Cancer-Related Fatigue - Experience and Outcomes

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ERRATA 2004-03-12

P. 42, Table 6, baseline;
Paper III, p. 26, Table 3, baseline;
Paper IV, p. 19, Table 3, baseline:

Should be	Reduced activity	0.84***
	Reduced motivation	0.68***
	Mental fatigue	0.60***

P. 42, Table 6, baseline;
Paper IV, p. 19, Table 3, baseline:

Should be	Loss of appetite	0.44***
	Nausea/vomiting	0.28*
	Pain	0.42***
	Insomnia	0.32*

Paper IV, p. 9, line 9, text:	… the same was seen for global quality of life ($p<0.001$) and loss of appetite ($p<0.01$).
Should be	… and loss of appetite ($p<0.001$), nausea/vomiting ($p<0.05$), pain ($p<0.001$) and insomnia ($p<0.05$).

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AKADEMISK AVHANDLING

som för avläggande av filosofie doktorsexamen med vederbörligt
tillstånd av Sahlgrenska Akademin vid GÖTEBORGS UNIVERSITET,
Vårdvetenskapliga fakulteten, offentligen försvaras i föreläsningssal
Inge Schiöler, Medicinaregatan 11, Göteborg,
fredagen den 12 mars 2004, kl. 09.00.

Fakultetsopponent är docent Carol Tishelman,
Institutionen för Omvårdnad, Karolinska Institutet, Huddinge.

Avhandlingen baseras på följande delarbeten:

I. Magnusson K, Möller A, Ekman T, Wallgren A (1999) A qualitative study to explore the experience of fatigue in cancer patients. European Journal of Cancer Care 8(4): 224-232.

II. Ahlberg K, Ekman T, Wallgren A, Gaston-Johansson F (2004) Fatigue, psychological distress, coping and quality of life in patients with uterine cancer. Journal of Advanced Nursing 45(2): 205-213.

III. Ahlberg K, Ekman T, Gaston-Johansson F Fatigue, psychological distress, coping resources and functional status during radiotherapy for uterine cancer – experience and relations. Oncology Nursing Forum, accepted for publication.

IV. Ahlberg K, Ekman T, Gaston-Johansson F The experience of fatigue, other symptoms and global quality of life during radiotherapy for uterine cancer. Submitted for publication.

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ABSTRACT
Cancer-related fatigue (CRF) is one of the most common and distressing symptoms in cancer patients and it may interfere with everyday aspects of life. Despite the recent significant increase in the literature on CRF it is nevertheless understudied, and several important questions involving experience, aetiology, assessment and interventions remain unanswered. The primary aim of this thesis was to advance the science of cancer-related fatigue and extend prior work by describing CRF over time and the relationship of fatigue to health-related quality of life in patients with uterine cancer who are receiving radiotherapy. Secondary aims were 1) to gain an understanding of the relationships between fatigue, other symptoms and selected physiological mechanisms associated with fatigue, and 2) to identify predictors of fatigue. The Conceptual Model of Symptom Management (Larson et al 1994; Dodd et al 2001) constituted the major theoretical framework for this dissertation. Both quantitative and qualitative methods have been used. In the qualitative study 15 respondents were included before data saturation was achieved. The data collection and data analysis took place in one simultaneous process in accordance with Grounded Theory. In the quantitative studies 60 patients with uterine cancer who were going to receive treatment with radiotherapy were included. Data was collected before start of radiotherapy, during radiotherapy and after completed radiotherapy mainly through self-rating instruments. The quantitative data was analysed with descriptive and non-parametric statistical methods.

The results of the studies indicated that fatigue is an experience of the whole person. The patients had a low level of experienced fatigue before starting radiotherapy. The fatigue level increased significantly during the course of radiation therapy and after completed treatment. During the period of treatment, between 77 and 89% experienced fatigue. Other symptoms (loss of appetite, nausea/vomiting, diarrhoea, pain) also increased significantly during treatment and the increases were significantly correlated with general fatigue. The patients' psychological distress (anxiety, depression) was low before start of treatment. Although the scores for depression had increased significantly after completed therapy, the levels were still within normal limits. The levels of coping resources, here defined as sense of coherence, were stable throughout the studies. The patients' health-related quality of life was high before start of treatment. The scores for global quality of life and social function decreased significantly over time. There was a significant relationship between general fatigue and global quality of life over time when measured at baseline, after 3 weeks of therapy, and after completed therapy. There was also a significant correlation over time between general fatigue and physical function, role function and cognitive function. There was no significant correlation between general fatigue and IL-1, TNF-alpha or haemoglobin. There was a significant negative correlation between the change in IL-6 and general fatigue.

The variation in the level of general fatigue after completed therapy was explained mainly by the level of experienced general fatigue at baseline.

The knowledge obtained in this thesis should lead to better understanding of the cancer-related fatigue experience, including influencing variables, responses and outcomes, in women with uterine cancer who are receiving radiotherapy. Nursing interventions to help patients with CRF may include careful assessment, identification of patients at risk, and management of problems before the initiation of therapy.

Key words: cancer-related fatigue, symptom experience, symptom assessment, symptom management, health-related quality of life, psychological distress, coping resources, cytokines, nursing, uterine cancer.

ISBN 91-628-5969-2

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To Håkan with love

ABSTRACT

Cancer-related fatigue (CRF) is one of the most common and distressing symptoms in cancer patients and it may interfere with everyday aspects of life. Despite the recent significant increase in the literature on CRF it is nevertheless understudied, and several important questions involving experience, aetiology, assessment and interventions remain unanswered. The primary aim of this thesis was to advance the science of cancer-related fatigue and extend prior work by describing CRF over time and the relationship of fatigue to health-related quality of life in patients with uterine cancer who are receiving radiotherapy. Secondary aims were 1) to gain an understanding of the relationships between fatigue, other symptoms and selected physiological mechanisms associated with fatigue, and 2) to identify predictors of fatigue. The Conceptual Model of Symptom Management (Larson et al 1994; Dodd et al 2001) constituted the major theoretical framework for this dissertation. Both quantitative and qualitative methods have been used. In the qualitative study 15 respondents were included before data saturation was achieved. The data collection and data analysis took place in one simultaneous process in accordance with Grounded Theory. In the quantitative studies 60 patients with uterine cancer who were going to receive treatment with radiotherapy were included. Data was collected before start of radiotherapy, during radiotherapy and after completed radiotherapy mainly through self-rating instruments. The quantitative data was analysed with descriptive and non-parametric statistical methods.

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ORIGINAL PAPERS

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CONTENT

INTRODUCTION

Symptom control has today become increasingly recognized as an important goal in patient care (Chang (2003). Patients with cancer may experience one or more symptoms involving both the occurrence and the distress associated with the symptom. Symptom experience may be seen as the perception of the frequency, intensity, distress, and meaning of symptoms as they occur and are expressed. Symptoms are multiplicative in nature and may act as catalysts for the occurrence of other symptoms. Antecedents to the experience of symptoms may include demographic, disease, and individual factors. Consequences may include the impact on mood state, psychological status, functional status, quality of life, disease progression, and survival (Armstrong 2003).

Fatigue is one of the most frequently reported unmanaged symptoms of cancer patients and affects around 70-100% of all cancer patients (Ahlberg et al 2003). Evidence suggests that high levels of fatigue lead to significant reductions in physical functioning (Jacobsen et al 1999; Given et al 2001), impairment in quality of life (Yellen et al 1997; Cella et al 1998; Redeker et al 2000; Curt 2000; Stone 2002), insomnia, and psychological distress (Redeker et al 2000). Many patients report that they cannot take part in activities as they did before, so they consequently lose control over parts of their life, and this can ultimately lead to feelings of loneliness and isolation and a further decrease in activity. This vicious cycle puts the patient in a distressing position (Flechtner & Bottomley 2003). Even cancer patients in their last period of life seem to experience fatigue. A study with the purpose to investigate symptom burden in the last week of life showed that fatigue was the most common experienced symptom, 83% of a sample of 270 was found to suffer from fatigue (Klinkenberg et al 2004).

The mechanisms responsible for the development of fatigue are poorly understood (Gutstein 2001) and correlations have received little attention (Knobel et al 2000). In a cancer setting, there may be many contributing or associated factors involved in the development of fatigue such as cancer itself, cancer treatment, depression or anxiety, some medications, pain, nausea, vomiting, diarrhoea, poor nutrition, anaemia, infections and insomnia (Tavio et al 2002).

To assess symptom experience adequately, it is essential to obtain information from patients about the occurrence and distress of the symptom experience (McDaniel & Rhodes 1995). Patients are often reluctant to report fatigue, and health-care professionals frequently do not screen for it because they are uncertain about how to treat it (Vogelzang et al 1997). Cancer patients report that their health-care professionals fail to recognise and adequately manage their fatigue (Stone et al 2000b). Health-care professionals have come to accept cancer-related fatigue (CRF) as expected and normal (Mock 2003). In a sample of 576 cancer patients, 52% had never reported their fatigue to the hospital doctor. There were three reasons that contributed to their not reporting fatigue: they thought it was inevitable (43%), unimportant (34%) or untreatable (27%) (Stone et al 2000b). In order to evaluate the problem in Sweden, a questionnaire was mailed to 442 registered nurses in the autumn of 1995. The aim was to determine cancer nurses' views concerning the nature and causes of cancer-related fatigue and the nursing interventions, if any, they employed in the management of this problem. The response rate was 49%. The responses showed that these nurses regarded fatigue as the most common symptom in cancer patients, but there were few established nursing interventions. It was also found that nurses wanted further education and tools for evaluating fatigue, its causes and treatment (Magnusson et al 1997). These results were confirmed by Knowles and colleagues (2000), who found that while nurses were able to describe a number of discrete components of fatigue, they did not necessarily acknowledge the intensity of the symptom or assess fatigue utilising a specific assessment tool. The majority of nurses in that study believed further education in this area would be beneficial in helping them to care for these patients. In their study, Miller & Kearney (2001) found that knowledge and practice on the part of nurses was poor regarding fatigue assessment and management. However, the nurses demonstrated good understanding of the impact of fatigue on cancer patients and an appreciation of the importance of the nurse’s role in fatigue management. Tiesinga and colleagues (2002) reported that nurses, as compared with the patients themselves, are still unable to accurately assess a patient’s fatigue (fair agreement), exertion fatigue (fair agreement) and types of fatigue (slight agreement). As a result, CRF is frequently underreported, underdiagnosed, and undertreated (Mock 2003). Even radiotherapy-induced fatigue is frequently underestimated by medical and nursing staff, only about 50% of patients discuss this problem with a health-care professional, and in one fourth of the cases no intervention is proposed to the patient (Jereczek-Fossa et al 2002).

Uterine cancer (also termed endometrial carcinoma) is one of the most common cancer disease in women. Uterine cancer is more frequent after the reproductive years as compared with other gynaecological cancers; 96% of the women are 45 years or older, with a median of 64 years in women aged 50 to 70 years, and it is often a slowly growing cancer. It can be detected early because it usually produces vaginal bleeding. Endometrial carcinomas comprise 97% of all cancers of the corpus uteri (versus uterine sarcomas, 3%) (Walczak 2000) and are surgically staged with a histological verification of grading and extent of the tumour based on guidelines from the FIGO committee on Gynaecological Oncology (Creasman et al 2001). Uterine cancer is the focus of this thesis.

In Sweden, uterine cancer is the third most common type of cancer in women, and approximately 1200 women receive this diagnosis each year (Cancer Incidence in Sweden 2001). The majority of patients are cured, but the treatment may induce alterations in functional status and quality of life. Retrospective studies have also reported high levels of psychological distress post-treatment (Cull et al 1993). Surgical hysterectomy is the primary treatment for endometrial cancer. In accordance with Swedish guidelines, the majority of patients are offered abdominal radiation therapy as consolidation after surgery. Diarrhoea and abdominal cramps are the most frequently reported side effects during such abdominal radiotherapy (Letschert 1995). There is still a lack of knowledge regarding the experience of fatigue and risk factors for developing fatigue in patients with uterine cancer who receive radiation therapy in a Swedish context.

PURPOSE

The major aim of this thesis was to obtain increased knowledge concerning cancer-related fatigue and extend prior work by describing fatigue over time and the relationship of fatigue and health-related quality of life in patients with uterine cancer who are receiving radiotherapy. Secondary aims were 1) to gain an understanding of the relationships between fatigue, other symptoms and selected physiological mechanisms associated with fatigue, and 2) to identify predictors of fatigue.

This information should lead to a better understanding of the fatigue experience in women with uterine cancer who are receiving radiotherapy among others and may contribute to the development of interventions that could be tested for future use in clinical cancer care.

CONCEPTUAL FRAMEWORK

The Conceptual Model of Symptom Management (Larson et al 1994; Dodd et al 2001a) was used as the major theoretical framework for this dissertation. The study of symptoms is based on the perception of the individual experiencing the symptom and his/her self report. A symptom may be defined as a subjective experience reflecting changes in the biopsychosocial functioning, sensations, or cognition of an individual. In contrast, a sign is defined as any abnormality indicative of disease that is detectable by the individual or by others (Dodd et al 2001a). Symptom management is a dynamic process; it is modified by individual outcomes and the influences of the nursing domains of person, health and illness and environment (Dodd et al 2001a).

The CMSM was chosen as the theoretical framework for this thesis since it is a broad and extensive model that can be used for understanding symptoms, designing and testing management strategies, and for evaluating outcomes. This model was chosen instead of other related models such as the Integrated Fatigue Model based on the work of Piper and colleagues (1987), a model that mainly addresses potential causes of CRF.

Conceptual Model of Symptom Management (CMSM)

The CMSM was developed in the School of Nursing at the University of California in San Francisco. The model was revised by Dodd and colleagues in 2001, see Figure 1. The model makes it possible to study a symptom from both a subjective and an objective perspective. Three interrelated dimensions are taken into consideration: 1) symptom experience, 2) symptom management strategies and 3) symptom outcomes. The model is based on the relation between these three dimensions and the result is that a symptom can be mapped, evaluated and treated. Person, environment and health and illness are variables believed to influence all the dimensions and reflect demographic and biopsychosocial factors. Environment is the aggregate of conditions or circumstances within which a symptom occurs. Health and illness are comprised of variables including health status, disease and injury (Dodd et al 2001b). The model does not distinguish between acute and chronic symptoms.

The symptom management model is based on six assumptions (Dodd et al 2001a):

1) That the gold standard for the study of symptoms is based on the perception of the individual experiencing the symptom and his/her self report.
2) That the symptom does not have to be experienced by an individual in order to apply this model; the individual may be at risk for the development of the symptom because of the impact of a context variable such as a work hazard. Intervention strategies may be initiated before an individual experiences the symptom.
3) That nonverbal patients may experience symptoms, and the interpretation made by a caregiver, for example, is assumed to be accurate for purposes of intervening.
4) That all troublesome symptoms need to be managed.
5) That management strategy may target the individual, a group, a family, or the work environment.
6) That symptom management is a dynamic process, i.e. it is modified by individual outcomes and the influences of the nursing domains of person, health/illness, and environment.

The domains of nursing science as they relate to the CMSM

In the model, the recognised domains of nursing science, person, health/illness and environment, are contextual variables influencing all three dimensions of the model (Dodd et al 2001a).

Person domain

The person variables include demographic, psychological, sociological and physiological components and are intrinsic to the way an individual views and responds to the symptom experience.

The health and illness domain

The health and illness domain is comprised of variables unique to the health or illness state of an individual and includes risk factors, injuries, or disabilities. Variables that are included in the health and illness domain have direct and indirect effects on symptom experience, management and outcomes.

Environmental domain

The environmental domain refers to the aggregate of conditions or the context within which a symptom occurs and includes physical, social and cultural variables. The physical environment may encompass home, work and hospital. The social environment may include the individual's social support network and interpersonal relationships. Cultural aspects of the environment are those beliefs, values and practices that are unique to the individual's identified ethnic, racial or religious group.

The symptom experience

The symptom experience includes an individual's perception of a symptom, evaluation of the meaning of a symptom, and response to a symptom (Dodd et al 2001a).

Perception of a symptom

Perception of a symptom refers to whether an individual notices a change from the way he or she usually feels or behaves. For a valid self-report of symptoms, the person reporting must be responding to a perception of the symptom.

Evaluation of a symptom

Evaluation of the meaning of a symptom can be understood as occurring when people evaluate their symptoms by making judgements about the severity, cause, treatability and the effect of the symptoms in their lives. Evaluation of symptoms entails a complex set of factors that characterise the symptom experience, including the symptom's intensity, location, temporal nature, frequency and, when appropriate, affective impact.

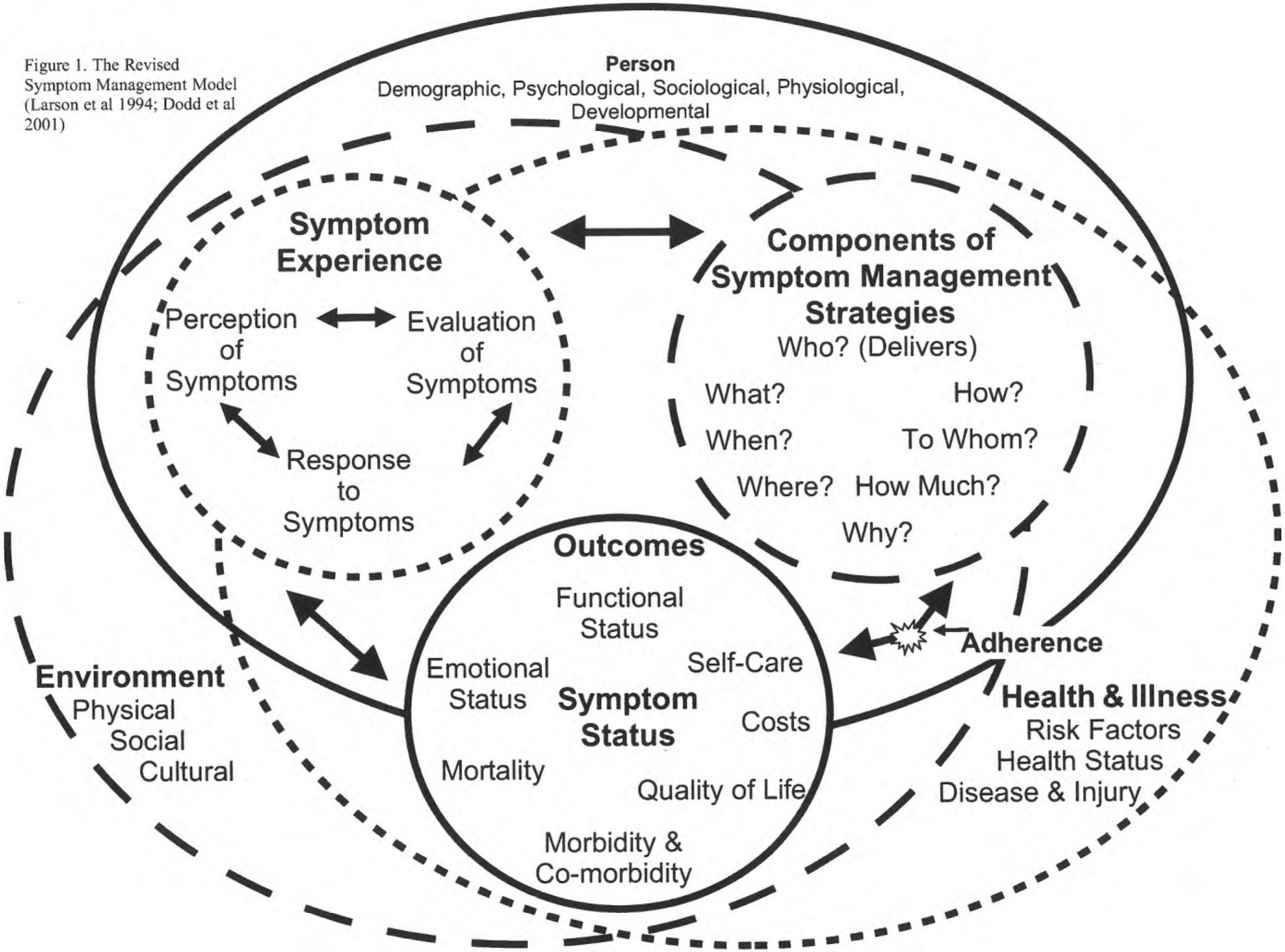
Response to a symptom

A person's response to a symptom includes physiological, psychological, sociocultural and behavioural components. One or more of any of these responses may be seen with a single symptom, for example fatigue.

The outcomes of a symptom

Outcomes emerge from symptom management strategies as well as from the symptom experience. In the model, the outcomes dimension focuses on eight factors: quality of life, functional status, emotional status, mortality, morbidity and co-morbidity, self-care and costs. There are no arrows indicating directionality between the multidimensional indicators and symptom status. All outcomes may be related to one another as well as to symptom status (Dodd et al 2001a).

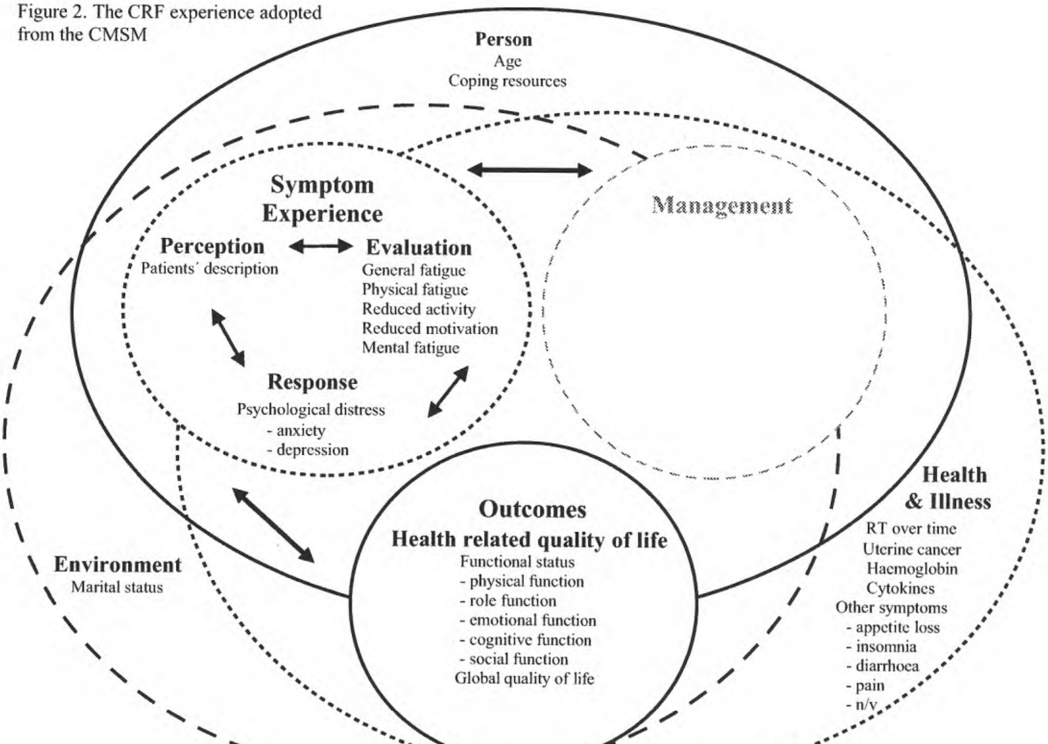
Figure 1. The Revised Symptom Management Model (Larson et al 1994; Dodd et al 2001)



The cancer-related fatigue experience adopted from the CMSM

The focus of this thesis involved selected aspects of the experience of CRF: influencing variables, perception, responses, evaluation and outcomes, see Figure 2. The symptoms management strategies dimension was not included in these non-intervention studies.

Figure 2. The CRF experience adopted from the CMSM



SPECIFIC AIMS AND RESEARCH QUESTIONS

Paper 1

Specific aim:

- To explore how cancer patients experience fatigue and to describe the categories and dimensions of fatigue.

Research question:

- How do cancer patients experience and describe fatigue?

Paper II

Specific aim:

- To provide a comprehensive description of the experience of fatigue, coping resources, psychological distress, other symptoms, and health-related quality of life in patients with uterine cancer before start of radiotherapy.

Research question:

- How do patients with uterine cancer describe the experience of fatigue, coping resources, psychological distress, other symptoms, and health-related quality of life before start of radiotherapy?

Paper III

Specific aims:

- To describe over time the experience of fatigue, coping resources, psychological distress and functional status.
- To determine the relationships among selected variables over time in patients with uterine cancer who are receiving radiotherapy.

Research questions:

- How do patients with uterine cancer who are receiving radiotherapy describe over time the experience of fatigue, coping resources, psychological distress and functional status?
- What is the relationship between fatigue and coping resources, psychological distress and functional status?

Paper IV

Specific aims:

- To describe over time the experience of fatigue, other symptoms (loss of appetite, nausea/vomiting, diarrhoea, pain, insomnia) and global quality of life.
- To describe over time the relationship between fatigue and other symptoms and global quality of life in patients with uterine cancer who are receiving radiotherapy.

Research questions:

- How do patients with uterine cancer who are receiving radiotherapy describe over time the experience of fatigue, other symptoms (loss of appetite, nausea/vomiting, diarrhoea, pain, insomnia) and global quality of life?

- What is the relationship between fatigue, other symptoms and global quality of life?
- Which of the following baseline variables (fatigue, coping resources, psychological distress, other symptoms, and health-related quality of life) account for the greatest variance in fatigue?

Paper V

Specific aim:

- To determine the relationship between fatigue, cytokines (IL-1, IL-6, TNF-alpha) and haemoglobin in patients with uterine cancer who are receiving radiotherapy.

Research question:

- What is the relationship between fatigue, cytokines and haemoglobin over time in patients with uterine cancer who are receiving radiotherapy?

SIGNIFICANCE

Fatigue is one of the most common and distressing symptoms in patients with cancer, and in these patients it is a long-lasting symptom that interferes with everyday aspects of life (Buchsel et al 2000). Despite significant increases in the literature on fatigue in the recent years, fatigue remains understudied and several important questions are still unanswered (Winningham & Barton-Burke 2000).

There is a lack of evidence about the experience and perception of CRF and correlations among selected variables over time in patients with uterine cancer who are receiving radiation therapy. The results obtained in this thesis can provide new knowledge about the experience of cancer-related fatigue, the relation between fatigue and other symptoms, and the outcomes of the symptom in a population of women with uterine cancer. The findings of this thesis could serve as a basis for future longitudinal studies where different prophylactic strategies, including nursing interventions, targeting CRF are prospectively studied. Furthermore, the results of this thesis will help nurses and other health-care professionals to better understand the fatigue experience in cancer patients.

THE STATE OF KNOWLEDGE

The review of the literature concentrates on current knowledge in the area of interest for this thesis. The review includes scientific literature related to the experience of fatigue including influencing variables, perception, responses, evaluation and outcomes as outlined by the conceptual framework derived from the CMSM, see Figure 2.

Cancer-related fatigue (CRF)

Patients and health-care professionals can generally differentiate "normal" fatigue experienced by the general population from fatigue associated with cancer or its treatment. Studies have shown that healthy individuals and persons with a disease experience fatigue in different ways, above all with respect to scope, degree, and recovery (Glaus et al 1996; Cella et al 2002). Fatigue in patients with cancer has only recently emerged as one of the major concomitants of cancer and its treatment, as it has a profound impact on decision making, on health-related quality of life and on numerous symptoms (Marty & Pecorelli 2001). CRF has a clearly detrimental effect on a cancer patient's ability to sustain his or her usual personal, professional, and social relationships (Morrow et al 2002). Although most patients with cancer report that fatigue is a major obstacle to maintaining normal daily activities and quality of life, it is seldom assessed and/or treated in clinical practice (Portenoy & Itri 1999).

The specific mechanisms responsible for the development of CRF are not completely known (Andrews & Morrow 2001), but the literature indicates that both physiological and psychosocial factors seem to be related to the symptom (Ahlberg et al 2003). Proposed mechanisms include abnormalities in energy metabolism related to increased requirements (e.g. due to tumour growth, infection, fever, or surgery), decreased availability of metabolic substrates (e.g. due to anaemia, hypoxaemia, or poor nutrition), and the abnormal production of substances that impair metabolism or normal functioning of muscles (e.g. cytokines or antibodies). There is no clear evidence in support of any of these mechanisms (Portenoy & Itri 1999). Post-operative fatigue has frequently been observed in patients who undergo surgery as a part of their cancer treatment, but there is little research that has examined the causes and correlates of this fatigue (Stasi et al 2003). Further research aimed at identifying the mechanism (s) of fatigue associated with cancer and its treatment requires studies that characterise the phenomenon of fatigue, supplemented by measurements of a range of physiological and biochemical parameters (Andrews & Morrow 2001). In healthy individuals, physical activity has been associated with fatigue (Chen 1986) and it may also be a cause of cancer-related fatigue (Winningham 1999). Fatigue is inversely correlated with activity level and with functional capacity. A consistent decrease in the level of daily activity over the often lengthy period

of cancer treatment may eventually lead to a reduced tolerance for normal activity and high levels of fatigue (Berger & Farr 1999).
Fatigue is symptomatic of a variety of conditions in patients with cancer (Curt 2000a). CRF occurs over a continuum, ranging from tiredness to exhaustion. But in contrast to "normal tiredness", CRF is perceived as being of greater magnitude, disproportionate to activity or exertion, and not completely relieved by rest. CRF is a condition in which a person with cancer experiences an overwhelming and sustained sense of exhaustion and has a decreased capacity for physical and mental work (Glaus et al 1996). Fatigue broadly refers to a sense of malaise, tiredness, exhaustion, or feeling sick (Flechtner & Bottomley 2003). There are conflicting data regarding the daily pattern of fatigue. According to King and others (1985), the experience of fatigue is worse in the afternoon. Glaus and colleagues contend that fatigue is of greater magnitude in the morning (Glaus 1993; Glaus et al 1996). Borthwick and colleagues (2003) found a clear trend indicating that patients with lung cancer who were receiving radiotherapy became more fatigued as the day progressed, and an indication that those who were more fatigued in the morning had rising levels of fatigue by late evening.

Only a few qualitative studies have been conducted with the aim of exploring the experience of fatigue from the cancer patient's perspective (e.g. Glaus et al 1996; Messias et al 1997). In the study by Glaus and colleagues, fatigue involved decreased physical performance, extreme, unusual tiredness, weakness and an unusual need for rest. The emerging concepts broke the concept of fatigue down into expressions of physical, affective and cognitive fatigue. The analysis by Messias and colleagues resulted in eight major thematic categories: (a) experiencing fatigue, (b) effects on well-being, (c) attribution of origin, (d) awareness and expectations, (e) emotional reactions, (f) activity, (g) the "biggest" concern, and (h) strategies and plans. The experience of cancer-related fatigue has never been investigated in a Swedish population using a qualitative method.

The most effective approach to symptom management is to identify the cause of the distressing symptom and correct it. However, in many cancer patients no cause for fatigue can be readily identified (Ahlberg et al 2003). The management of fatigue involves specific (targeting potentially reversible causes of fatigue) and symptomatic (targeting symptoms because no obvious aetiology or reversible cause for fatigue can be identified) intervention and treatment measures (Barnes & Bruera 2002). The management is cause-specific when conditions known to cause fatigue can be identified and treated (Mock et al 2000). The effective management of CRF may involve an informed and supportive team of health-care professionals that assesses patients' fatigue levels regularly and systematically and incorporates education and counselling regarding strategies for coping with fatigue (Johnson 1999), and that uses institutional fatigue management experts for referral of patients with unmanaged fatigue (Mock et al 2000). Two tested interventions with consistent results in terms of alleviating CRF have been reported in the literature:

treatment of cancer-related anaemia with erythropoietin agents (recombinant human erythropoietin and darbepotin alpha) and aerobic exercise (Ahlberg et al 2003, Stasi et al 2003). An exercise programme that combines high- and low-intensity physical activities may be used to prevent and/or minimise both CRF as well as physical inactivity, muscle wasting and energy loss in patients receiving chemotherapy (Adamsen et al 2003). Almost no well-designed clinical trials have been conducted to evaluate pharmacological agents, with the exception of erythropoietin, for the treatment of CRF.

There is a lack of knowledge regarding the experience and development of fatigue in patients with uterine cancer who are receiving radiotherapy that could serve as a base for managing fatigue in the population in question.

In this thesis cancer-related fatigue is defined as a subjective and multidimensional experience of tiredness and/or exhaustion, persistent over time that varies regarding occurrence and impact on health-related quality of life.

Variables that may influence the experience of CRF

Person and environment

Demographic characteristics

Relationships between CRF and demographic characteristics are not well defined. Some socio demographics seem to be associated with fatigue. Age is supposed to be a risk factor for developing fatigue but there is conflicting data. Many conditions that would not be considered normal in a younger population are routinely accepted in older people as a part of so-called "normal" ageing; among these are many chronic and debilitating conditions such as pain, insomnia, weakness and fatigue (Aapro et al 2002). In a study by Schwarz and Hinz (2001), it was found that younger people reported better functioning and fewer symptoms in general compared to older. Liao & Ferrell (2000) contend that fatigue is a symptom often found among older people. When fatigue was measured with a cancer-specific fatigue instrument (MFI-20) in a healthy population, all subscales showed a clear and nearly linear dependence on age, with higher fatigue values for older persons (Schwarz et al 2003). Regarding gender, female patients seem to report fatigue more often than men (Tiesinga 1999). The impact of age and gender may be of great importance in the interpretation of available data regarding prevalence and severity of fatigue in connection with cancer and cancer therapy.

A higher level of fatigue has been seen in unmarried patients with lower yearly income levels (Bower et al 2000). CRF has been consistently correlated with full time employment status (Akechi et al 1999).

Coping resources

Coping, a concept focusing on the situational context and changes within the context, may be simply defined as the effort to manage stress (Lazarus &

Folkman 1984; Lazarus 1999). Coping can be viewed as adaptation, i.e. routine modes of getting along under relatively difficult conditions (White 1985). What a person experiences as stressful depends on both the characteristics of the environment and the characteristics of the individual.

In 1979 Antonovsky presented a theoretical model designed to advance understanding of the relations among stressors, coping and health (Antonovsky 1979). This model later constituted the basis of a salutogenesis orientation called Sense of Coherence (SOC). The concept of SOC reflects the assumption that individuals have to cope with situations of distress and includes the following three components: comprehensibility, manageability and meaningfulness. Antonovsky hypothesised that the stronger the SOC, the more likely it is that a person will be coping successfully with life stressor situations. Theoretically, the SOC is assumed to be consistent in adult life (Antonovsky 1987), and it has been empirically shown that SOC is a relatively stable characteristic (Langius et al 1992; Schnyder et al 2000). On the other hand, one's SOC can quickly change in a negative direction, for example in connection with a traumatic event such as admission to a hospital (Antonovsky 1987; Schnyder et al 2000). SOC is defined by Antonovsky (1987) as "a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that the stimuli deriving from one's internal and external environments in the course of living are structured, predictable and explicable; the resources are available to one meet the demands posed by these stimuli; and these demands are challenges, worthy of investment and engagement".

Risk factors for poor adjustment when afflicted with gynaecological cancer have not been adequately investigated (Pearman 2003). A patient's SOC, here defined as coping resources, could be a factor influencing the experience of CRF.

Health and illness

The cancer itself

Although it seems reasonable to assume that the extent of tumour bulk or the presence of metastatic disease will influence the degree of fatigue, in several studies no correlation was found with either type of tumour or the presence of metastasis (Stone et al 1999; Okuyama et al 2001). This may have been because of the small number of patients representing each type and stage of disease in these studies. However, in one study of elderly patients with different types of newly diagnosed cancers, an effect of disease burden (early versus late clinical stage) on the degree of fatigue was reported (Given et al 2001). In a study on patients with lung cancer who were receiving radiotherapy, higher levels of fatigue were recorded in patients with more advanced disease (Borthwick et al 2003). Further studies are needed to confirm these results.

Radiotherapy

Radiation therapy causes damage to both normal cells and cancer cells by arresting the growth rate. Acute symptoms due to the effect upon rapidly dividing cells (e.g. mucosal cells) develop during radiotherapy. Depending on the areas involved in the radiation field, different symptoms may develop. Acute complications such as diarrhoea in women with uterine cancer who are treated with radiotherapy are usually manageable and resolve soon after irradiation is completed (Jereczek-Fossa 2001).

Fatigue is reported in up to 80% of patients receiving radiotherapy for lung cancer (Bardram et al 1996; Hickok et al 1996), prostate cancer (Stone et al 1997; Janda et al 2000) and breast cancer (Berger 1998). In patients with rectal cancer who were receiving radiotherapy, higher rates of fatigue were observed when radiotherapy was employed in postoperative rather than preoperative settings (Ooi et al 1999). The incidence and severity of fatigue depend on the irradiated volume and involved organs (Marty et al 2001) and/or on the length of radiation therapy (Maher 2000) and may include other symptoms (Harrison et al 2001).

Fatigue usually develops during the first week of treatment and then diminishes two to four weeks after completed therapy. In a study by Magnan & Mood (2003), the onset of fatigue varied widely; patients reported fatigue onset as early as the first and as late as the 38th day of treatment. Several studies have shown that fatigue is felt to be the worst side effect during the last week of treatment (Peck & Boland 1977; King et al 1985; Smets et al 1998a; Fürst & Åhnsberg 2001). The level of fatigue slowly decreases to pre-treatment levels by three months after treatment (Irvine et al 1998; Schwartz et al 2000).

Anaemia

As one of several factors contributing to the development of fatigue, the importance of anaemia has been studied prospectively. Potential mechanisms include haemorrhage, haemolysis, nutritional deficiencies, and the increased production of cytokines, which counteract the differentiation of erythroid precursors, reducing the production of erythropoietin and contributing to impaired iron utilisation (Heinz & Fritz 1998). Anaemia is a deficiency of red blood cells (RBCs) or haemoglobin, which leads to a reduction in the oxygen-carrying capacity of blood (Cella 1998). Anaemia, commonly defined as a haemoglobin level of <12 g/dL, occurs in over 30% of cancer patients at any point in time, and its incidence increases with treatment and progressive disease (Mercadante et al 2000). Untreated anaemia may counteract the efficacy of radiation therapy, and negatively affect activities of daily living, morbidity and mortality (Loney & Chernecky 2000), and quality of life (Loney & Chernecky 2000; Cella et al 2003; Eagleton & Littlewood 2003).

It would seem reasonable to assume that the degree of anaemia correlates with the intensity of fatigue in cancer patients. In a study by Glaus and Muller (2000), haemoglobin was measured in 444 cancer patients with different types and stages of cancer and treatment modalities. The results of this study suggested that cancer patients with a haemoglobin level below 11g/dl had higher levels of fatigue than patients with higher haemoglobin levels, indicating that fatigue was a function of the grade of anaemia. The correlation between fatigue and anaemia was most prominent with respect to physical fatigue such as reduced physical performance or weakness. Only prospective studies can define whether the degree of fatigue depends on the degree of anaemia or if there is simply a correlation between the two that is dependent on mutual factors such as disease stage.

CRF due to anaemia has been studied frequently in connection with chemotherapy, but not during and after radiotherapy in patients with uterine cancer.

Other symptoms

Fatigue has been associated with the coexistence of other symptoms. In this thesis the relationship between CRF and loss of appetite, nausea/vomiting, pain, insomnia, and diarrhoea was further investigated. Whether there is a relationship between CRF and these symptoms has not been adequately investigated in women with uterine cancer who are receiving radiotherapy. We do not know if any of these symptoms can be seen as a predictor of the experience of CRF.

Loss of appetite

The cancer anorexia syndrome, a clinical manifestation of cachexia, is common, occurs in up to 80% of patients with cancer, and is one of the most frequent causes of death in cancer patients (Nelson 2000). Involuntary weight loss may be a consequence of anorexia, and correlations between fatigue and weight loss in patients with cancer have been documented, but there is conflicting data. In a study by Beach and colleagues (2001), weight loss over the course of treatment was significant but did not correlate with fatigue; fatigue did not change significantly during the measurement period. Anorexia has a complex pathophysiology that correlates with poor outcomes and compromises the patient's quality of life. If anorexia, with ensuing malnutrition and weight loss, causes fatigue, efforts to maintain nutritional status can decrease or prevent some of the fatigue associated with cancer and its treatment (Kalman & Villani 1997).

Nausea/vomiting

Nausea is a subjective and unpleasant sensation that may or may not result in vomiting. Despite the development of efficacious pharmacological regimens, nausea remains a frequently reported adverse effect, especially in connection with anti-neoplastic therapy (Bender et al 2002). Abdominal and pelvic irradiation may result in nausea/vomiting (Maher 2000), which can drastically affect the patient's quality of life and physical well-being (Rhodes & McDaniel 2001). Some degree of anorexia usually accompanies nausea. As indicated earlier, nausea could contribute to the development of malnutrition and thus to the development of fatigue. Nausea may also prevent patients from getting enough rest (Bender et al 2002).

Diarrhoea

Diarrhoea is a symptom of major concern and a source of great discomfort for cancer patients. Patients with uterine cancer who receive radiation treatment may be afflicted with diarrhoea as a result (Maher 2000). Symptoms of acute radiation enteritis, predominantly diarrhoea and abdominal pain, occur in more than 70% of patients undergoing pelvic irradiation (Yavuz et al 2002). As would be expected due to the effects of radiation on the small bowel, Christman and colleagues (2001) found, in accordance with findings of King and colleagues (1985), that diarrhoea was prevalent by the second week of radiotherapy in patients with cervical or uterine cancer. The incidence of diarrhoea remained high throughout the last week of treatment. Poorly controlled diarrhoea may result in a range of physiological and psychological effects that extend beyond the patient to significant others and caregivers (Hogan 1998).

Pain

Pain is recognised as a personal experience and a symptom that has great impact on a patient's quality of life. Pain is one of the most common problems experienced by oncology patients. Of patients receiving active treatment, 30-50% experience pain on a daily basis (Ahles et al 1984; Miaskowski et al 1997; Miaskowski & Lee 1999). Pain and fatigue have several components in common, such as being subjective, prevalent in most patients with cancer, and being caused by multiple factors of both a physical and psychological nature (Kaasa et al 1999). A significant positive correlation between pain and fatigue has been reported in cancer patients (Blesch et al 1991). Burrows and colleagues (1998) found in their study that patients with pain, in this case somatic and visceral pain, had significantly higher fatigue scores than pain-free patients. In addition, patients with pain had significantly more symptom distress, lower levels of physical and psychological well-being and total quality of life than pain-free patients. (Burrows et al 1998).

Insomnia

There is limited research on insomnia in patients with cancer, but evidence is accumulating that sleep is often disturbed in these patients, probably owing to a variety of causes (Ancoli-Israel et al 2001). The bulk of research on insomnia has been performed in general populations rather than in patients who are ill. Clinical experience suggests that cancer, as well as cancer treatment and associated symptoms, results in sleep disturbances (Dodd el al 2001b). A study by Berger and Farr (1999), the aim of which was to identify indicators involving circadian activity/rest cycles associated with higher levels of cancer-related fatigue (CRF), showed that women who had increased night awakenings reported higher CRF levels, with the strongest association being number of night awakenings. In a study that evaluated pain, fatigue, and sleep disturbances in 24 outpatients with cancer who were receiving radiation therapy (Miaskowski & Lee 1999), patients reported significantly lower fatigue scores in the morning as compared to the evening. In addition, patients experienced significant sleep disturbances. Patients who had received a higher percentage of their radiation treatments reported more sleep disturbances. Ancoli-Israel and colleagues (2001) reported that some degree of cancer-related fatigue experienced during the day may be related to sleep/wake cycles or to the quality and quantity of sleep obtained at night. In women with breast cancer who were undergoing radiotherapy, fatigue and difficulty sleeping were positively correlated (Mock et al 1997).

Cytokines

One possible explanation for the development of fatigue in cancer patients has been proposed to be the increased secretion of pro-inflammatory cytokines (Greenberg et al 1993; Kurzrock 2001). Pro-inflammatory cytokines, e.g. interleukins, interferon and tumour necrosis factor, are proteins that mediate cell-to-cell communication and have been reported to be released in greater amounts in cancer patients as part of the host response to the tumour, in response to tissue damage, or due to depletion of immune cell subsets associated with treatment for the disease (Herskind et al 1998). This cytokine release may contribute to the development of fatigue by affecting the endocrine system and neurotransmitters (Anisman et al 1996), for example, as suggested in chronic fatigue syndrome (Moss et al 1999). High levels of tumour necrosis factor (TNF-alpha), interleukin-1 (IL-1) and interleukin-6 (IL-6) have been described in a variety of cancers and may contribute to the experience of being fatigued (Kurzrock 2001). There is still a lack of knowledge regarding the correlation between CRF and cytokines in patients with uterine cancer who are receiving radiotherapy.

Evaluation of CRF

The goals of a clinical assessment of fatigue differ from the ways in which fatigue is measured in research, but in both approaches instruments are needed that are sensitive to changes in levels of fatigue (Nail 2002). Validated multidimensional instruments provide a more sophisticated way of assessing fatigue, but they are difficult to use in clinical practice because of time limitations and the burden on the patient. Since fatigue is primarily a subjectively experienced symptom, self-report measures are the most commonly described type of instrument for measuring fatigue in connection with cancer. Available self-report instruments can basically be divided into so-called one-dimensional or multi-dimensional instruments. The response formats of these instruments include yes/no, Likert-type scales, and visual analogue scales.

One example of a specific instrument for CRF is the revised Piper Fatigue Scale (PFS) (Piper et al 1998) that covers four subjective dimensions (cognitive, behavioural, sensory, and affective dimensions) in addition to three open questions regarding cause, other symptoms, and relief measures. Another instrument is the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) (Yellen et al 1997). The FACT-F is designed to measure fatigue symptoms of cancer patients and consists of the 28 items from the FACT-General for assessing health-related quality of life and an additional 13 items for assessing fatigue. There is also an instrument that has been used mainly on patients receiving radiotherapy, i.e. the Multidimensional Fatigue Inventory (MFI-20) (Smets et al 1995; 1996). The MFI-20 is designed to cover five areas: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue, and consists of 20 items.

Responses to CRF

Psychological distress

Patients with cancer may experience psychological distress, e.g. anxiety and depression, at diagnosis, during treatment or over a long period of time as they adjust to life changes (Sivesind & Baile 2001). Anxiety may be defined as "an unpleasant subjective experience associated with the perception of real or imagined threat" (Walker 1990). While anxiety is a common psychological symptom in cancer patients, few patients are diagnosed or treated for the symptoms that can occur due to the debilitating nature of anxiety (Bottomley 1998a). Depression is a symptom that may exist secondary to a physical illness and it is common in patients with different types of cancer (Andrykowski et al 1998). Depression may be defined as "an abnormal mood state in which a person characteristically has a sense of worthlessness, despair, morbid thoughts, and psychomotor retardation or agitation" (Thompson 1999). It is estimated that 20-25% of cancer patients suffer often unrecognised and untreated long-term depression. Symptoms can include lack of sleep, loss of interest in life, anxiety, irritation, loss of concentration and, in severe cases, thoughts of suicide, thereby leading to an overall poor quality of life (Bottomley 1998b). Depressive symptoms can interfere with cancer treatment, increase length of hospital stay, reduce ability to care for oneself, impair quality of life, and possibly reduce overall survival time (McDaniel et al 1995).

CRF has been consistently correlated with psychological factors such as anxiety and depression (Mock et al 1997; Gaston-Johansson et al 1999). A significant association has been shown between fatigue and anxiety (Graydon 1994; Molassiotis et al 1996). There are conflicting data about the relationship between depression and fatigue, but depression seems to be prevalent in patients complaining of fatigue (Broeckel et al 1998; Barraclough 1999). A study by Tchekmedyian and colleagues (2003) examined the relationship between changes in depression and anxiety levels and changes in fatigue levels among anaemic patients with lung cancer. Improvements in fatigue were significantly associated with reductions in anxiety and depression. In a study with the aim of determining whether fatigue, depression, and pain were significant predictors of health status in breast cancer patients, a significant correlation was found between depression and fatigue (Gaston-Johansson et al 1999). Other studies in patients receiving radiotherapy have shown that psychological distress is related to post-treatment fatigue (Smets et al 1998a; Irvine et al 1998).

It must be remembered that fatigue is not only a symptom of many somatic illnesses but also one of the key symptoms of depression (Visser & Smets 1998). The difficulty in distinguishing between fatigue and depression has been discussed in the literature. According to Jacobsen and colleagues (2003), consideration of causal mechanisms suggests why this is difficult. In addition to fatigue being a possible cause of depression and depression being a possible cause of fatigue, both fatigue and depression can share a common cause, e.g. both the cancer itself and cancer treatment can cause both fatigue and depression. These different mechanisms have implications for efforts to distinguish between fatigue and depression and to identify appropriate treatments. For example, recently developed diagnostic criteria for a clinical syndrome of CRF might be useful in identifying fatigue that is caused by a major depressive disorder for which antidepressant therapy is generally indicated (Jacobsen et al 2003).

Relationship between the CRF experience and outcomes

Health-related quality of life

Quality of life (QOL) is an outcome indicator that is multidimensional and theoretically incorporates all aspects of an individual's life (Bowling 1995). Many definitions also include the notion that the patient is satisfied with his or her level of function in the various domains (Whalen & Ferrans, 2001). The concept of quality of life is particularly salient for oncology nursing, since health-care professionals have traditionally viewed patients from a holistic perspective, focusing on the quality of survival. Most quality of life definitions are based on the World Health Organisation's definition of health as not only the absence of disease or infirmity, but also a positive state of physical, mental and social well being (WHO 1993). When defining quality of life as it applies to health-care, the term "health-related" is commonly used to focus on the effects of illness or treatment on quality of life and to distinguish these from aspects beyond the realm of health-care, such as education, income and quality of the environment (Ferrans 2000). In this thesis, health-related quality of life is defined as a multidimensional experience, including various aspects of functioning and subjective appraisal of symptoms and well being (Muldoon et al 1998).

A large percentage of patients with CRF state that their fatigue affects their physical and psychosocial well-being and ability to work, which may lead to a decreased quality of life (Curt et al 2000). Likewise, pain, anxiety and depression have been shown to be associated with impaired quality of life (Smith et al 2003). Other modifying factors, e.g. physical condition, psychological state, coping and personality variables, may also affect the patient's quality of life (Ingham & Portenoy 1996). Quality of life is dependent upon the interpretation and perception of the individual. As cancer patients become too tired to participate fully in the roles and activities that make life

meaningful, the most important effect of cancer-related fatigue might be in the realm of quality of life (Ferrell et al 1996).
Functional status may be defined as the individual's ability to meet his or her basic needs, fulfil his or her usual roles, and maintain health and well-being (Leidy 1994). Functional status is frequently discussed as a key element of nursing practice and a critical outcome criterion, and yet this phenomenon is poorly understood because terms such as functional status, functional ability, health status, and quality of life have been used interchangeably (Leidy 1994). Assessing functional status in patients with CRF can provide information about the individual's functioning in routine undertakings and about the individual's well-being. Functional status is a significant concern for cancer patients, and impairment is often associated with symptoms such as fatigue (Yellen et al 1997; Cella et al 1998; Redeker et al 2000; Curt 2000) and insomnia and psychological distress (Redeker et al 2000).

Until recently, treatment for gynaecological malignancies focused almost exclusively on prolongation of life, and few research studies adequately addressed issues related to health-related quality of life (Pignata et al 2001). The relation between fatigue and health-related quality of life over time in women treated with radiotherapy for gynaecological cancer has not been adequately investigated.

METHODS

Designs

The research designs are as follows:
Paper I: descriptive (qualitative) design.
Paper II: descriptive, correlational design.
Papers III-V: longitudinal, descriptive, correlational design.

Setting

The study took place at the Department of Oncology, Sahlgrenska University Hospital, where patients from both the city of Göteborg and the Western Region (population 1.7 million) of Sweden are referred.

Sample size

In the qualitative study (Paper I) an open sampling was used initially, but in order to cover the variation in the fatigue experience it became more and more strategic. Respondents of different ages, genders and with different medical diagnoses were included. Fifteen patients were interviewed before data saturation was achieved.

The sample in the quantitative studies (Papers II-IV) was estimated at 55 patients at baseline according to the Wilcoxon Signed Rank test. This was calculated based on a statistical power of 80 % and a two-tailed probability of 0.05, assuming the mean change in the main variable general fatigue to be 1.5 with a SD of 3.77 (the estimations of the mean and SD were adopted from observations in earlier studies by Smets et al 1995; 1996) and an estimated 5% dropout of patients over time.

Paper V is a pilot study that will be used to develop further research questions and research designs (Burns & Grove 2001). Due to the high cost of performing cytokine measurements we decided before starting the study to explore the relationship between the variables of interest after 15 patients had been included. We estimated that with 15 patients we would be able to identify trends in the data.

Subjects

Paper I

The inclusion criteria for the first study were that the respondent:

- Was receiving therapy, in this case chemotherapy, as an outpatient
- Had spontaneously expressed to care staff that he or she was fatigued
- Was able to communicate about his/her experience
- Gave verbal consent to participate in the study.

Papers II-V

The inclusion criteria for the other studies were that the participants:

- Were women diagnosed with uterine cancer that, 4-6 weeks after surgical treatment (hysterectomy), were scheduled to receive external radiation therapy (46 Gy, 2 Gy/fraction, 4 days/week) as a curative treatment.
- Gave informed consent to participate
- Had the ability to understand, speak and read Swedish and understood the purpose of the study as well as the testing procedures involved.
- Were willing to have extra blood samples taken (V)

The exclusion criteria were:

- Evidence of dementia and a known history of a psychiatric disorder.

Of the 82 patients fulfilling the criteria for inclusion in Papers II-IV, 22 did not agree to participate. This group of 22 patients did not differ significantly from the study group with regard to demographic characteristics.

Concerning medications for symptoms that could influence the perception of fatigue, other symptoms or the patient's quality of life, only a few patients were treated for pain (n=1), insomnia (n=1) or depression (n=5). Before treatment started the mean Hgb value was 131 g/l. (SD=11.46).

Characteristics of the participants are presented in Tables 1 and 2.

Table 1. Demographic characteristics of the participants in Paper I

Characteristics	**Paper I** N=15	
Age (years)		
Mean	50	
Range	23-88	
	N	**%**
Gender		
Female	8	53
Male	7	47
Diagnosis		
Lymphoma	5	33
Breast cancer	3	20
Gastrointestinal cancer	2	13
Ovarian cancer	2	13
Myeloma	1	7
Pancreatic cancer	1	7
Malignant melanoma	1	7
Treatment intention		
Adjuvant/curative	8	53
Palliative	7	47

Table 2. Demographic characteristics of the participants in Papers II-V

Characteristics	**Papers II-IV** N=60 Baseline		**Paper V** N=15 Baseline	
Age (years)				
Mean	66		64	
SD	11		8	
Median	64		63	
Range	37-84		50-81	
	N	**%**	**N**	**%**
Gender				
Female	60	100	15	100
Marital status				
Married	36	60	10	62
Single / divorced	24	40	5	38
Education				
High school	42	70	9	60
Some college	4	7	1	7
College/graduate degree	14	23	5	33
Work status				
Employed, full-time	8	13		
Employed, half-time	6	10		
Unemployed	1	2		
Sick list	14	23		
Retired	31	52		
Children				
Yes	51	85		
No	9	15		
Children at home	3	5		
Diagnosis				
Uterine cancer	60	100	15	100
Cancer stage (FIGO)				
I	46	77	13	86
II	6	10	1	7
III	8	13	1	7

The Grounded Theory method (Paper I)

Grounded Theory (GT) is a qualitative method that has been developed in the discipline of sociology. The aim of a GT study is to generate theoretical frameworks (a set of explanatory concepts) that explain the collected data.
According to Glaser (1992), GT method is not specific to a particular discipline or type of data. For a long time this method is also seen as an important research approach for the study of nursing phenomena. GT has been used most frequently to study areas in which little previous research has been conducted and to gain a new viewpoint in familiar areas of research (Burnes & Groove 2001). An analysis of the CRF literature, especially that concerning tools for measuring fatigue, suggested that there is a lack of unbiased research (Glaus 1998). Since the experience of CRF is not yet thoroughly understood, the qualitative method of GT was an appropriate choice for Paper I.

Grounded Theory was originated by Glaser and Strauss in the mid to late 1960s (1967). With more post-positivistic underpinnings, Strauss and Corbin reformulated the classical version of the grounded theory in the late 1990s (1998). GT is based on the theoretic framework of symbolic interactionism (Blumer 1969). Symbolic interaction theory explores how people define reality and how their beliefs are related to their actions. People create reality through attaching meaning to situations. The meaning develops and is continuously modified through experience and interactions with others. The purpose of GT is to generate (Glaser 1978) or, as stated by Strauss and Corbin (1998), to develop concepts or a theory that is grounded in data. In Glaser & Strauss (1967), the method is described as inductive, and while in Strauss (1987) it is described as an inductive/deductive method. The interpretation of data is done on the basis of the researcher's previous experiences and understanding, but with an approach to the field of research that is as unprejudiced as possible. An important point is that data collection and open coding occur simultaneously. In other words, data collection and analysis are continuous and ongoing. Once theoretic saturation is obtained and data collection is terminated, then the researcher completes the axial and selective coding.

Analysis of the interview data (Paper I)

Data analysis and data collection took place in one simultaneous process and continued until saturation of information was achieved, i.e. nothing new appeared. An open question was used at the beginning of the interview ("What does fatigue mean to you?"), but the rest of the interview was unstructured. The analysis started soon after the first interview. Each interview was transcribed and read through once or twice before the open coding began.
Analysis of the data was done using an approach that was influenced by the instructions of Strauss and Corbin (1990). In the first step, line-by-line analysis of the transcripts was used, substantive codes related to the content of the data were written in the margin, and recurrent words or sentences were underlined (open coding). The substantive codes were then compared with one another to

find similarities and differences (substantive coding). The significant passages were extracted, marked with the number of the interview and page, and placed into preliminary categories. Each excerpt was then read several times and placed and replaced until the final categories could be determined. The categories were grouped until explicit categories appeared (axial coding). In the last step of the analysis, the categories formed were critically reviewed and when necessary revised to improve the reliability of the analysis (selective coding). Relationships between the dimensions were sought until a concept of fatigue had been arrived at.

Evaluation criteria

There are some specific criteria for judging the applicability of a GT theory: the theory must have fit and relevance and it must work. (Glaser 1978). These were achieved through openness, thoroughness in collecting the data, and consideration of all the data in the theory development phase. Also through that the data was collected until theoretic saturation was obtained. To reduce possible bias during the time of data collection and analysis of the data, frequent discussions took place between the first author and the method supervisor concerning the procedure for the interviews, the interviewer's way of behaving towards the respondents, and the work with the analysis of the data.

Field notes were taken regularly during the period of the interviews. The field notes consisted of thoughts regarding the respondent's expression of fatigue, how the respondent's explanations fit together, and the researcher's experience of the interview.

Measurements (Papers II-V)

All clinical and socio-demographic data were collected from the patients' medical records. An overview of variables and methods/instruments is presented in Table 3.

The following instruments were used in this thesis:

Multidimensional Fatigue Inventory

Fatigue was measured using the Swedish version (Fürst & Åhnsberg 2001) of the Multidimensional Fatigue Inventory (MFI-20) (Smets et al 1995; Smets et al 1996). It consists of 20 statements which cover five dimensions of fatigue based on different modes of expressing fatigue: 1) General fatigue includes general statements concerning the person's function such as "I feel rested", 2) Physical fatigue refers to the physical sensation related to the feeling of tiredness. Reduction in activities and lack of motivation to start an activity are covered by the reduced activities and lack of motivation to start an activity scales in the dimensions of 3) Reduced activity and 4) Reduced motivation, respectively. Finally, cognitive symptoms such as having difficulties concentrating are included in the dimension of 5) Mental fatigue. Each dimension contains four items, and the dimensions are balanced to reduce the influence of response tendencies as much as possible; each dimension contains two items indicative of fatigue and two items contra-indicative of fatigue. The response consists of five squares ranging from agreement with the accompanying statement, "yes, that is true", to disagreement, "no, that is not true". The statements refer to the situation of the last few days. For each scale a total score is calculated by summation of the scores of the individual items, and scores can range from a minimum of 4 to a maximum of 20. The instrument can be presented as a written questionnaire to be completed in the absence of the researcher.

The MFI-20 has been used in several studies of cancer patients and has demonstrated high reliability and validity when used with patients receiving radiotherapy (Smets et al 1995). The Swedish version of the MFI-20 has shown good internal consistency (Cronbach's alpha 0.75-0.94) (Fürst & Åhnsberg, 2001). A reliability analysis (internal consistency) was also performed for the five scales in present population before the start of radiotherapy. The satisfactory level of Cronbach´s alpha was above 0.82 for all the scales: general fatigue 0.89, physical fatigue 0.90, reduced activity 0.90, reduced motivation 0.82 and mental fatigue 0.87.

Hospital Anxiety and Depression Scale

The Swedish version of the Hospital Anxiety and Depression Scale (HAD) (Zigmond & Snaith 1983) is a 14-item screening tool that has been used to measure the degree of anxiety (HADA) and depression (HADD). HAD is specifically developed for the detection of anxiety and depression in medically ill patients by excluding items related to somatic symptoms. The HAD scale consists of brief scales of anxiety (7 items) and depression (7 items). Responses concern feelings during the past week. Scores on each subscale can range between 0 (no symptoms of depression / anxiety) to 21 (numerous and severe symptoms). The scale can be used to monitor change over time. The HAD has been used in studies involving general medical outpatients, individuals experiencing chronic illnesses, e.g. cancer, and cardiac conditions, and nonpatient community volunteers, (Grimm 1997). HAD scores are defined as follows: 0-7 = non-cases, 8-10 = doubtful cases and 11-21 = cases (Zigmond & Snaith 1983). The internal consistency is high with a Cronbach's alpha of 0.93 for anxiety and 0.90 for depression (Pasacreta 1997).

Sense of Coherence Scale

Coping resources, here defined as the concept of SOC, has been operationalised into the Sense of Coherence Scale (Antonovsky 1987; 1993). The SOC scale was designed to test the hypothesis that Sense of Coherence is causally related to health status and that it measures overall orientation towards demanding life situations (Antonovsky 1987). The scale measures perceived comprehensibility, manageability and meaningfulness. In this study the 29-item version (comprehensibility 11 items, manageability 10 items, meaningfulness 8 items) was used, and each item has a 7-point response scale. A high score on the scale indicates a high level of coping resources (range 29-203). Although the items on the three dimensions are visually separable, the SOC questionnaire was developed to measure the SOC as a global measure. The Swedish version of the SOC (29 items) has been tested and a Cronbach´s alpha ranging from 0.77 to 0.89 has been reported (Langius et al 1992; Lundman & Norberg 1993; Forsberg & Björvell 1996).

EORTC Quality of Life Questionnaire

The state of the art in relation to the assessment of quality of life in cancer patients is developmental; no measure satisfies a multidimensional model of quality of life (Bowling 1995). That implies that the administration of more than one scale is necessary in order to tap all the required dimensions.

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the QLQ-C30, version 3, (Aaronson et al 1993; Fayers et al 1995), is a disease-specific measure covering general aspects of health-related quality of life. The instrument has been translated and validated in 38 languages, with a Cronbach's alpha coefficient 0.70 (Aaronson et al 1993), and it has been used in more than 15000 studies worldwide (Kaasa & Loge 2003). The Swedish version of QLQ-C30 has been widely used and has demonstrated high reliability and validity in different groups of cancer patients.

The instrument consists of 30 items covering five functional scales (physical, role, cognitive, social, emotional function and social), three symptom scales (fatigue, pain and nausea/vomiting), and a global health and quality of life scale. Six single items are also included that measure other symptoms commonly reported by cancer patients (loss of appetite, insomnia, dyspnoea, diarrhoea, constipation, financial difficulties). Subjects are asked to rate each item on a four-point scale(?) ('not at all' to 'very much') with the exception of 'global quality of life', which ranges from 1 ('very poor') to 7 ('excellent'). Scores are then transformed into a 0-100 scale where a higher score represents a higher level of function ("better") or a higher level of symptoms ("worse").

The fatigue subscale is a brief measure with three items: have you felt weak, did you need a rest and have you felt tired? These items are based on the assumption that fatigue is a side effect of the disease process. A significant level of reliability has been found for the fatigue subscale, with Cronbach's alpha of 0.80 and above, and patient acceptability of the tool is high (Bottomley 2001).

In the quantitative studies within this thesis the instrument was used to measure fatigue, health-related quality of life and influencing symptoms (pain, nausea/vomiting, loss of appetite, insomnia, diarrhoea).

Measurement of cytokines

For cytokines measurements, peripheral venous blood samples were drawn into sterile blood collection tubes. The tubes were centrifuged for 20 minutes at 3000 rpm at 4°C. The plasma samples were frozen at -70°C until the analyses were performed. Plasma levels of IL-1 and TNF-alpha were determined by an

ELISA procedure (Medgenix, Fleurs, Belgium) using recombinant proteins to construct a standard curve. Plasma levels of IL-6 were analysed using a bioassay procedure, using cell line B13.29, subclone B9, known to be dependent on IL-6 for growth. The analysis of all samples was done at the same time point by the same person.

Table 3

Table 3. An overview of variables and methods/instruments

	Variable	Method/Instrument	Validity/Reliability
INFLUENCING VARIABLES			
Person	Age	Medical record	NA
	Coping resources	SOC	Cronbach's alpha 0.89
Environment	Marital status	Medical record	NA
Health & illness	Cancer stage	Medical record	NA
	RT over time	Medical record	NA
	Haemoglobin	Medical record	NA
	Other symptoms:		
	- loss of appetite	QLQ-C30	Cronbach's alpha 0.70
	- nausea / vomiting		
	- diarrhoea		
	- pain		
	- insomnia		
	Cytokines	Analysis of plasma	NA
	-IL-1, IL-6, TNF-alpha		
SYMPTOM EXPERIENCE			
Perception	Fatigue	Grounded Theory	NA
Evaluation	General fatigue	MFI-20	Cronbach's alpha 0.82-0.90
	Physical fatigue		
	Reduced activity		
	Reduced motivation		
	Mental fatigue		
	Fatigue as a side effect of the disease process	QLQ-C30	Cronbach's alpha 0.80
Responses	Anxiety	HAD	Cronbach's alpha 0.93
	Depression	HAD	Cronbach's alpha 0.90
OUTCOMES			
	Functional status	QLQ-C30	Cronbach's alpha 0.70
	Global quality of life	QLQ-C30	

Procedure

Potential subjects who met the inclusion criteria were identified by the nurses at the outpatient unit (I) or were consecutively identified by the project leader or the research nurses through the hospital's clinical database (II-V). All potential participants received verbal and written information. The participants who were included in the studies gave their informed consent in accordance with the ethics committee before any data were collected.

Paper I

The interviews took place in a quiet room at the hospital and were conducted by the first author between May 1997 and April 1998. Each interview took place during a single visit. All interviews were taped and transcribed verbatim by the same person (first author). Fifteen patients were interviewed before data saturation was achieved. Demographic and clinical data (age, cancer diagnosis, treatment intention) were extracted from the patients' medical records.

Papers II-IV

The data were collected within two weeks before start of radiotherapy (baseline), after 30 Gy (+ 3 weeks), and after completed treatment with 46 Gy (+5-6 weeks).

The first questionnaires (baseline) were given to the patients, instructions were given, and they were completed before the patients started their radiotherapy. Most of the subjects completed their questionnaires at the hospital. The remaining questionnaires (after 30 Gy and after completed therapy) were given directly to the patients when they visited the radiation unit or were sent to the patients' homes with a pre-stamped return envelope. When a patient completed the questionnaire in her home she was carefully instructed about how this should be done and about the importance of filling it in and sending it back as soon as it was completed. One reminder was handed or sent out.

Demographic and clinical data (age, level of education, marital and work status, cancer stage, other medication, haemoglobin) were extracted from the patients' medical records. The data were collected during the period 2000-2002.

Paper V

Fifteen patients were included in this pilot study. The data were collected before start of radiotherapy, after 30 Gy (+ 3 weeks) and after completed treatment with 46 Gy (+5-6 weeks). After receiving instructions the fatigue questionnaire (baseline) was completed by the patients in a private room at the hospital before they started radiotherapy treatment. The remaining questionnaires (after 30 Gy and 46 Gy) were given directly to the patients when they visited the radiation unit. Blood samples for the determination of cytokines and haemoglobin were taken when they visited the hospital, on the same day as the fatigue measurement. There were no missing data. All data were collected in 2002.

Analysis approach (Papers II-V)

Statistical methods

Mean (m), standard deviation (sd) median (md) and range were calculated for descriptive purposes. All tests were two-tailed and conducted at 5% significance level.

Papers II-IV

For comparison over time for each variable, Friedman's test with Tukey´s post-hoc test were used. Spearman's correlation coefficient (denoted as r) was used for all correlation analyses. For correlations between two variables over time, intra individual correlations were calculated and formally tested with the Wilcoxon signed rank test. Stepwise linear regression was used, after transforming the dependent variable to a normal distribution by calculating normal scores using Blom's method (1958), to find independent predictors related to change in General Fatigue and General Fatigue at baseline.

The reason a non-parametric test was chosen was that data obtained from the rating scales were ordered categorical responses designated as numerals. Due to the data distribution, the data are described as medians and ranges. However, since results of the MFI-20, HAD, SOC and QLQ-C30 are given as means (m) and standard deviations (SD) in reference studies, we also present data in that manner to facilitate comparisons.

Paper V

All correlations were analysed with Pitman's nonparametric Permutation Test (Good 2000a). In addition, Pearson's correlation coefficient was calculated for descriptive purposes. For comparison over time, Fisher's nonparametric permutation test for matched pairs (Good 2000b) was used.

Ethics

The World Medical Association's Declaration of Helsinki (WMA 2000), stipulates the ethical regulations regarding research involving human research subjects. Ethical considerations in this study concern individual autonomy, informed consent, and the risk of causing emotional injury through the questionnaires. All data from the investigation have been treated as confidential information and are stored in a safe place. The studies were approved by the Ethics Committee at Göteborg University.

RESULTS

The experience of fatigue in cancer patients (Paper I)

The results of the Grounded Theory study showed that the concept of fatigue could be understood as a process consisting of the experience of fatigue leading to consequences that result in actions. Three major categories were found: (1) experiences (of loss, need, malaise, psychological stress, emotional affection, abnormal weakness, difficulties in taking the initiative); (2) consequences (social limitation, affected self-esteem, affected quality of life); and (3) actions (coping activities). The categories were constructed on the basis of dimensions extracted from the data. The process contained a dynamic development within the categories.

The respondents tried to explain the experience of fatigue, but not everyone could find a word for it. Examples of the words used were "listless", "sluggish", "faint", "despondent", "apathetic", "tired", "slack", "indifferent", "paralysing fatigue". The use of metaphors instead of the term fatigue was also common, for example "my feet feel like lead" or "I couldn't run, my legs felt like spaghetti".

The experience of fatigue and selected variables in patients with uterine cancer *before* treatment with radiotherapy (Paper II)

The second study of the patients' experience of CRF before start of radiotherapy treatment showed that they experienced a low level of all dimensions of fatigue. The intensity levels of anxiety and depression were also low and defined as non-cases (0-7). The levels of other symptoms (appetite loss, nausea/vomiting, diarrhoea, pain, insomnia) were low and the scores for health-related quality of life were high.
Although the scores for fatigue mainly showed mild levels, 77% of the patients experienced some level of general fatigue before start of radiotherapy treatment. Other symptoms were also experienced to some degree: nausea/vomiting 22%, loss of appetite 18%, pain 37%, insomnia 55% and diarrhoea 15%, see Table 4.

Correlations among multiple variables (fatigue, psychological distress, coping resources and health-related quality of life) were analysed. Statistically significant correlations were found between general fatigue and anxiety ($r=0.36$, $p<0.01$), and between general fatigue and depression ($r=0.71$, $p<0.001$). The other dimensions of fatigue (mental and physical fatigue, reduced motivation and activity) were also found to be correlated with statistical significance to anxiety and depression. The correlation between general fatigue and coping resources was also statistically significant ($r=-0.49$, $p<0.001$). There was a significant negative correlation between general fatigue and global quality of life at baseline (r=-0.68, p<0.001). There were also significant negative correlations between general fatigue and the patients' physical function (r=-0.76, p<0.001), role function (r=-0.67, p<0.001), emotional function (r=-0.53, p<0.001), cognitive function (r=-0.44, p=<0.001) and social function (r=-0.39, p<0.01) at baseline.

A stepwise regression analysis performed *before* start of radiotherapy treatment, with anxiety, depression and coping resources as possible explanatory variables, resulted in a model with only depression as a significant explanatory variable of general fatigue. Depression explained 44% (R-square) of the variance in general fatigue (p<0.001). In addition, after adjustment for age, cancer stage and marital status, depression was still a significant independent explanatory variable for fatigue (R-Square 48%, p<0.001).

Table 4. Prevalence of fatigue and other symptoms over time

	Baseline N=60	**+30 Gy** N=47	**+46 Gy** N=53
General fatigue	77%	89%	87%
Nausea/vomiting	22%	64%	44%
Loss of appetite	18%	47%	45%
Pain	37%	55%	55%
Insomnia	55%	47%	51%
Diarrhoea	15%	94%	89%

Table 5 presents means, SDs, medians and ranges of all variables of interest at baseline. Table 6 presents correlations between all variables.

The experience of fatigue and selected variables over time in patients with uterine cancer *after* completed treatment with radiotherapy (Papers III-IV)

During the first three weeks of therapy the changes from baseline were significant for all the fatigue dimensions (p<0.05). After completed radiotherapy there were significant changes over time for general fatigue, physical fatigue, reduced activity and reduced motivation (p<0.05), but not for mental fatigue. The results showed that 87% of all patients experienced some level of fatigue after completed treatment, see Table 4.

The participants reported normal levels of anxiety and depression that were defined as non-cases (0-7) during and also after completed radiotherapy, although the change in depression from baseline to after 3 weeks of therapy and after completed therapy was significant ($p<0.05$). The scores for sense of coherence did not increase significantly over time. Appetite loss, nausea/vomiting, diarrhoea and pain increased significantly during the first three weeks of therapy ($p<0.05$). After completed therapy the changes from baseline were significant for loss of appetite, nausea/vomiting and diarrhoea ($p<0.05$), but not for pain. The score for insomnia showed small changes but the changes were never significant. The prevalence for diarrhoea over time indicated that between 89-94% of all patients experienced some level of diarrhoea during and after completed treatment. For the prevalence for the other symptoms over time, see Table 4.
During the three first weeks of treatment, physical function, cognitive function and social function decreased, but not significantly. The opposite was seen for role function and emotional function, which increased. After completed therapy all dimensions of function had decreased, and for social function the decrease was significant ($p<0.05$). During the first three weeks of treatment the score for global quality of life decreased significantly ($p<0.05$). The same significant decrease was seen after completed therapy ($p<0.05$).

The correlations over time between general fatigue and physical fatigue ($r=0.65$, $p<0.001$), reduced activity ($r=0.58$, $p<0.001$), reduced motivation ($r=0.55$, $p<0.01$), mental fatigue ($r=0.44$, $p<0.05$) and the fatigue subscale from the QLQ-C30 ($r=0.79$, $p<0.001$) were significant. The patients' coping resources did not correlate with general fatigue over time. With the exception of insomnia the correlation with general fatigue over time was significant for all symptoms: loss of appetite ($r=0.72$, $p<0.001$), nausea/vomiting ($r=0.65$, $p<0.001$), diarrhoea ($r=0.71$, $p<0.001$) and pain ($r=0.37$, $p<0.01$). The correlation over time between general fatigue and psychological distress was significant for depression ($r=0.51$, $p<0.001$) but not for anxiety. There was a significant negative correlation between general fatigue and global quality of life after completed therapy ($r=-0.57$, $p<0.001$). The correlation over time was also significant between general fatigue and physical function ($r=-0.44$, $p<0.001$), role function ($r=-0.48$, $p<0.01$), and cognitive function ($r=-0.46$, $p<0.01$), but not emotional function ($r=-0.10$) or social function ($r=-0.41$).

A stepwise regression analysis, with other symptoms (loss of appetite, nausea/vomiting, diarrhoea, pain, insomnia) and global quality of life at baseline as possible explanatory variables for general fatigue at baseline, showed that global quality of life at baseline explained 53% (R-square) ($p<0.001$) of the variation in general fatigue at baseline. Global quality of life was the only selected variable. Even after controlling for selected demographic factors (age, marital status and cancer stage), global quality of life was still significant. When anxiety, depression and functional status were investigated as possible explanatory variables for general fatigue, depression ($p<0.01$), physical function ($p<0.01$) and role function ($p<0.001$) explained 69% (R-square) of the variation in general fatigue at baseline. In addition, after adjustment for age, cancer stage and marital status the results were still significant.

When looking for predictors for the increase in the level of fatigue over time, with all variables as possible explanatory variables, general fatigue at baseline was the strongest predictor and accounted for over 50% of the variance in general fatigue after completed radiation therapy (R-square 53%, $p<0.001$).

Table 5 presents means, SDs, medians and ranges of all variables of interest over time. Table 6 presents correlations between all variables of interest.

Levels of fatigue compared to levels of cytokines and haemoglobin during and after radiotherapy (Paper V)

The fifth and last paper, which was a pilot study, described the relationship between fatigue and cytokines and haemoglobin. The cytokines measured were IL-1, IL-6 and TNF-alpha.

The levels of IL-1 remained below the detection limit during the entire study period. TNF-alpha increased above the detection limit after three weeks in 5 out of 15 patients ($p=0.94$), and in 4 out of 15 patients after completed therapy ($p=0.88$). The levels of IL-6 increased after 3 weeks of treatment in 7 patients and decreased in 8 patients ($p=0.59$). After completed therapy the numbers were the opposite; the values for 8 patients increased and for 7 they decreased ($p=0.72$). For 9 patients the level of IL-6 was higher from the beginning than the normal value (>85 pg/ml). Two of these patients had an increase in IL-6 after three weeks of therapy and 6 patients after completed therapy.

Correlations between general fatigue, IL-6 and TNF-alpha were performed. There was a significant negative correlation between the change from baseline to 3 weeks of treatment ($r=-0.65$, $p<0.01$) and to end of treatment ($r=-0.54$, $p<0.05$) between IL-6 and general fatigue. No significant correlation was found between fatigue and TNF-alpha in the changes from baseline to 3 weeks of treatment or to end of treatment.

Haemoglobin (normal range 116-149 g/l) decreased from 137 g/l (md) (range 128-147) at baseline, to 131 g/l (md) (range 118-144) after three weeks of therapy, and to 129 g/l (md) (range 114-144) after completed radiotherapy. These changes were significant ($p=<0.001$). There was no significant correlation between changes in general fatigue and haemoglobin from baseline to 3 weeks of therapy ($r = 0.04$, $p = 0.79$) or to completed therapy ($r=-0.18$, $p=0.23$).

Table 5: Scores for fatigue, coping resources, other symptoms, psychological distress, health-related quality of life at baseline, after 3 weeks of therapy (+30 Gy) and after completed therapy (+46 Gy)

	Baseline n=60		**After 3 weeks of therapy n=47**		**After completed therapy n=53**		**Reference values (healthy individuals)**
	m (SD)	**md (range)**	**m (SD)**	**md (range)**	**m (SD)**	**md (range)**	**m**
Fatigue							
General fatigue	10.4 (5.3)	9.5 (4-20)	12.7 (5.2)	12.0* (4-20)	13.1 (5.4)	14.0* (4-20)	7.8[a]
Physical fatigue	10.1 (5.2)	8.5 (4-20)	11.4 (5.5)	11.0* (4-20)	11.7 (5.8)	12.0* (4-20)	8.8[a]
Reduced activity	10.9 (5.4)	11.0 (4-20)	12.2 (5.3)	12.0* (4-20)	12.6 (6.0)	13.5* (4-20)	8.4[a]
Reduced motivation	8.8 (4.5)	8.0 (4-20)	9.3 (5.0)	8.0* (4-20)	9.7 (5.2)	9.0* (4-20)	5.0[a]
Mental fatigue	8.9 (4.7)	7.5 (4-20)	9.7 (5.2)	9.0* (4-20)	9.6 (5.2)	8.5 (4-20)	5.2[a]
Fatigue (QLQ-C30)	30.0 (24.3)	33.3 (0-88.9)	41.2 (27.8)	33.3* (0-100)	44.6 (30.3)	44.4 (0-100)	20.1[b]
Coping resources (SOC)							
Total Sense of Coherence	147.4 (21.6)	151.0 (76-179)	-	-	146.6 (21.4)	145.0 (91-181)	151[c]
Other symptoms							
Loss of appetite	8.9 (21.1)	0 (0-100)	22.7 (29.6)	0* (0-100)	25.2 (32.6)	0* (0-100)	4.1[b]
Nausea / vomiting	4.4 (9.6)	0 (0-50)	15.2 (15.5)	16.7* (0-66.7)	12.3 (17.9)	0* (0-83.3)	3.1[b]
Diarrhoea	5.6 (14.0)	0 (0-66.7)	59.6 (28.6)	66.7* (0-100)	56.6 (31.1)	66.6* (0-100)	4.6[b]
Pain	12.5 (21.2)	0 (0-83.3)	22.0 (27.8)	16.7* (0-100)	19.2 (16.7)	16.7 (0-83.3)	20.7[b]
Insomnia	25.6 (27.7)	33.3 (0-100)	22.0 (28.0)	0 (0-100)	26.4 (32.9)	33.0 (0-100)	22.6[b]
Psychological distress							
Anxiety	5.4 (4.6)	4.0 (0-19)	4.1 (3.6)	4.0 (0-13)	4.7 (4.4)	4.0 (0-15)	-
Depression	3.4 (3.7)	2.0 (0-17)	3.8 (3.9)	2.0* (0-14)	4.2 (4.3)	2.0* (0-18)	-
Global quality of life	75.0 (21.0)	83.3 (33.3-100)	62.2 (24.1)	66.7* (0-100)	64.0 (24.4)	66.7* (16.7-100)	77.5[b]
Functional status							
Physical function	75.9 (21.6)	80.0 (20-100)	74.8 (19.5)	80.0 (33-100)	74.0 (20.3)	80.0 (33.3-100)	86.7[b]
Role function	64.4 (33.5)	66.7 (0-100)	66.0 (66.7)	66.7 (0-100)	62.6 (31.8)	66.7 (0-100)	86.7[b]
Emotional function	75.8 (20.3)	75.0 (16.7-100)	80.1 (19.2)	83.3 (25-100)	78.8 (20.8)	83.3 (25-100)	83.5[b]
Cognitive function	86.1 (23.4)	100 (16.7-100)	84.0 (22.2)	100 (16.7-100)	82.1 (21.1)	83.3 (33.3-100)	90.0[b]
Social function	85.0 (21.8)	100 (0-100)	77.7 (26.3)	83.3 (0-100)	72.6 (27.0)	66.7* (0-100)	92.2[b]

*p<0.05 Friedman's test with Tukey´s post-hoc test

[a] Reference values from a healthy population, women and men, aged 60-69 years, n=181 (Watt et al 2000);[b] Reference values from a healthy population; women, aged 60-69 years, n=≥262 (Michelson et al 2000); [c] Reference values from a healthy population, women and men, n=145 (Langius & Björvell 1992).

Table 6. Correlations between general fatigue and other fatigue dimensions, coping resources, selected symptoms, psychological distress and health-related quality of life at baseline and over time.

	Baseline **n=60** **General fatigue**	**Over time** **n=47** **General fatigue**
	Spearman´s Rho	Spearman´s Rho[a] (means of intra individual correlation coefficients for all patients)
Fatigue		
Physical fatigue	0.87***	0.65***
Reduced activity	0.84	0.58***
Reduced motivation	0.68	0.55**
Mental fatigue	0.60	0.44*
Fatigue (QLQ-C-30)	0.88***	0.79***
Coping resources		
Sense of Coherence	-0.49***	-0.26
Other symptoms		
Loss of appetite	0.44**	0.72***
Nausea/vomiting	0.28	0.65***
Diarrhoea	0.13	0.71***
Pain	0.42	0.37**
Insomnia	0.32	0.09
Psychological distress		
Anxiety	0.36**	0.08
Depression	0.71***	0.51***
Global quality of life	-0.68***	-0.57***
Functional status		
Physical function	-0.76***	-0.44***
Role function	-0.67***	-0.48**
Emotional function	-0.53***	-0.10
Cognitive function	-0.44***	-0.46**
Social function	-0.39**	-0.41

* $p<0.05$, **$p<0.01$, ***$p<0.001$

[a] Formally tested with the Wilcoxon signed rank test

DISCUSSION

Symptom management is a challenging experience for health-care professionals including nurses. Without guidance, patients often adopt common-sense strategies that generally prove unsuccessful in alleviating a symptom such as fatigue. Within a nursing perspective, managing symptoms requires an understanding of the patient's experience of the symptom as well as the responses and the outcomes from the symptom experience. Health-care professionals have difficulty developing symptom management strategies that can be applied across acute and home-care settings because few models of symptom management have been tested empirically (Dodd et al 2001a).

The Conceptual Model of Symptom Management is applicable to practice and to research. According to Dodd and colleagues (2001a), the model may provide direction for selecting clinical interventions, performing research, bridging an array of symptoms associated with a variety of diseases and conditions, and allowing for the integration of findings from other fields. Within this thesis the CMSM was used when designing the studies and when formulating the research questions for the studies. The model for the CRF experience adopted from the CMSM was used to get a better understanding of the complexity of the fatigue experience. Further, to get a deeper understanding of the results from the studies when looking at influencing factors, responses and outcomes of CRF. The model will be used and tested in further studies of CRF.

The experience and perception of fatigue in patients with cancer

The results of this thesis indicate that fatigue is an experience of the whole person, both body and mind. This may be compared with results in the study by Glaus and colleagues (1996). They showed that physical signs of fatigue were more frequent than affective and cognitive signs in cancer patients as compared with healthy individuals. The experience of fatigue involved decreased physical performance, extreme, unusual tiredness, weakness and an unusual need for rest. Affective and cognitive distress was also more prominent in cancer patients. The emerging concepts in their study separate fatigue into expressions of physical, affective and cognitive fatigue. Our results in Paper I may indicate that it is not possible to consider fatigue as only an experience. This means that if a patient describes her experience of fatigue, she is as likely to talk about a change in her lifestyle and her self-esteem as about how she handles the occurrence of the symptom. For this reason, when talking to a patient who is suffering from fatigue the caregiver must have an open mind in order to carry out an adequate assessment and documentation. In Paper I, affected self-esteem was found to be a consequence of fatigue. This finding has not previously been reported in the literature. The way in which reduced self-esteem may affect a person experiencing cancer-related fatigue over time needs further investigation.

The dimensions of fatigue that emerged in Paper I are in good accord with further explanations found in the MFI-20 scales (Smets et al 1995). The scale concerning general fatigue corresponds to the remarks of a person concerning her functioning, “When my legs are tired I haven’t got any strength and then I easily stagger and fall”. Physical fatigue may be expressed as “When I’m out walking I have to stop much more often, my feet start aching very soon”. Mental fatigue refers to cognitive symptoms that may be expressed as follows: “You can’t concentrate, when my wife asks what I’ve been reading, I don’t know, I can’t remember”. Reduced motivation may describe a lack of motivation to start any activity, which in Paper I was expressed as “I lose all interest and lie down instead”. Finally, the scale measuring reduced activity refers to consequences of fatigue that were expressed in Paper I as “I can’t get involved with as many things as before”.

The fact that fatigue increases during radiation therapy has been demonstrated in several studies in other populations (e.g. Smets et al 1996; Smets et al 1998; Monga et al 1999; Fürst & Åhnsberg 2001). Stone and colleagues (2001) reported in a study on patients with prostate cancer who were receiving radiotherapy with curative intent that fatigue is a significant problem for patients receiving radiotherapy, even though its severity is relatively modest. The present thesis confirms that the increase in fatigue in other populations is comparable to the development of fatigue in women with uterine cancer. To be able to define cases of fatigue there is a need for cut-off values. The increases of the fatigue levels can be compared to the norm data that are shown as reference values in Table 5. Our result shows that patients with uterine cancer already before the start of treatment with radiotherapy have higher levels of fatigue compared with a healthy population. The prevalence over time indicated that 87-89% of the patients experienced some level of general fatigue. Other researchers have found a strong association between fatigue and both morbidity (Appels & Mulder 1988; Avlund et al 1998; Watt el al 2000) and mortality (Appels & Mulder 1988; Avlund et al 1998, Fang et al 2004) in longitudinal studies on different cancer populations. Measures of fatigue may therefore be used to identify patients susceptible to future morbidity who may be candidates for preventive interventions.

Variables that may influence the experience of CRF

Demographic characteristics

The literature indicated that disease stage (Given et al 2001; Marty et al 2001), age (Liao & Ferrell 2000) and marital status (Gaston-Johansson et al 1999) may have an impact on the experience of fatigue. For patients with lung cancer, for example, the stage of cancer at diagnosis is the best predictor of symptoms in general later in the disease (Gift et al 2003). When controlling for age, marital status and disease stage in the studies within this thesis, none of the variables was significant regarding the development of the experience of fatigue. When analysing the factors influencing fatigue in a patient with cancer, distinguishing between demographic factors and early and/or late consequences of therapy and the stage of the disease itself is probably very difficult. Based on the results of this thesis we cannot say whether or not demographic characteristics have an impact on the development of fatigue. Our findings showed that demographic characteristics did not influence the relation between general fatigue and other variables. The correlation between variables did not change based on age, disease stage or marital status.

Coping resources and strategies

The patients' levels of coping resources, here defined as Sense of Coherence, did not change significantly over time. Antonovsky contended that the SOC is consistent in adult life (1987) and it has been empirically shown that SOC is a relatively stable characteristic (Langius et al 1992; Schnyder et al 2000), which has been confirmed by the results of this thesis. The SOC did not change significantly over time. In the study by Forsberg & Björvell (1996) it was found that cancer patients with a strong SOC perceived their well-being as better than did the patients with a weaker SOC. We have not found any studies that have specifically looked at a possible correlation between the experience of fatigue and coping resources. Smets and colleagues (1998b) tested the hypothesis that a discrepancy between resources (e.g. optimism) and demands (e.g. the patient's perception of overall burden) explains most of the variance in fatigue in cancer patients undergoing radiotherapy. The hypothesis was not supported. In contrast, Servaes and colleagues (2003) found that severe fatigue at follow-up after treatment for malignant bone and soft tissue tumours was predicted by less optimism and more somatisation. Janda and colleagues (2000) reported that after radiotherapy for prostate carcinoma patients experienced a temporary deterioration in fatigue and role functioning. Despite physical deterioration, the authors observed an improvement in emotional functioning. The authors indicated that this might have been due to psychological adaptation and coping. A small study by Ream and colleagues (2002) was conducted to develop and test a nursing intervention to facilitate coping with fatigue by patients receiving chemotherapy. The intervention, termed the "Beating Fatigue" program, has four elements: assessment/monitoring, education, coaching in the management of fatigue, and provision of emotional support. Overall, patients were very positive about the program and perceived the opportunity to talk to someone about fatigue as the most beneficial strategy within the program.

How individuals cope with CRF may have the potential to influence their self-management and their experience of CRF. In the first paper within this thesis coping was one of the categories that was found. The respondents stated that they used coping strategies to deal with their fatigue, e.g. physical activity and planning and preparing for daily activities. Further studies are needed in order to find out if cancer patients use the same coping strategies over time when their level of fatigue is increasing and how effective these types of coping activities are in reducing fatigue and other symptoms.

Others symptoms

In the papers III-IV appetite loss, nausea/vomiting and diarrhoea increased significantly during treatment. We also found that the increases in gastro-intestinal (GI) symptoms were significantly correlated to the increase in general fatigue. These results confirm findings from other studies. A review by Maranzano (2001) showed that patients subjected to abdominal radiotherapy are at major risk for developing nausea and vomiting (71%). In studies by Jereczek-Fossa and colleagues (1998; 2003), 41-66 % of the patients receiving radiotherapy for endometrial cancer experienced bowel complications. In the study by King and colleagues (1985), fatigue, nausea, anorexia, and diarrhoea were the most frequently reported symptoms in the group of women receiving external radiotherapy for gynaecological cancer. The incidence of these symptoms increased during treatment and gradually decreased over a period of three months following treatment. At least 40% of the women in the study by Christman and colleagues (2001) reported difficulty sleeping, fatigue, diarrhoea, anorexia, and nausea in connection with radiation therapy for cervical or uterine cancer. Guren and colleagues (2003) showed in patients receiving radiotherapy for rectal cancer that the mean scores for diarrhoea, fatigue and appetite loss had significantly increased ($p<0.01$) at the end of treatment compared with pre-treatment, but this was not the case for nausea and pain scores. At the end of radiotherapy, diarrhoea, fatigue, appetite loss, physical function, social function and global quality of life were significantly worse than the population-based norms (Guren et al 2003).

It is important that patients with endometrial cancer who are receiving radiotherapy are informed of the expected changes, thereby giving them a chance to cope more effectively with these changes. Health-care professionals also need to include routines for assessment and evaluation of CRF and other symptoms. Because cancer patients who are receiving radiotherapy are seen frequently in the clinic, health-care professionals` use of a comprehensive approach for treating CRF and other symptoms can be of great importance.

Cytokines

The fifth paper showed that the degree of fatigue increased during radiotherapy without a significant change in serum levels of IL-1, IL-6 or TNF-alpha. There was no significant correlation between changes in general fatigue and the changes in IL-1 and TNF-alpha or haemoglobin. There was a significant negative correlation between the change in serum IL-6 and general fatigue.

The negative correlation between changes in serum IL-6 and fatigue was unexpected. Although this is a very preliminary finding, the negative correlation between general fatigue and IL-6 could verify that fatigue is associated with IL-6 in the immune system.

The mechanisms for the symptom of fatigue remain to be elucidated, and other influencing factors also need further investigation. For instance endogenous cortisol was found in a study by Lundström & Fürst (2003) to have a significant positive correlation to fatigue, appetite loss and nausea/vomiting. The findings in that study supported the view of a chronic stress condition in cancer. In addition, the possible influence of melatonin, a product of a tryptophan metabolism that is cyclic and exhibits a circadian (approximately 24 hrs.) rhythmicity (e.g. Reppert & Weaver, 1995; Brzezinski 1997), should be further investigated. Melatonin affects the timing and duration of sleep. In humans, it increases soon after the onset of darkness, peaking in the middle of the night (between 0200 and 0400), and gradually decreases during the second half of the night.

The findings within this thesis, together with the literature, indicates that a comprehensive assessment, including an understanding of the most likely etiologic factors, is necessary for further development of a therapeutic strategy for CRF.

Responses to CRF

Psychological distress: anxiety and depression

The patients' psychological distress (anxiety, depression) was low before start of treatment. During and also after completed radiotherapy the levels of anxiety and depression were still within normal limits. Depression was significantly correlated to general fatigue both at baseline and over time. Several studies that have found a positive correlation between fatigue and psychological distress, both in cancer patients (Smets et al 1996; Stone et al 2000a) and in healthy populations (Pawlikkowska et al 1994; Stone et al 2000a). The nature of the relationship between fatigue and anxiety and depression is complex. According to the literature, it is unclear whether fatigue results from prolonged emotional distress characterised by anxiety and depression, or whether high levels of fatigue cause patients to feel anxious and depressed about their reduced ability to take part in their usual activities. Both mechanisms seem probable (Ahlberg et al 2003). Dolbeault and colleagues (2001) contend that fatigue and depression do not follow the same clinical course and that the cause-and-effect relationship between these two variables has not been established (Dolbeault et al 2001). The same has been shown by Visser and Smets (1998), further by Watt with colleagues (2000). Others argue that fatigue and depression typically occur together in cancer patients, suggesting a common aetiology that may be based on serotonin. A randomised clinical trial tested whether paroxetine, a selective serotonin re-uptake inhibitor antidepressant known to modulate brain serotonin, would reduce fatigue in cancer patients and whether any reduction was related to depression (Morrow et al 2003). Their results showed that paroxetine had no influence on fatigue in patients receiving chemotherapy. A possible explanation is that cancer-related fatigue does not involve a reduction in brain 5-HT levels. Further research is needed.

The relationship between the fatigue experience and outcomes

In our studies the scores of functional subscales and global quality of life were high before start of treatment. Further, the patients' global quality of life and social function decreased significantly over time. There was a significant relationship between general fatigue and global quality of life over time when measured at baseline, after 3 weeks of therapy and after completed therapy. In our studies as well as in the study by Smets with colleagues (1998a), the patients' overall quality of life was negatively related to fatigue. These results were also confirmed by studies on women with gynaecological cancer (e.g. Holzner et al 2003). A study by Curt and colleagues (2000) indicated that the effect of fatigue on quality of life is more profound and prolonged than the effects of nausea, depression or pain on quality of life. Klee and Machin (2001) contended that radiotherapy for endometrial cancer exposes the patients to 1-3 months of adverse physical symptoms that impact on their daily lives. Flechtner and colleagues (1998) showed that the quality of life of lymphoma patients with high levels of fatigue remained substandard even 6-7 years after the end of treatment. Whether the situation is the same for patients with uterine cancer needs further investigation.

Predictors of fatigue

An important finding in one of our studies was that the variation in the level of general fatigue after completed radiotherapy was explained mainly by the level of experienced general fatigue at baseline. Smets and colleagues (1998) reported that the degree of fatigue before start of treatment might be the most powerful predictor of post-treatment fatigue. This means that the fatigue level before treatment may be an important variable when trying to find risk factors for the development of fatigue over the course of treatment. In a study aimed at identifying independent predictors of clinically significant fatigue based upon a multidimensional model, it was found that dyspnoea, pain, lack of appetite, feeling drowsy, feeling sad, and feeling irritable predicted fatigue independently. Physical and psychological symptoms independently predicted fatigue in the multidimensional model and superseded laboratory data. These findings support a symptom-oriented approach to assessment of CRF (Hwang et al 2003). Bower and colleagues (2000) found in their study of breast cancer survivors that depression and pain emerged as the strongest predictors of fatigue.
Our results concerning fatigue as its own predictor need further testing. If these findings are confirmed, the measurement of fatigue before treatment can be used as a tool to find patients at risk for developing CRF over time.

A high level of fatigue prevents patients from returning to work and from leading a normal life. A multidisciplinary group of practitioners, researchers, and patient advocates working to develop diagnosis and treatment guidelines, surveyed 379 patients who had undergone cancer treatment (Curt 2000a; Curt et al 2000b). Because of fatigue, 75% of the patients had to make changes in their employment status including a decrease in work hours (34%), the need to receive disability payments (23%), and discontinuation of work (28%). On average, patients reported missing almost a full week of work (4.2 days) during a typical month. Cancer treatment-related fatigue may result in an economic cost beyond lost work hours. Among respondents who experienced some level of fatigue, 50% reported needing help for everyday tasks such as cleaning the house or caring for children, which also increased monetary expenditures (Curt 2000a; Curt et al 2000b). It is important to clarify further the differences between patients at high risk for this outcome and those at low risk. As the number of people surviving cancer for extended periods of time continues to increase, the phenomenon of symptoms that persist following the completion of treatment needs to be recognised. The development of effective interventions for the treatment of CRF could profoundly affect the lives of many patients with cancer (Manzullo et al 2003).

CONCLUSIONS

The strength of this thesis is that it addresses a symptom of significance to cancer patients, the experience of CRF. Further, it provides valuable evidence concerning the nature of fatigue in one specific patient population. The Symptom Management Conceptual Model has been used in this thesis as the framework over time, which is an innovative approach. The clinical relevance of this research aimed at eliminating the gaps in scientific knowledge is improvement in health-care professionals' knowledge concerning the care of patients with uterine cancer who are receiving radiotherapy.

Our results indicate that we have confirmed existing knowledge in a new population of patients with cancer. We have also obtained new knowledge by describing fatigue, influencing variables, responses and outcomes over time that should lead to better understanding of cancer-related fatigue over time in women with uterine cancer who are receiving radiotherapy. Our findings need to be further investigated in other populations of cancer patients.

The results of this thesis showed that:

- Cancer-related fatigue is an experience of the whole person and that fatigue must be considered within the context of patients' daily lives. The experience of CRF may affect the patient's self-esteem.
- Before starting radiotherapy, patients with uterine cancer have a low level of experienced fatigue, other symptoms and psychological distress, and a high level of health-related quality of life.
- Cancer-related fatigue levels increased significantly during the course of radiation therapy and after completed treatment.

- Other symptoms (e.g. GI symptoms: appetite loss, nausea/vomiting and diarrhoea) increased significantly during treatment and the increases were significantly correlated to general fatigue.
- Psychological distress (anxiety and depression) remained within normal limits during and after completed radiotherapy.
- The patients' levels of coping resources, here defined as Sense of Coherence, did not change significantly over time.
- The patients' global quality of life and social function decreased significantly over time. There was a significant relationship over time between general fatigue and physical function, role function, cognitive function and global quality of life.
- There was no significant correlation between general fatigue and IL-1 and TNF-alpha. There was a significant negative correlation between the change in serum IL-6 and general fatigue. There was no significant correlation between general fatigue and haemoglobin.
- The variation in the level of general fatigue after completed therapy was only explained by the level of experienced general fatigue at baseline.

METHODOLOGICAL CONSIDERATIONS

Collection of quantitative data

The use of questionnaires to collect data in paper II-V has many advantages, but there are also some disadvantages. A questionnaire can be difficult to complete and the forced choice answers may not reflect an individual's experience. For practical reasons a minority of the patients in this study received the questionnaire by post instead of having it handed to them personally. This may have resulted in differences in the respondents' interpretation of the different questions. To avoid bias and to reduce the lack of personal contact, the person who was collecting the data tried to achieve good contact with the participants by telephone or at the patient's next visit at the hospital.

All instruments must possess two characteristics, validity and reliability. Concerns about reliability involve the consistency or repeatability of measurements made with the instrument. Cronbach´s alpha is a common reliability test that assesses the extent to which items in an instrument are related. On a scale of 0 to 1.0, higher values reflect a greater degree of internal consistency. Validity is briefly defined as indicating whether the tool measures what it is claimed to measure. All questionnaires used for this project had been used and tested frequently. The questionnaire in this thesis that had undergone the least use was the Swedish version of the MFI-20. Therefore a reliability analysis (internal consistency) was performed, and this showed highly satisfactory Cronbach´s alpha levels for all five scales.

Response-shift

How patients evaluate their experience, in this case of fatigue, other symptoms, psychological distress and health-related quality of life, may change over time. If patients experience extreme fatigue during treatment, they may judge the level of fatigue following this experience differently than they would have judged it before (Visser et al 2000). This paradox is now understood to reflect a psychological adaptation (a "response shift") that occurs in patients with cancer as well as in patients with other chronic diseases. The internal standard by which patients appraise their current state shifts and the same questionnaire items can elicit fundamentally different answers over time (Muldoon et al 1998). Due to a response shift, estimates of side effects of radiotherapy may be attenuated if patients adapt to treatment toxicities (Jansen et al 2000). For example, a lower frequency of fatigue in radiotherapy patients with previous surgery and chemotherapy has been observed in patients with lung cancer (Hickok et al 1996). In the study by Visser and co-workers (2000), fatigue was assessed before and after radiotherapy. Following completion of the post-test for fatigue, a then-test was administered where patients had to provide a renewed judgement of their pre-treatment level of fatigue. The response shift was assessed by the mean difference between the pre-test and then-test scores. Comparing the then-test with the pre-test scores, patients retrospectively minimised their pre-treatment level of fatigue. The then-test - post-test difference was significant, whereas the conventional pre-test - post-test difference was not. Therefore, reported changes in selected variables need not necessarily derive from actual changes in health or symptoms.

Sample size in Papers II-IV

The minimum acceptable power for a study is .80 (Burnes & Groove 2001). If a researcher does not have sufficient power to detect differences or relationships that exist in the population, one might question the advisability of conducting the study. Large sample sizes may be difficult to obtain in studies due to the requirement for long data collections periods and costs (Burnes & Groove 2001). In Papers II-IV we used the power of 80 % and two-tailed probability at 0.05, assuming the mean change in the main variable of general fatigue to be 1.5 with a SD of 3.77. The sample size needed was 55 patients. Our judgement was that the sample size would be sufficient for answering the research questions. The estimated 5% drop-out was a miscalculation, since we lost more respondents over time. Therefore the estimated sample size is not achieved over time, which may lead to a weaker power.

Of the 82 patients fulfilling the criteria for inclusion in Papers II-IV, 22 did not agree to participate. There is always a risk of missing important information when a cohort of the population is not included for different reasons. In a study like this, where the purpose was to describe patients' experience of fatigue, it could be that those who were the most tired were those who declined to participate. Although the demographic characteristics of the patients who were not included in the study were similar to those of the patients in the study, we cannot say anything about their level of fatigue. There is always a risk of missing a category of patients and thereby not covering all the dimensions of a concept, in this case fatigue.

IMPLICATIONS FOR NURSING PRACTICE

Evidence-based health-care aims to promote effectiveness and thereby improve quality. The challenge for cancer nursing is to continually evaluate what it does, retaining effective interventions and working to develop new ones and refine those interventions that require improvement, thereby enhancing both practice and patient outcomes (Richardson et al 2002). Although CRF is a prevalent symptom reported by cancer patients, evaluation and management of this distressing side effect of cancer and cancer treatment have been limited in clinical practice. This limitation is related to many factors, including a lack of understanding of the mechanisms responsible for CRF, a lack of awareness by cancer-care professionals of the significance of the problem, and a lack of evidence-based interventions for managing CRF. Nurses play a critical role in maintaining and improving the well-being and health-related quality of life of patients at risk for developing CRF by understanding their experience and influencing variables and outcomes. Nurses as well as other health-care professionals have very limited experience with systematically using evidence-based knowledge in defining and managing care for the patient. Although specific gaps in knowledge need to be addressed in order to guide future practice, nurses need to use existing knowledge in the care they are delivering. Adoption of evidence-based practice requires ongoing education of nurses and support from nursing colleagues, nursing researchers, nursing administration, and associated health-care professionals.

Assessment is one key to the recognition and management of cancer-related fatigue. The use of simple measurement scales greatly improves the symptom assessment process, it may help direct treatment choices, and it provides information about the effectiveness of interventions (Cleeland 2000). Fatigue assessment can be linked to evidence-based or best practice guidelines to expedite optimal treatment. The results obtained in this thesis, combined with findings reported in the literature, show that CRF is a symptom influenced by multiple factors comprising both biological and psychosocial domains. When evaluating CRF, the health-care professionals therefore need to include both subjective and objective data.

Portenoy and Itri (1999) suggest the routine use of three questions to help assess the severity of fatigue and its impact over time:
1. Are you experiencing any fatigue?
2. If so, how severe has it been, on average, during the past week?
If fatigue is present it is possible to use a simple 0 to 10 numeric rating scale where mild fatigue may be indicated as a score 0-3, moderate fatigue as 4 to 6, and severe fatigue as 7 to 10.

3. How does the fatigue interfere with your ability to function?
These three questions give the nurse some knowledge of the patient's status. This information may also indicate whether there is need for further investigation and serves as a baseline for future follow-up of the patient's experience of CRF. The 0 to 10 numeric rating scale however only provides a unidimensional assessment of the multidimensional concept fatigue. Other characteristics are similarly important, for example, onset, duration, severity, daily pattern, time course, exacerbating and reducing factors, and distress associated with fatigue (Ahlberg et al 2003).

Nurses and other health-care professionals need to identify cancer patients at risk for poor adjustment during the period illness and/or treatment. Pretreatment screening for fatigue and its influencing variables is needed to identify patients at risk for developing the symptom. In the United States, the National Comprehensive Cancer Network (NCCN) proposed in their Fatigue Practice Guidelines an algorithm in which patients are assessed regularly for fatigue using a brief screening instrument (Mock et al 2000). The algorithm included the following phases: screening, primary evaluation, intervention and re-evaluation. The screening for the presence and severity of CRF should occur at the patient's initial contact with an oncology provider, at appropriate intervals, and as clinically indicated. If fatigue is reported during screening, it should be quantified for future comparison. Data from a comprehensive assessment may suggest plausible hypotheses concerning pathogenesis, which in turn may suggest appropriate strategies. The guideline provides an overall framework for clinical practice but no outcomes research has been conducted to determine the effectiveness of the guideline on fatigue in cancer populations (Ahlberg et al 2003).

When measuring CRF there are several factors that should be considered. Because CRF fluctuates in severity over time it must be measured as a state rather than as a stable characteristic. Since CRF changes over time, evaluations of the experience of fatigue must be done repeatedly in relation to the disease, the therapy, the patient's situation, and treatment of CRF and other symptoms. Also potential confounding exists in the measurement of CRF because of its close association with other concepts linked to fatigue, e.g. depression. Furthermore, instrument reactivity is a critical issue with CRF, because respondent burden can induce the condition (Meek et al 2000)

Ream and Richardson (1999) contend that passive approaches frequently fail to reduce fatigue in patients with cancer. Instead, alternative approaches based on the growing body of theoretical and research evidence should be adopted. Patients require guidance in managing cancer-related fatigue, and nurses therefore need to develop and evaluate relief interventions, e.g. educational, attention-restoring, and psychosocial interventions (Ream & Richardson 1999). All of the interventions proposed in the literature for managing CRF are health policy challenges because they represent additions to usual care rather than changing existing components of care (Nail 2002). Wengström and Forsberg (1999) stated after reviewing the literature that since patients receiving radiation therapy often experience side effects and complications as a result of treatment, they need information about their treatment, general emotional support, and practical help with side effects. The first step in treating a cancer patient's fatigue may be to determine the patient's expectations and to set realistic goals (Berger 2003). The uncertainty regarding what to expect with a cancer diagnosis and the occurrence of side-effects such as fatigue from radiotherapy makes it difficult for patients to predict what it is going to be like or how they are going to feel (Wells 1998). This necessitates discussion with emphasis on the individual patient's experience.

Acknowledging fatigue as a common symptom in cancer patients receiving radiotherapy is important and may be the next step in management. Patients must be taught that fatigue is an expected effect of radiation treatment and that fatigue may be increased as a result of other influencing factors. Educating patients about CRF also includes helping them choose the most appropriate interventions for fighting fatigue. Efforts to manage fatigue in cancer patients should focus on correcting potential aetiologies and relieving symptoms (Mock et al 2003).

Guidelines for how to assess and manage symptoms and their outcomes need to be formulated. As earlier mentioned, the NCCN Fatigue Practice Guidelines Panel has reviewed the available evidence on CRF and the consensus of practitioners regarding the management of fatigue, and has developed clinical practice guidelines that are ready to use (Mock 2001), although further research is needed to support the use of the guidelines in clinical practice. Establishing special nursing care units within an oncology department, with sufficient time for nursing assessment, nursing interventions, and evaluation of symptoms and patient outcomes, and inclusion of these units in the overall treatment strategies of a multidisciplinary team, may be one way to offer better care to cancer patients suffering from CRF and other symptoms. Collaboration with other professionals is important as evaluation and treatment of CRF requires a multidisciplinary approach because of the multitude of possible aetiologies and contributing factors.

FURTHER RESEARCH

Although we were able to contribute new knowledge related to fatigue in patients with uterine cancer, there are some important gaps in our knowledge regarding the experience, mechanisms and management of CRF. Current studies of cancer-related fatigue interventions have focused predominately on breast cancer patients. Theories underlying the interventions being tested have not always been clearly explained, and thus our understanding of mediating mechanisms of CRF is insufficient. Study designs have been limited due to the lack of control groups and small sample sizes among other factors. Little research has been conducted on patients with advanced disease or patients who are elderly. These patients present obvious challenges as research subjects, as they are often more debilitated and have many co-morbidities and life demands

that make participation in research difficult, and that often confound findings (Ahlberg et al 2003).
Implications for future research include a follow-up study of the present data in studies II-IV after 3, 6, 9 and 12 months.

There is also a need for:

- Further investigations regarding the mechanisms underlying the development of fatigue
- Intervention-testing research including nursing interventions that may reduce CRF
- Intervention-testing research including nursing interventions that may reduce other symptoms (e.g. GI symptoms; anorexia, nausea/vomiting, diarrhoea) that are related to CRF
- Qualitative research with the aim to to understand what cancer-related fatigue means to the patient, the place it occupies in his/her life and how he/she interprets and relates to fatigue.
- Investigations concerning the occurrence of a response shift in CRF and health-related quality of life ratings over time and the implications for the outcomes and estimation of the effectiveness of interventions
- Investigations concerning the relationship between the experience of CRF, health-related quality of life and symptom distress

POPULÄRVETENSKAPLIG SAMMANFATTNING

Cancer-relaterad trötthet – upplevelse och konsekvenser

Bakgrund

Trötthet anses i dag som det mest frekvent rapporterade symtomet i samband med cancersjukdom. Symtomet förekommer över ett kontinuum som spänner från trötthet till utmattning. Det sista kan ses som ett tillstånd när man till och med vaknar utmattad efter en natts sömn. Studier visar att trötthet ofta upplevs som det mest besvärande symtomet. Olika faktorer har relaterats till trötthet i samband med cancersjukdom, t ex cancersjukdomen i sig, cancerbehandlingen samt andra symtom som till exempel smärta, oro, depression och anemi. Det saknas fortfarande kunskap om upplevelsen av trötthet över tid samt riskfaktorer för att utveckla trötthet hos patienter med cancersjukdom.

Syfte

Syftet med avhandlingen var att utveckla befintlig kunskap om cancerrelaterad trötthet genom att beskriva upplevelsen av trötthet, utvecklingen av trötthet över tid och relationen mellan trötthet och hälsorelaterad livskvalitet hos patienter med livmodercancer som får strålbehandling. Vidare att studera relationen mellan trötthet och andra symptom (smärta, illamående/kräkningar, aptitlöshet, diarré, sömnlöshet) liksom relationen mellan trötthet och fysiologiska mekanismer (anemi, frisättning av inflammatoriska ämnen som IL-1, IL-6, TNF-alfa) samt att identifiera riskfaktorer for utveckling av trötthet. Resultatet skall leda till en ökad förståelse samt ligga till grund för åtgärder för att förebygga eller minska cancerrelaterad trötthet.

Metod

Både kvalitativ och kvantitativ metod har använts. I den kvalitativa studien intervjuades 15 personer med cancersjukdom och analyserades med en kvalitativ metodik, Grounded Theory. I de kvantitativa studierna inkluderades 60 patienter med livmoderscancer som var planerade för strålbehandling. Data insamlades före, under samt efter avslutad behandling genom självskattningsinstrument och analyserades genom beskrivande och korrelerande statistiska metoder.

Resultat

Resultatet i den kvalitativa studien visade att tröttheten upplevdes som ett komplext fenomen med påverkan på bland annat vardaglig funktion och känslan av kontroll. Man beskrev till exempel en upplevelse av brist på energi, ett ökat behov av vila, en sjukdomskänsla, ett psykologiskt obehag, en känslomässig påverkan, en tyngdkänsla i kroppen, en onormal svaghet, svårigheter att tänka klart och att koncentrera sig samt svårigheter att ta initiativ. Upplevelsen ledde i sin tur till en social begränsning, påverkad självkänsla, en känsla av värdelöshet samt nedsatt livskvalitet.

Respondenterna försökte att på olika sätt hantera sin upplevelse av trötthet bland annat genom egenvårdsåtgärder såsom till exempel att vila extra eller att försöka tänka på annat.

Resultatet från de kvantitativa studierna visade att patienterna hade en lätt grad av trötthet före start av strålbehandling. Graden av trötthet ökade signifikant under pågående behandling och efter avslutad behandling. Under pågående behandling och efter avslutad behandling upplevde 77-89 % av inkluderade patienter någon grad av trötthet. Graden av andra symtom såsom aptitlöshet, illamående/kräkningar, diarré och smärta ökade också under pågående behandling, ökningen var signifikant korrelerad till graden av generell trötthet. Patienterna upplevde en lätt grad av psykologiska symtom såsom oro och depression före start av behandling. Även om graden av depression hade tilltagit efter avslutad strålbehandling låg värdena fortfarande inom gränsen för normalt tillstånd. Patienternas förmåga till hantering av sin situation, i avhandlingen definierat som känsla av sammanhang, var stabil genom hela undersökningen. Graden av hälsorelaterad livskvalitet var hög före start av behandling. En nedsättning uppmättes för skattningen av global livskvalitet samt social funktion över tid. Det fanns en signifikant relation mellan skattningen av ökad generell trötthet och nedsättningen av global livskvalitet före start av behandling, efter tre veckors behandling samt efter avslutad behandling. Det fanns också en signifikant korrelation mellan ökningen av generell trötthet och nedsättningen av fysisk funktion, rollfunktion samt kognitiv funktion.
Patienternas hemoglobinvärde minskade signifikant under pågående behandling, dock kvarstod de inom normala gränsvärden. Det fanns ingen signifikant korrelation mellan utvecklingen av generell trötthet och IL-1, TNF-alfa och hemoglobin. Det fanns en signifikant negativ korrelation mellan förändringen i IL-6 och generell trötthet. Variationen i graden av trötthet efter avslutad strålbehandling kunde i huvudsak förklaras av graden av generell trötthet före start av behandling.

Diskussion

Avhandlingen belyser ett symtom, cancer-relaterad trötthet, som har stor betydelse för patienter med cancersjukdom och studerar denna i en specifik population. Den kliniska relevansen är att resultatet kan förbättra omhändertagandet och omvårdnaden av patienter med livmodercancer som behandlas med strålbehandling. Avhandlingens resultat bekräftar befintlig kunskap samt ger ny kunskap genom beskrivningen av trötthet, påverkande faktorer och konsekvenser över tid. Trots att cancerrelaterad trötthet är ett vanligt förekommande symtom är det sällsynt att tröttheten systematiskt undersöks, behandlas eller utvärderas. Orsakerna till det är relaterat till flera faktorer, bland annat brist på förståelse för de mekanismer som orsakar tröttheten, brist på medvetenhet hos vårdpersonalen samt brist på evidensbaserade åtgärder. Sjuksköterskor har en viktig roll när det gäller att upprätthålla och förbättra hälsorelaterad livskvalitet hos patienter med risk att utveckla cancerrelaterad trötthet. Patienter bör informeras om risken för utveckling av cancerrelaterad trötthet över tid. Åtgärder för att minska cancerrelaterad trötthet skall baseras på en undersökning om dels graden av trötthet samt dels vilken påverkan tröttheten har på patienten. Upplevelsen av trötthet skall skattas av patienten själv. Resultatet i denna avhandling tillsammans med litteraturen visar att cancerrelaterad trötthet är ett symtom som kan påverkas av flera faktorer. Därför bör framtida undersökningar inkludera både subjektiva och objektiva data. För optimal undersökning, behandling och utvärdering av cancerrelaterad trötthet är ett multidisciplinärt förhållningssätt, på grund av antalet möjliga orsaker till uppkommen trötthet, att rekommendera.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all the people who have shared their experience and knowledge with me and thereby contributed to this thesis. I particularly wish to thank the following:

All patients in the studies for your willingness to participate. For offering your time to contribute and sharing experiences.

Professor Fannie Gaston-Johansson, main supervisor, for your great support, knowledge, guidance through the research process, constructive criticism and for believing in my capacity.

Associate professor Tor Ekman, supervisor, for sharing your knowledge with me, for inspiring discussions through out this work and for your genuine interest in my research. I thank you for your never-ending support and encouragement.

Professor Arne Wallgren, supervisor, for being my main supervisor in the beginning of the project and for all your advice during my period as a doctorial student. I thank you for believing in me from the very beginning.

Professor Anders Möller, supervisor, for helping me through the qualitative research process, for all the fruitful discussions we have had and for your friendship.

Gunnar Ekeroth, statistician, at the Statistical Consulting Group, Gothenburg, for excellent work and inspiring guidance in the field of statistics.

Sofie Jakobsson who helped me, always with a smile on your face and a professional performance, with the data collection. Also to Camilla Andhult who took over after Sofie. I am also grateful and happy for your support and friendship.

The staff at the Radiation Therapy Unit and Unit 56 at the Department of Oncology, Sahlgrenska University Hospital, for help during the data collection.

My friend and colleague Kristin Falk, doctorial candidate, who gave me a valuable input after taking the time over Christmas reading through the frame of this thesis and associate professor Ella Danielsson for valuable advice.

My friends and colleagues at the doctorial program at the Institute of Nursing, for constructive and helpful discussion during the courses and seminars and for all the fun that we have shared.

Eva Deutch among others at the Research Centre at the Faculty of Health and Caring Sciences and Åse Blennius and Kerstin Thalén at the Department of Oncology at the Institution of Selected Clinical Sciences for all your help and support.

My colleagues and friends that have inspired me and/or provided me with a lot of valuable support and advice over the years: Lasse Persson, Carola Skott, Victoria Mock, Joakim Öhlén, Inger Ekman, Clementine Molin, Ann Bengtson, Susan Strang, Peter Strang, Barb Karlsson, Ann-Kristin Holm, Ragnar Hultborn, Yvonne Wengström, Carina Lundh, Ulrika Östlund, Sussanne Börjeson, Elisabeth Karlsson and Catharina Palmblad among others.

My colleagues at the Unit for Research and Development and others at the Department of Oncology at Sahlgrenska University Hospital for your cheerful and friendly support. Also Marianne Andersson and Carina Bagge who are not longer working at the department but who showed me what is means to be a professional and caring nurse.

My friends and colleagues within the European Oncology Nursing Society (EONS) for support and friendship; Giel Vaessen, Jan Foubert, Agnes Glaus, Kathy Redmond among others. I thank you for all opportunities to collaboration with European colleagues.

My colleagues at the Institute of Nursing for fruitful discussion within the area of nursing.

My wonderful friends that I am most grateful to know: Susanne Eliasson, Thomas Björk-Eriksson, Anna-Karin Andersson, Annika Jakobsson and Gunnevi Hällstén Carlson among others.

My parents Stina och Dag and my sister Agneta since you always have a great place in my heart and for your support during life. Amanda and Isabelle for all the happiness and joy that you are giving me. “A trick or two makes life easier”.

My husband Håkan, for your never ending love, friendship, support, laughs and for sharing the same dreams. Lucky me who met you!

I am most grateful for the financial support from the King Gustaf V Jubilée Clinic Cancer Research Foundation, the Vårdal Institute and Cancer och Trafikskadades Riksförbund (CTRF). I wish to thank Jane Wigertz for revision of the English text.

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ISBN 91-628-5969-2