fatigue

in disease-free cancer patients

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Cover: Seña ontwerpers
Lay-out: Ria te Winkel

Printed by Ponsen & Looyen BV, Wageningen, the Netherlands

ISBN 90-9017086-3

FATIGUE IN DISEASE-FREE CANCER PATIENTS

Een wetenschappelijke proeve op het gebied
van de Medische Wetenschappen

Proefschrift
ter verkrijging van de graad van doctor aan de Katholieke Universiteit Nijmegen
op gezag van de Rector Magnificus Prof. Dr. C.W.P.M. Blom, volgens besluit
van het College van Decanen in het openbaar te verdedigen
op woensdag 10 september 2003 des namiddags om 3.30 uur precies

door

Petra Servaes
geboren op 26 februari 1970
te Capelle aan de IJssel

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The studies were supported by grant KUN 1997-1390 of the Dutch Cancer Society (Nederlandse Kankerbestrijding, KWF).

De publicatie van dit proefschrift kwam mede tot stand dankzij financiële steun van de afdeling Medische Psychologie en de Instrumentele Dienst van het Universitair Medisch Centrum St Radboud te Nijmegen, de Nederlandse Kankerbestrijding/ KWF en het Integraal Kanker Centrum Oost.

"I was lucky to be treated in a hospital that takes part in a study on fatigue
They can't do very much for me, but at least they show that
they understand and that's a great help"
(woman 51 years old, treated for breast cancer 4 years ago)

voor pappa en mamma

Contents

Chapter 1

Outline of this thesis

INTRODUCTION

The Expert Centre Chronic Fatigue of the University Medical Centre Nijmegen has focussed on the study of chronic fatigue since 1990. In the beginning the focus was mainly on Chronic Fatigue Syndrome, however during the years it expanded to chronic fatigue in several other specific patient groups. Nowadays it is a multidisciplinary collaboration of physicians, paediatricians, virologists, neurologists, neurophysiologists, neuroscientists, oncologists, and psychologists from several departments in the UMC Nijmegen.

In 1997 we began to focus on fatigue complaints in cancer survivors. With ‘cancer survivors’ we refer to persons who have been curatively treated for cancer and are disease-free at the time of participation in our studies. We conducted three studies in the last 5 years. All of these studies dealt with the natural presence and course of fatigue. We did not carry out any intervention studies. In our first study we asked a mixed group of cancer survivors to take part. In our second study, we extensively investigated a group of breast cancer survivors during a two-year period. Finally, in our third study, we investigated patients who were treated for a bone or soft tissue tumour.

The current thesis presents seven articles on the subject of fatigue complaints in cancer survivors: one literature review and six articles that resulted from the three above mentioned studies.

CONTENTS OF THIS THESIS

This thesis consists of nine chapters. In *Chapter 2* we start with a literature review of articles that were published between 1980 and 2001 on the subject of fatigue in cancer patients. We reviewed articles in which fatigue was investigated in patients in the active phase of their disease, and in disease-free patients who completed cancer treatment. In this review we focussed on what is known concerning: the prevalence of fatigue, the medical and psychosocial correlates of fatigue, and interventions to reduce fatigue.

In *Chapter 3* results of our first study are described. The main goal of this study was to assess the prevalence of fatigue in disease-free cancer patients with help of a validated fatigue questionnaire. Furthermore, we analysed the relationship between severe fatigue and former treatment modalities, problems of concentration and motivation, physical activity, functional impairment, depression and anxiety. Finally, we compared severely fatigued disease-free cancer patients to patients with Chronic Fatigue Syndrome (CFS).

Chapter 4 presents the baseline results of our longitudinal study on fatigue complaints in disease-free breast cancer patients. In this chapter we investigated the prevalence of severe fatigue in a sample of disease-free breast cancer patients who completed treatment for breast cancer for a minimum of 6 months and a maximum of 60 months before the study commenced. Further, we studied the relations between severe fatigue complaints and former treatment modalities, like type of operation, type of adjuvant therapy, duration of treatment and time since treatment ended. Finally, we described the ‘severely fatigued breast cancer patient’ on basis of measures of psychological well-being, functional impairment in daily life, sleep disturbances, physical activity, neuropsychological impairment, social functioning, social support and self-efficacy and causal attributions with respect to fatigue complaints. In this study an age-matched sample of women without a history of cancer was included.

Chapter 5, which is also based on baseline data of our longitudinal study on fatigue complaints in disease-free breast cancer patients, describes the relations between fatigue, neuropsychological functioning and physical activity after treatment for breast cancer. In this article a clear distinction has been made between different ways to measure neuropsychological functioning and physical activity. Both concepts were measured with general self-report questionnaires, daily self-report measures and by measures of actual behaviour (neuropsychological tests and actometer). In this article we investigated whether severely fatigued disease-free breast cancer patients, non- severely fatigued disease-free breast cancer patients and women without a cancer history showed differences in general self-reported, daily self-reported and objective neuropsychological and physical functioning.

In *Chapter 6*, similarities and differences between severely fatigued breast cancer patients and matched female Chronic Fatigue Syndrome patients are described. The purpose of this study was to examine to what extent a patient who experiences severe fatigue after treatment for cancer resembled a patient with CFS. This has been done in a much more profound way than it has been done in the study that is described in Chapter 3. In this study, results were based solely on general self-report questionnaires, while in the current study, results were based on general self-report questionnaires, daily self-report questionnaires and on measures of actual behaviour (neuropsychological tests and actometer). We compared severely fatigued breast cancer patients and female Chronic Fatigue Syndrome patients on self-efficacy, psychological well-being, sleep, concentration, physical activity, social support, and pain. The idea behind this comparison was to determine whether the same cognitive behavioural intervention to reduce fatigue in CFS patients would be appropriate as well for severely fatigued disease-free breast cancer patients.

In *Chapter 7* we widen our focus to fatigue complaints in patients who were treated for bone and soft tissue tumours, 1 to 15 years before accrual in this study. We thought this is of importance because this patient population has some characteristics that are different from our breast cancer patient population. First, within this population, patients have been treated for both malignant and benign tumours. Second, treatment for these kinds of tumours differs from treatment for breast cancer. Finally, time since end of treatment varied more widely within the investigated patient population than in our breast cancer patient population. The structure of this article is divided into two parts. In the first part baseline data were analysed. The prevalence of fatigue after treatment for malignant and benign bone and soft tissue tumours and the association between fatigue severity and former disease and treatment characteristics were described. Furthermore, we investigated whether patients who finished treatment relatively recently were more severely fatigued than patients who finished treatment longer ago. Finally we studied the association between fatigue severity and demographic, psychological and/or physical variables. In the second part we focussed on longitudinal data. In this part we investigated the course of fatigue during a two year period and the predictors of severe and heightened fatigue at follow-up.

In *Chapter 8* the focus is on the follow-up of our breast cancer patient cohort during a two-year period. In this chapter we investigated whether severe fatigue is a persistent problem and whether persistent fatigue was related to former treatment modalities. In addition, we studied to what extent psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions were able to predict persistent fatigue. Finally, we exploratory described the course of fatigue for those patients that developed a disease-recurrence during the two years of our study.

Finally, *Chapter 9* entails a general discussion of the studies presented in this thesis. Results are summarised, and shortcomings and implications are noted.

Chapter 2

Literature review

Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions

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European Journal of Cancer 2002; 38: 27-43

ABSTRACT

Research on the relationship between cancer and fatigue has increased considerably in recent years. In this review, we focus on fatigue observed in patients during and after treatment for cancer, using data from empirical studies. The results from these studies indicate that fatigue is mostly studied during active treatment for cancer, and is an important problem during this period. Studies that focussed on fatigue in disease-free cancer patients, although less prominent, also indicate fatigue is an important complaint in this time period. It is hard to draw conclusions with regard to the relationships between fatigue and disease- and treatment- related characteristics, because these relationships are seldom properly investigated. Relationships between fatigue and psychological, social, behavioural and physical factors have been established in several studies. However, most studies focussed on the depression-fatigue association. Finally, most intervention studies to reduce fatigue appear to be successful, but the follow-up analyses are lacking.

INTRODUCTION

Fatigue is a subjective experience that affects everybody. For healthy individuals, it might be a protective, sometimes even pleasant, regulatory response to physical or psychological stress. It seems to maintain a healthy balance between rest and activity. For people with specific diseases, fatigue often becomes a major distressing symptom and for people with cancer, fatigue has been described as a major concern during treatment, in the advanced stages of the disease and after curative treatment. Whereas healthy individuals report fatigue to be a pleasant, acute, normal, regulating phenomenon which helps them to schedule their daily rhythm and which disappears after a good night's sleep, cancer patients speak about chronic, unpleasant, distressing, life and activity-limiting fatigue throughout the day.

In various publications, different definitions to describe fatigue in patients with cancer have been used. From all these different descriptions, we conclude that fatigue is a subjective and multidimensional concept with several modes of expression: physical (e.g. diminished energy, need to rest), cognitive (e.g. diminished concentration or attention) and affective (e.g. decreased motivation or interest).

In this review, we focus on what is currently known about fatigue during and after treatment for cancer, based on empirical studies with reliable instruments. In the first part of our review (fatigue during treatment for cancer), studies are included in which fatigue was investigated in patients in the active phase of their disease. In the second part (fatigue after treatment for cancer), disease-free patients who completed cancer treatment are included. The prevalence of fatigue and correlates of fatigue are discussed. In addition, the literature concerning interventions to reduce fatigue in cancer patients is also examined. In Tables 1-3, all of the reviewed studies are summarised. Study characteristics and key findings are described and, when possible the effect size was calculated.

METHOD

We conducted a literature search in Medline, Current Contents (CC) and Psychlit for the period 1980- July 2001. In the first search, 154 different articles were found with the keywords FATIGUE and (CANCER or HODGKIN'S or TUMOR or TUMOUR or MALIGN* or HAEMATOLOG* or RADIOTHERAPY or RADIATION or CHEMOTHERAPY or HORMONE THERAPY) in the title. In a second search, we combined the words CANCER (or HODGKIN'S or TUMOR or TUMOUR or MALIGN* or HAEMATOLOG*) and (INTERVENTION or EXERCISE or PSYCHOTHERAPY or GROUP or COUNSEL*) in the title and the word FATIGUE in the title, keyword or abstract. This search resulted in 27 articles.

The following articles were excluded: 1) review articles, 2) editorials/ comments/ practical guidelines, 3) studies in which the sample size was less than 15, 4) studies investigating a sample of subjects other than adult cancer patients (e.g. children, caregivers), 5) studies in which evaluation of a fatigue-questionnaire was the only intention, 6) uncontrolled intervention studies, 7) studies published in a language other than English or Dutch and 8) studies in which fatigue was measured with only one or a few items from quality of life questionnaires. This last criterion was entered because these studies give a limited insight. The severity of the fatigue complaint is lacking and comparison with other groups is not possible.

Using these criteria, we had to exclude 127 articles (112 of the 154 and 15 of the 27), resulting in 54 articles to be reviewed. We checked the internal consistency of the fatigue questionnaires that were used in these 54 articles and concluded that they are all reasonable (alpha 0.70) to good (alpha 0.97).

FATIGUE DURING TREATMENT FOR CANCER

Description of the reviewed studies

In Table 1, 26 publications are summarised in which fatigue was investigated in a sample of cancer patients during or immediately after treatment for cancer[1-26].

Table 1. Fatigue during treatment for cancer

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire[#]
Blesch, 1991 (1)	In- and out patients (breast and lung cancer) receiving chemotherapy and/or radiotherapy (50% inpatients)	44 breast cancer patients, age 24-69, mean 51 (sd 11) 33 lung cancer patients, age 38-74, mean 58 (sd 9), 75% male	1	VAFS, POMS-fatigue
Key finding:	*Fatigue was present to some degree in 99% of the patients. Two- thirds rated their level of fatigue as moderate to severe.*			
Cimprich, 1992 **(2)**	Breast cancer patients during hospitalisation for surgery (mean 3 days after surgery)	32 patients, age 29-84, mean 54 (sd 14)	1	Attentional fatigue: digit span, alphabet backward, symbol digit modification test, letter cancellation
Key finding:	*Patients had a significantly decreased capacity to direct attention in comparison to norm scores.*			
Glaus, 1993 (3)	Patients with different cancer diagnoses during treatment with chemotherapy and/or radiotherapy	20 cancer patients age 31-85, mean 54 (sd 15), 30% male 30 healthy controls age 20-58, mean 33 (sd 10), 39% male	4 times daily during 7 days	VAFS
Key finding:	*The mean fatigue score was significantly higher for cancer patients than for healthy controls (effect size 0.31).*			
Irvine, 1994[A] (4)	Patients with lung, breast and gynaecological cancer during chemotherapy or radiotherapy	54 radiotherapy, 47 chemo-therapy, age 25-77, mean 55 (sd 11), 3% male 53 healthy controls, mean age 63, 0% male	2 (start and midpoint of a cycle of chemo-therapy or start and end of radiotherapy)	PBFFQ
Key finding	*61% experienced 'clinical fatigue'. Cancer patients experienced a significant increase in fatigue during therapy. Their fatigue scores were higher than scores of control subjects (effect size 0.65).*			

Table 1. continued

Author	**Diagnosis and treatment**	**Patient characteristics**	**Number of measurements**	**Fatigue questionnaire**[#]
Graydon, 1995[A] **(5)**	Patients with breast and gynaecological cancer during chemotherapy or radiotherapy	54 radiotherapy, 45 chemotherapy, age 25-77, mean 55 (sd 11)	2 (start and midpoint of a cycle of chemotherapy or start and end of radiotherapy)	PBFFQ
Key finding:	*At second assessment, patients were significantly more fatigued than they had been at first assessment.*			
Dean, 1995 (6)	Patients with malignant melanoma during treatment with interferon alpha	30 patients, age 20-85, mean 53 (sd 17), 67% male	5 (before treatment and at the end of each two weeks)	PFS
Key finding:	*Patients were significantly more fatigued mid- or post treatment than they had been at pre-treatment measurement.*			
Richardson, 1996 (7)	Patients with different cancer diagnoses during chemotherapy	129 patients, age 26-82, mean 58	Daily during one cycle of chemotherapy	VAFS
Key finding:	*90% reported fatigue at some point during a cycle of chemotherapy.*			
Dimeo, 1997 (8)	Patients with different cancer diagnoses in the period between receiving 1 to 4 chemotherapy cycles and hospital admission for high-dose chemotherapy with stem cell transplantation	78 patients, age 18-60, mean 40 (sd 11), 40% male	1	POMS-fatigue
Key finding:	*A weak correlation was found between fatigue and maximal physical performance (-.30).*			

Table 1. continued

Author	**Diagnosis and treatment**	**Patient characteristics**	**Number of measurements**	**Fatigue questionnaire**[#]
Irvine, 1998 (9)	Breast cancer patients during radiotherapy and at 3 and 6 months follow-up	76 patients, age 33-81, mean 60 (sd 11)	6 (before radiotherapy, 1 and 2 weeks later, during the last week, and 3 and 6 months later)	PBFFQ
Key finding:	*Fatigue increased over the course of treatment, was highest at the last week of treatment and returned to pre-treatment levels by 3 months after treatment.*			
Smets, 1998a [B] **(10)**	Patients with different cancer diagnoses during radiotherapy	250 patients, mean age 64 (sd 13), 58% male	2 (before start of treatment and 2 weeks after completion)	MFI-20
Key finding:	*Fatigue scores after radiotherapy were significantly higher than pre-treatment scores. After treatment 46% of the patients reported fatigue as among the three symptoms that caused them most distress.*			
Smets, 1998b [B] **(11)**	Patients with different cancer diagnoses during and after radiotherapy	250 patients, mean age 64 (sd 13), 58% male	3 (before start of treatment, 2 weeks and 9 months after completion)	MFI-20
Key finding:	*Fatigue during treatment with radiotherapy is best explained by treatment related demands (daily travel to hospital and confrontation with other patients) and demands of the social environment (work, children).*			
Visser, 1998 [B] **(12)**	Patients with different cancer diagnoses during and after radiotherapy	250 patients, mean age 64 (sd 13), 58% male	3 (before start of treatment, 2 weeks and 9 months after completion)	MFI-20
Key finding:	*Correlations between fatigue and depression were moderate. Depression scores did not change while fatigue scores rose over the course of cancer treatment.*			

Table 1. continued

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire[#]
Richardson, 1998 (13)	Patients with different cancer diagnoses during chemotherapy	109 patients, age 20-89, mean 59, 46% male	daily during one cycle of chemo-therapy (21 or 28 days)	VAFS
Key finding:	*89% reported fatigue at some point during a cycle of chemotherapy.*			
Berger, 1998 [C] **(14)**	Breast cancer patients during chemotherapy	72 patients, age 33-69, mean 50 (sd 9)	4 days at the start and 3 days at cycle midpoints during the first 3 cycles of chemotherapy	PFS
Key finding:	*Fatigue scores were significantly higher at the day of chemotherapy administration than between treatment courses, but fatigue did not increase over time.*			
Miaskowski, 1999 (15)	Patients with different cancer diagnoses with bone metastases during radiotherapy	24 patients, mean age 56 (sd 13), 50% male	during 2 days	LFS
Key finding:	*Patients reported moderately amounts of fatigue. Fatigue levels were higher at the end of the day and decreased in the morning following a night's rest.*			
Gaston-Johansson, 1999 (16)	Breast cancer patients in the period between receiving chemo-therapy and high-dose chemotherapy with stem cell transplantation	127 patients, age 22-60, mean 45 (sd 8)	1	PFS, VAFS
Key finding:	*91% reported fatigue at some point.*			

Table 1. continued

Author	**Diagnosis and treatment**	**Patient characteristics**	**Number of measurements**	**Fatigue questionnaire**[#]
Stone, 1999 (17)	Patients with different cancer diagnosis (advanced cancer, but currently not receiving chemotherapy or radiotherapy)	95 patients, age 30-89, mean 67, 43% male 98 healthy controls, age 41-85, mean 68, 38% male	2 (baseline and 2 weeks later)	FSS
Key finding:	*Prevalence of 'severe subjective fatigue' was found to be 75%.*			
Hann, 1999 (18)	Breast cancer patients receiving high-dose chemotherapy with bone marrow transplantation	31 patients, age 36-74, mean 51 (sd 15) 49 healthy controls, age 36-55, mean 51 (sd 8)	3 (prior to treatment, mid-treatment, near treatment completion)	POMS-fatigue, FSI
Key finding:	*Cancer patients reported significantly more frequent and severe fatigue than women with no cancer history (effect size POMS 0.75; FSI 0.61).*			
Monga, 1999 (19)	Prostate cancer patients during *and after* radiotherapy	36 patients, age 55-79, mean 67	4 (pre- , middle- and completion of treatment, and 4-5 weeks follow-up)	PFS
Key finding:	*Fatigue scores were significantly higher during and directly after radiotherapy (25%) than at pre-treatment (8%). At 5 week follow-up, fatigue scores were not higher anymore than scores at pre-treatment.*			
Jacobsen, 1999 (20)	Breast cancer patients during chemotherapy	54 cancer N=54, age 28-77, mean 51 (sd 10) 54 control, age 32-77, mean 54 (sd 11)	3 (before treatment and after completion of the second and third cycle)	POMS-fatigue, FSI
Key finding:	*Cancer patients experienced significant worse fatigue than women with no cancer history, before (effect size POMS 0.51) and during chemotherapy (effect size POMS 0.88).*			

Table 1. continued

Author	**Diagnosis and treatment**	**Patient characteristics**	**Number of measurements**	**Fatigue questionnaire**#
Berger, 1999 C **(21)**	Breast cancer patients during chemotherapy	72 patients, age 33-69, mean 50 (sd 9)	4 days at the start and 3 days at cycle midpoints during the first 3 cycles of chemotherapy	PFS
Key finding:	*Fatigue has been found to be associated with less daytime activity.*			
Stone, 2000a (22)	Patients with prostate cancer during treatment with hormone therapy	58 patients, age 55-80, median 69	2 (day they started therapy, 3 months later)	FSS
Key finding:	*Prevalence of severe fatigue was found to be 14% at baseline, before treatment started. Median FSS scores increased significantly after 3 months treatment.*			
Stone, 2000b (23)	Recently diagnosed patients with breast or prostate cancer awaiting therapy, patients with non-small-cell lung cancer referred for palliative chemo-therapy and patients with advanced cancer (but currently not receiving chemo- or radiotherapy)	227 patients, age 30-89, median 66, 56% male 98 control, age 41-85, median 68, 38% male	1	FSS
Key finding:	*Prevalence of severe fatigue was 48%. Median FSS of the combined patient group was significantly higher than that of the control group.*			
Stone, 2000c (24)	Patients with different cancer diagnosis, during different anti-cancer treatment	576 patients, age 18-89, median 59, 37% male	1	FACT-fatigue
Key finding:	*58% reported that fatigue had affected them in the past month. Fatigue affected patients significantly more than any other symptom.*			

Table 1. continued

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire#
Okuyama, 2001 (25)	Patients with advanced lung cancer (but currently not receiving anti-cancer treatment)	157 patients, age 27-80, mean 63, 71% male	1	CFS, FNS, questions on interference of fatigue with 7 domains of daily activity
Key finding:	*51% was found to experience clinical fatigue.*			
Ahsberg, 2001 (26)	Patients with different cancer diagnosis, during *and after* radiotherapy	81 patients, age 30-70, 9% male	4 (before treatment, at the last week of treatment, at 1 and 3 months after completion of treatment).	SOFI
Key finding:	*Patients were significantly more fatigued at the end of a course of radiotherapy than they had been before.*			

[A] different studies with almost the same sample of patients.
[B] different studies with the same sample of patients.
[C] different studies with the same sample of patients.

Fatigue Questionnaires: CFS- Cancer Fatigue Scale; FACT- Functional Assessment of Cancer Therapy; FNS- Fatigue Numerical Scale; FSI- Fatigue Symptom Inventory; FSS- Fatigue Severity Scale; LFS- Lee Fatigue Scale; MFI-20- Multidimensional Fatigue Inventory; PBFFQ- Pearson Byars Fatigue Feeling Questionnaire; PFS- Piper Fatigue Scale; POMS- Profile of Mood States; SOFI- Swedish Occupational Fatigue Inventory; VAFS- Visual Analogue Fatigue scale

These 26 publications were based on 22 studies. As indicated in Table 1, some studies were based on the same sample of patients, answering different research questions. In ten of these 22 studies, a homogenous group of cancer patients was investigated. In six studies, the sample consisted of breast cancer patients. In two studies, patients with prostate cancer were included. In one study, patients with malignant melanoma participated and finally, in one study, patients with advanced lung cancer participated. In the other 12 studies, samples consisted of patients with different cancer diagnoses.

Most studies (seven) investigated fatigue during treatment with chemotherapy. In three of these studies, patients were receiving high dose chemotherapy in combination with stem cell transplantation. More specifically, in one study patients were receiving high-dose chemotherapy at the moment of investigation, while in two other studies patient underwent chemotherapy recently, and were waiting to receive high dose chemotherapy. In five studies, patients were investigated during treatment with radiotherapy. In two studies, the investigation took place while patients were treated with hormonal therapy and in four studies while they were undergoing either chemo- or radiotherapy, or a combination of these treatments. Furthermore, in one study, in which attentional fatigue was the research subject, patients were investigated during hospitalisation after surgery for cancer. The idea behind this latter study was that the mental effort required to cope with the intense and competing demands imposed by a diagnosis of cancer may lead to attentional fatigue. In two studies, patients had advanced cancer, but they were not receiving treatment at the time of investigation and, finally, in one study, the sample consisted of recently diagnosed patients awaiting therapy, patients referred for palliative chemotherapy and patients with advanced cancer, not receiving treatment at the time of investigation.

A wide variety of instruments were used to measure fatigue. Frequently used were the Piper Fatigue Scale, the Fatigue Severity Scale, the fatigue subscale of the POMS and Visual Analogue Fatigue Scales.

The size of the investigated samples ranged from 20 to 576 cancer patients. The ages of the patients within these samples were within a range from 18 to 89, with means ranging from 40 to 67. In seven studies, patients were all female, in two studies patients were all male. In the majority of the other 13 studies, there was an equal distribution of men and women. A control group of healthy subjects was included in six studies only.

Prevalence and course of fatigue

Percentages of presence of fatigue differed in the reviewed studies. Twenty-five percent of a sample of prostate cancer patients reported fatigue during and directly after a course of radiotherapy[19]. Forty-six percent of a mixed sample of cancer patients reported fatigue among the three symptoms that caused them the most distress at the end of a course of radiotherapy[10]. The prevalence of severe fatigue (defined as fatigue greater than that experienced by 95% of the control group) in a combined group of patients with recently diagnosed breast or prostate cancer, patients with inoperable non small cell lung cancer and patients receiving inpatient palliative care was 48%[23]. In a Japanese study, 51% of a sample of patients with advanced lung cancer was found to experience clinical fatigue (which means that they complained of interference of fatigue with at least one domain of daily living activity)[25]. In another study, 58% of a sample of cancer patients undergoing anti-cancer therapy reported that fatigue had affected them in the past month, and that fatigue affected them significantly more than any other symptom[24]. Furthermore, 61% of a mixed sample of the cancer patients reported clinical fatigue (as defined by a score higher than the midpoint of the fatigue questionnaire) during chemotherapy or radiotherapy[4]. Finally, the prevalence of severe fatigue in patients with advanced cancer was found to be 75%[17]. Studies in which Visual Analogue Fatigue Scales were used, present even higher percentages of fatigue. In two studies in which a diary was used, 89 and 90% of the investigated patients reported fatigue at some point during a cycle of chemotherapy[7,13]. In two other studies, with only one measurement time, fatigue was present to some degree in 91%[16] and in 99%[1] of the investigated patients. In this last study, two thirds rated their fatigue as moderate to severe.

In all six studies in which cancer patients were compared with healthy control subjects, cancer patients reported more frequent and severe fatigue than healthy control subjects[3,4,17,18,20,23]. In addition, in a study in which attentional fatigue was measured during hospitalisation for breast cancer surgery, patients had a decreased capacity to direct attention compared with available norm scores[2]. In four of these studies, it was possible to calculate the effect size. The effect sizes were 0.31[3], 0.65[4], 0.75[18] and 0.88[20].

In ten studies, fatigue scores prior to treatment were compared with mid- or post-treatment fatigue scores. Nine studies reported that patients were significantly more fatigued mid- or post treatment than they had been at pre-treatment measurement[4,6,9,10,18-20,22,26]. In one study, contrary results were reported. In this study, fatigue was found to be significantly higher on the day of chemotherapy administration than between the treatment courses, but fatigue did not increase over time[14].

The course of fatigue during the day has been described in three studies only. In one study, the healthy population felt fit in the morning, with steadily increasing levels of fatigue over the day. In cancer patients, the daily profile was different: fatigue was continuously present, they already felt fatigued in the morning and, to a certain degree, over the whole day, but showed lower peak levels in the evening[3]. In the other two studies, results were contradictory. The authors found that fatigue in cancer patients varied throughout the day, more frequently occurring in the afternoon and early evening[13,15]. These contradictions could be due to the inclusion of dissimilar groups of patients; inpatients[3] versus outpatients[13,15].

Correlates of fatigue

Disease related variables

Results with regard to the relationship between fatigue and disease related variables have been reported in several of the reviewed studies. In seven of the ten studies, severity of fatigue appeared to be unrelated to cancer diagnosis, cancer stage at diagnosis, size of original tumour, number of nodes involved and presence and site of metastases[1,4,9,17,18,20,25]. However, in three studies, significant associations were found between fatigue and particular types of cancer. In a sample of radiotherapy patients with head and neck, gastrointestinal, gynaecological, lung, breast, urogenital and haematological cancer, lung cancer patients reported most fatigue, and patients with malignancies in the head and neck region reported least fatigue[10]. In another study, patients with small cell lung cancer were found to report less fatigue in contrast to patients with cholangiocarcinoma or pancreatic cancer, breast cancer, or a lymphoma during a cycle of chemotherapy[13]. Considering the fact that patients with small cell lung cancer quickly feel better after administration of chemotherapy, this result is not surprising. Finally, in a mixed sample of cancer patients, the prevalence of severe fatigue was found to be 15% among patients with recently diagnosed breast cancer, 16% among patients with recently diagnosed prostate cancer, 50% among patients with inoperable non small cell lung cancer and 78% among patients receiving inpatient palliative care[23].

Treatment related variables

It is generally accepted in clinical practice that fatigue complaints during treatment for cancer are a result of treatment with surgery, chemotherapy, radiotherapy or hormonal therapy. However, the association between the severity of fatigue and treatment related variables has been investigated in only a few studies. In two studies, fatigue scores were compared between patients receiving different kinds of surgery for breast cancer. No differences were found between patients who underwent mastectomy versus breast conservation surgery with regard to (attentional) fatigue[2,20]. Furthermore, no differences with regard to fatigue have been found between patients receiving chemotherapy versus radiotherapy[1,25]. In addition, in a sample of patients undergoing radiotherapy, no associations were found between fatigue and radiation dose or fractionation[10]. It should, however, be noted that in this study crude categorisations were used to have large enough groups for meaningful statistical analyses. In two studies in which patients underwent chemotherapy, the relationship between fatigue and type of conditioning has been investigated. Results of one study indicate that the type of conditioning regimen (61% received cyclophosphamide, thio-TEPA and carboplatin, 35 % received thio-TEPA, Novantrone and Taxol, and 4% received ifosfamide, carboplatin and etoposide) was unrelated to fatigue[18]. In the other study, fatigue was statistically associated with methods of drug administration. Patients receiving conventional 3 to 4 week cycles of chemotherapy experience high levels of fatigue for the first 4 to 5 days after treatment, which gradually decline. In contrast, patients receiving weekly injections of chemotherapy, experience moderate levels of fatigue that fluctuate cyclically[13].

Finally, anaemia is a frequent complication during the treatment of cancer. However, in the reviewed studies, only was a weak relationship found between haemoglobin level and fatigue[23]. On the contrary, in six studies no relationship could be found[1,3,4,9,17,25].

Demographic variables

In ten studies, relationships between the demographic variables and fatigue were investigated. In nine of these studies, no relationships were found between fatigue and age, gender, marital status, race and working status[5,10,12,17,18,20,22, 23,25]. Female patients were found to experience more fatigue in only one study[3]. However, this result has to be interpreted carefully, as the distribution of men and women was not equal.

Psychological, physical, social and behavioural variables

Feeling sad, depressed, anxious, confused and angry are normal reactions to the whole life-threatening situation of being diagnosed and treated for cancer. Emotional vulnerability and the endurance of heavy stress over prolonged periods of time may contribute to fatigue. In several studies, the intensity of fatigue showed a strong correlation with indicators of psychological distress such as depression, somatisation, and anxiety[1,4,8,9,10,15,16,18,20,23-26]. However, other studies present contradictory results. No correlation has been found between attentional fatigue and mood state after surgery for breast cancer[2]. Furthermore, severity of fatigue in patients with advanced cancer was unrelated to mood[17]. This discrepancy may partly be explained by the nature of the patient sample. All patients had advanced disease and most had multiple physical problems and a very short prognosis. Under these circumstances, it is probable that fatigue has a different origin to that occurring in patients with earlier stage disease. Finally, in three studies, although correlations between fatigue and depression were moderate, depression scores did not change while fatigue scores rose over the course of radiotherapy[12,19] and hormonal therapy[22].

With regard to the quality of sleep, results were unambiguous, suggesting higher fatigue is associated with more sleep problems[10,14,15,20,25]. In addition, a change in sleep patterns was among the most frequently mentioned symptoms to which patients attributed their fatigue[7]. The association between fatigue and pain has very rarely been the subject of investigation; in the studies we reviewed, however, results were similar. More severe fatigue before treatment was associated with pain in breast cancer patients[16,20]. In patients with advanced cancer, fatigue severity was also significantly associated with pain[15,17,23,25]. An association between fatigue and chemo- and radiotherapy side effects, like nausea, mouth sores, chills and vomiting has been found in two studies[7,17]. In addition, fatigue during treatment with radiotherapy is best explained by treatment related demands (daily travel to hospital and confrontation with other patients) and demands of the social environment (work, children)[11].

Finally, the relationship between fatigue and physical activity has been assessed in three studies. Results were identical. Fatigue was found to be associated with less daytime activity[21]. In another study, activity levels were significantly different over time in a mirror-image pattern of fatigue[14]. In addition, a weak association between fatigue and maximal physical performance has been found[8].

Summary

From the reviewed studies, it can be concluded that fatigue is an important complaint during treatment for cancer. Prevalence estimates of fatigue during treatment for cancer range from 25% to 75% in different samples of cancer patients, measured with different fatigue questionnaires. When Visual Analogue Fatigue Scales were used, percentages rose up to 99%. In studies in which a control group of healthy subjects was included, cancer patients reported more frequent and severe fatigue than healthy controls.

Most studies failed to find relationships between fatigue and disease related variables, such as diagnosis and stage at diagnosis. However, it is important to note that these negative results might be explained by the study characteristics. For instance, in studies investigating a small sample of patients coupled with a wide variation of disease-related variables, the chance of finding statistical differences is very small. However, studies of homogenous samples of cancer patients may also fail to find significant correlates of fatigue because of a lack of dispersion.

The relationship between fatigue and treatment related factors, such as type of surgery and type of adjuvant therapy, has rarely been investigated. Therefore, no conclusions can be drawn. Furthermore, results regarding the relationship between demographic variables and fatigue were unambiguous. In nine of the ten studies, no significant relationships were demonstrated. Finally, psychological distress, quality of sleep and a few other variables (pain, therapy side effects, and physical activity) were found to be related to fatigue.

FATIGUE AFTER TREATMENT FOR CANCER

Description of the reviewed studies

In Table 2, 16 publications are summarised in which the focus was on off-treatment fatigue[27-42]. These 16 publications were based on 13 studies. In these studies, fatigue complaints have been investigated in disease-free cancer patients, who completed curative treatment for cancer in the (recent) past. In seven of these 13 studies, a sample of breast cancer patients was investigated. In one study, Hodgkin's disease survivors, in one study, lymphoma patients and in one study, patients treated for haematological malignancies were investigated. Finally, in three studies, the sample consisted of patients treated for various kinds of cancer.

Mean time since completion of cancer treatment ranged from 9 months to 12 years. In one study, the time since diagnosis was mentioned (mean 2.5 years). In this study, because some patients were diagnosed with cancer only 6 months ago, there is a possibility that these patients were still in active treatment at the time of participation in the study[28].

Most studies made use of more than one fatigue questionnaire. Frequently used instruments were the Fatigue Symptom Inventory, the fatigue subscale of the Profile of Mood State, the Piper Fatigue Inventory and the Fatigue Questionnaire. Sample sizes of the disease-free cancer patients in the reviewed articles, ranged from 33 to 1975. The ages of disease-free cancer patients ranged from 18 to 90 years, with means ranging from 32 to 65 years. In seven studies, all of the patients were female, in one study, all the patients were male and, in the other five studies, the distribution of men and women was approximately equal.

In six studies, a control group was included. In five of these studies, the control group consisted of healthy subjects without a cancer history. In the sixth study, investigating fatigue after treatment for breast cancer, the control group consisted of women who were treated for benign breast problems. Furthermore, in four studies, norm scores were available for the fatigue questionnaire that was used[33,35,36,40].

Prevalence of 'off treatment-fatigue'

In five studies, percentages of patients suffering fatigue have been mentioned. In a study of cancer survivors who completed treatment more than 1 year ago, 17% met formal diagnostic criteria for cancer related fatigue[41]. In a sample of Hodgkin's survivors, 26% had substantial fatigue for 6 months or longer[33,39,42]. This percentage was significantly higher than the percentage among 2214 controls representative of the general Norwegian population (11%). In a study investigating a sample of patients who had been treated for various kinds of cancer, 29 percent experienced heightened feelings of fatigue compared with norm scores of healthy control subjects. Nineteen percent of the total sample even experienced severe fatigue[40]. Within a large sample of breast cancer survivors, 30 percent reported heightened levels of fatigue relative to women in the general population[36]. Finally, in a sample of cancer patients having a prior history of chemotherapy, 30% experienced fatigue on a daily basis. Ninety-one percent of those who experienced fatigue reported that it prevented a 'normal life' [38].

In six studies, fatigue scores of disease-free cancer patients have been compared with scores of control subjects. Four studies indicate that fatigue scores of disease-free cancer patients long after they finished treatment were significantly higher than fatigue scores of control subjects. In the first study, a group of disease-free breast cancer patients reported more fatigue, more weakness and less vitality relative to the benign breast problem group at the initial and the 4 month follow-up assessments[30]. In the second study, comparing former breast cancer patients with women with no history of cancer, patients reported more severe fatigue and worse quality of life because of fatigue[31]. In the third study, male patients treated for haematological malignancies had higher mean general fatigue, physical fatigue and mental fatigue scores compared with men without a cancer history[34]. Finally, in a study of former bone marrow transplantation recipients, patients reported significantly more fatigue, on significantly more days in the past week, as well as for a significantly greater part of the day, than the non-cancer comparison subjects[27]. The effect sizes in the above described studies range from 0.30 to 0.97. However, in two studies contradictory results have been described. Both of these studies compared disease-free cancer patients after a course of radiotherapy with a healthy control group. Results indicated that the fatigue experienced by patients after radiotherapy for cancer was not significantly different in intensity, duration or disruptiveness from fatigue experienced by healthy women[29,32]. In addition, three studies which were described in Table 1, conducted follow-up analyses of fatigue scores at 1 and 3 months after radiotherapy for different kinds of cancer[26], 3 and 6 months after radiotherapy for breast cancer[9] and 4-5 weeks after radiotherapy for prostate cancer[19]. All studies concluded that fatigue scores had returned to pre-treatment levels at follow-up.

Correlates of fatigue

Disease related variables

The relationship between off-treatment fatigue and disease related variables has been investigated in seven studies. In these studies, it was found that cancer diagnosis[29,34], disease stage at diagnosis[27,29,31-33,37], size of the original tumour[27,32,37], number of nodes involved[27] and having relapsed[33] were not significantly related to fatigue intensity.

Table 2. Fatigue after treatment for cancer

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire$^{\#}$
Hann, 1997 (27)	Breast cancer patients (3.5 to 62.5 months, mean 20 months) after treatment with high dose chemo-therapy with bone marrow transplantation	43 patients age 32-57, mean 44 (sd 6) 43 controls (noncancer) age 32-56, mean 47 (sd 6)	1	POMS-fatigue, FSI
Key finding:	*Women who had completed BMT reported significantly more frequent and severe fatigue than women with no cancer history (effect size POMS 0.46; FSI 0.40).*			
Woo, 1998 (28)	Breast cancer patients (6 months to 28 years after diagnosis, mean 30 months). Treated with chemotherapy, radiotherapy, hormonal therapy or a combination !! a few patients could have been in active treatment	332 patients, age 31-90, mean 52 (sd 10)	1	PFS
Key finding:	*Women who received combination therapy reported significant higher levels of fatigue compared with those treated with radiotherapy only (effect size 0.97).*			
Smets, 1998c (29)	Patients with different cancer diagnoses (9 months) after treatment with radiotherapy	154 patients, age 65 (sd 12), 57% male 139 healthy controls, age 46 (sd 16), 44% male	1	MFI-20
Key finding:	*Fatigue in patients did not differ significantly from fatigue in controls.*			

Table 2. continued

Author	**Diagnosis and treatment**	**Patient characteristics**	**Number of measurements**	**Fatigue questionnaire**$^{\#}$
Andrykowski, 1998 (30)	Breast cancer patients (3 to 60 months, mean 25 months) after treatment with chemotherapy, radiotherapy or a combination of these treatments	88 patients, age 35-76, mean 54 (sd 9) 88 controls with benign breast problems, age 37-76, mean 53 (sd 9)	2 (initial and 4 month follow-up)	MOS- vitality, CFS, PFS
Key finding:	*Breast cancer patients reported significantly more fatigue, more weakness and less vitality relative to the benign breast cancer patients at two assessment times (initial and 4 months follow-up) (effect size initial assessment MOS 0.30; CFS 0.15; PFS 0.30).*			
Broeckel, 1998 (31)	Breast cancer patients (3 to 36 months, mean 16 months) after treatment with chemotherapy (sometimes in combination with radiotherapy)	61 patients, age 52 (sd 11) 51 healthy controls, age 51 (sd 11)	1	POMS-fatigue, FSI, MFSI
Key finding:	*Patients reported more severe fatigue than healthy controls (effect size POMS 0.47; FSI 0.42; MFSI 0.42).*			
Hann, 1998 (32)	Breast cancer patients (5 to 88 months, mean 22 months) after treatment with radiotherapy	45 patients, age 36-86, mean 64 (sd 13) 44 healthy controls, age 47-77, mean 60 (sd 9)	1	POMS-F, FSI
Key finding:	*There were no significant differences between the groups on reported levels of fatigue severity, intensity, frequency, and disruptiveness.*			

Table 2. continued

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire#
Loge, 1999^{A} (33)	Hodgkin's disease survivors (mean observation period 12 years, sd 6)	459 patients, mean age 32 (sd 11), 56% male	1	FQ
Key finding:	*26% had substantial fatigue for 6 months or longer This percentage was significantly higher than the percentage among 2,214 controls representative of the general Norwegian population (11%) (effect size 0.51).*			
Howell, 2000 (34)	Patients treated for haematological malignancies (1-21 years, mean 8 years) after chemotherapy (sometimes in combination with radiotherapy)	66 patients, age 21-52, mean 40, 100% male 44 healthy controls, age 20-59, mean 40, 100% male	1	MFI-20
Key finding:	*Fatigue scores were higher in men treated for haematological malignancies in comparison to healthy men.*			
Knobel, 2000 (35)	Lymphoma patients (median 6 years) after high dose therapy supported by autologous bone marrow transplantation	33 patients, age 18-59, mean 39, 55% male	1	FQ
Key finding:	*Lymphoma patients were more fatigued than the Norwegian reference population.*			
Bower, 2000 (36)	Breast cancer patients (12 to 60 months, mean 35 months) after treatment with chemotherapy, radiotherapy or a combination of these treatments	1975 patients, mean age 55	1	Rand 36-energy/fatigue
Key finding:	*30% did report heightened levels of fatigue relative to women in the general population.*			

Table 2. continued

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire$^{\#}$
Okuyama, 2000 (37)	Breast cancer patients (mean 20 months) after treatment with surgery, chemotherapy, radiotherapy or a combination of these treatments	134 patients, age 28-86, mean 55 (sd 10)	1	CaFS
Key finding:	*Fatigue was significantly correlated with dyspnea, insufficient sleep and depression.*			
Curt, 2000^{B} (38)	Cancer survivors who completed treatment for chemotherapy (sometimes in combination with radiotherapy) more than 1 year ago	379 patients, mean age 63, 21% male	1	Telephone interview, 50 questions on fatigue
Key finding:	*30% experienced fatigue on a daily basis. 91% of those who experienced fatigue reported that it prevented a 'normal life'.*			
Loge, 2000^{A} (39)	Hodgkin's disease survivors (observation period 3 to 23 years)	421 patients, age 19-74, 56% males	1	FQ
Key finding:	*Fatigued HDS had higher levels of anxiety and depression than non-fatigued HDS.*			
Servaes, 2001 (40)	Patients with different cancer diagnoses (6 months to 12.5 years, mean 36 months) after treatment with chemotherapy and/or radiotherapy	85 patients, age 21-74, mean 48 (sd 14), 60% male	1	CIS
Key finding:	*19% of a sample of disease-free cancer patients experienced severe fatigue. Their mean fatigue score is significantly higher than a reference score of healthy adults (effect size 0.30).*			

Table 2. continued

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire[#]
Cella, 2001[B] (41)	Cancer survivors who completed treatment for chemotherapy (sometimes in combination with radiotherapy) more than 1 year ago	379 patients, mean age 63, 21% male	1	Telephone interview, 50 questions to establish cancer-related-fatigue
Key finding:	*17% met formal diagnostic criteria for cancer related fatigue.*			
Knobel, 2001[A] (42)	Hodgkin's disease survivors after radiotherapy (sometimes in combination with chemotherapy), mean observation time 9 years (sd 3)	92 patients, age 23-56, mean 37, 59% male	1	FQ
Key finding:	*Pulmonary dysfunction is associated with fatigue in HDS. Cardiac sequelae was not associated with fatigue in HDS.*			

[A] different studies with almost the same sample of patients
[B] different studies with the same sample of patients

[#] Fatigue Questionnaires: CaFS- Cancer Fatigue Scale; CFS- Chalder Fatigue Scale; CIS-20- Checklist Individual Strength; FQ- Fatigue Questionnaire; FSI- Fatigue Symptom Inventory; MFI-20- Multidimensional Fatigue Inventory; MFSI- Multidimensional Fatigue Symptom Inventory; MOS- Medical Outcome Studies; PFS- Piper Fatigue Scale; POMS- Profile of Mood States.

Treatment related variables

Relationships between off-treatment fatigue and certain treatment related variables were investigated in all the reviewed studies. No differences were found with regard to off-treatment fatigue between patients who underwent mastectomy versus patients who underwent breast conservation surgery[31,37].

The extent of adjuvant therapy patients underwent was unrelated to fatigue severity in eight articles in which this relationship was studied[29-34,37,40]. Current tamoxifen use turned out to be unrelated to fatigue severity as well[27,31,32,36,37]. In contrast, in two studies, severity of post treatment fatigue was related to the extent of treatment. In these studies, former chemotherapy patients (sometimes in combination with radiation and/or hormonal therapy) reported higher levels of fatigue compared with those treated with radiotherapy[28,36]. It should be noted, however, that in the study by Bower, the association between fatigue and type of treatment was only moderate. Treatment did not emerge as a significant predictor of fatigue in the regression analysis[36]. Furthermore, as noted before, in the study by Woo there is a possibility that some patients were still in active treatment at the time of participation in the study[28].

Time since treatment completion was unrelated to fatigue severity in eight of the nine studies in which this was investigated[30-34,36,37,40]. In the study that did reveal a relation between fatigue and time since treatment completion, this was the opposite of what was to be expected. The longer the time since treatment completion, the more severe was the fatigue reported[27].

Finally, possible long-lasting side effects of cancer treatment were investigated in two studies[35,42]. Hodgkin's disease survivors with pulmonary dysfunction were more fatigued than those with normal pulmonary function. Thyroid dysfunction and cardiac sequelae were not associated with fatigue in this patient population[42]. Furthermore, no statistical endocrinological or immunological association with fatigue could be demonstrated[35].

Demographic variables

In nine studies the relationships between off-treatment fatigue and age, educational level, marital status and ethnicity have been investigated. The authors of three studies found that none of the investigated demographic variables were significantly related to fatigue[27,31,32]. The association between gender and fatigue was investigated in three studies, in which a sample of both men and women was investigated. In one study, no differences were found between men and women[39], however in two studies women were found to experience more fatigue than men do[29, 35]. In three studies, fatigued breast cancer survivors were slightly younger than survivors in the non fatigued group[28,36,37]. An explanation could be that younger women are more often employed and often have the responsibility of caring for their families and young children.

Psychological, social, physical and behavioural variables

State and trait anxiety and depressive symptoms were significantly and positively correlated to fatigue severity in all studies. However, in one of the studies, the breast cancer group and benign breast problems group did not differ with regard to depressive symptoms, while they did differ with respect to fatigue scores[30].

Sleep quality was assessed in six studies. In all of these studies, poorer sleep quality was significantly related to fatigue[27,29-31,36,37]. Pain was registered in only two studies. In these studies fatigue was significantly associated with the pain rating[29,36].

Unlike in the studies investigating fatigue during treatment for cancer, the level of activity has hardly been studied in studies of off-treatment fatigue. An exception is one study, in which a negative relationship was found between fatigue and physical activity[40]. Furthermore, negative associations have been found between fatigue and physical functioning[32] and functional ability[29]. Finally, it is reported that severe fatigue among patients was significantly related to dyspnoea[37], menopausal symptoms[31,36], and the use of catastrophising as a coping strategy[31].

Summary

Studies of off-treatment fatigue mainly focussed on disease-free breast cancer patients. The majority of these studies conclude that fatigue is an important problem for approximately one third of the cancer survivors. With regard to the correlates of severe fatigue, it can be concluded that previous disease and treatment characteristics were unrelated to fatigue. Furthermore, only a few studies found that demographic variables (gender, age) were related to fatigue. Finally, fatigue turned out to be related to anxiety and depression, sleep quality, and a few physical variables (pain, dyspnoea, menopausal symptoms and physical activity/ physical functioning).

INTERVENTIONS TO REDUCE FATIGUE

Description of the reviewed studies

In Table 3, 12 controlled intervention studies are summarised. In five of these studies fatigue was the main dependent variable[48,50-52,54]. In the other seven studies, fatigue was one of the investigated outcome measures[43-47,49,53]. All studies took place while patients were undergoing treatment for cancer or, in one study, just after treatment for cancer had finished (surgery, without adjuvant therapy) To the best of our knowledge, no intervention studies have been conducted to reduce fatigue complaints long after treatment for cancer has finished.

With respect to the content of the interventions, three studies investigated the effect of a walking- or exercise program[50-52]. In these studies, patients walk or perform exercises on three to seven days a week for approximately 30 minutes. Five other studies described the effect of individual counselling by professionals[44,45,49,53] or by former cancer patients[46]. Contents of these individual sessions included preparatory information, improving coping skills, psychological support, health education, stress management, cognitive restructuring and relaxation. Two studies conducted an intervention study in which the effect of supportive group meetings[43] and psychiatric group meetings[47] were investigated. Furthermore, in one study the effect of an intervention to minimise attentional fatigue through regular participation in activities that engage fascination and have other restorative properties was investigated[48]. Finally, in one study, a virtual reality system was used. This system made patients feel that they were somewhere else in a virtual world, while they were given chemotherapy. Patients could chose a content (lake, forest, country town) and an aromatic essential oil[54].

The sample of patients in the reviewed studies, consisted mainly of breast cancer patients (in five studies). Other studies investigated patients with gynaecologic cancer, malignant melanoma or samples of patients with different cancer diagnoses. The POMS-fatigue was the most frequently used measurement of fatigue.

Effect of intervention

The studies that investigated the results of sports or walking programmes during treatment with radiotherapy or chemotherapy, reported positive results[50-52]. All studies found that after the end of the intervention patients felt less fatigued in comparison to patients who did not participate in the sports or walking program. None of these studies presented follow-up results.

In addition, in the four studies in which the effect of individual counselling by professionals on fatigue severity was investigated, positive results were found directly after the intervention[44,45,49,53]. Patients in the intervention groups reported significantly less fatigue than patients in the control group. In two studies these results lasted, at three[49] and six months follow-up[44] but, in the other study, the benefit was no longer present at a 4-week follow-up[45]. A study in which the results of counselling by former cancer patients was investigated failed to find a reduction in fatigue[46].

Furthermore, the studies in which the effects of a group intervention were tested, also reported positive results with regard to a reduction in fatigue[43,47]. In one study, the focus was on the effect of health education, enhancement of problem solving skills, stress management (e.g. relaxation) and psychological support. It was found that the intervention group reported less fatigue than a control group six months after the end of the intervention[47]. The other study compared a group of patients who were following weekly supportive group meetings compared with a group of patients who did not follow these meetings. Results indicate that the first group reported less fatigue than the second group[43].

Table 3. Interventions to reduce fatigue

Author	Diagnosis and treatment	Intervention	Patient characteristics	Number of measurements	Fatigue questionnaire[#]
Spiegel, 1981 (43)	Patients with metastatic breast cancer	Weekly supportive group meetings, during one year	16 intervention, mean age 54 14 control, mean age 55	4 (initial, and 4, 8, 12 months later)	POMS-fatigue
Key finding:	*Those who participated in the weekly group sessions experienced significantly less fatigue at all measurements than controls.*				
Worden, 1984 (44)	Patients with different cancer diagnoses, shortly after the time of initial diagnosis	6 week individual training to lower emotional distress and improve coping	59 intervention 58 control Patients were at risk for emotional distress and poor coping	3 (pre-intervention, 2 and 6 months follow-up)	POMS-fatigue
Key finding:	*Two and six months after the intervention, the intervention group was significantly less fatigued than the control group.*				
Forester, 1985 (45)	Patients with different cancer diagnoses, during radiotherapy.	Individual psychotherapy, weekly 10 times	48 intervention, age 23-78, mean 62, 54% men 52 control, age 25-81, mean 62, 46% men	5 (before psycho-therapy, week 3, week 6 (end of radiotherapy), week 10, week 14)	SADS-fatigue
Key finding:	*The intervention group reported significantly less fatigue directly after intervention, but the difference disappeared at follow-up (4 and 8 weeks later).*				

Table 3. continued

Author	Diagnosis and treatment	Intervention	Patient characteristics	Number of measurements	Fatigue questionnaire$^{\#}$
Houts, 1986 (46)	Gynaecologic cancer patients, shortly after the time of initial diagnosis	Individual counselling by former cancer patients (telephone), 10 weeks	14 intervention, mean age 48 18 control, mean age 51	3 (initial and 6 and 12 weeks after entering the study)	POMS-fatigue
Key finding:	*There were no differences in fatigue between the two groups at 6 and 12 weeks after beginning treatment.*				
Fawzy, 1990 (47)	Patients with malignant melanoma directly after surgery (no adjuvant therapy)	6 week psychiatric group intervention, postsurgical (health education, enhancement of problem solving skills, stress management and psychological support)	38 intervention, mean age 46, 47% male 28 control , mean age 38, 47% male	3 (pre, post intervention and 6 months follow-up)	POMS- fatigue
Key finding:	*Directly after the intervention, there were no differences in fatigue scores. At 6 month follow-up patients in the intervention group reported less fatigue than patients in the control group (effect size 0.61).*				
Cimprich, 1993 (48)	Breast cancer patients during treatment (radiotherapy/ chemotherapy/ antihormonal)	Regular participation in activities that engage fascination	16 intervention, age 29-84, mean 57 (sd 16) 16 control, age 32-77, mean 51 (sd 13)	4 (3, 18, 60 and 90 days after surgery)	Total Attention Score (sum of standardised objective attentional tests), Attentional Function Index
Key finding:.	*There was an interaction of experimental intervention and time on attentional capacity. Subjects in the intervention group showed significant improvement in attention capacity over the four time points.*				

Table 3. continued

Author	Diagnosis and treatment	Intervention	Patient characteristics	Number of measurements	Fatigue questionnaire[#]
Fawzy, 1995 (49)	Newly diagnosed patients with malignant melanoma	Nursing intervention, 3 hours of individual teaching on two occasions (health education, stress management, coping)	29 intervention, mean age 42, 52% male 33 control , mean age 46, 58% male	3 (baseline, 6 weeks and 3 months after the intervention)	POMS-fatigue
Key finding:	*Patients in the intervention groups reported significantly less fatigue than patients in the control group 3 months after the intervention (effect size 0.40).*				
Mock, 1997 (50)	Breast cancer patients during treatment with radiotherapy	20- 30 minutes walking 4 to 5 times a week	22 exercise, mean age 48 (sd 5) 24 control, mean age 50, (sd 8)	3 (pre, mid, and post exercise program)	PFS
Key finding:	*The intervention group reported less fatigue than the control group immediately after intervention.*				
Dimeo, 1999 (51)	Patients with different cancer diagnoses during hospitalisation for high dose chemotherapy with stem cell transplantation	Exercise program, 30 minutes daily	27 exercise, age 21-59, mean 40 (sd 11), 33 % male 32 control, age 20-56, mean 40 (sd 10), 40% male	2 (at hospital admission and hospital discharge)	POMS- fatigue
Key finding:	*By the time of hospital discharge, fatigue had increased significantly in the control group but not in the training group.*				

Table 3. continued

Author	Diagnosis and treatment	Intervention	Patient characteristics	Number of measurements	Fatigue questionnaire[#]
Schwartz, 2000 (52)	Patients with breast cancer, during the first 3 cycles of chemotherapy	8-week home-based exercise program, 3 to 4 days a week, 15 to 30 minutes	16 exercise, age 25-57, mean 47 11 control	2 (pre- and post exercise program)	VAFS
Key finding:	*Women who adopted exercise experienced fewer days of high fatigue levels than women who did not exercise.*				
Gaston-Johansson, 2000 (53)	Breast cancer patients undergoing autologous bone marrow transplantation (ABMT)	Comprehensive coping strategy program 2 weeks before hospital admission (preparatory information, cognitive restructuring, and relaxation)	52 intervention, age 21% 22-40, 50% 41-50, 29% >51 58 control, age 30% 22-40, 56% 41-50, 14% >51	2 (2 days before ABMT and 7 days after ABMT)	VAFS
Key finding:	*Patients in the intervention group reported significantly less fatigue than patients in the control group (effect size 0.35).*				
Oyama, 2000 (54)	Patients during a cycle of chemotherapy	Bed Wellness System – virtual reality: patients chose a preferred aromatic essential oil and content (lake, forest, country town)	15 intervention, age 29-73, mean 54, 20% male 15 control, age 29-73, mean 51, 20% male	2 (before chemotherapy and 3-5 days after chemotherapy)	CFS, VAFS
Key finding:	*Patients in the intervention group were statistically less fatigued three to five days after chemotherapy than patients in the control group.*				

[#] Fatigue Questionnaires: CFS- Cancer Fatigue Scale; PFS- Piper Fatigue Scale; POMS- Profile of Mood States; SADS- Schedule of Affective Disorders and Schizophrenia; VAFS- Visual Analogue Fatigue scale.

Furthermore, in the study that investigated an intervention to minimise attentional fatigue, the authors found that the intervention group improved significantly more than the control group[48]. Finally, patients who were in the virtual reality intervention group during the administration of chemotherapy, were statistically less fatigued three to five days after chemotherapy than patients in the control group[54].

Summary

All intervention studies were conducted with patients who were undergoing treatment or had just finished treatment at the time of the study. The interventions included individual counselling (5 studies), a walking- or exercise program (3 studies) or group meetings (two studies). In 10 of the 12 studies, positive effects on fatigue complaints were reported immediately after the intervention. Follow-up results were presented in only four studies. In three of these studies, the positive effect of the intervention was still apparent at three or six months follow-up.

DISCUSSION

In the last ten years, the amount of research on the relationship between cancer and fatigue has increased considerably. To give an indication, from the 181 articles we found using Medline, Current Contents and Psychlit, 20 were published between 1980 and 1990, and 161 were published between 1991 and 2001. From these 161 studies, 32 were published between 1991 and 1995 and 129 were published between 1996 and 2001. The conducted research has focussed mainly on fatigue complaints during treatment for cancer, while up to now only a few studies have attempted to investigate fatigue in cancer survivors.

The reviewed studies clearly indicate that fatigue is a problem for many cancer patients undergoing treatment for cancer. In studies that compared cancer patients to healthy control subjects, cancer patients have been found to report more frequent and severe fatigue than healthy controls. In addition, many studies reported a significant rise in fatigue when cancer patients are assessed just before treatment and again during or immediately after treatment. However, the percentages of fatigue during treatment for cancer showed broad variation, obviously depending on the way fatigue has been measured. Percentages of fatigue range from 25 percent to 99 percent in the reviewed studies. In studies in which a VAS scale was used to measure fatigue, the highest percentages were observed, indicating that fatigue is a problem for nearly all patients undergoing treatment for cancer. However, these percentages only indicate the amount of patients who experience fatigue to some degree. All patients who report fatigue on a VAS, no matter to which degree (a score greater than 0) are considered as fatigued. Thus, the meaning is limited, because is does not give an indication about the severity of the experienced fatigue.

Percentages of severe fatigue in disease-free cancer patients after they have finished curative treatment have been mentioned in only four studies and vary from 17 to 30 percent. The reason for this varying prevalence estimates probably has to do with the lack of consensus about what constitutes a case of severe fatigue after treatment for cancer.

Eight of the ten reviewed studies in which a control group or norm scores were available reported that fatigue scores were significantly higher for cancer survivors in comparison to control subjects without a cancer history or to norm scores. However, two studies reported contrary findings. In these studies, fatigue does not seem to be an important complaint for cancer patients (long) after they have finished treatment. In addition, in three studies fatigue scores had returned to pre-treatment levels at follow-up. A possible explanation for this contradiction, proposed by the authors of one of these studies, is a problem that has been denoted a "response shift". This means that the experience of fatigue during treatment for cancer, could have changed a patient's standard of measurement concerning fatigue. What has been perceived to be intense fatigue before treatment may be labelled 'slightly' fatigued after having experienced exhaustion during treatment. The term "response shift" thus refers to the change in a person's internal standard for determining his or her level of functioning on a given dimension[55]. However, if this hypothesis is right, it remains unclear why in most studies fatigue scores were significantly higher for cancer survivors in comparison to control subjects.

Another explanation could be that all five studies that did not find fatigue to be a serious problem after treatment for cancer, investigated a sample of patients who had received radiotherapy only. Moreover, in the studies in which it is was concluded that fatigue remained a problem long after cancer treatment, all patients were treated with chemotherapy, or with a combined anti-cancer therapy including chemotherapy.

Is it the receipt of chemotherapy or a combination of multiple therapies, that account for severe fatigue long after treatment? The results of two studies suggest that this might be the case[28,36]. However, eight studies did not find a relation between off-treatment fatigue and type/extent of former treatment. In addition, no relation has been found between fatigue and time since treatment. Obviously more controlled research should be conducted in the future in order to clear up these contradictions within the existing research.

For the disease related variables, in most studies, both during and after treatment for cancer, fatigue appeared to be unrelated to disease variables (e.g. cancer diagnosis, cancer stage at diagnosis, size of the original tumour, number of nodes involved and presence and site of metastases). However, as we have indicated before, certain study characteristics might explain these negative results.

Apart from the relationships between fatigue and disease- and treatment related variables, we looked at psychological, social, behaviour and physical correlates of fatigue. The results of many of the studies indicated that both during and after treatment for cancer, fatigue is associated with a negative affect. In addition, intervention studies which focussed on psychological well-being reported positive results with regard to fatigue. Still, the data are far from definitive in this regard. Most research has focused on the depression-fatigue association, which is a complex one. Feelings of depression may results from the fact that one has (or had) a possibly fatal disease, and a depressed state of mind may induce fatigue. However, depression could also be a result of persistent feelings of fatigue[56] probably especially when treatment for cancer has ended some time ago. Although, the depression-fatigue association cannot be ruled out as an explanation for the experience of fatigue during and after treatment for cancer, it is clearly an incomplete description of the underlying process. We found three indications in the reviewed studies to support this view. First, although correlations between fatigue and depression were moderate, depression scores did not change while fatigue scores rose over the course of cancer treatment[12,19,22]. Second, although breast cancer survivors differed with respect to fatigue scores from women with benign breast problems, the two groups did not differ with regard to depressive symptoms[30]. Thirdly, within a group of severely fatigued disease-free cancer patients, only 19% could be considered as clinically depressed[40].

An additional problem with regard to the relation between fatigue and depression is that most measures of depression contain items which overlap with items of fatigue questionnaires (for instance an item like ‘I have to push myself very hard to do anything’). High correlations between fatigue and depression may be due to these overlapping items.

The relationship between fatigue and physical activity has been investigated scarcely, and only during active treatment for cancer. There seems to be a negative relationship between physical activity and fatigue. In addition, sports or walking programs during treatment for cancer reported positive results. However, follow-up analyses were absent. In clinical practice, cancer patients are often being advised to reduce activities and take a lot of rest. With the discussed studies as a basis it would be better to encourage patients to maintain activity levels balanced with efficient rest periods. After treatment for cancer, rest may even be more ineffective in order to relieve chronic fatigue[40].

Disturbances in sleep have been found to be linked with fatigue, both during as well as after cancer. Causes of sleep problem have not been extensively investigated. It is possible that sleep problems are a result of the experience of tension, fear and anxiety that is related to the disease, the treatment and the uncertainty regarding the future. Furthermore, patients who are inactive, often have insomnia, which causes further fatigue complains. Finally, in breast cancer patients, who become menopausal because of chemotherapy, an increased frequency of night-time vasomotor symptoms (i.e. night sweats) could produce disruptive effects on sleep.

A few studies have reported correlations between fatigue and pain. The authors of the studies in which this relation was investigated did not however specify whether fatigue was caused by the pain itself or by pain medication. Therefore, this remains unclear.

A concept that has not been studied in the reviewed studies is the concept of social support. However, resource-related factors such as the perceived level of social support may be vital. It is important to understand the role social support plays in the perception and management of symptoms such as fatigue.

Finally, findings regarding the role of catastrophising suggest that the strategies patients use to cope with fatigue may also explain differences in fatigue severity. In our opinion, this is an area which deserves more attention in the future.

In this review, we decided to exclude studies in which fatigue has been measured with one or a few items within a quality of life instrument, because these measures are not suitable for in-depth studies of fatigue. However, we realise that many of the self-report fatigue scales that were used in the reviewed studies have shortcomings as well. More specific, most of the instruments are unidimensional (they simply measure fatigue intensity) opposite to multidimensional instruments (they attempt to gauge the quality of the symptoms as well as its severity). Examples of unidimensional fatigue scales are the Rhoten Fatigue Scale, the Pearson & Byars Fatigue Feeling Checklist, the Fatigue Questionnaire, the Visual Analogue Fatigue Scale and the fatigue scale of the Profile of Mood State. Examples of multidimensional fatigue scales are the Chalder Fatigue Scale, the Piper Fatigue Scale, the Fatigue Symptom Inventory, the Multidimensional Fatigue Inventory and the Checklist Individual Strength.

In future research, use of valid and reliable multidimensional fatigue instruments is recommended because fatigue is a subjective state with multiple dimensions (physical, cognitive and motivational). Fatigue questionnaires for which norm scores of healthy subjects and/or other patient populations are available should preferably be used. Another possibility is the inclusion of a matched control group. Otherwise there is no reliable way of ascertaining whether fatigue is any different for cancer patients than for healthy individuals or for patient with diseases other than cancer. Finally, longitudinal studies will better indicate factors that are correlated with the initiation or persistence of fatigue in cancer patients.

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Chapter 3

Fatigue in disease-free cancer patients compared with fatigue in patients with Chronic Fatigue Syndrome

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Supportive Care in Cancer 2001; 9: 11– 17

ABSTRACT

The goal of our work was to assess fatigue in disease-free cancer patients with help of a validated fatigue questionnaire. Furthermore, we wished to analyse the relationship between severe fatigue and former treatment modalities, problems of concentration and motivation, physical activity, functional impairment, depression and anxiety and finally, to compare severely fatigued disease-free cancer patients and patients with Chronic Fatigue Syndrome (CFS).

The participants were 85 adult cancer patients and 16 patients with CFS. The cancer patients were all disease-free and had been off treatment for a minimum of 6 months. They were asked to participate in this study by their physician when they came to the hospital for control visits. Patients who were willing to participate, completed four questionnaires. The Checklist Individual Strength was used to measure fatigue. In addition the Beck Depression Inventory, the Spielberger Trait Anxiety Inventory and the Nottingham Health Profile were used.

Results indicate that 19% of the disease-free cancer patients were severely fatigued. Their fatigue experience is comparable to that of patients with CFS. Severe fatigue is associated with problems of concentration and motivation, reduced physical activity, emotional health problems and pain. Furthermore, a relation was found between fatigue and depression and anxiety. No relation was found between fatigue and type of cancer, former treatment modalities, duration of treatment and time since treatment ended.

In conclusion, for one fifth of a group of disease-free cancer patients fatigue is a severe problem long after treatment. In addition to fatigue, these patients experience several psychological and physical problems.

INTRODUCTION

Fatigue is symptom that is frequently encountered in cancer patients, due to their illness or their treatment. The prevalence of fatigue in cancer patients undergoing chemotherapy and/or radiotherapy has been estimated to range from 70 to 96 percent[16,18].

Recently, several quality of life (QOL) studies in disease-free cancer patients also mention fatigue as a frequent complaint long after treatment has finished. Most of these studies investigate patients treated for Hodgkin's disease and breast cancer. The time elapsed since treatment varies from 1 to 10 years, and percentages of fatigue from 32% to 76%[4-6,8-11,14,17,23].

While these studies suggest the existence of off-treatment fatigue in cancer patients, they have been limited by rather crude, single-item measures of fatigue. In some of these studies fatigue has been scored on a yes/no format, in others on a four-point scale from 'not at all' to 'very much'. This might be an explanation for the variation in fatigue percentages.

Another limitation is the lack of comparisons with other patient groups or healthy control subjects. Both of these limitations were taken into account in five studies[1,7,12,13,19]. In these studies, fatigue has been measured in disease-free cancer patients and in subjects without a history of cancer, using specific fatigue questionnaires. Results indicate that disease-free cancer patients, following treatment for cancer respectively 28, 15 and 20 months before, report more fatigue than control subjects do[1,7,12]. However, in two studies no differences in fatigue scores were found between cancer patients, following treatment respectively 22 and 9 months before, and healthy comparison subjects[13,19].

The role of former treatment modalities in predicting post-treatment fatigue remains unclear in the studies mentioned above. In one study, former radiotherapy patients had significantly greater problems with decreased stamina than patients treated with chemotherapy[4]. In another study, fatigue was worse for patients who received a combination of radiotherapy and chemotherapy than in those who underwent radiotherapy only[10]. In contrast, in other studies no relations were found between present fatigue and former type and extent of treatment[1,7,13,17,19].

A relation between time since treatment and post-treatment fatigue was absent in four studies which investigated disease-free breast cancer patients[1,7,13] and patients after stem cell transplantation[14]. However, in another study the time since treatment in survivors of Hodgkin's disease who still suffered energy loss was less than in those with normal energy levels[10]. On the contrary, Hann et al. found that the longer the time since bone marrow transplantation for breast cancer, the more severe fatigue reported[12].

The relation between post-treatment fatigue and depression and anxiety in disease-free cancer has only been investigated in a few studies. A significant and positive correlation between anxiety and depressive symptoms and post-treatment fatigue has been found[1,7,10,12,13,19]. It is possible that fatigue is a symptom of depression or anxiety. Long after treatment, cancer patients could be clinically depressed as a result of being confronted with a life threatening illness or be anxious about the possibility of a relapse. Alternatively, prolonged fatigue in itself can lead to depression or anxiety.

Finally, other related problems of fatigue, such as problems with regard to concentration, motivation and physical activity, have never been investigated in the literature.

In the present study the prevalence of fatigue in a group of disease-free cancer patients is described, using a validated questionnaire. This questionnaire has been used extensively in research with patients with Chronic Fatigue Syndrome (CFS). This means it is possible to compare fatigue in disease-free cancer patients with fatigue in patients with CFS.

In this study the following research questions are addressed:

- How many disease-free cancer patients are severely fatigued long after treatment?
- Is fatigue severity long after treatment influenced by former treatment modalities?
- Is severe fatigue related to depression and anxiety?
- Is severe fatigue related to problems of concentration, motivation, physical activity and functional impairment?
- In what way(s) are severely fatigued disease-free cancer patients comparable to patients with CFS?

METHODS

Patients

The study used a cross-sectional design to assess fatigue in disease-free cancer patients in comparison to patients with CFS. Disease-free cancer patients were recruited from the Departments of Medical Oncology, Surgery and Gynaecology at the University Hospital Nijmegen in The Netherlands. The ethics committee of the hospital approved the study. During a period of 7 months in 1997, cancer patients who had been off treatment for a solid tumour for a minimum of 6 months were asked by their physicians to participate in this study when they came to the hospital for control visits. Patients who were willing to participate were asked to complete four questionnaires at home. After filling in the questionnaires, they were asked to send the questionnaires to the Department of Medical Psychology. Because physicians did not keep a record of patients who were unwilling to participate, the response rate in this study is unknown. Patients with breast cancer were not approached for participation because they are included in a longitudinal study concerning the course of post-treatment fatigue specifically in disease-free breast cancer patients.

For comparison, 16 patients with CFS, matched for age and gender with severely fatigued disease-free cancer patients (N=16) were recruited from the Department of Internal Medicine at the University Hospital Nijmegen.

Questionnaires

Participating patients were asked to complete the following four questionnaires.

The Checklist Individual Strength (CIS)[21]. This 20-item questionnaire is designed to measure four aspects of fatigue during the last 2 weeks: fatigue severity (8 items), concentration (5 items), motivation (4 items) and physical activity (3 items). Each item is scored on a 7-point Likert scale. High scores indicate a high level of fatigue, a high level of concentration problems, low motivation and a low level of physical activity. Reference scores recorded in several groups of patients

(CFS, MS, CVA, Cambodia- veterans) and healthy controls are available[22]. Based on research into CFS, a score of 35 or higher on the subscale 'fatigue severity' indicates severe feelings of fatigue[21]. Bases on scores in healthy controls, a score between 27 (mean score for healthy adults plus 1 sd) and 35 indicates a heightened experience of fatigue[22].

The Beck Depression Inventory (BDI)[2]. This standardised self-report questionnaire measures depression. A score of 16 or more is indicative of a clinical depression. For analyses of the data, also the Beck Depression Inventory for primary care (BDI-PC) was used, which has 7 items and is composed of cognitive and affective symptoms[3].

The Spielberger Trait Anxiety Inventory (STAI)[20]. This standardised self-report questionnaire measures trait anxiety. A score of 50 or more is considered indicative of clinical anxiety.

The Nottingham Health Profile (NHP)[15]. This questionnaire measures perceived physical, social and emotional health problems. It consists of six sub-scales: energy (3 items), pain (8 items), emotional reactions (9 items), sleep (5 items), social isolation (5 items) and physical mobility (8 items). All items use a yes/no answer format.

Statistical analyses

Analyses involved descriptive statistics for description of the sample. T-tests, chi-square and analyses of variance (ANOVA) were performed to test differences between groups.

RESULTS

Description of the sample

The sample in this study consists of 85 disease-free cancer patients, 48 men and 37 women. Their mean age is 47.5 (sd 14) years. Their education levels were determined according to a Dutch standardised scoring system (range 1–7). Thirty-seven patients (54%) completed elementary education (1-4), while 32 patients (46%) completed higher education (data about education were lacking for 16 patients). Data on the distinct cancer diagnoses (n=76), treatment modalities (n=80), duration of treatment (n=75) and time since treatment stopped (n=75) are listed in Table 1.

Seventy-eight patients (98%) underwent surgery. Sixty-three percent of these 78 patients also received adjuvant therapy. This adjuvant therapy was chemotherapy, radiotherapy, corticosteroids, immunotherapy, or a combination of two or more of these therapies. The mean duration of treatment was 5.8 months (sd 9.6) and the mean time since treatment stopped was 2.9 years (range 0.5 - 12.5).

The sample of 16 patients with CFS consists of 8 men and 8 women. Their mean age is 48.1 (sd 12) years.

Table 1. Cancer- and treatment related variables

Cancer diagnoses	Testis carcinoma	19 (25 %)
	Colorectal carcinoma	18 (23 %)
	Sarcoma	15 (20 %)
	Other	24 (32 %)
Treatment modalities*	Surgery	78 (98 %)
	Chemotherapy	38 (48 %)
	Radiotherapy	18 (23 %)
	Corticosteroids	27 (34 %)
	Immunotherapy	6 (8 %)
Duration of treatment	1 month	29 (39 %)
	Between 2 and 6 months	27 (36 %)
	Between 6 months and 1 year	9 (12 %)
	More than 1 year	10 (13 %)
Time since treatment finished	Less than 1 year	16 (21 %)
	Between 1 and 2 years	19 (25 %)
	Between 2 and 3 years	12 (16 %)
	Between 3 and 4 years	9 (12 %)
	Between 4 and 5 years	11 (15 %)
	More than 5 years	8 (11 %)

* Most patients are included in more than one treatment modality, because they received a combination of treatments.

Severe fatigue in disease-free cancer patients

The sample of 85 disease-free cancer patients has a mean score of 21.06 (sd 13.69) on the fatigue severity subscale of the CIS. Twenty-five patients (29%) score 27 or higher on this sub-scale, and 16 patients (19%) score 35 or higher. Twenty-five patients thus experience heightened feelings of fatigue compared with healthy control subjects. Sixteen patients even experience severe fatigue, comparable to fatigue patients with CFS experience.

Effect of former treatment on fatigue severity

Severely fatigued disease-free cancer patients (CIS-fatigue >= 35) are compared with non-severely fatigued disease-free cancer patients (CIS-fatigue < 35) to investigate whether severe fatigue was influenced by the duration of treatment and the time since treatment stopped (Table 2).

Results indicate no significant differences between severely fatigued disease-free cancer patients and non-severely fatigued disease-free cancer patients with regard to the mean time since treatment stopped and the mean duration of treatment.

Data about the impact of former treatment modalities on severe fatigue can be found in Figure 1.

Table 2. Effect of duration of treatment and time since end of treatment on fatigue severity

	Severely fatigued disease-free cancer patients (n=16)	Non-severely fatigued disease-free cancer patients (n=69)	p-value
	Mean (sd)	Mean (sd)	
Duration of treatment (months)	6.88 (7.18)	5.57 (10.32)	0.637
Time since treatment finished (years)	3.39 (2.56)	2.80 (2.20)	0.363

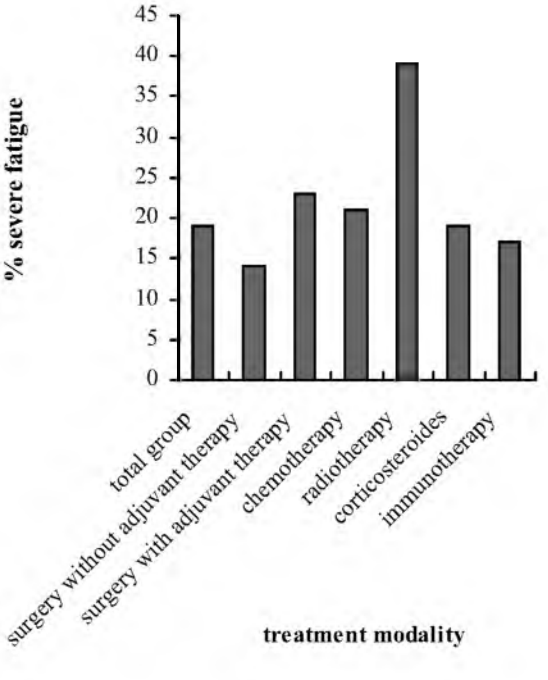

Figure 1. Relation between former treatment modalities and severe fatigue

In this figure, percentages of patients suffering severe fatigue following different treatment modalities are shown. The highest frequency of severe fatigue is found in patients treated with radiotherapy. Forty percent of the patients who received radiotherapy report severe fatigue while only 15 percent of the patients who did not receive radiotherapy report severe fatigue (Chi- Square, p=0.06).

Depression and anxiety in relation to severe fatigue

CIS-fatigue scores are significantly correlated with scores on the BDI (Spearman correlation=0.73), BDI-PC (Spearman correlation=0.58) and the STAI (Spearman correlation=0.60).

Table 3 compares mean depression and anxiety scores for non-severely fatigued disease-free cancer patients, severely fatigued disease-free cancer patients and patients with CFS. Severely fatigued disease-free cancer patients had significantly higher mean scores for depression and anxiety than non-severely fatigued disease-free cancer patients. There was no significant difference between severely fatigued disease-free cancer patients and patients with CFS with regard to mean depression scores.

Table 3 Mean depression and anxiety scores

	Non-severely fatigued disease-free cancer patients (n=69)	Severely fatigued disease-free cancer patients (n=16)	Patients with CFS (n=16)
	Mean (sd)	Mean (sd)	Mean (sd)
BDI-PC	0.43 (0.87)	2.25 (1.81)**	2.63 (1.82)
STAI	30.94 (9.37)	37.79 (10.97)*	no available data

* Significantly different from non-severely fatigued disease-free cancer patients, $p<0.05$

** Significantly different from non-severely fatigued disease-free cancer patients, $p<0.01$

CFS: Chronic Fatigue Syndrome, BDI: Beck Depression Inventory, STAI: Spielberger Trait Anxiety Inventory

Fatigue related problems (problems of concentration, motivation, physical activity and functional impairment)

To investigate whether fatigue was associated with other problems, comparisons were made between severely fatigued disease-free cancer patients and non-severely fatigued disease-free cancer patients. Three sub-scales of the CIS measure problems with concentration, motivation and physical activity. Scores on these three subscales were also compared against scores of patients with CFS. Functional impairment was measured by the NHP. Data are presented in Tables 4 and 5.

Severely fatigued disease-free cancer patients had more problems with concentration and reduced motivation and had a lower level of physical activity than non-severely fatigued disease-free cancer patients. Severely fatigued disease-free cancer patients also experienced more emotional health problems and pain than non-severely fatigued disease-free cancer patients. On the other hand, they did not experience more physical impairment (although there was a trend), sleep problems and social isolation.

Severely fatigued disease-free cancer patients were comparable to patients with CFS with regard to motivation problems and physical activity. However, patients with CFS experienced more problems with concentration.

Table 4. Fatigue related problems; concentration, motivation and physical activity

	Non-severely fatigued disease-free cancer patients (n=69)	Severely fatigued disease-free cancer patients (n=16)	Patients with CFS (n=16)
	Mean (sd)	Mean (sd)	Mean (sd)
CIS-concentration	10.18 (5.94)	15.81 (8.80)*	24.69 (8.05)**
CIS-motivation	7.51 (4.11)	15.38 (6.71)*	17.94 (5.81)
CIS-physical activity	5.88 (3.93)	15.12 (5.38)*	16.38 (3.96)

* significantly different from non-severely fatigued disease-free cancer patients, $p<0.01$

** significantly different from severely fatigued disease-free cancer patients, $p<0.01$

CIS: Checklist Individual Strength

Table 5. Fatigue related problems; functional impairment

	Non-severely fatigued disease-free cancer patients (n=69)	Severely fatigued disease-free cancer patients (n=16)	p-value
	Mean (sd)	Mean (sd)	
NHP- energy	0.19 (0.50)	1.75 (0.86)	0.000
NHP- pain	0.10 (0.52)	1.12 (1.89)	0.049
NHP- emotion	0.47 (1.04)	1.68 (1.40)	0.000
NHP- sleep	0.32 (0.85)	1.00 (1.51)	0.101
NHP- social interaction	0.13 (0.38)	0.38 (0.62)	0.151
NHP- physical	0.26 (0.64)	1.06 (1.57)	0.063
NHP- total	1.49 (2.58)	7.00 (3.90)	0.000

NHP: Nottingham Health Profile

DISCUSSION

This study shows that a considerable proportion of a sample of disease-free cancer patients were severely fatigued years after treatment. The severity of fatigue experienced by these patients was comparable to the severity of fatigue in patients with CFS. In addition, severe fatigue was associated with problems of concentration, reduced motivation, reduced physical activity, pain, and emotional health problems. The direction of the relation between these problems remains unclear. It is possible that fatigue causes the problems mentioned above: however, the relationship might also be the other way around, fatigue being a consequence of the problems mentioned above. Finally, for certain problems both can be true. For instance, because of fatigue, patients often reduce their level of physical activity. Because of a low level of physical activity, physical condition deteriorates and leads to even higher levels of fatigue.

There seems to be no relation between initial disease and treatment factors and severe fatigue in this study. First, the type of cancer is not associated with levels of post-treatment fatigue. Second, the duration of treatment and time since treatment finished are not associated with levels of post-treatment fatigue. This lack of association between fatigue and time since the end of treatment is in accordance with the results described in the majority of the studies mentioned in the Introduction[1,7,13,14]. Finally, no relation was found between former treatment modalities and fatigue. However, a strikingly high proportion of patients who had received radiotherapy were severely fatigued. Thus, radiotherapy might be a risk factor for severe fatigue long after treatment. This trend between radiotherapy and post-treatment fatigue should be interpreted with caution. As mentioned in the Introduction, results in studies that have investigated this relationship are contradictory. In addition, only a small proportion of the disease-free cancer patients in the current study (n=18) did receive radiotherapy, and some of these patients also underwent additional adjuvant therapy.

In accordance with results in the literature, severe fatigue is related to depression and anxiety. Results of this study reveal a significant difference between severely fatigued disease-free cancer patients and non-severely fatigued disease-free cancer patients with regard to mean depression and anxiety scores, severely fatigued disease-free cancer patients having the higher mean scores. The strength of the association between fatigue and depression is interesting considering that the measure of depression used in this study (BDI-PC) includes items that reflect cognitive and affective symptoms of depression but not somatic symptoms. Thus, the relationship can not be explained as overlap of the physical aspects of fatigue with somatic symptoms of depression. As a result of the cross-sectional design of this study no conclusions can be drawn about the direction of the causal relation between fatigue severity and depression and anxiety. However, even if depression and anxiety are causal factors in severe fatigue, other factors also play a part. In the group of severely fatigued disease-free cancer patients, only 19 percent can be considered to have been clinically depressed (BDI>16) and 14 percent clinically anxious (STAI>50). Severe fatigue thus cannot be fully explained by depression and anxiety.

When fatigued disease-free cancer patients are compared with patients with CFS there seem to be many similarities. The problems severely fatigued disease-free cancer patients experience in terms of depression, motivation and reduced physical activity are comparable in extent to the problems experienced by patients with CFS. However, patients with CFS report more problems with concentration.

The results presented in this study should be considered with some caution, since the number of disease-free cancer patients is small and the sample does not represent a well balanced disease-free cancer population. Also, there might be a selection bias because patients were asked by their physicians to take part. In the future, studies with a longitudinal design should focus on predictors of fatigue complained of long after treatment. Cancer and treatment for cancer might well lead to fatigue, but these factors seem not to explain levels of fatigue long after treatment. Anxiety and depression probably play a role in the maintenance of fatigue, but severe fatigue can not be fully explained by these factors. More knowledge, about (psychological) factors causing fatigue long after the end of treatment, will be useful in the development of interventions for severely fatigued cancer patients.

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Chapter 4

Determinants of chronic fatigue in disease-free breast cancer patients
a cross-sectional study

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Annals of Oncology 2002; 13: 589-598

ABSTRACT

Quality of life after cancer treatment becomes more important as the number of long-term survivors increases. This study aimed to investigate complaints of fatigue after treatment for breast cancer. The study patients were 150 women who had finished curative treatment for breast cancer by a mean of 29 months before commencement of this study. Measurements included computerised questionnaires and a daily Self Observation List. Thirty-eight percent of the sample were severely fatigued, compared with 11% in a matched sample of women without a history of cancer. No association was found between fatigue and former treatment. The 'severely fatigued disease-free breast cancer patient' scored more 'problematic' on psychological well-being, functional impairment, sleep disturbance, physical activity, social support, neuropsychological and social functioning compared with the 'non-severely fatigued disease-free breast cancer patient'. Furthermore, the severely fatigued patients had a lower sense of control with respect to their fatigue complaints and stronger breast cancer- and psychologically- related attributions with regard to the causes of fatigue compared with the non-severely fatigued patients. Regression analyses indicated that sleep disturbance, physical activity and causal attributions contributed significantly to the subjective experience of fatigue. In conclusion, severe fatigue is a problem for almost 40 percent of the sample of breast cancer survivors. Severe fatigue is related to physical, psychological, social, cognitive and behavioural factors.

INTRODUCTION

Fatigue is a subjective experience that affects everybody. For healthy individuals it might be a protective, sometimes even pleasant regulatory response to physical or psychological stress. It seems to maintain a healthy balance between rest and activity. Controversially, for people with specific diseases fatigue often becomes a major distressing symptom. Based on results of research with patients with Chronic Fatigue Syndrome, Multiple Scleroses and other chronic diseases we know that fatigue is a multidimensional phenomenon, which consists of physical, psychological, social, cognitive and behavioural aspects[1,2].

For patients with cancer, fatigue has been described as a major concern during treatment and in advanced stages of the disease[3,4]. In recent (quality of life) studies, fatigue has also been mentioned as a frequent complaint by disease-free cancer patients (long) after curative treatment for cancer has ended[5-13]. Furthermore, in three studies[14-16] patients who had been treated for breast cancer 20, 28 and 16 months before, respectively, scored significantly higher than non-cancer comparison subjects on standardised self-report measures of fatigue. In addition, in a large sample of breast cancer survivors, there was a subgroup of survivors who did report heightened levels of fatigue relative to women in the general population[17]. Contrary to these results, no differences in fatigue scores were found in two other studies[18-19] comparing disease-free cancer patients 9 and 22 months, respectively, following radiotherapy with healthy controls.

The possible causes of fatigue, long after treatment for cancer has finished, are still unknown. It is a logical expectation that fatigue can be predicted by preceding illness or former treatment modalities. However, most studies do not support a relationship between off-treatment fatigue and type of treatment, time since diagnosis, or treatment and disease-stage at diagnosis[7-9;13,15,16,18-20]. Nevertheless, these results have to be interpreted with caution because results might have been influenced by the research design. For instance, in a sample of patients who were all treated with radiotherapy, it is hard to demonstrate a relationship between off-treatment fatigue and radiotherapy.

Physical, psychological, social, cognitive and behavioural factors might also be related to fatigue, and play a role in the perpetuation of fatigue, long after treatment for cancer has finished. These relationships have been the object of investigation in only a few studies. In those studies post treatment fatigue seemed to be related to depression, anxiety, quality of sleep, use of catastrophizing as a coping strategy and menopausal symptoms[15-20].

In assessing chronic fatigue in patients with several chronic diseases, a multidimensional assessment method has identified nine dimensions, namely fatigue severity, psychological well-being, functional impairment in daily life, sleep disturbance, physical activity, neuropsychological impairment, social functioning/ social support, self-efficacy and causal attributions[1]. These dimensions appear to be relatively independent, meaning that each dimension uniquely contributes to the description of a patient. Based on clinical experience and indications in the literature, the object of the current study is to assess these nine dimensions of fatigue in a group of disease-free breast cancer patients. In addition, an age-matched sample of women without a history of cancer is included.

In this article we will answer the following four research questions. 1) How many disease-free breast cancer patients experience severe fatigue (long) after treatment for cancer was finished; 2) Is fatigue severity in disease-free breast cancer patients associated with former treatment modalities (type of operation, type of adjuvant therapy, duration of treatment and time since treatment ended); 3) How can the ‘severely fatigued disease-free breast cancer patient’ be described, with use of the above mentioned dimensions and 4) What is the contribution of the physical, psychological, social, cognitive and behavioural dimensions to the fatigue severity dimension in disease-free breast cancer patients?

PATIENTS AND METHODS

Sample

To select a relatively homogeneous group of patients, all patients had to be treated according to the protocol of the Comprehensive Cancer Centre East for premenopausal breast cancer patients. Furthermore, they had to be younger than 50 by the time of primary diagnosis and had to have completed treatment for breast cancer for a minimum of 6 months and a maximum of 70 months before the study commenced. They also had to have no evidence of disease recurrence at the time of participation. Finally, all patients had been checked for side effects of previous anti-cancer treatment within three months after treatment. None of the patients included in the study were anaemic at the time.

Most participating patients (120 of the 150) were asked to bring along a female family member, friend, or colleague who was not more than five years younger or older than the patient. This woman had to be healthy (no chronic disease) and had never to have been treated for cancer in the past.

Recruitment procedure

Patients were recruited from one university hospital and 6 regional hospitals. At the university hospital and three regional hospitals, all patients who met the eligibility criteria were initially informed about the study by mail with an introductory letter from their oncologist. At the other three regional hospitals, patients were informed by their oncologist during control-visits. In the following week, patients were contacted by telephone by the psychologist-researcher (P.S.). Those patients who agreed to take part in the study were invited to the department of Medical Psychology of the University Hospital Nijmegen. The ethics committee of all participating hospitals agreed with the study.

Measurement

Patients and their female friends were invited to the research institute where they were asked to fill out several computerised questionnaires. In addition, they filled out a daily Self Observation List (SOL) during a period of 12 days. Severity of fatigue was reported four times a day in this list. Furthermore, quality of sleep, level of activity, hours of household activities and hours of work outside the house were reported once a day.

Each of the nine investigated dimensions was represented by several measures. The reason behind this lies in the fact that each instrument contributed uniquely to a certain dimension.

Fatigue severity was measured by the fatigue severity subscale (CIS-fatigue) of the Checklist Individual Strength (CIS)[1]. The CIS is a 20-item questionnaire which was designed to measure four aspects of fatigue during the previous two weeks, namely: fatigue severity (8 items), concentration (5 items), motivation (4 items) and physical activity (3 items). Each item was scored on a 7-point Likert scale.

High scores indicated a high level of fatigue, a high level of problems with regard to concentration, low motivation and a low level of physical activity. Based on research with Chronic Fatigue Syndrome patients, a score of 35 or higher on the subscale fatigue severity indicates severe feelings of fatigue[1]. Based on scores of healthy controls, a score between 27 (mean score for healthy adults plus one standard deviation (sd)) and 35 indicated heightened experience of fatigue[21]. In addition fatigue was measured with the Daily Observed Fatigue (DOF) score of the SOL[22]. DOF was reported four times a day on a 5-point scale (0-4). Total scores range from 0 to 16. Available norm scores of 53 healthy subjects indicated that healthy adults have a mean DOF score of 1.6 (sd=1.4)[2].

Psychological well-being was been measured with the Beck Depression Inventory for primary care (BDI-PC), the Spielberger Trait Anxiety Inventory (STAI) and the Rosenberg Self Esteem Scale (RSE). The BDI-pc was used in analysing the data, to prevent an overlap between the physical aspects of fatigue with the somatic symptoms of depression. This shortened version of the BDI[23] had 7 items and was composed of cognitive and affective symptoms only[24]. A score of 4 or more was indicative of clinical depression. The STAI is a standardised self-report questionnaire designed to measure trait anxiety[25]. A score of 50 or more was considered indicative of clinical anxiety[26]. The RSE measured global self-esteem and consists of ten items[27]. Furthermore, the anxiety, agoraphobia, depression, somatisation, obsessive-compulsive behaviour, interpersonal sensitivity and hostility subscales of the Symptom Checklist (SCL-90) were used[28]. Finally, the emotional functioning subscale of the Quality of Life Questionnaire-C30 of the European Organisation for Research and Treatment of Cancer (QLQ-C30) was included[29].

Functional impairment was measured with the subscales home management, work, and recreation and pastimes from the Sickness Impact Profile (SIP)[30]. Furthermore, the role functioning subscale of the QLQ-C30 was used. In addition, hours of work (outside the home and household activities) were registered in the SOL.

Sleep disturbance was measured with the Groninger Sleep Quality Scale (GSQS)[31]. This questionnaire consisted of 14 items on problems with falling asleep, restless sleep, early awakenings in the morning and general quality of sleep. Each item was scored on a yes/no format. A total score of sleep disturbances was derived from this questionnaire. Furthermore, the sleep/rest subscale of the SIP and the sleep subscale of the SCL were used. Finally, quality of sleep (general quality of sleep, difficulties falling asleep, restless sleep and early awakenings) was registered daily in the SOL.

Physical activity was measured with the physical functioning subscale of the QLQ-C30, the physical activity subscale of the CIS, and the mobility and ambulation subscales of the SIP. In addition, physical activity was registered once a day in the SOL.

Neuropsychological functioning was measured with the cognitive functioning subscale of the QLQ-C30, the concentration subscale of the CIS and the alertness behaviour subscale of the SIP.

Social functioning/ Social support was measured with the social functioning subscale of the QLQ-C30, the social interaction subscale of the SIP and the van Sonderen Social Support Inventory (SSL)[32]. The SSL was divided into the SSL-I (amount of social support), the SSL-D (discrepancies between amount of social support and desired amount of social support), and the SSL-N (amount of negative interactions).

Self efficacy, a sense of control over fatigue symptoms, was measured with the subscale ‘internal locus of control’ of the Multidimensional Health Locus of Control (MHLC) and the Self Efficacy Questionnaire (SEQ). The MHLC measured control beliefs with respect to health in general[33,34]. The SEQ consisted of five questions that measured sense of control with respect to fatigue[35].

Causal attributions with regard to fatigue complaints were measured with the Causal Attribution List (CAL). This questionnaire consisted of 9 items divided over two subscales, psychological (e.g. ruminate, sleep problems) and breast cancer related attributions (e.g. surgery for breast cancer, adjuvant therapy for breast cancer). For each item, patients were asked to indicate their opinion regarding the cause of their fatigue complaints on a 4 point scale (1 very applicable to 4 not at all applicable). Internal reliability of this questionnaire was good. The subscales psychological- and breast cancer related attributions had alpha’s of .81 and .79, respectively.

Statistical analysis

Data analysis was performed using SPSS (version 8.0). Descriptive statistics were used for description of the sample. T-tests, chi-square and general linear model (GLM)-general factorial were performed testing the differences between groups. In order to examine the contribution of the physical, psychological, social, cognitive and behavioural dimensions to the dimension of fatigue severity, linear regression analyses (enter-method) was performed.

RESULTS

Description of the samples

Two-hundred and sixty-three disease-free breast cancer patients were contacted for this study. Most of these patients (248) were sent an introductory letter from their oncologist while only 15 patients were contacted during control visits. One hundred and fifty-five patients (59%) agreed to participate in the study. Non-participants did not differ from the participants with regard to age, type of surgery, radiotherapy and time since treatment completion. However the non-participants received chemotherapy less often: 41% compared with 66% (chi-square; $p<0.001$).

Therefore, duration of treatment was significantly lower for non-participants (4 compared with 6 months for participants; t-test; p<0.001). Reasons for non-participation were: participation takes to much time (n=24), too emotional to participate (n=12), wanting to move on with their lives (n=12), did not feel like taking part (n=9), concurrent major health problems (n=8), not able to contact (n=7), problems with transport (n=6), too tired to participate (n=1), other reasons (n=6) and unknown (n=23).

Table 1. Demographic characteristics of both samples

	Disease-free breast cancer patients (n=150)	Women without a cancer history (n=78)
Mean age	45.9 (sd 6.3)	48.1 (sd 6.2)
Marital status		
married	130 (87%)	67 (86%)
unmarried	7 (4%)	3 (4%)
divorced	10 (7%)	5 (6%)
widowed	3 (2%)	3 (4%)
Higher education (>= 12 years)	57 (38%)	32 (41%)
Employment		
work outside home	92 (61 %)	52 (67%)
voluntary work	33 (22%)	17 (22%)
disablement insurance act	18 (12%)	2 (3%)
partial disablement insurance act	20 (13%)	2 (3%)
sick leave	5 (3%)	1 (1%)

Table 2. Medical characteristics of the patient sample

	Disease-free breast cancer patients (n=150)
Mastectomy / Lumpectomy	95 (63%) / 55 (37%)
Adjuvant therapy	
none	20 (13%)
radiotherapy only	31 (21%)
chemotherapy only	33 (22%)
radio- and chemotherapy	66 (44%)
Duration of treatment (months)	Mean=6 (sd=3)
Time since diagnosis (months)	Mean=35 (sd=17)
Time since treatment (months)	Mean=29 (sd=17)

Five of the 155 participants were excluded for analyses since they dropped out during baseline assessment. One had concurrent major health problems (thyroid gland disorder), one had disease recurrence, one had medical problems with regard to breast reconstruction and two had major psychological problems.

Seventy-eight patients brought a female family member, friend, or colleague along to the hospital. Information about demographic characteristics of the two samples is listed in Table 1. The sample of disease-free breast cancer patients was comparable to the sample of control women with regard to age, marital status, education and employment. However, the percentage of disablement insurance act was higher in former breast cancer patients than in women without a cancer history.

Information about medical characteristics of the patient sample is listed in Table 2. The majority of the participating women were treated with mastectomy. A small group (13%) did not receive any adjuvant therapy while the others received radiotherapy, chemotherapy or both. Duration of treatment was defined as the period from the time of surgery until the end of adjuvant therapy. Time since diagnosis was defined as the day of diagnosis until the day of participation in the current study. Finally, time since treatment was defined as the period from the end of adjuvant therapy until the day of participation in the current study.

Research questions

How many disease-free breast cancer patients experience severe fatigue (long) after treatment for cancer was finished?

The mean CIS-fatigue score of the total patient sample was 28.5 (sd=13.6) compared with 19.4 (sd=11.0) in the sample of women without a history of cancer (t-test, $p<0.001$). Fifty- seven patients (38%) met the "cut-off" criteria for severe fatigue (i.e., CIS-fatigue >= 35) while an additional 24 patients (16%) had a score between 27 and 35. The group of patients who had a CIS-fatigue of 35 and higher will be referred to as "severely fatigued disease-free breast cancer patients", from now on. The other patients will be referred to as "non-severely fatigued disease-free breast cancer patients". In the control group, 9 women (11%) met the "cut-off" criteria for severe fatigue.

The mean DOF score of the total patient sample was 2.9 (sd=2.2, min=0 max=9.5). In comparison, the mean DOF score was 1.6 (sd=1.3, min=0, max=4.5) in the sample of women without a history of cancer (t-test, $p<0.001$). The mean DOF score of the severely fatigued disease-free breast cancer patients was 4.6 (sd=2.1) and that of the non-severely fatigued disease-free breast cancer patients was 1.9.

Is fatigue severity associated with former treatment modalities?

To test the association between fatigue severity on the one hand, and type of operation (lumpectomy or mastectomy) and type of adjuvant therapy (no adjuvant therapy, radiotherapy, chemotherapy or both) on the other hand, a GLM-general factorial was conducted. Dependent variable was the CIS-fatigue. Fixed factors were the variables type of operation and type of adjuvant therapy. Results indicated that there was no main effect of type of surgery (p=0.281), no main effect of adjuvant therapy (p=0.852) and no interaction effect (p=0.912). This meant that mean fatigue severity scores did not differ significantly for those patients who underwent mastectomy (mean CIS-fatigue 27) and those who underwent lumpectomy (mean CIS-fatigue 31). Furthermore, mean fatigue severity scores were equal for those patients who received radiotherapy (CIS-fatigue 28), chemotherapy (CIS-fatigue 28), both radiotherapy and chemotherapy (CIS-fatigue 29) and those who did not receive adjuvant therapy (CIS-fatigue 28).

The association between severe fatigue and length of treatment (1, 2-6 or more than 6 months) and time since treatment (6-12, 13-24, 25-36, 37-48, 49-60, or more than 60 months) was also tested with a GLM-general factorial. The dependent variable was the CIS-fatigue. Fixed factors were the variables length of treatment and time since treatment. No main effect of length of treatment (p=0.387), no main effect of time since treatment (p=0.938) and no interaction effect (p=0.950) were found.

How can the 'severely fatigued disease-free breast cancer patient' be described?

In Table 3, comparisons have been made between severely fatigued disease-free breast cancer patients, non-severely fatigued disease-free breast cancer patients and women without a history of cancer, with regard to the dimension of psychological well-being, functional impairment in daily life, sleep disturbance, physical activity, neuropsychological impairment, social functioning, self-efficacy and causal attributions.

Results with regard to the psychological well-being dimension are consistent. Severely fatigued disease-free breast cancer patients have a lower mean score of emotional functioning, they are significantly more depressed and more anxious than non-severely fatigued disease-free breast cancer patients. In addition, severely fatigued disease-free breast cancer patients have a lower self-esteem and higher scores on the agoraphobia, somatisation, obsessive-compulsive behaviour, interpersonal sensitivity and hostility subscales of the SCL, compared with the non-severely fatigued disease-free breast cancer patients. clinically depressed and 19 percent as both clinical depressed and anxious. These percentages are 2, 3, and 1%, respectively, for the group of non-severely fatigued disease-free breast cancer patients. Non-severely fatigued disease-free breast cancer patients are comparable with regard to psychological well-being to women without a cancer history.

Table 3. Dimensions of fatigue; comparisons between severely fatigued disease-free breast cancer patients, non-severely fatigued disease-free breast cancer patients and control women (General Linear Model-general factorial)

	A	B	C	
	Severely fatigued patients	Non-severely fatigued patients	Control women	p-value
	(n=57)	(n=93)	(n=78)	
	Mean (sd)	Mean (sd)	Mean (sd)	
Psychological well-being				
Emotional functioning (QLQ-C30)[1]	71.2 (21.8)	86.4 (15.0)	-	<0.001
Depression (BDI- PC)	2.8 (2.8)^{bc}	0.7 (1.4)^{a}	0.8 (1.3)^{a}	<0.001
Trait anxiety (STAI)	42.3 (11.0)^{bc}	31.7 (7.7)^{a}	31.2 (8.7)^{a}	<0.001
Self-esteem (RSE)	36.6 (7.3)^{bc}	42.2 (5.2)^{a}	40.8 (5.9)^{a}	<0.001
Depression (SCL)	28.9 (9.7)^{bc}	20.4 (4.7)^{a}	20.4 (4.7)^{a}	<0.001
Anxiety (SCL)	16.1 (6.3)^{bc}	12.1 (2.8)^{a}	12.5 (3.1)^{a}	<0.001
Agoraphobia (SCL)	8.8 (3.7)^{bc}	7.3 (0.8)^{a}	7.8 (1.5)^{a}	0.004
Somatisation (SCL)	23.4 (6.8)^{bc}	16.9 (5.0)^{a}	16.3 (4.0)^{a}	<0.001
Obsessive-comp. behaviour (SCL)	18.5 (7.2)^{bc}	12.4 (3.8)^{a}	12.7 (3.3)^{a}	<0.001
Interpersonal sensitivity (SCL)	29.0 (12.5)^{bc}	22.5 (4.9)^{a}	23.3 (4.8)^{a}	<0.001
Hostility (SCL)	8.3 (3.8)^{bc}	6.8 (1.1)^{a}	7.0 (1.2)^{a}	<0.001
Functional impairment in daily life				
Role functioning (QLQ-C30)[1]	71.4 (22.7)	89.3 (15.7)	-	<0.001
Home management (SIP)[2]	98.6 (64.5)^{bc}	52.0 (64.6)^{ac}	8.8 (32.0)^{ab}	<0.001
Work (SIP)[2]	91.4 (115.1)^{c}	63.1 (116.5)^{c}	12.7 (64.4)^{ab}	<0.001
Recreation and pastimes (SIP)[2]	72.4 (51.9)^{bc}	33.7 (46.6)^{ac}	6.7 (21.7)^{ab}	<0.001
Number of days working (SOL)	3.6 (3.4)	4.1 (3.4)	4.7 (3.4)	ns
Hours of work a day (SOL)	3.2 (3.1)^{c}	3.9 (3.1)^{c}	5.6 (2.1)^{ab}	<0.001
Number of days with household activities (SOL)	10.3 (2.2)	10.1 (2.4)	10.4 (2.2)	ns
Hours of household activities a day (SOL)	3.4 (1.9)	3.9 (2.1)	3.6 (1.9)	ns
Sleep disturbances				
Sleep disturbances (GSQS)	6.6 (4.0)^{bc}	3.5 (3.6)^{a}	3.6 (3.5)^{a}	<0.001
Sleep/ rest (SIP)[2]	65.8 (49.0)^{bc}	28.3 (43.8)^{ac}	11.4 (26.0)^{ab}	<0.001
Sleep (SCL)	7.1 (3.4)^{bc}	5.2 (2.6)^{a}	4.8 (1.9)^{a}	<0.001
Daily general quality of sleep (SOL)	0.58 (0.26)^{bc}	0.72 (0.25)^{a}	0.71 (0.28)^{a}	0.001
Daily difficulties falling asleep (SOL)	0.20 (0.26)^{bc}	0.10 (0.17)^{a}	0.11 (0.20)^{a}	0.007
Daily restless sleep (SOL)	0.30 (0.24)^{bc}	0.20 (0.21)^{a}	0.18 (0.24)^{a}	0.012
Daily early awakenings (SOL)	0.18 (0.21)	0.15 (0.22)	0.14 (0.24)	ns

Table 3. continued

	A Severely fatigued patients (n=57)	B Non-severely fatigued patients (n=93)	C Control women (n=78)	p-value
	Mean (sd)	Mean (sd)	Mean (sd)	
Physical activity				
Physical functioning (QLQ-C30)[1]	72.6 (18.8)	87.0 (13.4)	-	<0.001
Physical activity (CIS)[2]	12.1 (5.9)[bc]	6.8 (3.8)[a]	5.9 (3.7)[a]	<0.001
Mobility (SIP)[2]	16.5 (41.5)[bc]	4.9 (17.5)[a]	1.5 (8.7)[a]	0.003
Ambulation (SIP)[2]	25.4 (40.6)[bc]	6.9 (18.0)[a]	0.0 (0.0)[a]	<0.001
Daily activity score (SOL)	2.51 (0.52)[bc]	2.27 (0.46)[a]	2.29 (0.49)[a]	0.009
Neuropsychological impairment				
Cognitive functioning (QLQ-C30)[1]	73.7 (24.0)	88.8 (15.8)	-	<0.001
Concentration (CIS)[2]	20.3 (7.6)[bc]	14.1 (7.2)[a]	13.1 (7.5)[a]	<0.001
Alertness behaviour (SIP)[2]	150.9 (150.0)[bc]	56.5 (90.4)[a]	15.4 (78.8)[a]	<0.001
Social functioning and social support				
Social functioning (QLQ-C30)[1]	82.5 (22.8)	94.6 (12.1)	-	<0.001
Social interaction (SIP)[2]	173.5 (172.5)[bc]	64.3 (99.7)[ac]	9.0(26.9)[ab]	<0.001
Amount of social support (SSL-I)	168.1 (26.3)	170.3 (26.5)	165.7 (21.4)	ns
Amount of negative interactions (SSL-N)	10.54 (3.0)[bc]	9.4 (2.1)[a]	9.4 (1.9)[a]	0.005
Discrepancies social support (SSL-D)	47.89 (13.0)[bc]	42.3 (9.1)[a]	42.9 (8.1)[a]	0.002
Self-efficacy				
Self-efficacy (SEQ)*	17.3 (3.2)	19.2 (3.2)	-	0.002
Internal locus of control (MHLC-I)	13.9 (4.6)	13.8 (4.2)	-	ns
Causal attributions				
Psychological attributions (CAL)*[3]	2.9 (0.7)	3.3 (0.6)	-	0.001
Breast cancer related attributions (CAL)* [3]	2.1 (0.6)	2.7 (0.8)	-	<0.001

The QLQ-C30, SEQ, MHLC-I and CAL were not filled out by women in the control group.

[1] higher scores represent better functioning

[2] higher scores represent more impairment

[3] higher scores present less strong attributions

[a] significantly different from group A, Bonferroni $p<0.05$

[b] significantly different from group B, Bonferroni $p<0.05$

[c] significantly different from group C, Bonferroni $p<0.05$

* n=133 (these questionnaires have not been filled out by those patients who report that they never experience fatigue)

On the subscales of the QLQ-C30 and SIP that were used to measure functional impairment in daily life, severely fatigued disease-free breast cancer patients reported being more functionally impaired than did non-severely fatigued disease-free breast cancer patients. Furthermore, both patients groups (severely fatigued and non-severely fatigued) reported more functional impairment in daily life than women without history of cancer. On the SOL, no significant differences were found with regard to number of days working, number of days with household activities and hours of work or household activities per day within a 2-week period, between the three different samples. However, controls worked more hours per day in comparison with both patient groups.

On the sleep disturbance dimension, severely fatigued disease-free breast cancer patients report having more problems with sleep than non-severely fatigued disease-free breast cancer patients. The two groups did not differ in the frequency of early awakenings. Scores of non-severely fatigued disease-free breast cancer patients were comparable with scores of women without a cancer history, except for the sleep/rest subscale of the SIP. Non-severely fatigued disease-free breast cancer patients scored more problematic on this subscale in comparison with control women.

With regard to the physical activity dimension, severely fatigued disease-free breast cancer patients reported less physical functioning on all used measures compared with non-severely fatigued disease-free breast cancer patients. Non-severely fatigued disease-free breast cancer patients were comparable with respect to physical activity with women without a history of cancer.

The same applies for the dimension representing neuropsychological impairment. Scores on all subscales indicated that severely fatigued disease-free breast cancer patients reported having more problems with regard to memory and concentration than non-severely fatigued disease-free breast cancer patients. This latter group had comparable scores to women without a history of cancer.

On the social functioning/ social support dimension, severely fatigued disease-free breast cancer patients reported less social functioning and more impairment with regard to social interactions than non-severely disease-free breast cancer patients. In comparison with the control group, both patient groups reported significantly more problems on the social interaction scale of the SIP. With regard to social support all three groups reported having the same amount of social support. However, severely fatigued patients experience more negative interactions and a higher discrepancy between amount of social support and desired amount of social support than did the non-severely fatigued patients and control women. That is to say, severely fatigued patients wished they were receiving more social support than they felt they are actually receiving.

Within the self-efficacy dimension, no differences were found between severely fatigued disease-free breast cancer patients and non-severely fatigued disease-free breast cancer patients with respect to the internal locus of control of health in general. This means that patients in both groups believed to the same extent that they would remain healthy or ill as a result of their own behaviour. However, severely fatigued patients had a lower sense of control with respect to fatigue than non-severely fatigued patients. Thus, severely fatigued patients thought to a lesser extent, than non-severely fatigued patients, that they could exert influence on their fatigue complaints.

Finally, on the dimension of causal attributions, severely fatigued disease-free breast cancer patients, reported more psychological and more breast cancer-related attributions with regard to fatigue complaints than did non-severely fatigued disease-free breast cancer patients. In other words, patients who experienced severe fatigue attributed their fatigue complaints, more often, to the fact that they were diagnosed and treated for breast cancer in comparison with those who experienced only moderate fatigue. In addition, they also more often indicated that their fatigue complaints could be a result of the fact that they often ruminate, experience trouble sleeping etc.

Table 4. Linear regression analysis to predict fatigue

	Dependant variables			
	CIS-fatigue severity		Daily Observed Fatigue (DOF)	
	Beta	p	Beta	p
Independent variables				
SCL-depression	0.227	0.033	0.173	0.140
QLQ-C30-role functioning	-0.152	0.140	-0.041	0.720
SIP-sleep/rest	0.213	0.008	0.202	0.024
QLQ-C30-physical functioning	-0.072	0.384	-0.209	0.025
CIS-physical activity	0.317	<0.001	0.058	0.514
CIS-concentration	0.139	0.111	0.122	0.222
QLQ-C30-social functioning	0.177	0.098	0.123	0.305
SIP-social interaction	-0.043	0.645	0.023	0.829
SEQ-self efficacy	-0.061	0.448	-0.117	0.186
CAL-breast cancer related attributions	-0.205	0.023	-0.272	0.006
Total R^2 (adjusted)	0.523		0.427	

What is the contribution of the physical, psychological, social, cognitive and behavioural dimensions to the fatigue severity dimension in disease-free breast cancer patients?

Regression analyses have been performed to examine the contribution of psychological well-being, functional impairment in daily life, sleep disturbance, physical activity, neuropsychological impairment, social functioning, self-efficacy and causal attributions to fatigue severity. Two analyses were done, one with the CIS-fatigue severity score as the dependent variable, and the other using the DOF score as the dependent variable. Independent variables were those questionnaires or subscales of questionnaires within the other eight dimensions that correlated highest with one of the dependent variables. For the dimensions physical activity and social functioning two measures were selected for the regression analyses, because within these dimensions one measure correlated highest with the CIS-fatigue severity score and the other one with the DOF. Within all the other dimensions, one measure correlated highest with both the CIS-fatigue severity score and the DOF score.

Results indicate that in both analyses, questionnaires representing the dimensions of sleep disturbance (SIP-sleep/rest), physical functioning (CIS-activity or QLQ-C30-physical functioning) and causal attributions (breast cancer-related attributions) contributed significantly to the fatigue severity dimension. Furthermore, the dimension of psychological well-being (SCL-depression) contributed significantly to the CIS-fatigue severity score. In total, 52% of the fatigue severity subscale of the CIS were predicted, and 43% of the DOF score (Table 4).

DISCUSSION

In this study, a strikingly large part (38%) of a group of women who were treated for breast cancer in the past turned out to be severely fatigued. This is significantly higher than the percentage in a matched control group of women without a history of cancer. Although severe fatigue might have been associated with treatment modalities while patients were undergoing treatment, this association could not be found long after treatment for breast cancer was completed. Results failed to find significant associations between severe fatigue on the one hand, and type of operation, type of adjuvant therapy, length of treatment and time since treatment on the other hand. As mentioned in the Introduction, these results correspond to the majority of recent findings in the literature.

In an attempt to describe ‘the severely fatigued disease-free breast cancer patient’ on several dimensions, we found that severe fatigue long after completion of treatment for breast cancer is associated with several physical, psychological, social, cognitive and behavioural factors. The strength of the association observed between fatigue and depressive symptomatology is interesting in light of the fact that one of the measures of depression used in this study (BDI-pc) includes items that reflect cognitive and affective symptoms of depression but not somatic symptoms. Thus, the relationship cannot be explained as overlap of the physical aspects of fatigue with somatic symptoms of depression. However, our results suggest that, although in some patients the depression-fatigue association cannot be ruled out as a possible explanation for the experience of fatigue after treatment for cancer, it is an incomplete description of the underlying process. Within the group of severely fatigued disease-free breast cancer patients, 69 percent can not be considered as clinical depressed.

From results of the dimension ‘functional impairment’ it can be concluded that severely fatigued disease-free breast cancer patients see themselves as more impaired with regard to role functioning, home management and recreation and pastimes than do non-severely fatigued disease-free breast cancer patients. However, on the SOL, severely fatigued disease-free breast cancer patients reported the same amount of household activities and work outside the house as non-severely fatigued disease-free breast cancer patients. These results probably indicate that disease-free breast cancer patients have to resume their household activities, no matter whether they feel fatigued or not. Furthermore, it could be that it is very important for women in our society to resume their work outside the home after treatment for cancer (for financial or social reasons).

With regard to sleep disturbances, it seems logical that when one does not sleep well, fatigue complaints are maintained. Causes of sleep problems have not been extensively investigated. It is possible that sleep problems are a result of the experience of tension, fear and anxiety that is related to the uncertainty regarding the future. Furthermore, in breast cancer patients, who often become menopausal because of chemotherapy, an increased frequency of night-time vasomotor symptoms (i.e. night sweats) could produce disruptive effects on sleep[36]. Additional research is needed to clarify this issue.

The relationship between fatigue and physical activity has rarely been investigated in the literature, and only during active treatment for cancer[37-39]. Results suggest a negative relation between physical activity and fatigue. In addition, sports or walking programmes during treatment for cancer report positive results, although follow-up analyses are absent[40,41]. Results from our study also suggest that after treatment for cancer lower physical activity is related to more severe fatigue.

On the dimension of social support we found that severely fatigued disease-free breast cancer patients experienced less social support than they would like. This perceived lack of social support may result from the fact that family and friends do not expect their wife, mother or friend to experience fatigue or any other complaints more than a year after treatment for breast cancer.

In general, non-severely fatigued disease-free breast cancer patients are comparable to women without a cancer history on the above described dimensions. The only differences between these two groups were found on several subscales of the SIP (namely home management, work, recreation and pastimes, sleep/rest and social interaction) and on one subscale of the SOL (hours of work a day).

On the ‘self-efficacy’ dimension, severely fatigued disease-free breast cancer patients had a lower sense of control with respect to their fatigue complaints than did non-severely fatigued disease-free breast cancer patients. This finding is consistent with results of studies with chronic fatigue syndrome patients and multiple sclerosis patients. In these patient populations, a negative self-efficacy was found to have a direct negative causal effect on fatigue severity[35].

In summary, results from this study indicate that severe fatigue is a problem for nearly 40 percent of the disease-free breast cancer patients. Furthermore, there are no indications for a relationship between off-treatment fatigue and former treatment modalities. Finally, severe fatigue is associated with several physical, psychological, social, cognitive and behavioural factors. Regression analyses indicated that depression, physical inactivity, the need to sleep and rest during the day and the tendency to attribute fatigue complaints to the breast cancer experience, contribute significantly to the severity of fatigue.

Nevertheless, it is important to note that there are also many breast cancer survivors who have comparable scores to women without a history of cancer with respect to fatigue severity, psychological well-being, sleep disturbances, physical activity, neuropsychological impairment, social functioning and social support. These women thus seem to function quite well about two years after treatment for breast cancer.

The strengths of this study include the use of a comprehensive multidimensional assessment of fatigue and the reliance upon different self-report measures for each dimension. In addition, use of the SOL in which fatigue is registered four times a day, and sleep, activity and work are registered once a day, constituted an advance over entire reliance upon retrospective measures. Furthermore, we could use an empirically validated cut-off point for severe fatigue, based on norm scores of fatigue from several groups of patients and healthy controls[21]. Finally, the inclusion of an age and gender matched control group leads to useful results.

In the future, specific attention should be paid to the way physical, psychological, social, cognitive and behavioural factors contribute to the course of fatigue after successful treatment for cancer, using a longitudinal design. More knowledge about the perpetuating factors of off-treatment fatigue will enable us to develop interventions to reduce fatigue complaints in severely fatigued disease-free cancer patients.

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Chapter 5

Relations between fatigue, neuropsychological functioning and physical activity after treatment for breast carcinoma

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Cancer 2002; 95: 2017-2026

ABSTRACT

Previous research indicates that disease-free breast carcinoma survivors who experienced severe fatigue also had many problems with regard to neuropsychological functioning and physical activity, measured with general self-report questionnaires. Both neuropsychological functioning and physical activity can be measured with daily self-report measures in addition to measures of objective behaviour. The main objective of this study was to examine the relations between 1) fatigue and 2) daily self-reported and objective measures of neuropsychological functioning and physical activity. Disease-free breast carcinoma survivors and age-matched women with no history of breast carcinoma filled out a daily self-observation list and wore an actometer during a period of 12 days. Furthermore, they performed two standardised tests to assess neuropsychological functioning. No differences were found between severely fatigued disease-free breast carcinoma survivors, non-severely fatigued disease-free breast carcinoma survivors, and women in a control group with regard to daily self-reported and objective physical activity. The severely fatigued disease-free patients reported more impairment in neuropsychological functioning on daily questionnaires compared with non-severely fatigued disease-free patients and women in the control group. However, no differences were found between these three groups on a standardised concentration task. On a standardised reaction time task, no significant differences were found between the two groups of disease-free breast carcinoma survivors: However, women in the severely fatigued group had a significantly longer reaction time compared with women in the control group. We conclude that fatigue is correlated strongly with daily self-reported neuropsychological functioning, but not with objective neuropsychological functioning, in a laboratory setting. In the current study, fatigue was not correlated with daily self-reported and objective physical activity.

INTRODUCTION

During recent years, several articles have been published about fatigue complaints in disease-free patients long after curative treatment for malignant disease[1-9]. Although the results are not unambiguous, the majority of those studies concluded that fatigue is an important problem for about one-third of survivors of malignant disease.

Recently, our research group conducted a study to investigate fatigue in a sample of 150 disease-free breast carcinoma survivors[10]. The results indicated that 38% of these women experienced severe fatigue. Furthermore, it was found that, among this group of disease-free breast carcinoma survivors, severely fatigued patients experienced significant more problems in neuropsychological functioning (concentration and memory problems) and physical activity compared with non-severely fatigued patients and with a group of women who had no history of breast carcinoma, as measured with validated general self-report questionnaires.

There are several studies in which neuropsychological impairment is described in disease-free patients who previously had malignant disease[11-13], in patients undergoing treatment for malignant disease[14-16], in patients with terminal malignant disease[17-19], and in survivors of childhood malignancies[20,21]. However, with the exception of one article, the relation between fatigue and neuropsychological functioning was never investigated[12]. In that study, the patients who showed most impairment with respect to neuropsychological functioning also reported the most fatigue.

The relation between fatigue and physical activity has been investigated scarcely and only during active treatment for malignant disease[22-25]. During this period of active treatment, there seems to be a negative relation between physical activity and fatigue. In addition, patients with malignancies who participate in walking or exercise intervention programs report positive effects on fatigue[26,27]. No data are available concerning the relation between fatigue and physical activity in survivors of malignant disease.

In the current study, data are presented on the relation between 1) fatigue and 2) both neuropsychological functioning and physical activity. Results of general self-report questionnaires were reported previously[10]. However, neuropsychological functioning and physical activity can be measured as well with a daily self-observation list and by measures of objective behaviour. It is important to combine these different ways of measurement, because there is evidence that general self-report measures, daily self-report measures, and measures of objective behaviour do not always lead to the same conclusion[28].

To interpret data, an age-matched control group of women with no history of breast carcinoma was included. Furthermore, because clinical evidence suggests that radiotherapy of the breast can cause damage indirectly to the lungs, and because chemotherapy can have an effect on the nervous system, we investigated the influence of previous treatment on physical activity and neuropsychological functioning.

Three specific research questions were investigated: 1) Do severely fatigued disease-free breast carcinoma survivors, non-severely fatigued disease-free breast carcinoma survivors, and women with no history of breast carcinoma show differences in daily self-reported and objective neuropsychological functioning; 2) Do these three groups differ with regard to daily self-reported and objective physical activity; 3) Are the results of daily self-report measures and objective measures of neuropsychological functioning and physical activity consistent with the results of general self-report measures and 4) Are general self-reported, daily self-reported, and objective neuropsychological functioning and physical activity influenced by previous treatment for breast carcinoma?

METHODS

Sample

To select a relative homogeneous group of patients, all patients had to be treated according to the protocol of the Comprehensive Cancer Center East for premenopausal breast carcinoma. Furthermore, women had to be age < 50 years by the time of primary diagnosis and had to have completed treatment for breast carcinoma a minimum of 6 months and a maximum of 70 months prior to study entry. Finally, they could have no evidence of disease recurrence at the time of participation.

Participating patients were asked to bring along a female family member, friend, or colleague who was not > 4 years younger or > 4 years older than the patient. This woman had to be healthy (no chronic disease) and was never treated for malignant disease in the past.

Recruitment Procedure

Women were recruited from one university hospital and from six regional hospitals. At the university hospital and at three regional hospitals, all patients who met the eligibility criteria initially were informed about the study by mail with an introductory letter from their oncologist. At the other three regional hospitals, patients were informed by their oncologist during control visits. In the following week, patients were contacted by telephone by the psychologist-researcher (P.S.). The patients who agreed to take part in the study were invited (with their female family member, friend, or colleague) to the Department of Medical Psychology of the University Medical Center Nijmegen. The psychologist-researcher and one psychological assistant administered all measures. This was done during the period between January 1998 and June 1999. From all patients and control participants, informed consent was obtained. The ethics committee of all participating hospitals agreed with the study.

Measurement

Fatigue severity was measured with the Fatigue Severity subscale of the Checklist Individual Strength (CIS)[29]. The CIS is a 20-item questionnaire that was designed to measure fatigue severity (8 items), concentration (5 items), motivation (4 items), and physical activity (3 items). Each item is scored on a 7-point Likert scale, with high scores indicating a high level of fatigue, a high level of concentration problems, low motivation, and a low level of physical activity. Based on research with patients who have chronic fatigue syndrome, a score 35 on the Fatigue Severity subscale indicates severe feelings of fatigue[30].

Patients registered daily complaints of neuropsychological functioning and physical activity at home during a 12-day period in a daily self-observation list[31]. Memory and concentration both were registered four times daily (0, no; 1, yes). Total daily scores ranged from 0 to 4, with a higher score indicating more problems with memory and concentration. In addition, physical activity was registered 4 times daily, from 0 (not at all active) to 4 (very active). Total scores ranged from 0 to 16, with a higher score indicating more daily physical activity.

Objective physical activity was measured with the actometer, which is an apparatus about the size of a matchbox that was worn around the ankle both day and night during a 12-day period[28]. Specialised software was used to calculate several parameters. A general physical activity score reflected the physical activity level over the 12-day period and was expressed as the average number of accelerations per 5-minute period. Furthermore, the program calculated the 10 largest activity peaks. Both the average peak duration and average peak amplitude of these 10 largest peaks were calculated. Finally, the average duration of rest periods after these 10 largest peaks was calculated[32].

Objective neuropsychological functioning was measured with the Complex Reaction Time Task (CRT)[33] and the Symbol Digit subtest of the Wechsler Adult Intelligence Scale (WAIS)[34]. The CRT measures the speed of information processing and is comprised of three consecutive tasks. On a response board, five target buttons are situated in an arch around a start button. The target buttons are placed at equal distances from the start button. Each target button contains a stimulus light. In all tasks, the participant keeps the start button pressed until a stimulus button lights up. In the first task, only one stimulus button (the middle) can light up. In the second task, three different stimulus buttons (the middle three) can light up in random order. In the third task, three different stimulus buttons (the three buttons on the left) can light up in random order. In this task, participants are asked not to press the stimulus button that lights up (the first two tasks are considered the obvious response) but to press the button to the right of the stimulus button. Each task consists of 30 trials. To prevent anticipation effects, the time that elapses between pushing the start button and the lighting of the stimulus is varied between 0.5 seconds and 2.5 seconds (in random order). In the CRT, reaction time (speed of information processing) is registered by the computer. Reaction time is defined as the time elapsed between the moment the stimulus lights up and the moment the start button is released.

The Symbol Digit subtest of the WAIS assesses the ability to concentrate. This test consists of pairing numbers with nonsense symbols as quickly as possible. The higher the score on this test, the better a person is able to concentrate.

It should be noted that concentration and reaction time tap specific facets of neuropsychological functioning. These domains do not represent the complete area of cognitive functioning. The reason for choosing to focus on these domains is that previous research indicates that these domains often are problematic in long-term survivors of malignant disease[11,13,35].

General self-reported neuropsychological functioning was measured using the Concentration subscale of the CIS. Furthermore, the Alertness and Intellectual Functioning subscale of the Sickness Impact Profile (SIP-8) was used[36]. General self-reported physical activity was measured with the Physical Activity subscale of the CIS and the Mobility and Ambulation subscales of the SIP-8.

Statistical Analyses

Data analysis was performed using SPSS software (version 8.0; SPSS, Inc., Chicago, IL). Descriptive statistics were used to describe the samples. Chi-square tests and general linear model (GLM)-General Factorial tests were performed to determine differences between groups. In instances of an overall significance, the Bonferroni correction was applied to compare the three individual groups.

Table 1. Demographic characteristics

	Severely fatigued disease-free patients with breast carcinoma (n=57)	Non-severely fatigued disease-free patients with breast carcinoma (n=93)	Women without a history of carcinoma (n=78)
Mean age	45.2 (sd=6.2)	46.4 (sd=6.3)	48.1 (sd=6.2)
Marital status			
married	81%	90%	86%
unmarried	5%	4%	4%
divorced	10%	4%	6%
widowed	4%	1%	4%
Higher education (>=12 years)	37%	39%	41%
Employment			
work outside home	53%	67%	67%
voluntary work	14%	27%	22%
disablement insurance act	19%	7%	3%
partial disablement insurance act	21%	9%	3%
sick leave	7%	1%	1%

RESULTS

Description of the Sample

One hundred fifty disease-free breast carcinoma survivors participated in this study. The numbers of women who did not participate and their reasons for nonparticipation were described in an earlier publication[10]. Seventy-eight patients brought a female family member, friend, or colleague along to the hospital.

The sample of disease-free breast carcinoma survivors was divided into two groups: severely fatigued patients (i.e., a score 35 on the Fatigue Severity subscale of the CIS) and non-severely fatigued patients. Information about demographic characteristics of these two groups and the group of control women is listed in Table 1. No significant differences were found with regard to age, marital status, education, and employment between the three groups. However, the percentage of women on (partial) disability insurance was higher in the group of severely fatigued breast carcinoma survivors compared with the group of non-severely fatigued breast carcinoma survivors and the group of women with no history of breast carcinoma (GLM-General Factorial; $p<0.002$).

Information on the medical characteristics of the breast carcinoma survivors can be

Information on the medical characteristics of the breast carcinoma survivors can be
found in Table 2. Duration of treatment was defined as the period from the time of surgery until the end of adjuvant therapy. Time since diagnosis was defined as the month of diagnosis until the month of participation in the current study. Finally, time since treatment was defined as the period from the end of adjuvant therapy until the month of participation in the current study.

Table 2. Treatment characteristics

	Severely fatigued disease-free patients with breast carcinoma (n=57)	Non-severely fatigued disease-free patients with breast carcinoma (n=93)
mastectomy vs. lumpectomy	54% vs 46%	68% vs 32%
no adjuvant therapy	12%	14%
only radiotherapy	19%	21%
only chemotherapy	21%	23%
radiotherapy and chemotherapy	48%	42%
mean duration of treatment (months)	6 (sd 3)	6 (sd 3)
mean time since treatment (months)	27 (sd 16)	30 (sd 18)

Research Questions

Do severely fatigued disease-free breast carcinoma survivors, non-severely fatigued disease-free breast carcinoma survivors, and women with no history of breast carcinoma show differences in daily self-reported and objective neuropsychological functioning?

Results of daily self-reports (Table 3) indicated that severely fatigued disease-free breast carcinoma survivors (mean ± standard deviation CIS Fatigue Severity score, 43.0 ± 5.5) reported more daily concentration problems and more daily memory problems compared with non-severely fatigued disease-free breast carcinoma survivors (mean ± standard deviation CIS Fatigue Severity score, 19.6 ± 8.4) and women with no history of breast carcinoma. However, the difference between severely fatigued disease-free breast carcinoma survivors and non-severely fatigued disease-free breast carcinoma survivors with regard to daily memory problems did not reach significance ($p<0.06$). Non-severely fatigued disease-free breast carcinoma survivors and women with no history of breast carcinoma had equal scores.

Table 3. Neuropsychological functioning

	A	B	C	
	Severely fatigued disease-free patients with breast carcinoma	Non-severely fatigued disease-free patients with breast carcinoma	Women without a history of carcinoma	p-value
	(n=57)	(n=93)	(n=78)	
	Mean (sd)	Mean (sd)	Mean (sd)	
Daily self-report				
concentration	0.36 (0.79)[bc]	0.14 (0.37)[a]	0.04 (0.10)[a]	0.000
memory	0.22 (0.75)[c]	0.06 (0.27)	0.02 (0.08)[a]	0.016
Actual behaviour				
concentration (symbol digit)	54.5 (10.4)	55.7 (11.5)	55.4 (8.9)	0.795
reaction time (CRT1)	0.32 (0.06)[c]	0.30 (0.05)	0.29 (0.05)[a]	0.004
reaction time (CRT2)	0.36 (0.05)[c]	0.36 (0.14)[c]	0.32 (0.04)[ab]	0.009
reaction time (CRT3)	0.47 (0.08)[c]	0.45 (0.07)	0.42 (0.07)[a]	0.001
General self-report				
concentration (CIS)*	20.3 (7.6)[bc]	14.1 (7.2)[a]	13.1 (7.5)[a]	0.000
alertness behaviour (SIP)*	150.9 (150.0)[bc]	56.5 (90.4)[a]	15.4 (78.8)[a]	0.000

GLM-general factorial

[a] significantly different from group A, Bonferroni $p<0.05$

[b] significantly different from group B, Bonferroni $p<0.05$

[c] significantly different from group C, Bonferroni $p<0.05$

* also reported in Servaes et al.[10]

Furthermore, the speed of information processing (CRT) was slower for severely fatigued disease-free breast carcinoma survivors compared with for women in the control group. In addition, on one of the three subtests of the CRT, non-severely fatigued disease-free breast carcinoma survivors also were significantly slower compared with women in the control group. Severely fatigued disease-free breast carcinoma survivors and non-severely fatigued disease-free breast carcinoma survivors did not have significantly different scores. Finally, the ability to concentrate, as measured with the Symbol Digit subtest of the WAIS, did not reflect any differences between the three groups (Table 3).

Table 4. Physical activity

	A	B	C	
	Severely fatigued disease-free patients with breast carcinoma	Non-severely fatigued disease-free patients with breast carcinoma	Women without a history of carcinoma	p-value
	(n=57)	(n=93)	(n=78)	
	Mean (sd)	Mean (sd)	Mean (sd)	
Daily self-report				
physical activity	5.27 (1.71)	5.90 (2.04)	5.82 (1.88)	0.131
Actual behaviour				
general physical activity (actometer)[1]	76.1 (22.5)	79.1 (20.8)	76.9 (15.5)	0.613
peak amplitude (actometer)[1]	182.0 (29.7)	182.1 (23.1)	177.6 (22.3)	0.452
peak duration (actometer)[2]	125.7 (46.0)	136.7 (51.7)	129.5 (39.0)	0.344
rest duration after peak (actometer)[2]	71.2 (31.7)	63.9 (30.2)	68.2 (31.7)	0.369
General self-report				
physical activity (CIS)[3]	12.1(5.9)[bc]	6.8 (3.8)[a]	5.9 (3.7)[a]	0.000
mobility (SIP)[3]	16.5 (41.5)[bc]	4.9 (17.5)[a]	1.5 (8.7)[a]	0.003
ambulation (SIP)[3]	25.4 (40.6)[bc]	6.9 (18.0)[a]	0.0 (0.0)[a]	0.000

GLM-general factorial

[a] significantly different from group A, Bonferroni p< 0.05

[b] significantly different from group B, Bonferroni p< 0.05

[c] significantly different from group C, Bonferroni p< 0.05

[1] activity levels are expressed in the number of accelerations per 5-minute period

[2] peak and rest durations are expressed in minutes

[3] also reported in Servaes et al.[10]

Do severely fatigued disease-free breast carcinoma survivors, non-severely fatigued disease-free breast carcinoma survivors, and women with no history of breast carcinoma differ with regard to measures of daily self-reported and objective physical activity?

During a 12-day period, severely fatigued disease-free breast carcinoma survivors reported the same daily activity as non-severely fatigued disease-free breast carcinoma survivors and women in the control group. In addition, the three groups had equal scores for general physical activity, peak amplitude, peak duration, and duration of rest after an activity peak, as measured with the actometer (Table 4).

Are the results of daily self-report measures and objective measures of neuropsychological functioning and physical activity consistent with the results of general self-report measures?

In our previous publication, we found that severely fatigued disease-free breast carcinoma survivors experienced more impairment in neuropsychological functioning and in physical activity compared with non-severely fatigued disease-free breast carcinoma survivors and women with no history of breast carcinoma on all general self-report measures. Non-severely fatigued disease-free breast carcinoma survivors and women with no history of breast carcinoma had equal scores (see Tables 3 and 4). The results of daily self-reports of neuropsychological functioning were consistent with the previous results. Severely fatigued disease-free breast carcinoma survivors reported more daily problems with regard to neuropsychological functioning compared with non-severely fatigued disease-free breast carcinoma survivors and women with no history of breast carcinoma. Results of objective measurements of neuropsychological functioning were not entirely consistent with the results obtained by general self-report measures. Reaction time was longer for severely fatigued disease-free breast carcinoma survivors compared with women who had no history of breast carcinoma but not compared with non-severely fatigued disease-free breast carcinoma survivors. Furthermore, no differences were found between the three groups on the standardised concentration task.

The results of daily self-report and objective measurement of physical activity were not consistent at all with general self-reported physical activity results. Severely fatigued disease-free breast carcinoma survivors experienced more impairment in physical activity compared with non-severely fatigued disease-free breast carcinoma survivors and women with no history of breast carcinoma on all general self-report measures, as mentioned above. However, no differences between the three groups were found on daily self-reported activity or on the different parameters of the actometer.

Are general self-report, daily self-report, and objective neuropsychological functioning and physical activity influenced by previous treatments for breast carcinoma?

Neither general self-report, daily self-report, nor objective neuropsychological functioning and physical activity were influenced by previous treatment modalities. Patients who did not receive adjuvant therapy, patients who received chemotherapy only, patients who received radiotherapy only, and patients who received both chemotherapy and radiotherapy did not differ from one another on any of the general self-report, daily self-report, or standardised measures (Tables 5 and 6).

Table 5. Neuropsychological functioning for different former treatment

	both radio- and chemotherapy (n=66) Mean (sd)	no adjuvant therapy (n=20) Mean (sd)	chemo-therapy only (n=33) Mean (sd)	radio-therapy only (n=31) Mean (sd)	p-value
General self-report					
concentration (CIS)	17.5 (17.5)	14.9 (6.1)	15.6 (8.3)	15.9 (8.3)	0.460
alertness behaviour (SIP)	105.1 (143.7)	87.4 (85.5)	78.33 (100.1)	83.48 (123.2)	0.729
Daily self-report					
concentration	0.24 (0.55)	0.10 (0.18)	0.19 (0.42)	0.31(0.89)	0.620
memory	0.17 (0.64)	0.24 (0.75)	0.05 (0.15)	0.02 (0.08)	0.346
Actual behaviour					
concentration (symbol digit)	55.7 (10.3)	52.2 (10.8)	55.9 (8.6)	55.5 (14.8)	0.629
reaction time (CRT1)	0.30 (0.05)	0.31 (0.07)	0.32 (0.06)	0.31 (0.05)	0.671
reaction time (CRT2)	0.36 (0.17)	0.36 (0.05)	0.36 (0.04)	0.36 (0.05)	0.997
reaction time (CRT3)	0.45 (0.08)	0.45 (0.07)	0.46 (0.06)	0.47 (0.08)	0.815

GLM-general factorial

Table 6. Physical activity for different former treatment modalities

	both radio- and chemotherapy (n=66) Mean (sd)	no adjuvant therapy (n=20) Mean (sd)	chemo-therapy only (n=33) Mean (sd)	radio-therapy only (n=31) Mean (sd)	p-value
General self-report					
physical activity (CIS)	8.9 (5.5)	9.6 (4.9)	8.4 (5.5)	8.5 (5.3)	0.879
mobility (SIP)	9.5 (30.33)	3.6 (16.1)	10.5 (31.2)	11.2 (33.0)	0.822
ambulation (SIP)	16.8 (30.37)	1.8 (7.8)	8.6 (19.9)	21.5 (42.4)	0.073
Daily self-report					
physical activity	5.8 (2.0)	5.9 (1.6)	5.6 (2.0)	5.3 (1.8)	0.639
Actual behaviour					
general physical activity (actometer)[1]	77.8 (19.6)	78.5 (22.0)	80.2 (24.9)	75.7 (21.5)	0.873
peak amplitude (actometer)[1]	185.8 (25.9)	177.9 (28.2)	182.9 (24.6)	175.8 (24.0)	0.290
peak duration (actometer)[2]	131.2 (46.7)	134.3 (56.6)	136.6 (55.3)	130.2 (47.5)	0.952
rest duration after peak (actometer)[2]	67.8 (29.9)	63.3 (26.8)	65.0 (31.2)	68.0 (36.0)	0.923

GLM-general factorial

[1] activity levels are expressed in number of accelerations per 5-minute period

[2] peak and rest durations are expressed in minutes

DISCUSSION

This study was an attempt to expand knowledge of the relation between fatigue, neuropsychological functioning, and physical activity among disease-free breast carcinoma survivors by including daily self-report and standardised measures of neuropsychological functioning and physical activity in addition to general self-report measures of neuropsychological functioning and physical activity. With regard to neuropsychological functioning, it can be concluded that severely fatigued breast carcinoma survivors reported more impairment compared with non-severely fatigued breast carcinoma survivors and women with no history of breast carcinoma both on general measures and on daily self-report measures. Furthermore, severely fatigued breast carcinoma survivors had a slower speed of information processing compared with women in the control group and women in the group of non-severely fatigued breast carcinoma survivors. However, the differences between severely and non-severely fatigued breast carcinoma survivors did not reach significance. In the standardised concentration task, no differences were found between the two groups of breast carcinoma survivors and the comparison group. However, it should be noted that this standardised concentration task was done in a laboratory setting: The task has a duration of 90 seconds, so it does not measure the ability to concentrate during a longer period. In other words, we cannot draw conclusions about the possible differences between severely fatigued and non-severely fatigued disease-free breast carcinoma survivors and women with no history of breast carcinoma with respect to the endurance of the ability to concentrate.

With regard to the measurement of neuropsychological functioning, a few things have to be noted. First, we did not control for overall intelligence quotient (IQ), because we did not collect data pertaining to this variable. However, there is no reason to expect differences in IQ between the three groups; in addition, there were no differences with respect to education between the three groups. Second, it is important to note that the concentration task we used measures not only concentration but also incidental learning and visuomotor speed. Finally, it should be noted that we used only two tests of objective neuropsychological functioning; therefore, our conclusions with respect to objective neuropsychological functioning are limited to the concepts that were measured by these two tests.

No relation was found between type of previous treatment for breast carcinoma and neuropsychological performance. Patients who received chemotherapy had equal scores on general self-report, daily self-report, and standardised neuropsychological measures compared with patients who received radiotherapy and patients who did not receive any adjuvant therapy. This result is contrary to what was expected according to previous studies. In those studies, the types of treatment that affected the central nervous system (e.g., chemotherapy and prophylactic cranial irradiation) led to more neuropsychological impairment compared with antitumor treatments that did not affect the central nervous system directly[12,14,16,18,37]. However, there is an important difference between those studies and the current study. The samples investigated in the studies mentioned above consisted of patients who were undergoing treatment at the time of the study as well as terminal carcinoma survivors. In our study, all patients were disease-free and had finished treatment for breast carcinoma a mean of 2.5 years prior to the current investigation. Thus, it is possible that there was a relation between treatment and neuropsychological functioning during the period when patients were receiving treatment for breast carcinoma. However, this relation has disappeared over time.

With regard to physical activity, we knew previously that severely fatigued disease-free breast carcinoma survivors perceived themselves as more limited with regard to physical activity compared with non-severely fatigued disease-free breast carcinoma survivors and women in the control group. However, in a daily self-observation list, severely fatigued patients did not perceive themselves as less active compared with the two other groups. In addition, their objective physical activity pattern matched the pattern of the other groups. The expectation that patients who received radiotherapy were the most physically impaired was not confirmed. On all measurements (general self-report, daily self-report, and actometer), no differences were found between the four treatment groups.

What can explain the lack of correspondence between 1) general self-report measures and 2) daily self-report and standardised measures of physical activity? In other words, why do severely fatigued breast carcinoma survivors report less physical activity compared with non-severely fatigued breast carcinoma survivors and women in a healthy control group, although they seemed to function just as well as the other two groups during a 12-day period? One hypothesis that explains this lack of correspondence is that, due to the effort necessary to continue their physical activities, severely fatigued disease-free patients may experience themselves as less active. It is possible to imagine that, when a breast carcinoma survivor experiences severe fatigue, and when physical activity requires a lot of effort, the patient may perceive herself as physically less active compared with her activity level before she was diagnosed with breast carcinoma. In fact, she may have the same level of physical activity as a non-severely fatigued breast carcinoma survivor and a healthy control woman. In addition, it is possible that fatigued breast carcinoma survivors are too demanding of themselves. Thus, although they are just as active physically as non-severely fatigued breast carcinoma survivors and women in a healthy control group, they are not satisfied with their level of activity and, thus, perceive themselves as inactive. Finally, another possibility is that complaints of physical inactivity are indicative of emotional distress rather than actual reduced physical activity. In our data, relations between self-reported inactivity and emotional distress (measured with the Beck Depression Inventory and the Symptom Checklist) were significant statistically. Conversely, no significant relations were found between actual physical activity and emotional distress. The same was true for complaints of neuropsychological functioning. Statistically significant relations were found between self-reported neuropsychological problems and emotional distress, whereas there were no relations between actual neuropsychological functioning and emotional distress. In addition, in the literature, it is a common finding that objective test results and subjective reports of cognitive functioning are not related, whereas subjective reports of cognitive functioning are related strongly to anxiety and depression[12,38]. More data on emotional functioning in samples of disease-free breast carcinoma survivors can be found elsewhere[10].

To conclude, we want to emphasise that it is important to include different ways of measurement when possible. In our study, the inclusion of daily self-report and actual measurement, in addition to general self-report, provided better inside into fatigue and related problems.

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Chapter 6

Fatigue after breast cancer and in Chronic Fatigue Syndrome
similarities and differences

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Journal of Psychosomatic Research 2002; 52: 453-459

ABSTRACT

Fatigue is investigated in 57 severely fatigued disease-free breast cancer patients and in 57 gender- and age-matched patients with Chronic Fatigue Syndrome (CFS) using multidimensional and multimethod assessment. A comparison between these groups of patients is important to determine whether a cognitive behavioural intervention to reduce fatigue in CFS patients would be appropriate as well for severely fatigued disease-free breast cancer patients. Measurement included computerised questionnaires and a standardised neuropsychological test. Furthermore, patients filled out a daily Self-Observation List (SOL) and wore an actometer during a period of 12 days. Results indicate that in comparison to severely fatigued disease-free breast cancer patients, CFS patients score more problematic with regard to the level of fatigue, functional impairment, physical activity, pain and self-efficacy. However, a subgroup of severely fatigued disease-free breast cancer patients reports the same amount of problems as CFS patients with regard to psychological well-being, sleep and concentration. Finally, CFS patients and severely fatigued breast cancer patients score equal on measures of social support. In conclusion, there seem to be some similarities but also many differences between severely fatigued breast cancer survivors and females with CFS. Therefore, cognitive behaviour therapy (CBT) to reduce fatigue after treatment for cancer should also differ in certain aspects from cognitive behaviour therapy as it has been developed for patients with CFS.

INTRODUCTION

Fatigue is a complaint that is often reported by cancer patients while they are undergoing treatment for cancer[1]. In the last few years, several studies have demonstrated that many patients also experience fatigue (long) after curative treatment for cancer has been terminated[2-11]. At this moment, little is known about the factors that may cause or perpetuate fatigue. However, it seems that characteristics of the disease and treatment are not related to the severity of fatigue long after treatment has ended. A treatment for fatigue long after treatment for cancer is not available.

Another patient population with severe fatigue complaints, for which up until now no physical explanation has been found, are patients with chronic fatigue syndrome (CFS). CFS is characterised by persistent or recurrent fatigue that lasts for 6 or more consecutive months. Fatigue is not the result of constant exertion, does not improve by rest and has leaded to substantial decrease of former standards of professional, social and personal functioning[12]. There is increasing evidence that cognitive behaviour therapy (CBT) is effective for patients with CFS[13,14].

Our research group has developed a multidimensional assessment method to measure fatigue in patients with CFS[15]. Factor analyses has identified nine dimensions, namely fatigue severity, functional impairment, psychological well-being, sleep disturbances, neuropsychological impairment, physical activity, social support, causal attributions and self-efficacy. These dimensions appeared to be relatively independent, meaning that each dimension uniquely contributes to the description of a patient.

Using this assessment method, we are able to examine to what extent a patient who experiences severe fatigue after treatment for cancer resembles a patient with CFS. The purpose of this study is to compare, where possible, a group of severely fatigued disease-free cancer patients with a group of CFS patients on the above-described dimensions. We added the dimension "pain" in this study, because pain is a frequent complaint, besides fatigue, of CFS patients. A comparison between these groups of patients is important to determine whether a cognitive behavioural intervention to reduce fatigue in CFS patients would be appropriate as well for severely fatigued disease-free breast cancer patients.

The specific research questions we would like to answer are the following:

1) How many severely fatigued disease-free breast cancer patients fulfil the criteria (severity of fatigue and functional impairment) for CFS; 2) Do severely fatigued disease-free breast cancer patients (those who fulfil the criteria for CFS and those who do not fulfil these criteria) differ from CFS patients on the dimensions self-efficacy, psychological well-being, sleep, concentration, physical activity, social support and pain?

METHODS

Patients

In a longitudinal study investigating the course of fatigue after treatment for breast cancer, 150 disease-free breast cancer patients were included[33]. One of the inclusion criteria was that patients had to be treated according to the protocol of the Comprehensive Cancer Centre East in the Netherlands for premenopausal breast cancer patients. Furthermore, they had to be younger than 50 by the time of primary diagnosis and had to have completed treatment for breast cancer a minimum of 6 months and a maximum of 70 months before. Finally, they had to have no evidence of disease recurrence at the time of participation. On the basis of a cut-off score of 35 on the subscale "severity of fatigue" of the Checklist Individual Strength (CIS), 57 patients (38%) could be considered as severely fatigued 6-70 months (mean 2 years) after the end of treatment for cancer. Data of these severely fatigued disease-free breast cancer patients have been used for the present study.

In an intervention study, in which the effect of cognitive behaviour therapy on fatigue has been investigated, 270 patients with CFS participated (n=270)[14]. Participants had to be between the age of 18 and 60 years old. Furthermore, patients were selected for this intervention study on the basis of the operational criteria for CFS. This means a score of 40 or higher on the subscale "fatigue severity" of the CIS and a score of 800 or more on eight subscales of the Sickness Impact Profile (SIP-8). Finally, patients were excluded if they had participated in previous CFS research. From this sample of 270 patients, we selected 57 patients matched on age and gender with the 57 severely fatigued disease-free breast cancer patients.

From both samples, baseline data are used for the current study. The collected data consist of computerised questionnaires. Patients were asked to complete the self-report questionnaires mentioned below by computer at our department. Furthermore, patients performed a standardised neuropsychological test and filled out a daily Self-Observation List (SOL) during a period of 12 days. They also wore an actometer during this 12-day period.

Measures per dimension

Fatigue severity has been measured by the "fatigue severity" subscale of the CIS and the "Daily Observed Fatigue" (DOF) of the SOL. The CIS[15,16] is a 20-item questionnaire. Each item is scored on a seven-point Likert scale. The questionnaire was designed to measure four aspects of fatigue during the last 2 weeks, namely fatigue severity (eight items; 7-56), concentration (five items; 5-35), motivation (four items; 4-28) and physical activity (three items; 3-21). High scores indicate a high level of fatigue, a high level of concentration problems, low motivation and a low level of physical activity. The CIS has good reliability (Cronbach's alpha's varying from 0.83 to 0.92) and discriminative validity[15-17]. In the SOL, Daily Observed Fatigue is reported four times a day on a five-point scale (0-4). Total scores range from 0 to 16[18].

Functional impairment has been measured with eight subscales of the SIP-8: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work and recreation and pastimes[19,20]. The SIP is a widely used measure with good reliability and content validity[21].

Self-efficacy is measured with the Self-Efficacy Scale (SES)[22]. The SES consists of five questions that measure sense of control with respect to fatigue complaints. A total score ranges from 5 to 25, a higher score reflecting more sense of control. Cronbach's alpha reliability coefficients range from 0.70 to 0.77[14,22,23].

Psychological well-being has been measured with the Beck Depression Inventory for primary care (BDI-PC)[24] and with the subscales depression, anxiety, somatisation, interpersonal sensitivity and obsessive-compulsive behaviour of the Symptom Checklist (SCL-90)[25]. Lower scores reflect less problems in these subscales. The SCL-90 is widely used and the reliability and discriminating validity are good. The BDI-PC has seven items and is composed of cognitive and affective symptoms only. We used this shortened version of the BDI to prevent an overlap between the physical symptoms of chronic fatigue and the physical symptoms of depression. The BDI-PC has high internal consistency (Cronbach's alpha=0.86) and displays convergent validity[24].

Sleep has been measured with the sleep subscale of the SCL-90. Furthermore, quality of sleep (general quality of sleep, difficulties falling asleep, restless sleep and early awakenings) is registered daily (1=yes, 0=no) in the SOL. Concentration has been measured with the concentration subscale of the CIS. Additionally, the ability to concentrate has been assessed with the Symbol Digit subtest of the Wechsler Adult Intelligence Scale (WAIS)[26]. The test consists of pairing numbers with nonsense symbols as quickly as possible. The higher the score on this test, the better a person is able to concentrate.

Physical activity has been measured in three ways. Self-reported physical activity has been measured with the physical activity subscale of the CIS. In addition, physical activity is registered four times a day, on a five-point scale (0-4), in the SOL [Daily Observed Activity (DOA), range 0-16]. Finally, actual physical activity has been measured with the actometer. The actometer is a motion sensing device attached to the ankle and worn continuously for 12 days[27]. Specialised software was used to calculate several parameters. A general physical activity score reflects the physical activity level over the 12-day time period and is expressed in the average number of accelerations per 5-min period. Furthermore, the program calculates the 10 largest activity peaks. Both the average peak duration and average peak amplitude of these 10 largest peaks are calculated. In addition, the average duration of rest periods following these 10 largest peaks is calculated. Finally, pervasively passive patients were defined as those patients whose average daily physical activity scores stayed below the reference score (the mean general activity score of a sample of 277 CFS patients) in at least 11 of the 12 assessment days[28].

Social support has been measured with the van Sonderen Social Support Inventory (SSL)[29]. The SSL is divided into the SSL-I (amount of social support), the SSL-D (discrepancies between amount and desired amount of social support) and the SSL-N (amount of negative interactions). The SSL has good reliability (Cronbach's alpha=0.93 (SSLI) and 0.95 (SSLD)) and content validity[29].

Pain has been measured with the SOL. The presence and intensity of pain is scored four times a day on a 0-4 scale (range 0-16). In addition, patients register the presence of a headache or joint or muscle pain four times a day (1=yes, 0=no; max score=4).

Statistics

Data analysis was performed using SPSS (version 8.0). Descriptive statistics have been used for description of the samples. Differences between CFS patients, severely fatigued breast cancer patients who fulfil the CFS criteria and severely fatigued breast cancer patients who do not fulfil the CFS criteria, have been tested with GLM general factorial. In case of an overall significance, the Bonferroni correction was applied to compare the three individual groups.

RESULTS

Description of the patient samples

The group severely fatigued disease-free breast cancer patients consists of 57 women with a mean age of 45 (sd=6.2, range 29-55). Mean time since the ending of cancer treatment is 27 months (sd=16, range 6-70). The gender- and age-matched group of CFS patients (n=57) has a mean age of 45 (sd=6.3, range 29-59). The mean duration of complaints in this group is 90 months (sd=89, range 7-378). Despite the fact that the two groups were not matched on level of education, the mean level of education is equal for both groups.

Table 1. Comparisons with regard to fatigue severity and functional impairment (GLM-general factorial)

	A	**B**	**C**	
	CFS patients	Severely fatigued disease-free breast cancer patients	Severely fatigued disease-free breast cancer patients	F-value
		CFS criteria	no CFS criteria	
	(n=57)	(n=14)	(n=43)	
	Mean (sd)	Mean (sd)	Mean (sd)	
Fatigue				
CIS-fatigue severity	52.1 (4.1)[bc]	45.4 (3.9)[a]	42.2 (5.8)[a]	42.64**
SOL-daily fatigue	7.9 (2.2)[bc]	5.3 (2.4)[a]	4.3 (1.9)[a]	36.34**
Functional impairment (SIP-8)				
Home management	218.3 (117.5)[c]	152.7 (67.8)[c]	81.0 (53.2)[ab]	26.99**
Work	127.6 (149.5)	139.9 (101.3)	75.7 (116.0)	2.31
Mobility	168.4 (121.0)[bc]	41.3 (62.7)[a]	8.4 (28.4)[a]	41.02**
Ambulation	153.4 (96.7)[bc]	33.4 (48.5)[a]	22.8 (23.0)[a]	42.21**
Recreation and pastimes	180.2 (76.0)[bc]	110.8 (55.4)[ac]	59.9 (44.6)[ab]	44.43**
Sleep/ rest	163.9 (95.5)[bc]	103.7 (53.0)[ac]	54.7 (41.5)[ab]	26.38**
Alertness behaviour	353.2 (212.0)[c]	281.9 (188.6)[c]	108.3 (101.1)[ab]	24.16**
Social interaction	378.9 (205.6)[c]	331.4 (196.7)[c]	122.1 (129.1)[ab]	25.89**
Total	1744 (579.7)[bc]	1195 (275.8)[ac]	532.9 (247.9)[ab]	89.13**

** p<0.01
[a] significantly different from group A, Bonferroni p<0.05
[b] significantly different from group B, Bonferroni p<0.05
[c] significantly different from group C, Bonferroni p<0.05

Research questions

How many severely fatigued disease-free breast cancer patients fulfil the criteria for the CFS?

As described in the Methods, CFS patients are selected on a score of 40 or higher on the subscale "fatigue severity" of the CIS and a score of 800 or more on the SIP. Severely fatigued disease-free cancer patients are selected on basis of a score of 35 or higher on the subscale "fatigue severity" of the CIS.

Within the group of 57 severely fatigued disease-free breast cancer patients, 14 patients have a score of 40 or higher on the subscale "fatigue severity" of the CIS and a score of 800 or more on the SIP. This means that only 25% of the severely fatigued disease-free breast cancer patients fulfilled the fatigue severity and impairment criteria for CFS. The other 43 severely fatigued disease-free breast cancer patients do not fulfil these criteria and thus automatically experience less severe fatigue and functional impairment than the CFS patients. In Table 1, mean scores of these three different groups are presented. In this table, you can see that the severely fatigued disease-free cancer patients who fulfil the criteria for CFS also have lower scores with regard to fatigue and functional impairment in comparison to the CFS patients. In addition, severely fatigued disease-free cancer patients who fulfil the criteria for CFS experience the same amount of fatigue but more functional impairment than severely fatigued disease-free cancer patients who do not fulfil the criteria for CFS, except on restless sleep.

Do severely fatigued disease-free breast cancer patients (those who fulfil the criteria for CFS and those who do not fulfil these criteria) differ from CFS patients on the dimensions self-efficacy, psychological well-being, sleep, concentration, physical activity, social support and pain?

In Table 2, mean scores of the three different groups, on the measures that were used to describe the above-mentioned dimensions, are presented.

In the first place, severely fatigued disease-free breast cancer patients have a higher sense of control with respect to fatigue than CFS patients do. Secondly, severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS score highest on depression, interpersonal sensitivity and obsessive-compulsive behaviour. These differences are significant in comparison to severely fatigued disease-free breast cancer patients who do not fulfil the criteria for CFS but not significant in relation to CFS patients. Further, CFS patients score highest on somatisation. Their score is significantly higher than the score of severely fatigued disease-free breast cancer patients who do not fulfil the criteria for CFS but not significantly different to the score of severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS.

Comparisons with regard to anxiety indicate that severely fatigued disease-free breast cancer patients have a comparable score to CFS patients. The score of severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS is somewhat heightened in comparison to the two other groups. However, this difference is not significant (p<0.08).

Further, with regard to sleep and sleep quality, CFS patients and severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS experience more problems than severely fatigued disease-free breast cancer patients who do not fulfil the criteria for CFS, except on restless sleep.

Table 2. Comparisons with regard to self-efficacy, psychological well-being, sleep, concentration, physical activity, social support and pain (GLM-general factorial)

	A	**B**	**C**	
	CFS patients	Severely fatigued disease-free breast cancer patients	Severely fatigued disease-free breast cancer patients	F- value
		CFS criteria	no CFS criteria	
	(n=57)	(n=14)	(n=43)	
	Mean (sd)	Mean (sd)	Mean (sd)	
Self-efficacy with regard to fatigue				
Self Efficacy Scale	15.3 (3.3)^{bc}	17.4 (3.4)^{a}	17.3 (3.1)^{a}	5.45**
Psychological well-being				
BDI-PC	3.3 (2.6)	4.2 (3.9)	2.3 (2.2)	3.33*[3]
SCL-depression	31.6 (8.0)^{c}	36.9 (10.9)^{c}	26.3 (7.9)^{ab}	9.94**
SCL-anxiety	15.7 (5.0)	19.1 (7.0)	15.2 (5.9)	2.63
SCL-somatisation	29.8 (6.8)^{c}	26.9 (8.0)	22.2 (6.1)^{a}	15.7**
SCL-interpersonal sensitivity	28.1 (7.3)	35.0 (18.1)^{c}	27.0 (9.5)^{b}	3.52*
SCL-obsessive-compulsive behaviour	23.6 (5.4)^{c}	23.9 (8.9)^{c}	16.8 (5.7)^{ab}	17.23**
Sleep				
SCL-sleep	7.22 (3.1)	9.3 (4.1)^{c}	6.3 (2.8)^{b}	4.60*
SOL-general quality of sleep	0.5 (0.3)	0.5 (0.3)	0.6 (0.2)	3.15* [3]
SOL-difficulties falling asleep	0.4 (0.3)^{c}	0.4 (0.3)^{c}	0.2 (0.2)^{ab}	12.13**
SOL-restless sleep	0.3 (0.2)	0.4 (0.2)	0.3 (0.2)	1.98
SOL-early awakenings	0.3 (0.3)^{c}	0.2 (0.2)	0.2 (0.2)^{a}	3.96*
Concentration				
CIS-concentration	27.5 (7.4)^{c}	23.4 (6.0)	19.2 (7.8)^{a}	15.31**
WAIS-symbol digit	52.3 (10.6)	54.1 (12.8)	54.6 (9.7)	0.62

Table 2. continued

	A	B	C	
	CFS patients	Severely fatigued disease-free breast cancer patients	Severely fatigued disease-free breast cancer patients	F- value
		CFS criteria	no CFS criteria	
	(n=57)	(n=14)	(n=43)	
	Mean (sd)	Mean (sd)	Mean (sd)	
Physical activity				
CIS-physical activity	17.5 (3.9)[bc]	13.1 (7.0)[a]	11.7 (5.6)[a]	16.95**
SOL-daily observed activity	4.3 (0.2)[bc]	5.5 (0.5)[a]	5.2 (0.3)[a]	5.43**
Actometer-mean activity score[1]	62.4 (18.0)[c]	71.8 (23.3)	77.5 (22.3)[a]	6.72**
Actometer-peak amplitude[1]	183.0 (29.7)	183.0 (34.0)	192.7 (31.1)	1.19
Actometer-peak duration[2]	136.1 (49.2)[c]	150.0 (53.3)	165.6 (63.5)[a]	3.39**
Actometer-duration rest after peak[2]	89.9 (52.1)	73.7 (38.9)	73.7 (36.4)	1.35
Social support				
SSLI-total	166.2 (23.3)	172.1 (29.1)	166.2 (23.3)	0.32
SSLI-negative interactions	11.2 (3.2)	11.6 (3.8)	10.2 (2.6)	1.97
SSLD-total	51.1 (13.2)	49.3 (14.1)	47.4 (12.7)	0.96
Pain				
SOL-pain	5.8 (3.0)[bc]	3.7 (2.5)[a]	2.9 (2.8)[a]	13.35**
SOL-joint- or muscle pain	2.7 (1.4)[bc]	0.7 (1.1)[a]	0.5 (0.9)[a]	45.39**
SOL-headache	1.3 (1.2)[c]	0.8 (0.9)	0.5 (0.7)[a]	8.84**

** $p<0.01$

* $p<0.05$

[a] significantly different from group A, Bonferroni $p<0.05$

[b] significantly different from group B, Bonferroni $p<0.05$

[c] significantly different from group C, Bonferroni $p<0.05$

1 activity levels are expressed in number of accelerations per 5 minute period

2 peak and rest duration are expressed in minutes

3 in the post-hoc analyses no significant differences were found

CFS patients report the most problems with regard to concentration. Their mean score on the CIS concentration is significantly different from the mean score of severely fatigued disease-free breast cancer patients who do not fulfil the criteria for CFS but not significantly different to the mean score of severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS. This result does not come to the fore on the standardised concentration task (symbol digit WAIS). On this test, all groups have equal scores.

In reference to physical activity, severely fatigued disease-free breast cancer patients are more physically active than CFS patients are. On the self-report instruments, severely fatigued disease-free cancer patients report less problems with regard to activity than CFS patients do. In addition, measured with the actometer, they have a higher mean activity score and a longer peak duration in comparison to CFS patients. Also, the percentage of pervasively passive patients differs between the three groups. About 28% of the patients with CFS can be considered as pervasively passive compared to 23% in the group of severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS and only 8% in the group of severely fatigued disease-free breast cancer patients who do not fulfil the criteria for CFS ($F=9.98$, $p=0.041$). Mean peak amplitude and mean duration of rest after a peak are equal for all groups.

The subscales of the social support list indicate that amount of social support, amount of negative interactions and discrepancies between amount and desired amount of social support are equal for the three different groups.

Finally, concerning daily observed pain, results indicate that severely fatigued disease-free cancer patients experience significantly less pain than CFS patients do. Large differences can be seen as well when looking at the percentage of patients who do not experience pain at all during a period of 12 days. Within the sample of CFS patients, 2% does not experience pain (general), 9% does not experience joint or muscle pain and 5% does not experience a headache at all. For severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS, these percentages are 7%, 43% and 14%, respectively. Finally, for severely fatigued disease-free breast cancer patients who do not fulfil the criteria for CFS, these percentages are 14%, 50% and 33%, respectively ($F=5.77$, $p=0.056$; $F=21.91$, $p<0.001$; $F=13.70$, $p=0.001$).

DISCUSSION

In this study, multidimensional and multimethod assessment indicate that severely fatigued former breast cancer patients differ from CFS patients on certain important aspects. It is important to note that differences were found not only on general self-report questionnaires but also on daily self-report measures and when measured with the actometer. The only measure that did not reveal differences was the standardised concentration task. It should, however, be noticed that this concentration task was done in a laboratory setting. This task has a duration of 90 seconds, so it does not measure the ability to concentrate during a longer period of time. In other words, we cannot draw conclusions about the possible differences between severely fatigued former breast cancer patients and CFS patients with respect to the endurance of the ability to concentrate.

The group that we identified as severely fatigued disease-free breast cancer patients experiences fatigue to a lesser extent than a group of female CFS patients. In addition, the first-mentioned group experiences less limitations in several areas of daily life than the group of CFS patients. Within the group of severely fatigued breast cancer patients, only 25% fulfil criteria for CFS.

Further comparisons indicate that patients with CFS and severely fatigued breast cancer patients score equal on measures of social support. However, both groups experience more negative interactions and a higher discrepancy between the amount of social support and the desired amount of social support in comparison to a group of healthy women[33].

With regard to physical activity, pain and self-efficacy, patients with CFS score more problematic in comparison to severely fatigued breast cancer patients. In reference to sleep and concentration, the subgroup of severely fatigued disease-free breast cancer patients who fulfils the criteria for CFS reports the same amount of problems as CFS patients. However, all three groups score equal on the standardised concentration task (symbol digit). Nevertheless, these scores are significantly lower than mean scores (64.2) of healthy controls[30].

Depression and anxiety are somewhat heightened for severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS in comparison to CFS patients. These differences are, however, not significant, probably due to the small sample size of the severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS. It is possible that these former cancer patients interpret persistent feelings of severe fatigue as a sign of a disease-recurrence, associated with feelings of depression and anxiety and increasing fatigue. In the current group of severely fatigued disease-free breast cancer patients who fulfil the criteria for CFS, 50% had a score on the BDI-PC that is indicative of a clinical depression. In the group of CFS patients, this percentage is lower (35%).

As indicated in the Introduction, the findings of these study are important within the framework of the development of interventions to reduce fatigue. For patients with CFS, cognitive behaviour therapy has proven be to successful in reducing fatigue[14,31,32]. In one of these studies[14], cognitive behaviour therapy was based on a statistically tested model of perpetuating factors in CFS[22]. In this model, focussing on bodily symptoms, low physical activity and low sense of control contribute to increasing severity of fatigue and functional impairment. Cognitive behaviour therapy for patients with CFS is directed at these perpetuating factors.

It is very likely that a model of perpetuating factors for fatigue after treatment for cancer will differ from the CFS model. Based on the results of this current study, depression, sleep and concentration problems could possibly play important roles in this model. Therefore, cognitive behaviour therapy to reduce fatigue after treatment for cancer should also differ in certain aspects from cognitive behaviour therapy as it has been developed for patients with CFS. In addition, because there seem to be larger differences within the group of severely fatigued cancer patients than within the group of CFS patients, cognitive behaviour therapy to reduce fatigue after treatment for cancer should be adapted to each individual ex-cancer patient.

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Chapter 7

Fatigue after treatment for malignant and benign bone and soft tissue tumours

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Journal of Pain and Symptom Management, accepted for publication

ABSTRACT

Fatigue has been mentioned as an important complaint in several groups of disease-free patients after curative treatment for cancer. However, it has never been investigated in a sample of patients who have been treated for a bone or soft tissue tumours in the past. In the current study these patients participated. Measurement included posted questionnaires at baseline and at follow-up (two years later). Baseline results indicate that fatigue is a severe problem for 28 percent of the investigated patients. Percentages were equal for patients who were treated for malignant or benign tumours. Fatigue complaints seem to be most severe for patients who finished treatment relatively recently, and for patients who had to undergo more than one operation. In addition, fatigue is associated with several psychological and physical variables. At follow-up, the majority of all patients who were severely fatigued at baseline continued to be severely fatigued. Severe fatigue at follow-up is predicted by oncological complications after initial treatment, less optimism and more somatisation. It can be concluded that fatigue is an important problem for more than a quarter of a sample of patients who have been treated for a malignant or benign bone or soft tissue tumour in the past.

INTRODUCTION

The number of long-term survivors of bone and soft tissue tumours has gone up in the last decades. Because cancer treatment tends to produce troublesome long-term side effects, quality of life assessment after treatment for bone and soft tissue tumours becomes more important. Although most studies still solely concentrate on oncological and functional results, a few studies have been published recently in which quality of life has been assessed in survivors of bone sarcoma[1-8].

Fatigue is an important aspect of quality of life, which has been mentioned recently in several groups of disease-free patients long after they have finished treatment for cancer[9-19]. However, as far as we know, fatigue has never been investigated in a sample of disease-free patients who were treated for bone and soft tissue tumours. In addition, up till now no longitudinal studies have been published on the course of fatigue after successful treatment for cancer.

In the present prospective longitudinal study we will focus on fatigue complaints in a population of disease-free patients who were treated for bone and soft tissue tumours in the past. This patient population has a few specific characteristics that are different from cancer populations in which post-treatment fatigue complaints have been investigated up till now. First, within this population, patients have been treated for both malignant and benign tumours. It will be of interest to find out whether fatigue complaints differ between these two groups of patients. Second, treatment for these kinds of tumours differs from treatment for other kinds of tumours. Patients more often undergo extensive surgery that often leads to a certain level of physical impairment. In addition, although adjuvant chemotherapy is often utilised in osteo- and Ewing sarcoma, it is not used in chondrosarcoma and benign tumours. Furthermore, radiation therapy is used in soft tissue tumours and Ewing sarcoma but not curative in osteosarcoma or benign tumours. Finally, time since end of treatment varied widely within the investigated patient population. This makes it possible to compare the severity of fatigue complaints for patients who finished treatment relatively recently, versus patients who finished treatment longer ago.

The structure in this article is divided into two parts. In the first part baseline data will be analysed. The following specific research questions will be answered 1) What is the prevalence of fatigue after treatment for malignant and benign bone and soft tissue tumours, 2) Is fatigue severity associated with former disease and treatment characteristics, 3) Are patients who finished treatment relatively recently more severely fatigued than patients who finished treatment longer ago and 4) Is fatigue severity associated with demographic, psychological and/or physical variables?

In the second part we will focus on longitudinal data. In this part we will answer two more questions: 5) What is the course of fatigue during a two year period, and finally 6) Which variables are able to predict severe and heightened fatigue at follow-up?

METHODS

Patients

All patients who finished treatment for a bone or soft tissue tumour (malignant and benign) between 1 and 15 years ago at the University Medical Center Nijmegen were approached for this study. At the time of the study patients had to have a status of 'no evidence of disease' (NED) or 'continuing disease-free' (CDF). Furthermore, they had to be between the age of 18 and 60 at the time of this investigation.

Recruitment procedure

Patients were send a package of questionnaires, together with a letter of their physician, explaining the purpose of the study, and an informed consent form. Patients were asked to fill out the questionnaires and to send them back together with the signed informed consent form, to our medical center. Two years later, all patients who had returned the questionnaires at baseline and still had a status of NED or CDF, were send a second package of questionnaires. The ethics committee of our hospital approved with the study.

Measurement

Fatigue is measured by the Checklist Individual Strength (CIS). This is a 20-item questionnaire, which was designed to measure four aspects of fatigue, namely: fatigue severity (8 items), concentration (5 items), motivation (4 items) and physical activity (3 items)[20,21]. Each item is scored on a 7-point Likert scale. High scores indicate a high level of fatigue, a high level of concentration problems, low motivation and a low level of physical activity. Based on research with Chronic Fatigue Syndrome Patients, a score of 35 or higher on the subscale fatigue severity indicates severe experiences of fatigue[20]. Based on scores of healthy controls, a score between 27 (mean score for healthy adults plus one sd) and 35 indicates heightened experience of fatigue[21,22].

Psychological well-being is measured by the Symptom Checklist-90 (SCL-90)[23]. This 90-item indicator of psychopathology screens for anxiety, agoraphobia, depression, somatisation, obsessive-compulsive behaviour, interpersonal sensitivity, hostility and sleep disturbances.

Physical limitations are measured by the subscale physical functioning of the RAND-36[24,25]. This subscale consists of 10 items on 3-point Likert scale. Scores range from 0 to 100. Persons with lower scores are more severely limited with respect to physical functioning.

Optimism is measured by the Life Orientation Test (LOT)[26,27]. This questionnaire is a measure of dispositional optimism. It consists of 8 items (plus 4 filler items). The higher the scores, the more optimistic (range 0-32).

Quality of life is measured by the Quality of Life Questionnaire of the European Organisation for research and treatment of cancer (EORTC QLQ-C30)[28]. The content areas covered by this questionnaire reflect the multi-dimensionality of the quality of life construct. For this study, the five functional scales (physical-, role-, cognitive-, emotional-, and social functioning), and a general health status scale were used. Higher scores represent higher functioning and quality of life (range 0-100).

Acceptance of the experience of cancer is measured by the Cancer Acceptance Scale (CAS), a questionnaire of 7 statements (1 not at all applicable, 2 not applicable, 3 applicable, 4 very applicable). These statements are 1) I find it hard to believe that I had a bone tumour, 2) I often think back to the time that I had a bone tumour, 3) Treatment for my bone tumour has changed my life in a negative way, 4) I am worried about a tumour relapse, 5) I am angry about what happened to me 6) I am anxious about my health, 7) I am not able to forget about the period that I was treated for a bone tumour. A total score can be derived (range 7 to 28). High scores are indicative of low acceptance. Internal consistency is good (Chronbach's alpha=0.85).

Statistical analysis

Data analysis was performed using SPSS (version 8.0). Descriptive statistics have been used for description of the sample. T-tests, Chi-square and GLM-general factorial have been performed testing differences between groups. Pearson correlation analyses have been used to test the association between fatigue severity and demographic, psychological and/or physical variables. Finally, in order to examine the contribution of psychological-, physical- and disease- and treatment related variables to severe and heightened fatigue two years later, logistic regression was performed.

RESULTS

Description of the sample

We sent a package of questionnaires to 226 patients. The questionnaires were filled out and returned by 170 patients (75%). From these 170 patients 99 were treated for a benign tumour and 71 for a malignant tumour.

Two years later, the second package of questionnaires was send to 155 of these 170 patients (15 did no longer have the status of NED or CDF). Hundred and thirteen of these 155 patients returned the questionnaires (73%), from which 63 were treated for a benign tumour and 50 for a malignant tumour. Demographic characteristics of the sample are listed in Table 1. Patients treated for a benign tumour are significantly younger, and significantly less often receive disablement insurance act. Probably because of these differences, they are less often married, have received higher education and more often work outside the house.

Part 1 baseline measurement

1) What is the prevalence of severe fatigue after treatment for malignant and benign bone and soft tissue tumours?

The mean CIS-fatigue severity score of the total sample is 26.3 (sd=14.4). Forty-eight patients (28%) meet the cut-off criteria for severe fatigue (i.e., CIS-fatigue>= 35) while an additional 30 patients (18%) have heightened fatigue scores (i.e., CIS-fatigue between 27 and 35). Fatigue scores are not significantly different for patients treated for malignant and benign tumours. Patients who were treated for a malignant tumour have a CIS-fatigue score of 26.8 (sd=14.0). For patients who were treated for a benign tumour this score is 25.9 (sd=14.7). Percentages of patients with severe fatigue are respectively 27 and 29.

Table 1. Demographic characteristics

	Benign (n=99)	Malignant (n=71)	p-value
Gender	52 male (53%)	38 male (54%)	0.899
Age	34[*]	43[**]	<0.001
Married	57 (58%)	49 (70%)	0.032
Education (1=low; 7=high)	4.2	3.5	0.014
Work outside the home	67%	45%	0.005
Household work	12%	17%	0.340
Studying	19%	13%	0.282
Disablement insurance act	8%	29%	0.001

[*] sd=13, range=18-62, 68% <40 years

[**] sd=15, range=18-65, 39% <40 years

Table 2. Mean baseline CIS-fatigue scores and percentages of severe fatigue for different tumour types

	n	Mean CIS-fatigue baseline (sd)	% severe fatigue
Malignant tumours			
grades 1,2 chondrosarcoma (lgM)*	34	26.6 (14.6)	26
classical Osteosarcoma (hgM)	9	25.7 (10.0)	22
ewing's sarcoma (hgM)	7	24.4 (15.9)	29
synovial sarcoma (hgM)	6	29.2 (13.3)	17
other[1]	15	29.1 (15.2)	33
Benign tumours			
aneurysmal Bone Cyst	20	24.2 (15.3)	30
aggressive Enchondroma	15	33.7 (16.0)	53
giant cell tumour	14	23.5 (13.3)	21
osteoid osteoma	10	23.9 (15.2)	20
exostosis	9	21.9 (11.2)	11
chondroblastoma	6	25.8 (14.5)	17
fibrous dysplasia	6	18.7 (..8.5)	0
bone cyst	6	22.2 (18.5)	33
other[2]	13	29.9 (15.22)	46

[1] chordoma (n=2), lymphoma (n=2), grades 1,2 fibrosarcoma (n=1), clear cell chondrosarcoma (n=1), parosteal osteosarcoma (n=1), plasmacytoma (n=1), malignant schwannoma of bone (n=1), none bone tumour meta (n=1), liposarcoma (n=1), malignant fibrous histiocytoma (n=1), high grade hemangioendothelioma (n=1), hemangiopericytoma (n=1), malignant mesenchymoma (n=1)

[2] fibromatosis (n=3), osteoblastoma (n=2), histiocytic fibroma (n=1), chondroma (n=1),hemangioma (n=1), histiocytosis (n=1), schwannoma of bone (n=1), desmoid tumour (n=1), epithelioid hemangioma (n=1), neurofybroma (n=1)

* results on functional outcome according to the MSTS functional scoring system (Enneking, 1993) of this group of patients are reported in van de Geest et al., Journal of Surgical Oncology[31].

2) Is fatigue severity associated with former disease and treatment characteristics?
Mean fatigue severity scores and percentages of severe fatigue for the different diagnoses (only those with n>=5) are given in Table 2. Within the group of patients who were treated for malignant tumours mean fatigue severity scores range from 24.4 to 29.2. Within the benign tumours, mean fatigue scores range from 18.7 to 33.7. The highest mean fatigue score was in the group of patients who were treated for aggressive enchondroma (Enneking stage 3).

The association between post-treatment fatigue and the area of operation has been investigated. Three subgroups were identified: lower girdle (n=100; 24 hip, 66 knee, 10 ankle), upper girdle (n=39; 29 shoulder, 10 elbow) and axial skeleton (n=31; 21 pelvis, 10 spine). Within these three groups, mean fatigue scores are respectively 26.8 (sd=14.8), 23.6 (sd=14.4) and 27.8 (sd=12.9) (GLM-general factorial, p<0.406).

To analyse the association between post-treatment fatigue and the number of former operations, the group was divided into two groups, those who underwent only one operation (n=126), and those who had to undergo two or more operations (n=44). Mean baseline fatigue scores of these two groups are respectively 24.9 (sd=14.2) and 29.8 (sd=14.3). The relation between post-treatment fatigue and number of former operations almost reached significance (t-test, p<0.053). Percentages of severe fatigue for the two groups mentioned above are respectively 24 and 41 (Chi- square, p<0.034).

Table 3. The association between fatigue and type of procedure (t-tests)

	Yes		**No**		**p-value**
	n	mean CIS-fatigue baseline (SD)	n	mean CIS-fatigue baseline (SD)	
Procedure					
inc. biopsy	107	27.4 (14.6)	63	24.3 (13.8)	0.185
exc. biopsy	10	29.3 (15.9)	160	26.0 (14.3)	0.488
needle biopsy	1	-	169	-	-
curettage	74	26.9 (15.5)	96	25.7 (13.5)	0.625
debulking	5	22.6 (14.1)	165	26.3 (14.4)	0.567
en bloc resec.	81	26.1 (13.2)	89	26.4 (15.4)	0.889
amputation	9	21.9 (10.1)	161	26.5 (14.6)	0.352
mod amputation	1	-	169	-	-
cryosurgery	78	27.3 (15.0)	92	25.3 (13.9)	0.355
exploration	3	27.0 (15.6)	167	26.2 (14.4)	0.926
thoracotomy	5	28.2 (14.1)	165	26.2 (14.4)	0.757
osteosynthesis	16	29.9 (11.8)	154	25.9 (14.6)	0.280
cementation	2	14.5 (2.12)	168	26.4 (14.4)	0.246

To test the association between post-treatment fatigue on one hand and type of procedure during treatment on the other hand, several t-tests were performed. In all t-tests the dependent variable was the CIS-fatigue score at baseline. Independent variables were the different procedures. None of the t-test revealed significant differences in fatigue severity between those patients who underwent a certain procedure, and those who did not undergo that certain procedure (Table 3).

The association between post-treatment fatigue and former adjuvant therapy has been tested with a t-test. Dependent variable was the CIS-fatigue at baseline. Independent variable was former adjuvant therapy (no adjuvant therapy (n=145) versus adjuvant therapy (n=25; 6 radiotherapy, 13 chemotherapy and 6 both radiotherapy and chemotherapy). Mean baseline fatigue scores for these two groups are respectively 26.0 (sd=14.6) and 27.4 (sd=13.2). Results indicate that there is no effect of adjuvant therapy on the severity of fatigue (t-test, p<0.673).

Finally, we investigated the association between post-treatment fatigue and the prevalence of oncological complications after initial treatment. The total sample has been divided into two groups, those who did not have any oncological complications after initial treatment (n=146) and those who did have any oncological complications after initial treatment (n=24; 11 local recurrence, 9 residual tumour, 3 lung metastases and 1 node metastases). Mean baseline fatigue scores for these two groups are respectively 25.8 (sd=14.4) and 28.8 (sd=14.2) (t-test, p<0.348). Percentages of severe fatigue are respectively 27 and 38 (chi-square, p<0.277).

3) Are patients who finished treatment relatively recently more severely fatigued than patients who finished treatment longer ago?

The total sample has been divided into six groups: patients who finished treatment between 1 and 2 year ago (n=28), between 2 and 3 years ago (n=38), between 3 and 4 years ago (n=22), between 4 and 5 years ago (n=19), between 5 and 10 years ago (n=46) and more than 10 years ago (n=17). Mean baseline fatigue scores (sd) and percentages of severe fatigue for these six groups are shown in Table 4.

Table 4. Mean CIS-fatigue scores and percentages of fatigue for patients who finished treatment within a different time period

	Mean CIS-fatigue (sd)	% of severe fatigue
Patients who finished treatment …		
… between 1 and 2 year ago (n=28)	31.6 (15.5)	43
… between 2 and 3 years ago (n=38)	27.1 (15.4)	34
… between 3 and 4 years ago (n=22)	22.5 (15.0)	18
… between 4 and 5 years ago (n=19)	25.3 (13.0)	21
… between 5 and 10 years ago (n=46)	26.7 (13.2)	26
… more than 10 years ago (n=17)	20.1 (11.9)	18

Table 5. Correlations between fatigue severity (CIS-fatigue baseline) and demographic, psychological and physical factors

	Pearson correlation	p-value
Age	-0.009	0.912
Gender	0.017	0.830
Education	-0.052	0.509
Psychological well-being (SCL)		
depression	0.550	<0.001
anxiety	0.441	<0.001
somatisation	0.561	<0.001
agoraphobia	0.305	<0.001
obsessive-compulsive behaviour	0.430	<0.001
interpersonal sensitivity	0.364	<0.001
hostility	0.343	<0.001
sleep disturbances	0.276	<0.001
Physical functioning (RAND)	-0.393	<0.001
Optimism (LOT)	-0.398	<0.001
Quality of life (EORTC QLQ-C30)		
emotional functioning	-0.629	<0.001
physical functioning	-0.409	<0.001
role functioning	-0.417	<0.001
cognitive functioning	-0.319	<0.001
social functioning	-0.469	<0.001
general health status	-0.687	<0.001
Acceptance	0.337	<0.001

Statistical analyses indicate that there are no significant differences in mean fatigue scores (GLM-general factorial, $p<0.110$) and in percentages of severe fatigue (Chi-square $p<0.283$). However, results indicate that patients who finished treatment between one and two years ago are more severely fatigued than the rest of the patients (t-test, 31.6 (15.5) versus 25.2 (13.9), $p<0.029$). In addition, the correlation between the CIS fatigue score and time since treatment is -.146, and almost reaches significance ($p<0.057$).

4) Is fatigue severity associated with demographic, psychological and/or physical variables?

Fatigue severity is not correlated with age, gender or education. On the other hand, fatigue severity is negatively correlated with psychological well-being, physical well-being, optimism, quality of life and acceptance (Table 5).

Part 2 follow-up measurement

5) What is the course of fatigue during a two year period?

At follow-up CIS-fatigue severity score of the total sample is 25.7 (13.9). Twenty-six percent of all patients meet the cut-off criteria for severe fatigue (i.e., CIS-fatigue>=35) while an additional 16 percent experiences heightened fatigue (i.e., CIS-fatigue between 27 and 35). In accordance with baseline results, fatigue scores at follow-up are not significantly different for patients treated for malignant (CIS-fatigue=25.8 (sd=13.6)) and benign tumours (CIS-fatigue=25.1 (sd=13.9)).

The correlation between baseline and follow-up CIS-fatigue scores is 0.72 (p <0.01) for the whole sample. From the 48 patients who were identified as severely fatigued at baseline, 30 percent (n=14) is missing at second measurement. From the other 34 patients, 65 percent (n=22) is still identified as severely fatigued at follow-up. Thirty-five percent (n=12) is not severely fatigued anymore at second measurement. However, within this group that is not severely fatigued anymore at second measurement, 58 percent (n=7) still experiences heightened fatigue in comparison to healthy adults.

In addition, from the 122 patients who were identified as non-severely fatigued at baseline, 37 percent (n=45) is missing at second measurement. From the other 77 patients, 91 percent (n=70) is also identified as non-severely fatigued at follow-up, while 9 percent (n=7) has become severely fatigued at second measurement.

6) Which variables are able to predict severe fatigue and heightened fatigue at follow-up?

Two logistic regression analyses were performed. One with severe fatigue (CIS-fatigue>=35 versus CIS-fatigue<35), the other with heightened fatigue (CIS-fatigue>=27 versus CIS-fatigue<27) at follow-up as dependent variables. As predictors were entered the following disease and treatment characteristics: number of operations, adjuvant therapy (yes/no), number of oncological complications and time since treatment (in days). Also were entered the following baseline psychological and physical variables: Physical functioning (RAND), optimism (LOT) and acceptance (CAS). In addition, depression and somatisation (SCL) were entered to represent the construct of psychological well-being. Finally, general health status (EORTC QLQ-C30) was entered to represent the quality of life area. We have chosen for these specific subscales of the SCL and the EORTC QLQ-C30 because of their high correlations with the CIS-fatigue score at baseline (Table 5).

Results indicate severe fatigue at follow-up is predicted by more oncological complications after initial treatment, more somatisation and less optimism (Table 6). Heightened fatigue is predicted by the same variables, but also by lower general health status and less acceptance of the experience with a bone or soft tissue tumour.

Table 6. Logistic regression analysis (enter) to predict severe and heightened fatigue at follow-up

	Dependant variables (follow-up):			
	severe fatigue		heightened fatigue	
	Beta	p-value	Beta	p-value
Independent variables (baseline)				
former adjuvant therapy	-0.562	0.497	-0.158	0.868
number of operations	-0.931	0.154	-1.209	0.113
number of onc. complications	2.010	0.032	2.310	0.044
time since treatment	0.000	0.515	0.000	0.219
general health status (EORTC QLQ-C30)	-0.027	0.193	-0.101	0.001
physical functioning (RAND)	-0.001	0.473	-0.011	0.481
optimism (LOT)	-0.207	0.009	-0.259	0.003
acceptance (CAS)	-0.120	0.111	-0.197	0.015
depression (SCL)	0.002	0.978	-0.065	0.314
somatisation (SCL)	0.189	0.002	0.250	<0.001

DISCUSSION

In this study we found that about one third (28%) of a population of survivors of a bone or soft tissue tumour can be considered as severely fatigued long (mean=3.3 years) after they have finished treatment. This percentage is considerably higher than the prevalence of fatigue in a control group of persons without a cancer history (11%)[22]. Furthermore, this percentage is about equal to percentages of fatigue in several samples of cancer survivors, as reported in the literature. In a sample of Hodgkin's survivors 26% had substantial fatigue for 6 months or longer. This percentage was significantly higher than the percentage of 11 found among 2,214 controls representative of the general Norwegian population[18]. Within a sample of breast cancer survivors, 30 percent did report heightened levels of fatigue relative to women in the general population[16]. In another sample of breast cancer survivors, this percentage is even 38 percent[22]. Finally, in mixed samples of former cancer patients, 30% experiences fatigue on a daily basis[19], and 29% experiences heightened fatigue complaints in comparison to adults without a cancer history[17].

Surprisingly, we did not find any differences in fatigue scores between patients who were treated for a malignant or a benign tumour in the past. However, we found that patients who were treated for a malignant tumour were less often working outside their homes and did more often receive disablement insurance act than patients who were treated for a benign tumour. In addition, we also found differences in physical functioning (measured with the RAND and the EORTC QLQ-C30) between patients who were treated for malignant tumours and benign tumours. Patients in the malignant group experience significant more physical limitations than patients who were treated for benign tumours. Finally, patients in the malignant group also score significantly more problematic on the statement 'treatment for my bone tumour has changed my life in a negative way'.

On second thought, the similarity between fatigue scores of patients who were treated for malignant or benign tumour might thus be explained by the absence of work-related challenges that require either physical endurance, motivation or the ability to concentrate. It could be that not-working patients perceive themselves as less fatigued because they are not confronted with the consequences of their severe fatigue complaints in their jobs.

Furthermore, fatigue scores did not differ considerably between groups of patients with various diagnoses, with the exception of patients who were treated for aggressive enchondroma. A strikingly high fatigue severity score was found in this group. An explanation for this high fatigue score might be due to the fact that patients who are treated for aggressive enchondroma score significantly higher on the statements 'I am worried about a tumour relapse' ($p<0.01$) and 'I am anxious about my health' ($p<0.05$) than patients treated for other diagnoses. This may be explained by the fact that these patients know that although the chance of a relapse is low, it will most probably occur after a long observation period (5-10 years). None of the 15 aggressive enchondroma patients had experienced a recurrence after initial treatment, at the time of this study. Another possible explanation for the high fatigue severity within this group of former aggressive enchondroma patients could be that these patients finished treatment significantly less long ago (2.7 years) than the rest of the patients (4.9 years) ($p<0.001$).

One could think that the high fatigue severity scores within the group of aggressive enchondroma patients could be the reason why we failed to find a difference in fatigue severity between patients who were treated for a malignant tumour and patients who were treated for a benign tumour. However, this is not the case. When patients with aggressive enchondroma are excluded in the analysis, the mean CIS-fatigue score for patients with benign tumours is 24.3 (sd=14.1) and the mean CIS-fatigue score for patients with malignant tumours is 27.0 (sd=13.9) (t-test, $p<0.226$).

Except for the number of operations, no relations were found between post-treatment fatigue and former treatment. This result is consistent with results in the literature[29]. However, it is important to note that some of these negative results might be explained by small numbers of patients in several analyses. In addition, there is a trend for patients who did have oncological complications after initial treatment versus those who did not have oncological complications. The first group seems to experience more severe fatigue. In addition, results indicate that patients who finished treatment between 1 and 2 years ago experience more severe fatigue than patients for whom this was already longer ago.

It is important to note that the variables mentioned above are related to each other. Not surprisingly there is a high correlation between the number of oncological complications and the amount of operations (0.424, $p<0.001$). Furthermore, there is a moderate correlation between the amount of operations and time since last treatment (-0.219, $p<0.004$). This is why certain results are not always unambiguous to interpret. For instance, we concluded that patients who underwent only one operation experience less severe fatigue than those patients who had to undergo two or more operations. However, further analysis indicates that these groups also differ significantly with regard to time since treatment. For patients who underwent only one operation, time since treatment was 1867 days versus 1298 days for patients who had to undergo two or more operations (t-test, $p<0.005$).

Results with regard to the association between fatigue severity and psychological and physical variables indicate that fatigue is negatively correlated to psychological well-being, physical well-being, optimism, quality of life and acceptance. Highest correlations are found between fatigue and depression, somatisation, emotional functioning and general health status. These results are also similar to results found in various other studies in which these relations have been investigated in samples of disease-free cancer patients[29].

Finally, an important characteristic of this study is its longitudinal design. This enables us to discuss the course of fatigue and the perpetuating factors of fatigue. Results from this study indicate that fatigue complaints are more or less stable. Mean fatigue scores and percentages of severe fatigue and heightened fatigue of the total sample are about equal at baseline and follow-up. In addition, the majority of the patients who were identified as severely fatigued at baseline are still severely fatigue two years later. In our opinion the stability in fatigue complaints is due to the fact that the majority of patients were not in the first years after the completion of treatment anymore. Literature study shows that up to 99 percent of all cancer patients have to deal with some degree of fatigue during their treatment. We think that fatigue complaints wear off during the first years after treatment. For patients that still experience severe fatigue about 3 years later, there is a good chance that they continue to experience severe fatigue. Evidence for this early decrease in the fatigue incidence is found in the current study. As indicated above, patients who had finished treatment between one to two years prior to the study were significantly more severely fatigued than patients who had finished treatment considerably earlier.

With regard to these results, one could expect that those patients that are not severely fatigued anymore at follow-up, are patients who finished treatment only a short time ago. Analyses indicate that patients who were both severely fatigued at baseline and at follow-up, finished treatment 4.8 (sd=3.3) years ago, while patients who were severely fatigued at baseline, but not anymore at follow-up finished treatment 3.7 (sd=2.7) years ago. However, this difference does not reach significance (t-test, $p<0.341$).

With respect to the perpetuating factors of fatigue, severe fatigue seems to be predicted by more oncological complications after initial treatment for a bone or soft tissue tumour, less optimism and more somatisation (a high tendency to focus on bodily symptoms. These findings are important with respect to the development of interventions to reduce fatigue. For patients with Chronic Fatigue Syndrome (CFS), cognitive behaviour therapy has proven to be successful in reducing fatigue complaints[30,31]. In one of these studies[31], cognitive behaviour therapy was based on a statistically tested model of perpetuating factors in CFS[32]. In this model focussing on bodily symptoms, low physical activity, and low sense of control contributed to increasing severity of fatigue. Based on the results of the current study we might expect that, similar to the model for CFS patients, a strong focus on bodily symptoms might play a role in a model for severely fatigued survivors of bone and soft tissue tumours. In addition, oncological complications and low optimism may be other important perpetuating factors.

In summary, results from this study indicate that fatigue is a severe problem for more than a quarter of a sample of patients who were treated for malignant or benign bone and soft-tissue tumours in the past. Fatigue complaints seem to be most severe for patients who finished treatment only 1 to 2 years ago, and for patients who had to undergo more than one operation. Fatigue is not related to other former treatment modalities and demographic variables. Furthermore, it is associated with several psychological and physical variables. Finally, fatigue severity at follow-up is predicted by oncological complications after initial treatment, less optimism and more somatisation.

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Chapter 8

The course of severe fatigue in disease-free breast cancer patients

a longitudinal study

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Submitted for publication

ABSTRACT

In a previous cross-sectional study we concluded that severe fatigue was a problem for nearly 40 percent of a sample of disease-free breast cancer patients[1]. In the present article we report the results of a follow-up study. We investigated whether fatigue is a persistent problem, and whether persistent fatigue is related to former treatment modalities. In addition, we studied the predictors of persistent fatigue.

At baseline and at follow-up (two years later) patients were asked to fill out several computerised questionnaires on psychological, physical, social, cognitive and behavioural aspects and to perform two standardised tests to assess neuropsychological functioning. In addition they were asked to fill out a daily Self Observation List and to wear an actometer during a period of 12 days. During the two years in between patients were asked to fill out a fatigue questionnaire (CIS-fatigue) at the end of every month.

Results indicate that twenty-four percent of the disease-free breast cancer patients experienced persistent severe fatigue complaints during the two year observation period. Persistent fatigue seemed to be related to the duration of former treatment but unrelated to type of surgery, type of adjuvant therapy and time since treatment finished. High anxiety, high impairment in role functioning and low sense of control over fatigue symptoms at baseline were predictors of persistent fatigue.

We conclude that fatigue is a persistent problem for a quarter of a sample of disease-free breast cancer patients. It is important to be aware of the predictors of persistent fatigue.

INTRODUCTION

Based on many cross-sectional studies, we may conclude that fatigue is a frequent complaint in former cancer patients even up to ten years after successful treatment for cancer[2-9]. So far, the only longitudinal studies that have been published focussed on fatigue complaints in cancer patients while they were undergoing active treatment for cancer[10,12,13] and in the year after completion of treatment[11,14-16] Up until now, no longitudinal studies have been performed in which fatigue is examined over a longer period of time in cancer survivors.

In one of our previous publications we investigated and discussed the prevalence and correlates of severe fatigue in a group of disease-free breast cancer patients[1]. Results indicated that severe fatigue was a problem for nearly 40 percent of a sample of 150 breast cancer survivors who completed cancer treatment a mean of 29 months earlier, compared to 11% in a matched sample of women without a cancer history. In addition, severe fatigue appeared to be negatively related to psychological well-being, physical activity, neuropsychological functioning, social functioning, social support and self-efficacy. Furthermore, fatigue was positively related to functional impairment, sleep disturbances, and causal attributions.

The present study focuses on the follow-up of the same cohort of women during a two-year period. In this article we will answer three questions:

1. Is severe fatigue a persistent problem in disease-free breast cancer patients long after treatment for cancer?
2. Is persistent fatigue related to former treatment modalities?
3. To what extent are psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions able to predict persistent fatigue?

Furthermore, we will exploratory describe the course of fatigue for those patients that had a disease recurrence during the two years of our study.

METHODS

Sample

A relative homogeneous group of patients was selected for this study. All patients had to be treated according to the protocol of the Comprehensive Cancer Center East for premenopausal breast cancer patients. Furthermore, they had to be younger than 50 by the time of primary diagnosis and had to have completed treatment for breast cancer a minimum of 6 months and a maximum of 60 months before. Finally, they had to have no evidence of disease recurrence at the beginning of this study. During the two years of this study patients went to their own oncologist for medical follow-up. Patients that were found to have a disease recurrence during this two-year follow-up period dropped out of the study.

Recruitment procedure

Patients were recruited from one university hospital and 6 regional hospitals. At the university hospital and three regional hospitals, all patients who met the eligibility criteria were initially informed about the study by mail with an introductory letter from their oncologist. At the other three regional hospitals, patients were informed by their oncologist during control-visits. In the following week, patients were contacted by telephone by the psychologist-researcher (P.S.). Those patients who agreed to take part in the study were invited to the department of Medical Psychology of the University Hospital Nijmegen. Two years later, all patients that were still disease-free were invited to the department again for follow-up assessment. The ethics committee of all participating hospitals agreed with this study.

Measurement

At baseline and at the end of the study we investigated fatigue severity, psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions by validated questionnaires. Furthermore, patients performed two standardised tests to assess neuropsychological functioning. In addition, they were asked to fill out a daily Self Observation List and to wear an actometer during a period of 12 days at home. Finally, patients were asked to fill out a fatigue questionnaire (Checklist Individual Strength) at the end of every month, during the two-year period between baseline and follow-up assessment.

All measures are mentioned below. The fatigue scales and the measures that are not standard are extensively described. For a more detailed description of the other measures we refer to the articles in which the baseline data of the present study are described[1,17].

Fatigue severity has been measured by the fatigue severity subscale (CIS-fatigue) of the Checklist Individual Strength (CIS)[18]. The CIS is a 20-item questionnaire which was designed to measure four aspects of fatigue during the last two weeks, namely: fatigue severity (8 items), concentration (5 items), motivation (4 items) and physical activity (3 items). Each item is scored on a 7-point Likert scale. High scores indicate a high level of fatigue, a high level of concentration problems, low motivation and a low level of physical activity. Based on research with Chronic Fatigue Syndrome Patients, a score of 35 or higher on the subscale fatigue severity indicates severe feelings of fatigue[18]. Based on scores of healthy controls, a score between 27 (mean score for healthy adults plus one SD) and 35 indicates heightened experience of fatigue[20]. In addition fatigue has been measured with the Daily Observed Fatigue score (DOF) of the Self Observation List[19]. Daily Observed Fatigue is reported four times a day on a 5-point scale (0-4). Total scores range from 0 to 16.

Because patients filled out the CIS at the end of every months during the two years of our study we calculated a mean CIS-fatigue score over 24 months, which we refer to as the 'persistent fatigue score'. Patients with a persistent fatigue score of 35 or higher are referred to as persistently severely fatigued.

Psychological well-being has been measured with the Beck Depression Inventory for primary care (BDI-pc)[21], the Spielberger Trait Anxiety Inventory (STAI)[22,23] and the Rosenberg Self Esteem Scale (RSE)[24]. Furthermore, the anxiety, agoraphobia, depression, somatisation, interpersonal sensitivity and hostility subscales of the Symptom Checklist (SCL-90) were used[25]. Finally, the emotional functioning subscale of the Quality of Life Questionnaire-C30 of the European Organisation for Research and Treatment of Cancer (QLQ-C30) was included[26].

Functional impairment has been measured with the subscales home management, work, and recreation and pastimes from the Sickness Impact Profile (SIP)[27]. Furthermore, the role functioning subscale of the QLQ-C30 was used. In addition, hours of work (outside the home and household activities) are registered in the Self Observation List.

Sleep disturbances have been measured with the Groninger Sleep Quality Scale (GSQS)[28]. In the present study we decided to delete two items because these items strongly overlap with fatigue complaints (GSQS-2). Furthermore, the sleep/rest subscale of the SIP and the sleep subscale of the SCL were used. Finally, quality of sleep (general quality of sleep, difficulties falling asleep, restless sleep and early awakenings) is registered daily in the Self Observation List.

Physical activity has been measured with the physical functioning subscale of the QLQ-C30, the physical activity subscale of the CIS, and the mobility and ambulation subscales of the SIP. In addition, physical activity is registered once a day in the Self Observation List. Finally, actual physical activity has been measured with the actometer[29,30]. This is an apparatus about the size of a matchbox that was worn around the ankle both day and night during a 12-day period. Specialised software was used to calculate several parameters. A general physical activity score reflected the physical activity level over the 12-day period and was expressed as the average number of accelerations per 5-minute period. Furthermore, the program calculated the 10 largest activity peaks. Both the average peak duration of these 10 largest peaks, and the average duration of rest periods after these 10 largest peaks were calculated.

Neuropsychological functioning has been measured with the cognitive functioning subscale of the QLQ-C30, the concentration subscale of the CIS and the alertness behaviour subscale of the SIP. Furthermore, actual neuropsychological functioning is measured by the Complex Reaction Time task (CRT)[31] and the Symbol Digit subtest of the WAIS[32].

Social functioning and Social support have been measured with the social functioning subscale of the QLQ-C30, the social interaction subscale of the SIP and the van Sonderen Social Support Inventory (SSL)[33].

Self-efficacy has been measured with the subscale internal locus of control of the Multidimensional Health Locus of Control (MHLC)[34,35] and the Self Efficacy Questionnaire (SEQ)[36]. The SEQ consists of five questions that measure sense of control with respect to fatigue complaints. A total score ranges from 5 to 25, a higher score reflecting more sense of control. Cronbach's alpha coefficients range from 0.70 to 0.77[36,37,40].

Causal attributions with regard to fatigue complaints have been measured with the Causal Attribution List (CAL). This questionnaire consists of 9 items divided over two subscales, psychological (e.g. ruminate, sleep problems) and breast cancer related attributions (e.g. surgery for breast cancer, adjuvant therapy for breast cancer). For each item, patients were asked to indicate their opinion regarding the cause of their fatigue complaints on a 4 point scale (1 very applicable to 4 not at all applicable). Internal reliability of this questionnaire is good. The subscales psychological- and breast cancer related attributions respectively have alpha's of 0.81 and 0.79.

Statistical analysis

Data analysis was performed using SPSS (version 8.0). Paired sample T-tests were performed to analyse differences between baseline and follow-up percentages of severe fatigue. Pearson correlation was used to analyse the relation between fatigue at baseline and at follow-up. In addition, it was used to analyse the relation between the persistent fatigue score and the baseline measures. T-tests, and general linear model (GLM)- general factorial have been performed to test differences between groups. Finally, in order to examine the contribution of the baseline measures to persistent fatigue, linear regression analyses (enter-method) were performed.

RESULTS

Description of the sample

At baseline, 150 disease-free breast cancer patients participated in this study. Numbers and reasons for non-participation have been described in our previous publication[1]. From these 150 participating patients, 10 patients dropped out for several reasons during the 2-year period of this study (e.g. taking part in research takes too much time, family circumstances). Furthermore, 19 women had a disease recurrence during the 2-year period. Hundred-twenty-one patients thus completed the study. Compliance with respect to the completion of the monthly fatigue questionnaires was high. Fifty-six percent of the patients returned all 24 monthly questionnaires. Twenty-seven percent of the patients returned 20 to 23 questionnaires, and 17 percent returned 16 to 19 questionnaires.

Information on baseline demographic and medical characteristics of the patients can be found in Table 1. A division has been made between those women who stayed disease-free, those who had a disease recurrence during our study and those who dropped out for other reasons. The only significant difference between the three groups is that the first group is older than the third group.

Table 1. Baseline demographic characteristics and medical characteristics

	Disease-free breast cancer patients		**Drop-outs because of a tumour relapse**		**Drop-outs for other reasons**	
	(n=121)		**(n=19)**		**(n=10)**	
Mean age*	46.7	(5.9)	43.3	(6.2)	41.8	(8.3)
Marital status						
married	106	88%	16	84%	8	80%
unmarried	4	3%	2	11%	1	10%
divorced	8	7%	1	5%	1	10%
widowed	3	2%	-		-	
Higher education (>= 12 years)	45	37%	8	42%	4	40%
Employment						
paid work outside home	75	62%	10	53%	7	70%
home management	106	88%	15	79%	7	70%
disablement insurance act	15	12%	1	5%	2	20%
Surgery						
mastectomy	78	65%	12	63%	5	50%
lumpectomy	43	35%	7	37%	5	50%
Adjuvant therapy						
no adjuvant therapy	18	15%	1	6%	-	
only radiotherapy	24	20%	5	26%	2	20%
only chemotherapy	28	23%	4	21%	1	10%
radiotherapy and chemotherapy	51	42%	9	47%	7	70%
Duration of treatment (months)*,[1]	6	(3)	6	(3)	6	(2)
< 1 month	16	13%	-		2	20%
> 1 month, < 6 months	38	32%	12	63%	5	50%
> 6 months	67	55%	7	37%	3	3%
Time since treatment (months)*,[2]	30	(18)	25	(13)	26	(18)
between 6-12 months ago	12	10%	2	11%	1	10%
between 13-24 months ago	44	36%	10	52%	4	40%
between 25-36 months ago	26	22%	3	16%	1	10%
between 37-48 months ago	17	14%	3	16%	3	30%
between 49-60 months ago	11	9%	-		1	10%
more than 60 months ago	11	9%	1	5%	-	

data are numbers and percentages of participants or * mean (sd).

[1] defined as the period from the time of surgery until the end of adjuvant therapy.

[2] defined as the period from the end of adjuvant therapy until the day of participation in the current study.

Research questions

Is severe fatigue a persistent problem in disease-free breast cancer patients long after treatment for cancer?

For the total group of disease-free breast cancer patients the mean CIS-fatigue score at baseline was 28.9 (sd=13.5), and at follow-up 25.0 (sd=13.2) (paired sample T-test, $p<0.001$). The mean Daily Observed Fatigue score (DOF) at baseline was 2.9 (sd=2.2) and 2.9 (sd=2.5) at follow-up. The correlation between baseline and follow-up CIS-fatigue scores is 0.65 ($p<0.01$) and 0.73 ($p<0.01$) between baseline and follow-up DOF scores. Both the mean baseline and follow-up CIS-fatigue and DOF scores are significantly higher than the mean scores of healthy women without a cancer history (CIS-fatigue 19.4 (sd=11.0); DOF 1.6 (sd=1.3))[1].

The number of severely fatigued disease-free breast cancer patients was 47 (39%) at baseline. In addition, 21 patients (17%) experienced heightened fatigue. At follow-up, the number of severely fatigued patients was 28 (23%) and 26 patients experienced heightened fatigue (22%). The percentage of women who experienced heightened or severe fatigue had thus decreased from 56 to 45 percent (paired sample T-test, $p<0.01$).

In the left part of Table 2 we indicated the number (and percentages) of patients that were classified as severely, heightened or not fatigued at follow up, on basis of their classification as severely, heightened or not fatigued at baseline. Most important is the results that almost half of the patients (49%) that were identified as severely fatigued at baseline were also identified as severely fatigued at follow-up.

Table 2. Numbers (and percentages) of patients that were classified as severely, heightened or not fatigued at follow up, on basis of their classification as severely, heightened or not fatigued at baseline (left part of table) and persistent fatigue scores and numbers of persistently severely fatigued women (right part of table)

	n		persistent fatigue score	persistently severely fatigued women
Severe fatigue at baseline (n=47)				
severely fatigue at follow-up	23	49%	39.5	17
heightened fatigue at follow-up	13	28%	33.8	7
no fatigue at follow-up	11	23%	28.2	2
Heightened fatigue at baseline (n=21)				
heightened fatigue at follow-up	8	38%	29.5	1
no fatigue at follow-up	11	52%	23.7	-
severe fatigue at follow-up	2	10%	35.9	1
No fatigue at baseline (n=53)				
no fatigue at follow-up	45	85%	15.4	1
heightened fatigue at follow-up	5	9%	27.7	-
severe fatigue at follow-up	3	6%	31.2	-

In addition, 28 percent of these patients was identified as heightened fatigued at follow-up. Furthermore, most patients (85%) that were identified as not fatigued at baseline were also identified as not fatigued at follow-up.
The monthly CIS-fatigue scores of the total sample are depicted in Figure 1. In addition, the monthly CIS-fatigue scores are displayed for those women who were severely fatigued at baseline, and for those who were not severely fatigued at baseline. Results indicate that the monthly fatigue score dropped a little within a two year period. For the total group of 121 disease-free breast cancer patients, the monthly fatigue score dropped from 27 at first measurement to 25 at last measurement. This descent is due to the descent of fatigue scores in patients who were severely fatigued at baseline. Their monthly fatigue score dropped from 38 to 34. Monthly fatigue scores of patients who were not severely fatigued at baseline remained equal.

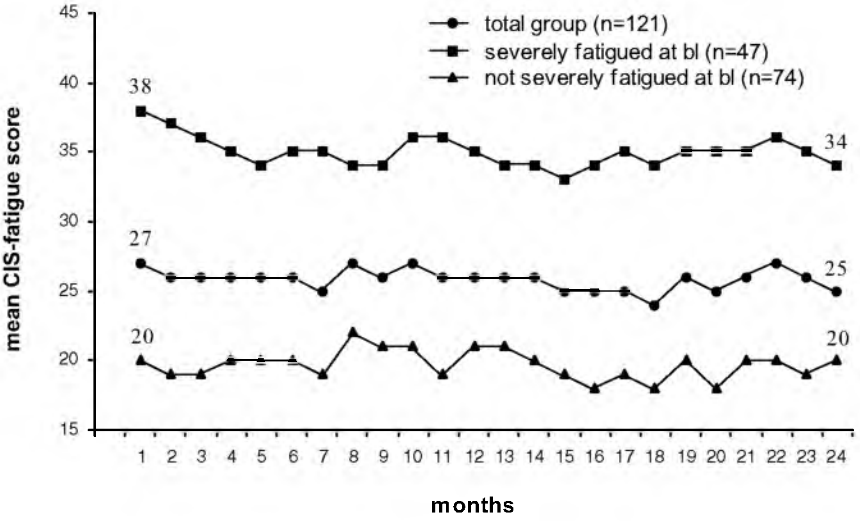

Figure 1. Mean CIS-fatigue scores over 24 months

The persistent fatigue score, which is the mean of all monthly fatigue scores, was 25.9 (sd=11.1) for the total sample. Further, the number of patients with a persistent fatigue score higher of 35 or higher was 29 (24%). In addition, 25 patients (21%) had a persistent fatigue score between 27 and 35. In the right part of Table 2 you can see that the highest persistent fatigue scores, and the greatest amount of persistently severely fatigued women, are within the categories ‘severe fatigue at baseline and severe fatigue at follow-up’ and ‘severe fatigue at baseline and heightened fatigue at follow-up’.

Is persistent fatigue related to former treatment modalities?

The mean persistent fatigue score did not differ significantly for those patients who underwent mastectomy (24.8 (sd=11.6)) and those who underwent lumpectomy (28.1 (sd=10.4)) (T-test; p=0.130).

Also for patients with different types of adjuvant therapy the mean persistent fatigue score was not statistically different, although patients who did not receive any kind of adjuvant therapy at all had a relatively low persistent fatigue score. The mean persistent fatigue score was 28.2 (sd=11.4) for patients who received radiotherapy, 24.9 (sd=11.4) for patients who received chemotherapy, 27.1 (sd=11.1) for patients who received both radiotherapy and chemotherapy, and 21.7 (10.5) for patients who did not receive adjuvant therapy (GLM-general factorial; p=0.244). Patients that used tamoxifen during a two year period (n=11) had equal fatigue scores to patients that did not use tamoxifen. Their fatigue score were respectively 23.5 (sd=11.8) and 26.2 (sd=11.2) (T-test; p=0.436).

Furthermore, there appeared to be a relation between persistent fatigue and the duration of cancer treatment. The mean persistent fatigue score was 19.5 (sd=8.7) for patients who finished treatment within one month, 27.0 (sd=11.3) for patients who finished treatment within 6 months and 27.0 (sd=11.3) for patients who were treated for cancer for more than 6 months (GLM-general factorial; p=0.045).

Finally, we found no relation between persistent fatigue and time since treatment finished. Patients who finished treatment 6-12, 13-24, 25-36, 37-48, 49-60, or more than 60 months ago had equal persistent fatigue scores (GLM-general factorial; p=0.997).

To what extent are psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions able to predict persistent fatigue?

In Table 3, correlations between the baseline scores (of all measures from the dimensions of psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions) and the persistent fatigue score are depicted.

Results indicate that within all different dimensions one or more baseline measure correlated significantly with the persistent fatigue score. In summary, women with higher persistent fatigue scores report more psychological distress, functional impairment, sleep disturbances, physical impairment, neuropsychological impairment and more problems with regard to social functioning and social support. Furthermore these women have a lower sense of control and stronger psychological and breast cancer related attributions with respect to their fatigue complaints.

Table 3. Pearson correlations between baseline measures and the persistent fatigue score persistent fatigue score

	persistent fatigue score
PSYCHOLOGICAL WELL-BEING	
emotional functioning (QLQ-C30)	-0.507***
depression (BDI- PC)	0.476***
trait anxiety (STAI)	0.612***
self-esteem (RSE)	-0.424***
depression (SCL)	0.560***
anxiety (SCL)	0.452***
agoraphobia (SCL)	0.375***
somatisation (SCL)	0.563***
interpersonal sensitivity (SCL)	0.375***
hostility (SCL)	0.206*
FUNCTIONAL IMPAIRMENT IN DAILY LIFE	
role functioning (QLQ-C30)	-0.537***
home management (SIP)	0.282**
work (SIP)	0.095
recreation and pastimes (SIP)	0.445***
number of days working (SOL)	-0.100
hours of work a day (SOL)	-0.099
number of days with household activities (SOL)	-0.061
hours of household activities a day (SOL)	-0.187
SLEEP DISTURBANCES	
sleep disturbances (GSQS-2)	0.412***
sleep/ rest (SIP)	0.379***
sleep (SCL)	0.438***
daily general quality of sleep (SOL)	-0.361***
daily difficulties falling asleep (SOL)	0.226*
daily restless sleep (SOL)	0.303**
daily early awakenings (SOL)	0.121
PHYSICAL ACTIVITY	
physical functioning (QLQ-C30)	-0.477***
physical activity (CIS)	0.512***
mobility (SIP)	0.011
ambulation (SIP)	0.302**
daily activity score (SOL)	-0.224*
mean activity (Actometer)	-0.194*
peak duration (Actometer)	-0.166
rest after peak (Actometer)	0.272**

Table 3. continued

NEUROPSYCHOLOGICAL FUNCTIONING	
cognitive functioning (QLQ-C30)	-0.514***
concentration (CIS)	0.470***
alertness behaviour (SIP)	0.454***
concentration (symbol digit)	0.059
reaction time (CRT1)	0.240**
reaction time (CRT2)	0.022
reaction time (CRT3)	0.164
SOCIAL FUNCTIONING	
social functioning (QLQ-C30)	-0.444***
social interaction (SIP)	0.304**
SOCIAL SUPPORT	
amount of social support (SSL-I)	0.063
amount of negative interactions (SSL-N)	0.337***
discrepancies social support (SSL-D)	0.279**
SELF-EFFICACY	
self-efficacy (SEQ)	-0.489***
internal locus of control (MHLC-I)	-0.044
CAUSAL ATTRIBUTIONS	
psychological attributions (CAL)	-0.476***
breast cancer related attributions (CAL)	-0.448***

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

To examine the contribution of the baseline measures mentioned above to persistent fatigue, a regression analyses was performed (Table 4). Independent variables were the CIS-fatigue score at baseline and those measures that correlated highest with the persistent fatigue score within the different dimensions. Results indicate that 51% of the persistent fatigue score was predicted by the baseline CIS-fatigue score. The other selected measures predicted an additional 11%. Results indicated that apart from a high baseline CIS-fatigue score, high persistent fatigue was also predicted by low self-efficacy. Thus, less perceived control over symptoms predicted higher persistent fatigue.

Because the CIS-fatigue score at baseline had the largest contribution to the prediction of the persistent fatigue score, a second regression analysis was performed without the baseline CIS-fatigue score. Results indicated that 53% of the persistent fatigue score was predicted by the selected measures. Higher persistent fatigue scores were significantly predicted by lower self-efficacy, more anxiety and more limitations in role functioning at baseline.

Table 4. Linear regression analyses to predict the persistent fatigue score (range 8-56); with baseline CIS-fatigue score (A) and without baseline CIS-fatigue score (B)

	A		B	
	Beta	**adj R^2**	**Beta**	**adj R^2**
fatigue (CIS)	0.413***	0.510		
trait anxiety (STAI)	0.121		0.286**	
role functioning (QLQ-C30)	-0.170		-0.258*	
sleep (SCL)	0.106		0.130	
physical activity (CIS)	-0.002		0.117	
cognitive functioning (QLQ-C30)	-0.130		-0.128	
social functioning (QLQ-C30)	0.075		0.162	
amount of negative interactions (SSL-N)	0.080		0.073	
self-efficacy (SEQ)	-0.199**		-0.306***	
psychological attributions (CAL)	-0.105	0.113	-0.096	0.534
total adj R^2		0.623		0.534

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

Description of the course of fatigue for those women that had a disease recurrence. The mean CIS-fatigue score at baseline for those women who had a disease recurrence within the two year period of our study was 23.9 (sd=14.5) at baseline. The mean Daily Observed Fatigue score (DOF) at baseline was 2.8 (sd=2.3). Further, the number of severely fatigued patients at baseline was five (26%). In addition, one patient (5%) experienced heightened fatigue.

In Figure 2 mean monthly fatigue scores are depicted for the 19 women who had a disease-recurrence during the study period. The CIS-fatigue scores rose from 23 (12 months before the diagnosis of a disease recurrence) to 31 in the month that the disease recurrence was diagnosed. In the same figure, mean monthly fatigue scores are depicted for a matched group of women who did not have a disease recurrence. The groups were matched on the baseline CIS-fatigue score. In addition, the two groups were comparable with respect to type of surgery, age, adjuvant therapy, duration of treatment and time since treatment. There was no clear rise of the monthly CIS-fatigue scores in this control group of persistent disease-free women. Their monthly CIS-fatigue score varied from 19 to 26.

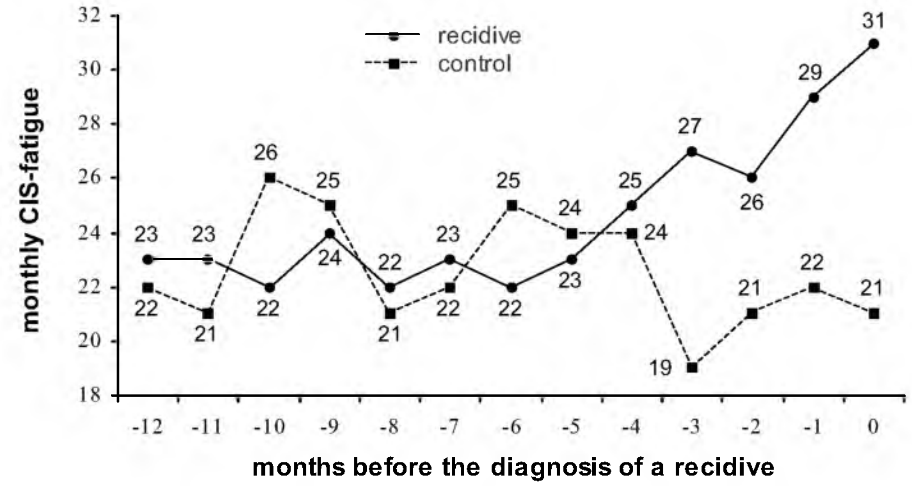

Figure 2. Mean monthly fatigue scores for women who developed a tumour relapse (n=19) in the 12 months before this was diagnosed
(n=19 at time 0, n=16 at time -3, n=14 at time -6, n=11 at time -9, n=10 at time -12)

DISCUSSION

The unique quality of this study lies in the fact that we studied fatigue in disease-free breast cancer patients during a longer period of time. Because of that we were able to take a closer look at the course of fatigue complaints and we were able to identify those patients that experienced persistent fatigue complaints. Based on the monthly fatigue scores we concluded that severe fatigue is a persistent problem for 24 percent of a group of disease-free breast cancer patients. For these women fatigue is thus a continuous severe problem, even years after treatment for cancer, and is associated with severe limitations in several areas of daily life. This percentage is comparable to percentages found in other samples of disease-free cancer patients[38].

To provide a measure for persistent fatigue we calculated the mean CIS-fatigue score over the 24 months that patients filled out the fatigue questionnaire. Patients with a persistent fatigue score of 35 or higher were referred to as 'persistently severely fatigued'. We realise that this technique has some shortcomings, for example, a few months of very high fatigue might place a person in the 'persistently severely fatigued' category even if most of her monthly scores fell below the cut point of 35. Because of this shortcoming we additionally calculated the persistent fatigue score according to another approach. We calculated the percentage of times that scores fell above the cut-point of 35. However, this technique has some shortcomings as well. For example, a person that has many fatigue scores just under 35, will not be labelled as persistently fatigued, while this is probably untrue. In spite of the shortcomings of both techniques it is reassuring to know that the Pearson correlation between these differently obtained persistent fatigue scores turned out to be very high; 0.90 ($p<0.001$).

Considering the relation to former treatment modalities, we can conclude that patients who did not receive any kind of adjuvant therapy and who did not experience any kind of complications during treatment, i.e. those patients that completed treatment for cancer within one month, are at lower risk for persistent fatigue. Furthermore, persistent fatigue seemed to be unrelated to type of surgery, type of adjuvant therapy and to time since treatment finished.

A possible explanation for the low persistent fatigue scores in patients whose treatment duration was short may be due to the fact that they had not been subjected to the harmful effects of adjuvant therapy and/or multiple operations (and anaesthetics) because of complications. In addition, for this group of patients the period of great uncertainty had been limited and they had been spared many hours of travelling to and from the hospital, which can cause exhaustion as well. Of course, there may be other explanations.

Furthermore, persistent fatigue was very well predicted by the questionnaires that we used to measure psychological well-being, functional impairment, sleep disturbances, physical activity, neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions. With use of several selected baseline measures, the percentage of explained variance was 62 percent. These findings are important with respect to the development of interventions to reduce fatigue. For patients with Chronic Fatigue Syndrome (CFS), cognitive behaviour therapy has proven to be successful in reducing fatigue complaints[39,40]. In one of these studies[40], cognitive behaviour therapy was based on a statistically tested model of perpetuating factors in CFS[36]. In this model, focussing on bodily symptoms, low physical activity, and low sense of control contributed to increasing severity of fatigue. Based on the results of the current study we might expect that, similar to the model for CFS patients, a low sense of control might play a role in a model for severely fatigued cancer survivors. In addition, anxiety and impairment in role functioning might be important perpetuating factors as well.

With respect to the relation between severe fatigue and disease recurrence it is important to note that at baseline severe fatigue was found both in patients who had a disease recurrence and in patients who remained disease-free. In our study the mean CIS-fatigue score and the percentage of severely fatigued patients at baseline were even lower in the group of patients who had a disease recurrence than in the patients that remained disease-free. In clinical practice severe fatigue complaints can thus not be interpreted as an indicator of a possible disease recurrence. However, there seems to be a rise of the fatigue score in the months preceding the diagnosis of the disease recurrence. Nevertheless, we should be careful in interpreting this finding because the group of women who had a disease recurrence is small.

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Chapter 9

General discussion

General discussion

INTRODUCTION

The results of the studies reported in the present thesis and of other studies published in the last five years make clear that fatigue (long) after curative treatment for cancer is a severe problem for a substantial part of disease-free cancer patients. Complaints of severe fatigue are often associated with serious limitations in daily life, for instance in the areas of work, household activities, social interactions or recreation and pastime. It is important to note that until recently the phenomenon 'post-cancer fatigue' was not recognised at all. In the past the focus within oncology was solely on survival. Often patients had to contend with the incomprehension from their physician, their boss, and even from family and friends, when they kept on experiencing severe fatigue complaints long after they had completed their cancer treatment. Fortunately, this one-sided focus is shifting and nowadays quality of life, and therefore also fatigue, is increasingly seen as an important aspect of (post-)cancer treatment.

In this final chapter we will summarise the results of the studies presented in the preceding chapters and place them into perspective, as well as describe the limitations of our investigations. The following topics will be discussed: the prevalence and course of post-cancer fatigue, a description of 'the severely fatigued disease-free cancer patient', the relationship between former disease and treatment characteristics and post-cancer fatigue, possible perpetuating factors of post-cancer fatigue, comparisons between severely fatigued disease-free cancer patients and Chronic Fatigue Syndrome (CFS) patients, and, finally, suggestions for a cognitive behavioural intervention to reduce post-cancer fatigue.

Prevalence and course of post-cancer fatigue

Our first goal was to assess the prevalence of fatigue in disease-free cancer patients by means of a validated fatigue questionnaire, the Checklist Individual Strength. It has excellent psychometric properties and, based on research of patients with Chronic Fatigue Syndrome and healthy controls, it enables us to determine severe and heightened feelings of fatigue[1-3].

It is important to start with the observation that of the patients that have been successfully treated for cancer not all will be confronted by long-lasting complaints of (severe) fatigue after they have completed treatment. Literature study shows that up to 99 percent of all cancer patients have to deal with some degree of fatigue during their treatment[4-6]. Based on the literature and our own experience we can conclude that more than one year after successful treatment this percentage is considerably lower, but still clinically relevant[4,7,8]. In the studies we carried out the proportion of severe fatigue varied from 19 to 38 percent in three different samples of cancer survivors. The percentage of heightened and severe fatigue ranged from 29 to 54 percent (Fig. 1).

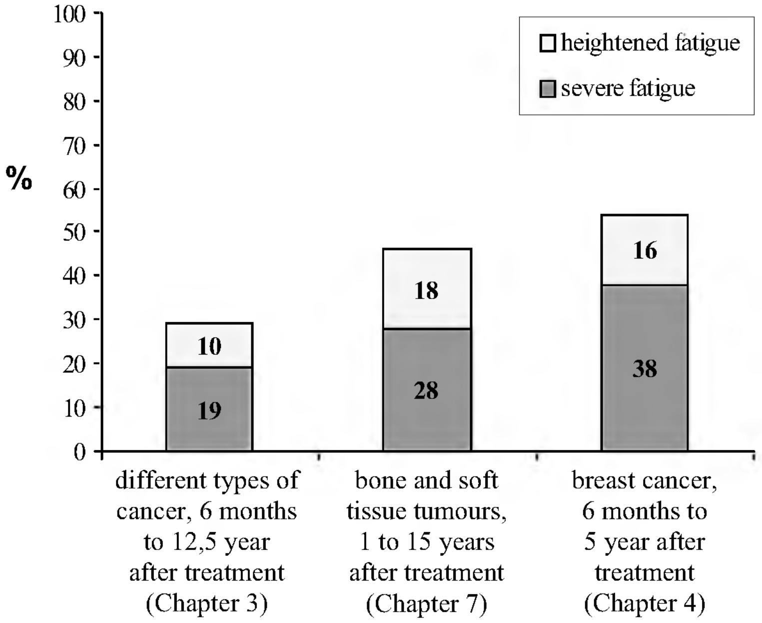

Figure 1. Percentages of cancer survivors with severe and heightened fatigue complaints

In two of these samples patients were assessed a second time after a period of two years. In the sample of patients treated for a bone or soft tissue tumour, the percentage of severe fatigue had remained about equal, namely 26%. However, in the sample of disease-free breast cancer patients the proportion had decreased from 38 to 23%. A possible explanation for this decrease could be that our breast cancer population had completed cancer treatment within a relatively short period (mean 2.5 years) before taking part in our study. These results seem to suggest that fatigue complaints continue to decrease during the first 3 to 4 years after successful treatment. Nevertheless, for about a quarter of the cancer survivors severe fatigue complaints are persistent. In the study of patients treated for a bone or soft tissue tumour we found evidence for an early decrease in the fatigue incidence. Here, patients who had finished treatment between one to two years prior to the study were significantly more severely fatigued than patients who had finished treatment considerably earlier.

There are a few limitations with respect to our conclusions on the prevalence of post-cancer fatigue. First, we only investigated patients with specific types of cancer, namely breast cancer, bone and soft tissue tumours, and a mixed cancer population in which a majority of the patients had testis carcinoma, colorectal carcinoma and sarcoma. However, based on the literature, there is no reason to expect that the prevalence will be different in the majority of other cancer survivor populations[4]. Second, our studies were limited to cancer survivors in a certain age category. The rationale was that we wanted to select more or less homogenous groups of patients. Mean ages of the breast cancer patients, the patients with bone and soft tissue tumours, and the mixed cancer population were 46 years (sd=6, range=28-55), 38 years (sd=14, range=18-65), and 48 years (sd=14, range=21-74), respectively. The presented results are thus not applicable to survivors of other age groups. We feel it will be of particular interest to also investigate fatigue complaints in older disease-free patients in the future. After all, fifty percent of all cancer patients are older than 65 years. Finally, our results do not apply to patients with advanced cancer. However, based on other research, we know that in the palliative setting fatigue is a very important problem as well. In their final stage of life the majority of cancer patients indicate fatigue as a serious complaint that interferes with their quality of life[9]. In contrast to the fatigue experience of disease-free cancer patients, patients with advanced cancer are confronted by numerous physical problems, which may aggravate their experience of fatigue.

Description of 'the severely fatigued disease-free cancer patient'

Besides the quantitative description of fatigue (the severity of fatigue) we have studied various qualitative aspects of fatigue in disease-free cancer patients. As indicated in Chapter 4, in our research department fatigue has been assessed in several samples (e.g. patients with chronic fatigue syndrome, multiple sclerosis, pancreatitis, neuromuscular disease and healthy controls) using a multidimensional assessment method. In addition to the dimension of fatigue severity this assessment method evaluates eight other dimensions, namely psychological well-being, functional impairment in daily life, sleep disturbances, physical activity, neuropsychological impairment, social functioning/social support, self-efficacy and causal attributions. These dimensions appeared to be relatively independent, implying that each dimension uniquely contributes to the description of a patient who experiences severe fatigue.

From the results of our collective studies we can conclude that severely fatigued disease-free cancer patients scored significantly higher on all eight dimensions compared to the non-severely fatigued disease-free cancer patients. Furthermore, non-severely fatigued disease-free cancer patients were comparable to matched healthy controls on most of the dimensions. It thus seems that fatigue is not an isolated problem. Cancer survivors that experienced severe fatigue also experienced numerous problems and limitations in several areas of life.

None of our studies yielded significant differences between severely fatigued disease-free cancer patients and non-severely fatigued disease-free cancer patients on demographic variables. The two groups were similar with respect to age, gender and level of education.

Relations between former disease and treatment characteristics and post-cancer fatigue

Starting from the hypothesis that post-cancer fatigue is initially caused by the cancer itself and/or the treatment for cancer, we were interested in finding out whether there are any correlations between post-cancer fatigue and initial disease- or treatment-related factors. One of our first studies had shown that there were no differences in severity between fatigued patients who were diagnosed with testis carcinoma, colorectal carcinoma, sarcoma or other types of cancer. Furthermore, in our study with patients that had been successfully treated for bone and soft-tissue tumours, there proved to be no differentiation in fatigue scores between patients treated for various types of malignant and those treated for benign tumours. Neither did we find any dissimilarities in fatigue scores in relation to the area of operation (lower girdle (hip, knee, ankle), upper girdle (shoulder, elbow) and axial skeleton (pelvis, spine)).

It may seem remarkable that the fatigue scores of the patients that were treated for malignant and those treated for benign tumours were similar. However, when you realise that patients with benign tumours also have to go through a period of uncertainty surrounding the discovery and diagnosis of their tumour, that they also have to undergo extensive surgery that always carries certain risks and might possibly lead to physical limitations, and that they also have to face the chance of disease recurrence, the similarity in scores is quite explainable.

With respect to treatment-related variables we did not find any significant relations between fatigue and former type of surgery (mastectomy versus lumpectomy; different orthopaedic procedures). In addition, there was no evidence for a relation between severe fatigue and type of adjuvant therapy. For instance, breast cancer patients treated with radiotherapy had post-cancer fatigue scores that were comparable to the fatigue scores of patients who had been treated with chemotherapy and to patients having received treatment consisting of a combination of radio- and chemotherapy. However, we did find that patients whose surgery had been without complications and who had not received any adjuvant therapy were less at risk of developing severe fatigue than other patients. In our longitudinal breast cancer study, patients that had completed treatment for cancer within one month, i.e. those patients that had undergone a surgical procedure without any complications and without any adjuvant therapy, experienced persistent fatigue significantly less often. Furthermore, in our study with patients treated for a bone or soft tissue tumour, the percentage of severe fatigue was significantly lower in patients that had undergone only one operation versus those who had had to undergo two or more procedures. This was relevant both for patients treated for malignant tumours and for patients treated for benign tumours.

It is our view that the lower fatigue scores in patients whose treatment duration was short may be due to the fact that they had not been subjected to the harmful effects of radiotherapy, chemotherapy, or multiple operations (and anaesthetics). In addition, the fact that for this group of patients the period of great uncertainty had been limited and that they had been spared many hours of travelling to and from the hospital, which can cause exhaustion as well, may have played a role here as well. This does not mean to say that these are the only reasons; there may be other explanations.

In conclusion, type of cancer, type of surgery and type of adjuvant treatment were not related to persistent fatigue complaints after treatment for cancer. However, patients that did not have to undergo adjuvant treatment at all, and for whom surgery was without complications, seemed to experience persistent fatigue less often than other patients.

Perpetuating factors of post-cancer fatigue

As described above, we did not find clear evidence for relationships between former disease and the majority of treatment characteristics on the one hand and post-cancer fatigue on the other hand. We therefore think that it is important to make a distinction between initiating factors and perpetuating factors of fatigue after cancer. We assume that post-cancer fatigue complaints originate in the diagnostic and treatment stages. In several reviews various factors have been pointed out as possible initiating factors of fatigue during active treatment for cancer. First, there is the primary influence of the tumour on the organs involved. Second, secondary effects of the tumour, like anaemia, can play a role. Third, the actual treatment (surgery, chemotherapy, radiotherapy) could be an important cause of fatigue, and finally, psychological factors like anxiety and depression could lead to complaints of fatigue[10-12]. After successful treatment for cancer fatigue complaints disappear in most cases. However, for a substantial part of cancer survivors they continue to exist. The factors that are responsible for these persistent complaints of fatigue are referred to as perpetuating factors. Because our studies of fatigue were all conducted some years after treatment had been completed, our investigations were restricted to the perpetuating factors of fatigue.

From our longitudinal studies we can conclude that low self-efficacy, elevated feelings of anxiety, serious limitations in role functioning, low sense of optimism and high tendency to focus on bodily symptoms seem to be perpetuating factors of fatigue complaints after successful treatment for cancer. It thus seems that patients that experience little control with respect to their fatigue complaints, patients that tend to be anxious, patients that experience difficulties in resuming their former roles at home and/or at work, patients that tend to be pessimistic and patients that tend to focus on bodily symptoms, are the ones that are most likely to experience persistent fatigue. Two of these factors, i.e. strong focus on bodily symptoms and low self-efficacy, have also been identified as perpetuating factors in a statistically tested model of perpetuating factors in Chronic Fatigue Syndrome[13].

In addition to these perpetuating factors of fatigue, the extent to which patients have come to terms with their disease (i.e. the acceptance of having been confronted with cancer), might be an important perpetuating factor as well. Initially, we assumed that for patients assessed more than one year after treatment completion, acceptance of their experience would no longer play an important role. However, based on the clinical knowledge acquired during the last few years and the literature[14-17] we now conclude that this assumption may not apply to all patients. It has become clear that some patients still experience difficulties with respect to the acceptance of the fact that they have had cancer, even years after treatment has been finished. In the study assessing patients treated for a bone or soft tissue tumour we reported data on the relationship between acceptance and fatigue (Chapter 7). The results indicated that heightened fatigue was predicted by lower levels of acceptance of the experience with cancer. This finding is consistent with unpublished results in our breast cancer population. Severely fatigued disease-free breast cancer patients had significantly lower acceptance scores than non-severely fatigued disease-free breast cancer patients.

Another possible perpetuating factor of fatigue after treatment for breast cancer is the menopause. Breast cancer patients often become menopausal as a result of chemotherapy. Although there still is an ongoing debate about exactly what symptoms are attributable to the menopause, most researchers consider the following symptoms to be menopausal in nature: vasomotor symptoms (e.g. hot flashes), symptoms related to vaginal atrophy (e.g. pain during intercourse), psychological symptoms (e.g. irritability) and other symptoms such as joint pains, trouble sleeping and heart palpitations[18]. In view of these assumed menopausal associations, it is very likely that these symptoms are additional perpetuating factors in the fatigue breast cancer survivors experience after they have become menopausal. This is all the more likely given that menopausal symptoms seem to be both more prevalent and severer in cancer survivors than in healthy women, and because physicians may be reluctant to prescribe hormone replacement therapy because of the potential increased risk of cancer recurrence[19,20].

Because of this likely influence of menopausal complaints we decided to include an item about the intensity of hot flashes in the self-observation list (Daily Observed Hot Flashes, DOHF). Patients were asked to report the intensity of hot flashes four times a day on a 5-point scale (0-4) during a 12-day period. Total DOHF scores ranged from 0 to 16. Because 41 patients had already completed the study by the time we included DOHF in the self-observation list, only 80 of our breast cancer patients filled out this question. The results do indeed suggest a relation between fatigue and hot flashes. Disease-free breast cancer patients with persistent, severe fatigue (n=21) had a mean DOHF score of 2.90 (sd=3.71) while the rest of the patients (n=59) had a mean DOHF score of 1.27 (sd=1.77). This difference approached significance (t-test $p<0.071$).

What we did not investigate in our studies were organic perpetuating factors of post-cancer fatigue because at the time we started our research there were no indications at all that organic factors could be of importance in disease-free cancer patients. However, in a recent article Bower[21] reported that fatigued breast cancer survivors had significantly higher serum levels of several markers associated with proinflammatory cytokine activity than non-fatigued survivors, including interleukin-1 receptor antagonist, soluble tumour necrosis factor receptor type II, and neopterin. Furthermore, they had significantly lower serum levels of cortisol than the non-fatigued group. Comparison with two lymphocyte populations also yielded differences.

As explained above, due to our study design we were only able to investigate the perpetuating factors of fatigue. However, we think it is important to also investigate the initiating factors of cancer-related fatigue in the future. This requires that patients are included in a longitudinal study from the moment of diagnosis and are assessed at various points in time for approximately 4 years. Such a research design will allow an evaluation of both the initiating and the perpetuating factors of fatigue during and long after treatment for cancer. Up until now, only a few longitudinal studies have been published in which patients were included from the moment of diagnosis[22-26]. Initiating factors of fatigue during and/or shortly after treatment were cancer diagnosis[23,25], depression[23,24,26], functional disability, quality of sleep and psychological distress[23]. However, none of these studies had a sufficient duration to allow an investigation of possible perpetuating factors of persistent fatigue complaints.

Similarities and differences between severely fatigued disease-free cancer patients and patients with Chronic Fatigue Syndrome

A comparison of severely fatigued disease-free cancer patients and CFS patients is of importance to determine whether a cognitive behavioural intervention designed to reduce fatigue in CFS patients would also be appropriate for severely fatigued disease-free breast cancer patients. In Chapters 3 and 6 of this thesis we investigated possible similarities and differences between severely fatigued cancer survivors and CFS patients. In Chapter 3 this was done on the basis of several general self-report questionnaires only, while in Chapter 6 we used a large battery of general and daily self-report questionnaires as well as measures of actual behaviour. The discussion below is therefore mainly based on the results described in Chapter 6 and thus on the results of our study involving severely fatigued former breast cancer patients.

With respect to the onset of the fatigue complaints it needs to be pointed out that there is an important difference between former cancer patients and CFS patients.

For patients with fatigue after cancer there is a distinct starting point, namely the period in which they were diagnosed and treated for cancer. For patients with CFS the onset differs per patient and is often vague or unknown. This automatically implies that the attributions relating to the causes of the fatigue are different for both groups. Severely fatigued disease-free cancer patients often attributed their fatigue complaints to the fact that they were diagnosed and treated for cancer, while CFS patients attribute their fatigue complaints to several other, mostly physical, factors. Another important difference in this respect is that cancer patients, besides their high cancer-related attributions, also had high psychologically related attributions. For instance, they attributed their fatigue complaints to their fear of a relapse, or to the fact that they tend to ruminate. By contrast, CFS patients often exclude the possibility of psychologically based causes of their fatigue complaints[27,28].

Furthermore, although many of the cancer survivors in our studies experienced severe fatigue, in general, they were less severely fatigued and less restricted in several areas of daily life than the CFS patients. Also, severely fatigued cancer survivors experienced fewer problems with respect to physical activity, concentration and pain and they reported to have more control over their fatigue complaints. However, the two groups seemed to have the same amount of problems as regards social support and sleep. And finally, levels of depression and anxiety tended to be somewhat heightened for severely fatigued cancer survivors in comparison to patients with CFS, which is also in line with our clinical experience. Some patients interpreted their persistent feelings of severe fatigue as a sign of disease recurrence, which was associated with anxiety and depression resulting in increasing fatigue.

Cognitive behavioural intervention to reduce post-cancer fatigue

Based on the above described results, and because differences within the group of severely fatigued cancer patients proved to be larger than within the group of CFS patients, it is likely that a model of perpetuating factors for former cancer patients differs from the CFS model, which has implications for therapeutic interventions aimed at reducing fatigue after treatment for cancer. Our findings indicate that the following aspects need to be taken into account when considering a cognitive behaviour therapy for fatigue after cancer: acceptance of the experience with cancer, cognitions associated with fatigue (attributions relating to the causes of fatigue, self-efficacy), sleep disturbances, regulation of physical, mental and social activities and social support and interactions. What the large differences we observed within the group of severely fatigued cancer patients have clearly shown is that cognitive behaviour therapy to reduce fatigue after successful treatment for cancer should, in any event, be adapted to each individual former cancer patient.

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Summary

This thesis consists of seven articles on the subject of fatigue complaints in cancer survivors.

In *Chapter 1* we briefly describe the history of the Expert Centre Chronic Fatigue of the University Medical Centre Nijmegen. Furthermore, we report that the research that is described in this thesis focuses on fatigue complaints in cancer survivors. With ‘cancer survivors’ we refer to persons who have received a curative treatment for cancer and are disease-free at the time of participation in our studies. Chapter 1 is completed with an outline of the contents of Chapters 2 to 9.

In *Chapter 2* we review the literature on the topic of fatigue complaints during and after treatment for cancer. Based on studies that were published between 1980 and 2001 we conclude that prevalence estimates of fatigue during cancer treatment range from 25% to 99%. For cancer survivors, it is found that for different samples of disease-free patients in 17% to 30% of the cases fatigue is an important problem. The majority of the studies on fatigue during and after cancer, fails to find relationships between fatigue on the one hand, and demographic variables and disease and treatment characteristics on the other hand. Nevertheless, fatigue seems to be related to psychological distress, sleep disturbance and limitations in physical functioning. Studies that focus on interventions to reduce fatigue are limited to interventions during or shortly after cancer treatment. These studies report positive effects on fatigue complaints immediately after the intervention.

In the reviewed articles a wide variety of instruments to measure fatigue have been used. Many of these instruments have not been tested on validity and reliability, and often reference scores are lacking. In addition, most of the instruments are unidimensional, i.e. they solely measure fatigue intensity, rather than multidimensional. In the latter case, the nature of the symptoms as well as their severity are gauged. Because of these shortcomings we state in the discussion of this article that it is important to use valid and reliable multidimensional fatigue instruments in future research, for which reference scores of healthy subjects and/or other patient populations are available. It is only with such instruments that that it can be ascertained whether fatigue is any different for cancer patients than for healthy individuals or for patients with diseases other than cancer. Furthermore, we suggest that it is important to conduct longitudinal studies that will allow the identification of initiating and perpetuating factors of fatigue complaints during and after treatment for cancer.

The goal of the article in *Chapter 3* was to assess fatigue with the use of a validated multidimensional fatigue questionnaire, i.e. the Checklist Individual Strength, in a mixed sample of 85 disease-free cancer patients. Reference scores recorded in several groups of patients and healthy controls are available for this questionnaire. We also wished to investigate whether relationships exist between severe fatigue on the one hand, and former treatment modalities, problems of concentration, motivational problems, decreased physical activity, functional impairment, depression and anxiety on the other hand. Finally, we were interested in finding out in what way(s) severely fatigued disease-free cancer patients were comparable with patients with Chronic Fatigue Syndrome (CFS). The disease-free cancer patients had completed cancer treatment 6 months to 12.5 years prior to our study. Nineteen percent of the disease-free cancer patients appeared to experience severe fatigue. No relationships were found between fatigue and type of cancer, type of former treatment modalities, duration of treatment and time since treatment completion. We did find correlations between severe fatigue and depression, anxiety, concentration problems, reduced motivation and reduced physical activity. Finally, severely fatigued cancer patients were comparable with a group of patients with CFS, matched for age and gender, with regard to depression, reduced motivation and reduced physical activity. CFS patients reported more concentration problems.

In *Chapter 4*, the results of a cross-sectional study of 150 disease-free breast cancer patients are reported. The aim of this study was also to assess severe fatigue, but this time in a larger, more homogeneous group of disease-free cancer patients. All women had undergone treatment for breast cancer, had been younger than 50 years at the time of primary diagnosis and had completed their treatment 6 to 70 months before participating in the study. We made use of a multidimensional assessment method consisting of nine dimensions, namely fatigue severity, psychological well-being, functional impairment in daily life, sleep disturbance, physical activity, neuropsychological impairment, social functioning/social support, self-efficacy and causal attributions. Thirty-eight percent of the sample turned out to be severely fatigued, compared with 11% in an age-matched sample of women without a history of cancer. Fatigue severity scores did not differ significantly for those patients who had undergone mastectomy and those who had had lumpectomy. Neither did we find differences in fatigue scores between patients who had received radiotherapy or chemotherapy or both. In addition, we did not find any differences between these three patient groups and patients who had not received adjuvant therapy at all. We elaborate on this latter finding in Chapter 8. The 'severely fatigued disease-free breast cancer patient' scored higher on several dimensions compared to the 'non-severely fatigued disease-free breast cancer patient'. Severely fatigued patients reported more psychological distress, experienced more functional impairment at home or at work, they more often had sleep disturbances and neuropsychological problems, were less physically active, and perceived to receive less social support. Finally, severe fatigue was highly related to a low sense of control with respect to the fatigue complaints and strong cancer- and psychologically related attributions with regard to the causes of the fatigue.

In *Chapter 5* a study is described in which the same 150 disease-free breast cancer patients participated. The goal of this study was to analyse the relationship between fatigue, neuropsychological functioning and physical activity. The results described in Chapter 4 had already shown that severe fatigue is related to self-reported problems of concentration, memory and physical functioning. However, it remained unclear whether this is truly the case. In the present study we therefore measured both neuropsychological functioning and physical activity in three ways: 1) with general self-report questionnaires, 2) with daily self-report questionnaires, and 3) by measures of actual behaviour. Neuropsychological tests were performed to measure speed of information processing and actual ability to concentrate. Actual physical activity was measured with the actometer, which is an apparatus about the size of a matchbox that was worn around the ankle both day and night during a 12-day period. Results indicated that fatigue was strongly related with general and daily self-reported neuropsychological functioning, but not with actual neuropsychological functioning in a laboratory setting. Furthermore, fatigue was strongly related with general self-reported physical activity but not with daily self-reported and actual physical activity.

The purpose of the study that is described in *Chapter 6* was to examine to what extent a patient who experiences severe fatigue after treatment for breast cancer resembled a patient with CFS. In this article we compared 57 severely fatigued disease-free breast cancer patients with 57 gender- and age-matched patients with CFS on the dimensions of fatigue severity, functional impairment, self-efficacy, psychological well-being, sleep disturbances, neuropsychological impairment, physical activity, social support, and pain. The CFS patients had higher fatigue scores, experienced more functional impairment, were less physically active, experienced more pain and had lower self-efficacy, in comparison to the severely fatigued disease-free breast cancer patients. However, a subgroup of the latter patient sample reported the same amount of psychological distress, sleep disturbances and concentration problems as the CFS patients. Finally, both the CFS and severely fatigued breast cancer patients had the same amount of problems with respect to social support. Based on these results, and because differences within the group of severely fatigued cancer patients seemed to be larger than the differences within the group of CFS patients, we assume that the model of perpetuating factors for the former cancer patients probably differs from the CFS model, which has implications for therapy aimed at reducing fatigue after treatment for cancer. Because of the large differences within the group of severely fatigued cancer patients it is concluded that cognitive behaviour therapy to reduce fatigue after cancer treatment should be adapted to each individual former cancer patient.

In *Chapter 7* the results of our longitudinal study on fatigue complaints in 170 patients who had received treatment for malignant and benign bone and soft tissue tumours 1 to 15 years prior to our study, are reported. One of the aims of this study was to investigate whether patients who were treated for malignant tumours experienced severe fatigue more often than patients treated for benign tumours. Because treatment for bone and soft tissue tumours differs from treatment for breast cancer, our second goal was to investigate the relationships between treatment characteristics and post-cancer fatigue in this population. In addition, because time since the end of treatment varied more widely within this patient population than in the populations we studied earlier, we were able to establish whether patients who had finished treatment relatively recently were more severely fatigued than patients for whom treatment completion was less recent. Finally, the longitudinal design of this study enabled us to investigate the perpetuating factors of fatigue. Severe fatigue complaints appeared to be a problem for 28 percent of the patients investigated. Percentages of severe fatigue were equal for patients who had been treated for malignant tumours and those treated for benign tumours. Fatigue complaints proved to be most severe for those patients who had finished treatment between 1 to 2 years ago, and for patients who had undergone more than one operation. At a two year follow-up the majority of the patients who had been severely fatigued at baseline were still severely fatigued. Oncological complications after initial treatment, low optimism and high somatisation appeared to be predictors of severe fatigue at follow-up.

Chapter 8 is a sequel of our cross-sectional breast cancer study of which the results were presented in Chapters 4 and 5. The sequel study was aimed at investigating whether severe fatigue after treatment for breast cancer was a persistent problem. In addition, we wished to find out whether persistent fatigue was related to former treatment characteristics. After baseline measurements, the patients were asked to fill out a monthly fatigue questionnaire during a two year period after which they were invited to our hospital for an extensive follow-up assessment. Of the 150 participating patients 121 women completed the study. Nineteen women had a disease recurrence during the 2-year period and 10 patients dropped out for several other reasons. Based on the monthly fatigue questionnaires we concluded that 24% of the disease-free breast cancer patients experienced persistent severe fatigue complaints. Persistent fatigue complaints were less severe in the patients that had not received any kind of adjuvant therapy and for whom, at the same time, surgery (mastectomy or lumpectomy) had been without complications. High anxiety, high impairment in role functioning and low sense of control over fatigue symptoms at baseline appeared to be predictors of persistent fatigue.

Finally, in *Chapter 9* we place the results of the studies presented in this thesis into perspective and discuss their shortcomings and implications. We conclude that for approximately 25 percent of all cancer survivors severe fatigue complaints are persistent. These severe fatigue complaints are associated with problems and limitations in different areas of life. Patients that had completed treatment within a relatively short time experienced persistent fatigue less often. None of these patients had had to undergo adjuvant treatment, and for all surgery had been without complications. Factors responsible for the perpetuation of severe fatigue were low self-efficacy, high feelings of anxiety, serious limitations in role functioning, low sense of optimism and high tendency to focus on bodily symptoms. Furthermore, our various findings indicate that it is plausible that menopausal complaints and difficulties in coping with the experience of having had cancer (i.e. acceptance) are important perpetuating factors as well.

Samenvatting

Dit proefschrift bestaat uit zeven artikelen over ernstige vermoeidheidsklachten bij ziekte-vrije kankerpatiënten.

In *Hoofdstuk 1* wordt in het kort de geschiedenis beschreven van het vermoeidheidsonderzoek dat we sinds 1990 binnen het Universitair Medisch Centrum St. Radboud doen. Verder geven we hier aan dat het in dit proefschrift gepresenteerde onderzoek zich richt op ziekte-vrije kankerpatiënten. Hiermee doelen we op patiënten die een curatieve behandeling voor kanker hebben afgesloten en bij wie op het moment van het onderzoek geen tekenen van een recidief aanwijsbaar waren. Tenslotte wordt in dit hoofdstuk kort aangegeven wat de inhoud is van de hoofdstukken 2 tot en met 9.

Hoofdstuk 2 bestaat uit een overzicht van de literatuur over vermoeidheidsklachten tijdens en na behandeling voor kanker. Gebaseerd op studies die tussen 1980 en 2001 zijn gepubliceerd, concluderen we dat de prevalentie van vermoeidheid tijdens behandeling voor kanker varieert van 25 tot 99 procent. Voor 17 tot 30 procent van de patiënten die de behandeling voor kanker reeds achter de rug heeft blijft vermoeidheid een belangrijk probleem. Dit is onderzocht in verschillende ziekte-vrije kankerpopulaties. In de meerderheid van de besproken onderzoeken naar vermoeidheid tijdens en na behandeling voor kanker wordt geen relatie gevonden tussen vermoeidheid aan de ene kant en demografische variabelen en ziekte- en behandelingskarakteristieken aan de andere kant. Wel blijkt dat vermoeidheidsklachten gerelateerd zijn aan psychische klachten zoals angst en depressie, problemen op het gebied van slaap en verminderd fysiek functioneren. Studies die zich richten op interventies om vermoeidheidsklachten te verminderen beperken zich tot interventies tijdens de behandeling voor kanker of vlak na het beëindigen van de behandeling. Deze studies rapporteren een positief effect op vermoeidheid, gemeten vlak na de interventie.

In de besproken artikelen werd gebruik gemaakt van een groot aantal verschillende vragenlijsten om vermoeidheid te meten. Veel van deze vragenlijsten zijn niet getoetst op validiteit en betrouwbaarheid en vaak waren er geen normgegevens beschikbaar. Bovendien zijn de meeste van deze vragenlijsten een-dimensioneel (ze meten slechts de intensiteit van vermoeidheid) in tegenstelling tot de multidimensionele vermoeidheidsvragenlijsten. Vanwege deze tekortkomingen stellen we in de discussie van dit artikel dat het belangrijk is om in toekomstig onderzoek gebruik te maken van valide en betrouwbare multidimensionele instrumenten om vermoeidheid te meten, voor welke normgegevens van gezonde controles en/of andere patiëntenpopulaties beschikbaar zijn. Alleen dan is het mogelijk om te kunnen vaststellen of de vermoeidheidsbeleving van (ziekte-vrije) kankerpatiënten, gezonde controles en andere patiëntengroepen verschilt. Tenslotte geven we aan dat het belangrijk is om longitudinale studies uit te voeren om initiërende en in stand houdende factoren van vermoeidheid tijdens en na behandeling voor kanker te achterhalen.

Het doel van het artikel in *Hoofdstuk 3* was het meten van vermoeidheid aan de hand van een gevalideerde multidimensionele vermoeidheidsvragenlijst, in een groep van 85 ziekte-vrije kankerpatiënten met uiteenlopende kankerdiagnoses. Van deze vragenlijst, de Checklist Individuele Spankracht, zijn normgegevens van gezonde controles en verschillende patiëntenpopulaties beschikbaar. Verder wilden we in deze studie de relatie onderzoeken tussen ernstige vermoeidheid enerzijds en eerdere behandeling voor kanker, concentratieproblemen, motivationele problemen, fysieke activiteit, functionele beperkingen, depressie en angst anderzijds. Tenslotte wilden we bekijken in hoeverre de ernstig vermoeide ziekte-vrije kankerpatiënten leken op patiënten met het Chronisch Vermoeidheids Syndroom (CVS). De ziekte-vrije kankerpatiënten hadden de behandeling voor kanker 6 maanden tot 12,5 jaar geleden afgesloten. Negentien procent van de ziekte-vrije kankerpatiënten bleek te kampen met ernstige vermoeidheidsklachten. Geen relaties konden worden aangetoond tussen ernstige vermoeidheid enerzijds en het soort kanker, type behandeling, duur van de behandeling en tijd sinds beëindiging van de behandeling, anderzijds. Wel vonden we dat ernstige vermoeidheid gepaard ging met concentratieproblemen, lage motivatie, afgenomen fysieke activiteit, depressie en angst. Tenslotte toonden we aan dat ernstig vermoeide ziekte-vrije kankerpatiënten vergelijkbaar waren met een op leeftijd en geslacht gematchte groep patiënten met CVS, voor wat betreft de hoogte van depressie, verminderde motivatie en afgenomen fysieke activiteit. CVS patiënten rapporteerden meer concentratieproblemen.

In *Hoofdstuk 4* worden de resultaten beschreven van een cross-sectioneel onderzoek waaraan 150 ziekte-vrije borstkankerpatiënten deelnamen. Het doel van dit onderzoek was eveneens het meten van ernstige vermoeidheid, maar nu in grotere, meer homogene groep ziekte-vrije patiënten. De patiënten in dit onderzoek waren allen behandeld voor borstkanker, waren jonger dan 50 jaar bij de diagnose en hadden hun behandeling voor borstkanker 6 tot 70 maanden geleden afgesloten. In dit onderzoek is gebruik gemaakt van een meetmethode om negen verschillende dimensies te meten, namelijk: ernst van de vermoeidheid, psychisch welbevinden, beperkingen in het dagelijks leven ten gevolge van de vermoeidheid, slaapproblemen, fysieke activiteit, concentratieproblemen, sociaal functioneren en sociale steun, attributies (waar de patiënt zijn klachten aan toeschrijft) en de verwachtingen over de eigen beïnvloedingsmogelijkheden van de vermoeidheid (self-efficacy). In de onderzochte groep bleek 38 procent ernstig vermoeid te zijn, vergeleken met 11 procent in een op leeftijd gematchte groep vrouwen die in hun leven nooit voor kanker waren behandeld. Vermoeidheidsscores waren niet significant verschillend voor patiënten die een borstbesparende operatie of een borstamputatie hadden ondergaan. Evenmin vonden we verschillen tussen de patiëntengroepen die radiotherapie, chemotherapie of een combinatie van radiotherapie en chemotherapie nodig hadden gehad na de operatie. Bovendien vonden we geen verschil tussen deze 3 patiëntengroepen en patiënten die geen nabehandeling hadden ondergaan, maar hier komen we in Hoofdstuk 8 op terug. De 'ernstig vermoeide ziekte-vrije borstkankerpatiënt' bleek op verschillende dimensies hoger te scoren dan de 'niet ernstig vermoeide ziekte-vrije borstkankerpatiënt'. Zo rapporteerden de ernstig vermoeide patiënten meer angst en depressie. Ze ervoeren meer problemen met betrekking tot het uitvoeren van hun dagelijkse activiteiten thuis of op hun werk. Ze hadden vaker last van slaap-, geheugen- en concentratiestoornissen, waren minder fysiek actief en ervoeren minder sociale steun. Tenslotte was ernstige vermoeidheid in sterke mate gerelateerd aan lage self-efficacy en aan sterke attributies met betrekking tot de behandeling voor borstkanker en psychische oorzaken, zoals piekeren.

In *Hoofdstuk 5* wordt een onderzoek beschreven dat is uitgevoerd bij dezelfde 150 ziekte-vrije borstkankerpatiënten. Het doel van dit onderzoek was het analyseren van de relatie tussen vermoeidheid enerzijds en neuropsychologisch functioneren en fysieke activiteit anderzijds. Uit het onderzoek van Hoofdstuk 4 wisten we al dat ernstige vermoeidheid samenging met zelfgerapporteerde problemen op het gebied van concentratie, geheugen en fysiek functioneren, maar onduidelijk blijft of dit ook werkelijk zo is, of dat dit slechts de beleving van de patiënt is. Daarom werden in het huidige onderzoek neuropsychologisch functioneren en fysieke activiteit op drie manieren gemeten: 1) aan de hand van algemene zelfrapportage vragenlijsten; 2) met dagelijkse zelfrapportage lijsten waarop patiënten 4 keer per dag aangeven of ze concentratie en/of geheugen problemen hebben ervaren en in welke mate ze fysiek actief zijn geweest; en 3) aan de hand van meetinstrumenten van het werkelijke gedrag. Neuropsychologisch testen werden afgenomen om concentratie en reactievermogen te meten. Bovendien droegen patiënten gedurende een periode van 12 dagen, een aktometer om hun enkel om werkelijke fysieke activiteit te meten. De aktometer is een apparaat ter grootte van een luciferdoosje, dat bewegingen registreert. Uit de resultaten bleek dat vermoeidheid in sterke mate gerelateerd is aan algemeen en dagelijks geregistreerd neuropsychologisch functioneren. Vermoeidheid bleek echter niet samen te hangen met de scores op de neuropsychologische testen. Met betrekking tot de relatie tussen vermoeidheid en fysieke activiteit, bleek er alleen een verband te zijn met de rapportage op algemene vragenlijsten. Vermoeidheid bleek niet gerelateerd aan dagelijks geregistreerde fysieke activiteit en aan werkelijke fysieke activiteit, gemeten met de aktometer.

Het doel van de studie in *Hoofdstuk 6* was om te onderzoeken in hoeverre ernstig vermoeide ziekte-vrije kankerpatiënten vergelijkbaar zijn met patiënten met het Chronisch Vermoeidheids Syndroom (CVS). In dit artikel werden 57 ernstig vermoeide ziekte-vrije borstkankerpatiënten vergeleken met 57 op leeftijd en geslacht gematchte CVS patiënten, op de dimensies ernst van vermoeidheid, mate van beperkingen in het dagelijks leven, self-efficacy, psychisch welbevinden, slaap, concentratie, lichamelijke activiteit, sociale steun en pijn. CVS patiënten bleken hogere vermoeidheidsscores te hebben, meer beperkingen te ervaren in het dagelijks functioneren, minder fysiek actief te zijn, meer pijn te ervaren en in mindere mate het idee te hebben dat ze zelf invloed kunnen uitoefenen op hun vermoeidheid, dan de vermoeide ziekte-vrije borstkankerpatiënten. Er was echter wel een subgroep binnen de groep ziekte-vrije kankerpatiënten die even hoog scoorde als de groep CVS patiënten op psychisch onwelbevinden, slaapproblemen en concentratiestoornissen. Tenslotte ervoeren de ziekte-vrije kankerpatiënten en de CVS patiënten evenveel problemen met betrekking tot de ervaren sociale steun. Gezien de hierboven genoemde verschillen en gezien het feit dat er binnen de groep kankerpatiënten een grotere spreiding is op de genoemde dimensies dan bij CVS patiënten, is het zeer waarschijnlijk dat een model van in stand houdende factoren voor vermoeidheid na kanker op enkele belangrijke punten zal verschillen van het CVS-model, hetgeen implicaties heeft voor de behandeling van vermoeidheid na behandeling voor kanker. Cognitieve gedragstherapie voor vermoeidheid na behandeling voor kanker zal in ieder geval, vanwege de grote spreiding in deze groep, in sterkere mate moeten worden aangepast aan elke individuele ex-kankerpatiënt dan bij CVS het geval is.

In *Hoofdstuk 7* wordt een longitudinaal onderzoek beschreven waaraan 170 patiënten, die 1 tot 15 jaar geleden behandeld waren voor een kwaad- of goedaardige bottumor, deelnamen. Een van de doelen van dit onderzoek was om te onderzoeken of vermoeidheid vaker voorkwam na behandeling van een kwaadaardige tumor dan na behandeling van een goedaardige tumor. Omdat de behandeling voor bottumoren verschilt van de behandeling voor borstkanker, wilden we in ook deze patiëntengroep onderzoeken of vermoeidheid gerelateerd was aan eerdere behandeling voor kanker. Bovendien was er in deze groep een groter bereik wat betreft de tijd sinds de beëindiging van de behandeling dan in onze borstkankerpopulatie. Dit gaf ons de mogelijkheid om te onderzoeken of patiënten die hun behandeling recent hadden afgesloten ernstiger moe waren dan patiënten voor wie dit langer geleden was. Tenslotte konden we vanwege het longitudinale karakter van deze studie de instandhoudende factoren van vermoeidheid onderzoeken. Ernstige vermoeidheidsklachten bleken voor te komen bij 28 procent van de 170 onderzochte ziekte-vrije patiënten. Er werden geen verschillen in vermoeidheidsscores gevonden tussen de groep die voor een kwaadaardige en de groep die voor een goedaardige tumor was behandeld. Vermoeidheidsklachten waren het meest ernstig voor patiënten die de behandeling voor kanker slechts 1 tot 2 jaar geleden hadden afgesloten en voor patiënten die meer dan 1 operatie hadden moeten ondergaan. Twee jaar na de eerste meting bleek dat de meerderheid van de patiënten die ernstig vermoeid was nog steeds ernstig vermoeid was. Oncologische complicaties na de primaire behandeling, weinig optimisme en gerichtheid op lichamelijke sensaties bleken voorspellers van ernstige vermoeidheid.

In *Hoofstuk 8* wordt het vervolg op de cross-sectionele borstkankerstudie (hoofdstuk 4 en 5) gepresenteerd. Het doel van dit vervolg was om te onderzoeken of ernstige vermoeidheid na behandeling van borstkanker een aanhoudend probleem was. Bovendien wilden we weten of aanhoudende vermoeidheid misschien wel gerelateerd was aan eerdere behandeling. En tenslotte wilde we onderzoeken welke factoren bijdroegen aan de instandhouding van ernstige vermoeidheidsklachten. Na de baseline-meting werd de groep ziekte-vrije borstkankerpatiënten gedurende een periode van 2 jaar gevraagd om elke maand een vermoeidheidsvragenlijst in te vullen en om na 2 jaar terug te komen voor een uitgebreide follow-up meting. Van de 150 patiënten hebben 121 patiënten de studie volledig afgerond. Negentien patiënten ontwikkelde een recidief tijdens de 2 onderzoeksjaren en 10 patiënten zijn voortijdig gestopt met het onderzoek om diverse redenen. Gebaseerd op de maandelijkse vermoeidheidsvragenlijsten vonden we dat 24 procent van de ziekte-vrije borstkankerpatiënten aanhoudende klachten van ernstige vermoeidheid ervoer. Deze aanhoudende vermoeidheid bleek minder voor te komen bij patiënten die geen nabehandeling (radiotherapie en/of chemotherapie) hadden ondergaan en bij wie tevens de operatie (borstbesparende operatie of amputatie) zonder complicaties was verlopen. Angst, beperkingen met betrekking tot het uitvoeren van dagelijkse activiteiten thuis of op het werk en het idee weinig controle te hebben over de vermoeidheidsklachten bleken voorspellers van aanhoudende vermoeidheid te zijn.

In *Hoofdstuk 9* tenslotte volgt een discussie omtrent de resultaten die in dit proefschrift genoemd worden. Bovendien worden er beperkingen en implicaties van het door ons uitgevoerde onderzoek besproken. We concluderen dat voor ongeveer 25 procent van de ziekte-vrije kanker patiënten ernstige vermoeidheid een aanhoudend probleem is, dat gepaard gaat met problemen en beperkingen op diverse terreinen. Aanhoudende vermoeidheidsklachten kwamen minder vaak voor bij patiënten voor wie de behandeling relatief kort had geduurd. Dit waren de patiënten die slechts 1 operatie zonder complicaties hadden ondergaan en bij die geen nabehandeling nodig was geweest. Factoren die verantwoordelijk waren voor de instandhouding van ernstige vermoeidheid waren lage self-efficacy, angst, beperkingen in het dagelijks functioneren, weinig optimisme en gerichtheid op lichamelijke sensaties. Verder is het aannemelijk dat ook menopausale klachten en moeite met de verwerking van de ervaring met kanker een rol spelen.

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