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NTNU
Norwegian University of
Science and Technology
Doctoral thesis
for the degree of philosophiae doctor
Faculty of Medicine
Department of Cancer Research and Molecular Medicine

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Innovation and Creativity

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To
Tore, Marte, and Sondre

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Abbreviations

BMI	= Body mass index
CFS	= Chronic fatigue syndrome
EORTC QLQ-C30	= The European Organisation for Research and Treatment of Cancer
FEV	= Forced expiratory volume
FEV_1	= Forced expiratory volume in one second
FQ	= Fatigue questionnaire
FVC	= Forced vital capacity
Gen-pop	= General population
HD	= Hodgkin's disease
HDSs	= Hodgkin's disease survivors
HDSs-NRH	= Sample recruited from Norwegian Radium Hospital
HDSs-St. Olavs	= Sample recruited from St. Olavs Hospital
HR	= Heart rate
HRQoL	= Health related quality of life
HUNT-2	= Second Health survey in North Trøndelag
HUNT-Q	= Questionnaire from the second Health survey in North Trøndelag
KPS	= Karnofsky performance status
LPA	= Level of physical activity
MF	= Mental fatigue
NRH	= Norwegian Radium Hospital
PF	= Physical fatigue
QoL	= Quality of life
RCT	= Randomised clinical trial
SE	= Self-reported evaluation
SF-36	= Short form-36
TF	= Total fatigue
VO_{2max}	= Maximal aerobic capacity

List of papers

I. Oldervoll LM, Kaasa S, Lydersen S, Fosså SD, Hjermstad MJ, Thorsen L, Jacobsen AB, Holthe H, Loge JH. Self reported level of physical activity, smoking habits and sleep pattern among Hodgkin's disease survivors compared to the general population. Submitted for publication

II. Oldervoll LM, Kaasa S, Knobel H, Loge JH.
Exercise reduces fatigue in chronic fatigued Hodgkin's disease survivors – results from a pilot study. European Journal of Cancer 2003, 39: 57-63

III. Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Hjermstad MJ, Kaasa S.
Are palliative cancer patients willing and able to participate in a physical exercise programme? Palliative and Supportive Care, 2006, 3: 281-287

IV. Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Wiken AaN, Hjermstad MJ, Kaasa S. The effects of a physical exercise programme in palliative care;a phase II study. Accepted for publication in Journal of Pain and Symptom Management, October 11th, 2005

Definitions and clarification of concepts

Physical activity is defined as any bodily movement produced by skeletal muscles and resulting in substantial energy expenditure above resting level (Bouchard C and Shepard RJ, 1994).

Leisure-time physical activity is defined as physical activity undertaken during discretionary time, with the key element being personal choice. This form of physical activity is often contrasted with occupational and household physical activity (Pedersen BK and Saltin B, 2003; Bouchard C and Shepard RJ, 1994).

Exercise and training is defined as leisure-time physical activity that is usually performed on a repeated basis over an extended period of time with the intention to improve fitness, performance and health. Training is repetitive bouts of exercise, conducted over periods of weeks or months, with the intention of developing physical and/or physiological fitness. Bouchard defines exercise as *"physical activity in leisure time that is repeated regularly and aim to improve physical capacity, performance or health"* (Bouchard C and Shepard RJ, 1994).

An exercise training prescription is described through the "dose concept" which includes the following four factors; 1: activity mode (e.g. walking, cycling, cross-country skiing, swimming) 2: volume (i.e. frequency, intensity, and duration), 3: progression or periodisation, and 4: context (i.e. physical and social environment) (Bouchard C and Shepard RJ, 1994).

Physical fitness is defined as the ability to perform muscular work satisfactorily and commonly includes the components of body composition, cardiorespiratory fitness, muscular fitness, flexibility, and agility/balance.

In this synthesis, the concept **functional status** covers both conditions that may be assessed subjectively, such as in self-reported physical functioning measured by questionnaires,

questionnaires of self-reported physical activity levels and objectively, such as physical fitness and performance.

Lifestyle comprises the aggregate of an individual's behaviours, actions and habits which can affect personal health (e.g. smoking, diet, sleep, physical activity) (Bouchard C and Shepard RJ, 1994)

Health related quality of life (HRQoL) is defined as the extent to which health impacts on an individual's ability to function and his/her perceived well-being in physical, mental and social domains of life (Ware, 1987; Aaronson, 1990; Cella and Tulsky, 1993). Many definitions of quality of life have been attempted, most including components of happiness and satisfaction with life. To distinguish between quality of life in its more general sense and quality of life is associated with clinical medicine or clinical trials, the term HRQoL is frequently used.

Fatigue is defined as a subjective feeling of tiredness, mentally and/or physically (Wessely, 1995).

Chronic fatigue is defined as an increased level of fatigue of duration 6 months or longer (Wessely, 1992a, Wessely, 1995).

1.0 Background

This thesis includes studies from two different cancer populations: long term cured cancer survivors (Hodgkin's disease survivors) and patients with incurable cancer (palliative care patients) with life expectancy below one year.

1.1 Preface

In 1999, while working with cardiac rehabilitation as an exercise physiologist at the Department of Physical Medicine and Rehabilitation, University Hospital in Trondheim, I was contacted and invited to take part in a study among Hodgkin's disease survivors treated at St. Olavs Hospital in the period 1987-1997. This study was initiated by professor Jon Håvard Loge who was at that time doing his post-doctoral work on fatigue in cancer patients: prevalence, correlates and intervention. In his doctoral thesis he found that Hodgkin's disease survivors were considerably more fatigued than the general population and that they reported fatigue of a substantially longer duration. Physical exercise has shown promising effects in terms of reducing the level of fatigue among patients with chronic fatigue syndrome and cancer patients suffering from fatigue during treatment (Fulcher and White, 1997; Mock *et al.*, 1997; Courneya *et al.*, 2003; Segal RJ *et al.*, 2003). We therefore completed a feasibility study (phase II-study) among the Hodgkin's disease survivors who reported chronic fatigue (paper II). As a follow-up, we started a project with professor Sophie Fosså, to study Hodgkin's disease survivors treated at the Norwegian Radium Hospital in the period 1971-1997. Part I of this project was a questionnaire-survey and data was collected in 2002. This questionnaire-survey has resulted in three papers, one of which is included in this thesis (paper I) (Hjermstad *et al.*, 2005; Hjermstad MJ *et al.*, 2006). Part II was planned as a randomised clinical trial investigating the effects of physical exercise in chronic fatigued survivors of Hodgkin's disease. However, due to practical reasons the randomised trial was postponed. As there is a 4-year maximum time limit on my doctoral thesis, we decided to carry out a systematic literature review of randomised clinical trials of exercise intervention studies in cancer patients. The reviewed studies indicated promising effects on both physiological and psychological outcomes during, and immediately after, cancer therapy, however the studies were small in size and mainly focused on breast cancer patients. Studies of incurable cancer patients were missing (Oldervoll *et al.*, 2004). Professor Stein Kaasa then

introduced me to the field of palliative medicine and I was fortunate to take part in and write a project description about physical exercise in incurable cancer patients. Although I was sceptical in the beginning, this project turned out to be very challenging and exciting. During 2003 and 2004, we collected data and completed an intervention study (phase II study) consisting of a group exercise programme among palliative cancer patients (paper III and IV in this thesis).

1.2 Physical exercise as part of the rehabilitation process

The evidence-based foundation for physical exercise among patients was for many years slight. Today physical exercise is indicated as part of the treatment or rehabilitation process among many medical diseases. Among chosen diseases, there is evidence that physical exercise is, in certain situations, more effective than the medical treatment or enhances the medical treatment (Pedersen BK and Saltin B, 2003).

Physical exercise may have a clinical effect, either by affecting the *disease pathogenesis*, improve dominant *symptoms* directly related to the diagnosis or by improving the cardiovascular capacity and muscular strength and thereby improving *quality of life* (Pedersen BK and Saltin B, 2003).

Cancer and heart disease are the two most important causes for early death in the western world. Cardiology was the first medical speciality in which exercise rehabilitation was implemented and evaluated. The investigation of cardiac rehabilitation in the 1960's showed, through a series of clinical studies, the benefits of early mobilisation after myocardial infarction (Clausen, 1976; Velasco Rami and Maroto Montero, 1995; Ewart *et al.*, 1983). Physical exercise is now commonly prescribed in cardiac patients and is integral in the rehabilitation programme. Psychological, social and physiological benefits of the physical exercise after myocardial infarction, coronary artery bypass grafting, heart transplantation and stable congestive heart disease are well documented (Belardinelli *et al.*, 2001; Nieuwland *et al.*, 2000). Systematic physical exercise is today a part of the routine in cardiac rehabilitation.

Today, physical exercise is also becoming more usual as an integral part in the rehabilitation process in different diseases. Physical exercise is an important component in the treatment of adipositas, hypertension, diabetes type II, metabolic syndromes, chronic obstructive lung

disease, cystic fibrosis, patients with fibromyalgia, chronic fatigue syndrome, etc. (Ross *et al.*, 2000; Whelton *et al.*, 2002; Albright *et al.*, 2000; Leon and Sanchez, 2001; Wigers *et al.*, 1996; O'Neill *et al.*, 1987; Wearden *et al.*, 1998). However, the type of exercise and intensity of exercise used in the different diseases differ. New scientific knowledge regarding activity mode and volume is produced regularly, especially in the field of exercise training in cardiac patients. Recently published studies among patients with coronary artery disease and congestive heart failure have demonstrated that high intensity training is superior to moderate exercise in improving aerobic- and metabolic fitness and endothelial function (Rognmo *et al.*, 2004; Kemi *et al.*, 2005; Slordahl *et al.*, 2005).

1.2.1 Cancer rehabilitation

The aim of rehabilitation in cancer care is to improve quality of life with maximal coping and against minimal dependence, regardless of expected lifetime (Dietz JH, 1981). Cancer rehabilitation is a process that assists the patient and their relatives to retain the best possible physical, social, psychological and occupational functions with the limitations that the cancer disease and treatment create (Gerber LH and Vargo M, 1998). Rehabilitation is in this respect a superior concept that contains physical exercise and recovery as a part of the rehabilitation. However, also other approaches are included, such as psychological and different activities helping the patients to regain social roles. This thesis is limited to physical exercise and activity among cancer patients at two stages of the disease trajectory as part of the rehabilitation process: (1) in longterm disease free cancer survivors and (2) in incurable cancer patients with life expectancy below one year.

Research assessing the possible effects of physical exercise among cancer patients and survivors is relatively new. The first studies were published in the mid 1980's. Maryl Winningham from Ohio State University in USA was a pioneer in this field and finished her doctoral dissertation in 1983 (Winningham ML, 1983). After this, sporadic works were published in the late 1980's and at the beginning of 1990. The research activity increased in the late 1990's when research programmes were launched in both North America and Europe.

1.3 Cancer patients

Despite the high mortality of different cancer types, survival rates have increased over the last decade and the chances to be cured from cancer has never been higher than today. In the periods 1958-62 and 1993-97, the five year survival rates have increased from 25 % to 52 % for males and from 39 % to 60 % for females (Cancer Registry of Norway, 2005).
Many of these patients have received intensive treatment combinations including intensive chemotherapy and radiotherapy. Of the 23,000 new cancer incidences in Norway every year about 50 % will be cured. 50 % of those dieing, will die within one year after being diagnosed with cancer (Cancer Registry of Norway, 2005). Today cancer can be recognised as a chronic disease. Hence, increased research efforts to improve quality of life, reduce the risk of relapse and increase survival in this patient population have emerged.

Cancer therapy, although increasingly effective for improving survival, are toxic in numerous ways and produce negative short and long term physiologic and/or psychological effects, including pain, reduced cardio-respiratory capacity, cancer-related fatigue, reduced health-related quality of life and suppressed immune function (Fobair *et al.*, 1986; Loge *et al.*, 1997; Fossa *et al.*, 2003; Meinardi *et al.*, 2000b; Meinardi *et al.*, 2000a). Physical exercise may contribute to modify and/or reduce the prevalence of some symptoms and maintain physical status in cancer patients.

1.3.1 Hodgkin's disease survivors

Hodgkin's disease (HD) is a malignant haemopoietic disease with an annual incidence of 2.1 per 100,000 of women and 3.3 per 100,000 of men. In Norway in 2003, 80 men and 53 women were diagnosed with HD (Cancer Registry of Norway, 2005). HD had been a fatal disease until the development of high-voltage radiotherapy and combination chemotherapy (Gilbert R, 1939). During the 1960's the prognosis for survival improved (De Vita VT *et al.*, 1970). This was mainly related to the introduction of improved (cancer) staging systems, better understanding of the spread and course of the disease, improved diagnostics and refined therapy. The therapeutic pessimism turned into optimism, and the clinicians dared to speak of cure. Cure was defined as follows: *"We can speak of cure when in time, probably a decade or so after treatment, there remains a group of disease-free survivors whose progressive death rate from all causes is similar to that of a normal population of the same sex and age constitution"* (Easson EC and Russel MH, 1963).

The incidence of new cases of HD in Norway is highest among the age group 20-29, as nearly 30 % of new cases are found in this age group. As a consequence of the improved treatment results, the prevalence of Hodgkin's disease survivors (HDSs) steadily increases (n = 1215, 1993 and n = 1725, 2003 in Norway) (Cancer Registry of Norway, 2005). The improved prognosis for survival achieved during the 1960's created an increasing number of survivors, and studies of possible late effects thereby became possible.

Today, HD is a disease mainly affecting young adults and with a good prognosis for survival (best among young patients) (Abrahamsen *et al.*, 1993). Consequently this cancer disease generates a population of survivors with a long life expectancy. In general the five-year survival rate for all patients with HD exceeds 80 %, and for patients ≤ 39 years of age more than 90 % are expected to live for 5 years or more after diagnosis (Aleman *et al.*, 2003). Consequently the prevalence of survivorship has steadily increased. Survivors treated for HD have been extensively studied in previous investigations as to their psychosocial morbidity and important aspects of their somatic health. Secondary malignancies such as cardiac, pulmonary and psychosocial problems have been identified as principle sequelae after treatment of HD, and their impact on health related quality of life have been described (van Rijswijk *et al.*, 1987; Abrahamsen *et al.*, 1999; Lund *et al.*, 1995; Knobel *et al.*, 2001; Loge *et al.*, 1999b; Loge *et al.*, 1999a). Late complications are therefore of special relevance because survivors will live most of their lives as "cured" cancer patients. Jon Håvard Loge concluded in his doctoral thesis that HRQoL in HDSs was affected many years after termination of curative treatment. Fatigue was the major problem, and the prevalence of chronic fatigue (elevated levels for six months) was more than doubled compared to the general Norwegian population (Loge *et al.*, 1999a).

Fatigue

Fatigue is defined as a subjective experience of being tired and/or worn out, both mentally and/or physically (Wessely, 1995). Fatigue has been difficult to operationalise and objective measuring methods do not exist. Consequently, fatigue is measured by asking the patients about subjectively experienced tiredness (Wessely, 1992b).

Tiredness is a normal and temporary condition occurring after physical and mental exertion and contributes to the regulation between activity and rest. In illness, fatigue occurs without

prior activity having taken place, is only slightly reduced by rest and is a more lasting condition. In chronic tiredness the regulation function is therefore weakened or absent, and fatigue is often associated with the underlying illness.

Fatigue may be a debut symptom in cancer disease, symptom of active or terminal disease, a side effect of treatment, late effect of disease or a covariance with one or more of these factors (Irvine *et al.*, 1991; Richardson, 1995). Fatigue is one of the most frequently and most distressing reported symptoms among cancer patients. About 70 % of people with cancer report fatigue during radiotherapy or chemotherapy or after surgery and it is the most prevalent symptom in palliative care (Dimeo, 2001; Stone *et al.*, 2000b; Stone *et al.*, 1999). Irrespective of the type of cancer, the cancer related fatigue influences all parts of a patient's quality of life and aggravates other distressing symptoms such as pain, nausea and dyspnoea (Winningham, 2001).

Earlier studies of cured cancer patients have shown that fatigue symptoms can persist for a considerable period of time (years) after the treatment is finalised. Different studies comparing HDSs to testicular cancer survivors (TCSs) and the general population, report that HDSs are more fatigued (26 %) than the TCSs (16 %) and the general population (11 %) (Bloom *et al.*, 1993; Loge *et al.*, 1999a; Ruffer *et al.*, 2003; Fossa *et al.*, 2003). No difference in fatigue levels are experienced among breast cancer survivors as compared to women in the general population (Bower *et al.*, 2000). Loge et al. have shown that patients cured of HD in the period 1971-91 and alive in 1994, had a significantly higher level of fatigue than the normal population 3-20 years after treatment (Loge *et al.*, 1999a). In the same cohort, 19 % of the patients of employment age were unable to work and received disability benefits, twice as many as in the normal population. It may therefore look like the high prevalence of fatigue is a more specific problem for long-term HDSs compared to breast cancer and testicular cancer survivors.

Evidence-based treatment of cancer related fatigue is missing, but is nevertheless relevant within rehabilitation of cancer patients, which today is mostly information/support-based. It is generally believed that fatigue cannot be treated and there is no consensus on how to prevent or alleviate fatigue. However, treatment studies with aerobic exercise have indicated that the level of fatigue can be considerably reduced among cancer patients during and immediately after treatment, among patients suffering from chronic fatigue syndrome and among patients

with fibromyalgia (Mock *et al.*, 1997; Courneya *et al.*, 2003; Segal RJ *et al.*, 2003; Wigers *et al.*, 1996; Wearden *et al.*, 1998; Dimeo *et al.*, 1999). In a randomised clinical trial (RCT), graded aerobic exercise significantly reduced fatigue, increased functional capacity and increased fitness in patients with chronic fatigue syndrome (CFS) without psychiatric or sleep disorders compared to flexibility exercises and relaxation therapy (Fulcher and White, 1997). Whiting et al. concluded in a systematic review of interventions for the treatment and management of chronic fatigue syndrome that cognitive behavioural therapy and graded exercise therapy are two interventions that show promising effects on fatigue levels (Whiting *et al.*, 2001). However, when we planned our study in 1999, no published study had addressed physical exercise as a possible mechanism to reduce chronic fatigue among long-term cancer survivors.

Mechanisms for fatigue in long term cancer survivors

The aetiology of fatigue in cancer disease is still unknown. A series of somatic conditions are related to fatigue during active cancer, such as metabolic conditions, nutritional status, immunological status, infections, anaemia, sleep disturbances, sedative medication and immobilisation (Smets *et al.*, 1993; Richardson, 1995). There is, however, limited knowledge about possible mechanisms that might explain the persistent fatigue in disease-free patients after successful treatment. Specific mechanisms associated with fatigue might be increased cytokines levels, endocrine dysfunction and anaemia (Morrow *et al.*, 2002). Few studies have explored the mechanisms behind chronic fatigue, but one study among HDSs found that pulmonary dysfunction was more prevalent among the chronically fatigued survivors than among non-fatigued survivors (Knobel *et al.*, 2001). Several underlying mechanisms have been proposed, such as disturbed sleep, physical inactivity and impaired functional status (Wessely, 2001). Few studies have addressed lifestyle variables such as physical activity levels, smoking habits and sleep patterns as possible mechanisms for persistent fatigue in long-term survivors.

1.3.2 Palliative cancer patients

Palliative medicine is the study and management of patients with active, progressive, far-advanced disease, for whom expected lifetime is limited and the focus of care is the quality of life (Doyle D *et al.*, 2004). The life prolonging, symptom-preventive and relieving phase when the treatment no longer has curative intent, is called the palliative phase. According to

European Association for Palliative Care (EAPC) palliative care is *"the active, total care of the patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of social, psychological and spiritual problems is paramount"* (http://www.eapcnet.org).

Most palliative patients have a complex clinical picture and symptomatology such as fatigue, pain, dyspnoea and nausea. The patients' physical functioning (functional capacity) will gradually decrease and the symptom level increase in the palliative phase. Jordhøy et al. found that physical and role functioning were the most severely affected functions, whereas fatigue was the highest rated symptom in palliative cancer patients 2-9 months before death (Jordhoy *et al.*, 2001). Cohen et al. found that physical functioning and physical conditions were among the most important determinants of palliative patients' quality of life (Cohen and Leis, 2002). The overall objective for all treatment in the palliative phase is to achieve the best possible quality of life for the patient and his/her relatives.

Physical exercise among cancer patients with short life expectancy may appear to be controversial. In spite of increasing interest in the quality of life among patients with advanced cancer disease, little attention has been directed towards maintenance of physical functioning. Among cancer patients the physical activity levels are generally reduced during the treatment period, with subsequent reduction in muscular strength and endurance. In addition, the cancer disease and treatment may also contribute to the catabolic effect on the muscular tissue. The contribution from inactivity, disease and treatment will probably depend on the cancer type, the disease dissemination and type of treatment. In addition, the individual's condition prior to treatment will also be of importance. Irrespective of the cause, the inactivity will result in a vicious circle with increased muscle atrophy, reduced muscle strength, reduced cardio-respiratory function and increased fatigue, which prevent the patients from being physically active. It has been estimated that as much as 1/3 of the reduction in a patients' performance is caused by inactivity (Dietz JH, 1981). All patients with advanced cancer or other incurable diseases experience physical decline. Recently published reviews suggest more research in the field of physical exercise among palliative cancer patients to maintain physical functioning and quality of life in different stages of the disease trajectory (Oldervoll *et al.*, 2004; Cheville, 2001; Santiago-Palma and Payne, 2001).

1.4 Physical activity and exercise

1.4.1 Effects of physical activity and exercise in general

Physical exercise and activity have documented favourable effect on physiological and psychological factors such as increased cardiorespiratory function (aerobic and metabolic fitness), improved skeletal muscle function (power, strength and endurance), motor function (agility, balance, coordination and speed of movement), skeleton and joints (joint structure and function, flexibility and bone density), metabolism (Aastrand PO 1987; Bouchard C and Shepard RJ, 1994) and on mental health such as reduced stress levels and depression (Martinsen *et al.*, 1985; Martinsen *et al.*, 1989).

Physical activity has been almost universally accepted as being relevant to health, although the pattern of activity (nature, intensity, frequency and duration of individual exercise bouts, cumulative years of participation) required to influence maximum health benefits remain uncertain. The health gain increases with increased levels of physical activity, but the relationship is not linear. Individuals with a high physical activity level at the starting point will attain smaller effects in health status by increasing physical activity by a given amount. Thus, individuals with low functional status are capable of attaining the greatest health effects, likewise for individuals with advanced age (US Department of Health and Human Services, 1997; Fiatarone *et al.*, 1994; Leon AS, 1997).

The dose-response between physical activity and health gain appear as a continuum with no lower limits. For patients and individuals physically immobilised because of disease, treatment or injury, nearly all physical activity will result in positive health effects. Consequently, being able to get out of bed and into a standing position, and further being able to walk represents a health gain. Furthermore, there are indications that regular physical activity may protect against a number of diseases and ailments such as development of cardiovascular disease, high blood pressure, type II diabetes, obesity and adipositas, colon and breast cancer (Blair *et al.*, 1996; Morris *et al.*, 1980; Petrella, 1998; Ornish *et al.*, 1990; Manson *et al.*, 1991; Friedenreich *et al.*, 1998; Thune and Lund, 1996; Thune and Furberg, 2001). Several studies, including one from Norway, conclude that good physical fitness is a significant prognostic factor for reduced risk of premature death due to disease and death (Paffenbarger *et al.*, 1993; Sandvik *et al.*, 1993). On the contrary, physical inactivity increases the chances of mortality and reduces functional capacity.

In addition to preventing a number of diseases, physical activity may positively influence our mental state; it may increase energy levels, reduce stress, improve the relationship to one's body image and promotes positive social relations. Possible mechanisms for this could be enhanced release of endorphins during physical activity which are involved in perception of euphoria, emotion, pain and pleasure (Allen, 1983). A well-established positive mental effect of physical activity is the feeling of well-being during and immediately after an exercise session (Dunn AL and Blair SN, 1997).

1.4.2 Recruitment and compliance

Recruitment, the process of screening and enrolling the patients into clinical trials, is in general a challenge and it may be influenced by several factors (Gotay, 1991; Hunninghake *et al.*, 1987; Lovato *et al.*, 1997). Motivation and attitude of both physicians and patients are important, along with the patient characteristics such as age, gender and performance status (Gotay, 1991). In a palliative setting, terminal illness, complex symptomatology, and patients' mental and physical exhaustion are likely to hinder trial entry, and successful recruitment to palliative interventions (McWhinney *et al.*, 1994).

Recruitment of patients into an exercise intervention may be even more challenging. Exercise presupposes personal commitment related to motivation, ability and will. Low participation rates in intervention programmes (e.g. compliance) and motivation to continue training influence the programme's impact.

Patient withdrawal (drop out) during the intervention is a general problem in experimental research, and of special relevance in physical exercise interventions. In healthy populations, approximately 50 % of those who start an exercise programme drop out during the first six months (Dishman DK, 1990). A large drop-out rate may reduce the sample's representation of the larger population, the strength of the findings and the ability to generalize from the result. Medically related drop-outs may be controlled through inclusion criteria; although strict inclusion criteria reduces drop out rates, it also decreases the ability to generalize from the results (Dishman DK, 1990; Pocock, 1996). A high drop-out rate may bias the results and/or influence the representativity (external validity) of the study and conclusions about the direct

clinical effects. High attrition rates have been presented as a major problem in palliative care trials (Ling *et al.*, 2000).

Courneya et al. conclude, in a review concerning physical exercise issues that exercise recruitment and adherence is a significant challenge in older cancer patients (Courneya *et al.*, 2004). However, few studies have addressed the challenges of recruitment, compliance, attrition and adherence in the exercise interventions among cancer patients at the different phases of disease trajectory when we planned our studies. Due to the known high attrition rate, the complex symptomatology and the majority of palliative patients being older, this problem was therefore addressed as primary outcomes in paper III in this thesis.

1.5 Documentation of the effectiveness of physical exercise in cancer patients

The primary outcomes in a physical activity program for cancer patients may vary according to several factors such as type of intervention and patient population i.e. curative or palliative. In addition clinical advice needs to be based on studies conducted on patients who are at a similar point of their cancer experience (pre-treatment, during treatment, and post-treatment). For example a study that reports physical exercise to be useful for alleviation of the fatigue among long-term cancer survivors does not necessarily make a clinician able to prescribe physical activity for cancer patients during treatment.

As this thesis includes physical exercise interventions among long-term cancer survivors and among palliation for those approaching the end of life, the following section gives a short overview of the literature. In addition a short overview of the results of physical exercise studies during and immediately after cancer treatment are presented.

1.5.1 Levels of physical activity among long-term survivors

Previous studies indicate that functional status is lowest immediately after treatment and tends to improve over time (Ko *et al.*, 2003). In older cancer survivors, regardless of duration after cancer diagnosis the presence of co-morbidity rather than history of cancer per se correlate with impaired functional status (Garman *et al.*, 2003).

Data regarding levels of physical activity (LPA) and cancer survivors are mixed, with some suggesting higher LPA (Demark-Wahnefried *et al.*, 2000; Hounshell *et al.*, 2001; Pinto *et al.*, 2002a; Thorsen *et al.*, 2003), some suggesting no difference (Blanchard *et al.*, 2003a; Gross *et al.*, 2002; Pinto *et al.*, 2002b) and some suggesting less (Blanchard *et al.*, 2003b) than before the cancer diagnosis or compared to the general population. Studies focusing on the LPA among long-term cancer survivors are rare. However, a recent finding by Thorsen et al was that testicular cancer survivors (11 years after treatment) had an increased odds ratio (1.32, 95 % CI, 1.10 to 1.58) for being physically active compared to the general population (Thorsen *et al.*, 2003). Among breast, colon and prostate survivors in one study, 70 % reported to exercise at least 30 minutes per day at least 5 days per week (Blanchard CM *et al.*, 2004). These conflicting data may be suspect due to both the general population and cancer survivors frequently overestimate their level of physical activity and the use of different measuring methods (Irwin and Ainsworth, 2004; Snyder *et al.*, 2004).

In a recent article, Ng et al. compared long-term survivors of HD (15 years after treatment) and their siblings on fatigue levels and factors predicting increased fatigue (Ng *et al.*, 2005). Factors significantly associated with increased fatigue in survivors were reports of cardiac disease, psychiatric condition, history of tobacco use and low exercise frequency. For siblings, the only independent factor associated with increased fatigue was low exercise frequency.

Previous studies of HRQoL among HDSs have demonstrated that they suffer from fatigue, have not regained energy and report reduced physical functioning compared to the general population (Loge *et al.*, 1999a; Loge *et al.*, 1999b). However, no study has addressed LPA and other lifestyle variables in fatigued and non-fatigued long-term HDSs and compared them to the general population. In addition, no physical exercise intervention has been published among cancer survivors addressing specific symptoms such as chronic fatigue in long-term cancer survivors.

1.5.2 Physical exercise in palliative cancer patients

Studies specifically dealing with physical exercise among incurable patients are few and most have methodological limitations such as small sample sizes, samples that are not representative and the intervention procedures are poorly described. Table 1 gives an

overview of the results from seven intervention studies in palliative patients and physical exercise (Yoshioka, 1994; Porock *et al.*, 2000; Crevenna *et al.*, 2003a; Crevenna *et al.*, 2002; Crevenna *et al.*, 2003b; Segal RJ *et al.*, 2003; Headley *et al.*, 2004). For identification of relevant publications in physical exercise interventions in palliative cancer patients, we performed a search in PubMed using the key words 'palliative AND exercise'. Of 242 hits (November 2005), seven papers were found relevant and had performed an exercise intervention among palliative cancer patients. Two of the studies were RCTs, three were single case studies with pre-post design and two studies had an experimental pre-post design. In the RCT published by Segal and coworkers, a total of 155 men with prostate cancer were randomised to resistance training or a control group (Segal RJ *et al.*, 2003). Sixty of these were palliative prostate cancer patients. The level of fatigue was significantly reduced and quality of life and muscular fitness improved. However, their expected lifetime was minimum 2-3 years, many projecting 4-5 years (personal communication) and the findings may therefore not be valid for patients with shorter life expectancy. However, no studies have addressed the effects of group exercise at the hospital (combined resistance and aerobic exercise) on subjective and objective outcomes in palliative cancer patients with different diagnosis and life expectancy below one year.

Table 1. Published trials on physical exercise in palliative cancer patients

Authors	Publ. date	Sample	N	Design	Type of intervention	Questionnaires and methods of measurement	Outcome measure	Results
Yoshioka H	1994	Mixed cancer types, terminal patients (advanced cancer with remaining life span of 6 months)	301	Experimental pre-post design	Package of physical therapy	BI and questionnaire to bereaved	ADL	BI increased by 27 %, 49 patients able to return to home
Porock et al.	2000	Mixed cancer types (life expectancy of at least one month)	11	Experimental pre-post design	Small exercise bouts several times a day for 28 days. Home based exercise (i.e. walking, dancing, perform arm exercises with rubber band) guided by a physiotherapist before start	MFI, SDS, HADS and Quality of Life Scale (QoL-scale)	Fatigue, QoL, psychological state and symptom distress	No increase in fatigue, trend towards increase in QoL and decrease in anxiety scores. The patients reported increased sense of satisfaction
Crevenna et al.	2002	Advanced hepacellular carcinoma (life expectancy not given)	1	Experimental pre-post design	Bicycle ergometer, twice a week for a 6-week period. Intensity: 60 % of the maximum work load at the exercise test for 20-35 min	SF-36, Grimsby's subjective score, symptom limited bicycle test, 6-minute walk test and self reported benefits	Feasibility, peak work capacity, self reported physical performance, HRQoL, self reported benefits	Improvement in HRQoL, pain, and vitality. Work capacity and 6-min walk increased by 20 %
Crevenna et al.	2002	Advanced breast cancer with inflammatory recurrence (life expectancy not given)	1	Experimental pre-post design	Cycle ergometer, 3 times a week for 4 weeks	SF-36 and EORTC-QLQ-C30, Grimsby's subjective score	HRQoL and work capacity	Improvement in all functional subscales, symptom scales fatigue, appetite loss, nausea and vomiting. VO_{2max} increased
Crevenna et al.	2003	Advanced breast cancer with metastatic disease (life expectancy not given)	1	Experimental pre-post design	Bicycle ergometer, 3 times per week, over 1 year, 60 % of the maximum work load at the exercise test	SF-36 and VO_{2max}	Feasibility and effects of aerobic exercise	HRQoL and VO_{2max} increased significantly from pre- to post-test

Authors	Publ. date	Sample	N	Design	Type of intervention	Questionnaires and methods of measurement	Outcome measure	Results
Segal et al.	2003	Palliative prostate cancer	60	RCT	Resistance training; 3 times per week, totally 12 weeks, 9 different exercises, 60-70 % of 1RM, 2 sets of 8-12 repetitions, control group	FACT-C and FACT-P, standard muscular fitness test, body weight, BMI, waist circumference, subcutaneous skinfold	Fatigue, HRQoL, muscular fitness and body composition	Significantly improvement in fatigue, HRQoL, muscular fitness and body composition in the intervention group compared to the controls
Headley et al.	2004	Advanced breast cancer	32	RCT	30 min seated exercise program at home (videotape), 3 times a week during 4 chemotherapy cycles, control group	FACIT-F	Fatigue and HRQoL	Significantly better physical wellbeing in the intervention group compared to the control group

BI = Barthel mobility Index, ADL = Activity of daily living, MFI = Multidimensional Fatigue Inventory, SDS = Symptom Distress Scale, HADS = Hospital Anxiety and Depression Scale, QOL scale = Quality of Life Scale, QoL = Quality of Life, SF-36 = Short form-36, HRQoL = Health Related Quality of Life, EORTC = Evaluation of Quality of Life, QLQ = Evaluation of Quality of Life, C 30 = Evaluation of Quality of Life, Grimsby's subjective score = Self-reported physical performance, VO_{2max} = Peak oxygen uptake, RCT = Randomised Clinical Trial, 1-RM = The maximum amount of weight that can be lifted once, FACT-C = Functional Assessment of Cancer Therapy-Fatigue, FACT-P = Functional Assessment of Cancer Therapy-Prostate scale, BMI = body mass index, FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue version

1.5.3 Physical exercise during cancer treatment

Several studies with both RCTs with usual–care controls and pre-post test designs with no controls, have examined the effects of exercise *during* cancer treatment. Female breast cancer patients are the most frequently studied patient group, but also groups of mixed cancers (e.g., breast, testicular, non-Hodgkin's lymphoma, Hodgkin's lymphoma and multiple myeloma), leukaemia patients, stomach cancer after surgery and colorectal cancer patients are studied. The most frequently tested intervention is aerobic exercise (Dimeo *et al.*, 1998; Dimeo *et al.*, 2004; Segal *et al.*, 2001; Courneya *et al.*, 2003), but resistance exercise has been tested in a few studies (Cunningham *et al.*, 1986; Segal RJ *et al.*, 2003). Studies on physical exercise during cancer treatment are of generally good quality consisting of RCT designs with appropriate controls, structured exercise and have an appropriate exercise stimulus (Oldervoll *et al.*, 2004; Courneya, 2003). The studies use a wide range of instruments to assess HRQoL and physical fitness. However, the studies indicate promising effects on both physiological and psychological outcomes. Schmitz el al. recently published a systematic review and the first meta-analysis of controlled physical exercise trials in cancer survivors (Schmitz *et al.*, 2005). Data from 32 studies were abstracted and weighted mean effect sizes were calculated from 22 high-quality studies. Because effect size could not be computed for all of the studies, a qualitative approach was also used to collate the data. These criteria indicated that there was strong evidence of a positive effect if there were at least three high quality studies with consistent statistically significant results (e.g., 75 % of the studies with statistically significant result, $p < .05$) and weak evidence if there were at least three high quality studies, with inconsistent results. They concluded that there is strong evidence of the effect on physiological outcomes and symptoms/side effects and weak to moderate evidence on the effects on cardiorespiratory fitness, quality of life, body size (goal to reduce), anxiety and depression, multiple constructs in cancer patients during treatment (Schmitz *et al.*, 2005).

1.5.4 Physical exercise immediately post-treatment

Few randomised studies of physical exercise in cancer patients have focused on the effect of exercise immediately *after* the treatment period (Thorsen *et al.*, 2005b; Courneya *et al.*, 2003; Burnham TR and Wilcox A, 2002). These three studies all found statistically improved cardio-respiratory fitness following the exercise period in the exercise groups compared to the control groups. Two of the studies found increased overall QoL and energy after exercise.

According to Schmitz's there is strong evidence for the effect on cardiorespiratory fitness and QoL and a weak to moderate evidence for effect on fatigue, vigour/vitality, psychosocial outcomes, body size (goal to reduce), depression and anxiety following a physical exercise programme after cancer treatment (Schmitz *et al.*, 2005).

2.0 Aims of the thesis

The aims of this thesis are to investigate the physical activity of Hodgkin's disease survivors (HDSs), as well as to investigate the feasibility and the effects of physical training in HDSs and in palliative cancer patients.

The research questions are as follows:

- What is the level of physical activity in HDSs with and without chronic fatigue compared to the general population?

- What is the effect of an aerobic exercise programme in chronic fatigued HDSs?

- Are palliative cancer patients willing and able to participate in an exercise programme and what are the effects of such a programme?

3.0 Material and methods

This thesis includes one cross-sectional study and two clinical intervention studies (A, B and C) presented in four papers (I-IV).

3.1 Study populations

Table 2 lists the samples, the number of patients in each study, the response rate, gender distribution and study design of the four in the thesis.

Table 2. Overview of samples included in the four papers

Sample	N	Response rate (%)	Gender (%) (M/F)	Design	Paper
General population	56999	71	47/53	Cross-sectional	I
HDSs-NRH	494	81	56/44	Cross-sectional	I
HDSs-St. Olavs	53	85	60/40	Intervention	II
Palliative patients	90	89	58/42	Intervention	III/IV

M = male, F = female

3.1.1 Hodgkin's disease survivors (HDSs-NRH)

The Hodgkin's disease survivors in paper I were recruited from the Norwegian Radium Hospital (NRH) in 2002. The eligibility criteria for this study included patients diagnosed for Hodgkin's disease in the period 1971-1997, who were 15 or older at the time of diagnosis and aged 18-74 in 2002. All patients should be in complete remission, without signs of secondary cancers and should not have received any treatment for Hodgkin's disease during the previous three years.

A total of 611 patients met the inclusion criteria. Ten patients were no longer registered at the Norwegian Census Bureau and could not be contacted. Another ten patients had recently participated in another postal survey on psychosocial late effects in another health region and

were therefore not contacted (study B). Hence, the 591 eligible patients were contacted by mail and received a questionnaire packet. A total of 479 patients returned the questionnaire. However, three patients had failed to fill in Fatigue questionnaire (FQ), and were excluded from the analyses. The overall response rate was 81 % (476/591).

3.1.2 Hodgkin's disease survivors (HDSs-St. Olavs)

The Hodgkin's disease survivors in paper II were recruited from the University Hospital in Trondheim. During a ten year period (1987-1997), patients treated for HD and alive without active disease in 1999 were invited to participate in this study. We identified 62 patients aged between 19 and 74. The study included three phases; phase 1 is a survey; phase 2 is an exercise- and medical examination and phase 3 is an intervention study (Fig. 2). They were approached by mail, and 53 patients completed the questionnaires after one written reminder (85 %). 18 of the 53 patients reported chronic fatigue (34 %) (*phase I*). These were invited to participate in medical examinations and physical exercise testing. 15 of the 18 chronic fatigued patients gave their consent to participate at this stage. The reasons for not participating were living too far away from the hospital (n = 2) and unknown reason (n = 1). 12 of the 15 patients completed the physical exercise testing and the medical examinations. One person did not show up in spite of two reminders. Two subjects underwent the medical examination, but were not able to perform the physical exercise test because of a splint in the leg (n = 1), and relapse of the malignant disease (n = 1) (*phase II*). After the medical examination and the exercise test, the cohort was invited to participate in an intervention consisting of aerobic exercise three times a week for 20 weeks. Nine of the 12 patients (4 women and 5 men) gave written informed consent and entered the intervention (*phase III*). Two men wanted to perform individual exercise themselves, but did not want to attend the programme. One woman was too ill to take part in the exercise programme. Immediately after the exercise period the same exercise test and questionnaire package as upon inclusion were completed.

Among the 35 non-fatigued HDSs who had completed the questionnaire, 15 patients of same gender and age ± 2years were drawn as controls. The controls underwent exercise testing and medical examinations identical to the one in the chronic fatigued survivors, but were not offered the training programme.

3.1.3 Palliative Cancer Patients

The patients in paper III and IV were recruited from two hospitals: (1) the outpatient departments at the palliative and the oncological unit at St. Olavs Hospital in Trondheim and (2) Hospice Lovisenberg day care centre in Oslo, Norway. Both curative and palliative patients are treated at the outpatient clinic at the oncological unit in Trondheim. Patients with incurable diseases, short life expectancy and multiple symptoms that require close medical and psychosocial follow-up are referred to the Palliative Unit. Patients at the hospice day care centre in Oslo are palliative patients referred from oncological wards, general practitioners or the patients themselves initiate the contact.

In two consecutive periods of five months, the outpatient lists at the palliative and oncological units were searched for patients receiving palliative cancer treatment with any cancer diagnosis and place of residence less than 30 minutes by car from the hospital. In the same period, a physiotherapist searched for patients at the hospice day care centre. The patient's medical consultant was contacted and sent a written request as to whether the patient filled the following inclusion criteria; palliative cancer patients with a life expectancy between three and twelve months, Karnofsky performance status (KPS) ≥ 60, who had adequate pain relief (score less than three on a 0 - 10 numerical rating scale), place of residence less than 30 minutes from the hospital, ability to walk or travel by themselves to and from the hospital by taxi, bus or private car. The patients were asked if they were willing to receive written information about the study. If so, information about the exercise study and an informed consent form was sent, and the patients were asked to provide information about cancer type, age and gender. If they did not want to attend, they were also asked to specify why. A stamped addressed envelope was enclosed. A total of 101 patients from both hospitals fulfilled the criteria.

The patients who returned the informed consent form and agreed to participate were contacted, included in the study and went through a physical examination and answered a questionnaire packet including FQ, EORTC QLQ-C30 and questions from the second cross sectional health survey in North-Trøndelag (HUNT 2) concerning level of physical activity and smoking (HUNT-Q). The same physical examination and questionnaires as upon inclusion were immediately after completing the exercise programme.

3.2 Reference population

3.2.1 General population

From 1995-1997, all inhabitants aged 18 and older in North-Trøndelag County were invited to participate in the second cross sectional health study of this county (HUNT-2) (www.hunt.ntnu.no). An invitation letter and a questionnaire packet that covered demographic variables, general health and lifestyle were sent by mail. Among those invited, approximately 65,000 responded (response rate 71 %) (Holmen *et al.*, 2003). Men and women aged between 21 and 74 when answering the questionnaire were included in paper I.

3.3 Outcome measures

Different objective and subjective outcome measures were used in this thesis and were adjusted to the different patient materials and study designs. The primary and secondary outcomes used in the papers are presented in Table 3. Further, the different questionnaires and measuring methods are presented in Table 5.

Table 3. Primary and secondary outcomes in papers I – IV

	I	II	III	IV
Patient recruitment and compliance		x	x	
Feasibility		x		x
Level of fatigue		x		x
Chronic fatigue	x	x		
Physical fitness		x		x
Physical functioning		x		x
HRQoL				x
LPA	x		x	
Sleep-pattern	x			
Smoking habits	x			
Patients subjective experiences of exercise				x

3.3.1 Objective outcome measures

Aerobic power (maximal oxygen uptake) (Study B, paper II)

Maximal oxygen uptake (VO_{2max}) was determined while the patients were walking/running on a treadmill. VO_{2max} was measured by use of a cardiopulmonary exercise testing instrument (Vmax29, Sensomedics, Netherlands).The Oslo protocol was used for assessment of VO_{2max} (Fredriksen *et al.*, 1998). The test protocol is presented in Table 4 and was carried out until exhaustion. Oxygen uptake and heart rate (HR) were measured continuously on each speed and inclination. The heart rate was measured continuously during the test using a Polar Sport tester PE 3000.

Table 4. Treadmill protocol

Minutes	2	4	6	8	10	12	14	16	18	20
Km/h / % inclin.	5/2	6/2	6/5	7/5	7/8.5	8/8.5	8/10.5	9/10.5	9/13	10/13
VO_2/kg										
HR										

Lung function measurements (Study B, paper II)

The lung function test included dynamic spirometer, i.e. the determination of ventilatory capacity per time unit. The subjects breathed into a low resistance spirometer. For the determination of forced expiratory volume (FEV), the subjects first took a deep breath and inspired maximally. The subject then exhaled as forcefully and completely as possible. In this way it is determined how much of a person's vital capacity can be exhaled in the course of 1 s (FEV_1) is determined, and this volume is expressed as a percentage of the individual's entire vital capacity. The tests were performed using Vmax29 testing instrument (Vmax29, Sensomedics, Netherlands). Spirometric variables were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and FEV_1 expressed as percent of FVC (FEV_1 %).

Simmonds' test battery (Study C, paper IV)

In paper IV, physical performance was measured by three tests (6-minute walk, sit to stand and functional reach) from a performance test battery developed for patients with cancer (Simmonds, 2002). The testing order of sit to stand and functional reach were random, the 6-minute walk was always performed as the last test.

6-minute walk test

This test measures the distance covered by walking for 6 minutes. The test was originally developed to assess tolerance among individuals with respiratory disease. Patients were instructed to walk as long and fast as they could for six minutes. The subjects walked back and forth a 50 meter long corridor. Patients were allowed to rest as necessary during the 6-minute period. The heart rate was monitored continuously during the test using a Polar Sport tester PE 3000. The heart rate was monitored during the test and immediately after they stopped. Rating of perceived exertion was monitored and the distance walked in meters at the end of the 6-minutes was registered.

Timed sit-to-stand (STS)

Subjects sat on a 46-cm high hardback chair without armrests, with their arms folded. Patients who were unable to rise from the chair with their arms folded were allowed to use their arms. The patients were instructed to use their arms as little as possible. They were told to stand up and sit down twice as fast as they were able to. A stop watch was used to record the time. The test was repeated three times with a brief rest between each test and the average time of the two last trials was used as the outcome.

Functional reach (measure of balance)

Functional reach was measured using the simple clinical apparatus consisting of a levelled meter stick, which had been mounted horizontally to the wall at right acromion height of the patient. In order to maintain identical foot placement during all testing conditions, the foot position was traced on a sheet of paper attached to the floor. The patients were asked to make a fist and extend their right arm forward and the position of the third metacarpal was recorded (position 1). Alternatively the left arm was used in case of limitations with the right arm. Patients were then asked to reach as far forward as they could without losing their balance or taking a step (position 2), and the placement of the end of the third metacarpal was again recorded. No attempt was made to control the subjects' methods of reach. Functional reach

was defined as the mean difference in centimetres between position 1 and 2. The test was repeated three times with a brief rest between each test and the average length of the two last trials was used as the outcome.

3.3.2 Subjective outcome measures

Fatigue questionnaire (FQ) (Study A, B and C, paper I, II and IV)

Fatigue was assessed by the Norwegian version of the Fatigue Questionnaire (FQ) (Chalder *et al.*, 1993). The FQ is a domain specific, self-reported instrument for the assessment of fatigue including symptoms experienced during the last month, compared with how the subject felt when last feeling well. Additionally, two items ask about the duration and extent of fatigue. FQ measures physical fatigue (PF) (seven items) and mental fatigue (MF) (four items). All 11 items are designated total fatigue (TF). Each item has four response choices with a Likert-scoring (0, 1, 2, 3) for summarising PF, MF and TF respectively. Higher scores imply more fatigue. A dichotomised score (0, 0, 1, 1) is used for the definition of chronic fatigue, which is defined by the sum of dichotomised scores ≥ 4 and a duration of six months or longer. In this thesis the definition chronic fatigue is used in papers I and II, while we report mean levels of MF, PF and TF in papers II and IV. The FQ has originally been validated in primary care and has shown good face and discriminant validity. No specific validation study has been performed in cancer patients. However, the FQ has been used in studies among HDSs and in patients with prostate cancer receiving hormonal therapy (Loge *et al.*, 1999a; Stone *et al.*, 2000a). The psychometric properties demonstrated in these studies correspond well with reports from a validation study and from the studies in non-cancer populations. Fatigue was the primary outcome in paper II and secondary outcome in paper IV. Number of patients with chronic fatigue is reported in papers I and III.

Table 5. Self-report questionnaires and measuring methods used in papers I – IV

	I	II	III	IV
FQ	x	x		x
SF-36		x		
EORTC QLQ-C30				x
Spirometer		x		
Simmonds' test battery				x
HUNT-Q	x		x	
VO_{2max}		x		
SE			x	

Short Form-36 (SF-36) (Study B, paper II)

The SF-36 is a widely used generic HRQoL-measure (Ware *et al.*, 1995). The items are grouped into eight subscales: physical functioning (PF), role limitations due to physical problems (RP), social functioning (SF), role limitations due to emotional problems (RE), bodily pain (BP), mental health (MH), vitality (VT) and general health perceptions (GH). An additional item (HT) reports health transition. The responses were summed and transformed to a 0 - 100 scale (0 = worst health state, 100 = best health state) according to the SF-36 algorithm (1994). The subscale PF was a secondary outcome in paper II and was assessed before and immediately after the intervention.

The European Organisation for Research and Treatment in Cancer (EORTC QLQ-C30) (Study C, paper IV)

In paper IV, health related quality of life was assessed by the EORTC QLQ-C30, version 3.0 immediately before and after the intervention. The EORTC QLQ-C30 includes a total of 30 items and is composed of scales that evaluate physical function (5 items), emotional (4 items), role (2 items), cognitive (2 items) and social (2 items), as well as global health status (2 items). Higher scores on these scales represent better functioning. There are three symptom scales measuring nausea and vomiting (2 items), fatigue (3 items) and pain (2 items), and six

single items assessing financial impact and various physical symptoms. Higher mean values on the symptom scales/items mean more symptoms. Before statistical analyses are made, the raw EORTC QLQ-C30 scores are linearly transformed to 0 – 100 scales (Kaasa *et al.*, 1995; Aaronson *et al.*, 1993). A mean change in scores of five to 10 has been found to represent little subjective change to the patients, while a change of 10 to 20 represents a moderate change, thus differences of 10 points or more may be regarded as clinically significant (Osoba *et al.*, 1998). Physical- and emotional functioning and fatigue were defined as the HRQoL endpoints in paper IV.

Level of physical activity (LPA) (Study A and C, paper I and III)

LPA was assessed by a single question: "How has your physical activity level in your leisure time been the last year?" (Estimate a weekly average for the year, walking to work counts as leisure time). The response categories reflect two *intensities* (levels) of activity; one describing a low-level activity (not leading to sweating and breathlessness) such as walking, and the other a high level activity that leads to sweating and breathlessness. The response categories reflect four levels of *duration* of physical activity per week, no activity, less than one hour a week, between one and two hours per week and three hours or more per week. The four levels are no activity, less than one hour a week, between one and two hours per week and three hours and more per week (Fig. 1) (Thorsen *et al.*, 2003).

Question: How has your physical activity level been in your leisure time the last year? (Estimate a weekly average for the year, walking to work counts as leisure time)

Response categories	Hours per week			
	No	< 1	1-2	≥ 3
Low-level activity (not sweaty/breathless)				
High-level activity (sweaty/breathless)				

"Inactive" "Minimally active" "Highly active"

Figure 1. Level of physical activity (LPA)

Smoking-habits and sleep-pattern (Study A, paper I)

To investigate daily smoking habits (yes versus no) and sleep pattern, questions were chosen from the HUNT-2 study (http://www.hunt.ntnu.no) with identical wording (Holmen *et al.*, 2003).

Self-reported Evaluation (SE) (Study C, paper III)

In paper III, the patient's experience of attending the exercise program was registered by seven questions specifically designed for this study. The following questions were included:

1. How satisfied were you with attending the exercise sessions? Response alternatives: 1 was 'extremely satisfied' to 7 'not satisfied'.
2. Where would you prefer to do the exercise programme? Response alternatives (a) at home (b) at the hospital or hospice (c) combination of hospital, hospice and at home (d) out patient clinic, rehabilitation clinic, somewhere else
3. Would you recommend group exercise to others who are in a similar situation as yourself?
4. Would you prefer individual follow-up instead of in a group

5. Would you consider continuing with a similar type of physical exercise?
   Response alternatives for questions 3, 4 and 5 were 'yes' or 'no'.
6. Is there anything you can manage now that you couldn't manage before you started in the exercise group?
7. Comments.
   Questions 6 and 7 were open-ended.

3.3.3 Other background measures

In the analyses we also included demographic variables such as gender, age, marital status, educational level, work situation and weight and/or body mass index (BMI = bodyweight/(height)^2). Relevant clinical variables in the two HDSs-samples, such as date of diagnosis, stage, histology, treatment and current disease status (relapse or not) were retrieved from the Hodgkin's database at respectively NRH and St. Olavs Hospital.

Among the sample of palliative cancer patients, information about primary cancer diagnosis, Karnofsky Performance Status Scale (KPS), previous and ongoing tumour treatment, metastatic disease, medication and co-morbidity were extracted from the patients' medical records. The patients provided supplementary demographic information at a pre-assessment session in the week before start of the intervention. A blood sample was taken to determine haemoglobin-, albumin- and C-reactive protein (CRP)-levels before entering the programme.

The KPS is an observer rated scale which is frequently used to evaluate the physical function in patients and their medical care requirements. It is a general measure of patients' independence and has been widely used as a general assessment of patient with cancer. It contains 11 categories going from 0 % which means death to 100 % which indicates normal performance. The KPS has shown good validity as a global indicator of the functional status of patients with cancer (Yates *et al.*, 1980). The KPS was filled in by clinicians before inclusion in study C.

3.4 Intervention procedures

Two different physical exercise interventions on two different cancer populations were tested in this thesis: a home-base exercise programme among chronically fatigued HDSs (study B)

and a hospital-based group exercise programme among palliative cancer care patients (study C).

3.4.1 Aerobic exercise intervention (HDSs-St. Olav)

The patients lived in south- and north Trøndelag and Møre and Romsdal counties. An exercise instructor visited the patients in their local community at the start of the intervention period. The patients were given instructions and advice for their home-based exercise programme. Every patient received a Polar Sport Tester which recorded and stored the heart rate (HR) every fifteenth second during the exercise session. Follow-up phone calls were made regularly to motivate, guide and regulate the intensity of the exercise programme.

The aerobic endurance exercise programme consisted of 20 weeks with an exercise session of 40-60 min continuous work using large muscle groups at an intensity of 65-80 % of the subjects' target heart rate (measured at the first test) three times a week. Instructions were given to divide the session up into intervals with low to moderate/high intensity during the session. An exercise diary filled in by the patients contained information on the duration, type of activity as well as the patients' experience of the exercise sessions classified as 'easy', 'somewhat strenuous' or 'strenuous'. The activities included brisk walking, jogging, cycling, aerobics, cross-country skiing or swimming. The attainment target for compliance was 75 % of the aerobic exercise programme. This is considered to be the minimum attendance accepted in other, similar studies.

3.4.2 Circuit training intervention (palliative patients)

The participants met with the physiotherapist to start in the intervention group within a week after the pre-assessment session and were introduced to their personalised circuit-training programme. Six different exercises were included in the circuit. The programme consisted of exercises in groups of 3-8 patients. The patients participated twice a week, for approximately 50 minutes each session for a total of six weeks. An important aim for the group training was to make exercises individually tailored with respect to type as well as level of difficulty. The programme consisted of a warm up session (10 minutes), circuit-training with six stations (30 minutes) and relaxation/stretching sessions (10 minutes). At each of the six stations, exercises were performed for 2 minutes, with a 30-second pause moving on to the next station. The

main focus was mainly on lower and upper limb muscle strength, in addition to standing balance and aerobic endurance. Each station had a "set" series of exercises, with the possibility for adjustments according to the individual patient's physical function. The warm-up session was aerobic exercise using large muscle groups in an upright or sitting position, alternatively using a static exercise bike. The six stations in the circuit programme were as follow; (1) different strength exercises for the lower limbs (2) balance exercises on trampoline/thick mat (3) resistance exercises for the arms using pullies or rubber bands (4) rise and descend from/to the floor. Alternatively for patients who were able to, abdominal and back exercises with progression were included (5) step up and down on a step (6) use of an exercise bike. To be included in the analyses, the patients should have participated in a minimum of six sessions.

3.5 Ethics

The Regional Committee for Medical Research Ethics in Central and Southern Norway approved the protocol for participants reported in study A, B and C. Participants in these studies provided written informed consent.

3.6 Statistical analyses

All statistical analyses was performed using the SPSS statistical software versions 8.0 and 12.0 (SPSS inc., Chicago, Il, USA). The statistical methods are described in each of the four papers. Comparisons between groups were performed by Fisher's exact test for nominal variables and chi square test for trend (linear-by-linear test) for ordinal variables, and t-tests for scale variables. Paired sample t-tests were used to detect differences from pre to post in the two intervention studies. The .05 criteria were used to define statistically significant effects.

In study B, analysis was carried out on an intention to treat basis. Since both study B and C were phase II studies, we broadly wanted to study whether it was possible to note changes in any effect measures. Any formal sample size calculation was therefore not completed in preparation for these studies.

Comparisons between groups were performed by Fisher's exact test for nominal variables, chi square test for trend (linear-by-linear test) for ordinal variables, and t-tests for scale variables. P-values < .05 were considered statistically significant.

In study A, a logistic regression analysis with physically active (yes versus no) as the dependent variable was performed in the analysis comparing the HUNT-2 population with the HDSs, adjusting for the covariates age, group (HDSs/HUNT-2) and educational level. The odds ratio (OR) are presented as estimates and 95 % Confidence Intervals (95 % CI). All tests are two-sided. The analysis was assessed in the entire population (men and women) and men and women separately. Possible interactions were checked, as well as linearity in age. Significant interactions (only including gender) were accounted for by using separate analyses for men and women.

4.0 Main results (summary of papers)

4.1 Paper I

Self-reported levels of physical activity, smoking habits and sleep pattern in Hodgkin's disease survivors compared to the general population

This study addresses whether life-style parameters such as level of physical activity, smoking and sleep disruption may be associated with chronic fatigue in HDSs. We also compared the results from the HDSs to the general population (Gen-pop). The level of physical activity, smoking habits and sleep pattern did not differ between HDSs with and without chronic fatigue. The fatigued and the non-fatigued HDS were therefore combined into one group and compared with men and women from the general population. The two cohorts did not differ in age, however, there was a significantly higher proportion of men (56 % vs. 44 %), more individuals with higher education (37 % vs.21 %), a lower proportion of smokers (25 % vs. 31 %) and significantly more individuals who were highly active (48 % vs. 25 %) among HDSs compared to the general population. On the contrary, the HDSs reported significantly more problems falling asleep and more early wakening than the general population. Because of interaction, separate analyses were done for men and women. A multivariate logistical regression analysis with physical active (yes/no) as the dependent variable, adjusting for age, education, smoking and early wakening showed that HDSs males were significantly more physically active than Gen-pop (76 % vs. 86 %), OR = 1.5, (95 % CI 1.04 – 2.17), $p = .031$, while no such difference was found among females (73 % vs. 78 %), OR = 1.2 (95 % CI 0.83 – 1.74)., $p = .33$. In the entire sample, the level of physical activity increased with increasing level of education, decreased with increasing age, was lower among smokers, and physically active individuals reported less sleep disturbance than inactive. These results indicate that the chronic fatigue in HDSs is not due to excessive rest.

4.2 Paper II

Exercise reduces fatigue in chronic fatigued Hodgkin's disease survivors – results from a pilot study

In this study aerobic exercise capacity (VO_{2peak}) and lung function (spirometric variables) were tested in a group of chronic fatigued HDSs (n = 12) and compared to the results from a group of age and gender matched HDSs (n = 15) without chronic fatigue. Further, we investigated the effects of a 20 weeks home-based aerobic endurance exercise program on fatigue levels (measured by Fatigue Questionnaire), self reported physical functioning (measured by physical functioning subscale in SF-36) and VO_{2peak} in the group of chronic fatigued HDSs. The flow chart of the survey and the intervention patients is presented in Fig. 2. No statistically significant differences were seen in VO_{2peak} between the chronic fatigued versus the non-fatigued survivors. Spirometric variables did not differ significantly, except for forced vital capacity (FVC), being significantly lower in the HDS group without fatigue. However, both groups scored within the normal range. Following the intervention period, the total (TF), physical (PF) and mental fatigue (MF) scores were all significantly and clinically reduced (44 %), TF: 21.5 to12.1 (min 0 – max 33); PF: 14.0 to 7.9 (min 0 – max 21) and MF: 7.5 to 4.2 (min 0 – max 12). Seven of the nine patients were below the threshold for chronic fatigue after completing the intervention. VO_{2peak} increased from 33.9 $mlkg^{-1}min^{-1}$ to 36 $mlkg^{-1}min^{-1}$ and time to exhaustion on treadmill increased by 110 seconds (p = .04) from before to after the intervention. Self-reported physical functioning improved significantly from 82.2 to 89.4 on a 0 - 100 scale (p = .04). Aerobic exercise had a positive effect upon total-, physical- and metal fatigue in HDSs, however, the number of patients in the trial was low and the study needs confirmation in a randomised trial.

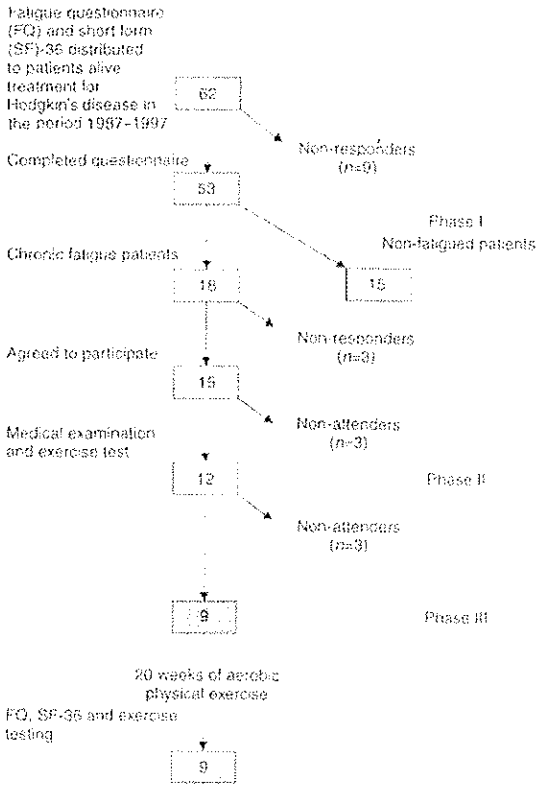

Figure 2. Flow chart of the survey and intervention patients in study B

4.3 Paper III

Are palliative cancer patients willing and able to participate in a physical exercise programme?

This study addresses the challenge of recruitment, attrition and compliance concerning participation in a physical exercise programme among palliative care patients with life expectancy of less than one year. Flow chart of patient recruitment, attrition and compliance is presented in Fig. 3. The invited sample consisted of 101 patients, 42 males and 59 females with mean age 66 and KPS 81. Sixty-three patients agreed to participate. Hence, a total of thirty-eight patients did not respond (n = 11) or did not want to participate (n = 27) and were significantly older than those who agreed to participate. No significant differences were found with gender and KPS. Sixteen of the 63 patients, 12 males/4 females, mean age 65 and KPS 82 dropped out after consent was given, but before the programme started due to medical or social reasons or death. Thus 47 patients started in the exercise intervention. Thirteen patients (28 %) dropped out during the exercise period due to sudden death (n = 1), medical (n = 10) or social reasons (n = 2). The most frequent reasons for withdrawal were considerable disease progression (n = 5) and pain (n = 5). Thirty-four patients (19 females and 15 males) completed the exercise programme (mean age 65 and KPS 83). No significant differences were found with KPS, gender, motivation and previous physical activity habits. Seventy-three % of the patients reported to be extremely satisfied attending the programme and all would recommend other patients in same situation to attend. Seventy seven percent of the patients preferred to do the exercises in a group with other patients. The compliers reported that they found the exercise programme useful, that it gave them improved coping skills and increased their well-being. A high proportion of incurable cancer patients are willing to participate (63 %) in a structured exercise programme. The attrition rate was high, but despite being severely ill, 54 % of the patients completed the exercise period.

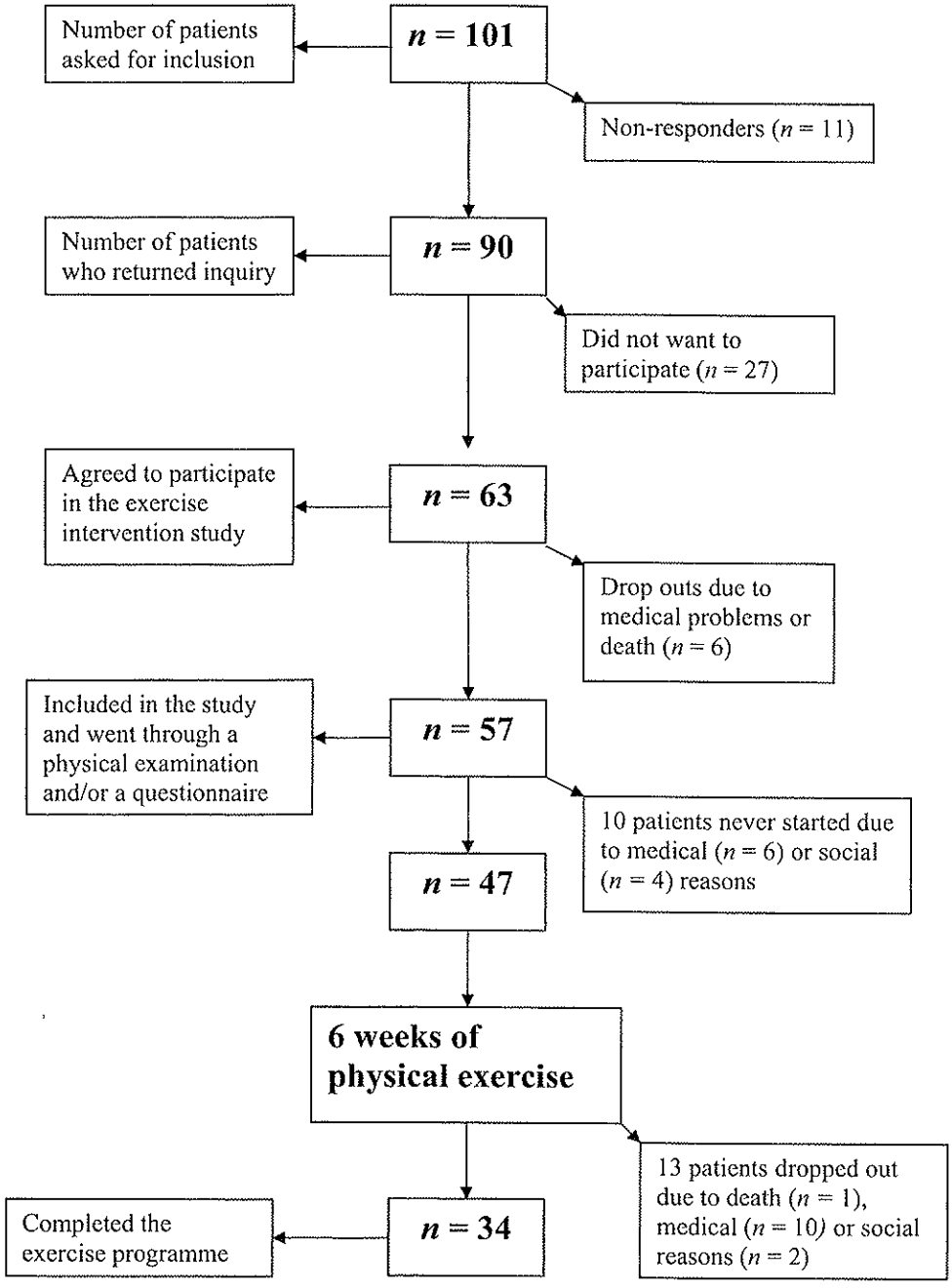

Figure 3. Flow chart of patient recruitment, attrition and compliance in study C

4.4 Paper IV

The effect of a physical exercise programme in palliative care; a phase II study

In this pilot study we investigated the effects of a six-week physical exercise programme on physical fitness and quality of life (QoL) on incurable cancer patients with short life expectancy. The patient sample consisted of 15 males and 19 females with a mean age of 65. Four patients were working full or part time, while the remaining patients were not employed. The median KPS was 80 and the population consisted of different cancer types with gastrointestinal cancer as the most frequent. During the six-week period the mean adherence rate to exercise sessions was 10.6 sessions. Following the exercise intervention period, emotional functioning was improved from 69 to 79 ($p = .002$). The mean score on the fatigue subscale of the EORTC QLQ-C30 went down from 51 to 43 ($p = .06$), and mean scores on the FQ subscales for physical fatigue and total fatigue were reduced from 12.2 to 10.4 ($p = .04$) and 17.5 to 15.5 ($p = .06$) respectively. Mental fatigue scores remained unchanged. Physical functioning and global QoL remained stable. Dyspnoea was reduced from 42 to 30 ($p = .006$), role functioning and social functioning improved from 50 to 63 ($p = .02$) and from 55 to 65 ($p = .008$) respectively. The walk length (6-min walk) increased by 29 meters from 481 meters to 510 meters ($p = .007$) and "timed repeated sit to stand" was reduced from 5 seconds to 4 seconds ($p = .001$). The results from the study are promising and physical exercise seems to be a feasible way to improve well-being and physical fitness among incurable cancer patients. However, future randomised trials with fewer and more specific endpoints are needed to confirm the results.

5.0 Discussion

This thesis includes one study with cross-sectional design and two clinical studies. The overall aim is to increase the knowledge of the impact of physical exercise on cancer survivors as well as cancer patients in a palliative stage of their disease. The following section discusses the methodological strengths and limitations related to the study designs, recruitment process into the intervention (representability of the samples) and the assessment issues related to the outcome measures. Finally, the discussion rounds up with the main findings and clinical implications of the various studies in the thesis.

5.1 Methodological considerations

The **validity** of a study is often divided into **internal and external** validity. The internal validity is defined as the degree to which the results are representative for the particular cohort being studied. External validity is about whether the results are applicable to other populations (Benestad HB and Laake P, 2004). Both aspects of validity are important to determine whether clinical studies can be used to guide clinical practice.

5.1.1 Study design

Cross-sectional study

Cross-sectional studies are suitable for descriptive analysis and for detection of differences between samples. Further, the cross-sectional design may be used to estimate associations between variables that are measured at the same time, but is unsuitable for conclusions about cause and effect (Rothman K and Greenland S, 1998; Pocock, 1996; Altman DG, 1997). Thus, this design can generate hypotheses about causal effects to be investigated in studies with other designs, for example RCTs. The cross-sectional design was considered appropriate for the aims in paper I. However, the cross-sectional design in this study imposes limitations regarding *response rate and inclusion criteria.* A representative sample can never be "guaranteed" and the ability to generalise the results from the study may be limited. Non-responders can cause a possible bias, because those who do not respond to the questionnaire

(non-responders) are usually less healthy, sometimes described as *volunteer bias* (Benestad HB and Laake P, 2004).

Many cross-sectional studies obtain all or most of their information from postal questionnaires. The recruitment of patients in papers I and II was performed by postal questionnaires with one written reminder if they did not respond after the first mailing. In paper I, the response rate was 81 % in the HDSs population,which is considered to be fairly high. This response rate is similar to other studies with cross sectional designs among cancer patients (Thorsen *et al.*, 2003; Thorsen *et al.*, 2005a; Nord *et al.*, 2005).There were more males than females among the non-responders (21 % v 14.5 %; $p < .05$), whereas no significant differences were found with age, observation time, primary treatment, and relapse between responders and non-responders (Hjermstad *et al.*, 2005). The response rate to the questionnaire in paper II (HDSs-St. Olavs) was 85 %. The non-respondents tended to be younger than the respondents (35 vs 42), but the difference did not reach statistical significance. There were no statistically significant differences between responders and non-responders regarding gender, stage/substage, primary treatment, primary treatment or time from diagnosis. Since the response rate was fairly high in both studies I and II, we believe that results from these two studies are valid for HDSs in general. However, we do not know whether the non-responders are less healthy than the responders, for instance whether they report more or less fatigue, or report being less physically active than the responders.

Due to the cross-sectional design of paper I, we cannot conclude about the stability of the findings. This may relate to the measures or the states being measured. However, in both FQ and LPA there is a question about duration (respectively the last year and 6 months or more). This might indicate that the measures included in these instruments are relatively stable.

The reference population used in study A was from the HUNT-2 survey. The response rate was 70 % which is considered highly satisfactory for a general population survey. The non-participants in HUNT-2 survey were mostly relatively young or old and unmarried compared to the participants (Holmen *et al.*, 1990). North-Trøndelag County is located in the middle of Norway. The population of North-Trøndelag County was 127,500 in 1995 (a total of 4.4 million in Norway). The population is relatively stable and the geographic, demographic and occupational structure is fairly representative of the whole of Norway. However, the county has coastal and inland areas, but lacks densely populated areas and larger cities above 50,000

residents. The educational- and income level is lower than the national average. Despite these limitations, findings from two previous HUNT-surveys are used for extensive generalisation to the Norwegian population at large, and a new HUNT survey is currently being launched. The HUNT-2 survey was completed in 1995, while the HDSs survey was completed in 2001. Data from the HUNT-2 may therefore have influenced the results, in particular regarding physical activity. Our way of living has changed over the last 10-20 years, spending more time in cars and in front of the televisions and computers. Daily demands of physical capacity, activities of daily living and physical activity patterns have changed. Studies report that daily physical activities have decreased, while exercise leading to sweating has increased during this period (Kurtze N *et al.*, 2001). As regards to the reference data used in study A, collected in the period 1995 to 1997, these data may be out of date.

Clinical intervention trials

Randomised controlled trials (RCT) are usually taken as the "gold standard" to prove causality in clinical trials. The advantages with controlled clinical trials compared to epidemiological studies are that the randomisation and blinding exclude external factors that affect/influence the results from the study (confounding) (Pocock, 1996). It is possible to draw conclusions about a direct association between the intervention and the effect. Against this background, one can say that controlled clinical trials have a high **internal validity.** A drawback in controlled clinical trials is that they may have a **low external validity**. In clinical trials strict criteria for inclusion of patients, regarding age, co-morbidity, performance status, etc. is a threat to the external validity and may reduce the generalisability of the results. It may be reasonable to question the generalisation of a study if only a small number of the relevant patients who fulfil the inclusion/exclusion criteria are included. Some patients refuse inclusion, other times the patient's doctor may have an opinion that this treatment is not useful for the patient (so called 'gatekeeping'). Such exclusions may lead to **selection bias** that may weaken the generalisation of the results from the clinical trials. Thus, strict inclusion criteria result in a selective group with special properties of the target patient population and it is not obvious that the result can be applied to the target population as a whole.

A blinded design is preferred in a therapeutic RCT. However, blinded RCTs in physical exercise interventions are generally not feasible. The consciousness of being randomised into a physical exercise study may influence the physical activity level of the patients included in the trial.

In this thesis, both intervention trials are phase II studies. Phase II trials are initial clinical investigations for treatment effect (Pocock, 1996). These are fairly small-scale investigations that are completed before starting a randomised controlled trial. Phase II studies are required to test the feasibility, effectiveness and safety of a specific intervention and are necessary to complete before a full-scale evaluation of the treatment can be actuated (phase III studies). After an intervention is shown to be reasonably effective, it is essential to compare it with the current standard treatment for the same condition in a large trial involving a substantial number of patients (such as a RCT).

Based on the few intervention studies published in both long term cancer survivors and palliative cancer patients, we initiated phase II studies to test the feasibility of the physical exercise interventions in these two patient populations. Since phase II studies are primarily feasibility studies, there are several limitations that should be considered concerning the effects on psychological and physiological outcomes from such studies. The two intervention studies in this thesis have a pre-post design with no control group. The results from the studies should be interpreted with caution, because of the small number of patients included in the studies and the lack of a control group. We cannot rule out that the effects are due to the attention the patients received from the health personnel or simply the consciousness of being included in a physical exercise trial. Thus, the positive effects of the intervention programmes could be explained by one or both of the following factors: 1) the content of the exercise programme and/or 2) psycho-social effects. It is possible that the patients who took part in the training regarded the project as a positive venture, something that, again, led to increased physical and psychological well-being.

Two different intervention procedures were tested in this thesis. Patients with chronic fatigue received a home visit and exercised *individually* at home (study B). They received regular phone calls from an exercise physiologist during the exercise period. They also completed an exercise diary and a pulse watch was used to record the intensity of each exercise sessions. Consequently, they received attention and support which may have influenced the results. In study C the patients attended a *group exercise* lead by a physiotherapist. One ought to consider the practical and psychological support which participants in the exercise group are able to give to each other, in addition to the relationship to and support from the physiotherapists. Thus, this could be considered a possible Hawthorne-effect (non-specific

placebo effect) in both of the intervention studies. The psychological and physiological effects from the two intervention studies in this thesis are therefore considered to be preliminary results that need replication in randomised designs.

5.1.2 Recruitment process

Exercise presupposes personal commitment related to motivation, ability and will. Low participation rates in intervention programmes (e.g. compliance) and motivation to continue training may influence the programme's impact.

The recruitment process in the two intervention studies differed. In study B, the recruitment of patients was through postal questionnaires, whereas the patients in study C were mainly recruited via the patients' medical records and medical consultant (paper III and IV). In paper II,, the primary aim was to study the effect of physical exercise on fatigue among chronic fatigued HDSs. Thus, we selected those patients who reported having high levels of fatigue for six months or more. Eighteen of 53 patients (34 %) who returned the FQ reported chronic fatigue. 15 of them agreed to participate, and 12 of 15 completed the physical exercise testing. Nine of these 18 patients started and completed the 20 weeks exercise intervention. Consequently 50 % of the chronic fatigued dropped out or did not agree to participate. This raises one important question, whether the exercise training was performed for a selected group only? Is it a selective group of "pleasers" who enter in and complete the programme? Except for a borderline significance of a higher proportion of university education in the intervention group ($N = 9$) compared to the non-attendees ($N = 9$), no differences were found with gender, age, relapse, primary treatment, marital status, work situation, time since treatment, fatigue scores, physical functioning or work situation. Attendance in exercise depends on factors such as motivation, education, knowledge of, and belief in the beneficial health effects of physical exercise (Dishman DK, 1990). Unfortunately, we do not have information about earlier exercise habits among the patients in study B. It is therefore reasonable to assume that the results from the study pertain to a somewhat selected population of chronic fatigued HDSs who are motivated to exercise. But it does not necessarily underscore the potential benefit of such a training programme to others – if one is able to motivate the entire cohort.

The recruitment of palliative care patients into study C was challenging. However, due to a relatively thorough procedure, we believe that the sample in this study is fairly representative for the palliative population. The inclusion criteria were wide and the patients were included from two different hospitals; Hospice Lovisenberg and St. Olavs Hospital. Patients at Hospice Lovisenberg day care centre are palliative patients referred from oncological wards; general practitioners or patients themselves initiate the contact. During their stay at the day care centre (twice a week) they are offered to take part in different activities. Because of the self-selection to the day care centre the patients may not be representative for the palliative population at large. At St. Olavs Hospital, the outpatient lists at the palliative and oncological units were searched for patients receiving palliative cancer treatment and place of residence less than 30 minutes from the hospital. The patient's medical consultant was contacted with a written request as to whether the patient filled the inclusion criteria of the study. The medical doctor then returned the request, and noted if the patient filled the inclusion criteria of the study. We then called up the patients, gave them information about the ongoing study and asked if they consented to written information being sent to them. They then returned the form and were asked to specify why if they did not want to attend. Because of this recruitment strategy, we believe the cohort is fairly representative for the palliative cancer care population. However, we cannot rule out the incidence of 'gatekeeping', since we do not have exact information about how many number of forms that were not returned. One could suspect that we have a selected sample being especially interested in physical activity. However, compared to the HUNT population, the self-reported level of physical activity was at about the same level (paper I).

Recruitment of cancer patients into physical exercise studies demonstrate that a high percentage of the patients that were assessed for eligibility, declined for various reasons (57 %) (Oldervoll *et al.*, 2004). However, different studies differ greatly in their descriptions of recruitment and adherence. There is no reason to believe/expect that all patients wish to attend a physical exercise programme and results from exercise studies may pertain to a selected population of cancer patients. However, we were surprised at how many patients who expressed a wish to train and get fit again after different treatment regimens, and the group was heterogeneous with regard to age, fitness level, education and life time expectancy.

5.1.3 Assessment related to outcome measures

An important issue in research is to choose an instrument in accordance with the research questions. Instruments should capture those factors that the intervention is likely to affect. When planning and completing a physical exercise intervention, there is a need to choose outcome measures that are related to the type of exercise performed and the aim of the study.

Level of physical activity (LPA)

Level of physical activity was the primary outcome in paper I and was used as a background variable in paper III. The physical activity items were chosen from the HUNT survey, to be able to compare the data on a physical activity level against the general population. To obtain valid and objective estimates of physical activity levels in large populations are difficult, and the only useful method in practice is self-reported questionnaires. The main weaknesses in paper I relate to the accuracy of the physical activity measurement. The questions were not validated when we started our study, however a post doctoral student (Kurtze) at the research department at the North-Trøndelag health survey is at the moment undertaking a validation study on the physical activity items in HUNT-2 against VO_{2max}, ActiReg and the International Activity Questionnaire (IPAQ) (Anderssen SA and Andersen LB, 2004; Hustvedt *et al.*, 2004). In the present study, LPA was evaluated by frequency, duration, intensity and regularity of physical activity using a two-step question. One major limit with these questions is that the items give no information about the type of activity the individuals undertake. In the logistic regression analysis, patients were divided into 'physically active' and 'physically inactive' individuals. This is considered to be as valid as using more detailed answer categories (Schechtman *et al.*, 1991; Gionet and Godin, 1989). However, it is possible that this division is too broad to notice the important differences in this study.

However, the ability to remember is a particular drawback in questionnaires measuring physical activity. It is more reasonable to believe that individuals have better memory regarding high-level activities than low-level activities such as gardening, household work and walking. Although this might cause a recall bias, there is no reason to believe that HDSs report differently from the general population. However, we cannot exclude the possibility that cancer survivors after a life-threatening disease become more health conscious and therefore are more prone to report physical activity.

A possible misclassification may exist in that the two populations may have interpreted the LPA questions differently. In another publication from the same sample, we found a significantly poorer QoL measured by SF-36 compared to the normal population. They had lower scores on six of eight SF-36 scales including physical functioning (Hjermstad MJ *et al.*, 2006). HDSs might therefore report a high LPA, since they become sweaty and breathless earlier due to reduced general health condition.

Physical fitness

VO $_{2max}$ measured directly is the "gold standard" of a person's cardiovascular capacity. The test is strenuous and based on a maximal effort on treadmill or static bicycle (Åstrand PO and Rodahl K, 1986). In paper II VO_{2max} was used as a proxy outcome to measure the effect of the exercise programme on cardiovascular capacity. However, different test procedures measuring heart rate on sub-maximal load before and after an intervention may be a useful tool for evaluating whether the training programme has been effective in improving the patient's circulatory capacity. The advantage in measuring the VO_{2max} directly is that the results can be used to compare the individual's own performance to the other individuals. Measuring VO_{2max} gives useful information about the physiological effects of the programme, but yields no direct information about the patient's symptoms and well-being. Based on these considerations, we believe that aerobic capacity is best regarded as a proxy variable, and not as a primary endpoint in intervention studies among cancer patients.

Choosing tests to measure the effects of an exercise program on physical fitness in palliative cancer patients were challenging. In paper IV, we chose to use three tests from a performance battery of nine physical performance tests for cancer patients were (Simmonds, 2002). The tests were simple and easy for clinicians to use and acceptable to the patients.The psychometric properties have been tested, yielding excellent inter-rater and test-retest reliability and discriminative validity (Simmonds, 2002). Correlations between self-reports of function and performance of functional tests are found to be moderate. It is therefore suggested that the two methods of measuring function are to be complementary and both should be used for assessment and as outcome measures.

Future studies should also monitor physical activity during the day with monitoring devices such as pedometers, ActiReg or similar methods (Hustvedt *et al.*, 2004; Najafi *et al.*, 2003). These systems are unique and combine recordings of body position and motions alone, or

combined with heart rate to calculate energy expenditure and express physical activity. Consequently, they record the time spent in different body positions and different LPA, and may be a useful tool in measuring effect of physical exercise interventions and in validation studies of objectively and subjectively measurements of functional status.

Fatigue

In papers I, II and IV fatigue was measured by the domain specific questionnaire FQ. Fatigue was also measured by EORTC QLQ-C30 in paper IV. A fatigue specific questionnaire is recommended when fatigue is the primary endpoint of the study (Knobel *et al.*, 2003) as in paper II and we therefore used FQ. In paper I, we chose the FQ because it assesses chronic fatigue. We chose to use FQ in paper II, because fatigue was the primary outcome.

Subjective physical functioning

Subjective physical functioning was the outcome measure in paper II and IV, using respectively the generic questionnaire SF-36 (paper II) and the cancer specific EORTC-QLQ-C30 (paper IV). It is important that the subscale of physical functioning is responsive and sensitive to change due to the specific intervention. We believe that the items in SF-36 are relevant for the purpose of paper II. However, we are questioning the ability of the physical functioning scale in EORTC-QLQ-C30 to detect changes. Compared to the SF-36, the EORTC-QLQ-C30 has fewer measurement levels (16 vs 21), which decreases precision and hence the possibility to detect changes. In our opinion, the results might indicate a need for a more appropriate instrument to measure self-reported physical function in palliative care.

5.2 Discussion of the main findings

5.2.1 Interventions

The content of the exercise programme in the two intervention studies in this thesis differed due to different groups of patients and the aims of the studies. The primary aim in study B was to reduce fatigue in HDSs, while the aims in study C were two fold; investigate palliative patients' ability and willingness to attend and complete an exercise programme and evaluate the effects of the exercise on HRQoL and physical performance/fitness.

We believe that the strength of this thesis is the choice of type and content of interventions. It was based on results from studies among patients with similar symptoms (study B), clinical experience from the palliative patient group and the patients' specific needs (study C). The aerobic exercise programme was designed based on earlier findings of aerobic exercise being one of the few promising interventions in patients with chronic fatigue syndrome (Whiting *et al.*, 2001) and also in cancer patients during and after treatment (Mock *et al.*, 1997; Dimeo *et al.*, 1997). Important factors when planning the study were also the feasibility of the programme and the transferability to real life situation. Our study cannot conclude whether another exercise strategy would have been more beneficial. Exercise studies comparing different types of physical exercise specifically with fatigue as a primary endpoint are few. However, one study found no difference between relaxation training and aerobic exercise on reduction of fatigue among cancer patients after cancer surgery (Dimeo *et al.*, 2004). Future intervention studies are needed to explore what type, frequency and intensity are most suitable for alleviation of cancer fatigue after treatment.

Retaining physical function and independence in activities of daily living are important factors in palliative patients (Cohen and Leis, 2002; Cheville, 2001). All patients with advanced cancer or other incurable disease experience physical decline (Jordhoy *et al.*, 2001). This may be caused by more general effects of disease progression, such as cachexia, weight loss, fatigue and inactivity. Thus, a vicious circle often leads to reduction in functional status among palliative cancer patients. Physical strength and the ability to do what one wants are highly ranked by both cancer patients and their spouses with respect to overall quality of life. Furthermore an association between physical deterioration and lower patients scores on role, social, emotional and cognitive function has been demonstrated (Jordhoy *et al.*, 2001). In study C we therefore made a programme suited to improve and/or maintain muscular strength and endurance. The programme needed to be adjusted for the palliative patient group and several factors had to be taken into account. The inclusion criteria were wide giving a heterogeneous group with respect to diagnoses, age, functional status and earlier exercise habits. This resulted in the selection of a circuit training programme with strength and aerobic exercises aiming to maintain and increase physical function important for activities of daily living. We aimed at making exercises without expensive equipments so that the exercises could be completed at home and in other settings. It was therefore a challenge to make a programme tailored to the individual patient while they were doing the exercises in a group setting. We did not prescribe a specific intensity of the exercises.

The results from paper II indicate that structured physical exercise in Hodgkin's disease survivors suffering from chronic fatigue was feasible and reduced fatigue. The strength of study B is that patients with a specific symptom like chronic fatigue may be more likely to benefit from physical exercise compared with the entire HDSs sample in the study. Selecting patients most likely to benefit from physical exercise increase the effect size. Furthermore, targeted interventions are also a more cost-effective approach.

The intervention study among incurable cancer patients in this thesis is the first to investigate the recruitment and compliance of palliative patients into a physical exercise programme. Surprisingly many palliative patients reported to be interested in attending an exercise programme. However, we are not able to advice the establishment of physical exercise rehabilitation for palliative cancer patients, primarily because of a small sample size, lack of a control group and high attrition. Futures prospective studies should identify the research needs for, and the best possible organisation of such a programme. It is not reasonably to believe that physical exercise suits all patients. We believe that physical rehabilitation primarily should be offered to those patients who suffer from specific functional symptoms and reduced physical fitness. The outcome measures should be those that are most likely to be improved by physical exercise.

5.2.2 Functional status

As described on page 7 in this thesis, functional status covers both conditions that may be assessed subjectively, such as in self-reported physical functioning measured by questionnaires and self-report questionnaires of physical activity levels, and objectively, such as physical fitness.

In this thesis the *functional status* in Hodgkins's disease survivors is measured by SF-36 (physical functioning subscale) (paper II), self report of physical activity level (questions from the HUNT-2 survey) (paper I) and cardiovascular fitness (VO_{2max}) (paper II).

Previous studies of HRQoL among Hodgkin's disease survivors have demonstrated that they suffer from fatigue, do not regain energy and experience reduced *physical functioning* compared to normal populations (Loge *et al.*, 1999a; Loge *et al.*, 1999b; Ruffer *et al.*, 2003). Physical functioning measured by SF-36 in study B was significantly lower in fatigued

compared to non-fatigued HDSs (79 vs 89) (unpublished results).This finding is confirmed in a recent publication from our group concluding that the HDSs in study A in this thesis, report lower physical functioning than the general population, in particular HDSs with chronic fatigue (Hjermstad MJ *et al.*, 2006). Their physical functioning was similar to that of general population subjects with CF, but HDSs had significantly better mental status. Thus, chronic fatigue in long term survivors may be associated with more physical than psychological aspects of long term survivorship. Is this because they are more physically inactive than the non-fatigued survivors? Can the survivors' lifestyle help to explain the increased pattern of fatigue?

In paper I we demonstrated that the self-reported level of physical activity did not differ significantly between HDS with and without chronic fatigue. Compared to the general population, more male HDSs reported to be physically active than males the normal population. No such difference was found among the females. Further, no significant difference in cardiorespiratory fitness (VO_{2max}) was found between HDSs with and without fatigue (paper II). However, 20 weeks of structured physical exercise, VO_{2max} increased significantly, the fatigue levels were reduced and physical functioning increased to the same levels as the sample from the general population (Loge *et al.*, 1998; Loge *et al.*, 1999b).

This highlights the difficulty of comparing different measures of functional status or capacity and shows the importance of measuring functional status using both self report and objective measuring methods.

In conclusion, fatigued HDSs report to have reduced physical functioning compared to the non-fatigued survivors and the normal population. On the contrary, fatigued survivors report to be equally physically active as non-fatigued survivors and the cardiovascular capacity did not differ in the two groups. The fatigued HDSs report same levels of physical activity as the non-fatigued survivors. Compared to the general population, a significantly higher proportion of the HDSs reported to be highly active (48 % vs 25 %) and fewer reported to smoke. This was contrary to our hypothesis, stating that fatigued HDSs report lower level of physical activity than the non-fatigued survivors and the general population. However, comparison of cardiovascular capacity to the general population is difficult because the number of patients in our study was low and heterogeneous regarding age and gender. In addition, the reference material concerning VO_{2max} in the general population is old (Åstrand I, 1960). Consequently,

physical inactivity does not seem to be a particular issue among cured Hodgkin's disease survivors suffering from chronic fatigue years after treatment.

One interesting additional finding was the significantly higher level of sleeping problems among the cancer survivors. This finding should be investigated more thoroughly in future studies.

Physical decline is experienced by all palliative care patients, affects most aspects of life and is among the most distressing concerns. In study C, functional status among the palliative patients (study C) was measured by the EORTC QLQ-C30 (physical functioning subscale), self report of level physical activity (questions from the HUNT-2 survey) and physical fitness (muscular fitness, balance and cardiovascular capacity/walking mobility). The level of physical fitness increased significantly in two of three on the performance test. However, contrary to our hypothesis, no change in physical functioning as measured by EORTC QLQ-C30 was found. LPA was measured before start of the intervention. Large discrepancy between subjective and objective measures concerning physical status has been revealed earlier, and the relationship between reported physical functioning and detectable physiological changes is not fully understood (Lindholm *et al.*, 2004). In palliative care the aim is to improve QoL and preserve normal functions for as long as possible. Thus, there are major and multiple reasons to focus on patients' physical function both in assessment and care. However, there is no consensus on how physical functioning should be measured or which instrument to use.

6.0 Conclusions

The answers to the research questions addressed in the present thesis are indicated in the following conclusions:

- Physical inactivity does not seem to be a particular issue among cured Hodgkin's disease survivors suffering from chronic fatigue compared to non fatigued survivors 3-12 years after treatment
- Generally, the HDSs report to have a healthy lifestyle compared to the general population. The prevalence of physically active men was higher among HDSs than in the general population, while the prevalence of physically active females in the two populations was similar. The HDSs reported to smoke less, however they are more bothered with disrupted sleep than the general population
- A structured home-based physical exercise programme in Hodgkin's disease survivors suffering from chronic fatigue is a feasible intervention to reduce fatigue and increase physical functioning
- A high proportion of palliative cancer patients reported to be interested in attending an exercise programme (63 %), the attrition rate was high, but 54 % of the patients completed the exercise period
- A group exercise programme tailored to individual patient is feasible in a palliative cancer population
- The results from the exercise intervention indicate promising results and provide a basis for future research. However, the results on physical fitness, HRQoL and fatigue do not give scientific evidence to advise incurable patients to exercise in order to maintain or improve functional status.

8.0 Future research

In conclusion, the findings from the studies in this thesis are promising and call for future research in both cured cancer patients, as well as in palliative care patients. Future trials, preferably with a randomised design, are needed to see if the promising results from our studies can be reproduced. Physical training interventions need to be further developed and tested according to specific targeted cancer populations. In palliative cancer care patients, based upon our findings from the phase II study, a controlled randomised study seems to be the next step. There is also a need to further develop the content of the physical training programme, as well as optimal outcomes in these types of studies targeting the population in question. Due to various reasons, not all patients will benefit from physical training and such factors need to be further investigated.

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Erratum

In paper II, in the fifteenth line, the second paragraph in the introduction: "Many chronic diseases such as cognitive heart failure....."Cognitive" should be replaced by "congestive".

Papers

Self-reported level of physical activity, smoking habits and sleep pattern among Hodgkin's disease survivors compared to a general population sample

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Abstract

It is well documented that Hodgkin's disease survivors (HDSs) report more chronic fatigue (CF), defined as elevated levels for more than 6 months, relative to other cancer survivors. The mechanisms behind are poorly understood, but lifestyle variables may help to explain this pattern of increased fatigue. The primary objective was therefore to compare self-reported levels of physical activity (LPA), smoking habits and sleep pattern in HDSs with and without CF. The scores were compared to a large cohort from the general population. The secondary aim was to identify parameters that influenced the level of physical activity. The Fatigue Questionnaire (FQ) was completed by 476 HDSs from the Radiumhospitalet-Rikshospitalet Trust (RR) and 56.999 inhabitants from a Norwegian county in (HUNT-Pop). LPA, smoking habits and sleep pattern did not differ significantly between HDSs with and without CF. A significantly higher proportion of the HDSs reported to be highly physically active (48 % versus 25 %, $p < .0001$) and fewer reported to smoke (25 % versus 31 %, $p = .005$) compared to the HUNT-Pop. However, the HDSs reported more sleeping problems (27 % versus 8 %, $p < .0001$) than the general population. The HDSs report a general healthy lifestyle concerning physical activity habits and smoking compared to a sample from the general population. However, future studies should investigate their sleep patterns more thoroughly, for instance in terms of duration of sleep during a 24 hour period.

Introduction

Fatigue is a non-specific and subjective feeling of tiredness, physically and/or mentally, and a common symptom among cancer patients and cancer survivors (Wessely, 1995;Fobair *et al.*, 1986;Irvine *et al.*, 1991;Stone *et al.*, 2000). For the majority of the patients, the levels of fatigue decline after termination of chemotherapy and/or radiation therapy (Greenberg *et al.*, 1992). However, for some patients the fatigue level persists for months or even years after the treatment, even when there is no sign of recurrent disease (Loge *et al.*, 1999a;Bloom *et al.*, 1993).

The prevalence of chronic fatigue (CF), defined as elevated levels of fatigue for more than 6 months, is higher in Hodgkin lymphoma survivors (HDSs) than in other cancer survivors and in the general population (Loge JH *et al.*, 2001;Ruffer *et al.*, 2003;Loge *et al.*, 1999c). Different studies comparing HDSs to testicular cancer survivors (TCSs) and to the general population report that HDSs are more fatigued (25-26 %) than TCSs (16 %) and the general population (10-11 %) (Ruffer *et al.*, 2003;Bloom *et al.*, 1993;Loge *et al.*, 1999b;Fossa *et al.*, 2003). No difference in fatigue levels is experienced among breast cancer survivors as compared to women in the general population (Bower *et al.*, 2000). In addition, no excess fatigue in young adult survivors of childhood cancer was demonstrated in another study (Langeveld *et al.*, 2003).

There is limited knowledge about possible mechanisms that might explain the persistent fatigue in disease-free patients after successful treatment. Specific mechanisms associated with fatigue might be elevated levels of cytokine, endocrine dysfunction (disturbances in hypothalamic pituitary (HPA)-axis) and anaemia (Morrow *et al.*, 2002). Few studies have explored specific mechanisms and possible aetiologic explanations for fatigue in HDSs. Gonadal dysfunction was prevalent among HDSs in one study, but no correlation between endocrinological or immunological parameters and fatigue could be demonstrated (Knobel *et al.*, 2000). However, HDSs with pulmonary dysfunction were found to be more fatigued than

HDSs with normal pulmonary function (Knobel *et al.*, 2001). Several other underlying mechanisms have also been proposed, such as, disturbed sleep, physical inactivity, reduced physical fitness and psychological distress (Wessely, 2001;Lucia *et al.*, 2003). Perceived high levels of fatigue were associated with decreased walking ability in one study comparing lymphoma patients and healthy controls (Lee *et al.*, 2003).

Theoretically, acute fatigue most probably starts with a biological process ensued from the disease and/or its treatment. Most patients interpret fatigue as a signal to limit their activity and rest. These strategies may be effective in relation to acute fatigue in order to regulate the balance between rest and activity, resulting in restoration when needed. However, the experience of fatigue may provoke psychological and biological reactions that maintain or exacerbate fatigue into a vicious circle. Increased fatigue, somatic sequelae and psychological distress separately or in combination may lead to decreased level of physical activity. Sedentary activity habits can make chronic fatigue become a self-perpetuating condition. Generally, moderate to high levels of physical activity are associated with feeling of physical and emotional well-being (Crews *et al.*, 2004).

Among patients with chronic fatigue syndrome (CFS) characterised by persistent medically unexplained fatigue, cancer patients suffering from fatigue and chronic fatigued HDSS, graded exercise has shown promising effects in terms of reducing the level of fatigue (Fulcher and White, 1997;Segal RJ *et al.*, 2003;Mock *et al.*, 1997;Wigers *et al.*, 1996;Oldervoll *et al.*, 2003). However, to our knowledge, no one has investigated the self-reported level of physical activity among HDSs suffering from chronic fatigue.

Disturbed sleep is common in cancer patients, but relatively few studies concerning sleeping patterns have been published (Ancoli-Israel *et al.*, 2001). The relationship between sleep disturbance and fatigue is inadequately investigated (Lee, 2001). Patients with fatigue are often advised to get additional rest and sleep (Vogelzang *et al.*, 1997). However, patients who tried additional rest and sleep to reduce fatigue did not report it to be effective (Berger and Farr, 1999). Sleep disorders are generally accompanied by day-time fatigue. Among chronic fatigued patients, hypersomnia and

unrefreshing sleep are prevalent (Cleare, 2003). A recent study demonstrated that fatigue, mood and depression were significantly associated with concurrent changes in the circadian rhythm in breast cancer patients (Roscoe *et al.*, 2002). Our clinical experience indicates that HDSs with chronic fatigue report hypersomnia and sleep disruptions and feel indisposed when they wake up. However, no empirical studies have addressed this possible association.

Lung tissue injury is a common side effect induced by treatment of Hodgkin's disease. Impaired lung function will be further aggravated among patients who smoke. Smoking-induced elevations in the carbon monoxide (CO) can reduce exercise tolerance and contribute to fatigue in smokers compared to non-smokers. In a recent German study of HDSs compared to age and gender matched normal controls, a significantly higher percentage smokers were found among the patients (33% versus 25%) (Ruffer *et al.*, 2003).

To our knowledge, no study has addressed if lifestyle-parameters such as physical activity, smoking and sleep disruptions may be associated with chronic fatigue among HDSs. In the present cross sectional study the main purpose was to evaluate the level of physical activity among HDSs suffering from chronic fatigue and compare them to non fatigued survivors. We also explored smoking habits and sleep pattern in the same populations. Secondly, we compared the results with observations from men and women in the same age range in the general population. In addition we tried to identify parameters that influenced the level of physical activity. The hypothesis was that fatigued HDSs report lower level of physical activity than the non-fatigued survivors and the general population.

Patients and methods

2.1 Study samples

This study included data from two cross sectional studies: one in Hodgkin's disease survivors and one in a general population survey. From 1971 all patients with Hodgkin's lymphoma patients treated at the Radiumhospitalet-Rikshospitalet Trust (RR) are registered in a Hodgkin's database. Survivors for the present study were identified from this database. Data from a large population study collected in the county of North-Trøndelag in Norway served as general population controls

(www.hunt.ntnu.no). Both the survivors and the controls were contacted by mail and received a self report questionnaire. All patients received one written reminder if they did not respond after the first mailing.

2.1.1 Hodgkin disease survivors (HDSs)

Before 1980 the majority (92 %) of Norwegian cancer patients in the age group between 15 and 39 years of age who were diagnosed with Hodgkin's disease received their treatment at the RR. The corresponding percentages in the age groups 40-59 years and above, were 80 % and 53 % respectively (Abrahamsen *et al.*, 1997). After 1980, the treatment of Hodgkin's disease gradually became more decentralised, although the NRH still serve as the referral hospital for a health region that includes about 50% of Norway's total population. The eligibility criteria in the present study included patients diagnosed for Hodgkin's disease in the period 1971-1997, 15 years or older at time of diagnosis and aged 18-74 years in 2002. All patients should be in complete remission, without signs of invasive secondary cancers and they should not have received any treatment for Hodgkin's disease during the previous three years.

A total of 611 adult patients met the inclusion criteria. Ten patients were no longer registered at the Norwegian Census Bureau and could not be contacted. Ten patients who had received the majority of their treatment in another health region and who had recently participated in another postal survey on psychosocial late effects were not contacted. The 591 eligible patients were contacted by mail. They received a questionnaire packet consisting of among other the Fatigue Questionnaire (Chalder *et al.*, 1993). A total of 479 returned the questionnaire packets. However, three patients had failed to fill on the FQ, and were excluded from analysis in this report. Thus, the response rate for the FQ overall was 81% (476/591). The respondents had a mean age of 46 years (range 21-73) and 56% were males ($N = 267$).

Missing items on the completed forms were less than .05 %. To avoid omitting patients with partially incomplete data, mean imputation was used for scale scores when patients completed at least 50 % of the scale, as recommended by the EORTC Manual (Fayers P *et al.*, 1995). All clinical variables were retrieved from the lymphoma data base at the RR.

One hundred forty three of the 476 HDSs reported chronic fatigue (30 %) compared to 11.5 % in a Norwegian normal population (Loge *et al.*, 1998;Hjermstad *et al.*, 2005). No significant differences in the basic characteristics between the fatigued and the non-fatigued groups were found, except for stage/substage and a trend towards a shorter observational time since treatment among the fatigued survivors (204 versus 189 months, $p = .07$) (Table 1).

2.1.2 HUNT-population (HUNT-Pop)

From 1995 to 1997, all inhabitants in the county of Nord-Trøndelag, Norway aged 18 years and above were invited to participate in a large cross-sectional study of physical and psychosocial health (www.hunt.ntnu.no). The individuals were asked to complete a questionnaire packet and to undergo a physical examination, including an assessment of height and weight. The participation rate was 71 %. The eligibility criteria for this study included men and women between 21 and 73 years when answering the questionnaire.

2.2 Measures

All HDSs received a self-report questionnaire including several standardised questionnaire. Relevant clinical variables among the HDSs, such as, date of diagnosis, stage, histology, treatment and current disease status (relapse or not) were retrieved from the Hodgkin database at the RR. Additional variables in the questionnaire were gender, age, educational level (years), marital status, daily smoking (no versus yes), sleeping pattern and level of physical activity. These questions were identical to those used in the North-Trøndelag health study (The HUNT study) in Norway (http://www.hunt.ntnu.no) with identical wording (Holmen J *et al.*, 2003). The packet included the Fatigue Questionnaire (FQ) for use in the present study (Chalder *et al.*, 1993).

Fatigue was assessed by the Norwegian version of the Fatigue Questionnaire (FQ). The FQ is a self-report instrument for assessment of fatigue symptoms experienced during the last month, compared with how the subject felt when last feeling well. Additionally, two items ask about the duration and the extent of fatigue. FQ measures physical fatigue (PF) (seven items) and mental fatigue (MF) (four items). The sum of

all 11 items is designated total fatigue (TF). Each item has four response choices. Likert-scoring (0, 1, 2, 3) is used for construction of PF, MF and TF, with higher scores implying more fatigue. A dichotomised score (0, 0, 1, 1) is used for the definition of chronic fatigue; defined by the sum of dichotomised scores ≥ 4 and a duration of six months or longer. The FQ was originally validated in primary care, and has demonstrated good face and discriminant validity and good and stable psychometric properties across populations (Chalder *et al.*, 1993).

The main study outcome was level of physical activity (LPA), and was assessed by one question, which described two sublevels of physical activity. The first described a low level of activity, such as walking, the other a high level of activity that leads to sweating and breathlessness. Forms with missing values for both responses were excluded from analyses. The participants were divided into three groups, according to their level of physical activity (LPA) (see Figure 1) (Thorsen *et al.*, 2003):

Group 1. 'Inactive': no low-level activity or low-level activity < 1h per week and no high-level activity.
Group 2. 'Minimally active': low-level activity ≥ 1 h per week, and either no high-level activity or < 1h per week.
Group 3. 'Highly active': independent of the level of low-level activity, high-level activity ≥ 1h per week.

Groups 2 and 3 were combined into one representing the physically active group and compared with group 1 (inactive group) in the logistic regression analysis.

period 1995 to 1997, these data may be out of date when comparing with a cohort of cancer patients evaluated 7 years later.

The North-Trøndelag county has a population that is considered representative of population in Norway. However, it is a rural district and lacks densely populated areas and larger cities with more than 50.000 residents. The level of education and income is lower than the national average. Low education and low income are shown to be associated with low levels of physical activity (Sogaard *et al.*, 2000). In accordance with these limitations, extensive generalisation to Norway may be limited. A possible underreporting of the level of physical activity may also exist in this population. They may be physically active in their work and daily activities, but do not think of it as being physically active.

Earlier data regarding physical activity and cancer survivors are mixed, with most studies suggesting higher levels of activity, some suggesting no difference and one suggesting less (Demark-Wahnefried *et al.*, 2005). Support to our findings, Thorsen and colleagues recently reported similar results in testicular cancer survivors (TCSs), they were significantly more physically active than the general population (Thorsen *et al.*, 2003). Other recently published studies suggested that breast cancer survivors and a group of mixed cancer survivors were equally physical active relative to healthy controls (Blanchard *et al.*, 2003;Nord *et al.*, 2005a). Among a group of lymphoma/leukaemia patients compared to controls, there was a trend towards more controls being physically inactive than the cancer survivors (Nord *et al.*, 2005b).

Among HDSs, 25 % reported to be daily smokers, versus 31 % in the HUNT-Pop. As opposed to our findings, Ruffer et al. found a higher percentage smokers among HDSs compared to a matched control group (Ruffer *et al.*, 2003). Unfortunately, they did not report on physical activity levels among their patients. A higher proportion of smokers among TCSs compared to healthy controls was also found by Thorsen et al. (Thorsen *et al.*, 2003). Contrary, Nord et al. found no significant difference in smoking comparing a group of mixed cancer survivors to matched controls. However, a sub analysis investigating lymphoma/leukaemia patients show similar results as our study with significantly lower percentage smokers (13 % versus 29 %) (Nord *et al.*, 2005b)

Newly published results indicate that cancer survivors are likely to make lifestyle changes, however, those who are male, older and less educated are less likely to adopt these changes (Demark-Wahnefried *et al.*, 2005;Patterson *et al.*, 2003). In our study, the HDSs reported to smoke less and exercise more than the general population. The life-threatening cancer disease may have led to a healthier lifestyle. This is important since the risk of developing late effects (caused by radiation and/or chemotherapy treatment) like cardiovascular disease may be even higher than the risk of relapse or secondary malignancies (Gustavsson *et al.*, 2003;Adams *et al.*, 2003;Mert *et al.*, 2003). Because of this notable risk in Hodgkin's lymphoma survivors, it is important to obtain more insight in the level of physical activity and the physical fitness these patients have.

The majority of patients with Hodgkin's disease are young (< 40 years) and most are cured. Increasing physical activity has clearly been shown to attenuate cardiovascular risk in men, although other unfavourable coronary risk factors remains unchanged (Erikssen *et al.*, 1998;Wannamethee *et al.*, 1998). Because of the demonstrated benefit of physical activity, oncologists may play an important role in encouraging the patients to be physically active. Breast cancer patients randomly assigned receiving an oncologist's recommendation to exercise report an increased activity level per week, compared to those not receiving a similar message (Jones *et al.*, 2005)

Conclusions

Although a high proportion of HDSs report chronic fatigue, they report same levels of physical activity, smoking and sleeping problems as the non-fatigued individual. Compared to a sample from the general population, they smoke less and a higher proportion of the HDSs are physically active. However, our results indicate that HDSs are more bothered with disrupted sleep and problems to get to sleep at night. Future studies should therefore look further into the association between sleep patterns and fatigue.

Figure 1: Level of physical activity (LPA)

Question: How has your physical activity level been in your leisure time the last year? (Estimate a weekly average for the year, walking to work counts as leisure time)

Response categories	Hours per week			
	No	< 1	1-2	≥ 3
Low-level activity (not sweaty/breathless)				
High-level activity (sweaty/breathless)				

"Inactive" "Minimally active" "Highly active"

Two questions were used to survey sleep pattern in this study: 1) "during the last month, have you had trouble falling asleep? and 2)"during the last month, did you wake up early and were not able to get back to sleep?" The answer categories were 'never', 'sometimes', 'often' and 'almost every night'. In the final analysis the answers were dichotomised to a yes/no variable with never/sometimes categorised into 'no' (not having sleeping problems) and often/almost every night categorised into 'yes' (having sleeping problems).

One question was used to map smoking habits: 'Do you smoke cigarettes or cigars daily?' with the answer alternatives being yes/no.

2.3 Statistical analysis

Comparisons between groups were performed by Fisher's exact test for nominal variables, chi square test for trend (linear-by-linear test) for ordinal variables, and t-tests for scale variables. P-values < 0.05 criteria were considered statistically significant.

A logistic regression analysis with physically active (yes versus no) as the dependent variable was performed in the analysis comparing the HUNT-Pop with the HDSs, adjusting for the covariates age, group (HDSs/HUNT-Pop) and educational level. The odds ratio (OR) are presented as estimates and 95% Confidence Intervals (95% CI). All tests are two-sided. The analysis was assessed in the entire population (men and women) and men and women separately. Possible interactions were checked, as well as linearity in age. Significant interactions (only including gender) were accounted for by using separate analysis for men and women. All analyses were performed using the SPSS for Windows (PC version 12.0).

Results

Basic characteristics among fatigued and non-fatigued HDSs are presented in Table 1. Self-reported physical activity level, smoking habits and sleep problems did not differ significantly between HDSs with and without fatigue (presented in table 2). Logistic regression with physical activity (yes/no), smoke (yes/no) and sleep disturbance (yes/no) as dependent variables adjusting for age, gender and level of education gave similar results, no differences in self-reported physical activity level between the groups (results not included here).

The fatigued and the non-fatigued HDSs were therefore combined into one group (HDSs) and compared with the HUNT-Pop in the subsequent analyses (Table 3). There were no significant differences in age between groups, however there were a significantly higher proportion of men in the HDSs group, 56 % versus 44 % ($p < 0.0001$). Among the HDSs, there were significantly more individuals with high education, respectively 37 % and 21 %, ($p < 0.0001$). A significantly lower proportion of smokers were found in the HDSs compared to the HUNT-Pop, 25 % versus 31 %, ($p = 0.005$). Furthermore, HDSs reported higher level of physical activity compared to the HUNT-Pop, respectively 48 % and 25 % were highly active, ($p < 0.0001$) (see figure 2). Contrary, the HDSs reported significantly more problems to get to sleep and early wakening than the HUNT-population.

A multivariate logistic regression analysis with physical active (yes/no) as the dependent variable and group (HUNT/HDSs), age, education, smoking (yes/no) and

early wakening (yes/no) as covariates was performed. Because of interaction, separate analyses were done for men and women. Being male HDSs increased the chance of being physically active by 50 % compared to males in the HUNT-population, (OR = 1.50, CI 1.04 – 2.17), p = .031 (table 4), while no significant difference was found among females (OR = 1.20, CI = 0.83 – 1.74), p = .33, (Table 4). For both genders, the level of physical activity increased with increasing level of education, decreased with increasing age, was lower among smokers than non-smokers and finally physical active persons reported less sleep disturbance than inactive individuals.

Discussion

In this study, the level of physical activity and other self-reported life-style variables (i.e. smoking and sleep disruptions) did not differ between chronic fatigued and non-fatigued HDSs. Furthermore, more male HDSs were physically active than the general population, however no such difference was found among the females. Both genders reported to smoke less, but have more sleep disruptions than the general population. There were significant associations between the level of physical activity and the level of education, age, smoking and sleeping problems.

The strength in our study is the use of the same questionnaire regarding the level of physical activity, smoking and sleep in the two populations, and the large sample size in both groups. However, all types of self reporting are vulnerable to bias. Measuring physical activity habits by a self reporting questionnaire is problematic with a view to validity. So far, there is no standardised method for assessment of physical activity and we still miss a "gold standard" that other methods can be validated against. One recently published study show that the use of different numerical response scales have significant impact on the estimated percentage of regular exercisers (Courneya *et al.*, 2003). Earlier studies have recommended to divide the level of physical activity into two main groups reflecting respectively 'physical active' and 'physically inactive' individuals (Schechtman *et al.*, 1991). We believe that for the purpose of this study, in which the main purpose was to evaluate whether fatigued survivors reported a lower level of physical activity than non-fatigued individuals and to provide descriptive information about physical activity levels between HDSs and the general population a self report questionnaire with two final response categories was sufficient.

However, we cannot exclude the possibility that people who have been seriously ill are especially aware concerning their health status, and therefore report to be more physically active than those without a history of cancer. Although the risk of misclassification of level of physical activity cannot be excluded, its impact is estimated to be limited.

Our finding that the fatigued and non-fatigued HDSs reported same levels of physical activity was somewhat surprising. Exercise training is one of the few interventions suggested to prevent or alleviate fatigue among cancer patients and survivors, but so far the research supporting this suggestions and mechanisms behind are still limited (Dimeo *et al.*, 1996;Dimeo *et al.*, 1999;Mock *et al.*, 1997;Dimeo *et al.*, 1998;Schwartz *et al.*, 2001;Oldervoll *et al.*, 2003;Burnham TR and Wilcox A, 2002). Support to our findings about equal physical activity levels in fatigued and non-fatigued survivors, no significant difference in peak exercise capacity (VO_2 peak) was found between the fatigued and the non-fatigued HDSs in one study (Oldervoll *et al.*, 2003). However, the number of patients in this study was low and a possible type II error may exist.

Self-reported physical activity may give an indicator of how much physical exercise/activity individuals perform (categorised as being physically active or not active). However, complementary data on type, frequency and content of physical exercise/activity are necessary to draw any conclusions, especially regarding possible interventions against fatigue. Future studies should therefore be designed in order to thoroughly and objectively assess physical performance in chronic fatigued and non-fatigued cancer survivors by for instance measuring maximal oxygen capacity, muscle strength and/or to monitor physical activity with monitoring devices during the day (Najafi *et al.*, 2003).

Our society and way of living have changed during the last years, and daily demands to physical capacity, activities in daily life and physical activity pattern have changed dramatically. Studies report that daily physical activities have decreased, while exercise leading to sweating has increased during this period (Kurtze N *et al.*, 2001). As regards to the reference data used in the present study which was collected in the

Table 1. Basic characteristics among fatigued and non-fatigued HDSs

	HDSs with chronic fatigue (*N* = 143)	**HDSs without chronic fatigue (*N* = 333)**	***p-value***
Gender (N (%))			.87
Male	81 (56)	186 (57)	
Female	62 (44)	147 (43)	
Age at time of the study (years)(mean ±SD)	47 (11.3)	46 (11.8)	.37
Age at diagnosis (years)(mean ±SD)	30 (10.6)	30 (10.6)	.98
Observational time (months)(mean ±SD)	204 (89.5)	189 (82.6)	.07
Marital status (N (%))			.47
Single	21 (14)	38 (11.)	
Married/cohabitant	105 (73)	250 (75)	
Divorced/separated	3 (2)	9 (3)	
Widow/widower	14 (10)	35 (11)	
Educational Level (N (%))			.11
≤ 10 years	29 (20)	60 (18)	
≥ 11 years,	54 (38)	151 (46)	
University < 4 years	21 (15)	67 (21)	
University ≥ 4 years	38 (27)	49 (15)	
Stage/substage N (%)			.05
IA/IIA	60 (42)	171 (51)	
IB/IIB	30 (21)	39 (12)	
IIIA/IVA	23 (16)	58 (17)	
IIIB/IVB	29 (20)	65 (20)	
Primary treatment (N (%))			.18
Chemotherapy	26 (18)	55 (16)	
Radiotherapy	39 (27)	108 (32)	
Radiotherapy +Chemotherapy	76 (53)	168 (51)	
Other treatment	1 (1)	1 (1)	
Missing	1	3	
Relapse N (%)	16 (1)	38 (11)	.81
Non-CR	11 (8)	23 (7)	

Table 2. Comparison between HDSs with fatigue and HDSs without fatigue in self reported physical activity, smoking habits and sleep pattern

	HDSs with chronic fatigue (*N* = 143)	**HDSs without chronic fatigue (*N* = 333)**	***p*-value**
Smoker N (%)	39 (28)	77 (24)	.38
Missing	5	17	
Physical activity (N (%))			.52
'Inactive'	22 (15)	55 (17)	
'Minimally active'	48 (34)	120 (36)	
'Highly active'	73 (51)	158 (47)	
Problems to get to sleep (N (%))			.49
'Never/sometimes'	98 (70)	243 (73)	
'Often/almost every night'	42 (30)	88 (27)	
Missing	3	2	
Early wakening (N(%))			.43
'Never/sometimes'	98 (70)	244 (74)	
'Often/almost every night'	42 (30)	87 (26)	
Missing	3	2	

Table 3. Comparison between HDSs and the general population sample

	HDSs ($N = 476$)	**HUNT-Pop** ($N = 56999$)	***p*-value**
Age at questionnaire (years)(mean ±SD)	46 (11.6)	47 (14.3)	.19
Gender N (%)			< .0001
Male	267 (56)	27082 (47)	
Female	209 (44)	29917 (53)	
Smoker N (%)	115 (25)	16916 (31)	.005
Education			< .0001
'< 10 years'	89 (19)	18453 (34)	
'> 11 years'	204 (44)	24611 (44)	
'University < 4 years'	88 (19)	7144 (13)	
'University ≥ 4 years'	87 (19)	4595 (8)	
Physical activity (N (%))			< .0001
'Inactive'	77 (16)	14510 (26)	
'Minimally active'	167 (35)	27973 (49)	
'Highly active'	231 (49)	14516 (25)	
Problems to get to sleep (N (%))			< .0001
'Never/sometimes'	341 (72)	43394 (92)	
'Often/almost every night'	130 (28)	3903 (8)	
Early wakening (N(%))			< .0001
'Never/sometimes'	342 (73)	43139 (91)	
'Often/almost every night'	129 (27)	4254 (9)	

Table 4. Multivariate logistic regression analysis among men with physical active (yes/no) as the dependent variable

	'Physical active'			
	No (0)	Yes (1)	OR (95%CI)	p-value
All				
HUNT-Pop (0)		20715 (77)	1.0	.031
HDSs (1)	6367 (23)	231 (87)	1.50 (1.04 – 2.17)	
	36 (13)			
Age (years) (SD)	50 (14.6)	47 (14.0)	0.993 (0.991 – 0.996)	< .001
Education				
Primary/secondary school (0)	2516 (32)	5342 (68)	1.0	< .001
High school (1)	2706 (21)	10209 (79)	1.58 (1.47 – 1.72)	
College/university < 4 years (2)	416 (13)	2838 (87)	2.87 (2.51 – 3.29)	
College/university ≥ 4 years (3)	220 (9)	2157 (91)	3.81 (3.22 – 4.50)	
Sleeping problems				
No (0)	4520 (22)	16145 (78)	1.0	< .001
Yes (1)	397 (29)	974 (71)	0.74 (0.65 – 0.85)	
Smoking				
No (0)	3761 (21)	14468 (79)	1.0	< .001
Yes (1)	2214 (29)	5418 (71)	0.71 (0.66 – 0.77)	

Table 5. Multivariate logistic regression analysis among women with physical active (yes/no) as the dependent variable

	'Physical active'			
	No (0)	Yes (1)	OR (95%CI)	p-value
All	8184	21941		
HUNT-Pop (0)	8143 (27)	21774 (73)	1.0	
HDSs (1)	41 (21)	167 (79)	1.20 (0.83 - 1.74)	.33
Age (years) (SD)	53 (14.6)	45 (13.7)	0.977 (0.975 – 0.979)	< .001
Education				
Primary/secondary school (0)	4026 (38)	6658 (62)	1.0	
High school (1)	2480 (21)	9420 (79)	1.64 (1.53 – 1.77)	
College/university < 4 years (2)	552 (14)	3426 (86)	2.49 (2.21 – 2.80)	< .001
College/university ≥ 4 years (3)	259 (11)	2046 (89)	3.16 (2.71 – 3.69)	
Sleeping problems				< .001
No (0)	5662 (24)	17408 (76)	1.0	
Yes (1)	956 (36)	1706 (64)	0.76 (0.69 – 0.83)	
Smoking				
No (0)	4797 (25)	14141 (75)	1.0	
Yes (1)	2801 (30)	6598 (70)	0.78 (0.69 – 0.83)	< .001

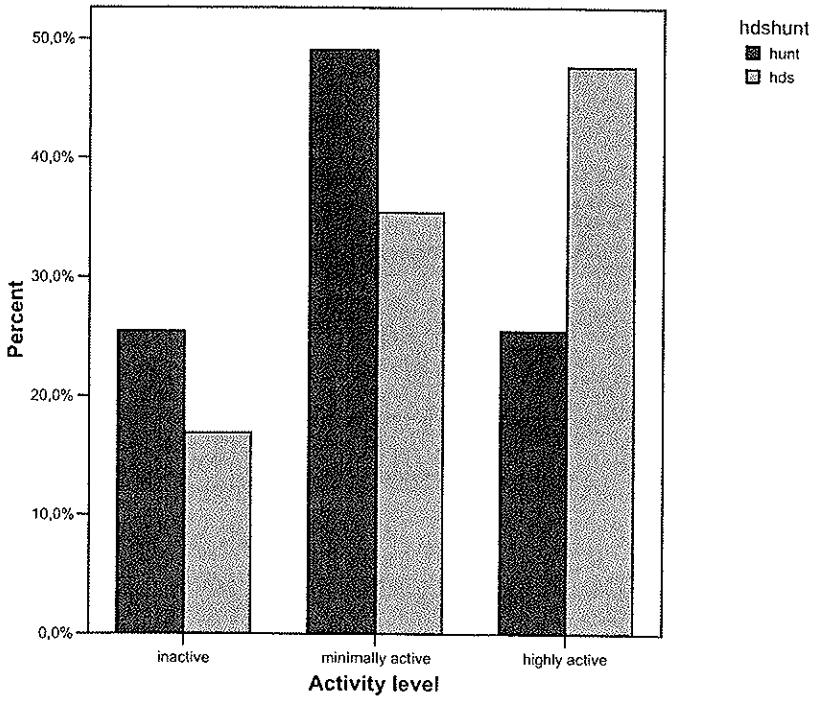

Figure 2. Comparisons between Hodgkin's disease survivors (HDSs) and normal controls in self reported physical activity divided into three levels (inactive, minimally active and highly active.

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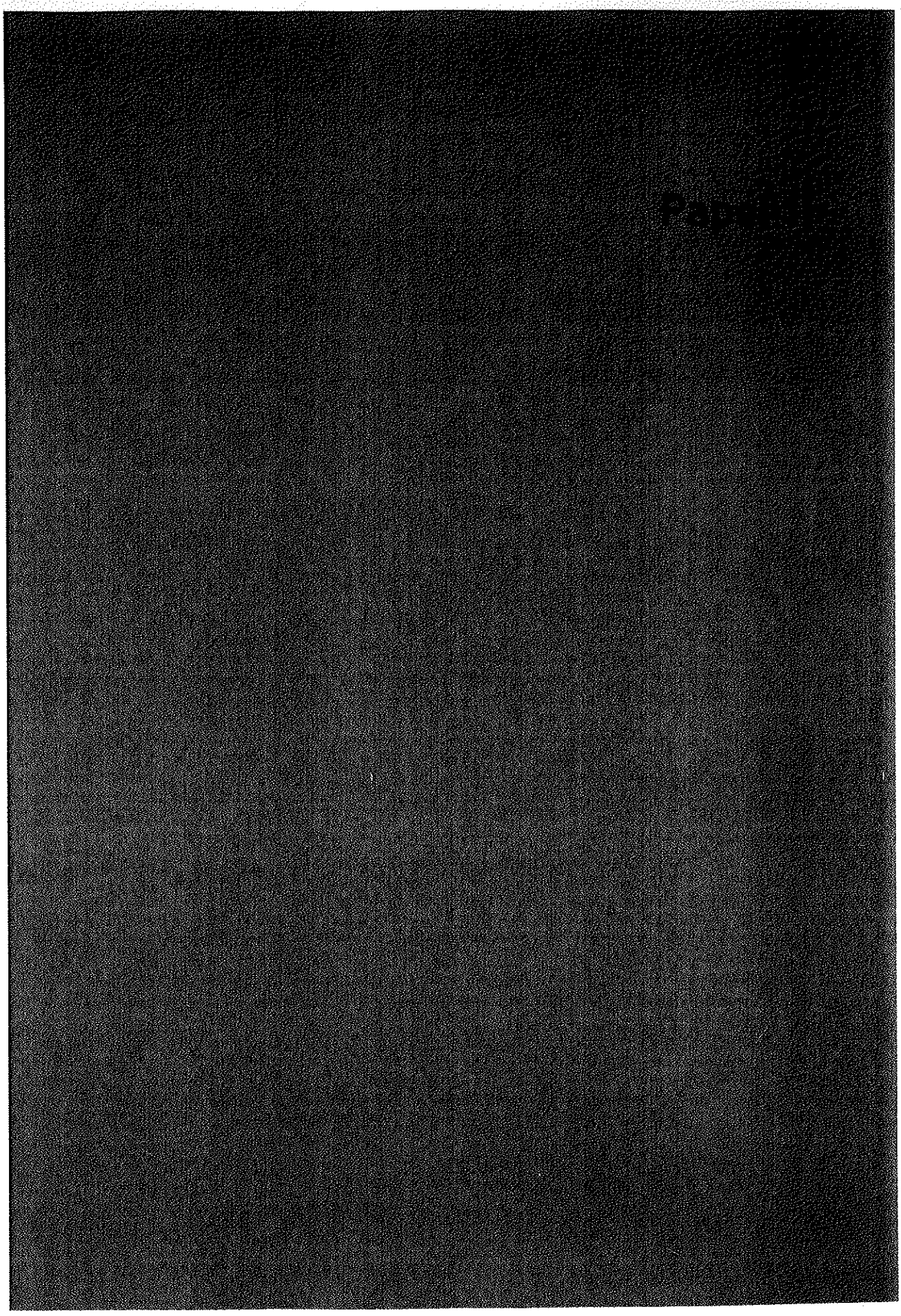

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Exercise reduces fatigue in chronic fatigued Hodgkins disease survivors—results from a pilot study

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Abstract

The aims of this pilot study were to compare aerobic capacity in non-fatigued and fatigued Hodgkin's disease survivors (HDS) and to assess the feasibility of an exercise-programme and its effects upon fatigue, physical functioning and aerobic capacity in chronic fatigued HDS. 53 HDS (85%) of originally 62 survivors treated at the Trondheim University Hospital in the period 1987–1997 completed a questionnaire including the Fatigue Questionnaire (FQ). 18 subjects were identified with chronic fatigue. 15 non-fatigued HDS matched for gender and age were drawn as controls. Both groups were invited to medical examination and exercise tests. All 15 fifteen non-fatigued HDS showed up to the medical examination. 12 of the 18 patients with chronic fatigue completed the tests and nine agreed to enter a home-based exercise intervention. Outcome measures were aerobic capacity, fatigue and physical functioning. No significant difference in aerobic capacity was found between the chronic fatigued HDS and the controls. Fatigue, physical functioning and maximal aerobic capacity were significantly improved after the intervention. Aerobic exercise had a positive effect upon chronic fatigue in HDS. However, the study is a pilot study and needs confirmation in a larger group of subjects. The intervention was well accepted, and the majority of the patients adhered to the programme.

Keywords: Exercise; Fatigue; Intervention study; Hodgkin's disease

1. Introduction

The prevalence of chronic fatigue among Hodgkin's disease survivors (HDS) is 25–30% compared with 11% in the general population [1]. Fatigue seems to be more prevalent in HDS than in other cancer survivors [2]. Chronic fatigue in this particular group of cancer survivors is relatively poorly understood, but an association between fatigue and pulmonary dysfunction has recently been demonstrated [3].

Fatigue is a normal and passing experience after physical and mental exertions, and contributes to regulate the balance between rest and activity, resulting in restoration when needed. For example, some days of rest are a normal and effective strategy in the restitution after an acute infectious disease. Patients undergoing treatment for cancer are often advised to limit their activity and get enough rest. These strategies may be effective in acute situations of fatigue. However, for patients suffering from chronic fatigue, rest will result in physical deconditioning and probably increased fatigue. Most individuals with chronic disease or disability become less physically active, and this may lead to a cycle of deconditioning of multiple physiological systems [4]. Many chronic diseases such as cognitive heart failure, multiple sclerosis, systemic lupus erythematosus and patients with psychiatric disorders are accompanied by fatigue [5–8]. Like in chronic pain, the experience of fatigue in chronic disease may provoke psychological and biological reactions that maintain or exacerbate fatigue in a vicious circle. Furthermore, prolonged rest or inactivity can lead to skeletal muscle atrophy and

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further reduction in exercise tolerance. Today, however, there is increasing consensus among professionals that persistent rest may worsen fatigue in sufferers of the chronic fatigue syndrome (CFS) [9].

There is no consensus on how to prevent or alleviate fatigue. In a randomised clinical trial (RCT), graded aerobic exercise significantly improved fatigue, functional capacity and fitness in CFS patients without psychiatric or sleep disorders compared with flexibility exercises and relaxation therapy [10].

Exercise is one of the few interventions suggested to prevent or decrease fatigue among cancer patients, but the research supporting this is limited [11–13]. Dimeo and colleagues concluded that an aerobic exercise programme improved maximal physical performance and reduced fatigue in fatigued cancer patients. However, these studies mainly included cancer patients during and immediately after chemotherapy or radiotherapy [13,14].

To our knowledge, no published study has so far tested exercise capacity among chronic fatigued HDS or the effects of physical exercise in chronic fatigued cancer survivors. On this basis, the present quasi-experimental pilot study was conducted to examine the level of aerobic capacity among chronic fatigued HDS compared with HDS without chronic fatigue. Further aims were to assess the effects of an aerobic training programme upon fatigue, physical functioning and aerobic capacity in chronic fatigued HDS and to evaluate the feasibility of the programme as a preparative step for a larger randomised study.

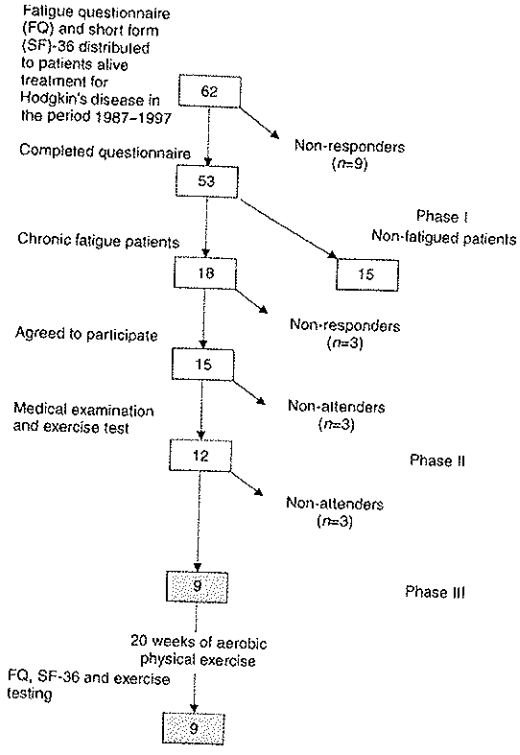

Fig. 1. Flow chart of the survey and intervention patients.

2. Material and methods

2.1. Sampling

Fig. 1 shows the flowchart of the study and the patient selection. The study included three phases; phase 1 is a survey; phase 2 is an exercise testing and medical examination and phase 3 is an intervention study. 62 patients (aged 19–74 years) were treated for Hodgkin's disease at the University Hospital in Trondheim in the period 1987–1997 and were alive without active disease in 1999. They were approached by mail, and 53 patients completed the questionnaires after one written reminder (85%). 18 of the 53 patients reported chronic fatigue (34%) (*phase I*). These were invited to participate in medical examinations and physical exercise testing. 15 of the 18 chronic fatigued patients gave their consent to participate at this stage. The reasons for not participating were living too far away from the hospital ($n=2$) and unknown reason ($n=1$). 12 of the 15 patients completed the physical exercise testing and the medical examinations. One person did not show up in spite of two reminders. Two subjects underwent the medical examination, but were not able to perform the physical exercise test because of a splint in the leg ($n=1$), and relapse of the malignant disease ($n=1$) (*phase II*). After the medical examinations and the exercise test the cohort was invited to participate in an intervention consisting of aerobic exercise three times a week for 20 weeks. 9 of the 12 patients (4 women and 5 men) gave written informed consent and entered the intervention (*phase III*). Two men wanted to perform individual exercise by themselves, but did not want to attend the programme. One woman was too ill to take part in the exercise programme.

From the 35 non-fatigued HDS who had completed the questionnaire, 15 patients of same gender and age ±2 years were drawn as controls (see Fig. 1). After giving written informed consent, the controls underwent exercise testing and medical examinations identical to the chronic fatigued survivors, but were not offered the training programme.

Patient characteristics in the non-fatigued and the fatigued HDS are presented in Table 1. The distribution of the demographic characteristics and time since treatment was well balanced between the two groups.

2.2. Subjective health assessments

Fatigue was assessed by the Norwegian version of the Fatigue Questionnaire (FQ) [15]. The FQ is a self-report

Table 1
Samples characteristics

	HDS with fatigue $N=12$	HDS without fatigue $N=15$	P value
Age (years)			
Mean (S.D.) (range)	41 (11.3) 24–58	40 (11.0) 25–60	NS
Gender (N (%))			
Male	7 (58)	9 (60)	NS
Female	5 (42)	6 (40)	
Educational level N (%)			
≤10 years	6 (50)	9 (60)	
≥11 years, university <4 years	3 (25)	2 (13)	NS
University ≥4 years	3 (25)	4 (27)	
Stage/substage N (%)			
IA/IIA	9 (75)	10 (67)	
IB/IIB	1 (8)		NS
IIIA/IVA		3 (20)	
IIIB/IVB	2 (17)	2 (13)	
Primary treatment N (%)			
Radiotherapy	5 (42)	5 (33)	
Chemotherapy	4 (33)	3 (20)	NS
Radiotherapy + chemotherapy	3 (25)	7 (47)	
Relapse	2 (17)	3 (20)	NS
Smoker	5 (42)	2 (13)	NS
Work situation			
Paid work/trader	9	13	
Disabled/rehabilitation[a]	2	1	NS
House work	1.0	1	
Marital status			
Married/cohabitant	10	13	
Single/widowed	2	2	NS
Time since treatment (months)			
Mean (S.D.)	79 (35)	59 (32)	NS

S.D., standard deviation; HDS, Hodgkin's disease survivors; NS, non-significant.
[a] One person had a 50% disability pension and was also in paid work.

instrument for the assessment of fatigue including symptoms experienced during the last month, compared with how the subject felt when last feeling well. Additionally, two items ask about the duration and the extent of fatigue. FQ measures physical fatigue (PF) (seven items) and mental fatigue (MF) (four items). All 11 items are designated total fatigue (TF). Each item has four response choices. Likert-scoring (0, 1, 2, 3) is used for construction of PF, MF and TF. Higher scores imply more fatigue. A dichotomised score (0, 0, 1, 1) is used for the definition of chronic fatigue, which is defined by sum of dichotomised scores ≥4 and duration 6 months or longer. The FQ has originally been validated in primary care and has shown good face and discriminant validity. No specific validation study has been performed in cancer patients. However, the FQ has been used in studies among Hodgkins disease survivors and in patients with prostate cancer receiving hormonal therapy [1,16]. The psychometric properties demonstrated in these studies correspond with reports from the validation study and from the studies in non-cancer populations. The FQ was filled in before (*phase 1*) and immediately after the intervention period (end of *phase 3*) and was defined as the primary outcome of the intervention.

The SF-36 was completed before (*phase 1*) and immediately after the intervention period (end of *phase 3*) [17]. The sub-scale 'physical functioning' (10 items) was used as a secondary outcome-measure in the intervention. The responses were summed and transformed to a 0–100 scale (0 = worst health state, 100 = best health state) according to the SF-36 algorithm [18].

2.3. Physiological assessments

The patients height, weight, resting heart rate, resting blood pressure, maximal oxygen consumption (VO_{2max}), total walking distance/time to exhaustion and heart rate at sub-maximal and maximal speed were measured immediately before and after the intervention programme. The patients were instructed not to perform heavy exercise training nor to smoke or eat 2 h before the test. Lung function was measured before the clinical examination in both groups.

2.4. Physical exercise capacity

VO_{2max} was measured by use of a cardiopulmonary exercise testing instrument (Vmax29, Sensomedics, Netherlands). The patients were walking and running on a treadmill. The heart rate was measured continuously during the test using a Polar Sport tester PE 3000.

For assessment of maximal physical performance the Oslo protocol was used [19]. The test protocol (speed and elevation increment) was carried out until exhaustion.

2.5. Lung function measurements

The lung function test included dynamic spirometry. Spirometric variables were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and FEV_1 expressed as percent of FVC (FEV_1%). The tests were performed using Vmax29 testing instrument (Sensomedics, The Netherlands).

2.6. Intervention procedure

An exercise instructor visited the patients in their local community at the start of the exercise period. The patients were given instructions and advice in their home-based exercise programme. The Polar Sport Tester recorded and stored the pulse rate every fifteenth second during the exercise session. Follow-up phone calls were done regularly to motivate, guide and regulate the intensity of the exercise programme.

Table 2
Physiological comparisons of the fatigued and non-fatigued patients

	HDS with chronic fatigue ($n=12$) (mean) (95% CI)	HDS without chronic fatigue ($n=15$) (mean) (95% CI)	P value
Weight (kg)	78.2 (72.8–83.6)	74.7 (67.8–81.5)	NS
Height (cm)	176 (170–182)	173.7 (170–177.5)	NS
BMI (kg/m^2)	25.2 (24.8–26.4)	24.7 (22.8–26.6)	NS
VO_2 peak (ml kg^{-1} min^{-1})	32.7 (27.1–38.2)	34.0 (29.5–38.6)	NS
Resting heart rate (beats/min)	81 (72–91)	79 (68–89)	NS
Lung function variables[a]			
FVC	104 (90–118)	94 (84–103)	0.04
FEV_1	97 (85–110)	93 (83–104)	NS
FEV_1%	78 (76–81)	82 (78–87)	NS
Maximal heart rate (beats/min)	184 (174–194)	185 (170–194)	NS

BMI, Body Mass index; 95% CI, 95% Confidence Interval.
[a] Lung function values are presented as percentage of predicted normal values.

2.7. Aerobic endurance exercise programme

The aerobic endurance exercise programme consisted of 20 weeks with an exercise session of 40–60 min continuous work using large muscle groups at an intensity of 65–80% of the subjects target heart rate (measured at the first test) three times a week. An exercise diary filled in by the patients contained information on the duration, type of activity as well as the patients' experience of the exercise session classified as 'easy', 'somewhat strenuous' or 'strenuous'. The activities could be chosen and included brisk walking, jogging, bicycling, aerobics, cross-country skiing or swimming. The attainment target for compliance was 75% of the aerobic exercise programme. This is considered to be minimum attendance accepted in other similar studies [20].

2.8. Data scores and statistical analysis

All statistical analysis was performed using the Statistical Package for the Social Services (SPSS) software package (8.0 for Windows) with two tailed tests for estimates of P values. The 0.05 criteria were used to define statistically significant effects. The statistical analysis included Chi-tests statistics (categorial variables) and Student t-tests were used to assess pair-wise group differences. Analysis was carried out on an intention-to-treat basis.

3. Results

3.1. Fatigued versus non-fatigued HDS

Results from physiological comparisons of the fatigued and the non-fatigued HDS are presented in Table 2. No statistically significant differences were seen between the two groups in physiological measures: body mass index (BMI), VO_2 peak, resting heart rate, maximal heart rate or resting blood pressure. Spirometric variables did not differ significantly between the two groups, except for FVC ($P=0.04$). The FVC mean value of the chronic fatigued HDS was 4% above the mean normal value, while the controls' mean value was 6% below the mean normal value. However, both groups scored within the FVC normal range as recommended by the European Respiratory Society [21].

All the 9 patients who attended the intervention completed the pre- and posttests. There were no statistically significant differences between patients who completed the intervention programme ($n=9$) and the non-respondents/non-attenders ($n=9$) by gender, age, relapse, primary treatment, marital status, work situation, time since treatment, fatigue scores, physical function or work situation. However, the education level among the two groups indicated a borderline significant difference in favour of a higher proportion of university education in the intervention group ($P=0.06$). Time since antitumour therapy and inclusion in the study was 82 months standard deviation (S.D.) 41.6) in the intervention group.

6 of the 9 patients adhered to the prescribed programme according to the results from the Polar Sport tester, the written exercise diary, regularity and compliance of 75% of the instructed exercise hours. The 3 others exercised more sporadically.

3.2. Effects of intervention upon subjective outcomes

After the training period, the TF score was reduced by 43.7% in the intervention group ($n=9$) from 21.5 before the intervention to 12.1 after the intervention ($P=0.001$). PF was reduced by 43.6% from 14.0 to 7.9 ($P<0.001$). MF was reduced by 44.0% from 7.5 to 4.2 ($P=0.01$). (Table 3). 7 of the 9 patients scored below the

Table 3
Subjective health effects of the intervention

	Before exercise ($N=9$) (95% CI)	After exercise ($N=9$) (95% CI)	P value
Total fatigue (mean)	21.5 (18.7–24.4)	12.1 (9.6–14.6)	$P=0.001$
Mental fatigue (mean)	7.5 (5.7–9.4)	4.2 (3.3–5.1)	$P=0.01$
Physical fatigue (mean)	14.0 (12.4–15.6)	7.9 (5.6–10.1)	$P<0.001$
Physical function (mean)	82.2 (72.6–91.8)	89.4 (80.7–98.1)	$P=0.04$

95% CI, 95% Confidence Interval.

threshold (dichotomised score ≥ 4) for chronic fatigue after completing the intervention. All 6 patients who adhered to the exercise program were among these. The score on the physical functioning scale was improved from 82.2 before start of the exercise period to 89.4 postintervention ($P=0.04$).

3.3. Physiological effects of the intervention

VO_{2max} increased from 33.9 ml kg^{-1} min^{-1} (pre) to 36.0 ml kg^{-1} min^{-1} (post) ($P=0.04$) (Table 4). Time to exhaustion on the treadmill increased from 11 min and 30 s to 13 min and 20 s ($P=0.04$). The sub-maximal heart rate in all sub-maximal speeds and inclinations were reduced from before to after the exercise period at 20 weeks. Body mass index, resting heart rate, target heart rate under exercise testing did not show any significant differences from pre- to post-test.

4. Discussion

Exercise capacity (VO_{2max}) did not differ between the chronic fatigued HDS and HDS without chronic fatigue. Therefore, aerobic exercise capacity does not seem to play an important role in the pathophysiology of chronic fatigue in HDS. The reduction of fatigue after 20 weeks of aerobic exercise indicate that home-based physical exercise may be an alternative treatment for chronic fatigued HDS. Furthermore, the feasibility and adherence rate compare with well to similar exercise intervention studies [22]. VO_{2max} was significantly improved after the intervention.

Interpreting the clinical significance of differences is of greater relevance than the statistical significance level *per se*. According to Osoba's division of difference in health related quality of life scores (HRQOL scores) on a 0–100 scale, scores between 5 and 9 are little differences 10–20 moderate and >20 large differences. Improvement in previous studies of 10–15% was considered clinically significant [23]. The improvement in physical functioning from 82.2 to 89.4 is statistically significant at the 0.05 level in our study. However, according to Osoba the clinical significance is low. Nevertheless, the reduction in all three fatigue scores (FT, PF and MF) of approximately 44% should be considered clinically significant. Similar numerical reductions in fatigue in randomised trials among sufferers of the CFS have been found after cognitive behaviour therapy and graded physical exercise [10,24]. The level of fatigue after the intervention in the present study is at the same level as in the general Norwegian population [1].

An aerobic exercise programme can break the circle of inactivity, impaired performance and increased fatigability [11]. However, the specific mechanisms for the effects are still not fully understood. One could speculate whether subjects without chronic fatigue already use physical exercise as a means to reduce fatigue. Dimeo and colleagues observed an improvement in maximal physical performance and a clear reduction in fatigue after daily walking on a treadmill in five cancer survivors [25]. However, the cohort was heterogeneous with regard to cancer diagnoses and the patients were studied relatively close to termination of cancer-specific treatment (8 weeks–9 months). The improvement may therefore reflect the natural course of fatigue after termination of cancer treatment.

No study has to our knowledge investigated differences in physical exercise capacity among HDS with and without chronic fatigue. Studies on exercise capacity and related cardiopulmonary variables in CFS patients have produced contradictory results [26]. However, CFS-patients show significantly lower exercise capacity than healthy subjects [27,28]. The present results did not confirm such a pattern in HDS.

All 15 patients among non-fatigued HDS attended the tests. A possible reason for the 100% attendance rate in

Table 4
Physical effects of the intervention

	Before exercise ($N=9$) (mean) (95% CI)	After exercise ($N=9$) (mean) (95% CI)	P value
VO_{2peak} (ml kg^{-1} min^{-1})	33.9 (29.9–37.9)	36.0 (31.0–41.1)	$P=0.04$
Maximal walking time (min.s)	11.30 (9.30–12.40)	13.20 (11.10–15.40)	$P=0.04$
Weight (kg)	77.3 (70.0–84.7)	77.0 (69.0–85.0)	NS
Resting heart rate (beats/min)	80 (72–89)	76 (69–83)	NS
Maximal heart rate (beats/min)	192 (180–198)	189 (181–197)	NS

CI, 95% Confidence Interval; NS, non significant.

the control group is less additional medical problems, which is supported by the observation/fact that the fatigued patients gave various medical reasons for not attending the study.

Completion of training depends on factors such as motivation, education, knowledge of, and belief in the beneficial effects of physical activity on health, weight and mental health [29]. Our finding towards a higher educational level in the intervention group supports this. This raises the important question of whether exercise intervention/rehabilitation is for a selected group. Other interventions may be more suitable for other patients. Unfortunately, we do not have any information about earlier exercise habits in the subject group. The drop-out rate in the intervention group is quite similar to other exercise studies [30]. Studies on healthy populations have consistently shown that 50% of individuals who begin a structured exercise programme will drop out within the first 6 months [22]. 6 of the 9 patients who entered the intervention adhered to the prescribed programme. Thus the total drop-out rate was 33%. The three drop-outs completed the objective and subjective pre- and posttests, but were more sporadic exercisers according to the exercise diaries and stored pulse rate results.

The absence of a control group limits the possibility of drawing firm conclusions on the effects of aerobic exercise. The effects could be a Hawthorne-effect (non-specific placebo effect). However, previous reports have shown that aerobic exercise significantly improves physical performance, reduces levels of fatigue and increases quality of life in both CFS patients and patients in early rehabilitation after cancer treatment [10,14,31]. Furthermore, the documented adherence to the programme and the improved physical capacity also weaken the probability for a Hawthorne effect explaining our findings.

Instructed home exercise was chosen before group exercise because most of the patients lived too far away from the hospital. In addition, we wanted to simulate real life conditions in order to assess the feasibility of the intervention.

Rehabilitation programmes of cured cancer patients has been proposed to be a standard offer. However, extensive research may be needed. In studies evaluating such programmes, costs should be taken into considerations along with primary outcome of the effect of the intervention. The physical exercise programme in the present intervention is cheap and easy to carry out for selected and motivated patients. In addition to the favourable health effects, the home-based programme demonstrated feasibility comparable to more extensive and expensive programmes [32,33].

The generalisability of the findings is limited for several reasons. Firstly, this is a small pilot study. The number of patients was low ($n = 9$), and the strength of the statistical analysis is therefore limited. Although the effect size is great and must be considered as clinically significant, studies with a comparable and randomised design are necessary in order to confirm these findings. Future studies are also needed to assess the feasibility of such an intervention and attempts should be made to simulate real life conditions.

Furthermore, this selected group should be followed over time to observe any possible long-term effects.

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Paper 11

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Are palliative cancer patients willing and able to participate in a physical exercise program?

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ABSTRACT

Objective: The primary aim of the present article was to identify palliative care patient populations who are willing to participate in and able to complete a group exercise/physical training program designed specifically for the individual patient.

Method: We conducted a prospective phase II intervention study examining the willingness and ability of palliative care cancer patients to participate in a group exercise physical training program. Patients who were diagnosed with incurable cancer and had a life expectancy of less than 1 year at two outpatient clinics were invited to participate in an exercise program in the hospitals. The groups met twice a week over a 6-week period.

Results: One hundred one consecutive patients were asked for inclusion. Sixty-three patients agreed to participate. Sixteen (25%) of the 63 patients dropped out after consent was given, but before the program started due to medical problems, social reasons, or death. Thus, 47 patients started the exercise program. Thirteen patients withdrew during the program due to sudden death, medical problems, or social reasons. The most frequent reasons for withdrawal were increased pain or other symptoms. Thirty-four patients completed the exercise program.

Significance of results: A high proportion of incurable cancer patients were willing to participate (63%) in a structured exercise program. The attrition rate was high, but despite being severely ill, 54% of the patients completed the exercise period. This shows that a physical exercise program tailored to the individual patient is feasible in this population.

KEYWORDS: Clinical trials, Palliative care, Physical exercise, Intervention, Recruitment

INTRODUCTION

Physical exercise has become common in oncology rehabilitation and has also been proposed for use in palliative care during the past years. However, empirical foundation for such a proposal is limited, and recent reviews ask for more research within physical rehabilitation of palliative care patients (Cheville, 2001; DeLisa, 2001; Santiago-Palma & Payne, 2001).

In general, the recruitment of patients into exercise interventions is a complex process and is influenced by several factors such as health status, earlier

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physical exercise habits, education, gender, age, and relatives (significant others). Participation in physical exercise presupposes personal commitment related to motivation, ability, and will. In healthy populations, approximately 50% of those who start an exercise program drop out during the first 6 months (Dishman, 1990).

The challenges of recruitment and retention of patients in palliative research are well documented (Rinck et al., 1997; Jordhoy et al., 1999). One reason for these difficulties may be that the health professionals caring for the patients see themselves as "gatekeepers." They want to protect the patients from unnecessary and exhausting strains. "Gatekeeping" therefore represents a challenge for researchers seeking to obtain a representative study sample and may introduce a selection bias. Other factors that are related to limited recruitment are unwillingness from the patients or relatives to attend and patients being too frail. However, a recent study of factors influencing participation in palliative care research in a major cancer center found that the majority of patients agreed to enter trials, but that the attrition rate was high (Ling et al., 2000).

It is therefore a special challenge to implement a physical exercise program in a palliative care population. Patient withdrawal during the intervention is a general problem in experimental research *per se*, and of special relevance to both palliative care patients and physical exercise interventions. The external validity of any study depends on size and representativity of the sample, as these factors determine if any effect can be reliably demonstrated and whether the findings generalized. Hence, low recruitment and a large drop-out rate may reduce the sample's representativeness, the strength of the findings, and thereby the ability to generalize from the results.

Palliative cancer patients with short life expectancy experience multiple symptoms, and the clinical presentation is often complex. In theory, the patients would profit from attending a physical exercise intervention to maintain physical functions important for everyday functioning and independence. However, little is known about the patients' interest and ability in attending such a program. Physical exercise studies among palliative cancer patients are few, and description of the recruitment process is not clearly described (Porock et al., 2000; Yoshioka et al., 1994). Thorsen et al. (2005) found that shortly after completing curative chemotherapy, 63% of the approached patients agreed to participate in a home-based flexible exercise program. In two other studies among cancer patients undergoing treatment, about 30% of the approached patients agreed to participate in a resistance exercise program and a cycle ergometer training program, respectively (Courneya et al., 2003; Segal et al., 2003). In preparation for a larger randomized study we therefore completed a phase II study where we wanted to study the recruitment process and the adherence rate to an individualized physical exercise program among palliative cancer patients with short life expectancy.

The research question in the present descriptive report was twofold. The primary aim was to study how many of the palliative cancer patients with short life expectancy ($\leq$12 months) were willing and able to participate in and complete a 6-week group exercise program tailored to the individual patient. Secondary aims were to evaluate the patients' subjective experiences and opinions in attending the program.

PATIENTS AND METHODS

The patients were recruited from the outpatient departments at the palliative and the oncological unit at St. Olavs Hospital in Trondheim and Hospice Lovisenberg day care center in Oslo, Norway. Both curative and palliative patients are treated at the outpatient clinic at the oncological unit. Patients with incurable disease, short life expectancy, and multiple symptoms that require close medical and psychosocial follow-up are referred to the Palliative Unit. Patients at the hospice day care center are palliative patients referred from oncological wards or general practitioners or the patients themselves initiate the contact. In two consecutive periods of 5 months, the outpatient lists at the palliative and oncological units were searched for patients receiving palliative cancer treatment with any cancer diagnoses and place of residence less than 30 min by car from the hospital. In the same period, a physiotherapist searched for patients at the hospice day care center. The patient's medical consultant was contacted and sent a written request as to whether the patient met the following inclusion criteria; palliative cancer patients with a life expectancy between 3 and 12 months, Karnofsky performance status (KPS) $\geq$ 60, who had adequate pain relief (score less than 3 on a 0–10 numerical rating scale), place of residence less than 30 min from the hospital, ability to walk and travel by themselves to and from the hospital by taxi, bus, or private car. The patients were asked if they consented to written information about the study being sent to them. Information about the exercise study and an informed consent form were sent, and the patients were asked to fill in information about cancer type, age, and gender. If they did not want to attend, they

were also asked to specify why. A stamped addressed envelope was enclosed. A total of 101 patients from both hospitals met the criteria and were contacted and given brief information about the study.

The patients who returned the informed consent form and agreed to participate were contacted, included in the study, and went through a physical examination and answered a questionnaire described elsewhere (Oldervoll et al., 2005). The same physical examination and questionnaire were completed immediately after completion of the exercise program. Information about usual physical activity habits the last year (Thorsen et al., 2003) and motivation for attending an exercise program was also filled in by the patients on a numerical rating scale (0–10) before they started in the intervention group. Level of physical activity (LPA) was assessed by the following question: "How has your physical activity level been in your leisure time over the past year?" and had two sublevels of physical activity. The first described a low level of activity, such as walking, the other a high level of activity that leads to sweating and breathlessness. The participants were divided into three groups, depending on their level of physical activity. Group 1 was described as "inactive": low-level activity < 1 h per week and no high level activity. Group 2 was described as "low active": low-level activity ≥ 1 h per week and either no high level activity or < 1 h per week. Group 3 was described as "highly active": independent of the level of low-level activity, high level activity ≥ 1 h per week (Fig. 1).

The intervention program consisted of exercises in groups (3–8 patients in each group) in the gymnasium at the hospital or in the living room at the palliative care day center. The patients participated twice a week, 50 min per session for a 6-week period. The program consisted of a warm-up session (10 min), circuit training with six stations (30 min), and a relaxation/stretching session (10 min). Details of the exercise program are described elsewhere (Oldervoll et al., 2005).

Self-Reported Evaluation Questionnaire

After completing the intervention, the individual patient's experience of the exercise program was registered by seven questions that were designed specifically for this study. The questionnaire included the following seven questions: (1) "How satisfied were you with attending the group?" Response alternatives were from 1 to 7, where 1 was *extremely satisfied* and 7 was *not satisfied*. (2) "Where would you prefer to do the exercise program?" Response alternatives were: (a) at home, (b) at the hospital or hospice, (c) combination of hospital, hospice, and at home, and (d) outpatient clinic, rehabilitation clinic, somewhere else. (3) "Would you recommend group exercise to others who are in a similar situation to yourself?" (4) "Would you prefer individual follow-up instead of in a group?" (5) "Would you consider continuing with a similar type of physical exercise?" Questions (3), (4), and (5) had response alternatives "yes" or "no." In addition the following two open-ended questions were included: (6) Is there anything you manage now that you didn't manage before you started in the group? (7) Comments.

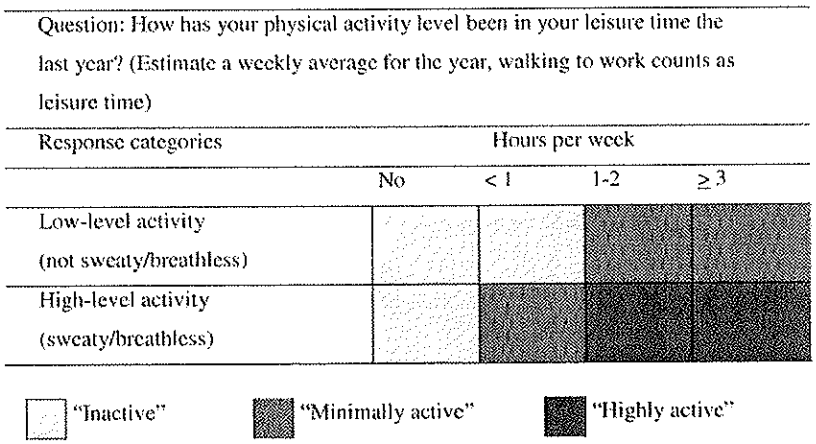

Fig. 1. Level of physical activity (LPA).

Ethics

The study was conducted according to the guidelines of the Helsinki Declaration. The Regional Committee for Medical Research Ethics, Health Region IV approved the study. Appropriate informed consent was obtained from all patients.

Statistical Analysis

All statistical analysis was performed using the SPSS statistical software version 12.0 (SPSS Inc., Chicago, IL). Comparisons between groups were performed by Fisher's exact test for nominal variables and chi square test for trend (linear-by-linear test) for ordinal variables, and t tests for scale variables. The 0.05 criteria were used to define statistically significant effects.

RESULTS

Recruitment

One hundred one patients were invited to attend the study (Fig. 2). The sample consisted of 42 men and 59 women with mean age 66 (SD = 11.1) and KPS 81 (SD = 11.5). Thirty-eight patients either did not respond (n = 11) to the letter being sent to them or did not want to participate (n = 27). These 38 patients were significantly older than those who agreed to participate (64 vs. 70 years, p = 0.007). No significant differences were found according to gender or KPS. Seventeen of the 27 patients provided a reason for their refusal. The reasons were too burdensome to get to the hospital (n = 5), social reason (n = 1), were already engaged in an exercise program (n = 3), lack of energy and mobility (n = 4), and 4 of the patients could not come to the hospice more than once a week. Sixteen of the 63 patients (12 men/4 women, mean age 65 and KPS 82) dropped out after consent was given but before the program started due to medical problems, social reasons, or death. Thus 47 patients started in the exercise intervention. Thirteen patients (28%) dropped out during the exercise period due to due sudden death (n = 1), medical problems (n = 10), or social reasons (n = 2). The most frequent reasons for withdrawal were due to considerable disease progression (n = 5) and pain (n = 5). Thirty-four patients (19 women and 15 men) completed the exercise program with mean age 65 and KPS 83. No significant differences were found according to KPS, gender, motivation, and earlier physical activity habits among those who withdrew and the patients who completed the program (Table 1). However, those who dropped out tended to be younger than those who completed (58 vs. 65 years, p = 0.06).

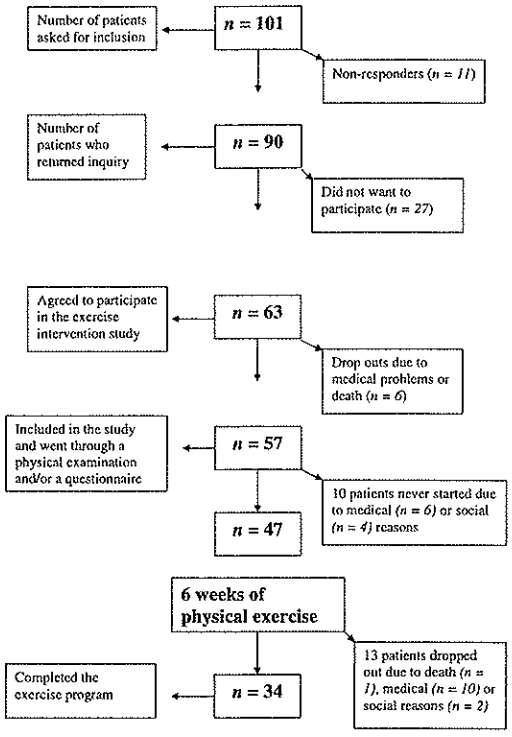

Fig. 2. Flow chart of patient recruitment, attrition, and compliance.

Patient Evaluation

Thirty-three of the patients (97%) who completed the exercise program filled in the evaluation ques-

Table 1. *Characteristics of completers and drop outs in the intervention*

	Completers (n = 34)	Drop outs (n = 13)	p value
Age (years)	65.2 (11.5)	58.1 (11.0)	0.06
KPS	82.9 (13.2)	81.7 (10.5)	0.76
Gender (N (%))			
Male	15 (44)	3 (23)	0.19
Female	19 (56)	10 (77)	
Physical activity level (N (%))			
Inactive	9 (27)	3 (22)	0.55
Minimally active	14 (41)	5 (39)	
Highly active	7 (21)	4 (31)	
Missing	4 (11)	1 (8)	
Motivation	7.8 (1.9)	7.1 (2.8)	0.31
Missing	3	2	

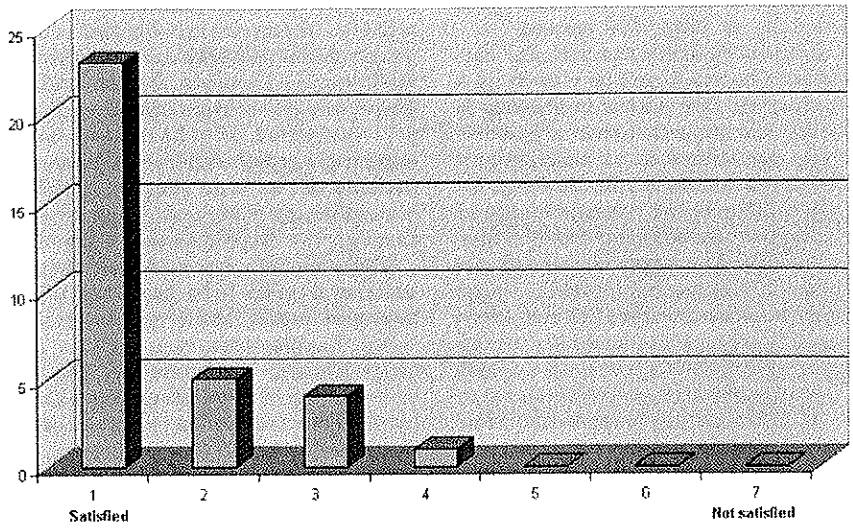

Fig. 3. Self-reported patient satisfaction after attending the exercise program.

tionnaire. Twenty-three patients (73%) reported they were extremely satisfied with the exercise program (results presented in Fig. 3). All participants would recommend the exercise program to other patients in the same situation. Twenty-six patients (77%) reported that they preferred doing the exercises in groups, whereas 5 patients preferred individual training. Twenty-seven patients (80%) reported a desire to continue in a similar program (Table 2). Only 1 patient preferred to do the exercises at home, and 12 patients (36%) preferred to do the exercises in combination at home and at the hospital. Sixteen of the patients (47%) preferred to do the program at the hospital, whereas 3 patients would prefer to exercise at a physiotherapy institute. Eighteen of the 33 patients (55%) reported having increased energy, physical endurance, and increased muscle strength, were able to do more house work, and relied more on their own physical abilities.

Table 2. *Self-reported evaluation of the exercise program*

	Yes *N* (%)	No *N* (%)	Missing
Recommend exercise to other patients in same situation?	33 (97)		1
Individual follow-up to group exercise	5	26 (77)	3
Desire to continue in a similar program?	27 (80)	5	2

DISCUSSION

This study is unique, as no other trials have studied the recruitment process into and retention in a physical exercise program among incurable cancer patients with life expectancy below 12 months. A high proportion of incurable cancer patients (63%) were willing to participate in the structured exercise program. Despite being severely ill, the patients expressed a desire to engage in activities that increased their functional well-being.

In comparison to other intervention studies with physical exercise among cancer patients earlier in the disease trajectory, a similar proportion of the palliative patients were willing to attend (Segal et al., 2003; Pinto et al., 2005). As in other intervention studies, limited information exists about those who did not want to participate except for age, KPS, and gender. No difference in performance status and gender was found between the patients who agreed to participate and those who did not. However, the participants were significantly younger. Among those who gave a reason for not attending, the majority claimed lack of energy and mobility and that it was too burdensome to get to the hospital as major causes. This might indicate a need for specially tailored interventions for the older

patient, for example, in the form of home-based exercises adjusted for the individual patient.

The lack of information about the patients' earlier physical activity habits might be viewed as a limitation of this report. Our clinical impression is that those patients who are accustomed to exercise are more likely to participate in an exercise program even when they are seriously ill. However, we experienced that as long as the patients managed to get to the hospital without too much trouble, they were willing to attend. Furthermore, we did not find any difference in exercise habits the last year when comparing those who completed and those who dropped out. Future studies should try to map earlier physical exercise habits (not only the last year) among participants and nonparticipants to see if this has significance for whether palliative patients want to participate in an exercise intervention.

We do not have information about the number of potentially eligible patients that were in the three different departments during the recruitment period. Therefore, we cannot rule out the possibility of a selection bias such as gatekeeping. However, we believe that the patients asked for inclusion are representative of the palliative population. The completers were a heterogeneous group with respect to age, performance status, and cancer diagnosis. The youngest patient was 40 years old, the oldest being 80, 19 of the 34 patients had a KPS $\leq$ 80 and patients with 10 different diagnoses were represented. Prior to the present study, we included 4 patients in a prestudy to test the feasibility of the exercise intervention. Here we experienced problems to recruit patients into the study from the outpatient clinic at the cancer department. Although the doctors and nurses were well informed about the study, the high-tempo, busy routine made recruitment by doctors and nurses difficult. Hence, making plans for the present study, it was important to generate a suitable recruitment process to find the eligible patients, keeping the problems with gatekeepers in mind.

In palliative care, the attrition rate is high in any study lasting more than a few weeks (Ling et al., 2000). According to earlier studies, attrition rates of 50% over an 8-week period are not uncommon (Dahele & Fearon, 2004). In our study, 54% of the patients who agreed to participate in the exercise study completed the program. As expected, a slightly higher attrition/withdrawal rate was found in our study (46%) compared to other physical exercise studies among cancer patients earlier in the disease trajectory. The drop-out rates across different studies in physical exercise studies among curative cancer patients range from 0% to 34% (Oldervoll et al., 2004). However, no higher withdrawal was registered in our exercise intervention when compared to a randomized trial with aromatherapy massage (aromatherapy and usual care) attending a specialist palliative care day center (Wilcock et al., 2004). During a 4-week period, 11 of 23 patients (48%) in the aromatherapy group withdrew, compared to 5 of the 23 patients in the usual care group (22%). In spite of aromatherapy being less demanding than physical exercise, the dropouts were at a similar level.

The compliers reported that they regarded the exercise program to be useful and that it gave them improved coping skills and increased their well-being. Furthermore, the patients felt that their general health was improved. One of the patients expressed that attending the exercise sessions brought out the healthy side of her, although she was close to death. One patient expressed: "I discovered that it is much better to get out and do something physical even if you're in a situation where you're feeling in bad shape and fatigued. Just to get out and do something else, you nearly forget that things are so bad." The majority of the patients voiced a preference for group exercise as opposed to individual follow up. They felt the group as a commitment and one patient expressed that "it was good to get forced into doing something, it was an appointment you had to attend. It's a problem to get started by yourself, it's really getting more and more of an effort."

In conclusion, although the recruitment process was challenging, a high proportion of the incurable cancer patients were interested in attending structured exercise. The attrition rate was high and it is important to keep this in mind when making power calculations for future randomized studies with physical exercise in palliative populations. Due to a high attrition rate, multicenter studies are advisable to ensure enough patients are recruited within a reasonable period of time.

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Paper IV

The Effect of a Physical Exercise Program in Palliative Care; a Phase II Study

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Abstract

The purpose of this pilot study was to assess the effects of a physical exercise program on physical performance and quality of life (QOL) in incurable cancer patients with short life expectancy. Thirty-four patients participated in a 50 minutes group exercise program twice a week for six weeks. Physical performance was measured by three tests; "6-minute walk test", "timed repeated sit to stand" and "functional reach". Fatigue was measured by the Fatigue Questionnaire (FQ). QOL was assessed by the European Organization for Research and Treatment on Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). The outcome variables were assessed before and after the intervention. The walk length increased and the "timed repeated sit to stand" was reduced ($p < .05$). Emotional functioning improved and physical fatigue was reduced ($p < .05$). Physical exercise seems to be a feasible way to improve well-being among incurable cancer patients. Future randomised trials are needed to confirm the results.

Key Words

Physical exercise, palliative patients, intervention, physical function, physical performance

Running Title

Physical exercise among palliative patients

Introduction

Physical exercise has attracted increased interest in rehabilitation of oncological patients in general and also in palliative care[1]. Still, maintenance and recovery of physical function in incurable cancer patients with limited life expectancy has received relatively little attention in palliative care research and in clinical practice. This is in contrast to patients priorities, Cohen et al found that physical functioning and physical condition were among the most important determinants of palliative patients' quality of life [2]. Most palliative patients experience multiple symptoms such as fatigue, pain, dyspnoea and nausea which may all contribute to reduced physical activity or even inactivity and thereby reduce physical functioning[3]. However, cancer patients treated with opioids for moderate to severe pain achieved pain reduction, but no improvement in physical, social and emotional functioning was observed [4]. The patients remained physically inactive in spite of a significant reduction of pain. These findings calls for the need of a systematic approach (program) in order to motivate and help the patients to improve physical performance.

The majority of cancer patients express a wish to remain physically independent as long as possible and want to maintain strength and endurance throughout the course of their disease. It has been estimated that about 1/3 of cancer patients' reduction in physical functioning may be attributable to physical inactivity [5]. In addition, the cancer disease and treatment often have catabolic effects on muscular strength. The contribution from inactivity, the cancer disease and treatment upon physical function will probably vary across cancer types, dissemination of the disease and treatment regimens.

In general, physical activity and nutrition are important in order to maintain a sense of well-being and enhance quality of life. Exercise rehabilitation during or after curative or life prolonging treatment is now considered as an effective means of restoring physical and psychological function [6].

Randomised clinical trials among curative cancer patients attending physical exercise program show significant increase in cardiovascular capacity, overall health related quality of life (HRQOL), reduction in fatigue and sleeping problems, increased self-reported physical functioning, general well-being, self-esteem, and energy [7;8]. Even seriously ill bedridden cancer patients can profit from exercise [9].

Many palliative patients ask for advice about how they can improve their situation, regarding physical exercise and nutrition. Our clinical impression is that many patients feel especially uncertain about how much and what type of physical activity they can participate in, and they also report that the doctor's answers are vague and unsatisfactory. Studies specifically dealing with physical exercise among incurable patients are few and have methodological limitations such as small sample sizes, samples that are not representative and poor description of the intervention procedures [10-12]. It is thus difficult to determine specifically which patient group may benefit from physical exercise and also what type of exercise that is suitable for patients in different stages of the palliative phase. Segal et al. recently published a randomised intervention study of resistance exercise in both curative and palliative prostate cancer patients [13]. The level of fatigue was significantly reduced and the quality of life and the muscular fitness improved among both the palliative and curative groups as compared to the controls. However, the palliative patients were early in disease trajectory (minimum of 2-3

years of expected survival, many projecting over 4-5 years (personal communication)). The findings may therefore not be valid for patients with shorter life expectancy.

Based on these findings a phase II pilot study was performed in order to evaluate the effects of a six week structured exercise program on HRQOL, fatigue and "objective measured" physical performance in male and female cancer patients with short life expectancy (more than three months and less than one year). The hypothesis was that physical exercise enhances subjective physical and emotional functioning, general well-being, reduces the level of subjective fatigue and maintains "objectively measured" physical performance in palliative cancer patients.

Material and methods

Definitions

In this article the term *self-reported physical functioning* is used to describe subjective physical functioning measured by health related quality of life questionnaires. *Physical performance* is used to describe objective measures of physical function.

Sampling

Patients were recruited from the palliative unit and the oncological outpatient clinic at St. Olavs Hospital in Trondheim ($n = 20$) and from Hospice Lovisenberg (day care patients) in Oslo ($n = 14$). The eligibility criteria included palliative cancer patients with a life expectancy between three and twelve months, Karnofsky performance score (KPS) ≥ 60, who had adequate pain relief (score less than three on 0 - 10 numerical rating scale), lived less than 30 minutes from the hospital, who were able to walk and get to and from the hospital by taxi, bus or private car. A total number of 101 consecutive patients were asked to participate. Sixty

three patients agreed to participate. Twenty nine patients dropped out before entering ($n = 11$) or during ($n = 18$) the program due to sudden death, medical and social reasons. Thirty four patients entered and completed the exercise intervention. Details about the recruitment procedure, drop outs at different stages in the trial and content of the exercise program are described in a separate paper [14].

Subjective and physiological health assessments

Information about primary cancer diagnosis, KPS, previous and ongoing tumour treatment, metastatic disease, medication and comorbidity were registered based upon the patients' medical records. Supplementary demographic information was completed by the patients at a pre-assessment session in the week before start of the intervention.

The European Organization for Research and Treatment of Cancer (EORTC QLQ-30), version 3.0, [15;16] the Fatigue Questionnaire (FQ)[17] and the physical performance tests [18] were completed prior to (at the pre-assessment session) and immediately after the intervention period. To describe the patients' nutritional status and morbidity, a blood sample was taken to determine haemoglobin-, albumin- and C-reactive protein (CRP)-levels before entering the program. None of these variables were used to determine eligibility for the study.

The EORTC QLQ-C30 has 30 items and is composed of scales that assess physical functioning, emotional functioning, role functioning, cognitive functioning, social functioning, as well as global health status. Higher mean scores on these scales represent better functioning. The questionnaire also includes three symptom scales measuring nausea and vomiting, fatigue, and pain, and six single items assessing financial impact and various physical symptoms. Higher scores on the symptom scales/items mean more symptoms. The

raw EORTC QLQ-C30 scores were linearly transformed to 0 to 100 scales. Based on previous publications differences of 10 points or more is regarded as clinically significant [19].

Fatigue was assessed by the Fatigue Questionnaire (FQ). FQ measures physical fatigue (PF) (seven items) and mental fatigue (MF) (four items). All 11 items are designated total fatigue (TF). Higher scores imply more fatigue [17;20;21]

The patients' body weight and height were measured. The body mass index was calculated as the weight in kilograms divided by the height in meters squared. Physical performance was measured by three tests from a performance test battery in patients with cancer [18].

Three physical performance measures were used:

1. *Distance walked in 6 minutes (6-minute walk)*: Patients were instructed to walk as long and fast as they could for six minutes. The subjects walked back and forth a 50 meters long corridor. The distance walked was measured after six minutes. Patients were allowed to rest as necessary during the 6-minute period. Patients who normally utilised walking aids, used them during the test, both pre- and post. The heart rate was monitored continuously during the test using a Polar Sport tester PE 3000. The heart rate and the distance walked in meters at the end of the 6 minute walk were registered.
2. *Timed sit-to-stand (STS):* Subjects sat on a 46-cm high hardback chair without armrest, with their arms folded. Patients who were unable to rise from the chair with their arms folded were allowed to use their arms. The patients were instructed to use their arms as little as possible. They were told to stand up and sit down as fast as they were able to twice. A stop watch was used to record the time. The test was repeated

three times with a brief rest between each test and the average time of the two last trials was used as the outcome.

3. *Functional reach (measure of balance):* Functional reach was measured using the simple clinical apparatus consisting of a levelled meter stick which had been mounted horizontally to the wall at right acromion height of the patient. In order to maintain identical foot placement during all testing conditions, the foot position was traced on a sheet of paper attached to the floor. The patients were asked to make a fist and extend their right arm forward and the position of the third metacarpal was recorded (position 1). The left arm was used where there were limitations with the right arm. Patients were then asked to reach as far forward as they could without losing their balance or taking a step (position 2), and the placement of the end of the third metacarpal was again recorded. No attempt was made to control the subjects' methods of reach. Functional reach was defined as the mean difference in centimeters between position 1 and 2. The test was repeated three times with a brief rest between each test and the average length of the two last trials was used as the outcome.

The testing order of sit to stand and functional reach were random, the 6-minute walk was always performed as the last test.

Exercise procedure

The participants met with the physiotherapist to start in the intervention group within a week after the pre assessment session and were introduced to their personalised circuit training program consisting of six different exercises. The program consisted of exercises in groups (3-8 patients in each group) in the gymnasium at the hospital or in the living room at the palliative care day center. The patients participated twice a week, 50 minutes each session for

a six week period. The program consisted of a warm-up session (10 minutes), circuit training with six stations (30 minutes) and a relaxation/stretching session (10 minutes). At each of the 6 stations, exercises were performed for 2 minutes, with a 30 second interval/pause moving on to the next station. Main focus was mainly on lower and upper limb muscle strength, in addition standing balance and aerobic endurance. Each station had a "set" series of exercises, with the possibility for adjustments according to the individual patients' physical function. The warm up session was aerobic exercises using large muscle groups in upright or sitting position, alternatively exercise bicycling. The six stations in the circuit program were as follows; Station 1: Strength lower limb: "step up": step up and down on a step. Station 2: Balance: Trampoline/thick mat: weight transfer. Station 3: Pull down, resistance exercise for arms. Station 4: Start in standing position, descend to the floor, lie on back, then roll from side to side and stand up again. For patients who were able to, abdominal and back exercises with progression were included. Station 5: Sit on bench, stand up and sit down again. Station 6: Exercise bicycling. To be included in the analysis, the patients should have participated in a minimum of six sessions.

Ethics

The study was conducted according to the guidelines of the Helsinki Declaration. The Regional Committee for Medical Research Ethics, Health Region IV approved the study. Appropriate informed consent was obtained from all patients.

Statistical analysis

All statistical analysis was performed using the SPSS statistical software version 12.0 (SPSS inc., Chicago, Il, USA). The patients from hospice ($n = 14$) and the outpatient clinic ($n = 20$) were combined into one group in the statistical analysis. Since this was a phase II study we

broadly wanted to study whether it was possible to note changes in any effect measures. Any formal sample size calculation was therefore not completed in preparation for this study. The .05 criteria were used to define statistically significant effects. The statistical analysis included frequency analysis, Chi-square-tests (categorical variables) while paired sample t-tests were used to detect differences from pre to post intervention. Two tailed tests for estimates of *P* values were used.

Results

The patient sample was mainly Caucasians, consisted of 15 males and 19 females with a mean age of 65 (Table 1). Thirty of the patients (88 %) were not employed (retired, disabled or on sick leave), while 4 patients (12 %) were working part or full-time. The median KPS was 80 (73 % of the patients had a score $\geq$ 80). The patients recruited from hospice had a significantly lower KPS, compared with the patients from the outpatient clinic, 74 versus 88 (p = .003). Seventy-nine percent of the patients at the hospice were female compared to 40 % at the outpatient clinic (p = .03). The population consisted of patients with different cancer types, with gastrointestinal cancer as the most frequent (n = 16). Other cancer types included breast cancer (n = 5), genitourinary (includes prostate, ovary and kidney) (n = 5), lung cancer (n = 1) and miscellaneous (sarcoma, haematological cancer, lymphoma (n = 7). Eighteen patients (53 %) used opioids or other analgesics (data not tabulated). Metastatic disease was reported in 80 % of the patients, with bone-, lymphatic and lung metastases as the most frequent. During the 6 week period, the mean adherence rate to exercise sessions was 10.6 sessions (maximum = 12). No serious adverse events were encountered during the exercise period. Four patients were still able to work full or part time. In Norway, there is a high level of acceptance for flexibility at work for those with serious illness. Hence it was possible for those in full and part time employment to attend.

[Insert Table 1 about here]

Effects upon self-reported outcomes (EORTQ QLQ-C30 and FQ)

There was a significant improvement in emotional functioning from 69 before intervention to 78 post intervention ($p = .002$). The fatigue score of the EORTC QLQ-C30 decreased from 51 to 43 ($p = .06$), indicating less fatigue (Table 2). The physical fatigue score of the FQ decreased from 12.2 to 10.4 ($p = .04$), the total fatigue score decreased marginally from 17.5 to 15.5 ($p = .06$) while the mental fatigue score remained unchanged from baseline assessment to post intervention (Table 3).

Physical functioning (PF) and global QOL remained stable. The changes in the other scales and items of are presented in table 2. Dyspnoea was reduced from 42 to 30 ($p = .006$). Role- and social functioning improved from 50 to 63 ($p = .02$) and from 55 to 65 ($p = .008$) respectively.

[Insert Table 2 and 3 about here]

Effects upon physical performance

Three patients used their cane at both pre and post test. There was a significant increase in walking length by 29 meters from pre to post test ($p = .007$). A significant decrease in timed "sit to stand" from 5.1 to 4.1 seconds ($p = .001$) was assessed. Finally, measuring balance by "functional reach" improved from 30.4 to 32.8 cm, but failed to reach significance ($p = .07$) (Table 4).

[Insert Table 4 about here]

Discussion

This phase II study shows that a structured physical exercise program is a promising intervention for palliative cancer patients with short life-expectancy. Following the 6-week intervention there was a significant decrease in physical fatigue, an improvement in emotional functioning and an improvement in physical performance among the patients who attended.

To our knowledge this is one of the first studies to systematically test a structured group exercise program in a broad sample of cancer patients with short life-expectancy. The group exercise program was feasible for this group despite the fact that the patients were heterogeneous with regard to age, cancer diagnoses, disease progression and physical functional status. Experienced physiotherapists were responsible for the training sessions and the exercises were tailored for the individual patient's level of physical function to achieve the best possible effect.

The training program was made with main focus on strength promoting activities and exercises to maintain independence and mobility. Although we included one station with treadmill walking/stationary cycling, aerobic endurance exercise was not the main focus of the exercise program. Maintaining physical function and independence in activities of daily living are important factors in palliative patients. In our study we therefore included elements we believe important for independent functioning and general wellbeing. Due to the heterogeneity of the patients regarding physical function, adjustments to the individual patients exercise program was one of the basic features of the intervention.

Although promising, the main limitation of the present study is the lack of a control group. Other factors than the intervention per se might therefore account for the observed improvements. As seen in earlier exercise studies the effects on emotional outcomes may be an effect of being in a group setting. The patients might also have been at a stage of their disease where they irrespective of the intervention, would have improved on health related dimensions. Hence, ongoing oncological treatment and disease progression are important variables that need to be controlled for. As in other intervention studies among palliative patients, this was a challenge which was not addressed optimally in the present study. Future randomised studies are therefore needed to confirm the positive findings of the present study.

Six weeks exercise intervention may be long time in a palliative setting, but short with respect to assess effects in work physiological tests. Although aerobic endurance exercises were included in the programme, the intensity was low and the duration limited. Aerobic capacity (VO_{2max}) was therefore not chosen as a relevant outcome measure since it was not reasonable to assume that major improvement in aerobic/cardiovascular capacity could be achieved. The training program mainly focused on strength promoting activities and exercises to maintain independence and mobility. The ability to stand up and sit down (that requires sufficient strength in lower limbs), walking capacity and balance are fundamental functions for every day life functioning. Relevant tests to measure these abilities were therefore important. Thus, we chose to assess physical function by three tests from a performance battery measuring physical function in patients with cancer [18,22]. Although these tests are a composite of physical functions, they reflect important functions for activities of daily living. It was important that the tests could be performed in any hospital setting and did not require specific instruments, hence making them feasible for clinical use. Other specific tests could have given more precise information concerning aerobic capacity and muscular strength. Therefore we cannot

define specifically how the improvements occurred. For example, the increased walking length may reflect an increased ability to conduct a maximal effort, increased confidence to own capacity or increased muscular strength in the lower limbs. At the pre-test some of the patients had extremely weak thigh muscles. In our clinical practice we have observed that even small doses of strength exercises improve muscular strength in palliative patients. The sample was too small to perform subgroup analyses, but it is our impression that the improvement in muscular strength was highest among the patients with extremely weak thigh muscles at baseline.

The patients were tested twice, before and after the intervention. Theoretically the positive results may therefore be an improvement in how to perform the tests. However, the tests were performed twice with a six-week interval and the improvements also occurred on the subjective measures. We therefore do not think this explains the positive results, although a practice session prior should ideally have been performed prior to the first test to make the patients familiar with the tests.

Contrary to our hypothesis, no change in self-reported physical functioning as measured by the EORTC QLQ-C30 was found. One possible explanation could be that the intensity, frequency and duration of the exercise were not sufficient to give effect upon self-reported physical function. However, improvements were observed in two of the three physical performance tests. Our result is in accordance with the findings of others who observed improved physical performance, but no effect in self reported physical function assessed by the EORTC QLQ-C30 in cancer patients undergoing exercise during and after chemotherapy [23 24]. On the other hand, the Short-Form 36 (SF-36) has been widely used to study effects after physical exercise interventions in cancer patients, and the scale has intercepted changes after

similar interventions[7;10;25-27]. Large discrepancy between subjective and objective measures concerning physical functioning has been revealed, and at present the relation between self-reported physical functioning and detectable physiological changes is not fully understood [28]. It is therefore of interest to consider possible explanations for such discrepancies.

A possible interpretation relates to the properties of the physical functioning scale of the EORTC QLQ-C30. In the present study this scale was chosen because it is cancer specific. Both the content and the number of measurement levels (i.e. the precision) of a scale affect the scale's capability to detect changes. The physical functioning scale of the EORTC QLQ-C30 includes the following items "Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?", "Do you have any trouble taking a long walk?", "Do you have any trouble taking a short walk outside the house?", "Do you have to stay in bed or a chair for most of the day?" and "Do you need help eating, dressing, washing yourself or using the toilet?". The content and the measurement levels differ between the physical functioning scales of the EORTC and the SF-36. The SF-36 physical functioning scale asks for limitations in doing activities during a usual day such as vigorous and moderate activities, lifting or carrying groceries, climbing several flights of stairs, climbing one flight of stairs, bending, kneeling or stooping, walking more than one mile, walking several blocks, walking one block, bathing and dressing. By inspection, the physical functioning scale of the SF-36 includes more items that are relevant to capture changes in functions important for patients' daily functioning. This difference in content can indicate that our choice of physical functioning scale was not optimal. More of the items in the SF-36 physical functioning scale concern strength, which we regard as essential for palliative patients and also reflect the content of the present intervention.

The SF-36 physical functioning also has more measurement levels than the physical functioning scale of the EORTC QLQ- C30 (21 vs. 16), which increases precision and hence the possibility to detect changes. In our opinion, the results of the present study indicate a need for a more appropriate instrument. Other instruments need to be tested in future studies to see if they better capture possible improvements in self-reported physical functioning when such improvements are detected by objective measures.

Because this was a phase II study our intention was to study whether it was possible to detect changes by the chosen effect measures. The Fatigue Questionnaire (FQ) was added because the validity of the fatigue subscale in the EORTC QLQ-C30 has been questioned for use in palliative care patients [29]. The FQ is a more precise measure, measure physical fatigue which is essential among the palliative patients and has more measurements level than the fatigue scale in EORTC-QLQ-C30. Our findings support this in that the physical fatigue scale of the FQ revealed significant and clinically relevant reduction in the levels of fatigue as opposed to the fatigue subscale of the EORTC QLQ-C30. Mental fatigue measures subjective cognitive function and is not influenced by interventions among palliative patients unless subjective cognitive function is of particular interest such as demonstrated in relation to opioid treatment [29]. The results of this study indicate that this dimension of fatigue is of less relevance in palliative patients. The improvement in the level of fatigue and well-being compares well to findings in other studies of palliative patients [11;13;30]. Earlier studies have included breast cancer[30], prostate cancer [13] and mixed cancer [11], which compare well to our sample. However, only one study used resistance exercises in their intervention [13]. Other studies have used ergometer cycling, mixed endurance/resistance exercises and home-based exercises seated in chair, however no activities for strength or resistance [10;11;30]. Although some of the prostate cancer patients included in the study by Segal et al was palliative, their disease was far less

advanced (minimum of 2-3 years of expected survival, many projecting over 4-5 years (personal communication)). The findings may therefore not be valid for patients with shorter life expectancy.

The subject population in the present study received receiving palliative treatment and had a life expectancy between three and twelve months, hence they were not terminal or dying. According to the inclusion criteria they were able to come to the hospice or the hospital twice weekly. However, their age and physical performance status varied and it was therefore important the program was tailored the individual patient. Not all the patients were able to do all the exercises in the circuit every session, and adjustments were made both from one session to another and within each session.

Complete knowledge about the type of physical exercise most beneficial for patients at different stages of the disease progression is still lacking. Most exercise studies among cancer patients up to now have used aerobic exercise as intervention. Recently published reviews suggest that more studies are needed to investigate the potential benefits of resistance exercise or anabolic exercise as the exercise modality to counteract some of the side effects of cancer treatment and disease progression on quality of life and physical function [7 31]. Interventions concerning maintenance of physical functioning among palliative patients have been understudied, and the complete knowledge about type of physical exercise most beneficial for patients at different stages of disease progression is still lacking. Future studies should try to identify the type of exercise most helpful and relevant to people at the end stage of their disease.

In conclusion, although challenging, physical exercise is a feasible intervention in a palliative care setting. The effects on subjective and objective outcomes are encouraging and future studies at different stages of the disease trajectory are warranted. However, randomised controlled trials are needed to confirm the effects of physical exercise in palliative patients.

Table1. Demographic and medical characteristics of the sample

	All patients (n = 34)	
	n	%
Gender		
Female	19	56
Male	15	44
Age (years) Mean (SD) (min-max)	65 (11.5) (40-82)	
Karnofsky status Mean (SD) (min-max)	83 (13.2) (60-100)	
Marital status		
Married/cohabitant	18	53
Single	3	9
Divorced or widowed	10	29
Missing	3	9
Educational level		
≤ 10 years	7	21
≥ 11 years	11	32
University	14	26
Missing	2	6
Smoker		
Yes	5	15
No	24	71
Missing	5	14

Previous cancer treatment		
Chemotherapy	3	9
Radiotherapy	2	6
Hormone	2	6
Surgery	11	33
Combined treatments	11	33
No treatment	2	6
Missing	3	9
Ongoing cancer treatment		
Chemotherapy	9	27
Radiotherapy	0	0
Hormone	3	9
Comorbidity		
Cardiovascular disease	7	20
Pulmonary disease	1	3
Diabetes	3	10
Others	9	27
Blood samples Mean (SD) (min-max)		
Haemoglobin (G/DL)	12.6 (1.6) (9.3-14.8)	
Albumin (G/L)	39.7 (4.2) (28-48)	
CRP (MG/L)	20.6 (30.5) (5-148)	

Table 2. Changes in functioning- and symptom scales in EORTC QLQ-C30 before and after 6 weeks of physical exercise

	Pre	Post	Significance
	Mean (SD)		*p* - value
Functional scales			
Physical	65 (20)	67 (22)	.62
Role	50 (32)	63 (32)	.02
Emotional	69 (25)	78 (20)	.002
Cognitive	72 (24)	75 (30)	.30
Social	55 (30)	65 (29)	.008
Global QOL	61 (21)	64 (20)	.26
Symptom scales			
Fatigue	51 (32)	43 (26)	.06
Nausea/vomiting	18 (25)	14 (19)	.26
Pain	41 (35)	37 (34)	.36
Single items			
Dyspnoea	42 (33)	30 (31)	.006
Sleep disturbance	44 (34)	36 (34)	.16
Appetite loss	37 (38)	28 (35)	.07
Constipation	39 (39)	37 (37)	.74
Diarrhoea	22 (28)	18 (25)	.40
Financial impact	14 (29)	11 (27)	.18

Table 3. Changes in FQ pre and post exercise in all patients

	All patients(n = 34)		
	Mean (SD)		
	Pre	Post	p - value
Total fatigue	17.5 (4.7)	15.5 (5.8)	.06
Mental fatigue	5.3 (1.7)	5.1 (2.0)	.42
Physical fatigue	12.2 (3.6)	10.4 (4.1)	.04

Table 4. Changes in weight, BMI and physical performance before and after exercise

	All (n = 34)		
	Mean (SD)		
	Pre	Post	p - value
Weight (kg)	74 (11.5)	73.6 (12.4)	.10
BMI	25.2 (3.4)	25 (3.1)	.08
Heart rate (beats/min)	119 (26)	122 (28)	.24
6 minute walk (meters)	481 (144)	510 (156)	.007
"Sit to stand" (seconds)	5.1 (2.3)	4.1 (1.4)	.001
Functional reach (cm)	30.4 (6.9)	32.8 (8.3)	.07

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Appendices

62505

SF-36 Spørreskjema om helse

Dato for utfylling: ☐☐.☐☐.☐☐ Pasient nr. ☐☐☐ Hodgkin nr. ☐☐☐☐

INSTRUKSJON: Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.
Hvert spørsmål skal besvares ved å sette et kryss x i den boksen som passer best for deg. Hvis du er usikker på hva du vil svare, vennligst svar så godt du kan.

---

47. Stort sett, vil du si at din helse er

- ☐ Utmerket
- ☐ Meget god
- ☐ God
- ☐ Nokså god
- ☐ Dårlig

48. Sammenlignet med for ett år siden, hvordan vil du si at helsen din stort sett er nå ?

- ☐ Mye bedre nå enn for ett år siden
- ☐ Litt bedre nå enn for ett år siden
- ☐ Omtrent den samme som for ett år siden
- ☐ Litt dårligere nå enn for ett år siden
- ☐ Mye dårligere nå enn for ett år siden

49. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
a. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	☐	☐	☐
b. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid	☐	☐	☐
c. Løfte eller bære en handlekurv	☐	☐	☐
d. Gå opp trappen flere etasjer	☐	☐	☐
e. Gå opp trappen én etasje	☐	☐	☐
f. Bøye deg eller sitte på huk	☐	☐	☐
g. Gå mer enn to kilometer	☐	☐	☐
h. Gå noen hundre meter	☐	☐	☐
i. Gå hundre meter	☐	☐	☐
j. Vaske eller kle på deg	☐	☐	☐

Snu arket!

62505

50. I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

	Ja	Nei
a. Du har måttet **redusere tiden** du har brukt på arbeid eller på andre gjøremål	☐	☐
b. Du har **utrettet mindre** enn du hadde ønsket	☐	☐
c. Du har vært hindret i å utføre **visse typer** arbeid eller gjøremål	☐	☐
d. Du har hatt **problemer** med å gjennomføre arbeidet eller andre gjøremål (for eksempel fordi det krevde ekstra anstrengelser)	☐	☐

51. I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som for eksempel å være deprimert eller engstelig)?

	Ja	Nei
a. Du har måttet **redusere tiden** du har brukt på arbeidet ditt eller på andre gjøremål	☐	☐
b. Du har **utrettet mindre** enn du hadde ønsket	☐	☐
c. Du har utført arbeidet eller andre gjøremål **mindre grundig** enn vanlig	☐	☐

52. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

☐ Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye

53. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene?

☐ Ingen ☐ Meget svake ☐ Svake ☐ Moderate ☐ Sterke ☐ Meget sterke

54. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

☐ Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye

55. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

	Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Følt deg full av tiltakslyst?	☐	☐	☐	☐	☐	☐
b. Følt deg veldig nervøs?	☐	☐	☐	☐	☐	☐
c. Vært så langt nede at ingenting har kunnet muntre deg opp?	☐	☐	☐	☐	☐	☐
d. Følt deg rolig og harmonisk?	☐	☐	☐	☐	☐	☐
e. Hatt mye overskudd?	☐	☐	☐	☐	☐	☐
f. Følt deg nedfor og trist?	☐	☐	☐	☐	☐	☐
g. Følt deg sliten?	☐	☐	☐	☐	☐	☐
h. Følt deg glad?	☐	☐	☐	☐	☐	☐
i. Følt deg trett?	☐	☐	☐	☐	☐	☐

56. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.) ?

☐ Hele tiden ☐ Nesten hele tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

57. Hvor RIKTIG eller GAL er hver av de følgende påstander for deg ?

	Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
a. Det virker som om jeg blir syk litt lettere enn andre	☐	☐	☐	☐	☐
b. Jeg er like frisk som de fleste jeg kjenner	☐	☐	☐	☐	☐
c. Jeg tror at helsen min vil forverres	☐	☐	☐	☐	☐
d. Jeg har utmerket helse	☐	☐	☐	☐	☐

Kreftpasienter og fysisk aktivitet
Kontaktperson fysiolog / stipendiat Line M. Oldervoll
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Tlf. 73 86 72 64

Dato for utfylling ☐☐.☐☐.☐☐☐☐

EORTC QLQ-C30 (Versjon 3.0)

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss x i den boksen som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar. Alle opplysningene vil bli behandlet konfidensielt.

	Ikke i det hele tatt	Litt	En del	Svært mye
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	☐	☐	☐	☐
2. Har du vanskeligheter med å gå en lang tur?	☐	☐	☐	☐
3. Har du vanskeligheter med å gå en kort tur utendørs?	☐	☐	☐	☐
4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐	☐	☐
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐	☐	☐

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
8. Har du vært tung i pusten?	☐	☐	☐	☐
9. Har du hatt smerter?	☐	☐	☐	☐
10. Har du hatt behov for å hvile?	☐	☐	☐	☐
11. Har du hatt søvnproblemer?	☐	☐	☐	☐
12. Har du følt deg slapp?	☐	☐	☐	☐
13. Har du hatt dårlig matlyst?	☐	☐	☐	☐
14. Har du vært kvalm?	☐	☐	☐	☐

Bla om til neste side

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
15. Har du kastet opp?	☐	☐	☐	☐
16. Har du hatt treg mage?	☐	☐	☐	☐
17. Har du hatt løs mage?	☐	☐	☐	☐
18. Har du følt deg trett?	☐	☐	☐	☐
19. Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	☐	☐	☐	☐
21. Har du følt deg anspent?	☐	☐	☐	☐
22. Har du vært engstelig?	☐	☐	☐	☐
23. Har du følt deg irritabel?	☐	☐	☐	☐
24. Har du følt deg deprimert?	☐	☐	☐	☐
25. Har du hatt problemer med å huske ting?	☐	☐	☐	☐
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1 til 7 som best beskriver din tilstand.

29. Hvordan har din helse vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig Helt utmerket

Dato for utfylling: ☐☐.☐☐.☐☐ Pasient nr. ☐☐☐

Dag Mnd År

Kreftpasienter og fysisk aktivitet
Kontaktperson fysiolog / stipendiat Line M. Oldervoll
Institutt for kreftforskning og molekylærmedisin, NTNU
Tlf. 73 86 72 64

Fatigue

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

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

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

- Mindre enn en uke ☐
- Mindre enn tre måneder ☐
- Mellom tre og seks måneder ☐
- Seks måneder eller mer ☐

Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (ett kryss)

- 25% av tiden ☐
- 50% av tiden ☐
- 75% av tiden ☐
- Hele tiden ☐

56614

Vennligst kontroller at du har besvart alle spørsmålene

Karnofsky performance status

Utfører normal aktivitet, trenger ikke spesielt stell	100%	Normal. Ingen plager eller subjektive tegn på sykdom
	90%	Klarer normal aktivitet, sykdommen gir lite symptomer
	80%	Klarer med nød normal aktivitet. Sykdommen gir en del symptomer
Ute av stand til å arbeide. Klarer seg hjemme, greier personlig stell. Trenger varierende grad av hjelp	70%	Klarer seg selv, ute av stand til normal aktivitet eller aktivt arbeid
	60%	Trenger noe hjelp, men klarer stort sett å tilfredsstille egne behov
	50%	Trenger betydelig hjelp og stadig medisinsk omsorg
Ute av stand til å greie seg selv. Avhengig av pleie. Sykdommen i progresjon	40%	Ufør, trenger spesiell hjelp og omsorg
	30%	Helt ufør, hospitalisering nødvendig, men fare for død er ikke overhengende
	20%	Svært syk, hospitalisering og understøttende behandling nødvendig
	10%	Moribund, dødsprosessen er i rask frammasj
	0%	Død

Kreftpasienter og fysisk aktivitet
Kontaktperson fysiolog / stipendiat Line M. Oldervoll
Institutt for kreftforskning og molekylærbiologi, NTNU, 7489 Trondheim
Tlf. 73 86 72 64

IDnr: ☐☐

Evaluering

1. Hvor tilfreds har du vært med opplegget i gruppen?

Svært tilfreds — Ikke tilfreds

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

2. Vil du anbefale fysisk trening i gruppe til andre i samme situasjon? ☐ Ja ☐ Nei

3. Ville du foretrukket individuell oppfølging fremfor gruppe? ☐ Ja ☐ Nei

4. Ville du foretrekke å gjøre opplegget
   - ☐ Hjemme
   - ☐ På sykehus/hospice
   - ☐ Kombinasjon sykehus/hospice og hjemme
   - ☐ Fysikalsk institutt/rehabiliteringsinstitusjon/noe annet

5. Kunne du tenke deg å fortsette med et lignende aktivitetstilbud? ☐ Ja ☐ Nei

6. Er det ting du føler du klarer nå som du ikke klarte før du startet treningen?

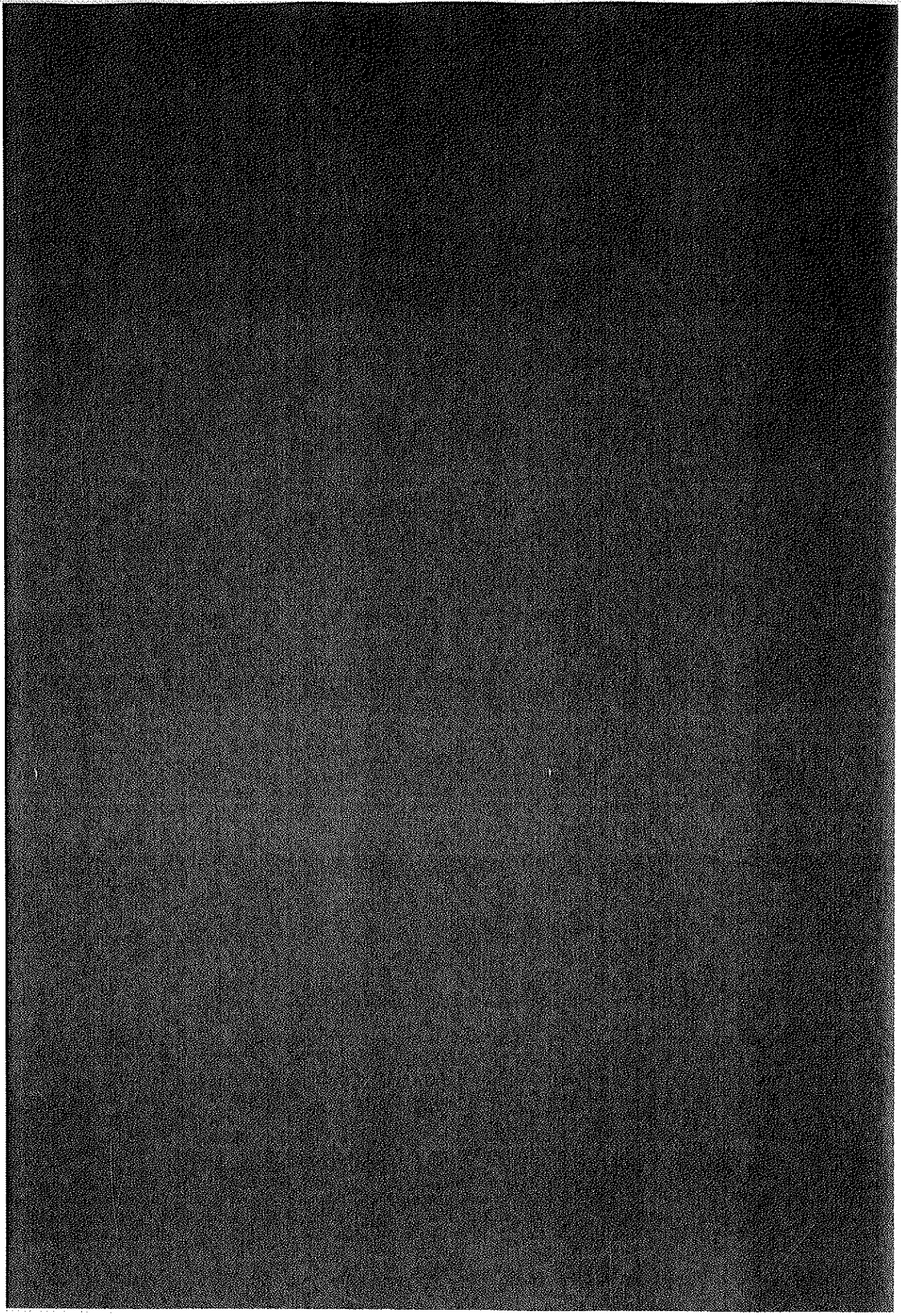
_____

_____

7. Kommentarer

_____

_____



Dissertations at the Faculty of Medicine, NTNU

1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980

6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983

9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984

11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AN STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987

27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988

30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.

33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
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60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
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68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN'S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
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80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
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86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
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1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
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103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
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107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
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109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

1997

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO.*
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR TNF AND LPS: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.

139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
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