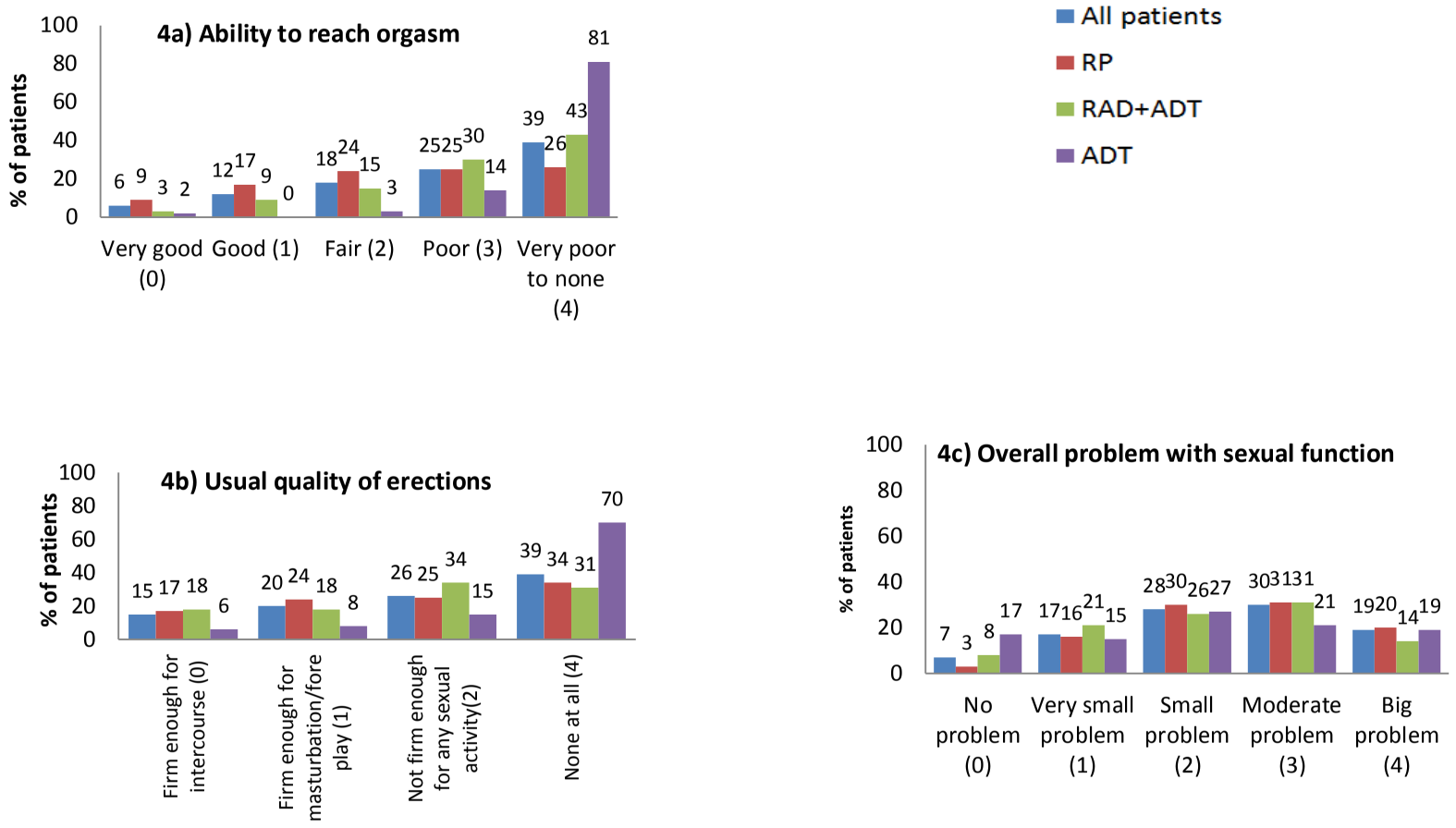
RP=radical prostatectomy. RAD+ADT=radiotherapy+(neo)-adjuvant androgen deprivation therapy. ADT=androgen deprivation therapy. Item score range from 0 to 4.
Percentages may not add up to 100 because of rounding.

Fig. 3a-3c: Responses to the items in EPIC-CP bowel symptom score (%)



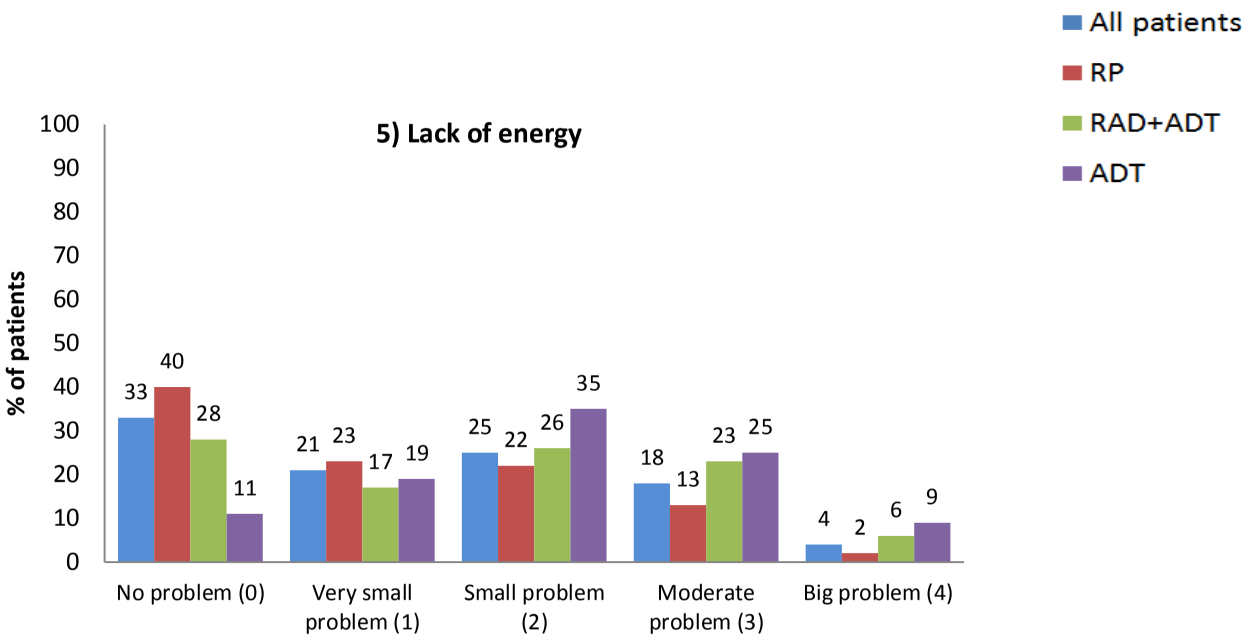
RP=radical prostatectomy. RAD+ADT=radiotherapy+(neo)-adjuvant androgen deprivation therapy. ADT=androgen deprivation therapy. Item score range from 0 to 4.
Percentages may not add up to 100 because of rounding.

Fig. 4a-4c: Responses to the items in EPIC-CP sexual symptoms score (%)



RP=radical prostatectomy. RAD+ADT=radiotherapy+(neo)-adjuvant androgen deprivation therapy. ADT=androgen deprivation therapy. Item score range from 0 to 4.
Percentages may not add up to 100 because of rounding.

Fig. 5: Lack of energy (%). Extracted from the EPIC-CP vitality/hormonal symptoms score



RP=radical prostatectomy. RAD+ADT=radiotherapy+(neo)-adjuvant androgen deprivation therapy. ADT=androgen deprivation therapy. Item score range from 0 to 4.
Percentages may not add up to 100 because of rounding.

Paper II

Lifestyle among long-term survivors of cancers in young adulthood

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Running head: lifestyle in young adult cancer survivors

Keywords: late effects, unhealthy lifestyle, physical activity, overweight, smoking

Abstract:

Purpose: To investigate lifestyle of a population-based sample of long-term (> 5 years since diagnosis) young adult cancer survivors (YACSs) and explore factors associated with not meeting the public guidelines regarding physical activity (PA), body mass index (BMI) and smoking.

Methods: YACSs (n=3558) with breast cancer (BC), colorectal cancer (CRC), non-Hodgkin lymphoma (NHL), acute lymphoblastic leukaemia (ALL) or localized malignant melanoma (MM) diagnosed at the age of 19 to 39 years and treated between 1985 and 2009 completed a mailed questionnaire. Survivors of localized MM treated with limited skin surgery served as a comparison group.

Results: The response rate was 42 %, and 1056 YACSs were included in the present study (74 % females, mean age at survey 49 years, mean 15 years since diagnosis). There were no differences in adherence to lifestyle guidelines between YACSs treated for BC, CRC, NHL or ALL (n=810) and the comparison group (n=246). Forty-three per cent did not meet PA guidelines, 49 % reported BMI ≥ 25 and 20 % smoked. Male gender, education ≤ 13 years, comorbidity, lymphedema, pain, chronic fatigue and depressive symptoms were associated with not meeting single and/or an increasing number of lifestyle guidelines.

Conclusion: A large proportion of long-term YACSs did not meet the public lifestyle guidelines for PA, BMI and/or smoking. Non-adherence to guidelines was associated with several late effects and comorbidity. Interventions aimed at improving the lifestyle of YACSs should focus specifically on these conditions.

Introduction

Each year, approximately 130 000 individuals aged 20 to 39 years are diagnosed with cancer in Europe (1). Improvements in detection and treatment have led to a relative 5-year survival rate of more than 80 %, thus creating a rapidly growing population of long-term (> 5 years since diagnosis) young adult cancer survivors (YACSs) (2, 3). Their life-saving treatment, however, place long-term YACSs at risk of late effects, such as fatigue, cardiovascular and pulmonary diseases and second cancer (3-6).

Growing evidence suggests that a healthy lifestyle may reduce the risk of late effects and improve health in cancer survivors in general. Physical activity (PA), a healthy body mass index (BMI) and non-smoking are associated with a lower risk of cancer recurrence, morbidity and mortality (7-10). Similar to the population in general, cancer survivors are therefore recommended to be physically active for at least 150 minutes with moderate intensity or 75 minutes high intensity per week, maintain a healthy BMI, avoid smoking and consume at least five daily servings of vegetables and fruits (5-a-day) (11, 12).

Despite the well-known health benefits of meeting these guidelines, a large proportion of cancer survivors are physically inactive, overweight and do not meet 5-a-day, and few cancer survivors meet several lifestyle guidelines (7-40 %) (13, 14). To date, however, this research is predominantly based on populations diagnosed with cancer after the age of 50, who are less than 5 years since diagnosis (13, 14).

The few studies which have investigated lifestyle in YACSs have mostly included populations less than 5 years since diagnosis (15-20). Two recent studies from the United States (U.S.) investigated lifestyle exclusively among long-term adolescent and YACSs, and found that 56-65 % were not meeting the PA guidelines, and one of three was smoking (21, 22). Generalizability of these findings to European long-term YACS is, however, problematic due

to differences in culture and health care systems. Demographic and medical characteristics have been linked to unhealthy lifestyle behaviors among survivors diagnosed with cancer at a young age (23), but associations between lifestyle and specific cancer-related information, such as treatments and late effects, are scarcely explored in long-term YACSs.

On this basis the overall aim of the present study was to investigate lifestyle among long-term YACSs, extracting data from a large population based cross-sectional survey named The Norwegian childhood, adolescent and young adult cancer survivor study (The NOR-CAYACS study) (24). Specific aims were to:

1) Investigate and compare the adherence to lifestyle guidelines between Norwegian long-term YACSs treated for breast cancer (BC), colorectal cancer (CRC), non-Hodgkin lymphoma (NHL) or acute lymphoblastic leukemia (ALL), and survivors of localized malignant melanoma (MM) treated with limited skin surgery (comparison group)
2) Explore demographic and cancer-related factors associated with not meeting the guidelines of PA, BMI and smoking separately, and factors associated with not meeting an increasing number of these guidelines

Methods

Design and study population

Details on design and study population have been described previously (24). In brief, YACSs diagnosed with BC, CRC, NHL and ALL, as well as a randomly selected sample of MM, at the age of 19 to 39 years between 1985 and 2009 were identified by the Cancer Registry of Norway (CRN), and invited to participate (n=3558). Selection of cancer types were based on the relative frequent occurrence during young adulthood and good prognosis. YACSs of other relevant cancer types such as testicular cancer, Hodgkin lymphoma and cervix cancer were

not invited because of participation in ongoing studies at our research unit at the time of survey. Exclusion criteria for the present study are described in Figure 1.

Comparison group: due to the lack of data from the general population, we compared the lifestyle of YACSs treated for BC, CRC, NHL or ALL with participants treated with limited surgery for localized MM (comparison group).

Variables and measurements

Lifestyle

Physical inactivity was defined as not meeting the guidelines of ≥150 minutes of moderate intensity, 75 minutes high intensity, or an equivalent combination of moderate and high intensity PA per week (11). A modified version of the Godin Leisure Time Exercise Questionnaire was used to sum the total minutes spent on moderate or high intensity PA per week (25).

BMI (kg/m^2) was calculated from self-reported height and weight and categorized as underweight (< 18.5), healthy weight (18.5-24.9), overweight (25-29.9) and obese (≥ 30) (26).

Current smoking ("daily" or "now and then") and *5-a-day* were assessed by questions modified from the Nord-Trøndelag Health (HUNT) Study (27).

A more unhealthy lifestyle: the number of lifestyle guidelines not met in terms of PA, BMI and smoking were summed for each participant (score 0 to 3).

Because of the large proportion not adhering to 5-a-day (92 %), we chose not to explore associated factors nor include 5-a-day in the score of a more unhealthy lifestyle.

Explanatory variables

Participants self-reported on demographic, cancer treatment and health variables, while information on cancer type and stage was obtained from the CRN.

Living with a partner included marriage and cohabitation. *Education level* was dichotomized into ≤ 13 years (up to high school) versus >13 years (college/university).

Treatments were categorized into: 1) limited surgery for localized MM (surgical removal of the skin lesion; comparison group), 2) surgery and/or radiotherapy, 3) systemic treatment only and 4) systemic treatment combined with radiotherapy and/or surgery.

Number of comorbid conditions was assessed using a modified version of the Charlson comorbidity index (28). For each participant, the number of the following comorbid conditions ever experienced was summed and categorized as "no comorbidity", "1-2 comorbid conditions" and "> 2 comorbid conditions": cardiovascular- and pulmonary diseases, diabetes, kidney disease, gastro-intestinal disease, rheumatic disease, arthrosis, muscle/joint pain, epilepsy and thyroid diseases.

Presence of numbness in hands/feet and *lymphedema* were categorized as yes/no. *Pain* was assessed by the pain item in the 12-Item Short Form Survey (SF-12) (29). Responses were dichotomized into no ("not at all"/"a little bit"/ "moderately") versus yes ("quite a bit"/"extremely"). Using questions modified from the HUNT-study (27), *trouble sleeping* was defined as experiencing one of more of the following symptoms several times per week: difficulties falling asleep at night, waking up repeatedly during the night and/or waking up too early without being able to go back to sleep.

Depressive symptoms were assessed using the nine-item Patient Health Questionnaire-9 (PHQ-9) (30), with response categories ranging from 0 to 3. Increasing sum score (0 to 27)

indicates higher level of depressive symptoms. *Anxiety symptoms* were measured by the seven-item anxiety subscale of The Hospital Anxiety and Depression Scale (HADS-A) (31), with response categories from 0 to 3. An increasing sum score (0 to 21) indicates higher level of anxiety symptoms. Cronbach's alpha's were 0.87 for PHQ-9 and 0.83 for HADS-A in the present study population.

Chronic fatigue was assessed by the Fatigue Questionnaire (FQ) (32). Each of the 11 items is scored from 0 to 3, with increasing total score (0 to 33) implying higher levels of fatigue. To identify chronic fatigue, raw scores of each item were dichotomized (0=0, 1=0, 2=1, 3= 1). Chronic fatigue was defined by a dichotomized sum score ≥ 4 and ≥ 6 months duration of fatigue (32). Cronbach's alpha for the present study population was 0.91 (physical subscale), 0.84 (mental subscale) and 0.92 (the whole scale).

Statistical analyses

Continuous variables were described using mean and standard deviation (SD), and categorical variables were presented as numbers and percentages. Comparisons across diagnostic groups were performed with chi-square tests or one-way analysis of variance. Uni- and multivariable logistic regression analyses identified factors associated with not meeting single guidelines of PA, overweight and smoking. Ordinal regression analyses were applied to identify factors associated with not meeting an increasing number of lifestyle guidelines (0 to 3). Variables statistically significant associated with the dependent variable in unadjusted analyses ($p < 0.05$) were included as independent variables in the multivariable ordinal logistic regression analyses.

Because of overlapping content in the items in FQ and PHQ-9, only chronic fatigue was included in multivariable analyses if both variables were statistically significant associated with the outcome variable in unadjusted analyses. For the ordinal regressions analyses, the

proportional odds assumption was confirmed by the test of parallel lines. Results from the multivariable analyses are presented as adjusted odds ratios (aOR) with 95 % confidence intervals (95 % CI). P-values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS statistics version 25.0.

Ethics

The study was approved by the South East Regional Committee for Medical and Health Research Ethics (no: 2015/232), the Norwegian Data Protection Authority (no: 15/00395-2/CGN), the Data Protection Officer at Oslo University Hospital and the CRN. All participants signed an informed consent form.

Results

Characteristics of participants

A total of 1488 (42 %) YACSs responded. After exclusion of 432 responders (Figure 1), 1056 evaluable participants were included. Characteristics of non-responders are described in Supplementary file.

Of included participants, 74 % were female, 40 % were diagnosed with BC, 11 % with CRC, 16 % with NHL, 10 % with ALL and 23 % with MM (Table 1). Mean age at survey was 49 years (SD 8), and time since diagnosis was 15 years (SD 7). Forty-seven per cent of the participants had received systemic treatment in combination with radiotherapy and/or surgery and 72 % reported at least one comorbid condition (Table 1).

Adherence to lifestyle guidelines

Among the YACSs treated for BC, CRC, NHL or ALL (n=810), 43 % were physically inactive, 49 % were overweight, 20 % were current smokers, and 92 % did not eat 5-a-day (Table 2). There were no statistically significant difference in lifestyle between these YACSs

and the comparison group (Table 2). Twenty-six per cent of the YACSs treated for BC, CRC, NHL or ALL met all three guidelines of PA, BMI and smoking guidelines versus 24 % of the comparison group (Figure 2). Details about the combinations lifestyle guidelines not met are shown in Figure 3.

Factors associated with not meeting lifestyle guidelines

Factors associated with physical inactivity, overweight or smoking in unadjusted analyses are shown in Table 3.

In multivariable analyses, only chronic fatigue was associated with physical inactivity (aOR 1.50, 95 % CI 1.11-2.03) (Table 3). Male gender (aOR 2.50, 95 % CI 1.80-3.45), >2 comorbid conditions (aOR 1.99, 95 % CI 1.31-3.04), lymphedema (aOR 1.77, 95 % CI 1.25-2.50) and increasing levels of depressive symptoms (aOR 1.03, 95 % CI 1.01-1.06) were associated with being overweight. Systemic treatment combined with surgery and/or radiotherapy was negatively associated with being overweight (aOR.62, 95 % CI 0.44-0.89). Not living with a partner (aOR 1.50, 95 % CI 1.02-2.21), education ≤ 13 years (aOR 1.63, 95 % CI 1.18-2.27) and lymphedema (aOR 1.67, 95 % CI 1.15-2.41) were associated with smoking (Table 3).

Factors associated with a more unhealthy lifestyle in unadjusted analyses are shown in Table 4. Male gender (aOR 1.80, 95 % CI 1.37-2.37), education ≤ 13 years (aOR 1.44, 95 % CI 1.13-1.84), >2 comorbid conditions (aOR 1.57, 95 % CI 1.08-2.29), lymphedema (aOR 1.37, 95 % CI=1.02-1.84) and pain (aOR 1.54, 95 % CI 1.0-2.35) were associated with a more unhealthy lifestyle in multivariable ordinal regression analyses.

Discussion

This large population-based study on lifestyle among long-term YACSs indicate that the majority is physically inactive, overweight and/or not meeting 5-a-day, and one of five is smoking. YACSs with comorbid conditions, lymphedema, pain, increasing levels of

depressive symptoms or chronic fatigue were less likely to meet single or an increasing number of the lifestyle guidelines, as well as males, individuals living without a partner or with education ≤ 13 years.

Importantly, the diversity of measures, population characteristics and cultural differences across studies limit direct comparison of our findings with previous studies on lifestyle among cancer survivors. Taking this into account, long-term YACSs in our study seemed to be equally or more adherent to lifestyle guidelines than cancer survivors in general (13, 14, 18, 21, 23). Compared to Warner et al., who found that 56-65 % of U.S. long-term adolescent and YACSs were physically inactive, we observed a lower proportion not meeting PA guidelines (43 %) (21). In agreement with our findings, using the same PA questionnaire, Bélanger et al. (18) found that 48 % were physically inactive in a sample of Canadian YACSs of various cancer types diagnosed at age 20 to 44 years. However, most of these participants were < 5 years since diagnosis. The proportion not meeting PA guidelines in our study is also lower than previously found among survivors diagnosed with cancer at an older age (50-75 %) (13, 14, 33). The prevalence of overweight in our study (49 %) is also in agreement with Bélanger et al.'s study (18) (53 %), and findings among U.S BC and CRC cancer survivors diagnosed before the age of 50 and mean 9 years since diagnosis (55 %) (34). Higher proportions of overweight have been found among survivors diagnosed with cancer further into adulthood (60-75 %) (13, 33). For smoking, the proportion of 20 % in our study was lower than reported among female adolescent and YACSs in U.S studies (≈30 %) (21, 22), but higher than found among older adult cancer survivors and the YACSs in the study by Bélanger et al. (13 %) (13, 18).

Assuming that long-term YACSs are aware of their risk for late effects following treatment, one could expect that they would be more motivated for a healthy lifestyle than the general population. In our study, lifestyle did not differ between the comparison group, which we

expected to be comparable to the population in general, and long-term YACSs who had received more intensive cancer treatment. Our results are also similar to self-reported prevalence of overweight (48 %) and smoking (women 17 %, men 22 %) in the Norwegian general population, while the proportion of physically inactive in the general population (33 %) is somewhat lower than among the YACSs (43 %) (35, 36). In sum, our findings suggest that long-term YACSs are not more likely of a healthy lifestyle than the general population, despite their increased risk of a poorer health. On the other hand, two Norwegian studies on long-term Hodgkin lymphoma and testicular cancer survivors diagnosed predominantly during young adulthood, found that these cancer survivors were significantly more physically active than the general population (37, 38).

Lifestyle interventions in cancer survivors must be targeted towards the unique needs and challenges existing across the broad spectrum of populations of cancer survivors (39). Not meeting PA guidelines was associated with chronic fatigue, which is in line with previous research on fatigue and PA in survivors of lymphoma (40, 41), CRC (42) and BC (43). Fatigue is also one of the most commonly reported barriers for being physically active among cancer survivors in general (44). PA is, however, also recommended to improve fatigue among cancer survivors, as physical inactivity and subsequent loss of muscle mass and physical function may worsen fatigue (45).

In agreement with previous studies among cancer survivors in general, overweight was associated with male gender (33, 46), comorbid conditions (41) and depressive symptoms (23, 46). Our finding that long-term YACSs who had received multimodal therapy were less likely to be overweight than MM survivors treated with limited surgery is in line with a recent study by our group reporting that three or more treatment regimens were associated with a decreased risk of being overweight in long-term lymphoma survivors treated with high dose chemotherapy with autologous stem cell support (41). However, research in BC survivors has

reported large variations in weight change (gain, maintenance and loss) during and after adjuvant systemic treatments (47, 48).

As far as we know, our study is the first to investigate the adherence to a combination of several lifestyle guidelines in long-term YACSs. The finding that only one of four long-term YACSs were physically active combined with a healthy BMI and non-smoking is comparable with the findings of Spector et al., who reported that 20 % of long-term NHL survivors met these three guidelines (49). Also congruent with our findings, a recent systematic review on health behavior among adult cancer survivors estimated that 23 % met a combination of several lifestyle recommendations (13). Considering their long life expectancy with risk of late effects and future health challenges associated with aging, adhering to a combination of several lifestyle guidelines might be particularly important for YACSs. Interventions aimed at improving lifestyle among YACSs should therefore include a comprehensive focus on lifestyle; i.e. increasing PA in combination with a healthy nutrition and weight, and when needed, smoking cessation.

Our study revealed several associations between lifestyle, comorbid conditions and late effects. In Norway, formal oncological follow-up care of cancer survivors is usually discontinued 5-10 years after treatment. Health problems will then be managed primarily by a general practitioner, which could be problematic as previous research has demonstrated limited knowledge about late effects among both cancer survivors (50, 51) and general practitioners (52, 53). A significant proportion of long-term YACSs might therefore lack knowledge about their risk of late effects and the benefits of having a healthy lifestyle. Thus, our findings indicate a need to inform YACSs and general practitioners about the benefits of a healthy lifestyle also as a preventive measure against late effects.

The main strength of this study is the large national population-based sample of YACSs, which is an understudied population in terms of long-term cancer survivorship (54). Our study contributes with new knowledge about lifestyle and its associations to late effects, assessed with established patient-reported outcome measures. Limitations include the cross-sectional design precluding causal conclusions, and the reliance on self-reported treatment data. The response rate of 42 % and the high proportion of females and BC survivors might increase the risk of bias. However, Lie et al recently found low risk of non-response bias in the NOR-CAYACS study on a wide range of survey outcomes, including lifestyle and late effects (24). Finally, our study lacks a control group, but by using the MM survivors as a comparison group, we partly overcome this limitation.

Conclusion

There is a large potential to improve the lifestyle of long-term YACSs, and interventions should focus specifically on survivors with late effects and comorbid conditions. YACSs should be informed about the benefits of a healthy lifestyle on long-term health.

Author Disclosure Statement

No competing financial interests exist.

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Figure legends

Figure 1: Flow chart of included participants. BC=breast cancer, CRC=colorectal cancer, NHL=non-Hodgkin lymphoma, ALL=acute lymphoblastic leukaemia, MM=malignant melanoma. *BC survivors undergoing hormone therapy were retained in the sample (n=22)

Figure 2: Proportions of participants adhering to 0, 1, 2 or 3 guidelines in terms of physical activity, body mass index < 25 kg/m^2 and smoking. YACSs=young adult cancer survivors. MM=malignant melanoma. BC =breast cancer. CRC=Colorectal cancer. NHL=non-Hodgkin lymphoma. ALL=acute lymphoblastic leukemia.*Comparison group not included **Comparison group. Percentages may not add up to 100 because of rounding.

Figure 3: Proportions of survivors not adhering to 3, 2 and 1 lifestyle guidelines in terms of physical activity, body mass index (< 25 kg/m^2) and smoking. The comparison group (limited surgery for malignant melanoma) was not included in Figure 3.

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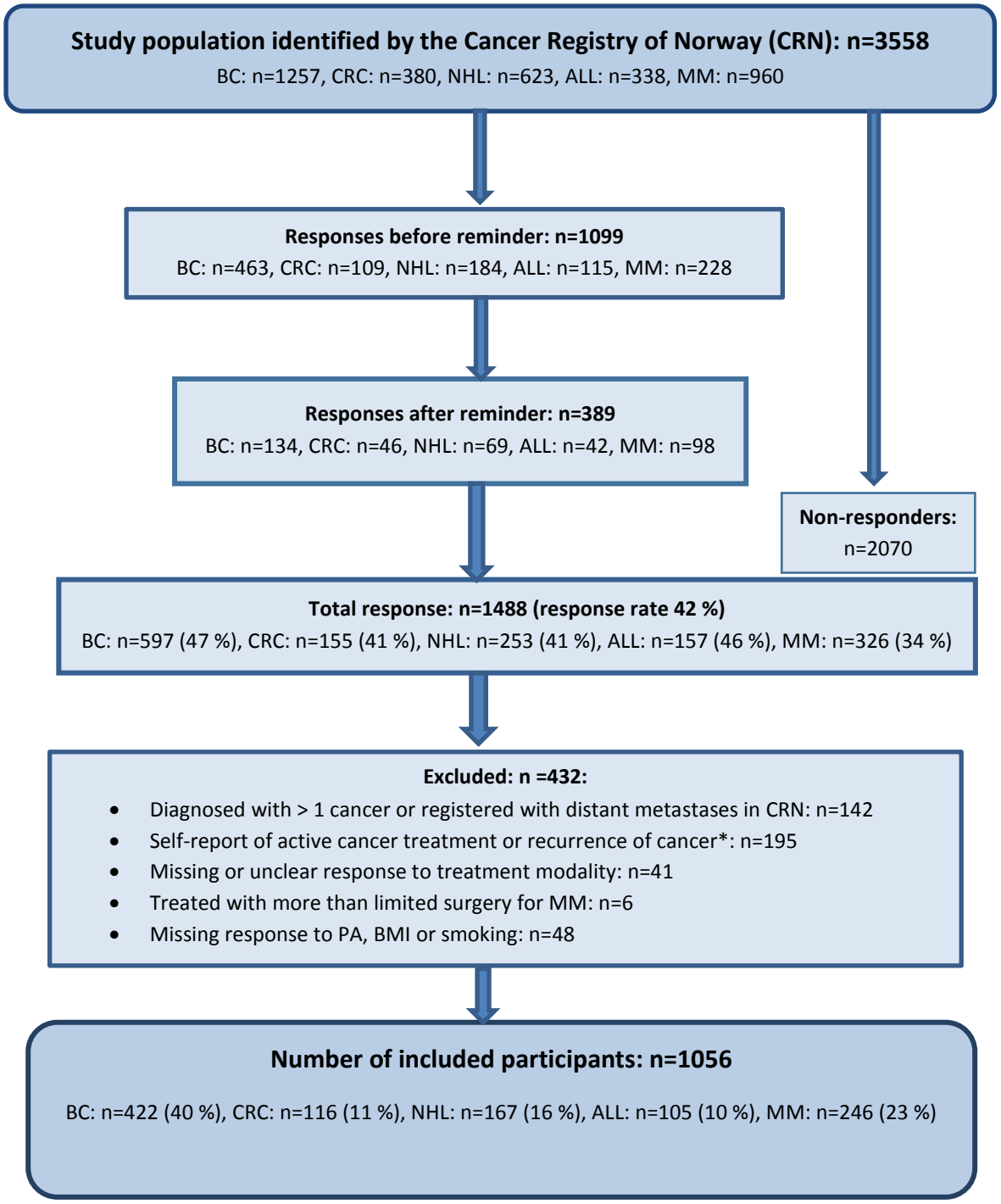
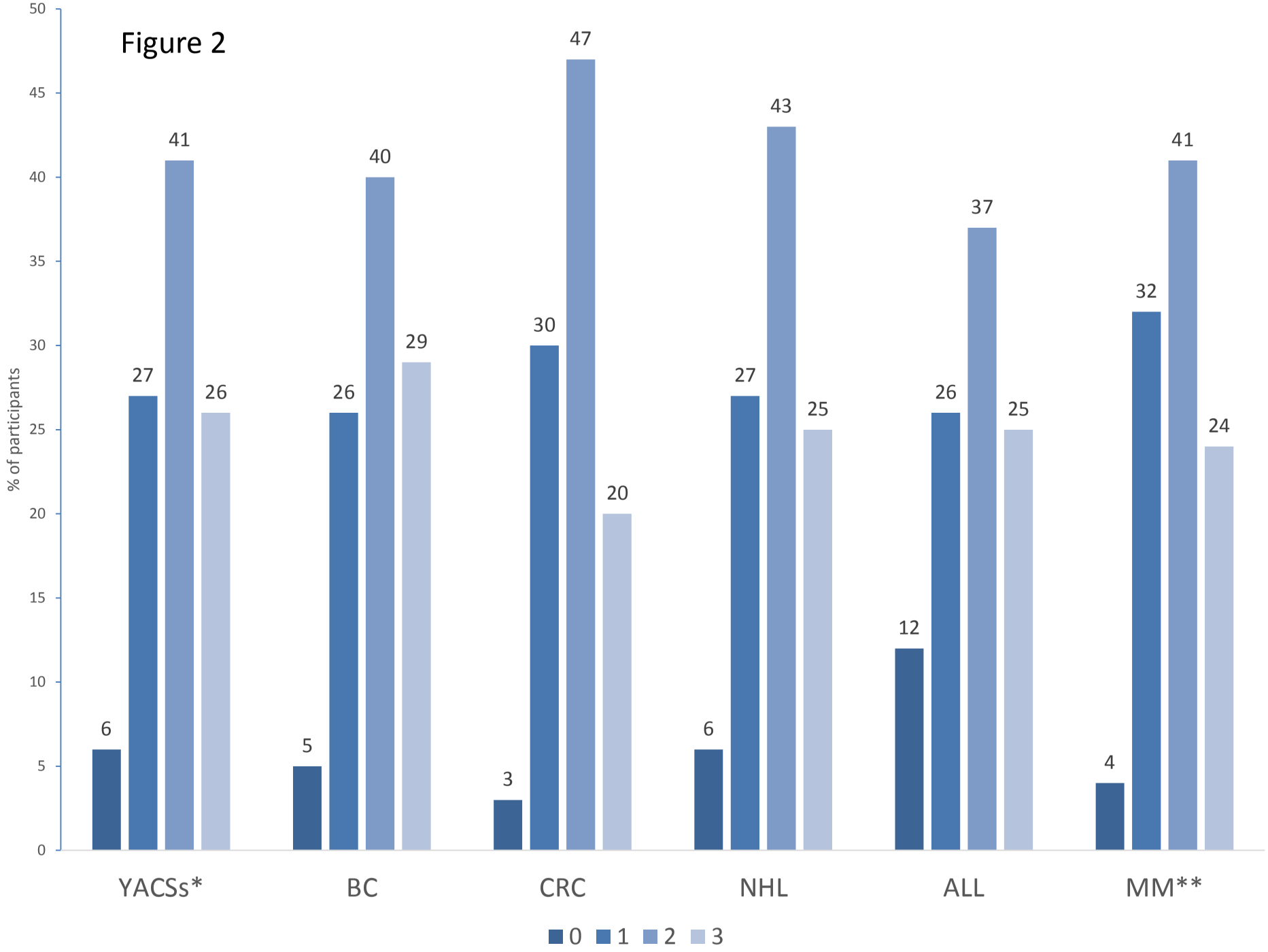

Study population identified by the Cancer Registry of Norway (CRN): n=3558
BC: n=1257, CRC: n=380, NHL: n=623, ALL: n=338, MM: n=960
Responses before reminder: n=1099
BC: n=463, CRC: n=109, NHL: n=184, ALL: n=115, MM: n=228
Responses after reminder: n=389
BC: n=134, CRC: n=46, NHL: n=69, ALL: n=42, MM: n=98
Non-responders:
n=2070
Total response: n=1488 (response rate 42 %)
BC: n=597 (47 %), CRC: n=155 (41 %), NHL: n=253 (41 %), ALL: n=157 (46 %), MM: n=326 (34 %)
Excluded: n =432:
Diagnosed with > 1 cancer or registered with distant metastases in CRN: n=142
Self-report of active cancer treatment or recurrence of cancer*: n=195
Missing or unclear response to treatment modality: n=41
Treated with more than limited surgery for MM: n=6
Missing response to PA, BMI or smoking: n=48
Number of included participants: n=1056
BC: n=422 (40 %), CRC: n=116 (11 %), NHL: n=167 (16 %), ALL: n=105 (10 %), MM: n=246 (23 %)

Figure 2


50
45
40
35
30
25
20
15
10
5
0
% of participants
6
27
41
26
5
26
40
29
3
30
47
20
6
27
43
25
12
26
37
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24
YACSs*
BC
CRC
NHL
ALL
MM**
0
1
2
3

Figure 3

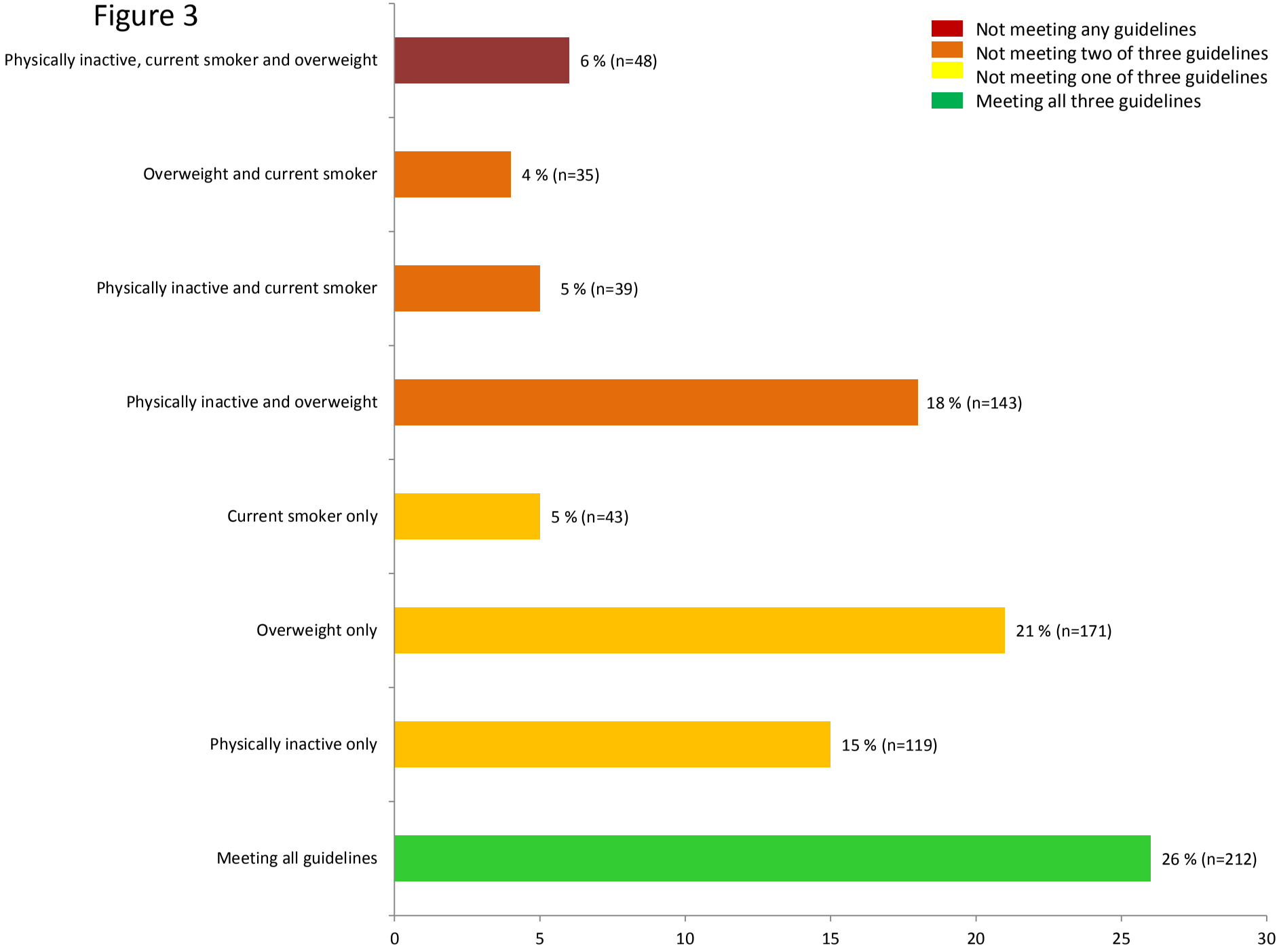
Not meeting any guidelines
Not meeting two of three guidelines
Not meeting one of three guidelines
Meeting all three guidelines
Physically inactive, current smoker and overweight
6 % (n=48)
Overweight and current smoker
4 % (n=35)
Physically inactive and current smoker
5 % (n=39)
Physically inactive and overweight
18 % (n=143)
Current smoker only
5 % (n=43)
Overweight only
21 % (n=171)
Physically inactive only
15 % (n=119)
Meeting all guidelines
26 % (n=212)
0
5
10
15
20
25
30

Table 1: Demographic, cancer-related and health characteristics of the participants by cancer type

Variables	Total n=1056	BC n=422	CRC n=116	NHL n=167	ALL n=105	MM n=246	P-value
Demographic variables							
Female gender, n (%)	783 (74)	422 (100)	59 (51)	78 (47)	49 (47)	175 (71)	<.001
Age at survey, mean (SD)	49.0 (7.7)	49.2 (6.7)	48.7 (9.2)	48.3 (8.3)	47.3 (7.9)	50.3 (8.1)	.011
Living with a partner[a], n (%)	841 (80)	337 (80)	89 (77)	132 (80)	83 (79)	200 (81)	.897
Living with children[b], n (%)	415 (39)	166 (39)	45 (39)	63 (38)	48 (46)	93 (38)	.703
Education > 13 years[c], n (%)	624 (60)	246 (59)	75 (65)	99 (60)	53 (51)	151 (62)	.279
Cancer-related variables							
Age at diagnosis, mean (SD)	32.8 (5.4)	35.2 (3.4)	33.4 (5.2)	30.5 (5.7)	29.1 (5.9)	31.6 (5.8)	<.001
Years since diagnosis, mean (SD)	15.2 (6.8)	13.0 (5.8)	14.3 (7.5)	16.8 (6.9)	17.2 (6.3)	17.7 (6.9)	<.001
Treatment modality, n (%)							
Limited surgery for MM	246 (23)	0	0	0	0	246 (100)	<.001
Surgery and/or radiotherapy	166 (16)	67 (16)	79 (68)	20 (12)	0	0	
Systemic treatment alone	144 (14)	0	0	47 (28)	97 (92)	0	
Systemic treatment combined with radiotherapy and/or surgery	500 (47)	355 (84)	37 (32)	100 (60)	8 (8)	0	
Health variables							
Number of comorbid conditions, n (%)							.010
None	292 (28)	121 (29)	28 (24)	31 (19)	26 (25)	86 (35)	
1-2	560 (53)	230 (55)	65 (56)	92 (55)	55 (52)	118 (48)	
>2	202 (19)	70 (17)	23 (20)	44 (26)	24 (23)	41 (17)	
Numbness in hands/feet, n (%)	174 (18)	66 (17)	19 (19)	58 (37)	30 (31)	1 (0.5)	<.001
Lymphedema, n (%)	213 (22)	165 (40)	7 (7)	25 (16)	10 (10)	6 (3)	<.001
Pain[d], n (%)	106 (10)	46 (11)	12 (11)	18 (11)	10 (10)	20 (8)	.827
Trouble sleeping[e], n (%)	469 (44)	212 (50)	54 (47)	77 (46)	31 (30)	95 (39)	.001
PHQ-9 score[f], mean (SD)	5.3 (4.8)	6.0 (5.3)	5.3 (4.8)	5.8 (4.6)	4.9 (5.0)	4.0 (4.1)	<.001
HADS-A score[g], mean (SD)	4.7 (3.7)	5 (4)	4 (4)	5 (4)	4 (4)	4 (3)	.017
Chronic fatigue[h], n (%)	257 (25)	123 (29)	33 (29)	43 (26)	22 (21)	36 (15)	.001

Abbreviations: BC= breast cancer, CRC= colorectal cancer, NHL= non-Hodgkin lymphoma, ALL=acute lymphoblastic leukemia, MM=malignant melanoma. SD= standard deviation.
Missing data as follows: living with a partner/with children n=2; education level n=8; comorbid conditions n =2; numbness in hands/feet n=79; lymphedema n=63; pain n=9; trouble sleeping n=1; PHQ-9 n=5; HADS-A n=4; chronic fatigue n=16.
[a] married or cohabitant, [b] aged < 18 years, [c] college/university, [d] defined as pain interfering quite a bit or extremely with normal work, [e]experiencing difficulties falling asleep at night, waking up repeatedly during the night and/or waking up too early without being able to go back to sleep several times per week, [f]The Patient Health Questionnaire-9, range 0-27. Increasing score implies higher level of depressive symptoms. [g] The Hospital Anxiety and Depression Scale, anxiety subscale. Range 0-21. Increasing score implies higher level of anxiety, [h] elevated fatigue symptoms of at least 6 months duration.
Percentages may not add up to 100 because of rounding.

Table 2: Adherence to lifestyle guidelines by cancer type

Variables	Comparison group ** n=246	YACSs* n=810	BC n=422	CRC n=116	NHL n=167	ALL n=105	P-value***
Lifestyle variables, n (%)							
Physically inactive[a],	111 (45)	349 (43)	175 (42)	50 (43)	69 (41)	55 (52)	.573
BMI							.244[c]
Underweight	2 (1)	3 (.4)	3 (.7)	0	0	0	
Healthy weight	113 (46)	410 (51)	232 (55)	54 (47)	77 (46)	47 (45)	
Overweight	89 (36)	267 (33)	127 (30)	43 (37)	56 (34)	41 (39)	
Obese	42 (17)	130 (16)	60 (14)	19 (16)	34 (20)	17 (16)	
Current smoker	43 (18)	165 (20)	92 (22)	22 (19)	32 (19)	19 (18)	.318
Not meeting 5-a-day[b] (n=1051)	221 (91)	744 (92)	381 (91)	106 (91)	156 (93)	101 (97)	.419

Abbreviations: YACSs= young adult cancer survivors. BC =breast cancer. CRC=Colorectal cancer. NHL=non-Hodgkin lymphoma. ALL=acute lymphoblastic leukemia. BMI=body mass index (kg/m^2).
*Survivors of BC, CRC, NHL or ALL
**Survivors of localized malignant melanoma treated with limited skin surgery
*** YACSs versus comparison group
[a]Defined as not meeting physical activity guidelines of at least 150 minutes moderate exercise per week or 75 minutes of high-intensity exercise or an equivalent combination
[b]Defined as consuming at least 5 daily servings of fruits and vegetables.
[c]Comparing the proportion of participants with BMI <25 versus BMI ≥25 kg/m^2
Percentages may not add up to 100 because of rounding.

Table 3 is displayed on the next page

Table 3: Characteristics of physically inactive, overweight and currently smoking participants and factors associated with these behaviors

	Physical inactivity[a]						Overweight (BMI ≥25 kg/m^2)						Current smoking (daily or now and then)					
		Unadjusted		Adjusted				Unadjusted		Adjusted				Unadjusted		Adjusted		
Variables	N (%)	cOR	95 % CI	aOR	95 % CI	P	N (%)	cOR	95 % CI	aOR	95 % CI	P	N (%)	cOR	95 % CI	aOR	95 % CI	P
Socio-demographic variables																		
Sex, n (%)																		
Female (ref.)	340 (43)	1.0					348 (44)	1.0		1.0			163 (21)	1.0				
Male	120 (44)	1.02	.77-1.35				180 (66)	2.42	**1.82-3.22*** **	2.50	**1.80-3.45**	**<.001**	45 (17)	.75	.52-1.08			
Age at survey, mean (SD)	48.2 (8.0)	.99	.98-1.01				49.4 (7.5)	1.01	.99-1.03				49.4 (7.0)	1.01	.99-1.03			
Living with a partner, n (%)																		
Yes (ref.)	359 (43)	1.0					428 (51)	1.0					149 (18)	1.0		1.0		
No	101 (47)	1.21	.90-1.64				99 (47)	.84	.62-1.13				58 (27)	1.74	**1.23-2.47****	1.50	**1.02-2.21**	**.041**
Living with children < 18 years, n (%)																		
Yes (ref)	169 (41)	1.0					192 (46)	1.0					69 (17)	1.0		1.0		
No	291 (46)	1.22	.95-1.56				335 (52)	1.28	.99-1.64				138 (22)	1.38	**1.0-1.90***	1.10	.78-1.54	.604
Education level																		
>13 years (ref.)	253 (41)	1.0		1.0			295 (47)	1.0		1.0			98 (16)	1.0		1.0		
≤13 years	203 (48)	1.35	**1.05-1.73***	1.26	.97-1.63	.082	227 (54)	1.29	**1.0-1.65***	1.14	.87-1.49	.353	108 (26)	1.83	**1.35-2.49*****	1.63	**1.18-2.27**	**.003**
Cancer-related variables																		
Years since diagnosis, mean (SD)	15.5 (7.0)	1.01	.99-1.03				15.5 (6.8)	1.01	.99-1.03				15.4 (6.8)	1.01	.98-1.03			
Treatment modality, n (%)																		
Reference[b]	111 (45)	1.0					131 (53)	1.0		1.0			43 (18)	1.0				
Surgery and/or radiotherapy	76 (46)	1.03	.69-1.53				88 (53)	.99	.67-1.47	.81	.52-1.25	.336	27 (16)	.92	.54-1.55			
Systemic treatment alone	72 (50)	1.22	.81-1.84				83 (58)	1.19	.79-1.81	.88	.56-1.40	.599	30 (21)	1.24	.74-2.09			
Systemic treatment with radiotherapy and/or surgery	201 (40)	.82	.60-1.11				226 (45)	.72	**.53-.98***	.62	**.44-.89**	**.009**	108 (22)	1.30	.88-1.93			
Health variables, n (%)																		
Number of comorbid conditions																		
None (ref.)	116 (40)	1.0		1.0			131 (45)	1.0		1.0			53 (18)	1.0				
1-2	237 (42)	1.11	.84-1.49	.93	.69-1.26	.637	267 (48)	1.12	.84-1.49	.99	.73-1.35	.948	106 (19)	1.05	.73-1.52			
>2	105 (52)	1.64	**1.14-2.36****	1.19	.80-1.76	.390	130 (64)	2.22	**1.53-3.21*****	1.99	**1.31-3.04**	**.001**	48 (24)	1.41	.91-2.18			

Numbness in hands/feet																		
No (ref.)	352 (44)	1.0					398 (50)	1.0					151 (19)	1.0				
Yes	81 (47)	1.12	.80-1.55				83 (48)	.93	.67-1.29				37 (21)	1.17	.78-1.75			
Lymphedema																		
No (ref.)	342 (44)	1.0					372 (48)	1.0		1.0			135 (17)	1.0		1.0		
Yes	94 (44)	1.01	.75-1.37				121 (57)	1.44	**1.06-1.96***	1.77	**1.25-2.50**	**.001**	57 (27)	1.75	**1.22-2.49****	1.67	**1.15-2.41**	**.007**
Pain interfering with normal work																		
No (ref.)	393 (42)	1.0		1.0			460 (49)	1.0		1.0			177 (19)	1.0				
Yes	61 (58)	1.89	**1.26-2.84****	1.39	.89-2.16	.151	63 (59)	1.53	**1.02-2.30***	1.13	.69-1.83	.633	28 (26)	1.55	.98-2.46			
Trouble sleeping																		
No (ref.)	233 (40)	1.0		1.0			288 (49)	1.0					106 (18)	1.0				
Yes	227 (48)	1.42	**1.11-1.82****	1.24	.95-1.61	.114	240 (51)	1.08	.85-1.38				102 (22)	1.26	.93-1.71			
PHQ-9 score[c], mean (SD)	6.1 (5.1)	1.07	**1.04-1.10***** [f]				5.7 (4.9)	1.04	**1.01-1.06****	1.03	**1.0-1.06**	**.042**	6.1 (5.0)	1.04	**1.01-1.07****	1.0	.96-1.05	.941
HADS-A score[d], mean (SD)	4.8 (3.8)	1.02	.99-1.06				4.7 (3.8)	1.01	.98-1.04				5.3 (3.8)	1.05	**1.01-1.10***	1.04	.98-1.10	.236
Chronic fatigue[e], n (%)																		
No (ref.)	314 (40)	1.0		1.0			393 (50)	1.0					149 (19)	1.0				
Yes	138 (54)	1.73	**1.30-2.30*****	1.50	**1.11-2.03**	**.009**	130 (51)	1.02	.77-1.35				53 (21)	1.11	.78-1.57			

Abbreviations: BMI=body mass index. 95 % CI= 95 % confidence interval. SD=standard deviation. cOR=crude odds ratio. aOR=adjusted odds ratio. Ref.=reference.
[a]Physical inactivity defined as not meeting physical activity guidelines of at least 150 minutes moderate or 75 minutes vigorous physical activity per week.
[b]Limited skin surgery for malignant melanoma. [c]The Patient Health Questionnaire-9 Range 0-27. Increasing score implies higher level of depressive symptoms. [d] The Hospital Anxiety and Depression Scale, anxiety subscale. Range 0-21. Increasing score implies higher level of anxiety. [e] defined as elevated level of fatigue of at least 6 months duration. [f]Not included in multivariable analyses due to overlap with chronic fatigue.

Bold: statistically significant result ($p<0.05$)
*=$p<0.05$
**=$p<0.01$
***=$p<0.001$.
Numbers included in adjusted multivariable analyses were 1024 for physically inactive, 981 for overweight and 985 for smoking.

Table 4: Ordinal logistic regression analyses of potential associated factors of not meeting an increasing number of guidelines in terms of physical activity, body mass index and smoking.

	Unadjusted			Adjusted*		
	cOR	95 % CI	p	aOR	95 % CI	P
Sex, n (%)						
Female (ref.)	1.0			1.0		
Male	1.46	1.14-1.88	**.003**	1.80	1.37-2.37	**< .001**
Age at survey, mean (SD)	1.01	.99-1.02	.306			
Living with a partner, n (%)						
Yes (ref.)	1.0					
No	1.26	.96-1.66	.100			
Living with children < 18 years, n (%)						
Yes (ref)	1.0			1.0		
No	1.43	1.14-1.80	**.002**	1.21	.94-1.54	.137
Education level, n (%)						
> 13 years (ref.)	1.0			1.0		
≤ 13 years	1.65	1.31-2.07	**<.001**	1.44	1.13-1.84	**.003**
Cancer-related variables						
Years since diagnosis, mean (SD)	1.01	.99-1.03	.110			
Treatment modality, n (%)						
Reference[a]	1.0					
Surgery and/or radiotherapy	.99	.70-1.43	.987			
Systemic treatment alone	1.24	.85-1.80	.269			
Systemic treatment with radiotherapy and/or surgery	.80	.61-1.06	.120			
Health variables						
Number of comorbid conditions, n (%)						
None (ref.)	1.0			1.0		
1-2	1.11	.86-1.44	.435	.94	.71-1.24	.641
>2	2.17	1.16-3.03	**<.001**	1.57	1.08-2.29	**.018**
Numbness in hands/feet, n (%)						
No (ref.)	1.0					
Yes	1.05	.78-1.41	.764			
Lymphedema, n (%)						
No (ref.)	1.0			1.0		
Yes	1.46	1.10-1.93	**.008**	1.37	1.02-1.84	**.037**
Pain interfering with normal work, n (%)						
No (ref.)	1.0			1.0		
Yes	2.10	1.45-3.05	**<.001**	1.54	1.0-2.35	**.048**
Trouble sleeping, n (%)						
No (ref.)	1.0			1.0		
Yes	1.35	1.08-1.68	**.009**	1.10	.86-1.42	.450
PHQ-9 score[b], mean (SD)	1.07	1.05-1.10	**<.001**[c]			
HADS-A score[c], mean (SD)	1.03	1.0-1.07	**.026**	1.02	.98-1.05	.357
Chronic fatigue[d], n (%)						
No (ref.)	1.0			1.0		
Yes	1.38	1.06-1.79	**.015**	1.09	.81-1.46	.573

Abbreviations: 95 % CI= 95 % confidence interval. SD= standard deviation. cOR=crude odds ratio. aOR=adjusted odds ratio. Ref.=reference. *Numbers included in multivariable analyses were 968. Variables associated (p<.05) (**bold)** with not meeting an increasing number of guidelines in unadjusted analyses were included as explanatory variables in the adjusted analyses [a]Limited surgery for malignant melanoma [b]The Patient Health Questionnaire-9 [c] The Hospital Anxiety and Depression Scale, anxiety subscale. [c]Not included in multivariable analyses due to overlap with chronic fatigue, [d] elevated fatigue symptoms of at least 6 months duration

Supplementary file: characteristics of non-responders versus responders

	Non-responders (n=1838)*	Included responders (n=1056)	P-value
Sex, (n, %)			
Female	1279 (70)	783 (74)	.009
Male	559 (30)	273 (26)	
Age at survey, mean (SD)	48 (8)	49 (8)	.001
Age at diagnosis, mean (SD)	33 (5)	33 (5)	.476
Time since diagnosis, mean (SD)	14 (7)	15 (7)	.001
Cancer type, n (%)			
BC	563 (31)	422 (40)	<.001
CRC	184 (10)	116 (11)	
NHL	342 (19)	167 (16)	
ALL	178 (10)	105 (10)	
MM	571 (31)	246 (23)	

Abbreviations: BC=breast cancer. CRC=colorectal cancer. NHL=non-Hodgkin lymphoma. ALL=acute lymphoblastic leukemia. MM=malignant melanoma.

*Non-responders with >1 cancer diagnosis, recurrence or distant metastasis excluded from non-responders (n=232).

Appendix

Appendix A: selected items from the questionnaire used in sub-study I

Treatment:

Hva var den første behandlingen du fikk?

□ Åpen operasjon med fjerning av prostata

□ Robotoperasjon med fjerning av prostata

□ Annen type operasjon med fjerning av prostata

□ Strålebehandling uten hormonbehandling

□ Strålebehandling med hormonbehandling i for- og etterkant

□ Bare hormonbehandling som tabletter eller sprøyter

□ Fjerning av testiklene

□ Vente-og-se opplegg med tett oppfølging hos spesialist

□ Vente-og-se opplegg med vesentlig oppfølging hos fastlegen

Etterbehandling etter avsluttet første-behandling: Har det vært nødvendig å starte med ny/annen behandling? □ Nei □ Ja

Level of physical activity:

Med mosjon menes at du for eksempel gå på ski, svømmer eller driver trening/idrett slik at du blir andpusten eller blir svett. Hvor ofte driver du mosjon? (Ta et gjennomsnitt)

□Aldri

□ Sjeldnere enn en gang i uka

□ En gang i uka

□ 2-3 ganger i uka

□ Omtrent hver dag

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)

1.Samlet sett hvor stort problem har du hatt med urinfunksjonen?

☐Ikke noe problem ☐Svært lite problem ☐Lite problem ☐Nokså stort problem ☐Stort problem

2.Hvordan vil du beskrive din kontroll over vannlatingen?

☐Total kontroll ☐Dråpelekkasje av og til ☐Hyppig lekkasje ☐Ingen kontroll

3.Hvor mange truseinnlegg, bind eller bleier har du vanligvis brukt *per dag* for lekkasje?

☐Ingen ☐En per dag ☐To per dag ☐Tre eller flere per dag

4.Hvor stort problem har urinlekkasje vært for deg?

☐Ikke noe problem ☐Svært lite problem ☐Lite problem ☐Nokså stort problem ☐Stort problem

5.Hvor stort problem har det følgende vært for deg?	**Ikke noe problem**	**Veldig lite problem**	**Lite problem**	**Nokså stort problem**	**Stort problem**
a. Smerte eller brennende følelse ved vannlating	☐	☐	☐	☐	☐
b. Svak urinstråle eller vansker med å tømme blæra?.....	☐	☐	☐	☐	☐
c. Hyppig vannlating.....	☐	☐	☐	☐	☐

6.Hvor stort problem har det følgende vært for deg?	**Ikke noe problem**	**Veldig lite problem**	**Lite problem**	**Nokså stort problem**	**Stort problem**
a. Smerter i endetarmen eller umiddelbar avføringstrang.....	☐	☐	☐	☐	☐
b. Hyppig avføring.....	☐	☐	☐	☐	☐
c. Samlede problemer med dine avføringsvaner...	☐	☐	☐	☐	☐

7.Hvordan vil du gradere din evne til å oppnå orgasme (klimaks)?

☐Svært god ☐God ☐Rimelig ☐Dårlig ☐Svært dårlig/ingen

8.Hvordan vil du beskrive den vanlige kvaliteten på ereksjonen din?

☐Tilstrekkelig stivhet for samleie ☐Bare stiv nok til onanering og forspill ☐Ikke stiv nok til noen seksuell aktivitet ☐Ingen ereksjon (reisning)

9.Samlet sett hvor stort problem har din seksualfunksjon eller mangel på seksualfunksjon vært for deg?

☐Ikke noe problem ☐Svært lite problem ☐Lite problem ☐Nokså stort problem ☐Stort problem

10.Hvor stort problem har det følgende vært for deg?	**Ikke noe problem**	**Veldig lite problem**	**Lite problem**	**Nokså stort problem**	**Stort problem**
a. Hetetokter eller ømme/svulne bryster.....	☐	☐	☐	☐	☐
b. Følt deg nedstemt.....	☐	☐	☐	☐	☐
c. Mangel på energi.....	☐	☐	☐	☐	☐

Appendix B: selected items from the questionnaire used in sub-study II (The NOR-CAYACS study)

3. Hva slags behandling fikk du?	Ja	Nei	Vet ikke
a. Cellegift	☐	☐	☐
b. Strålebehandling	☐	☐	☐
c. Kreftbehandling med hormoner/anti-hormoner	☐	☐	☐
d. Operasjon	☐	☐	☐
e. Høydosebehandling med stamcellestøtte/benmargstransplantasjon	☐	☐	☐
f. Antistoffbehandling	☐	☐	☐
g. Annen behandling	☐	☐	☐

16. Er du klar over at visse former for kreftbehandling kan gi seneffekter som:	Ja – har erfart selv	Ja – vet om det	Nei
a. Hormonforandringer	☐	☐	☐
b. Redusert fruktbarhet	☐	☐	☐
c. Hjerte/karsykdommer	☐	☐	☐
d. Lungeproblemer	☐	☐	☐
e. Kronisk tretthet/utmattelse (fatigue)	☐	☐	☐
f. Tannhelseproblemer	☐	☐	☐
g. Vansker med hukommelse og konsentrasjon	☐	☐	☐
h. Problemer med hørsel	☐	☐	☐
i. Muskelkramper	☐	☐	☐
j. Nervesmerter	☐	☐	☐
k. Nummenhet i hender/fotsåler	☐	☐	☐
l. Ny kreft	☐	☐	☐
m. Problemer med seksuallivet	☐	☐	☐
n. Osteoporose (benskjørhet)	☐	☐	☐
o. Lymfødem (væskeansamlinger f.eks. i arm, ben, andre kroppsdeler)	☐	☐	☐
p. Psykologiske reaksjoner	☐	☐	☐
q. Stråleskader i hud, bindevev og muskler	☐	☐	☐
r. Andre seneffekter, spesifiser:			

32. Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene?	**Har du eller har du hatt denne plagen/sykdommen?**		**Begrenser plagen/sykdommen deg i aktiviteter i dag?**	
	Ja	**Nei**	**Ja**	**Nei**
a. Hjertesykdom (som hjerteinfarkt, hjertesvikt, hjertekrampe (angina pectoris))	☐	☐	☐	☐
b. Høyt blodtrykk	☐	☐	☐	☐
c. Kronisk lungesykdom (som astma, kronisk bronkitt eller kols)	☐	☐	☐	☐
d. Diabetes (sukkersyke)	☐	☐	☐	☐
e. Nyresykdom	☐	☐	☐	☐
f. Leversykdom	☐	☐	☐	☐
g. Magesår eller tarmsykdom (som Crohns sykdom, ulcerøs kolitt)	☐	☐	☐	☐
h. Reumatisk sykdom (som leddgikt, Bekhterevs sykdom)	☐	☐	☐	☐
i. Slitasjegikt (artrose)	☐	☐	☐	☐
j. Andre muskel/skjelett plager	☐	☐	☐	☐
j. Epilepsi	☐	☐	☐	☐
k. Hjerneslag / hjerneblødning / blodpropp i hjernen	☐	☐	☐	☐
l. Depresjon som du har søkt hjelp for	☐	☐	☐	☐
m. Andre psykiske plager som du har søkt hjelp for	☐	☐	☐	☐
n. Anemi (lav blodprosent)	☐	☐	☐	☐
o. Lavt stoffskifte (hypothyreose)	☐	☐	☐	☐
p. Høyt stoffskifte (hyperthyreose)	☐	☐	☐	☐

33. Hva er din høyde? ☐☐☐ cm **34. Hva er din vekt?** ☐☐☐ kg

41. Hvor ofte spiser du vanligvis minst 5 porsjoner med grønnsaker, frukt og bær på en dag?

En porsjon tilsvarer 100 gr. Ikke ta med poteter.

☐ Mindre enn en gang i uka ☐ 4-6 dager i uka
☐ 1-3 dager i uka ☐ Hver dag

43. Røyker du? (sett ett kryss)

☐ Nei, jeg har aldri røykt ☐ Ja, røyker av og til (fest/ ferie, ikke daglig)
☐ Nei, jeg har sluttet å røyke ☐ Ja, røyker daglig

50. Hvor ofte har det hendt i løpet av de siste <u>3 måneder</u> at du:

	Sjelden/ aldri	Av og til	Flere ganger i uken
a. Har vanskelig for å sovne om kvelden.....	☐	☐	☐
b. Våkner gjentatte ganger om natten.....	☐	☐	☐
c. Våkner for tidlig og får ikke sove igjen.....	☐	☐	☐

The Godin Leisure Time Exercise Questionnaire

Fysisk aktivitet

Når du skal svare på de neste **tre** spørsmålene ber vi deg tenke på **din gjennomsnittlige ukentlige trening i løpet av den siste måneden**. Når du svarer på spørsmålene under skal du merke deg følgende:

- Ta bare med treningsøkter som varte **10 minutter eller lenger**.
- Ta bare med trening du har gjort **i løpet av fritiden** (altså ikke i arbeidstiden eller husarbeid).
- Merk deg at hovedforskjellen mellom de tre treningskategoriene er **intensiteten**.

Skriv ned hvor mange ganger per uke i gjennomsnitt du gjorde en aktivitet i første kolonne, og hvor lenge du holdt på per gang i gjennomsnittet på andre kolonne.

46. Tenk tilbake på din gjennomsnittlige ukentlige trening den siste måneden. Hvor mange ganger i løpet av en vanlig 7-dagers uke gjennomførte du følgende trening:

	Ganger per uke i gjennomsnitt	Hvor lenge per gang gjennomsnitt (antall min.)
a) HARD TRENING **(Veldig anstrengende - hjertet slår fort)** (f. eks. løping, jogging, ishockey, fotball, squash, basketball, skigåing, judo, rulleskøyter, rask svømming, rask sykling over lange avstander)	☐☐ ganger	☐☐☐ minutter
b) MODERAT TRENING **(Moderat anstrengende)** (f. eks. rask gange, tennis, lett sykling, volleyball, badminton, rolig svømming, slalåm, folkedans)	☐☐ ganger	☐☐☐ minutter
c) LETT TRENING **(Minimalt anstrengende)** (f. eks. lett gange, yoga, bueskyting, fiske, bowling, golf, snøscooterkjøring)	☐☐ ganger	☐☐☐ minutter

The Chalder Fatigue Questionnaire

57. Tretthet/utmattelse

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd **den siste måneden.** Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Vi spør om hvordan du har følt deg i det siste og ikke om 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.

a. Har du problemer med at du føler deg sliten?	☐	Mindre enn vanlig	☐	Ikke mer enn vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
b. Trenger du mer hvile?	☐	Nei, mindre enn vanlig	☐	Ikke mer enn vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
c. Føler du deg søvnig eller døsig?	☐	Mindre enn vanlig	☐	Ikke mer enn vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
d. Har du problemer med å komme i gang med ting?	☐	Mindre enn vanlig	☐	Ikke mer enn vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
e. Mangler du overskudd?	☐	Ikke i det hele tatt	☐	Ikke mer enn vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
f. Har du redusert styrke i musklene dine?	☐	Ikke i det hele tatt	☐	Ikke mer enn vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
g. Føler du deg svak?	☐	Mindre enn vanlig	☐	Som vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
h. Har du vansker med å konsentrere deg?	☐	Mindre enn vanlig	☐	Som vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
i. Forsnakker du deg i samtaler?	☐	Mindre enn vanlig	☐	Ikke mer enn vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
j. Er det vanskeligere å finne det rette ordet?	☐	Mindre enn vanlig	☐	Ikke mer enn vanlig	☐	Mer enn vanlig	☐	Mye mer enn vanlig
k. Hvordan er hukommelsen din?	☐	Bedre enn vanlig	☐	Ikke verre enn vanlig	☐	Verre enn vanlig	☐	Mye verre enn vanlig

58. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? *Sett ett kryss.*

Mindre enn en uke..... ☐
Mindre enn tre måneder..... ☐
Mellom tre og seks måneder..... ☐
Mellom seks måneder og ett år..... ☐
Mellom 1 år og 5 år..... ☐
5 år eller mer..... ☐

59. Har du følt deg sliten helt siden du ble behandlet for kreft? Ja ☐ Nei ☐

60. Hvis ja, hvordan har det i så fall utviklet seg over tid?

Ingen forandring..... ☐
Blitt bedre over tid ..... ☐
Blitt verre over tid ..... ☐

The Hospital Anxiety and Depression Scale, anxiety subscale (HADS-A)

53. Her kommer noen utsagn om hvordan du har følt deg den siste uken. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uken.

a. Jeg føler meg nervøs og urolig	☐ Mesteparten av tiden	☐ Mye av tiden	☐ Fra tid til annen	☐ Ikke i det hele tatt
b. Jeg har en urofølelse som om noe forferdelig kommer til å skje	☐ Ja, og noe svært ille	☐ Ja, ikke så veldig ille	☐ Litt, bekymrer meg lite	☐ Ikke i det hele tatt
c. Jeg har hodet fullt av bekymringer	☐ Veldig ofte	☐ Ganske ofte	☐ Av og til	☐ En gang i blant
d. Jeg kan sitte i fred og ro og kjenne meg avslappet	☐ Ja, helt klart	☐ Vanligvis	☐ Ikke så ofte	☐ Ikke i det hele tatt
e. Jeg føler meg urolig som om jeg har sommerfugler i magen	☐ Ikke i det hele tatt	☐ Fra tid til annen	☐ Ganske ofte	☐ Svært ofte
f. Jeg er rastløs som om jeg stadig må være aktiv	☐ Uten tvil svært mye	☐ Ganske mye	☐ Ikke så veldig mye	☐ Ikke i det hele tatt
g. Jeg kan plutselig få en følelse av panikk	☐ Uten tvil svært ofte	☐ Ganske ofte	☐ Ikke så veldig ofte	☐ Ikke i det hele tatt

The Patient Health Questionnaire-9 (PHQ-9)

55. I løpet av de siste 2 ukene, hvor ofte har du vært plaget av ett eller flere av de følgende problemene?

	Ikke i det hele tatt	Noen dager	Mer enn 7 dager	Nesten hver dag
a. Lite interesse for eller glede over å gjøre ting	☐	☐	☐	☐
b. Følt deg nedfor, deprimert eller fylt av håpløshet	☐	☐	☐	☐
c. Vansker med å sovne eller med å sove natten gjennom uten å våkne - eller å sove for mye	☐	☐	☐	☐
d. Følt deg trett eller slapp	☐	☐	☐	☐
e. Dårlig appetitt eller å spise for mye	☐	☐	☐	☐
f. Vært misfornøyd med deg selv eller følt deg mislykket – eller følt at du har sviktet deg selv eller familien din	☐	☐	☐	☐
g. Vansker med å konsentrere deg om ting, slik som å lese avisen eller se på TV	☐	☐	☐	☐
h. Beveget deg eller snakket så langsomt at andre kan ha merket det? Eller motsatt - følt deg så urolig eller rastløs at du har vært mye mer i bevegelse enn vanlig	☐	☐	☐	☐
i. Tanker om at du like gjerne kunne vært død eller på annen måte ville skade deg selv	☐	☐	☐	☐

Errata

Page	Line	Original text	Type of correction	Corrected text
5	14	..has been..	Cor	..have been..
5	17	..is a…	Cor	..are..
9	4	…associated an…	Cor	…associated with an..
12	24	..PSA, findings on a digital rectal exam level…	Cor	..PSA level, findings on a digital rectal exam …
2т	3	Obesity place…	Cor	Obesity places…
28	16	Current knowledge gaps (…) is	Cor	Current knowledge gaps (…) are
64	17	…an increased risk CF…	Cor	…an increased risk of CF…
Paper I, page 3	Statistics, second paragraph	…test continuous variables…	Cor	…test on continuous variables…
Paper II, page 2	20	..lifestyle YACSs…	Cor	…lifestyle of YACSs…
Paper II, page 3	10	… and non-smoking is…	Cor	…and non-smoking are…
Paper II, page 4	4	…is scarcely…	Cor	…are scarcely…
Paper II, table 4			Table 4 was turned from horizontal to vertical	

Cor – correction of language