Exploring Fatigue in Cancer Patients

From diagnosis until one year after cancer treatment

Martine M. Goedendorp

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Martine Margaretha Goedendorp
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- Promotoren: Prof. dr. G. Bleijenberg
  Prof. dr. W.T.A. van der Graaf

- Copromoteren: Dr. C.A.H.H.V.M. Verhagen
  Dr. M.F.M. Gielissen

- Manuscriptcommissie: Prof. dr. K.C.P. Vissers (voorzitter)
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Voor

Paps en Mams

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Chapter 1

General introduction

HISTORY OF CANCER

The earliest descriptions of patients with cancer were found in pieces of writing by Hippocrates, the Greek physician who lived 25 centuries ago. He described patients with lumps on the skin, nose and breasts. Inspired by the shapes of these lumps he spoke about karkinos (crab) or karcinoma.

Hippocrates was very reluctant in treating cancer: "When the lump is not septic, one should just leave it at that", he said. A wise decision, because cutting it away, at that time the only possible treatment, was a very risky and painful procedure.

The causes of diseases were explained by humouralism. This theory held that when a person is healthy the four basic substances of the human body; blood, yellow bile, black bile and phlegm are supposed to be in balance. "Cancer originated by local accumulation of the black bile" raised the physician Galenos in the second century A.D. The treatment of cancer remained similar until the 19th century; diets, laxatives, and phlebotomy (bloodletting).

Since the 19th century the theories about health and diseases changed radically after the discovery of organs, tissues and cells of the human body. With the use of newfound anaesthetics and insights in hygiene, the possibilities for surgical interventions and later radiotherapy and chemotherapy changed the chances for increased survival strongly. Cancer is uppermost a disease of modern times. In the Netherlands cancer is nowadays the most frequent cause of death[1].

SOME NUMBERS

Cancer is a collective term for more than hundred different diseases. Al these different types of cancer have one shared characteristic: abnormal uncontrolled growth of cells, loss of function and dissemination[2]. In 2005 at least 81.000 new

cases were diagnosed with cancer in the Netherlands, 42.000 were men, 39.000 were women. The total prevalence of cancer in the Netherlands was estimated around 400.000 patients, 2.5% of the population. Breast cancer is the most common type of cancer followed by skin cancer, colon cancer and prostate cancer. Compared to 2004 the number of new cases rose, mainly because of growth and aging of the population. The changes of survival depend on the type and stage of cancer. Approximately half of all patients who are diagnosed with cancer receive oncological treatment with the intent to cure. The chances of survival have increased slowly but steady in the last decennia[3].

FATIGUE IN CANCER SURVIVORS

Research at the Expert Centre for Chronic Fatigue

Now that the prevalence of cancer is increasing and more patients survive, more people have to deal with the consequences of cancer. Fatigue is the first mentioned consequence by the Dutch Cancer Society. Not only for patients who are living with cancer[4], but also as a long term consequence for cancer survivors[5].

The Expert Centre Chronic Fatigue, as a part of the Radboud University Nijmegen Medical Centre, was founded in 1990. It started as a collaboration of scientists from different disciplines to study incidence and origin of chronic fatigue and chronic fatigue syndrome, and in later years also the treatment and implementation of treatment strategies. Since then it also focused on fatigue in other groups, for example among employees[6], Cambodia veterans[7], in patients with neuromuscular disorders[8, 9], multiple sclerosis[10], and rheumatoid arthritis[11].

In 1996 the Expert Centre started to study fatigue in cancer survivors. A review, based on studies between 1980 and 2001, showed that the prevalence of fatigue during cancer treatment varied between 25% and 99% in different samples of cancer patients and measured with different questionnaires. In disease-free cancer patients fatigue remained problematic in about 20% to 40%[12,13].

Fatigue was studied in several groups of disease-free cancer patients, who finished treatment at least 6 months before participation. These studies showed

that severely fatigued cancer survivors experienced numerous problems and limitations in several areas of life, such as psychological well-being, functional impairment in daily life, sleep disturbances, physical activity, neuropsychological impairment, social functioning/social support, self-efficacy and causal attributions[14]. A longitudinal study, that followed fatigued in breast cancer survivors for two years found that, women who only received surgery without complications were at lower risk for persistent fatigue. Persistent fatigue was unrelated to type of surgery, type of adjuvant therapy and to time since treatment was finished[15].

Physicians and other care providers now recognize that fatigue after successful cancer treatment is a serious problem. Patient organizations and individual cancer survivors accomplished a lot to get this problem acknowledged[16]. Unfortunately many cancer survivors are told that severe fatigue is a consequence of their former oncological treatment and that they "just have to live with it". Contrary to this message, cancer survivors should be informed about the treatment options for ongoing severe fatigue. An effective treatment option is individually tailored cognitive behaviour therapy (CBT) for post cancer fatigue.

Cognitive Behaviour Therapy for postcancer fatigue

For a proper understanding of chronic fatigue following successful cancer treatment a model of precipitating and perpetuating factors was introduced. The assumption is that the cancer itself and the treatment might have triggered fatigue, but as it was demonstrated that disease and treatment characteristics were unrelated to the severity of post-cancer fatigue[12, 17-21], it is plausible that over time other factors caused fatigue to persist. To treat chronic fatigue in cancer survivors a specific kind of CBT was developed directed at the perpetuating factors. The treatment protocol encompasses six modules that coincide with the following perpetuating factors: 1) Poor coping with cancer and cancer treatment, 2) Excessive fear of disease recurrence[20, 21], 3) Dysfunctional cognitions regarding fatigue, such as somatic attributions, non-acceptance of symptoms / impairments, catastropising[22] and negative self-efficacy, 4)

Dysregulatory sleep-wake cycle[12, 19, 21], 5) Dysregulatory activities, such as physical mental and social activities, 6) low social support and negative interactions[23]. A RCT showed that CBT was a highly clinically and significantly effective treatment for long term cancer survivors suffering from severe fatigue. This effect was maintained after about two year follow-up period. CBT for postcancer fatigue elicited a clinically relevant reduction in fatigue and functional impairments in long term cancer survivors. in severely fatigued cancer survivors who finished cancer treatment about five years earlier [24, 25].

Although severe fatigue in long term cancer survivors can be treated successfully with CBT it would be more desirable to prevent fatigue in cancer survivors by an intervention in an earlier stage. Therefore, one of the aims of this research project was to evaluate whether an intervention during treatment of cancer was effective in managing fatigue and whether it could prevent persistent fatigue in cancer survivors.

The course of fatigue in cancer patients

In the literature a few longitudinal studies on fatigue in cancer patients have been reported. For example, fatigue was investigated in breast cancer patients who received chemotherapy[26] or radiotherapy[27]. In both studies women were assessed before these oncological treatments and in the years thereafter. In the study of Nieboer et al. (2005) women were assessed 1, 2 and 3 years after chemotherapy, and in the study of Geinitz et al. (2004) 2,5 years after radiotherapy. It is generally assumed that the level of fatigue increases from the pre- to the post-treatment period, but both studies found not change in fatigue. This inconsistency could be the result of methodological flaws, such as fatigue not being assessed frequently enough to detect fluctuations[28]. The finding that no change in fatigue was found could also be due to the relatively homogeneous characteristics of the sample, or the fact that most women were not treatment naïve at baseline.

Two other studies investigated fatigue in a group of cancer patients treated for various malignancies. In the study of Given et al., (2001) older cancer patients were observed at 6-8, 12-16, 24-30, and 52 weeks[29]. In the study of Smets et al.,

(1998)[30] fatigue was examined in disease-free cancer patients 9 months after being treated with radiotherapy. Both studies did find an effect of disease characteristics on fatigue. For example, lung cancer patients had the most fatigue. It should be noted that the baseline assessment took place incongruent with the phases of the oncological treatments. None of these longitudinal studies provided insight in the course of fatigue from diagnosis into the year after cancer treatment.

It is generally assumed that fatigue arises during active cancer treatment, as a consequence of the oncological treatment, the disease itself, and possibly associated distress.

Many cancer patients experience fatigue in the period during active treatment for cancer. Prevalences of 90% or higher have even been reported[12, 19]. When cancer treatment is finished most cancer survivors recover spontaneously from the direct effects of the oncological treatment. Based on the study of Servaes et al. (2007) it was expected that a relatively large group of cancer patients would be severely fatigued shortly after cancer treatment, about 40 - 50%. It is assumed that the occurrence of severe fatigue decreases during the first year after cancer treatment to about 30% - 40% and would stabilize in the years thereafter to about 25%[15]. These assumptions however were never been confirmed in longitudinal studies with assessments before the start of any oncological treatments.

The design of the studies described in this thesis was as follows: patients who just received the diagnosis cancer were assessed before the start of cancer treatment, shortly after cancer treatment, and monthly for a year thereafter. Patients were asked to participate in a RCT in which they would be assigned to one of three conditions: 1) CBT intervention, 2) brief nursing intervention 3) usual oncological care. With the RCT we could test the short and long term effectiveness of these two interventions in reducing fatigue during curative cancer treatment. With this design also other questions could be answered such as; a) Is severe fatigue already an issue before the start of cancer treatment? b) What is the natural course of fatigue in the year after cancer treatment is finished? c) Can we identify predictors of persistent fatigue after successful

cancer treatment? These and other research questions are outlined in this dissertation.

OUTLINE OF THIS DISSERTATION

When this research project started the literature was lacking solid evidence to what extent psychosocial interventions could be effective to reduce fatigue in patients who were actively treated for cancer. There were some reviews that included psychosocial interventions as a strategy to manage fatigue, but these reviews were based on interventions for cancer patients irrespective of the phase of cancer treatment. Thus the reviews were based on studies that included patients during cancer treatment, patients who finished cancer treatment, or both. The *second chapter* describes the systematic review that evaluated if psychosocial interventions were effective in reducing fatigue in cancer patients receiving active treatment for cancer. Additionally it was determined which specific types of psychosocial interventions during cancer treatment were the most effective in reducing fatigue.

Studying the literature revealed that fatigue in cancer patients prior to treatment was seldom investigated, although there were indications that fatigue could already be problematic particularly at that stage. Therefore we investigated the occurrence of severely fatigued after being diagnosed with various types of malignancies, but before initiation of any medical treatment for cancer. Secondly, it could be established which factors contributed to severe fatigue in treatment naïve cancer patients. The results of this study are presented in *chapter three*.

In the *fourth chapter* two interventions for fatigue during curative cancer treatment were evaluated and compared to usual care in a randomised controlled trial. The first intervention was a brief nursing intervention (BNI), the latter cognitive behaviour therapy (CBT).

The BNI focused only on physical activity. Intervening on physical activity to reduce fatigue is based on the assumption that a lack of physical activity and

deconditioning during cancer treatment can worsen fatigue. When patients are diagnosed with cancer, their activity pattern changes and they become physically less active, possible leading to deconditioning. It is presumed that this is the result of a negative spiral, because when patients become physically less active they become more easily fatigued, and when patients experience fatigue they react by becoming physically even less active. With the BNI it was intended to avoid or break this negative spiral.

The CBT was, in addition to breaking the negative spiral of physical activity, focused on other elements such as changing dysfunctional cognitions about fatigue, changing a distorted sleep-wake rhythm, and on coping with the consequences of having cancer. In this study it was investigated if fatigue shortly after cancer treatment could be reduced early or prevented with these interventions given during cancer treatment.

It is generally assumed that increasing physical activity is important in reducing fatigue during cancer treatment. However, the contribution of physical activity in interventions was previously not established. Therefore we aimed to investigate if increasing physical activity had a mediating role on the reduction in fatigue.

The intervention study focused on a broad group of participants. Patients with various malignancies, receiving treatment with curative intent participated, but also with different pre-treatment levels of fatigue and other symptoms. Therefore it was expected that some groups of patients would benefit more from an intervention for fatigue during cancer treatment than others. *In chapter five* an exploratory study is presented that identified which patients benefitted the most from the intervention. As fatigue was assessed every month during a year after the post-intervention assessment the long term effects of the interventions in the year post-intervention could be investigated too. The follow-up results of the interventions are also presented in this chapter.

In *chapter six* we describe the natural course of fatigue in cancer survivors in a prospective follow-up study from diagnosis into the year after successful cancer

treatment. The first aim of this study was to determine the occurrence of severe persistent fatigue in the year after successful cancer treatment. Early identification and treatment of cancer patients at risk for persistent fatigue could shorten the period of invalidating persistent fatigue. Therefore our second aim was to explore which pre-treatment, post-treatment and cancer-related factors predicted persistent fatigue.

Our last aim was to investigate if the known fatigue perpetuating factors found in long term cancer survivors (described above in detail) also have a predictive value for persistent fatigue in the year after cancer treatment? More specifically, can the six fatigue perpetuating factors assessed shortly after cancer treatment predict persistent fatigue? If this would be the case, cancer survivors suffering from severe fatigue might already be treated with CBT for postcancer fatigue at an earlier stage, shortly after successful cancer treatment.

In the final *chapter seven*, our results are put in a broader daylight and learning points are discussed.

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Chapter 2

Psychosocial interventions for reducing fatigue during cancer treatment in adults

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Martine Goedendorp, Marieke Gielissen, Stans Verhagen, Gijs Bleijenberg.

ABSTRACT

Background: Fatigue is a common symptom in cancer patients receiving active treatment. There are a limited number of reviews evaluating interventions for fatigue *during* active treatment, and they are restricted to patients with advanced cancer, or to patients during radiotherapy. To date there is no systematic review on psychosocial interventions for fatigue during cancer treatment.

Objectives: To evaluate if psychosocial interventions are effective in reducing fatigue in cancer patients receiving active treatment for cancer, and which types of psychosocial interventions are the most effective.

Search methods: In September 2008 we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), PUBMED, MEDLINE, EMBASE, CINAHL and PsycINFO, and checked the reference lists.

Selection criteria: Randomised controlled trials (RCTs) were included which evaluated psychosocial interventions in adult cancer patients during treatment, with fatigue as an outcome measure.

Data collection and analysis: Three review authors independently extracted data from the selected studies, and assessed the methodological quality using several quality rating scales and additional criteria.

Results: Twenty-seven studies met the inclusion criteria with a total of 3324 participants, and seven studies reported significant effects of the psychosocial intervention on fatigue. In three studies the effect was maintained at follow-up. The quality of the studies was generally moderate. Effect sizes varied between 0.17 to 1.07. The effectiveness of interventions specific for fatigue was significantly higher (80%) compared to interventions not specific for fatigue (14%). In five studies the interventions were specifically focused on fatigue, with four being effective. The five interventions were brief, consisting of three individual sessions, provided by (oncology) nurses. In general, during these interventions participants were educated about fatigue, were taught in self-care or coping techniques, and learned activity management. Of the remaining 22 studies only three were effective in reducing fatigue, and these interventions had a more general approach. These interventions were aimed at psychological distress, mood and physical symptoms, and varied strongly in duration and content.

Authors' conclusions: There is limited evidence that psychosocial interventions during cancer treatment are effective in reducing fatigue. At present, psychosocial interventions specifically for fatigue are a promising type of intervention. However, there is no solid evidence for the effectiveness of interventions not specific for fatigue. Most aspects of the included studies were heterogeneous, and therefore it could not be established which other types of interventions, or elements were essential in reducing fatigue.

PLAIN LANGUAGE SUMMARY

There is limited evidence that psychosocial interventions are effective in reducing fatigue during active treatment in cancer patients. Most promising are psychosocial interventions specifically designed to treat fatigue. In general, during these interventions patients were educated about fatigue, were taught in self-care or coping techniques, and learned to manage their activity. Interventions that did not focus on fatigue were rarely effective in reducing fatigue.

BACKGROUND

In recent years the treatment of cancer has changed, as more people are treated and an increasing number survive the disease. The primary focus of treatment for cancer is survival, but alongside this the management of symptoms and quality of life of patients are also becoming important. Fatigue is one of the symptoms most commonly reported by cancer patients and is gaining more recognition by oncologists. In addition to this scientific knowledge about fatigue in cancer patients is growing. Fatigue can be described in terms of perceived energy, mental capacity and psychological status and is therefore a multidimensional concept[1, 2]. Fatigue is sometimes seen as a continuum, ranging from tiredness to exhaustion[3].

Cancer-related fatigue (CRF) is a term that is frequently used. The National Comprehensive Cancer Network (NCCN) defines CRF as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion, related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning[4]. Cancer patients can experience fatigue at different stages, for example, during cancer treatment or shortly after finishing treatment. Disease-free cancer patients can also experience fatigue. The prevalence of fatigue during cancer treatment ranges from 25% to 99% depending on the sample and on the type of instrument used to measure fatigue[5]. After successful cancer treatment, fatigue can still be a problem in up to 38% of cancer survivors and can persist for many years[6]. It is important to note that the term CRF does not make a distinction between fatigue during cancer treatment, and fatigue after finishing treatment, but covers the whole period.

Efforts to manage fatigue should first focus on identifying and treating the comorbidities that may cause it, for example, anaemia or hypothyroidism. However, often no specific cause for fatigue can be identified in patients during cancer treatment, other than the cancer or the treatment itself. In these situations the management of fatigue usually involves multiple strategies. The

strategies are often divided into pharmacological and non-pharmacological interventions.

Minton (2008) reviewed drug therapy for the management of CRF and concluded that erythropoietin and darbopoetin, drugs that improve anaemia, are effective in managing CRF in patients who are anaemic as a result of chemotherapy[7]. However, currently concerns are raised about the safety of these drugs as a series of recent, randomised placebo-controlled clinical trials reported adverse effects including enhanced tumour progression and increased mortality[8, 9]. Methylphenidate was also effective, but more research is needed to confirm this. No data currently supports the use of paroxetine or progestational steroids for treatment of CRF[7]. This review included studies that recruited participants at any point of the cancer treatment spectrum. A Cochrane review is also in progress evaluating drugs for the treatment of fatigue in palliative care[10].

There are an increasing number of studies with exercise as a non-pharmacological intervention for cancer patients. Current literature suggests that exercise is likely to be beneficial, but the latest reviews draw conflicting conclusions about the role of exercise on managing fatigue[11]. Some reviews concluded that exercise had a positive effect on fatigue[12, 13] while others found no effect of exercise on fatigue[14-16]. In addition a Cochrane review investigating exercise for fatigue in cancer patients is also now published[17].

All reviews mentioned above were based on studies that included cancer patients during active treatment and disease-free survivors. In the review of Ahlberg (2003) a distinction was made between studies evaluating exercise during cancer treatment and after treatment, and concluded that in all studies the exercise groups had lower levels of fatigue[3]. Contrary to this, the Cochrane review of Markes (2006) concluded that exercise had no effect on fatigue in breast cancer patients during adjuvant therapy[18].

In recent years more studies have evaluated psychosocial interventions for the management of fatigue. The aim of a psychosocial intervention is to influence or change cognitions, emotions, behaviour, the social environment or a combination of these, with the ultimate goal to decrease fatigue.

Some reviews have included psychosocial interventions as a subgroup for managing fatigue in cancer patients and these interventions have been regarded as some of the more promising treatments, but further research was recommended [19, 20]. A recent meta-analysis is less positive and concluded that there is limited support for the clinical use for psychological interventions for CRF[14]. However, these reviews were based on studies that included patients during the whole spectrum of cancer treatment, as well as disease-free survivors.

There are only a limited number of reviews that evaluated interventions for fatigue in patients who received active treatment. These reviews were restricted to certain patient groups, for example to patients with advanced cancer[21], metastatic breast cancer[22], or to patients during radiotherapy[23, 24].

To date, no systematic review has been published evaluating the effectiveness of psychosocial interventions for fatigue during cancer treatment, which was the goal of this review. In this review we identified studies that tested the effectiveness of psychosocial interventions in randomised controlled trials (RCT). First we described which psychosocial interventions were effective in reducing fatigue, and how strong the effects were by using effect sizes. Secondly, the quality of the studies was evaluated. Finally, the more promising psychosocial interventions for reducing fatigue during cancer treatment are discussed.

OBJECTIVES

The primary objective was to evaluate if psychosocial interventions are effective in reducing fatigue in cancer patients receiving active treatment for cancer. The secondary objective was to consider which specific types of psychosocial interventions during cancer treatment are the most effective in reducing fatigue.

METHODS

Criteria for considering studies for this review

Types of intervention

Only RCTs were included in this review. In addition, studies with small sample sizes (less than ten participants) were excluded, as this causes a lack of power to demonstrate the effect of an intervention. This means that when no significant effect of an intervention is found, this doesn't necessarily mean that the intervention is not effective at all. Finding no effect of the intervention can be explained by the small sample size of the studies. Thus the results of these studies can be misinterpreted easily.

Types of participants

Adult (those aged 16 years and above) cancer patients of either sex, receiving active treatment for cancer, with curative or palliative intention. This review focused only on patients receiving active cancer treatment and not on patients who finished cancer treatment. Although some cancer survivors, specifically breast cancer survivors, continue to receive hormone therapy for several years, in this review this group of survivors was considered as a group who finished the active period of receiving cancer treatment.

Types of interventions

A broad range of interventions were considered, such as psychotherapy, psycho-education and also interventions containing elements such as; education, cognitive restructuring and changing coping strategies. Interventions focusing on behavioural changes were included, for example; behavioural therapy, self-help or self-care. In addition other intervention types such as; support groups, relaxation, energy conservation, or stress management, and interventions combining psychosocial elements with physical activity were included. Both individual and group-focused interventions were included.

The psychosocial intervention needed to fulfil the following conditions:

- the interventions involved a systematic treatment consisting of a process between the patient and the person giving the intervention;
- the interventions consisted of at least two contacts between the patient and the care provider who gave the intervention;
- during the intervention a care provider gave the patient some kind of personal feedback concerning the changes they were trying to achieve, for example, in the first session a care provider could advise a patient to change their coping behaviour aiming to reduce fatigue, whilst discussing the progress of the patient and giving feedback on their behaviour in later sessions.

Types of outcome measures

In the included studies, fatigue was at least one of the outcome measures. Studies were included when fatigue was measured with a questionnaire specifically designed to evaluate fatigue, or other instruments used by authors to evaluate fatigue. For example, fatigue was measured as part of a quality of life instrument, with a visual analogue scale (VAS), or as part of a symptom list and scored as 'present' or 'absent'.

Search methods for identification of studies

1) Electronic databases

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, September 2008), PUBMED (1950 to September 2008), MEDLINE (1966 to September 2008), EMBASE (1980 to September 2008), CINAHL (1982 to September 2008) and PsycINFO (1806 to September 2008).

We identified studies for this review using search strategies based on the MEDLINE (via OVID) strategy set out in Appendix 1, which uses a combination of MeSH and free text terms. MeSH terms were exploded. Terms were searched in the title, abstract, summary, heading or keywords. We applied the Cochrane Collaboration filter for the identification of RCTs, as published in the Cochrane

Handbook for Systematic Reviews of Interventions[25]. We adjusted the search strategy appropriately for each database searched.

2) Reference search

We checked the reference lists of relevant articles for additional studies, and applied backward and forward searching to the relevant articles.

3) Journals

When no digital articles are available, we hand searched the journals.

4) Communications

We contacted authors of several studies to require additional information.

5) Ongoing studies

We checked The Australian New Zealand Clinical Trials Registry, the ClinicalTrials.gov registry, the ISRCT register, UMIN Clinical Trials Registry, and the Dutch Trial Register, for ongoing studies. We searched each register for the keywords 'cancer' and 'fatigue', and selected studies that were currently recruiting participants. There was no language restriction on studies.

Data collection and analysis

Selection of trials

One review author (MMG) screened titles and abstracts and eliminated those clearly not relevant to this review. When the title and abstract did not provide all the information concerning the criteria, full paper copies were retrieved and screened. Authors of studies were contacted when additional information was required to assess if the studies met the criteria for inclusion. Three review authors (MMG, MG and GB) screened the remaining studies for their eligibility and discussed in accordance with the above defined criteria, if the studies were included or excluded. Disagreement about the selection of a trial was resolved by consensus. The review authors were already familiar with some of the studies, and therefore the relevant studies were not blinded for assessment.

Quality assessment

Three review authors (MMG, MG and GB) independently assessed the methodological quality of the selected studies. The RCTs were evaluated using a Quality Rating Scale. This scale contained all the criteria of the Oxford Quality Scale[26], the Delphi list[27] and additional criteria listed by Van Tulder (1997)[28]. The following aspects of the selected studies were scored to evaluate the methodological quality:

- random assignment;
- losses to follow-up;
- blind analysis;
- intention-to-treat analysis;
- participants adherence;
- adverse effects of the intervention;
- eligibility criteria;
- follow-up measurements;
- power calculation;
- possible differences between the treatment group and the control group, and in the timing of the assessments;
- concealed allocation;
- contamination.

Concealment of allocation was evaluated using the criteria defined in The Cochrane Handbook[25]. When nothing was described about concealment of allocation in the studies, concealed allocation was evaluated as 'unclear'. To investigate the effectiveness of an intervention it is important to minimize contamination. Contamination means that patients in the control group get informed about the intervention and its content, and subsequently use this information. When this happens the effect of the intervention itself is harder to demonstrate. To minimize contamination it is advisable to avoid contact between patients in the control condition, and care providers giving the intervention, or other staff informed about the intervention.

Additional aspects were scored to evaluate the quality of the intervention:

- how many care providers gave the intervention;
- if care providers were trained;
- if care providers were supervised;
- if an intervention protocol was used;
- if an integrity check was described.

In most quality rating scales blinding is evaluated on several levels, such as blinding of patients and care providers. These scales are often used to test the quality of placebo-controlled medication studies. However, the nature of RCTs testing psychosocial interventions is different. In these trials it is nearly impossible to blind the patients to the intervention they were assigned to. In addition it is also impossible to blind the care providers to the intervention they are giving to the patients. Thus, blinding of patients and care providers were not scored in the Quality Rating Scale.

The three review authors met to discuss all items of the Quality Rating Scale of the studies, and to reach a final quality score by consensus. The total score of the Quality Rating Scale varied between one and 25 and was divided into three categories. When the total score was between one and nine, the quality was rated as poor, when between ten and 17 as moderate, and when between 18 and 25 as good.

Data extraction

Three review authors (MMG, MG and GB) independently extracted data from the selected studies using data extraction forms. The data extraction form was designed using listed criteria described by Van Tulder (1997)[28], and a scale to evaluate RCTs developed by the EBRO-forum[29], and was expanded with necessary information on the psychosocial interventions to be evaluated. Any disagreement was resolved through consensus.

From each selected study the following data was extracted:

Patient characteristics:

- Demographic characteristics such as age and gender.

- Disease characteristics such as type of cancer, stage of cancer, types and duration of treatment.

Intervention characteristics:

- Duration of the intervention, total number of sessions and duration of each session.
- The nature and content of the psychosocial intervention.
- The number of care providers and the profession.
- Duration and nature of training and supervision given to the care providers.
- Patient compliance and contamination.

Information on statistics:

- Number of participants in each arm.
- Duration of short-term follow-up and, if available, long-term follow-up.
- Instruments used, key outcomes and description of missing data.

Data synthesis and effect of psychosocial interventions

A narrative overview of the included RCTs was provided in this review. We assessed which interventions during cancer treatment were effective in reducing fatigue, and described explanations for the effectiveness where possible. To determine the magnitude of the effect, effect sizes were calculated of the studies that were effective in reducing fatigue. The size of the effect is calculated in a standardized way, and therefore the effect sizes across the various studies can be compared. The effect sizes were calculated by using the means and standard deviations of two groups (experimental group and control group) of the post-intervention or follow-up measurement, in the following way:

Effect size = $M_1 - M_2/\sigma_{pooled}$

where $\sigma_{pooled} = \sqrt{[(\sigma_1^2 + \sigma_2^2)/2]}$

As the characteristics of the included studies, the instruments, and the interventions were very diverse, we concluded that a meta-analysis or a subgroup analysis was not sensible or appropriate.

RESULTS

Description of studies

Excluded studies

The search of the electronic databases retrieved 2210 publications. After eliminating the duplicates 1753 publications were identified for further consideration. After screening the titles and electronic available abstracts 1668 publications were excluded. Reasons for excluding publications were the following:

- studies were no intervention studies, for example studies were reviews, or comments;
- studies evaluated no psychosocial interventions, for example medical treatments, exercise, or massage;
- studies were no RCTs, for example studies did not have a control group, or participants were not randomised;
- studies did not focus on cancer patients or only a part of the sample were cancer patients;
- studies evaluated interventions in cancer patients after finishing cancer treatment;
- fatigue was not assessed as an outcome measure.

After this initial screening, the full-text articles were retrieved of the remaining 85 potential studies. From these full-text articles 56 studies were excluded leaving 29 studies to review. These 56 studies were excluded for the following reasons; 15 studies were excluded because the interventions were given to participants after finishing cancer treatment. One study was excluded because most participants did not receive cancer treatment during the intervention. Five studies did not describe if participants received cancer treatment during the intervention. One study focused on participants receiving colorectal surgery and did not only include cancer patients, but also patients with other types of diseases. Six studies were not RCTs. Two studies had less than ten participants in each condition. In four studies fatigue was not measured and three studies did

not describe separate results on fatigue. Nineteen studies identified did not include psychosocial interventions. In two studies the intervention was mainly focused on changing exercise behaviour. In three studies nutritional behaviour was the focus of the intervention and one focused on medication. In 13 studies the interventions were not psychosocial interventions according to our definition described in 'Types of intervention'. The interventions did not consist of a systematic process between the patient and the person giving the intervention. The excluded studies are described in more detail in Table 1: Characteristics of excluded studies.

Ongoing studies

The search for ongoing studies found eight RCTs that are currently recruiting participants. Three of these studies are evaluating different types of yoga intervention (Cohen, 2007a; Cohen, 2007b; Oh, 2008b). Purcell (2008) is evaluating a group education and support intervention, and Savard (2008) a self help treatment for insomnia. Two studies are evaluating two interventions compared to usual care. Cohen (2004a) is evaluating mindfulness relaxation, and music relaxation. Goedendorp (2005) is evaluating cognitive behaviour therapy and a nursing intervention. Cohen (2006) is also evaluating a cognitive behaviour intervention. The ongoing studies are described in more detail in Table 2: Characteristic of ongoing studies.

Included studies

Two remarks should be made with regards to the 29 included studies. In the Sandgren (2003)[30] study the immediate effects of the intervention are described whereas the duplicate study Sandgren (2007)[31] includes the follow-up. Goodwin (2001)[32] and it's duplicate study Bordeleau (2003)[33] described the effects of the same intervention, but presented results on different outcome measures. Therefore these 29 publications were evaluated as 27 separate included studies.

Participants

Disease characteristics

A majority of the studies, 13, focused on patients with one type of malignancy, mainly patients with breast cancer. In eleven studies participants were patients with breast cancer, however, with different stages of cancer. Three studies included breast cancer patients with stages I-II[34-36]. Sandgren (2003)[30] and Moadel (2007)[37] included patients with stages I-III, and Gaston-Johansson (2000)[38] included patients with stages II-IV. Two studies focused on patients with other types of cancer, such as prostate cancer[39], or malignant melanoma[40]. Six studies included only metastatic cancer patients[32, 41-45]. Five of these studies included patients with metastatic breast cancer[32, 41, 43-45], and one; patients with metastatic renal cell carcinoma[42].

The remaining studies included cancer patients with more than one diagnosis. Two studies focused on patients with two types of cancer. The first study included patients being treated for prostate or bladder cancer[46]. The second study included patients receiving treatment for gastric or colon cancer[47]. Rawl (2002) included patients with three different types of cancer: breast, colorectal and lung cancer[48]. Ten studies focused on cancer patients in general and included patients with several types of cancer, such as lymphoma's, breast, lung, colorectal, prostate, gynaecologic, testicular cancer, and other solid tumours[49-57], however, one study excluded patients with abdominal cancer[58].

One study explicitly described that patients were treated with curative intent[50], and Brown (2006)[51] focused on patients with advanced cancer. Eleven studies included cancer patients with various stages of cancer, with or without metastasis[46-49, 52-58].

Cancer treatment

All 27 included studies described results of interventions given to patients during cancer treatment. In 15 studies all patients were receiving cancer treatment during the intervention [30, 34, 36, 38, 42, 46-51, 54, 55, 57, 58]. In ten studies most, but not all, patients were receiving active cancer treatment during the intervention[32, 35,

[37, 39-41, 43, 52, 53, 56]. The percentage of patients receiving active treatment during the intervention varied from at least 44%[35] to 91%[53]. Edelman (1999), Savard (2006) and Spiegel (1981) did not describe how many patients actually received cancer treatment during the intervention[43-45]. However, these studies focused on patients with metastatic cancer, and therefore it is expected that these patients would have received treatment sometime during the intervention.

In most studies the interventions were given to patients receiving chemotherapy only[36, 47-49, 55, 57], or radiotherapy only [46, 51, 54, 58]. Four studies included participants receiving chemotherapy or radiotherapy [34, 35, 50], or chemotherapy or hormone therapy[41]. Five studies included participants with several treatment regimes. One study included participants who had surgery, radiotherapy or hormone therapy[39]. Five studies included participants receiving chemotherapy, radiotherapy or hormone therapy [30, 32, 52], or additionally surgery or other treatment [37, 53]. In one study some participants received chemotherapy, but it is unclear if participants also received other types of treatment[56]. Three studies focused on other treatments[38, 40, 42]. The first study included patients receiving immunotherapy[40]. The second study focused on patients receiving nephrectomy and vaccine treatment[42] and the third study included patients receiving bone marrow transplantation[38].

Other criteria for inclusion

In two studies the participant sample was strikingly different than the other studies. De Wit (1997)[53] included only participants with cancer related pain, and Savard (2006)[44] focused on depressed metastatic breast cancer patients.

Two studies described inclusion criteria for fatigue. Armes (2007)[49] explicitly described that cancer patients with significant fatigue were included, and Given (2002)[55] included patients reporting both fatigue and pain at baseline. As patients were included during chemotherapy, it is expected that the majority of the patients would experience symptoms at time of accrual.

Most studies described additional exclusion criteria. Participants were excluded for several reasons. Some reasons were cancer or treatment related. Three studies excluded cancer patients with previous[40, 41] or other cancer[39]. Six

studies excluded patients who received previous cancer treatment[47], such as chemotherapy[42, 57], radiotherapy[54], cytokine treatment[49], or immunotherapy[42]. One study excluded patients if their treatment plan included stem cell transplantation, interleukins, interferons, or tumour necrosis factor[50].

Other additional criteria were also described. Most studies excluded cancer patients with other comorbidities[30, 32, 39, 41-43, 47, 49, 50, 56], or current or a history of psychiatric illnesses [32, 34, 39, 40, 44, 47, 49, 51, 54, 56, 57]. Eight studies excluded cancer patients involved in intervention studies[50, 51], or other types of care programs[44], such as support groups[32, 39], attending yoga[37] or medical qigong[56], or receiving psychotherapy[49]. Six studies did not describe additional criteria[35, 36, 45, 46, 52, 57].

Interventions

Studies were only included in this review if participants received the intervention during cancer treatment.

In most studies the intervention was started during cancer treatment, although it often remained unclear at what stage of cancer treatment the interventions ended. Of the studies that evaluated short interventions (four weeks or less) it is likely that participants continued with cancer treatment after the intervention[36, 42, 50, 51]. When the duration of the intervention was longer it remained unclear how many participants continued with cancer treatment after the intervention. Only four studies described explicitly at what stage of cancer treatment the intervention ended. In Faithfull (2001) the intervention started at the beginning of cancer treatment and ended at the end of the treatment[46]. In three studies the intervention continued after participants finished cancer treatment[38, 47, 58].

Format

In most studies the intervention was administered by nurses[30, 36, 40, 46-50, 53, 55, 57]. In the study of Oh (2008)[56] an experienced instructor gave medical qigong. In the study of Moadel (2007)[37] the yoga instructor was also an oncologist. In the remaining studies the intervention was administered by social workers[34, 38], (psycho)therapists[43, 58], psychologists[44], or graduate students[35, 52, 54]. In five

studies the intervention was multidisciplinary[32, 39, 41, 45, 51]. In seven studies there was one care provider giving the intervention[34, 37, 48, 49, 52, 56, 58]. In three studies it was unclear how many care providers gave the intervention[38, 40, 46], but it may have been only one. In all other studies more than one care provider gave the intervention.

In ten studies the intervention was given in groups[32, 34, 37, 39, 41, 43, 45, 51, 52, 56], in the remaining studies the intervention was given individually. The individual sessions were mostly face-to-face, but seven were exceptions. In the studies of Sandgren[30, 35] and Barsevick (2004)[50] the participants received only telephone sessions. Three studies combined face-to-face contact and telephone calls in the intervention[36, 53, 55]. In one study participants received individual writing instructions, for several occasions[42]. The instructions stimulated participants to write about their thoughts, feelings and consequences on their lives. We decided to include this study as change of cognitions and behaviour were the focus of the intervention.

In 14 studies additional information materials were given to the participants[34, 36-38, 41, 43, 46, 47, 49, 51-54, 56]. In eight studies participants received written information [36, 43, 46, 47, 49, 51, 53, 56]. In one study participants received audiotapes[37], and in five studies participants received both written information and audiotapes[34, 38, 52, 54] and additional videotapes[41].

Duration

The number of sessions was described in 22 studies, but there was a lot of variation. Among these studies the number of sessions varied from two to 12, with a median of six sessions. In two studies the number of sessions was not fixed for participants[37, 56]. In the remaining three studies the intervention consisted of weekly 90 minute sessions, for the duration of at least one year, but the actual number of sessions was not given. The number of sessions could be estimated to be around 50[32, 41, 45].

Four studies failed to describe the duration of each session [38, 43, 47, 57]. Among the remaining 23 studies the duration of the sessions varied from ten minutes to

three hours. The most common duration was 30 minutes for individual sessions and 90 minutes for group sessions.

The duration of the full intervention was described in 20 studies or could be estimated. The total duration of the interventions varied from two weeks[36] to 20 weeks[43, 55], with three exceptions having a duration of at least one year[32, 41, 45]. From six studies the actual length of the intervention was not clear, but depended on the cancer treatment participants had received. For example the sessions took place on specific points in patients' treatment regimes[38, 46, 47, 57], took place during patients' clinic visits[40], or depended on the duration of the hospital admission[53]. One study did not describe the total length of the intervention[54].

Content

In only five studies the intervention was specifically focused on fatigue[36, 47, 49, 50, 57]. All the other interventions focused on other aspects. Eight interventions aimed to influence depression[44], depression and anxiety[39], or mood states in general[41-43, 45, 52, 54]. Some interventions focused on symptoms, such as pain[53], or on symptoms and side-effects in general[34, 38, 46, 48, 55, 58]. Interventions also focused on distress[30, 34, 35, 40-42, 52, 58] and quality of life [32, 35, 37, 39, 46, 51, 56].

The elements of the intervention varied among the studies. Some interventions were based on one or two elements, while others used multiple techniques. Four studies focused on the expression of emotions[30, 42], on providing social support[45], or a combination of these two[32]. Yoga was evaluated in two studies, with elements such as meditation, and physical stretching. Yoga also falls within complementary medicine, but as general discussion and relaxation were also parts of the intervention, it was decided to include these studies[37, 56]. All other studies used a combination of several elements in the intervention. Teaching, giving patients information and education on cancer and treatment is often used as one of the elements. In two studies exercise was actually performed[39, 51], but activities were more often one of the topics, for example activity management, or energy conservation. Relaxation or guided imagery were sometimes used as techniques to manage stress. Problem solving or teaching

patients coping strategies were also elements of several interventions. In four studies cognitive (behavioural) therapy was the intervention[34, 43, 44], or psychotherapy[58].

Control group

In 18 studies participants in the control group did not receive the intervention, but received standard care and standard information[30, 32, 34, 35, 38-40, 43, 47-49, 51, 53-58]. In the studies of Savard (2006)[44] and Moadel (2007)[37] participants in the control group were assigned to a waiting list. One study did not specify the control group[45]. In six studies the control condition involved more than standard care. In the study of Classen (2001)[41] participants were provided with self-directed education materials. In four studies participants in the control group received an intervention with the same number and duration of sessions, but received different information. In the first study the control condition comprised supportive discussion alone[52]. In the second study participants in the control group received information on nutrition[50]. In the third study the control condition was a 'neutral writing' condition[42]. In the fourth study participants received general information on living with cancer[36]. In one study participants in the control group had more moments of contact than in the intervention group[46]. Participants in the control group received routine ten minute weekly appointments for patients with bladder cancer, or ten minute two-weekly appointments for patients with prostate cancer, led by physicians.

Outcomes

Studies were only included when they were RCTs. Thus, all the studies had a baseline assessment and a post-intervention assessment. However, the total number of assessments varied between two and six assessments, with a median of three. Studies with more than two measurements, also assessed participants during the intervention, or had a follow-up measurement. Twelve studies had one or more follow-up measurements[30, 34-36, 40, 42, 43, 49, 50, 52, 53, 58], and ten studies assessed participants once or more during the intervention[32, 38, 39, 41, 43, 45, 47, 48, 55, 58].

The timing of the measurements varied a lot across the studies. In most studies participants were assessed immediately or within a few days after the intervention was completed. In two studies the time between the end of the intervention and the assessment of participants was longer; one month[48] and six weeks[40] after the intervention. The actual time between the end of the intervention and the assessment was not obvious in five studies[30, 36, 46, 49, 50]. In two of these studies the actual time between the end of the intervention and the follow-up assessment was also unclear[46, 50]. In Barsevick (2004) and Yates (2005) the post- and follow-up assessment depended on the treatment regimes, radiotherapy or chemotherapy[36, 50]. Five studies had a short period between the post-intervention assessment and the follow-up, of four weeks or less[42, 49, 52, 53, 58]. Three of these five studies had additional follow-up measurements at eight weeks[53], at six, eight, and ten weeks[42], and nine months after recruitment[49]. In five other studies the time between post-intervention and follow-up was longer varying between three to eight months[30, 34, 35, 40, 43].

Five studies explicitly described that the post-intervention assessment took place after participants finished their cancer treatments [38, 47, 49, 53, 58], and three of these studies also had a follow-up assessment[49, 53, 58]. In two studies it was described that part of the participants finished cancer treatment at the time of follow-up measurement[36, 50].

Most studies used one instrument to measure fatigue, but six studies used two to four instruments[32, 36, 46, 49-51] (see Table 3: Outcomes). Five instruments were used in multiple trials. The most frequently used instrument was the POMS sub-scale fatigue/inertia, and was used in 12 studies to measure fatigue[30, 32, 35, 40-43, 45, 50-52, 54]. The VAS was used in five studies[38, 46, 49, 51, 57] and the EORTC QLQ-C30[32, 39, 46, 49, 53, 56] was used in six studies. The FACT-F [36, 47] and the MFI[44, 49] were used in two studies. All other instruments were only used in a single study.

A minority of the studies, only five, used specific questionnaires designed to measure fatigue, such as the MFI, SCFS, GFS, FSI, PFS. The most frequently used instruments were used to measure mood states, or quality of life. Fatigue in these instruments was measured with a sub-scale, or with only one item.

Other study characteristics

The sample size of the 27 included studies varied between 30 and 396, with a total of 3324 participants. Most studies described the sample at randomisation. Five studies described the number of participants at baseline[36, 43], or used for analysis[34, 38, 54]. The mean sample size was 123 (standard deviation (s.d.) 87). Twelve studies had a sample size smaller than 100 [34, 35, 40, 42-45, 47, 49, 52, 54, 56], and ten studies between 100 and 200[36-38, 41, 46, 48, 51, 55, 57, 58]. Five studies had a larger sample than 200 [30, 32, 39, 50, 53].

Methodological Quality

The results of the methodological quality assessment are described in Table 4: Quality Assessment. A majority of the studies scored one or two on the Oxford Quality Scale[26] within the range of one to five. Only three studies scored three[36, 48, 57]. On the Delphi List[27] seven studies scored above three [30, 32, 34, 36, 38, 50, 57] and none of these were published before the year 2000. Looking at the scores on internal validity as suggested by Van Tulder (1997)[28], only one study had a good evaluation with a score of five[36]. All other studies scored lower than five.

The majority of the studies had a moderate methodological quality, varying between ten and 17. In three studies the quality was graded a nine, being regarded as poor[39, 45, 46]. The methodological quality of the study of Barsevick (2004)[50] was rated as 18, being good.

One of the items of the Quality Rating Scale was concealment of allocation and the evaluation is described in Table 5: Characteristics of included studies. Eight studies suggested that concealed allocation was used[32, 36, 44, 46-49, 57] and in five studies the allocation was concealed adequately[36, 46, 48, 57], with one study changing the procedure during recruitment[49]. In the remaining studies it was not described which procedure was used to conceal allocation.

Barsevick (2004) was the only study in which an intention-to-treat analysis was used[50]. Two other studies described that intention-to-treat analysis was used, however, this remained unclear from the described analysis and results[32, 39]. In most studies the analysis was performed with participants who completed all assessments.

Three studies explicitly described that actions were taken to prevent contamination. In the study of Sandgren (2003) nurses gave both interventions, but the authors attempted to avoid contamination by informing the nurses about the risks of contamination[30]. In two other studies it was explicitly mentioned that the persons administering the intervention were different from the persons in contact with participants in the control condition[36, 57]. In the study that evaluated medical qigong, patients in the control group were asked to refrain from joining an outside qigong class[56].

An important aspect when evaluating the effectiveness of psychosocial interventions is the adherence of patients, however, in only 12 studies this was described. In eight studies the attendance of participants joining the sessions was described[32, 36, 37, 41, 42, 49, 51, 53] and in four studies adherence was assessed in other ways. Two studies measured if participants used the behaviours learned during the intervention[36, 50]. Two studies asked participants if they read the provided brochures[53], or practiced at home[34].

Risk of bias in included studies

The possibility of bias could be found in the characteristics of the sample. The exclusion criteria varied a lot between the included studies, for example some studies excluded patients with other comorbidities, while some studies did not describe additional exclusion criteria. The methodological quality might also cause a bias, however, this is described in the discussion in more detail.

Effects of interventions

Seven of the included studies reported a significant effect of the interventions on fatigue at a 0.05 level. The seven studies and their results are briefly described in part A and B of Table 6: Summary of findings: Effective studies. The effect sizes varied between 0.17[50] and 1.07[34]. The smallest effect size was found in the study of Barsevick (2004), but this could be due to the use of intention-to-treat analysis not applied in other studies[50]. In two studies it was not possible to obtain all relevant data to calculate effect sizes[45, 58].

Of the seven studies which found a significant effect of the interventions on fatigue, three found significant time-by-group interaction effects at follow-up [34, 49, 50] on at least one instrument that measured fatigue. In the studies of Armes (2007) and Barsevick (2004) the follow-up period was short, up to one month[49, 50]. The follow-up period in the study of Cohen (2007) was longer, lasting four months[34]. In the study of Armes (2007) participants were measured additionally at nine months after recruitment[49]. Of these seven studies two studies found a significant effect immediately post-intervention, but these results were not maintained at follow-up[36, 58]. In the study of Spiegel (1981) significant results were found post-intervention, but no follow-up assessment was described[45]. The study of Ream (2006) found a significant effect on fatigue comparing the post-intervention scores with a t-test without controlling for baseline differences. No follow-up measurement was carried out. The use of a *t*-test was justified in this study as baseline fatigue scores of the control and the intervention group were not significantly different[57]. These seven studies are further referred to as the 'effective' studies[34, 36, 45, 49, 50, 57, 58].

The remaining 20 included studies were regarded as not effective. In 17 studies no significant effects of the intervention on fatigue were found, although in four of these 17 studies the authors concluded that the results were in the expected direction[32, 55, 56] or significant on a 0.1 level[52]. Three of the 20 studies found a significant effect of the intervention when measured with a *t*-test, immediately post-intervention[38, 54] or at follow-up[40]. In the first study, Gaston-Johansson (2000) reported that the difference between the intervention group and control group disappeared after controlling for demographic variables and fatigue at baseline[38]. In the second study of Decker (1992) a statistically significant difference in the pre- versus post-test scores was found, where control patients became more fatigued. However, no significant results on treatment by repeated measures interaction were found on fatigue. In addition, when looking at the results fatigue scores were higher in the experimental group compared to the control group, at baseline and post-intervention[54]. In the third study, Fawzy (1995) found significant results on fatigue on the within-group analysis and the between-group analysis, but reported no significant result of the analysis of

covariance on fatigue[40]. Thus, using a t-test to evaluate the intervention was not justified in the last three studies and therefore we concluded that in 20 studies the intervention was not effective for fatigue.

Comparing effective and non-effective interventions for fatigue

The quality of the seven effective studies did not differ from the non-effective studies (P = 0.231). The mean quality score of the effective studies was 14.0 (s.d. 3.6) compared to 12.2 (s.d. 2.0) of the non-effective studies. No difference was found in the mean number of participants (P = 0.598). The mean number of participants of the effective studies was 138 (s.d. 115) compared to 118 (s.d. 78) of the non-effective studies.

The psychosocial interventions could be distinguished into interventions specific for fatigue and interventions not specific for fatigue. The effectiveness of interventions specific for fatigue was significantly higher at 80% (four out of five) compared to interventions not specific for fatigue at 14% (three out of 22) (P < 0.01). Two studies were specific interventions for pain[53], and depression[44], but were not effective for fatigue. The other interventions not specific for fatigue had a more general approach and focused on distress, mood states, quality of life, or symptoms or side effects in general. Of these 20 studies, three studies were effective in reducing fatigue[34, 45, 58].

The five specific interventions for fatigue were short interventions, consisting of three individual sessions with a duration varying between ten and 60 minutes. These interventions were to a large extent based on the same elements. In all interventions participants were; 1) educated about fatigue; 2) taught in self-care or coping techniques; 3) taught activity management, learning to balance between activities and rest. In addition to these elements Ream (2006) emphasised emotional support[57]. In these five studies (oncology) nurses administered the interventions and were trained. All studies included participants with various malignancies and stages of cancer. In the study described by Armes (2007), the first author was also the nurse administering the intervention[49]. The study of Godino (2006) was the only intervention specific for fatigue, that was not effective[47]. The most obvious difference between this study

and the effective studies is the smaller number of participants. Godino (2006) randomised 40 participants, while the sample size of the effective studies was between 60 and nearly 400 participants.

The three effective studies not specific for fatigue were longer interventions compared to the interventions specific for fatigue. The study of Cohen (2007) consisted of nine weekly sessions of 90 minutes[34]. The study of Forester (1985) consisted of ten weekly 30 minute sessions[58]. The intervention in the study of Spiegel (1981) lasted at least a year, in which participants met weekly for 90 minutes[45]. The duration of these three interventions fall within the range of all other interventions that were not specific for fatigue, varying between four weeks and a year. The content of these three interventions varied among each other. The intervention groups in the study of Spiegel (1981) was primarily supportive and aimed to benefit patients psychologically[45]. The intervention of Forester (1985) was individual unstructured supportive psychotherapy designed to reduce patients emotional distress and physical symptoms, regarding treatment[58]. Cohen (2007) studied the effects of two group interventions on psychological distress and physical symptoms[34]. The first was a cognitive behaviour group intervention and the second consisted of relaxation and guided imagery. Only the relaxation and guided imagery intervention appeared to be effective on fatigue. In the studies of Cohen (2007) and Forester (1985) the first authors were also the only care provider giving the intervention[34, 58]. The effectiveness of the three studies probably couldn't be explained by a larger sample size or by a better quality. The quality scores of the studies by Cohen (2007), Forester (1985), and Spiegel (1981) ranged between nine and 13, while the quality score of the non-effective studies not specific for fatigue ranged from nine to 17[34, 45, 58]. Thus the quality scores were within the range of the effective studies not specific for fatigue, and even a bit lower. The number of participants of the three effective studies ranged between 86 and 114, and was within the range of 30 to 313 of the non-effective studies not specific for fatigue.

DISCUSSION

The aim of this review was to provide an overview of psychosocial interventions for fatigue during cancer treatment, and to evaluate the effectiveness of these interventions. In our search 27 psychosocial interventions were found, in which the effect on fatigue was tested in a RCT. The sample size of the 27 included studies varied between 30 and 396, with a total of 3324 participants. The quality was generally evaluated as moderate.

In general, there is limited evidence that psychosocial interventions during treatment are effective in reducing fatigue in cancer patients. In only seven studies were the psychosocial interventions effective in reducing fatigue. In only three studies was the effect of the intervention on fatigue maintained during the follow-up period[34, 49, 50]. The quality and the mean number of participants of the effective studies did not differ from the non-effective studies. The effect sizes of the effective studies were generally medium[59]. In the studies with a large effect size, the intervention was provided by only one care provider, also being the first author[34, 49].

Overall the 27 studies were very heterogeneous on most aspects of the studies, on patient and treatment characteristics, types of interventions, and outcome measures. This made it difficult to establish if certain types of intervention or elements could be essential for reducing fatigue. Attempts were made to draw additional conclusions about certain types of interventions or subgroups of patients. For example a lot of studies were carried out with only breast cancer patients, but these studies were also too heterogeneous to draw additional conclusions about interventions for this specific group. Psychosocial interventions for patients with prostate cancer or other common types of cancer, are less often tested in RCTs, as also previously established[14]. However, it was possible to distinguish interventions that were specifically designed to treat fatigue during cancer treatment, and interventions not specific for fatigue.

This review showed that the effectiveness of interventions specific for fatigue was significantly higher than interventions not specific for fatigue. To

conclude, at present psychosocial interventions specifically for fatigue is the more promising type of intervention for reducing fatigue during cancer treatment. However, there is currently no solid evidence for the effectiveness of interventions not specific for fatigue.

Of the five interventions specific for fatigue, four were effective in reducing fatigue during cancer treatment[36, 49, 50, 57]. In two studies the effects were maintained in the follow-up period that lasted up to a month[49, 50]. One study was not effective[47], but the small sample size might be an explanation why no significant result was found.

It seems promising that four out of five interventions specifically designed for fatigue were effective, but the stability of the evidence is questionable for three reasons. First, in two studies there was only an immediate effect on fatigue after the intervention, but the effect disappeared at follow-up[36], or no follow-up assessment was performed[57]. Second, when more than one instrument was used to assess fatigue, the effects were not visible on all instruments. Third, in the study of Armes (2007)[49] the intervention was provided by only one care giver, also being the first author.

Looking at the characteristics of the five studies that evaluated interventions specifically designed to treat fatigue, revealed two obvious features. Firstly, these studies included patients with various malignancies and stages of cancer. Secondly, these interventions were brief, consisting of three sessions lasting up to 60 minutes each, and containing to a large extent the same elements. In all interventions participants were; 1) educated about fatigue; 2) taught in self-care or coping techniques; 3) taught about activity management, learning to balance between activities and rest. Based on this limited number of five studies it could not be established which format or elements of an intervention were essential for reducing fatigue. For example, it could not be established if sessions should be based on face-to-face contact, or if telephone sessions might be an alternative.

Three out of 22 psychosocial interventions not specially designed to manage fatigue were effective in reducing fatigue during cancer treatment[34, 45, 58]. In one study the effect on fatigue was maintained during the four month follow-up

period. These three interventions had a more general approach aimed at psychological distress, mood and physical symptoms. There is no obvious reason why these three interventions were effective, while 19 other studies were not. No explanation could be found in the sample size, the quality of the studies or characteristics of the interventions.

There are several reasons that support the conclusion that interventions with a general approach are rarely effective. First, in the studies of Cohen (2007) and Forester (1985) the first author was also the care provider administering the intervention[34, 58]. Second, in only one study the effect was maintained at follow-up. In addition, one of these three studies was an early study of Spiegel (1981)[45] and was replicated in later studies[32, 41]. However, the effect on fatigue demonstrated by Spiegel (1981), was not confirmed in the later two studies[45].

Interventions that did not focus on fatigue, for example interventions that aimed to reduce depression or pain, showed that fatigue did not decrease with depression or pain, and therefore we can conclude that these interventions are not effective for reducing fatigue.

Limitation of the studies

During the evaluation of the included studies several shortcomings were noticed. In most studies it was difficult to get a clear picture of the complete cancer treatment participants received, such as types of treatments and total duration. As a result it also remained unclear when during cancer treatment the assessments and the sessions took place. Often it was uncertain if participants continued with cancer treatment after the intervention.

The evaluation of the quality of the included studies revealed additional limitations. In the majority of the studies it was not described if a procedure was used to conceal allocation, not even in the most recent publications. In addition, only one study applied an intention-to-treat analysis. Recommendations for improving the quality of RCTs are provided in the CONSORT guidelines[60].

Several methodological elements of the psychosocial intervention studies could be improved. For example, avoiding the risk of contamination, and testing

the adherence of participants. Training the care providers, supervising them, and applying an integrity check would help improve an intervention study.

In some studies the intervention was provided by only one care provider also being the author, but there might be a conflict of interest in performing the intervention at the one hand, and publishing the results at the other. The care provider might work hard to get positive outcomes, resulting in a large effect size. Despite the good intentions of realising a good intervention, with only one practising care provider it could be difficult to transfer the intervention to others, and to replicate the study. Thus it is recommended that the intervention should be given to participants by more than one person.

Limitation of the review

A limitation of this review is that RCTs were excluded when it was unclear if cancer patients were receiving treatment at the time of the intervention. To clarify this issue we contacted the experts and researchers who performed the studies. In addition the possibility remains that trials with negative results might not have been published at all, and therefore are missed during our search. Although we are unaware that relevant studies were missed, the possibility that a relevant study exists cannot be ruled out.

AUTHORS' CONCLUSIONS

Implications for practice

When cancer patients experience fatigue during cancer treatment there are several options to treat fatigue. In clinical practice an intervention with a general approach is usually chosen when intervening for fatigue, although at present there is no solid evidence for the effectiveness of psychosocial interventions not specific for fatigue. This review showed that interventions with a general approach were rarely effective in reducing fatigue, and these interventions focused on psychological distress, mood and physical symptoms. When other types of psychosocial intervention are offered to cancer patients, for example with

the aim of reducing depression or pain, it is not likely that symptoms of fatigue automatically decrease with depression or pain.

The effectiveness of psychosocial interventions specifically designed to treat fatigue was significantly higher than interventions not specific for fatigue, and is currently the more promising type of intervention for reducing fatigue during cancer treatment. The interventions specific for fatigue contained, to a large extent, the same elements. In all interventions patients were: 1) educated about fatigue; 2) taught in self-care or coping techniques; 3) taught activity management, learning to balance between activities and rest. However, currently with only a limited number of studies it could not be established which format or elements are essential to reduce fatigue during cancer treatment.

It is important to note that psychosocial interventions during active cancer treatment were the focus of this review. Our results are therefore not applicable to cancer patients who have completed their cancer treatment.

Implications for research

This review showed that there is limited support for psychosocial interventions for fatigue during cancer treatment. At present the effectiveness of psychosocial interventions specifically designed to treat fatigue is high, but there is no solid evidence for the effectiveness of psychosocial interventions not specific for fatigue.

As the RCTs were very heterogeneous in nature, and the number of psychosocial interventions specific for fatigue were limited, there are still some questions that need to be answered. First, it is important to know why some psychosocial interventions work, and therefore interventions should preferably be based on a theory or model. To find essential components that are necessary to reduce fatigue it is advisable to assess if factors that are expected to reduce fatigue also change during the intervention. In addition, the optimal duration of the intervention needs to be established, and the best method to provide the intervention. For example, it is unclear if telephone or face-to-face sessions are equally effective. Also there are no RCTs that evaluated the effectiveness of group interventions specific for fatigue.

As the included studies were very heterogeneous it was not possible to identify high risk groups. Thus, the question remains whether patients with specific malignancies, or patients receiving specific types of treatments are at risk of becoming more fatigued, although some studies point in that direction[24]. Some studies found that the prevalence of fatigue depended on the diagnosis. For example, patients with prostate carcinoma reported the least severe fatigue during radiotherapy and patients with lung, alimentary, and head and neck carcinoma reported the most severe fatigue[61]. Levels of fatigue also depended on diagnosis in patients receiving chemotherapy. In a group of cancer patients receiving cytotoxic treatment, lung and breast cancer patients experienced the highest degree of fatigue[62].

There are also indications that the prevalence of fatigue depends on the type of treatment cancer patients receive. For example, breast cancer patients who had a mastectomy operation were more fatigued than women who underwent a lumpectomy. Receiving radiotherapy supplementary to chemotherapy led to an increase in fatigue in women with breast cancer[63].

In addition the course of fatigue appears to depend on the type of treatment cancer patients receive. For example, the course of fatigue in patients receiving chemotherapy seems to be different from the course of fatigue in patients receiving radiotherapy. After the start of chemotherapy the prevalence of fatigue increases, remaining stable during chemotherapy treatment[63, 64]. During radiotherapy the occurrence of fatigue increases with the number of weeks patients are treated with radiotherapy[61, 65].

If high risk groups can be identified it is important to know if these groups need adapted psychosocial interventions. In current guidelines for CRF, interventions for patients on active treatment are distinguished from interventions for patients at the end of life[4] although, the effectiveness of interventions specific for fatigue in this sample still needs to be demonstrated.

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CONTRIBUTIONS OF AUTHORS

Draft the protocol, develop the search strategy, search for trials, obtain copies of trials: M Goedendorp, M Gielissen, G Bleijenberg

Select which trials to include: M Goedendorp, G Bleijenberg, C Verhagen

Extract data from trials: M Goedendorp, M Gielissen

Enter data into RevMan: M Goedendorp, G Bleijenberg

Carry out the analysis: M Goedendorp

Interpret the analysis: M Goedendorp, M Gielissen, G Bleijenberg and researchers of the 'Expert Centre for Chronic Fatigue'

Draft the final review: M Goedendorp, M Gielissen, G Bleijenberg

Update the review: M Goedendorp, M Gielissen, G Bleijenberg

DECLARATIONS OF INTEREST

None known

Table 1: Characteristics of excluded studies

Study	Reason for exclusion
Badger 2005[66]	In a previous study of Badger 2001, participants were randomised between six conditions, five experimental groups and a control group. In this study participants of the five experimental groups were taken together as one, and compared with the control group on fatigue. This was not considered to be a RCT.
Bennet 2007[67]	Intervention was conducted after cancer treatment was completed.
Berglund 1994[68]	Intervention was conducted after cancer treatment was completed.
Boesen 2005[69]	Intervention was conducted after cancer treatment was completed.
Burns 2008[70]	No psychosocial intervention. Participants were educated about the use of music imagery and relaxation. Thus no feedback was given on their behaviour.
Campbell 2005[71]	No psychosocial intervention. The emphasis was placed on exercise.
Campbell 2007[72]	Intervention was conducted after cancer treatment was completed.
Carlson 2005[73]	In this study there was no control or normal care group.
Cimprich 1993[74]	Fatigue was not measured.
Cimprich 2003[75]	Fatigue was not measured.
Clark 2006[76]	No psychosocial intervention. During the intervention participants listened to music, but no feedback was received on their behaviour.
Cohen 2004[77]	Most participants (71%) did not receive cancer treatment during the intervention.
Courneya 2003[78]	Unclear if participants received cancer treatment during the intervention.
Crooks 2004[79]	Participants were not randomised between the conditions.
Culos-Reed 2006[80]	Intervention was conducted after cancer treatment was completed.
Daley 2004[81]	Intervention was conducted after cancer treatment was completed.
Dalton 2004[82]	Fatigue was not measured.
Dimeo 1999[83]	No psychosocial intervention. The emphasis was placed on exercise.
Dimeo 2004[84]	Intervention was conducted after cancer treatment was completed.
Doorenbos 2005[85]	Fatigue was mentioned as one of the symptoms. Results on the total number of symptoms were described, and not separated for fatigue.
Fawzy 1990[86]	Cancer participants undergoing treatment were excluded.
Gielissen 2006[87]	The intervention was conducted after cancer treatment was completed

Table 1: Characteristics of excluded studies

Study	Reason for exclusion
Given 2004[88]	Fatigue was mentioned as one of the symptoms. Results on the total number of symptoms were described, and not separated for fatigue.
Given 2005[89]	No psychosocial intervention. The effect of neutropenia was tested.
Haase 2005[90]	No psychosocial intervention. This study evaluated guided imagery and group relaxation. Participants were provided with tapes and instructions, but no feedback on their behaviour was given.
Hack 2003[91]	Consultation was recorded and participants received an audiotape.
Hanna 2008[92]	In this study there was no control or usual care group.
Hoekstra 2006[93]	No psychosocial intervention. This study evaluated a symptom monitor. Participants monitored their symptoms, but no additional feedback on their behaviour was provided.
Houborg 2006[94]	Not only cancer participants were included (participants undergoing colorectal surgery also included).
Jacobsen 2002[95]	No psychosocial intervention. This study evaluated two types of stress management consisting of only one session. This intervention is not a systematic process.
Kim 2002[96]	No psychosocial intervention. In this intervention participants received tapes with information on self-help. Thus feedback was lacking.
Kim 2005[97]	No psychosocial intervention. In this intervention participants received tapes for exercise in bed and relaxation breathing exercise, but there was no additional feedback.
Korstjens 2008[98]	Intervention was conducted after cancer treatment was finished.
Laidlaw 2005[99]	Less than 10 participants for each condition (n = 7 self hypnosis group, n = 4 Johrei group, n = 3 control group).
Lindemalm 2008[100]	Intervention was conducted after cancer treatment was finished.
Mock 1994[101]	Less than 10 participants for each condition (n = 9 experimental group, n = 5 control group).
Ollenschlager 1992[102]	No psychosocial intervention. The emphasis was placed on changing nutritional behaviour.
Ovesen 1993[103]	Fatigue was not measured.
Oyama 2000[104]	No psychosocial intervention. This study evaluated a Bedside wellness system, including aromatic oil and virtual reality using sound systems. Thus feedback was lacking.
Persson 2002[105]	Four conditions were described, but participants were randomised between two of the four groups. There was no control for these two groups.
Post-White 2003[106]	In this study there was no control or normal care group.
Ravasco 2005[107]	No psychosocial intervention. The emphasis was placed on changing nutritional behaviour.
Ravasco 2005a[108]	No psychosocial intervention. The emphasis was placed on changing nutritional behaviour.

Table 1: Characteristics of excluded studies

Study	Reason for exclusion
Roscoe 2005[109]	No psychosocial intervention. This study evaluated polarity, but feedback on their behaviour was lacking.
Savard 2005[110]	Intervention was conducted after cancer treatment was completed.
Sherwood 2005[111]	Fatigue was mentioned as one of the symptoms. Results on the total number of symptoms were described, but was not separated for fatigue.
Speca 2000[112]	Unclear if participants received cancer treatment during the intervention.
Stanton 2005[113]	Intervention was conducted after cancer treatment was completed.
Stiegelis 2004[114]	Intervention was conducted after cancer treatment was completed.
Strong 2008[115]	Cancer patients with concurrent chemotherapy or radiotherapy were excluded.
Telch 1986[116]	Unclear if participants received cancer treatment during the intervention.
Vos 2004[117]	Unclear if participants received cancer treatment during the intervention.
Wenzel 1995[118]	Unclear if participants received cancer treatment during the intervention.
Williams 2004[119]	No psychosocial intervention. In this intervention participants were educated using audiotapes. Thus feedback was lacking.
Williams 2005[120]	No psychosocial intervention. In this intervention participants were educated using audiotapes. Thus feedback was lacking.
Wydra 2001[121]	No psychosocial intervention. This intervention evaluated self-care management giving participants an interactive videodisc module, but received no feedback from a care provider.

Table 2: Characteristics of ongoing studies

Cohen 2004a

Study name	Mindfulness relaxation compared with relaxing music and standard symptom management education in treating patients who are undergoing chemotherapy for newly diagnosed solid tumors.
Methods	Randomized phase: Patients are randomized to 1 of 3 treatment arms; Arm I: Patients undergo mindfulness relaxation therapy (MR); Arm II: Patients listen to relaxing music; Arm III: Patients receive standard symptom management education. Nausea and vomiting, mental health (anxiety, depression, and distress), and quality of life (cancer-related symptoms, fatigue, sleep, and pain) are assessed at baseline, in the middle of chemotherapy (course 2 of a 4-course chemotherapy protocol OR course 3 of a 6-course chemotherapy protocol), at the end of treatment, and then at 3 months.
Participants	Patients who are undergoing chemotherapy for newly diagnosed solid tumors.
Interventions	Arm I: Patients undergo mindfulness relaxation (MR) therapy comprising listening to instructions on breathing techniques and other mind and body relaxation practices on compact disc for 30 minutes before and during each chemotherapy session and at least once daily for the entire duration of chemotherapy treatment. Arm II: Patients listen to relaxing music (with no instructions on relaxation techniques) for 30 minutes before and during each chemotherapy session and at least once daily for the entire duration of chemotherapy treatment. Arm III: Patients receive standard symptom management education.
Outcomes	Conditioned nausea and vomiting as measured by Morrow assessment of nausea and emesis (MANE); Distress as measured by Impact of Event Scale (IES); Fatigue as measured by brief fatigue inventory (BFI); Anxiety as measured by Spielberger State/Trait Anxiety Scale (STAI); Depression as measured by Center for Epidemiology-Depression (CES-D); Sleep as measured by Pittsburgh Sleep Quality Index (PSQI); Pain as measured by brief pain inventory (BPI); Quality of life as measured by Functional Assessment of Cancer Therapy.
Starting date	March 2006
Contact information	Lorenzo Cohen: U.T.M.D. Anderson Cancer Center USA
Notes	

Table 2: Characteristics of ongoing studies

Cohen 2006

Study name	Evaluation of the effect of cognitive behavior intervention on psychological distress of cancer patients and their family members.
Methods	Study Design: Randomized, Active Control Study. Questionnaires will be answered by the participants pre-, post-intervention and after four months.
Participants	Cancer patients.
Interventions	Cognitive behavior group intervention.
Outcomes	Brief Symptom Inventory, Fatigue inventory, Mini Sleep Questionnaire and repression-sensitization questionnaire.
Starting date	July 2006
Contact information	cohenm@research.haifa.ac.il
Notes	

Cohen 2007a

Study name	Effects of Tibetan yoga on fatigue and sleep in cancer.
Methods	Participants are randomly assigned to three groups: a Tibetan Yoga (TY) group; stretching group (SG); or a usual care group (UC). Measures will be obtained prior to randomization and 1 week, 1 month, 6 months, and 12 months, after the last intervention session.
Participants	Women with breast cancer undergoing chemotherapy.
Interventions	Participants in the TY and SG groups will participate in seven weekly group sessions (60 minutes) or 4 sessions every 3 weeks (90 minutes). TY: Deep breathing exercises and performing different stretching and movement exercises. SG: Simple stretching exercises.
Outcomes	Fatigue and sleep disturbances.
Starting date	November 2006
Contact information	Lorenzo Cohen: U.T.M.D. Anderson Cancer Center USA
Notes	

Table 2: Characteristics of ongoing studies

Cohen 2007b

Study name	Effects of yoga in breast cancer patients.
Methods	Participants are randomly assigned to three groups: a Yoga group (YG) group; stretching group (ST); or a waitlist control group (WL). Measures will be obtained prior to randomization, a brief assessment during the middle of radiation therapy, during the last week of radiation therapy and 1 month, 3 months, and 6 months, after the last radiation session.
Participants	Women with breast cancer undergoing radiotherapy.
Interventions	Participants in the YG and ST groups will attend three sessions (60 minutes) each week throughout their 6-week radiotherapy schedule. TY: Deep breathing exercises and performing different movements and meditation. SG: Simple stretching exercises.
Outcomes	Fatigue and sleep disturbances (self-report and actigraphy).
Starting date	March 2006
Contact information	Lorenzo Cohen: U.T.M.D. Anderson Cancer Center USA
Notes	

Goedendorp 2005

Study name	Evaluation of intervention strategies to manage fatigue during active treatment and to prevent persistent fatigue after curative treatment for cancer.
Methods	Participants are randomly assigned to three groups: the minimal intervention; the CBT intervention; and a usual care group. Patients will be assessed before cancer treatment (T0), shortly after cancer treatment (at least 6 months after baseline) (T1), and one year after T1.
Participants	Patients just have been diagnosed for breast cancer, colorectal cancer, cervix cancer, uterus cancer, testis cancer, Hodgkin and non-Hodgkin disease. Patients in preparation of receiving therapy with curative intention.
Intervention	1) The nursing intervention consists of a booklet with easily understood general information about two components. In two one hour session the research nurse will explain the booklet and help the patient to applicate this to their situation. General information about fatigue during active treatment will be given. The second component consists of physical activity instructions. In the second session also the adherence of the patients to the instructions will be discussed.

Table 2: Characteristics of ongoing studies

continued Goedendorp 2005

Interventions	2) CBT condition will also get and discuss the booklet given in the minimal intervention condition. Additional they get individual treatment that consists of 10 sessions with a psychotherapist of the Expert Centre Chronic Fatigue in about six months. Patients will; learn to cope with emotions evoked by having a life-threatening disease; be thought how to get a more regular sleep/wake cycle; learn to regulate activities; learn to regulate support of others, emotionally or instrumentally; engaging in activities that give mental rest and relief; integrate the learned way of thinking and behaving in daily life.
Outcomes	Fatigue severity will be measured using the Checklist Individual Strength.
Starting date	1-11-2005
Contact information	m.goedendorp@nkcv.umcn.nl; g.bleijenberg@nkcv.umcn.nl
Notes	

Oh 2008b

Study name	Randomized Clinical Trial: The impact of medical qigong (traditional Chinese medicine) on fatigue, quality of life, side effects, mood status and inflammation of cancer patients.
Methods	Participants are randomly assigned to two groups: a control group that receive usual health care and an intervention group who participate in a Medical Qigong (MQ) program in addition to receiving usual health care at the hospital. Randomisation was stratified by completion of cancer treatment or under active cancer treatment. Patients completed measures before and after the program.
Participants	Patients diagnosed with a range of cancers.
Interventions	The 10 week MQ program consists of, coordination of gentle exercise and relaxation through meditation and breathing exercise based on the Chinese Medicine theory of energy channels.
Outcomes	Cancer related fatigue was measured by FACT-F, quality of life and symptoms were measured by the FACT-G, mood status by POMS. The inflammatory marker serum C-reactive protein (CRP) was also monitored serially.
Starting date	Unclear. In September 2008 almost 162 participants were recruited.
Contact information	byeongsangoh@health.usyd.edu.au
Notes	An abstract can be found at the American Society of Clinical Oncology: 08-AB-32678-ASCOAM

Table 2: Characteristics of ongoing studies

Purcell 2008

Study name	A randomised control trial investigating the effects of group education and support in reducing cancer-related fatigue and improving quality of life in patients undergoing radiotherapy.
Methods	Patients will be randomised into one of four group using a 2x2 factorial design. These groups will attend a fatigue education and support (FES) group either once at the start of treatment, once at the end of treatment or twice at both the start and end of treatment. These three interventions will be compared to a control group who receive standard care (no FES group). Patients will be assessed at three time points; once at the start of treatment, once at the end of treatment, and once six weeks after the completion of treatment.
Participants	Patients diagnosed with a range of cancers.
Interventions	Participants receive education about radiotherapy process, what to expect from treatment, side effects and strategies to use to minimise side effects.
Outcomes	Fatigue using the Multidimensional Fatigue Inventory.
Starting date	01-04-2008
Contact information	Amanda_purcell@health.qld.gov.au
Notes	

Savard 2008

Study name	Self-Help treatment for insomnia in breast cancer patients.
Methods	Study Design: Randomized, Active Control Study with three study arms: two forms of cognitive-behavioral therapy (CBT) and a the control condition (i.e., usual care). Timeframe: pre-treatment, post-treatment, 4 follow-up.
Participants	Cancer patients.
Interventions	1: professionally administered cognitive-behavioral therapy, consisting of six weekly sessions. 2: self-administered form of cognitive behavioral therapy, consisting of six short booklets and videotapes.
Outcomes	sleep diary indices, actigraphy, Insomnia Severity Index.
Starting date	April 2008
Contact information	josee.savard@psy.ulaval.ca; julie.villa@crhdq.ulaval.ca
Notes	

Table 3: Outcomes

Author and year	Instruments used to measure fatigue	Number of instruments used to measure fatigue
Armes 2007[49]	Visual Analogue Scale (VAS-f) of global fatigue. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), sub-scale fatigue. Multidimensional Fatigue Inventory (MFI).	3
Barsevick 2004[50]	Short Form of the Profile of Mood States (POMS), sub-scale Fatigue. Schwartz Cancer Fatigue Scale (SCFS). General Fatigue Scale (GFS).	3
Berglund 2007[39]	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), sub-scale fatigue.	1
Brown 2006[51]	Single item Linear Analogue Self Assessment (LASA). Profile of Mood States (POMS), Fatigue-Inertia sub-scale. STAI question 26, Symptom Distress Scale (SDS) fatigue question.	4
Classen 2001[41]	Profile of Mood States (POMS), Fatigue-Inertia sub-scale.	1
Cohen 2007[34]	Fatigue Symptom Inventory (FSI).	1
Cunningham 1989[52]	Profile of Mood States (POMS), Fatigue-Inertia sub-scale.	1
Decker 1992[54]	Profile of Mood States (POMS), Fatigue-Inertia sub-scale.	1
De Moor 2002[42]	Profile of Mood States (POMS), Fatigue-Inertia sub-scale.	1
De Wit 1997[53]	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), sub-scale fatigue.	1
Edelman 1999[43]	Profile of Mood States (POMS), Fatigue-Inertia sub-scale.	1
Faithfull 2001[46]	Visual Analogue Scale (VAS). European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), sub-scale fatigue.	2
Fawzy 1995[40]	Profile of Mood States (POMS), Fatigue-Inertia sub-scale.	1
Forester 1985[58]	Schedule of Affective Disorders and Schizophrenia (SADS), item Fatigue.	1

Tables 3: Outcomes

Author and year	Instruments used to measure fatigue	Number of instruments used to measure fatigue
Gaston-Johansson 2000[38]	Visual Analogue Scale (VAS).	1
Given 2002[55]	Symptom Experience Scale (SES), item Fatigue.	1
Godino 2006[47]	Functional Assessment of Cancer Therapy Fatigue (FACT-F).	1
Goodwin 2001[32]	Profile of Mood States (POMS), Fatigue-Inertia sub-scale. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), sub-scale fatigue.	2
Moadel 2007[37]	Functional Assessment of Chronic Ilness Therapy - Fatigue (FACIT-F).	1
Oh 2008[56]	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), sub-scale fatigue.	1
Rawl 2002[48]	SF-36 Vitality.	1
Ream 2006[57]	Visual Analogue Scale (VAS), SF-36 sub-scale vitality.	2
Sandgren 2000[35]	Profile of Mood States (POMS), Fatigue sub-scale.	1
Sandgren 2003[30]	Profile of Mood States (POMS), Fatigue-Inertia sub-scale.	1
Savard 2006[44]	Multidimensional Fatigue Inventory (MFI).	1
Spiegel 1981[45]	Profile of Mood States (POMS), Fatigue sub-scale.	1
Yates 2005[36]	Revised Piper Fatigue Scale (PFS). Functional Assessment of Cancer Therapy Fatigue (FACT-F). Four 11-point numeric fatigue rating scales (NFRS) assessing levels of fatigue at worst, best, and average in the past week, and currently.	6

Table 4: Quality Assessment

Scales	Armes 2007[4]9	Barsevick 2004[5]0	Bergl und 2007[3]9	Brown 2006[5]1	Classen 2001[4]1	Cohen 2007[3]4	Cunningham 1989[5]2
randomisation	1	1	1	1	1	1	1
concealment of allocation	0	0	0	0	0	0	0
blinded outcome assessor	0	0	0	0	0	1	0
power calculation	1	0	0	0	0	0	0
intention to treat	0	1	0	0	0	0	0
group similarity at baseline	0	1	1	0	1	1	1
specified eligibility criteria	1	1	1	1	1	1	0
drop-out	1	0	1	0	1	0	1
selective lost to follow-up	0	1	0	0	0	0	0
co-intervention avoided	1	1	1	1	1	1	1
compliance	1	1	0	1	1	1	0
relevant measures	1	1	1	1	1	1	1
timing assessments	1	1	0	1	1	0	0
equally treatment	1	1	1	0	1	1	1
contamination	0	0	0	0	0	0	1
protocol	1	1	0	1	1	1	1
training	1	1	0	1	0	0	0
integrity check	1	1	0	0	0	0	0
adverse effects	0	0	0	0	0	0	0
sample size	1	0	0	0	1	1	1
missing values	0	1	0	0	0	0	0
standard deviation	1	1	0	0	0	1	0
desc. of index & control intervention	1	1	1	1	1	1	1
long term follow-up measurement	1	1	1	1	0	1	1
supervision	1	1	0	0	1	0	0
Oxford Quality Scale[26]	2	1	2	1	2	1	2
Delphi list[27]	2,5	3,5	2,5	1,5	2,5	3,5	1,5
Internal Validity[28]	4,5	4,5	3,5	3,5	4,5	4,5	3,5
Total (25)	17	18	9	10	13	13	11

Footnotes
Oxford Quality Scale[26]: randomisation, concealed allocation, drop-out (0-3).
Delphi list[27]: randomisation (0,5 points), concealed allocation (0,5 points), blinded outcome assessor, power calculation, intention to treat, group similarity at baseline, specified eligibility criteria (0-6).
Internal validity[28]: randomisation, concealed allocation, blinded outcome assessor, intention to treat, drop-out, co-intervention avoided, compliance, timing assessments. (0-8)
Yes= 1, No= 0, Not enough information to answer this question= 0
desc. = description

Table 4: Quality Assessment

Scales	Decker 1992[54]	De Moor 2002[42]	De Wit 1997[53]	Edelman 1999[43]	Faithfull 2001[46]	Fawzy 1995[40]
randomisation	1	1	1	1	1	1
concealment of allocation	0	0	0	0	0	0
blinded outcome assessor	1	0	0	0	0	0
power calculation	0	0	0	0	1	0
intention to treat	0	0	0	0	0	0
group similarity at baseline	0	1	1	1	0	1
specified eligibility criteria	1	1	1	1	1	1
drop-out	0	1	1	1	0	0
selective lost to follow-up	1	0	-1*	0	0	0
co-intervention avoided	1	1	1	1	1	1
compliance	0	1	1	0	0	0
relevant measures	1	1	1	1	1	1
timing assessments	1	1	1	1	1	0
equally treatment	1	1	1	1	1	1
contamination	0	0	0	0	0	0
protocol	1	1	1	1	0	1
training	0	0	1	0	0	0
integrity check	0	0	0	0	0	0
adverse effects	0	0	0	0	0	0
sample size	0	0	1	1	1	0
missing values	0	0	0	0	0	0
standard deviation	1	0	1	0	0	1
desc. of index & control intervention	1	1	1	1	1	1
long term follow-up measurement	1	1	1	1	0	1
supervision	1	0	0	0	0	0
Oxford Quality Scale[26]	1	2	2	2	1	1
Delphi list[27]	2,5	2,5	2,5	2,5	2,5	2,5
Internal Validity[28]	3,5	4,5	4,5	3,5	2,5	2,5
Total (25)	13	12	14	12	9	10

Table 4: Quality Assessment

Scales	Forester 1985[58]	Gaston-Johansson 2000[38]	Given 2002[55]	Godino 2006[47]	Goodwin 2001[32]	Moadel 2007[37]	Oh 2008[56]
randomisation	1	1	1	1	1	1	1
concealment of allocation	0	0	0	0	0	0	0
blinded outcome assessor	0	0	0	0	0	0	0
power calculation	0	1	0	0	1	1	0
intention to treat	0	0	0	0	0	0	0
group similarity at baseline	1	1	1	0	1	1	0
specified eligibility criteria	1	1	1	1	1	1	1
drop-out	0	0	0	1	1	1	1
selective lost to follow-up	0	0	1	0	1	-1*	0
co-intervention avoided	1	1	1	1	1	1	1
compliance	0	0	0	0	1	1	0
relevant measures	1	1	1	1	1	1	1
timing assessments	1	1	0	1	1	1	1
equally treatment	1	1	1	1	1	1	1
contamination	0	0	0	0	0	0	0
protocol	0	1	1	1	1	0	0
training	0	0	1	1	1	1	1
integrity check	0	0	0	0	1	0	0
adverse effects	0	0	0	0	0	0	0
sample size	1	1	1	1	1	1	1
missing values	0	0	0	0	0	0	0
standard deviation	0	1	0	1	1	1	0
desc. of index & control intervention	1	1	1	1	1	1	1
long term follow-up measurement	1	0	0	0	0	0	0
supervision	0	0	0	0	0	0	0
Oxford Quality Scale[26]	1	1	1	2	2	2	2
Delphi list[27]	2,5	3,5	2,5	1,5	3,5	3,5	1,5
Internal Validity[28]	2,5	2,5	2,5	3,5	4,5	4,5	3,5
Total (25)	10	12	11	12	17	13	10

Footnotes

* -1: in this study selective lost to follow-up was present

Table 4: Quality Assessment

Scales	Rawl 2002[4 8]	Ream 2006[5 7]	Sandgren 2000[35]	Sandgren 2003[30]	Savard 2006[44]	Spiegel 1981[45]	Yates 2005[36]
randomisation	1	1	1	1	1	1	1
concealment of allocation	1	1	0	0	0	0	1
blinded outcome assessor	0	0	0	0	0	0	0
power calculation	0	1	0	0	0	0	1
intention to treat	0	0	0	1	0	0	0
group similarity at baseline	1	1	1	0	0	0	1
specified eligibility criteria	1	1	1	1	1	0	1
drop-out	1	1	1	1	1	0	1
selective lost to follow-up	0	0	0	1	0	0	0
co-intervention avoided	1	1	1	-1	1	1	1
compliance	0	0	0	1	0	0	1
relevant measures	1	1	1	0	1	1	1
timing assessments	1	1	1	1	1	0	1
equally treatment	0	1	1	1	1	0	1
contamination	0	0	0	1	0	0	0
protocol	1	1	0	1	0	1	1
training	1	0	1	1	0	1	1
integrity check	1	0	0	1	1	0	0
adverse effects	0	0	0	0	0	0	0
sample size	0	1	1	0	1	1	1
missing values	0	0	0	0	0	1	0
standard deviation	0	1	0	0	1	0	1
desc. of index & control intervention	1	1	1	1	1	1	1
long term follow-up measurement	1	0	1	1	1	0	1
supervision	0	0	1	1	0	1	0
Oxford Quality Scale[26]	3	3	2	2	2	1	3
Delphi list[27]	3	4	2,5	3,5	1,5	0,5	4
Internal Validity[28]	4	4	3,5	3,5	3,5	2,5	5
Total (25)	13	14	13	15	12	9	17

Footnotes
* -1: in this study selective lost to follow-up was present

Table 5: Characteristics of included studies

Armes (2007)[49]

Methods	RCT. Originally starting with minimization on basis of age, sex, site, and stage of cancer, and HADS scores. After 10 patients were allocated, simple random permuted block randomization was implemented. Sixty participants were randomized, 30 to both groups, the final sample size was 55. Of the experimental group (EG) 28 completed baseline questionnaires (T0 = cycle 3 of CT), 21 participants completed T1 assessment (end of cytotoxic treatment), 22 participants completed T2 assessment (4 weeks after the end of cytotoxic treatment), and 17 participants completed T3 assessment (9 months after recruitment). Of the control group (CG) 27 participants completed T0, 16 completed T1, 22 completed T2, 19 completed T3. Non response rate varied across assessment from 16 to 5. At T3 14 participants died and 5 were non-responders (EG 7 died, 4 non response; CG 7 died, 1 non response).
Participants	Patients who were attending for chemotherapy treatment were screened for eligibility at 2 cancer centres in South London. Patients were excluded who 1) were aged < 18 years; 2) did not have histologically proven cancer or were not aware of their cancer diagnosis; 3) were receiving the last half of the planned course of cytotoxic treatment; 4) were unable to speak and understand English; 5) did not report significant fatigue; 6) had a poor Eastern Cooperative Oncology Group performance status (>3); 7) had a previous history of psychotic disorder; 8) had evidence of cognitive impairment or central nervous system metastases; 9) were receiving psychotherapy or CBT; 10) were receiving cytokine treatment; or 11) had an uncontrolled infection at the time of recruitment. The mean age of the 55 participants was 59 years. A majority were women (n=33) and were white British (n=46). Of these, 27 had a diagnosis of colorectal cancer, 44 had stage III or IV, and 42 had at least 1 metastasis.
Interventions	One trained research fellow (nurse) (first author) provided the intervention, consisting of 3 individual, face-to-face, 60 minute sessions at 3 to 4 weekly intervals (coinciding with chemotherapy). The components of the intervention were education of CRF, written information on CRF, discussing effectiveness of coping strategies; goal setting, activity scheduling, graded task management, self monitoring and modification; distraction, cognitive restructuring, praise and encouragement. The control group received standard care.
Outcomes	Three primary outcomes were measured. Fatigue was assessed using a VAS of global fatigue, physical functioning (sub-scale of EORTC-QLQ-C30), fatigue-related distress was measured with a Fatigue Outcome Measure designed specifically for the study. Secondary outcomes were MFI, HADS, and the EORTC-QLQ-C30.
Notes	The duration of the cytostatic treatment is not described.
Allocation concealment?	Yes, Not concealed at the start of the study (see methods)

Footnotes: CBT: cognitive behavioural therapy; CRF: cancer related fatigue

Table 5: Characteristics of included studies

Barsevick 2004[50]

Methods	RCT. Participants were stratified by job status (working versus Nonworking), type of treatment (CTX versus. radiotherapy versus concurrent therapy), and diagnosis (breast versus non-breast cancer). Questionnaires were administered at three points. Baseline assessment occurred before the start of cancer treatment. For participants receiving CTX or concurrent therapies assessment occurred 48 hours after the second and third CTX. For participants receiving RT assessment occurred during the last week of treatment and one month after completion of treatment. 396 participants were included in the study.
Participants	Individuals were eligible if they were currently beginning treatment intended for cure of local control, for breast, lung, colorectal, advanced prostate, gynaecologic, or testicular cancer or lymphoma and if they planned to receive > 3 cycles of high-dose chemotherapy (CTX), 6 weeks of radiotherapy (RT) or current RT and CTX. Other treatment other than surgery had to be completed one month previously. Exclusion criteria were if the treatment plan included stem cell transplantation, interleukins, interferons, or tumour necrosis factor, patients with chronic fatigue syndrome, patients who enrolled on to other studies involving psycho-educational interventions, patients with a psychiatric disorder, and patients receiving treatment for anaemia or depression. The mean age of the 396 participants was 56.3 years, the majority were female (85%), Caucasian (91%) and college educated (65%). The study was conducted at a university health science centre and a comprehensive cancer centre.
Interventions	Participants allocated to the energy conservation and activity management (ECAM) condition received three telephone sessions from a trained oncology nurse. Participants were given information on cancer-related fatigue and learned energy conservation skills. An energy conservation plan was created (coping stage), evaluated and revised (appraisal stage). The control group received three telephone sessions with information on nutrition, informing and discussing maintenance of a healthy diet, use of vitamins and minerals. Planned duration for both conditions of the first two sessions was 30 minutes and the third session 15 minutes. For participants receiving CTX or concurrent therapy the intervention was administered during the first 3 weeks of treatment. For participants receiving RT the intervention occurred during week 3 to 5 of treatment.
Outcomes	Fatigue was measured with three scales (POMS-sf, SCFS and GFS). An other outcome was functional performance (FPI).
Notes	How many patients were randomised to the two conditions and how many were lost to follow up is not described. In addition a description what was done with missing values is lacking.
Allocation concealment?	Unclear

Footnotes: ECAM: energy conservation and activity management

Table 5: Characteristics of included studies

Berglund 2007[39]

Methods	RCT. After stratification on stage of disease, curative treatment and age, 211 participants were randomised to Physical training (Phys) (n=53), Information (Info) (n=55), information plus physical training (PhysInfo) (n=52) or a control group (C) (n=51). Questionnaires were completed by 194 participants at baseline, 166 participants at 6 months follow-up, and 158 participants at 12 months follow-up. Some participants (n=23) dropped-out after randomisation, others in a later stage for the following reasons; dissatisfied with group assignment, could not arrange transportation. In addition some questionnaires were not returned, at 6 months follow-up or at 12 months follow-up.
Participants	Within six months after diagnosis prostate cancer were included at the university hospital in Uppsala, Sweden. Participants were excluded if they had another cancer diagnosis, participated in other studies, were patients in other care programmes, had severe hearing or vision impairment, were not Swedish speaking, or were physically or mentally disabled. Overall 20% of the participants had metastasis, the most frequent curative treatment was radical prostatectomy (24%), and 36% did not had active treatment (watchful waiting). The average age was 69 years, 80% was married and 24% had a university degree.
Interventions	Each intervention program included 7 weekly sessions, with group sizes varying from 3 to 10 participants. Phys: A physiotherapist led 60-minute physical training session followed by a 15 minute coffee break. The programme included light physical training with movement and fitness training, relaxation and breathing exercises. A booster session was held 2 months after the conclusion of the training exercises. Info: A nurse led 60 minute information sessions followed by a 15 minute coffee break. Emphasis was laid on giving the information about prostate cancer, its treatment (lecture given by an urologist) and potential side effects and how to deal with side effects. PhysInfo: combination of Phys and Info programs. Participants were given physical training and then information in the same session, consisting of seven 135-minute sessions. The control group received standard care, i.e. the information and care that was available at that time.
Outcomes	The HADS and EORTC-QLQ-C30 were used. Fatigue was assessed with the fatigue sub-scale of the EORTC QLQ-C30.
Notes	Unclear how many patients completed questionnaires at 12 months follow-up as numbers in the figure are different from the tables.
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Brown 2006[51]

Methods	RCT: stratification for tumour type, age, gender, and ECOG score. Of the 115, 57 were randomised to the experimental condition 58 to the control condition. Before assessment 3 participants cancelled due to illness. 55 participants in the experimental condition completed baseline assessment, 57 in the control condition. Of the experimental condition 46 completed the assessment at week 4, 6 were found ineligible due to lack of session attendance. Of the control condition 54 completed the assessment at week 4.
Participants	Eligible participants were adult advanced cancer patients scheduled to undergo radiation therapy, recruited at the division of radiation oncology mayo clinic Rochester. Participants had to be diagnosed with cancer in the past 12 months, have an expected survival of at least 6 months, but a 5-year survival probability of no more than 50%, and recommended radiotherapy for at least two weeks. Exclusion criteria was a MMSE-score less than 20, an ECOG performance score of 3 or more, active alcohol or substance dependence, active thought disorder, suicidal plans, or participation in a psychosocial trial. The mean age of the 115 participants was 59.6 and 66 of the participants were male.
Interventions	In the structured multidisciplinary intervention participants attended eight 90-minute sessions over the first 4 weeks after enrolment. A psychiatrist or a psychologist led each session; depending on the theme (mental, emotional, physical, social, spatial), an advanced practice nurse, a chaplain, or a social worker co-facilitated each session. Sessions began with 20 minutes of exercise conducted by a physical therapist followed by educational information, cognitive-behavioral strategies, discussion, and support. Sessions concluded with a 10 to 20 minute guided relaxation exercise. Participants received a manual and specific education brochures. The control group received standard medical care.
Outcomes	Fatigue was assessed as a secondary outcome, measured with LASA, POMS, and SDS at baseline and at week 4, 8, 27 and STAI at baseline. In addition raw scores were transformed to a 0 to 100 point scale as fatigue QOL.
Notes	Not described how many patients completed the assessment at week 8 and 27.
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Classen 2001[41]

Methods	On completion of baseline testing, participants were randomised to intervention or control conditions using the adaptive randomisation biased coin-design method. The adaptive randomisation method used the following variables: 1 dominant site of metastasis at study entry, 2 estrogen receptor status, 3 disease-free interval, metastasis or recurrence, 4 age at study entry, 5 systemic treatment received since metastasis, 6 institution. 102 women were included in the data analysis, with patients who completed a pre-randomisation baseline measure and at least 1 post baseline assessment. 23 of the 125 women randomised into the study did not complete any post-baseline assessments: 15 of these 23 participants were too ill to complete questionnaires (4 treatment and 11 control participants), 2 were too busy (both control participants), 4 withdrew from the study because they were not assigned to a support group, 1 withdrew because she did not like the support group, and 1 assigned to the treatment condition withdrew for no stated reason. 64 women were randomised to the intervention arm of the study and 61 to the control arm. Post-baseline assessments were conducted every 4 months during the first year and every 6 months thereafter.
Participants	Women with confirmed metastatic or locally recurrent breast cancer were recruited through the Oncology Day Care Center at Stanford University Medical Center. Patients were eligible if they had a Karnofsky score of at least 70%, were proficient enough in English to be able to respond to questionnaires and participate in a support group. Women were not included with positive supraclavicular lymph nodes as the only metastatic lesion at the time of initial diagnosis; active cancers within the past 10 years other than breast cancer, basal cell or squamous cell carcinomas of the skin, in situ cancer of the cervix, or melanoma with a Breslow depth less than 0.76 mm; or concurrent medical conditions likely to affect short-term survival. At study entry 41% of the control group received chemotherapy and 84% hormone therapy. Of the treatment group 43% received chemotherapy and 81% received hormone therapy. The mean age of the control group was 54, the mean education was 19 years, and 80% was white. The mean age of the treatment group was 53, the mean education was 16 years, and 91% was white.

Table 5: Characteristics of included studies

continuation Classen 2001[41]

Interventions	Participants in the treatment group, the size ranging from 3 to 15, met weekly for 90-minute sessions. The intended duration of treatment was 1 year. The therapy sessions were facilitated by 2 therapists. Therapists included a psychiatrist, psychologists, and social workers. The supportive-expressive therapy model involved the creation of a supportive environment in which participants were encouraged to confront their problems, strengthen their relationships, and find enhanced meaning in their lives. Psycho education was provided in a similar fashion, with group members sharing knowledge they gathered about the illness and related issues. The intervention was unstructured, neither coping strategies nor psycho education was taught in a didactic manner. Each session ended with a self-hypnosis exercise to help participants manage stress and deal with pain. Participants were encouraged to use this exercise at home. All participants (also from the control group) were offered self-directed education materials. They were given a list of materials to select from and to take home on loan. The selection of 30 books, 15 pamphlets, 5 videotapes, and 7 audiotapes covered a wide range of topics related to breast cancer.
Outcomes	The Profile of Mood States (POMS) was used to assess mood disturbance, including the sub-scale fatigue. The Impact of Event Scale (IES) was used to assess trauma symptoms.
Notes	Results of the six months follow-up measurements after the intervention are not described.
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Cohen 2007[34]

Methods	RCT. The number of participants was 38 in the cognitive-behavior (CB) group, 39 in the relaxation and guided imagery (RGI) group, and 37 in the control group (CG). Participants completed questionnaires at three time point: pre-intervention, post-intervention, and at the end of a 4-month follow-up after the CB and RGI groups concluded. Several women did not complete the post-intervention or follow-up questionnaires: 3 from the RGI group, 1 from the CB group, and 6 from the CG.
Participants	Breast cancer patients, stages I and II, who were 2 to 12 months since surgery and receiving treatment (chemotherapy or radiotherapy) were invited to participate in the outpatient unit of the oncology centre. Inclusion criteria were fluent spoken Hebrew and absence of a psychiatric illness known to the oncology staff. The mean age of the women was 55.9 (CB), 51.8 (RGI), and 52.9 (CG). The mean education in years was 13.5 (CB), 13.2 (RGI) and 12.8 (CG). The majority were married 76.3% (CB), 64.1% (RGI), and 81.1% (CG). The time since diagnosis was 6.9 (CB), 7.2 (RGI), 6.5 (CG) months. A majority received chemotherapy 60.5 (CB), 64.1 (RGI), 56.8 (CG).
Interventions	The interventions were conducted by the first author, a senior social worker and expert in psycho-oncology, with training and experience in CB techniques. Each group of 6 to 8 participants met weekly, for nine 90-minute sessions. CB: Cognitive components focused on learning to elicit negative thinking patterns and restructure them into adaptive patterns and stress-reducing thoughts. In addition mental distraction, problem-solving, and decision-making strategies were taught. Behavioral components focused on activity scheduling, graded task assignment and behavioral distraction. Practicing at home was emphasized, with homework exercises, and written material was provided. RGI: Systematic learning of deep RGI, practicing deep breathing and autogenic relaxation. Experience of practice at home was discussed to give reassurance and work on problems in the relaxation process. Participants also practiced anxiety, pain, and nausea reduction, and strategies to overcome sleep problems. Participants were provided with RGI audio cassettes or compact disks for activity at home. Patients in the control group received standard care in the oncology unit.
Outcomes	The Fatigue Symptom Inventory (FSI) was used to measure fatigue. Other instruments used were the Brief Symptom Inventory, the Perceived Stress Scale, the Mini Sleep Questionnaire, and the Multidimensional Health Locus of Control.
Notes	The two interventions could overlap in the use of a behavioral strategy such as distraction. Group processes, such as mutual support, exchange of information, and expression of feelings, took place in both groups.
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Cunningham 1989[52]

Methods	RCT. 60 participants were randomly assigned into one of the two treatment arms: (30 to both groups). They were stratified by the authors according to age, sex and apparent seriousness of disease. Seven dropped out of the therapy (three dying during the program, three being too ill to attend, and one for unknown reasons), leaving 53, 28 in the psycho educational therapy plus supportive discussion, 25 in supportive discussion only. All assessments were being administered, by the authors, at the beginning of the first weekly session of each intervention, at the end of the last weekly session, and for a third time 2 to 3 weeks later.
Participants	The participants were consecutive admissions to an ongoing coping skills training program at a large metropolitan cancer centre. They were referred by a variety of health professionals, or self-referred. The group was heterogeneous in demographic and disease characteristics, about half having recurrent disease, and half being on some form of medical treatment (chemotherapy, radiotherapy or hormone treatment) at the time the interventions began. Of the psycho educations group (n=28), 20 were female, the mean age was 48, 13 had breast cancer, and 16 did not receive treatment at start of the groups. Of the discussion control group (n=25), 19 were female, the mean age was 49, 12 had breast cancer, and 12 did not receive treatment at start of the groups.
Interventions	Both interventions occupied 6 weekly, 2-hour sessions with groups from 7 to 10 participants and a single leader. The psycho educational intervention included in addition to supportive discussions, education in coping skills. The training comprised two sessions of relaxation, two sessions on the use of positive mental imagery and one session each centred around goal-setting and on general lifestyle management. Where coping techniques were taught, they were practised first in the group after which participants were asked to continue the practice at home with the aid of a workbook and two audiotapes. These groups were conducted by the first author, at that time a graduate student in clinical psychology. The control intervention consisted of supportive discussion, ventilation of feelings, general problem solving and information sharing. The leader was the second author, a senior nurse.
Outcomes	The POMS was used, including the sub-scale fatigue. The symptom checklist (SCL-90-R) was also used.
Notes	
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

De Moor 2002[42]

Methods	RCT. On the day of the first vaccine treatment, 42 participants completed questionnaires and were then randomly assigned to an expressive writing (EW) group or a neutral writing (NW) group using minimization. Patient characteristics used for assignment were: gender, number of metastases, and non-lung metastatic involvement. Participants completed follow-up assessments on the day of the fourth writing session and 4, 6, 8 and 10 weeks later. Of the 21 participants in the EW group 2 dropped out prior to the follow-up, and one participant died during the study. Of the 21 participants in the NW group 3 dropped out and two died during the study.
Participants	Patients with newly diagnosed stage IV renal cell carcinoma were recruited from a Phase II trial. Inclusion criteria for the Phase II trial were that all participants had a life expectancy of > 4 months, a Zubrod performance status of 2, no serious intercurrent illnesses, and no brain metastases. Prior to enrolment participants could not have received any chemotherapy, or immunotherapy. Participants underwent a nephrectomy and vaccine treatment. In both groups, the average age was 56 years, 86% were male, and 76% had two or more metastases. Participants with non-lung involvement was 76% in the EW group and 71% in the NW group.
Interventions	The writing sessions for both groups were conducted at each of the first four weekly clinic visits while the participants waited to receive their vaccine treatment. Participants were given verbal and written instructions. Participants in the EW group were instructed to write for 15 minutes about their deepest thoughts and feelings about their cancer. The instructions remained essentially the same for each assignment. The participants in the NW group were instructed to write about a different health behaviour at each session, which comprised diet, physical activity, substance use and sleep.
Outcomes	The outcome measures were symptoms of distress (IES), perceived stress (PSS), mood disturbance (POMS), and sleep disturbances (PSQI). Fatigue was measured with a sub-scale of the POMS.
Notes	The results represented the overall group means averaged across the five follow-up measures, for both groups. In addition it was not described how many participants the statistical analysis was performed upon.
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

De Wit 1997[53]

Methods	Cancer patients who would receive district nursing at home and patients who would not receive district nursing were studied separately. Both patient groups were randomly assigned to a control or an intervention group, after stratifying for three variables: gender, age, and metastatic sites. Summarizing, four study groups were distinguished: 1) a control group without district nursing (n=103); 2) an intervention group without district nursing (n=106); 3) a control group with district nursing (n=51); and 4) an intervention group with district nursing (n=53). Patients were approached to participate after admission to the hospital. All participants were followed up by telephone at 2 (T1), 4 (T2), and 8 weeks postdischarge (T3). (Group (1) T1: N=94, T2: N=86, T3: N=78. Group (2) T1: N=100, T2: N=97, T3: N=85. Group (3) T1: N=44, T2: N=43, T3: N=41. Group (4) T1: N=39, T2: N=33, T3: N=31).
Participants	The study was carried out in the Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands. The following inclusion and exclusion criteria were used: 1) pain related to cancer, cancer therapy, or illness; 2) pain duration of at least 1 month; 3) life expectancy of at least 3 months; (4) able to read and speak Dutch; (5) accessible by telephone; and (6) not residing in a nursing home or retirement home. Participants had various types of primary tumours and extent of the disease. At baseline 22.4% of the participants did not receive cancer treatment, 62.6% were female, 25.9% had a higher education and the mean age was 55.5 years.
Interventions	Three nurses gave the Pain Education Program (PEP). The PEP consists of three components:1) Enhancing patients' knowledge about pain and pain treatment. A patient was instructed about a specific pain topic only when that topic was assessed as applicable to the patient, and only when the patient's knowledge about pain and pain treatment was assessed as insufficient. This tailored information was provided on a one-to-one setting lasting between 30 and 60 minutes. The verbal instruction was accompanied by a pain brochure consisted of two parts: (A) a section with general information aimed at all cancer pain patients, and (B) a loose-leaf part given to patients when applicable, including supplementary sheets with information about different cancer pain treatments.2) Participants were instructed on how to register their Present Pain Intensity twice daily in a pain diary for a period of 2 months. In addition, participants were instructed to document changes on type of pain and use of (non-)pharmacological pain treatment. 3) Stimulating patients' help-seeking behavior. Participants were instructed on how to use simple non-pharmacological pain management techniques, such as cold, heat, relaxation, and massage, at home when pain relief was insufficient. They were encouraged to contact health care providers if necessary.

Table 5: Characteristics of included studies

continuation De Wit 1997[53]

Continuation Interventions	Besides the instruction provided in the hospital, participants were called at home at 3 and 7 days post-discharge by the same nurse to determine whether the instruction was fully understood, and to offer the opportunity to ask questions. These phone calls took 5 to 15 minutes each
Outcomes	Pain experience was measured with the MCGill Pain Questionnaire Dutch Language Version (MPQ-DLV). Present and Average Pain Intensity was measured with a numeric rating scale. Pain knowledge was measured with PKQ-DLV. Quality of life was measured with the EORTC-QLQ. Fatigue was measured with the symptom list of the EORTC-QLQ.
Notes	Drop out rate in the intervention group with district nursing was much higher compared to the other three groups, thus possible selective drop-out.
Allocation concealment?	Unclear

Decker 1992[54]

Methods	RCT. Baseline assessment took place prior to radiation therapy. The post intervention assessment took place at the sixth session, for both groups. 34 participants of the relaxation group completed the post-intervention assessment, 29 of the control group.
Participants	Eligible participants were recently diagnosed cancer patients scheduled to receive external beam radiation. Patients with prior cancer were excluded, those who received prior radiation therapy, in-patients, or those with suicidal ideas. 74 were treated with curative intent, 8 with palliative intent. Of the 82 patients randomised 30 were males, the mean age was 61 years.
Interventions	Participants receiving relaxation treatment met individually for six 1-hour sessions with a graduate student supervised by the first author. In addition to relaxation training, support focused on concerns related to cancer radiation treatment and its effects on physical and emotional sensations. Participants were instructed to perform relaxation each day at home and were provided with a relaxation tape and written instructions. The control group completed the assessment and received standard education and support along with the radiation therapy. All participants received the usual services during radiation therapy.
Outcomes	Fatigue was measured with the POMS sub-scale fatigue.
Notes	
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Edelman 1999[43]

Methods	RCT. For every 20 participants that were recruited a block randomisation procedure took place, with ten to each condition. Of the 124 participants recruited 32 were classified as dropouts (16 died, 10 due to illness, 3 were found not have metastatic disease, 3 other reasons. Ninety-two completed baseline questionnaires, 43 in the CBT group and 49 in the control group (CG). The 3 month assessments was completed by 36 CBT and 37 CG. The 6 month assessment was completed by 31 CBT and 32 CG.
Participants	This study focused on metastatic breast cancer patients recruited from the Royal North Shore Hospital Sydney. Eligibility criteria included: ability to attend group sessions; no concurrent psychiatric disorder, organic brain disorder or drug/alcohol dependency; ability to speak and read English; and aged between 30 and 65 years. Of the recruited participants 47% were between 41 and 50 years old, 63% was married. It was not described whether participants received treatment during the intervention.
Interventions	Therapy recipients attended eight weekly sessions of group CBT, followed by a family night, and three further monthly sessions. The programme was led by two therapists and incorporated the use of cognitive and behavioural techniques, encouraging the expression of feelings and building of group support. Participants received a manual, handouts and homework exercises at every session. In the first few sessions participants were taught basic cognitive skills, including how to identify and challenge maladaptive thoughts and beliefs. Behavioural techniques were introduced in the second sessions, with a discussion on deep relaxation/meditation as a tool for managing anxiety. Participants received a relaxation tape and were encouraged to practise. The no-therapy control group received standard oncological care.
Outcomes	The POMS was used to measure mood, including the sub-scale fatigue. The Coopersmith Self-esteem Inventory-Adult form was also used to measure self-esteem.
Notes	
Allocation concealment?	Unclear

Footnotes: CBT: cognitive behavioural therapy

Table 5: Characteristics of included studies

Faithfull 2001[46]

Methods	RCT. 115 men were randomised and stratified to provide a balanced representation of men with prostate and bladder cancer. Both groups were assessed within the first week of starting RT, week 3, 6, and at 12 weeks following start of RT. There was a decrease in completion of questionnaires over time (88% at week 6). 81% of the EORTC QLQ was returned at week 12.
Participants	Men included in the study were those undergoing radical (greater than 60 Gy) radiotherapy for prostate (83%) or bladder cancer (17%). The mean age of the men was 70 in both groups.
Interventions	The nurse-led care (intervention) was organised for within the first week and last week of RT. Appointments were for 20 minutes and further appointments could be negotiated as required. The nurse explored the individual's understanding of their diagnosis, symptoms and the meaning of the illness. The intervention provided participants with information and practical advice on how to recognise early symptoms, what to expect from treatment and how to manage existing problems. The nurse also provided men and their families with leaflets on healthy eating, RT and how to manage urinary symptoms during RT. The control group received conventional care consisting of routine medical appointments lasting 10 minutes. These were arranged at the start of RT, continuing weekly for patients with bladder cancer, or 2-weekly for patients with prostate cancer, throughout the duration of RT, and led with a group of 6 physicians.
Outcomes	Data collected were observer-rated toxicity scores (RTOG/EORTC), self-assessment of symptoms (VAS), quality of life (EORTC QLQ-C30), satisfaction with clinical care (based on Newcastle satisfaction with nursing scale), costs. Fatigue was measured with a VAS and a sub-scale of EORTC QLQ-C30.
Notes	Missing data were removed from analysis. Therefore the number of participants varies from 56 at week 1 to 25 at week 12, in the intervention group (SES)
Allocation concealment?	Yes, adequate

Footnote: RT: Radiotherapy

Table 5: Characteristics of included studies

Fawzy 1995[40]

Methods	RCT. Stage I patients were recruited at time of their postoperative checkup and stage II patients when they began immunotherapy protocols. At recruitment participants were asked to fill in the baseline questionnaires. At baseline (t0) 31 participants were randomised to the intervention group and 32 to the control group. Follow-up Questionnaires were mailed to all participants, six weeks (t1) and 3 months (t2) after completion of the intervention. At t2 three participants were lost to follow-up, leaving 28 participants in the intervention group and 32 in the control group.
Participants	This study focused on patients with malignant melanoma, stage I or II. Any Breslow depth and Clark levels I-V were acceptable. Participants had to be at least 18 and no older than 70, able to speak and read English and have no previous history of cancer or psychiatric treatment. The mean age of the experimental condition (n=29) was 42, all were white, 15 were males, and 24 had a college degree or higher. The mean age of the control group (n=33) was 46, 30 were white, 19 were males, and 19 had a college degree or higher.
Interventions	Participants randomised to the psycho educational nursing intervention received an educational manual and 3 hours of individualized teaching on two separate occasions from an oncology nurse. The first session was after baseline testing, the second was made coinciding with the patients' next clinic visit. The intervention consisted of three specific nursing goals and strategies. Health education, stress management, including teaching about stress, stress monitoring and relaxation exercises, and enhancement of coping skills. Participants were called by the nurse prior to the second appointment to remind them of the appointment and to do the reading and relaxation exercises. The control group did not receive the intervention but completed the questionnaires.
Outcomes	Affective state was measured with the BSI and POMS, which includes the sub-scale fatigue/inertia. The Dealing with Illness Inventory was used to asses health seeking and coping behaviours.
Notes	The numbers of patients participating is not clear. Different numbers are described at baseline, and the numbers at t1 are not described.
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Forester 1985[58]

Methods	RCT. 48 participants were randomly selected from the 100 patients to receive psychotherapy, the other 52 participants served as control subjects. Assessments were made at five points, at baseline (week 0), midpoint in radiotherapy (RT) (week 3), end of RT (week 6), 4 weeks after RT (week 10), 8 weeks after RT (week 14).
Participants	Participants were randomly selected before they received 6 weeks of radiotherapy for cancer. Patients with abdominal cancer were excluded. The mean age of the participants given psychotherapy was 62.4 years (n=52), 54% were men and 71% was married; of the control group (n=48) the mean age was 61.5 years, 46% were men and 67% were married.
Interventions	Participants given the intervention were given weekly supportive psychotherapy for 10 weeks (4 weeks beyond completion of RT). The sessions were provided by the first author and lasted 30 minutes. The content was unstructured and focused on perceived patients needs, helping them deal with their emotions regarding treatment. For the majority the sessions were composed of supportive psychotherapy with explanatory, educational, interpretive, and cathartic components. The control group received only RT.
Outcomes	The outcome measure was a SADS interview measuring emotional symptoms, physical symptoms, including a anorexia, nausea and vomiting, and a fatigue scale.
Notes	It seems that of the 100 participants all assessment were available. Nothing is mentioned on missing data or loss to follow up.
Allocation concealment?	Unclear

Footnote: RT: Radiotherapy

Table 5: Characteristics of included studies

Gaston-Johansson 2000[38]

Methods	RCT. The final sample was 110 participants with 52 in the intervention group (IG) and 58 in the control group (CG). The participants completed the questionnaires at baseline, 2 days before autologous bone marrow/peripheral blood stem cell transplantation (ABMT), and 7 days after the ABMT provided by the BMT clinical nurse specialist.
Participants	Eligibility criteria for the participants required a diagnosis of stage II, III or IV breast cancer; a scheduled ABMT at an urban National Cancer Institute-designated comprehensive cancer centre; age of 18 years or older; and ability to read and write English. Most participants were between 41 and 50 years old (50% in the IG and 56% in the CG). Most participants had a college or graduate degree (65% in the IG and 51% in the CG) and were white (89% in the IG and 83% in the CG).
Interventions	The comprehensive coping strategy program (CCSP) was taught to participants by a clinical social worker at least 2 weeks before hospital admission for treatment with high-dose chemotherapy and ABMT. During the intervention preparatory information was presented explaining that adequate control of pain can lead to decreased psychological distress and a decrease in physical symptoms such as fatigue. Several handouts were given explaining theoretical considerations and the use of relaxation exercise with guided imagery, and coping self-statements. Cognitive restructuring information focused on the avoidance of catastrophising distorted thinking. Relaxation with guided imagery was presented via live model and participants were given an audiotape and recorder with earphones to guide them through the relaxation exercise. Participants were instructed to use it every day and before stressful events. The CCSP was reinforced by an ABMT oncology nurse, the principal investigator or the project director, on the day patients were admitted to hospital, 2 days after completing of chemotherapy, and 7-9 days after ABMT. The control group did not receive CCSP.
Outcomes	The outcome measures were pain (POM), nausea (VAS), fatigue (VAS), psychological distress (anxiety (STAI) and depression (BDI)).
Notes	
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Given 2002[55]

Methods	RCT. 113 participants were randomised, 53 to the experimental condition (EG), 60 to the control group (CG), and were interviewed for baseline assessment, within eight weeks of the participants initiating chemotherapy. The second interview, 10 weeks following baseline was completed by 42 participants of the EG and 48 of the CG. The third interview, 20 weeks following baseline was completed by 35 participants of the EG and 43 of the CG.
Participants	Participants were eligible when they were within 56 days of the first cycle of chemotherapy, after a new cancer diagnosis, for colon, breast, lung cancer, non-Hodgkin lymphoma or other solid tumours. Participants had to be at least 40 years of age, and had to report both pain and fatigue at baseline. In addition participants had to be cognitive intact and able to read English. Patients were excluded when they were not expected to survive the duration of the study. Four out-patient cancer treatment sites were used for this study. Two sites were affiliated with comprehensive cancer centres, and two were community cancer treatment clinics. The mean age of the sample was 58 years, 28% was male, and 73% had some college education. About 70% had advanced cancer (stages III of IV).
Interventions	The intervention given by nurses with a certification in oncology, was a 20-week during intervention with 10 sessions at two weeks interval. Six sessions were in person, lasting one hour, and four were via telephone, lasting 20 minutes. With the use of a computer assisted protocol, symptoms were assessed, including fatigue. For each problematic symptom an intervention strategy was created and in later sessions modified, changed or deleted depending on the result. Intervention strategies were categorized as teaching, counselling and support, coordination and communication. The control group did not receive the intervention, but did completed the interview assessments.
Outcomes	Symptoms, the primary outcomes, were measured with the SES, with fatigue as one of the symptoms. Functioning was measured with the SF-36 (short-form) as secondary outcome.
Notes	
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Godino 2006[47]

Methods	RCT. Participants were stratified based on diagnosis and treatment with mono-chemo therapy or multi-chemotherapy schedule. 40 participants were randomised, 23 to the intervention, 17 to the control condition. A second assessment was available from 16 participants, from the experimental condition only. The third assessment was available from 13 participants who received the intervention and 7 participants from the control condition. Part of the participants were lost to follow-up because they declined in health. The three assessment were carried out at the same time as the sessions of the intervention.
Participants	Eligible participants were diagnosed with gastric or colon cancer, and who were undergoing chemotherapy at time of the study. Other inclusion criteria were Karnofsky Index >70 and willing to sign the consent form. Exclusion criteria were previous cancer treatment, including surgery, radiotherapy or chemotherapy; presence of respiratory; cardiac or hepatic dysfunctions; learning disability and central nervous system metastasis. The mean age of the experimental group was 58.5 years (30 to 75), of the 23 participants 12 were men and 11 had primary school as education. The mean age of the control group was 62.7 years, of the 17 participants were 9 men and 8 had primary school as education. The study was carried out in a comprehensive cancer centre in Barcelona.
Interventions	The experimental group received an individualised intervention over three sessions given by an experienced nurse. The first session during the first cycle of chemotherapy, the second session during the second cycle of chemotherapy, the third session one month after finishing treatment. The issues discussed during the sessions included nutrition, stress management, rest and sleep, activity to maintain energy, lifestyle changes and adjustment. Family members could attend and written information was provided to participants. Control group received the usual information provided to patients by cancer nurses and data were collected during the first and the third session.
Outcomes	Fatigue was measured with the FACT-F as primary outcome. Satisfaction with the nursing intervention was assessed with a self-completed questionnaire consisting of 10 items.
Notes	The differences in fatigue scores were not significant, but results are not described.
Allocation concealment?	Yes, not adequate

Table 5: Characteristics of included studies

Goodwin 2001[32]

Methods	Randomisation was performed centrally with the use of sealed envelopes containing allocations form a computer generated table of random numbers, was stratified according to the centre (7 sites) and the presence or absence of visceral metastases. A 2:1 ratio (intervention/control) was used. Of the 237 women randomly assigned. Two of them were found ineligible - one woman (control group) did not have metastases, and one woman (intervention group) had a carcinoid tumour. These women were excluded from the analysis. The analyses included the 218 women who completed baseline questionnaires during the four months before randomisation (146 in the intervention group and 72 in the control group). After one year, 102 completed the POMS in the intervention group, and 45 in the control group.
Participants	Inclusion criteria: histologic confirmation of breast cancer at the time of diagnosis, presence of metastatic disease outside of the breast and ipsilateral axilla, consent of the most responsible treating physician. Exclusion criteria: central nervous system metastases, life expectancy of less than 3 months as assessed by the treating oncologist; active psychosis, untreated major depression, or severe character disorder; inability to speak and read English; planned participation in a therapist-led support group for patients with metastatic breast cancer outside of the study centre; and residence of more than 1 hour from the study centre. At randomisation 73.9% of the women in the intervention group were currently married, and the mean age was 49.5. Currently 41.1% received chemotherapy, 43.0% hormone therapy, and 3.2% radiotherapy. In the control group 69.3% of the women were currently married, and the mean age was 51.5. and 14.3% did not had active treatment. Currently 39.0% received chemotherapy, 46.8% hormone therapy, and 6.5% radiotherapy.
Interventions	Women in the intervention group participated in a weekly 90-minute therapist-led group of supportive-expressive therapy. Each group consisted of 8 to 12 women and two leaders. The leaders were psychiatrists, psychologists, social workers, or nurse clinicians who were experienced in leading group therapy.

Table 5: Characteristics of included studies

continuation Goodwin 2001[32]

Interventions	The supportive-expressive therapy was intended to foster support among group members and to encourage the expression of emotions about cancer and its broad ranging effects on their lives. Women were encouraged to interact with each other and to support each other outside of the group sessions. Participants were given the opportunity and support to speak about the effects of the illness, its treatment, and changes in their self-image, roles, and relationships with family members, friends, coworkers, health care providers, and others. The women also discussed the life-altering nature of the illness and strategies for coping and communicating. They were asked to attend the group sessions for at least one year. A monthly 90-minute session was provided for family and friends. Women in the control arm did not participate in a support group. Every 6 months, all women received educational materials about breast cancer and its treatment, relaxation, and nutrition.
Outcomes	The primary outcome for this trial was survival. Psychosocial function was assessed by self-reported questionnaires including the POMS fatigue-inertia sub-scale. Pain and suffering was measured with a VAS.
Notes	
Allocation concealment?	Yes, not adequate

Table 5: Characteristics of included studies

Moadel 2007[37]

Methods	RCT: After baseline assessment, participants were randomly assigned to start classes either immediately or in 3 months. The baseline assessment was conducted in person, the follow-up assessment by telephone on a day when participants did not attend a yoga class previous to the assessment. 164 women consented to participate. Random assignment was in a 2:1 ratio to intervention (n=108) or control (n=56) after stratification by treatment (chemotherapy or antiestrogen therapy). 128 (78%) completed the baseline and follow-up assessment (yoga=84, control=44). In the yoga group 24 participants were study drop-out, 16 were lost to follow-up, 5 refused, and 3 had a change in health status. In the control group 12 participants were study drop-out, 8 were lost to follow-up, 3 refused, and 1 had a change in health status.
Participants	Eligibility included age ≥ 18 years, new/recurrent (stage I to III) breast cancer diagnosis within previous 5 years, high performance status (Eastern Cooperative Oncology Group performance status of < 3), ability to speak English or Spanish, and not actively practicing yoga. Throughout the study 48% of the participants were receiving medical treatment. Of the sample (n=128) 27 received CT, 30 received antiestrogen therapy and 10 received radiation treatment at baseline. Participants were 42% African American, 31% Hispanic, and 23% white; mean age was 54,8 years, and 69% of patients were not currently married. Three quarters of the sample earned up to, but no greater than, a high school degree.
Interventions	The yoga intervention consisted of 12 1,5-hour weekly classes. Participants were permitted to attend more than one class per week. The yoga intervention was developed for use with breast cancer patients by one of the co-authors (C.S.), an oncologist and certified yoga instructor, in consultation with experts in India and the USA. Based on Hatha yoga techniques, the intervention incorporated the following three major yoga components: physical stretches and poses; breathing exercises; and meditation. Participants were asked to practice yoga at home daily and given an audiotape/compact disk for guidance. The control group started classed after 3 months.
Outcomes	QOL was measured with FACT. The FACIT-fatigue was used to assess limitations in daily activity and energy level. The FACIT-spiritual was used to assess spiritual and existential well-being. A Distressed Mood Index was developed using 19 feelings-state descriptive adjectives from the Profile of Mood States.
Notes	
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Oh 2008[56]

Methods	RCT: 30 participants were randomly assigned into the intervention group (n=15), and the control group (n=15). The randomization was stratified by treatment at baseline (currently ongoing chemotherapy or completed the cancer treatment). Randomization was done by a computer program. 18 participants completed the study, 8 from the intervention group (MQ) and 10 from the control group. Reasons were the time schedule was not suitable (n=3), family holiday (n=2) and sickness (n=2). Five participants of the control group did not respond to the questionnaires and were not reachable to provide reasons. At the end of the program all participants were assessed.
Participants	Inclusion criteria were: a confirmed diagnosis of cancer at any stage, 18 years of age or older, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-3, an expected survival length of more than 12 months, and ability to complete all questionnaires. Exclusion criteria were: diagnosis of other major medical or psychiatric disorders, a history of epilepsy, brain metastasis, delirium or dementia, medical contraindication for exercise and already practicing Qigong. Participants ranged in age from 35 to 75 years old (mean 54, s.d. 9). Most were females (75%), living with a partner (67%), and of Caucasian ethnicity (84%). Of the participants 53% were on active treatment.
Interventions	The intervention was a Medical Qigong (MQ) group therapy program, modified to specifically target the needs of cancer patients to control emotion and stress as well as improve physical function. The MQ group was lead by an experienced MQ instructor. Participants attended class once or twice a week for eight weeks that lasted totally 90 minutes, and it was recommended that they carried out practice at home every day for at least an hour. Each session consisted of 15 minutes of general discussion, including the philosophy and principle behind the intervention, patients' feelings and experiences of treatment; 30 minutes of stretching and body movements; 15 minutes movement in seated posture; and 30 minutes of breathing exercise, meditation and visualization. The control group received usual care and were asked to refrain from joining an outside Qigong class.
Outcomes	Participants completed the EORTC QLQ-C30, including the symptom scales (fatigue, pain, and nausea and vomiting).
Notes	Change scores of side effects were only tested within groups. Not between groups. Change scores for the MQ group and the control group were not significant for fatigue.
Allocation concealment?	Unclear Randomization was done by a computer program.

Table 5: Characteristics of included studies

Rawl 2002[48]

Methods	RCT. 120 participants were randomised, 31 did not continue in the study (21 in the intervention group (IG), 10 in the standard care group (CG)). 109 patients provided data for analysis, at baseline, 94 (55 IG, 54 CG), 94 at time 2, which was midway through the intervention (9 weeks), and 77 at time 3 which was one month post intervention (24 weeks). Group assignment was generated via computer and stratified according to, site of recruitment, site of the patients' cancer, and care givers' employment status.
Participants	Patients newly diagnosed with breast, colorectal, or lung cancer who were undergoing chemotherapy were approached within 56 days of initiating chemotherapy, in a tertiary-cancer centre or a community-based cancer centre. Participants were eligible if they were 18 or older and spoke English. Of the 109 participants 91% were Caucasian, 77% were female. 51% had breast cancer, 23% colorectal cancer, and 27% lung cancer. The average age was 55.7 years. The sample was distributed evenly between early (stage I or II) and late (stage III or IV) cancers. Education levels were fairly heterogeneous.
Interventions	The intervention was a computer-based nursing intervention and occurred over 18 weeks consisting of nine visits (five in person (1 hour) and four via telephone (20 minutes) with a masters'-prepared oncology nurse specialist. It was a menu-driven computer program that guided clinical assessment, problem identification, selection of interventions, and measurement of outcomes. Symptom experience was assessed for 38 symptoms, including frequency, severity, limitations, and level of distress. Interventions were tailored individually to address up to four symptoms that were prioritised as problems by the participant. The nurse provided objective information about the management and monitoring of the symptom, but also provided emotional support and counselling during each session. Control group participants received any education normally delivered during chemotherapy.
Outcomes	The Medical Outcomes Study Short Form (SF-36) was used. The sub-scale vitality was used to measure fatigue. Other instruments were also used. The Center for Epidemiological Studies Depression-20 scale and the State-Trait Anxiety Inventory.
Notes	
Allocation concealment?	Yes, adequate

Table 5: Characteristics of included studies

Ream 2006[57]

Methods	RCT. Participants were stratified according to the centre they were treated and the chemotherapy regimen they were given. 103 participants were randomised, 48 allocated to the intervention, 55 to the control condition. In the intervention condition 5 participants were lost to follow-up (1 withdrew, 4 declined in health). In the control condition 12 participants were lost to follow-up (3 withdrew, 9 declined in health). In both conditions 43 participants were available for analysis. Pre-intervention measurement took place prior to the chemotherapy. The post-intervention measurement took place prior to the fourth treatment cycle.
Participants	Eligible participants had been diagnosed with, non-Hodgkin's lymphoma or gastrointestinal, non-small cell, lung, colorectal, breast, or unknown primary cancer, and were chemotherapy-naive. They had to understand, speak, read, and write English. Patients were excluded when treated for psychiatric illness. The mean age of the sample was 56.5 years (18 to 70) and 55% was male. Participants were recruited from the inpatient or outpatient service prior to commencing their first cycle of treatment.
Interventions	The intervention program was provided by an experienced cancer nurse visiting participants at home, over the first three treatment cycles (3 sessions). The intervention comprised: assessment/monitoring of fatigue; education on fatigue including an investigator-designed information pack; coaching in self-care; and provision of emotional support. Control group received usual care and fatigue assessments.
Outcomes	Fatigue (four VAS'), as primary outcome. Other outcomes were Emotional well-being (HADS), General health status (SF-36) and coping (VAS and COPE).
Notes	
Allocation concealment?	Yes, adequate.

Table 5: Characteristics of included studies

Sandgren 2000[35]

Methods	RCT. Participants first completed baseline questionnaires. For women in the experimental group, telephone therapy began the week following the return of the questionnaires. Questionnaires were mailed at 1 month (not presented), 4 and 10 month intervals. Data presented came from 53 of the original 62 participants, 24 therapy participants and 29 control participants. Four women failed to complete measures at some intervals, and five dropped out of the study (one died, others unknown).
Participants	Women with stage I or II breast cancer initially were recruited through a tertiary cancer treatment centre serving rural eastern North Dakota and western Minnesota. Women diagnosed within the prior three to four months were eligible. All but five women underwent adjuvant treatment, and were in the midst of such treatment during the study. All had completed chemotherapy and radiation before the 10-month follow-up. Ages ranged from 30 to 82 (mean 51). Nearly all (92%) of the sample had completed high school, and 30% completed a college education (mean 13.5 years). All participants were Caucasian except for one Native American.
Interventions	Treatment participants received up to 10 telephone calls (mean=9). Therapy was administered once a week for four weeks and then every other week for six more sessions (4 months). Phone sessions lasted up to 30 minutes, averaging 20 to 25 minutes. Therapy included providing support, teaching coping skills, managing anxiety and stress, and helping to solve patients-generated problems. Cognitive restructuring was used, a technique that involves identifying erroneous beliefs, over-generalization, or catastrophic thinking. Therapists also encouraged emotional expression, and relaxation techniques. Three female clinical psychology master's candidates conducted the therapy. The control group had assessments only.
Outcomes	The POMS was used to measure distress. It assesses six moods, including fatigue. The Coping Response Indices-Revised scale was used to measure coping, and the Medical Outcome Scale (MOS) short-form was used to measure quality of life.
Notes	
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Sandgren 2003[30]

Methods	RCT. Of the 235 participants who began the study 13 dropped out. A total of 222 participants completed the study. Random assignment to a condition was based on a 2:2:1 ratio. 55 participants in the standard care completed the study, 78 of the health education intervention, and 89 of the emotional expression intervention. Participants were blocked by cancer stage. Measures were collected immediately before the intervention, which was typically after surgery, but during adjuvant treatment. Follow-up took place approximately 5 months later.
Participants	Eligibility criteria included diagnosis of stages I-III breast cancer, ability to speak English and to talk by phone, absence of serious comorbid conditions, and undergoing adjuvant treatment. Adjuvant treatment included any combination of chemotherapy, radiotherapy, and hormone therapy. Patients were recruited from two cancer treatment clinics, 1-3 months after diagnosis. The average age of the sample was 54.5 years, most participants (78%) were married and Caucasian (97%).
Interventions	Both interventions included 5 weekly 30 min phone calls, with a sixth follow-up 3 months later, about the time adjuvant chemotherapy typically ended. Participants in the health education intervention received a structured curriculum. The topics included understanding breast cancer and treatment (chemotherapy, radiation therapy, and hormone therapy), managing post-surgical changes and treatment side effects and fatigue, and maintaining a healthy lifestyle. Participants in the emotional expression were asked to talk about thoughts, feelings and emotional issues and stressful experiences. Trained nurses participated in both treatment conditions. Participants in the control group received standard care in which the usual nurse help line would be available.
Outcomes	Outcome measures included quality of life (FACT-B) and additionally POMS. Fatigue was measured as the fatigue/inertia sub-scale of the POMS.
Notes	Not described how many participants were randomised and what was done with any missing values.
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Savard 2006[44]

Methods	Participants were first stratified according to the cancer clinic they were recruited to. 45 participants were then randomly assigned either to the CT (25) or WLC (20) condition. Pre-treatment measures were completed by 21 participants of the CT and 16 of the WLC. Post-treatment measures were completed by 15 (CT) and 13 (WLC). 3-month follow-up measures were completed by 14 (CT) and 10 (WLC). 6-month follow-up measures were completed by 12 (CT) and 9 (WLC). Reasons for lost to follow-up were, study or therapy too burdensome, lost interest, due to chemotherapy side effects, terminal stage or death.
Participants	Inclusion criteria: 1) a diagnosis of metastatic breast cancer (stage IV) and 2) a score of 7 or more on the HADS-D or 15 or more on the BDI. Exclusion criteria: 1) life expectancy of less than 2 months, 2) meeting DSM-IV criteria for a severe psychiatric disorder other than major depression, 3) presenting severe suicidal ideas with a risk of acting out, 4) having recently started an antidepressant medication or recently altered the dosage, 5) currently receiving a psychological intervention targeting depression. Participants were recruited in three cancer clinics. All participants were Caucasian. In the experimental condition 57% was married, 48% completed university and the mean age was 51. In the waiting-list control condition 50% were married, 31% completed university and the mean age was 52. (not described how many participants received treatment).
Interventions	Cognitive therapy (CT) was administered individually and involved eight weekly sessions of 60 to 90 minutes, with three booster sessions of CT every 3 weeks following treatment. Two psychologists with experience in the application of CT conducted the sessions. The ultimate goal was to develop an optimistic but realistic attitude towards their situation. CT began with the presentation of a cognitive theory of emotions. Then participants were encouraged to increase their level of daily activities. Participants were then trained to identify their negative thoughts and to use cognitive restructuring to modify dysfunctional or irrational cognitions. Participants were then encouraged to redefine their life goals. Finally, future high-risk situations were identified, as well as strategies to cope with them. Patients in the waiting-list control (WLC) condition were scheduled 10 weeks later for CT.
Outcomes	Fatigue was measured with the MFI. Other instruments used were Hospital Anxiety and Depression Scale, Beck Depression Inventory, Insomnia Severity Index, Quality of life questionnaires: QLQ-C33, QLQ BR-23, and List of Life Events.
Notes	
Allocation concealment?	Yes, not adequate

Table 5: Characteristics of included studies

Spiegel 1981[45]

Methods	RCT. 109 women were referred to the study by their oncologists, and 86 completed the first questionnaire. More participants were randomised to the experimental group (EG=50) than to the control group (CG=36). Of the EG 14 were too weak or too ill to participate and 2 moved away. Of the CG 12 participants were lost; 4 were too ill, 2 died, 4 refused, 2 were out of contact. The final EG consisted of 34 women, and the final CG of 24 women. Follow-up testing was done at four-month intervals for a total of a year. The analysis considered 16 (EG) and 14 (CG) that completed all four assessments.
Participants	Participants with documented metastatic carcinoma of the breast were included. The average age of the treatment group was 54 years, and the control group 55 years. 75% of the treatment group and 70% of the control group were married. Two members of the treatment group and three of the control group lived alone. The average length of time since diagnosis of recurrence was 54 months for the treatment group and 68 months for the control group. Members of the treatment and control group received equivalent amounts of chemotherapy during the period of study. At onset of the study it was noted that the members of the treatment group were of significantly higher social status than were members of the control group.
Interventions	The psychological support groups met weekly in outpatient settings for 1 1/2 hours and were composed of seven to ten women. Although the period of measurement was one year, no termination time was set for the groups. Three groups were formed; each group had two leaders, a psychiatrist or a social worker and a counsellor who had had breast cancer. The groups were designed primarily to be supportive. There was a high degree of cohesion and relatively little confrontation and here-and-now interpersonal exploration. Interaction in the group often contained a considerable amount of self disclosure and sharing of mutual fears and concerns. Unlike a therapy group, there were few process interpretations; the focus was more on content, which included discussion of death and dying, related daily problems, difficulties in obtaining treatment, issues of communication with physicians, and living as richly as possible in the face of a terminal illness.
Outcomes	Fatigue was measured with the POMS sub-scale fatigue. In addition Health Locus of control, Maladaptive coping response and denial was measured. Self-esteem was assessed with the Janis-Field Scale and Phobias with a checklist.
Notes	No description of the control condition.
Allocation concealment?	Unclear

Table 5: Characteristics of included studies

Yates 2005[36]

Methods	RCT: Baseline assessments were completed at the first treatment visit (week1) (53 of the intervention group (IG) and 57 of the control group (CG)). The first follow-up assessment (t2) was conducted at the third course of chemotherapy (CT) (week 7-9) (50 of IG and 54 of CG). The second follow-up (t3) was conducted at the fourth course of CT or for participants receiving radiotherapy (RT) assessment was conducted on the first day of RT (week10-13) (50 of IG and 50 of CG). The third follow-up (t4) was conducted at the fifth course of CT or for participants receiving radiotherapy (RT) assessment was conducted on the first day of RT. Participants receiving RT at t3, assessment was conducted two weeks after RT (week 13-21) (49 of IG and 48 of CG).
Participants	Women more than 18 years of age with stage I or II breast cancer who were commencing adjuvant chemotherapy at one of 5 day-treatment units were approached and admitted if they had an ECOG performance rating of one or two and their haemoglobin level was at least 11.6 g/mL at recruitment. The mean age of the participants was 49.4, and approximately 65% of the sample had post-high school qualifications. Most of the women were married (77% in the IG and 73% in the CG).
Interventions	The psycho educational intervention, given by an oncology nurse (2), aimed to improve patients knowledge and skills in performing self-care behaviours to minimize fatigue, based on Green's PRECEDE model of health behaviours. Effective strategies to reduce fatigue included promoting: sleep and rest, a balance between activity and exercise, conserving energy, and restorative activities. The first session, a face to face contact of 20 minutes, focused on the participants specific needs and to target influencing these factors. The second and third session, a telephone call of 10 minutes, were aimed to review the patients' fatigue management plan, and reinforcement. The intervention was given at the start of the second cycle of chemotherapy with one week between each session. In addition patients received a booklet with specific information. Participants in the control group received general cancer education sessions equivalent in number and timing and also given by the same oncology nurses. The education focused on talking about general issues associated with living with cancer. Participants also received a booklet with general information.
Outcomes	The primary end points for the study included use of fatigue-management behaviours, confidence with managing fatigue, and fatigue experiences (levels of fatigue at worst, best, average in the past week and currently, PFS, and FACT-F).
Notes	Not described what was done with missing values.
Allocation concealment?	Yes, adequate

Footnote: RT: Radiotherapy

Table 6: Summary of findings: Effective studies Part A

Author	Intervention	Duration	Patients	Quality (0-25)	N (total)
Armes 2007[49]	A brief behaviorally oriented intervention for cancer-related fatigue, given by one nurse (the first author).	Three individual, face-to-face, 60 minute sessions at 3 to 4 weekly intervals (coinciding with chemotherapy).	Cancer patients who were attending for chemotherapy treatment.	17	60
Barsevick 2004[50]	ECAM intervention for cancer related fatigue.	Three 3 telephone sessions with an oncology nurse, during the first 3-5 weeks of treatment. Duration of the first two sessions was 30 minutes, the third session 15 minutes.	Cancer patients currently beginning chemotherapy, radiotherapy, or both, intended for cure.	18 i.t.t	396
Cohen 2007[34]	Two group interventions: cognitive-behaviour group, and RGI group. Goal decreasing psychological distress and physical symptoms (general approach).	The interventions were conducted by a senior social worker (the first author). Each group of 6-8 participants met weekly, for nine 90-minute sessions.	Breast cancer patients, stages I and II, receiving chemotherapy or radiotherapy.	13	114
Forester 1985[58]	Unstructured individually supportive psychotherapy provided by a psychiatrist (first author), focusing on emotions and physical symptoms (general approach).	The 30 minute sessions were given weekly, for 10 weeks (4 weeks beyond completion of radiotherapy).	Cancer patients before they received 6 weeks of radiotherapy. Patients with abdominal cancer were excluded.	10	100

Table 6: Summary of findings: Effective studies Part A

Author	Intervention	Duration	Patients	Quality (0-25)	N (total)
Ream 2006[57]	The supportive intervention for fatigue was provided by a cancer nurse who visited individual patients at home.	Three sessions, over the first 3 treatment cycles, duration not described.	Cancer patients during chemotherapy.	14	103
Spiegel 1981[45]	Psychological support groups (3 groups). Each group had two leaders, a psychiatrist or a social worker and a counsellor. (general approach).	The groups met weekly for 1 1/2 hours, during at least one year.	Patients with metastatic breast cancer	9	86
Yates 2005[36]	An individual psycho educational intervention for fatigue, given by an oncology nurse.	Three sessions. The first session, was a face to face contact of 20 minutes, the second and third session was a telephone call of 10 minutes. The intervention was given at the start of the second cycle of chemotherapy with one week between each session.	Women receiving adjuvant chemotherapy for early stage breast cancer (stage I & II).	17	110

Footnotes
T0 = pre-intervention, T1 = post-intervention, T2 = follow-up, T3 = second follow-up.
- = not assessed, n.s. = not significant, n.a. = not applicable, S.E.M. = Standard error of the mean.
RGI = relaxation and guided imagery.
ECAM = energy conservation and activity management.

Table 6: Summary of findings: Effective studies Part B

Author	Results	Instruments *	Fatigue scores mean (s.d.) T0	Fatigue scores mean (s.d.) T1	Fatigue scores mean (s.d.) T2	Fatigue scores mean (s.d.) T3	Effect size post-intervention (T1)	Effect size follow-up (T2)	Effect size follow-up (T3)
Armes 2007[49]	An interaction between group and time for MFI-fatigue, (P = 0.03).	MFI physical fatigue.	EG 15,4 (3,7) CG 15,2 (3,7) (NA)	EG 14,3 (4,6) CG 14,6 (3,6)	EG 12,3 (4,5) CG 14,7 (3,3)	EG 10,2 (4,6) CG 13,5 (4,2)	T1 = 0	T2=0,61 (MFI physical fatigue) (follow-up period 4 weeks).	T3=0,75 (MFI physical fatigue) (follow-up period 9 months after recruitment)
Barsevick 2004[50]	A group-by-time interaction effect was found on GFS (P < 0.01), SCFS (P < 0.05) and POMS-F (< 0.05), examined in a separate repeated-measures ANOVA, with cancer treatment as covariate. After bonferroni correction+ only GFS was significant.	GFS	EG 3,3 (1,8) CG 3,3 (1,8)	EG 4,6 (2,2) CG 4,6 (2,0)	EG 4,1 (2,2) CG 4,7 (2,1)	-	T1 = 0	T2=0,28 (follow-up period up to 4 weeks)	-
		POMS	EG 1,9 (0,72) CG 1,9 (0,76)	EG 2,5 (1,1) CG 2,5 (1,1)	EG 2,4 (1,1) CG 2,6 (1,1)	-	T1 = 0	T2= 0,17	-
		SCFS	EG 1,8 (0,70) CG 1,8 (0,73)	EG 2,4 (0,95) CG 2,4 (0,94)	EG 2,3 (0,99) CG 2,5 (1,0)	-	T1 = 0	T2= 0,20	-
Cohen 2007[34]	Repeated measures MANOVA (3 group x 3 times x 6 variables) revealed significant group x time effects. For fatigue P < 0.001. Only the reduction in the RGI group from pre-to post-intervention was significant.	FSI	RGI 4,89 (0,96) CG 4,50 (1,30)	RGI 3,01 (1,13) CG 4,32 (1,31)	RGI 2,86 (0,89) CG 3,72 (1,19)	-	RGI T1 = 1,07	RGI T2= 0,82	-

Table 6: Summary of findings: Effective studies Part B

Author	Results	Instruments *	Fatigue scores mean (s.d.) T0	Fatigue scores mean (s.d.) T1	Fatigue scores mean (s.d.) T2	Fatigue scores mean (s.d.) T3	Effect size post-intervention (T1)	Effect size follow-up (T2)	Effect size follow-up (T3)
Forester 1985[58]	For fatigue a significant effect was found at T1 (P = < 0.01) found with repeated measures, analysis of variance. No significant effect was found at T2.	SADS	EG 3,8 CG 4,0 (s.d. not reported)	EG 2,3 CG 3,3	EG 3,1 CG 3,5	-	? (unknown s.d.)	n.s.	-
Ream 2006[57]	Significant results on t-test for between-group differences post intervention. VAS P = 0.04, SF36 P = < 0.05.	VAS	EG 38,8 (28,9) CG 42,6 (28,8) P = 0.51	EG 30,6 (27,7) CG 41,6 (29,4)	-	-	T1 = 0,39	-	-
		SF36 vitality	Mean rank EG 46,3 CG 42,6 P = 0.53	EG 47,1 CG 38,2	-	-	? (unknown s.d.)	-	-
Spiegel 1981[45]	For fatigue a significant effect was found after one year (completers) P < 0.05. Additional slope analysis of patients who completed two assessments, showed a significant effect (P < 0.01).	POMS	Slopes: EG: -1,06 (s.e.m 0,34) CG 1,55 (s.e.m. 0,45)		-	-	? (no mean and s.d. described)	-	-

Table 6: Summary of findings: Effective studies Part B

Author	Results	Instruments *	Fatigue scores mean (s.d.) T0	Fatigue scores mean (s.d.) T1	Fatigue scores mean (s.d.) T2	Fatigue scores mean (s.d.) T3	Effect size post-intervention (T1)	Effect size follow-up (T2)	Effect size follow-up (T3)
Yates 2005[36]	On 4 of the 6 fatigue measures a significant effect was found at T1. (Analysis of covariance of the change scores controlling for baseline values). Follow-up measures were not significant.	NFRS fatigue at worst in the past week.	EG 2,6 (3,0) CG 1,8 (2,5)	EG 3,5 (3,2) CG 4,5 (3,1)	·	·	T1 = 0,32	n.s.	·
		NFRS average fatigue in the past week.	EG 2,0 (2,5) CG 1,2 (1,7)	EG 2,9 (2,8) CG 3,5 (2,5)	·	·	T1 = 0,22	n.s.	·
		PFS sub-scale fatigue severity.	EG 1,8 (2,6) CG 0,9 (1,4)	EG 2,7 (3,0) CG 3,6 (3,0)	·	·	T1 = 0,30		
		FACT-F	EG 1,1 (0,3) CG 1,0 (0,4)	EG 1,1 (0,4) CG 1,3 (0,6)	·	·	T1= 0,39	n.s.	·

Footnotes
* = the instruments and abbreviations are explained in Table 3: Outcomes
Bonferroni correction⁺ = This correction is applied for multiple testing. In this study three separate ANOVA's were preformed. Results on all three outcomes significant on a 0.05 level.
After Bonferroni correction (0.05/3) only the result on GFS was significant.
T0 = pre-intervention, T1 = post-intervention, T2 = follow-up, T3 = second follow-up.
· = not assessed, n.s. = not significant, n.a. = not applicable, S.E.M. = Standard error of the mean.
EG = experimental group, CG = control group.

Appendix 1

MEDLINE search strategy
MEDLINE (via OVID)

1. Exp NEOPLASMS
2. BONE MARROW TRANSPLANTATION
3. Exp STEM CELL TRANSPLANTATION
4. (neoplas$ or cancer$ or carcinoma$ or tumour$ or adenocarcinoma$ or leukemi$ or leukaemia$ or lymphoma$ or tumor$ or malignan$ or melanoma$ or sarcoma$ or "bone marrow transplant$" or "stem cell transplant$")
5. OR/1-4
6. FATIGUE/
7. (fatigue$ or asthenia or asthenic or astheni$)
8. (exhaustion or exhausted)
9. ((loss adj4 energy) or (loss adj4 vitality))
10. (weary or weariness or weakness)
11. (apathy or apathetic or lassitude or lethargic or lethargy)
12. (sleepy or sleepiness or drowsy or drowsiness)
13. (tired or tiredness)
14. OR/6-13
15. Exp PSYCHOLOGY, SOCIAL/
16. Exp PSYCHOTHERAPY/
17. (psychosocial$ or psycho-social$)
18. (counsel$ or (behaviour$ adj4 therap$) or "autogenic training" or (behavior$ adj4 therap$) or (relax$ adj4 therap$) or (relax$ adj4 treatment$) or (support$ adj4 group$) or imagery or "energy conservation" or "stress management" or psychotherapy$ or "self care" or "self help" or biofeedback or educati$ or psychoeducat$ or relaxation therap$ or "nursing intervention" or "nursing support")
19. OR/15-18

20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized controlled trials.sh.
23. random allocation.sh.
24. double blind method.sh.
25. single blind method.sh.
26. or/1-6
27. (ANIMALS not HUMANS).sh.
28. 7 not 8
29. clinical trial.pt.
30. Exp CLINICAL TRIALS
31. (clin$ adj25 trial$).ti,ab.
32. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
33. placebos.sh.
34. placebo$.ti,ab.
35. random$.ti,ab.
36. research design.sh.
37. or/10-17
38. 18 not 8
39. 19 not 9
40. 9 or 19
41. 5 AND 14 AND 19 AND 40

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Chapter 3

Severe fatigue and related factors in cancer patients before the initiation of treatment

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Martine Goedendorp, Marieke Gielissen, Stans Verhagen, Marlies Peters, Gijs Bleijenberg.

ABSTRACT

It is generally known that fatigue is a common symptom during cancer treatment, and in cancer survivors. However, fatigue was never studied after diagnosis, before cancer treatment was initiated. This study investigated the prevalence of severe fatigue, and related factors, in cancer patients before the initiation of treatment. One hundred and seventy-nine patients with various malignancies were assessed before start of treatment with curative intention, including the Checklist Individual Strength, Sickness Impact Profile, Beck Depression Inventory Primary Care, Symptom Checklist-90, and six Numeric Rating Scales to measure fatigue, pain and physical activity. To test which factors contributed to severe fatigue a logistic regression analysis was performed. In total 23.5% patients were severely fatigued, varying between diagnoses; prostate cancer (14.3%), breast cancer (20.3%), gastrointestinal cancer (28.1%). Currently lower physical activity ($P = 0.013$), more depressive mood ($P = 0.014$), impaired sleep and rest during the day and night ($P = 0.045$), and fatigue 1 year before diagnosis ($P = 0.005$) contributed to severe fatigue. Relatively large numbers of cancer patients already experience severe fatigue before initiation of treatment, varying between 14-28%. The factors that contributed to severe fatigue at this stage were physical activity, depressive mood, impaired sleep and rest, and fatigue 1 year before diagnosis.

INTRODUCTION

Fatigue is a frequent reported symptom in cancer patients and when severe, it is a distressing symptom interfering with daily functioning. Cancer patients experience fatigue at different stages during their illness. The prevalence of fatigue during cancer treatment ranges from 25% to 99% in different samples[1]. After successful cancer treatment severe fatigue remains problematic in 19 - 38% of the disease free cancer survivors[1, 2].

It is generally thought that during the active period of cancer treatment, symptoms of fatigue arise as a consequence of the cancer itself, and the treatments patients receive, such as surgery, chemotherapy and radiotherapy. Other factors are also suggested to influence fatigue during cancer treatment. Psychological distress, such as depression, somatisation, anxiety, and also sleep quality were previously found to relate with fatigue[1, 3]. It is suggested that the experience of receiving cancer treatment in itself contributes to the development of fatigue[4].

Fatigue in cancer patients prior to treatment has seldom been investigated. Some studies investigated fatigue before start of chemotherapy[5-7] or radiotherapy[4, 8, 9], but looking at these studies more closely revealed that most patients were not treatment naive. The majority of patients already received treatment that could have contributed to fatigue, such as surgery, hormone therapy, or chemotherapy.

Results of three quality of life studies indicate that fatigue might be problematic in treatment naive cancer patients[10-12]. The first study found that lung cancer patients before surgery reported significant more fatigue compared with age-matched control subjects[11]. Two other studies concluded that fatigue contributed to increased distress and impaired quality of life in newly diagnosed cancer patients[10, 12].

Cancer patients report that the period of diagnosis was very distressing, and research does confirm this. At diagnosis emotional functioning, anxiety, and sleep problems were the most problematic in patients with oral and oropharyngeal cancer[13]. In newly diagnosed breast cancer patients, disturbances in mood states

and insomnia were also found, in addition to loss of concentration[10]. Thus, newly diagnosed cancer patients have been studied in the past, but research specifically aimed at fatigue in this group is lacking.

The first objective of this study is to determine how many cancer patients report severe fatigue after being diagnosed, but before initiation of any medical treatment for cancer. If patient do report severe fatigue, the second objective is to establish which factors contribute to severe fatigue before cancer treatment, and whether mood, such as anxiety and depression, and sleep problems contribute to fatigue.

MATERIALS AND METHODS

Patients and procedure

Patients were recruited from one university hospital and six regional hospitals in the period from November 2005 until August 2007. Patients were included in this study after being diagnosed with a primary tumour and before initiation of treatment with curative intention. Treatment could be surgery, radiotherapy, chemotherapy, or a combination of these. Patients could additionally receive hormone therapy. In concordance with national and regional guidelines of the comprehensive cancer centre, the curability of a patient with cancer was determined, and the treatment procedure was chosen. All treatment options were discussed in the multi disciplinary working party for the specific tumour group, before the treatment procedure was decided. Patients in this study were recruited as part of a larger ongoing intervention study for fatigue during cancer treatment, and preventing chronic fatigue after finishing cancer treatment. To minimize drop out and exclusion during the ongoing study, patients with lung cancer, and head and neck cancer were not included. Patients were included if they were between 18 and 75 years old, and able to speak, read and write Dutch. Patients were excluded when having a co-morbidity that could cause fatigue, or when patients indicated to be severely fatigued for several years or have been seeking treatment for their fatigue. In addition, patients who were receiving psychiatric of psychological treatment in the last 3 months were excluded.

Eligible patients were informed about the study by their physicians and were asked if a researcher could approach them. When a specialised cancer unit was present in a hospital, such as a mamma care or colon care unit, specialised nurses checked for eligibility and informed patients. When patients agreed the physician informed the researcher. Patients who agreed to be approached received written information on the study and were contacted by telephone by the researcher or a test-assistant. When patients agreed to participate an appointment was made for the baseline assessment. The baseline assessment took place, at the Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre, at the hospital where patients would receive treatment, or at the patients' home. All participants gave their written informed consent before baseline assessment. The ethics committees from all seven involved hospitals gave approval for the study.

The data presented in this study are based on cancer patients who were treatment naive, and were assessed before initiation of treatment.

INSTRUMENTS

Information on age, gender and diagnosis was provided by the patient's physician from patients who agreed to be approached, also from patients who did not participate eventually. From all participating cancer patients demographic and medical characteristics were gathered by self-report using questionnaires. Information on marital status and level of education were collected as part of the demographic data. The following information on medical characteristics was obtained: medication use in the past month, and medical history on co-morbidities, and receiving psychological and psychiatric treatment during patients' lifetime.

Fatigue severity was assessed by the subscale fatigue of the Checklist Individual Strength (CIS)[14, 15]. The CIS is a well-validated instrument among patients with chronic fatigue syndrome (CFS) and in the working population[16, 17]. The fatigue subscale consists of eight items scored on a seven-point Likert scale, with scores ranging from eight to 56. Based on research with CFS patients a

score of 35 or higher indicate severe fatigue[15]. A score between 27 (mean score for healthy adults plus one s.d.) and 35 indicate a heightened experience of fatigue[14]. The CIS was used in earlier research investigating cancer survivors[18-21].

Depression was assessed with the Beck Depression Inventory Primary Care (BDI-PC)[22]. This is a seven item questionnaire with scores ranging from zero to 21. A score of four or higher on the BDI-PC is indicative for a clinical depression[23]. The BDI-PC is based on a set of non-somatic items from the BDI-II[24].

Depressive mood was measured with the Symptom Checklist-90 (SCL-90)[25], subscale depression. Sixteen items measure depressive mood, with scores ranging from 16 to 80. Higher scores indicated a stronger depressive mood.

Anxiety was measured with the SCL-90 subscale anxiety. Ten items measure anxiety with scores from 10 to 50. Higher scores indicated more anxiety.

Quality of nocturnal sleep was measured with the SCL-90 subscale sleep. Three items measure sleep with scores from three to 15. Higher scores indicated lower quality of sleep. In addition, the impact of the disease on sleep and rest during the night and day was measured with the subscale sleep/rest of the Sickness Impact Profile –8 (SIP)[26, 27]. Higher scores on this subscale was an indication of more impairment on sleep/rest. Seven items measured impairments on sleep/rest, with scores ranging from zero to 499.

Physical activity was measured with an 11-point Numeric Rating Scale (NRS) ranging from zero to 10. Patients were asked how physically active they were in the period since diagnosis. Zero indicated 'not physically active' and ten 'physically very active'.

Pain was also measured with an 11-point NRS. Patients were asked how much pain they had experienced in the period since diagnosis, on a scale from zero to 10. Zero indicated 'no pain' and ten 'very much pain'.

Patients were asked additionally to indicate their level of fatigue, physical activity, and pain before diagnosis retrospectively, 1 year before diagnosis and 3 years before diagnosis. Thus, in total six 11-point NRS' were used, ranging from zero to 10.

Statistical analysis

All data analysis was performed with SPSS (version 14.0). Differences between participating and non-participating cancer patients were tested with χ^2. For the first objective descriptive statistics were used to describe demographic characteristics of treatment naive cancer patients, and the data on the presence of severe fatigue. Differences on demographic and medical characteristic between severely and non-severely fatigued cancer patients were tested with χ^2. For the second objective, to find the contributing factors, two steps were taken. The first step was to test the differences between severely fatigued cancer patients and non-severely fatigued cancer patients on the contributing factors with a *t*-test for independent samples. For the second step a logistic regression analysis was performed using Stepwise Forward method. This method was chosen, as it was an exploratory data analysis. Significant factors found in the first step were put in the logistic regression as independent variables, with significant demographic and medical variables as covariates. The dimensions of depression and sleep were each measured with two instruments, although measuring different aspects. When both instruments showed significant results in the first step, the instrument with the largest significant difference was put into the logistic regression. Variables that applied to the period before diagnosis were entered into the first block, and variables that applied to the current period were entered into the second block. Two persons with missing data on the BDI-PC or SCL-90 were excluded from the analysis. A two-sided $P < 0.05$ was considered significant.

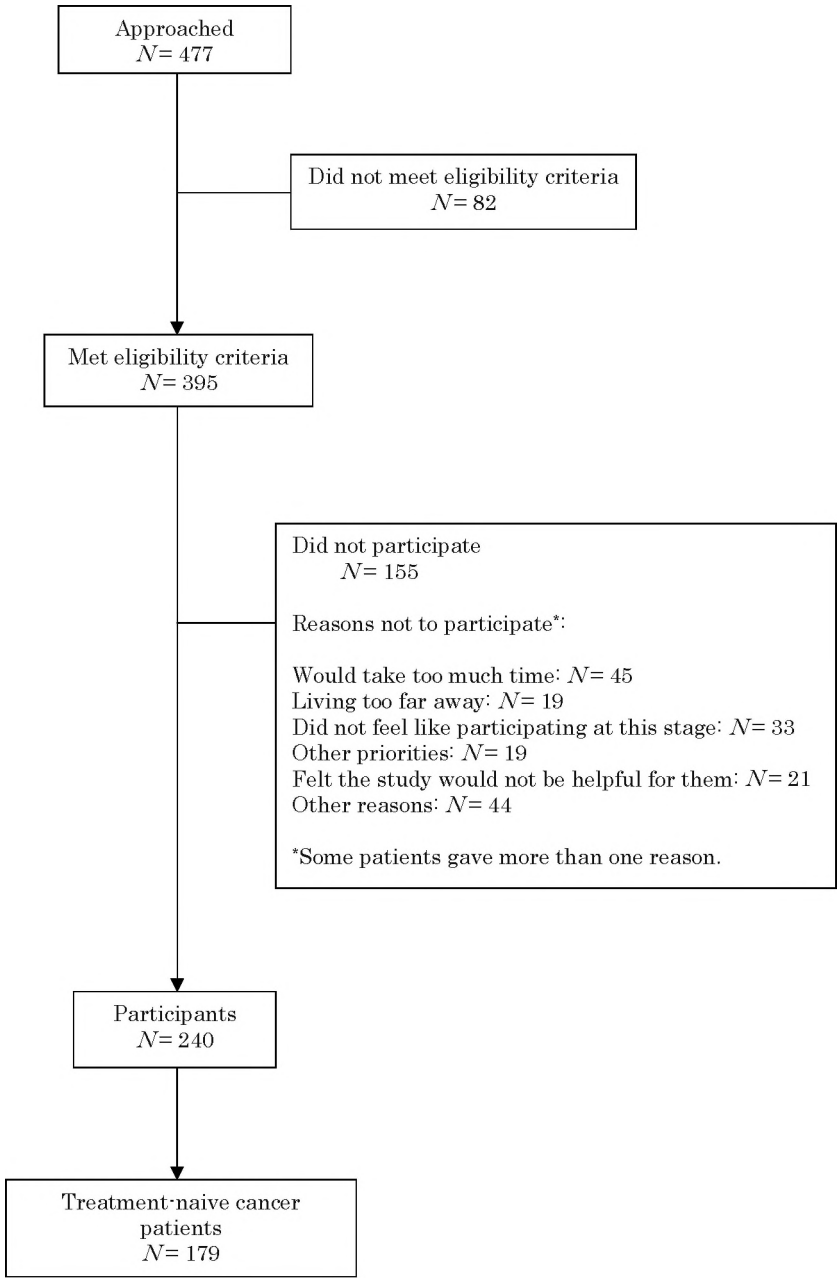

Figure 1: Flow chart showing the accrual of patients.

RESULTS

In total 477 patients agreed to be approached and were contacted by telephone. During the telephone conversations an additional 82 patients were excluded who did not meet the eligibility criteria. The most common reasons for exclusion were: having a co-morbidity that could cause fatigue, and being severely fatigued for several years. Of the 395 patients who met the inclusion criteria 155 refused to participate for different reasons (see Figure 1). In total 240 patients participated and completed baseline assessments. The characteristics of participants were compared with non-participants (see Table 1).

Table 1: Differences between participants and non-participants.

Characteristics	Participants	Non-participants	P-value
Total (n)	240	155	
	Mean (s.d.)	**Mean (s.d.)**	
Age (years)	56.8 (11.1)	59.7 (10.9)	**0.010**
	n (%)	**n (%)**	
Sex			0.219
Male	92 (38.3)	50 (32.3)	
Female	148 (61.7)	105 (67.7)	
Diagnosis[a]			0.310
Breast cancer	109 (45.4)	81 (52.3)	
Prostate cancer	57 (23.8)	28 (17.4)	
Other tumours	76 (31.7)	47 (30.3)	
Gastrointestinal	33	26	
Urogenital	16	9	
Gynaecological	13	10	
Lymphomas	7	0	
Sarcoma	3	2	
Melanoma	2	0	
Thyroid carcinoma	2	0	

[a] Three patients were diagnosed with both bladder and prostate cancer and were categorized as urogenital tumours of the other tumours. A two-sided $P < 0.05$ was considered significant.

Results showed that cancer patients who refused to participate were significantly older compared to patients who participated. No differences were found on gender or diagnosis between participants and non-participants. Patients usually start with cancer treatment relatively fast after being diagnosed. As a consequence of this short time span baseline assessments sometimes took place when cancer treatment had just started. For example, some breast cancer patients were assessed after surgery, but before adjuvant radiotherapy or chemotherapy.Of the 240 participants 61 patients were assessed when their cancer treatments had just started, but their data were not used in the analysis. Thus data presented in this study are based on 179 cancer patients who were treatment naive.

Patient Characteristics

Most of the 179 patients were diagnosed with breast cancer or prostate cancer, 54% were female, and 82% were married (see Table 2). The mean age of the sample was 56.6 (s.d. 10.9) years, and the mean education level was 4.1 (s.d. 1.7) ranging between one and seven (data not shown). No differences were found between severely and non-severely fatigued cancer patients on demographic variables such as sex, age, education or marital status, although the difference between males and females nearly reached significance. In addition, differences were tested on several medical variables between severely fatigued cancer patients and non-severely fatigued cancer patients. No significant differences were found on current medication use, and on the medical history of co-morbidities, and receiving psychological or psychiatric treatment in patients' lifetime (all $P > 0.971$) (data not shown).

The presence of severe fatigue in cancer patients before treatment

In the total sample 23.5% of the cancer patients were severely fatigued, but this percentage varied between diagnoses (see Table 2). The presence of severe fatigue was the lowest in patients with prostate cancer (14.3%), but higher in breast cancer patients (20.3%).

Table 2: Data of demographic variables, diagnosis and presence of severe fatigue.

Characteristics	Total sample n	Non-severely fatigued cancer patients n (%)	Severely fatigued cancer patients n (%)	Difference[a] P-value
Total	179	137 (76.5)	42 (23.5)	
Sex				0.064
Male	82	68 (82.9)	14 (17.1)	
Female	97	69 (71.1)	28 (28.9)	
Age (years)				0.237
Younger age group (≤ 57 years)	88	64 (72.7)	24 (27.3)	
Older age group (> 58 years)	91	73 (80.2)	18 (19.8)	
Education level				0.269
Lower education (≤ 4)	111	88 (79.3)	23 (20.7)	
Higher education (>4)	68	49 (72.1)	19 (27.9)	
Marital status				0.568
Married / cohabiting	146	113 (77.4)	33 (22.6)	
Other status (unmarried/divorced/ widowed)	33	24 (72.7)	9 (27.3)	
Diagnosis [b]				**0.044**
Breast cancer	64	51 (79.7)	13 (20.3)	
Prostate cancer	49	42 (85.7)	7 (14.3)	
Other tumours	68	46 (67.7)	22 (33.3)	
Gastrointestinal	32	23 (71.9)	9 (28.1)	
Urogenital	14		6	
Gynaecological	10		3	
Lymphomas	5		2	
Sarcoma	3		1	
Melanoma	2		1	
Thyroid carcinoma	2		1	

[a]Difference between severely and non-severely cancer patients, tested with χ^2.
[b]Two patients were diagnosed with both bladder and prostate cancer and were categorized as urogenital tumours of the other tumours. A two-sided $P < 0.05$ was considered significant.

In the group of patients with other tumours the presence of severe fatigue was the highest (33.3%). When patients with gastrointestinal cancer were considered as a separate group, fatigue in this specific group was 28.1%. In patients with other tumours without gastrointestinal cancer severe fatigue even rose to 38.2%. A significant overall effect of diagnosis on severe fatigue was found using the χ^2 test ($P = 0.044$). In addition, we tested if the means of the three diagnosis groups were different on the CIS using ANOVA, and also a significant overall effect was found ($P = 0.014$). Using a *post hoc* test we tested which of the three groups (breast cancer (mean 23.5, s.d. 12.4), prostate cancer (mean 19.9, s.d. 12.0), or other tumours including gastrointestinal cancer (mean 27.1, s.d. 13.9)) differed from each other, and found one significant difference. Patients with prostate cancer were significantly less fatigued compared with the group of patients with other tumours ($P = 0.011$) (data not shown).

Contributing factors to severe fatigue before cancer treatment

In Table 3 the differences on contributing factors between severely fatigued cancer patients and non-severely fatigued cancer patients are described.

Severely fatigued cancer patients reported to have more fatigue in the period before diagnosis, more pain, and being less physically active. These differences were significant for both periods, 1 and 3 years before diagnosis. Severely fatigued cancer patients also reported currently more pain and being less physically active, than non-severely fatigued cancer patients. In addition, they reported significantly more sleeping problems, and more feelings of depression and anxiety.

Table 3: Contributing factors to severe fatigue before cancer treatment tested with a *t*-test.

Factors	Non-severely fatigued mean (s.d.)	Severely fatigued mean (s.d.)	t	df	p
Period before diagnosis					
Fatigue 1 year before diagnosis[a]	1.71 (2.43)	3.86 (2.89)	4.786	177	<0.001
Fatigue 3 years before diagnosis	1.32 (2.14)	2.93 (2.67)	3.563	177	0.001
Physical activity 1 year before diagnosis	7.06 (2.34)	6.17 (2.66)	-2.094	177	0.038
Physical activity 3 years before diagnosis[a]	7.28 (2.24)	6.17 (2.63)	-2.711	177	0.007
Pain 1 year before diagnosis	0.89 (1.91)	1.95 (2.68)	2.391	177	0.020
Pain 3 years before diagnosis[a]	0.73 (1.66)	1.76 (2.43)	2.577	177	0.013
Current period before cancer treatment					
Pain[a]	1.28 (2.14)	3.24 (3.04)	3.900	177	<0.001
Anxiety[a]	13.1 (3.77)	17.0 (6.91)	3.502	176	0.001
Sleep quality (SCL-sleep)	4.91 (2.23)	6.91 (2.93)	4.061	176	<0.001
Impairments on sleep/rest (SIP-SR)[a]	34.7 (46.4)	85.1 (70.4)	4.358	177	<0.001
Physical activity[a]	6.66 (2.42)	4.69 (2.37)	-4.636	177	<0.001
Depressive mood (SCL-90)[a]	20.8 (5.86)	27.5 (9.54)	4.360	176	<0.001
	% (n)	% (n)			
Clinical depression (BDI-PC)[b]	2.9 (4)	17.1 (7)			0.004

[a]Factors that were put into the logistic regression analysis as separate factors.
[b]Difference on clinical depression was tested with Fisher's Exact Test.

The results of the logistic regression are described in Table 4. Four factors contributed uniquely to severe fatigue in cancer patients before treatment. First fatigue 1 year before diagnosis contributed significantly. Three factors of the current period contributed significantly to severe fatigue. Lower physical activity contributed the most, followed by depressive mood and impairments on sleep and rest.

Two factors, diagnosis and physical activity 3 years before diagnosis, did not contribute significantly to severe fatigue. Anxiety and pain were not part of the linear regression.

Table 4: Contributing factors to severe fatigue

Contributing factors	B (SE)	Exp b	P-value	95% CI
Diagnosis group			0.374	
Diagnosis group (1) (breast cancer)	0.783 (0.609)	2.187	0.199	0.663 – 7.218
Diagnosis group (2) (prostate cancer)	0.270 (0.606)	1.310	0.656	0.399 – 4.297
Period before diagnosis				
Fatigue 1 year before diagnosis	0.218 (0.077)	1.244	**0.005**	1.070 – 1.446
Physical activity 3 years before diagnosis	0.020 (0.111)	1.020	0.855	0.822 – 1.267
Current period before treatment				
Depressive mood (SCL-90)	0.076 (0.031)	1.079	**0.014**	1.015 – 1.147
Impairments on sleep/rest (SIP-SR)	0.008 (0.004)	1.008	**0.045**	1.000 – 1.015
Physical activity	-0.284 (0.115)	0.752	**0.013**	0.601 – 0.943
Constant	-2.986 (1.040)	0.051	0.004	

(R^2 was 0.274 (Cox & Snell) and 0.412 (Nagelkerke)). A two-sided $P < 0.05$ was considered significant.

DISCUSSION

This is the first study specifically aimed at investigating fatigue in patients who were recently being diagnosed with cancer, before initiation of any treatment for cancer. The first goal of this study was to establish how many cancer patients report severe fatigue before receiving treatment. In the whole sample 24% of the cancer patients were severely fatigued, ranging from 14 to 28%. The presence of severe fatigue was the lowest in patients with prostate cancer (14%), but higher in breast cancer patients (20%), and gastrointestinal cancer patients (28%).

The prevalence of severe fatigue in our study is surprisingly high, in perspective to results in other samples. Reviewing the results of seven different studies fatigue in cancer survivors appears to vary between 16 and 38%, compared with 10 - 11% in a control group[28]. The prevalence of severe fatigue in cancer survivors with various cancer diagnoses was about 22[18, 19, 29]. Thus severe fatigue in cancer patients before treatment seems two times as high compared with people without a history of cancer, and reaching the level of severe fatigue in cancer survivors long after cancer treatment.

As patients in this study were recruited as part of a larger intervention study, the question rises if this could be a biased sample. In the general Dutch population more males are diagnosed with cancer than females. In addition, breast cancer is the most common type of cancer, followed by colorectal cancer, lung cancer, and prostate cancer[30]. So the sample in this study does not reflect the incidence and types of cancer in the Dutch population, as more females were included and prostate cancer was more common than gastrointestinal cancer in this sample. These differences cannot be explained from the characteristics of the patients who refused to participate, as no significant differences were found between participants and non-participants on sex and diagnosis. The following reasons might explain these differences. One reason might be, because this sample is a selected group of cancer patients who would be treated with curative intent. Another reason might be that patients with colorectal cancer are more often diagnosed in an acute phase requesting immediate treatment, whereas patients with breast or prostate cancer receive treatment in a more planned manner. Patients diagnosed and treated in this acute phase were more difficult to approach and to include into the study. This also explains the small numbers of patients with testis cancer in this study, who also receive surgery in an acute phase. The organisation of the recruitment might also explain the differences between our sample and the Dutch population. For example, in most hospitals specialised mamma care units were involved with recruiting patients, which might explain the large numbers of patients with breast cancer.

The question rose if severe fatigue was more common in this sample as patients were recruited for an intervention study on fatigue during cancer treatment. We do not expect that patients with severe fatigue are over-represented in this sample. Firstly, physicians excluded patients with co-morbidities that could have caused fatigue, for example patients with rheumatic arthritis or heart disease. Secondly, patients were informed that prevention of severe fatigue was the main goal of the study, and patients who indicated seeking help for severe fatigue were not included in the study. Thirdly, although patients were excluded when receiving psychiatric or psychological treatment in the last 3 months based on self-report, patients were not excluded based on taking psychotropic medicines. However, only one participant took psychotropic medicine, so it is improbable that this is an explanation for the prevalence of severe fatigue. The prevalence of severe fatigue might even be underestimated. More patients with prostate cancer (who are less frequently severely fatigued), and less patients with colorectal cancer (who are more often severely fatigued) participated in this study, compared with the Dutch population.

Our second goal was to investigate which factors influenced severe fatigue before cancer treatment, and four factors were found. More fatigue 1 year before diagnosis, currently lower physical activity, depressive mood and more impaired sleep and rest appeared to be related to fatigue prior to treatment. Although differences were found in the prevalence of severe fatigue among various groups of diagnoses, results showed that diagnosis did not uniquely contribute to severe fatigue. In light of this result, TNM classification of each tumour was considered not useful. Further classification would increase the number of subgroups, making it even harder to demonstrate a potential relationship between diagnosis and fatigue. The four mentioned factors are thus stronger related to severe fatigue than diagnosis, and also stronger than anxiety, pain or physical activity 3 years before diagnosis.

Lower physical activity was related to fatigue in cancer patients during treatment[31-33] and in cancer survivors[19, 26] as previous studies revealed.

A new finding is that this relationship between physical activity and fatigue was now found in cancer patients before initiation of treatment.

Two studies that investigated the quality of life in newly diagnosed cancer patients found that sleeping problems affected patients before cancer treatment[10, 13]; however, it remained unclear which aspects of sleep were affected. Looking at our results on the subscale sleep/rest of the SIP more closely revealed four differences between severely and non-severely fatigued cancer patients. Severely fatigued cancer patients indicated to sleep less at night, sleep or nap more during the day, sit during much of the day, and lie down to rest more often during the day. Thus, not only the nocturnal sleep was affected in severely fatigued cancer patients, but their daily sleep and rest was affected too.

One of the symptoms of clinical depression can be fatigue. However, the prevalence of clinical depression in our sample is low (6.2%) and within the normal range of the adult Dutch population (5.7 – 6.6%)[34]. Thus, clinical depression cannot be an explanation for the high prevalence of severe fatigue in this study. In addition our results showed the necessity to distinguish clinical depression from depressive mood, with the latter clearly being a mood state. Although no structured psychiatric interview was used to diagnose mood disorders.

Fatigue 1 year before diagnosis was evaluated retrospectively by patients, and not measured at that specific time. This evaluation probably reflects patients' recollection of fatigue 1 year before diagnosis, rather than actual fatigue at that time.

Contrary to what was expected anxiety was not found as a fatigue-contributing factor. Receiving the diagnosis cancer can inflict strong feelings of anxiety[10, 35], although these high levels appeared to decrease within 2 weeks[13]. This trend was also found in patients receiving chemotherapy. High level of anxiety prior to chemotherapy decreased as soon as individuals started treatment[36, 37]. Thus, feelings of anxiety are a common reaction on being diagnosed with cancer, and the prospect of receiving chemotherapy, but feeling of anxiety are not related to severe fatigue in treatment naive cancer patients.

No previous research was done to investigate the relationship between

fatigue and pain in treatment naive cancer patients, but no evidence was found that pain contributed to severe fatigue in this study.

One of the limitations in this study is the reliance on cross-sectional data. Therefore, we cannot make any claims for causality between fatigue and the related factors, impaired sleep and rest, depressive mood, and physical activity.

In this study questionnaires were used to measure physical activity, but asking people to estimate their level of physical activity has its limitations. Previous research showed that there is a lack of correspondence between self-reported physical activity and objective physical activity[38, 39]. Probably the perception of physical activity does not always reflect the actual level of physical activity. Thus in our study it is more likely that the perceived level of physical activity was related to severe fatigue rather than the actual level.

In summary, it is generally known that most cancer patients will experience fatigue during treatment, but fatigue in treatment naive cancer patients was not previously investigated. This study showed that a large number of cancer patients already experience severe fatigue before initiation of cancer treatment. One might expect that the course of fatigue during and after cancer treatment could be different for patients with severe fatigue or patients without severe fatigue before cancer treatment. In addition, it remains a question if patients with severe fatigue before cancer treatment should receive a kind of early fatigue intervention at this stage. These will be topics for future research.

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Chapter 4

Is increasing physical activity necessary to diminish fatigue during cancer treatment? Comparing cognitive behavior therapy and a brief nursing intervention with usual care in a multicenter randomized cntrolled trial

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Martine Goedendorp, Marlies Peters, Marieke Gielissen, Fred Witjes, Jan Willem Leer, Stans Verhagen, Gijs Bleijenberg.

ABSTRACT

Background. Two interventions for fatigue were given during curative cancer treatment. The aim of this multicenter randomized controlled trial (RCT) with three conditions was to demonstrate the efficacy and to determine the contribution of physical activity.

Methods. Recruited from seven hospitals, 220 patients with various malignancies participated in a RCT. The brief nursing intervention (BNI) consisted of two one-hour sessions, three months apart, given by 12 trained nurses, focusing only on physical activity. Cognitive behavior therapy (CBT) consisted of up to ten one-hour sessions, within six months, provided by two therapists, focusing on physical activity and psychosocial elements. The control group received only usual care (UC). Assessments took place before and at least two months after cancer treatment, when patients had recovered from acute fatigue. Fatigue was the primary outcome. Efficacy was tested using analyses of covariance. A

nonparametric bootstrap approach was used to test whether the effect on fatigue was mediated by physical activity.

Results. The CBT group was significantly less fatigued than the UC group. Between the BNI and the UC groups, no significant difference was found in fatigue. The mediation hypothesis was rejected.

Discussion. CBT given during curative cancer treatment proved to be an effective intervention to reduce fatigue at least two months after cancer treatment. The BNI was not effective. Contrary to what was expected, physical activity did not mediate the effect of CBT on fatigue. Thus, the reduction in fatigue elicited by CBT was realized without a lasting increase in physical activity.

INTRODUCTION

Fatigue is one of the most common and distressing symptoms in cancer patients, and when severe it has a large impact on daily functioning and quality of life[1-3]. It is assumed that levels of fatigue are low before the start of cancer treatment and high during cancer treatment. Prevalence estimates of fatigue during treatment are in the range of 25%–75%, in different samples and measured with different questionnaires[4]. Several studies even reported a prevalence ≥ 90%[5-9]. Fatigue continues to be problematic for many patients after cancer treatment is finished, because the number of patients with substantial fatigue is higher than that in control groups[4, 10]. Therefore, it is important to intervene during active cancer treatment in order to reduce severe fatigue after cancer treatment. Because nearly all cancer patients experience fatigue during active cancer treatment, we assumed that most patients could benefit from an intervention for fatigue.

Exercise and psychosocial interventions have the strongest evidence base for managing fatigue during cancer treatment[11], but clearly not all interventions generate similar effects. Psychosocial interventions specifically aimed at fatigue during cancer treatment were found to be more effective than psychosocial interventions not aimed at fatigue[12-14]. However, the number of randomized

controlled trial (RCT) interventions specifically for fatigue during cancer treatment is limited[13].

Reviews demonstrate that interventions for fatigue and assessments take place during different phases of cancer treatment[12-14]. For example, in some RCTs, participants still received chemotherapy after the postintervention assessment[15-17]. Such a design is unsuitable to demonstrate whether the level of fatigue after finishing cancer treatment returns to the pretreatment level. To the best of our knowledge, there is no fatigue interventional RCT during cancer treatment that assessed patients at clinically relevant moments—before the start of cancer treatment and shortly after finishing cancer treatment.

Exercise interventions are solely aimed at physical activity, whereas psychosocial interventions often have a physical activity component, such as activity management. Intervening with physical activity to reduce fatigue is based on the assumption that a lack of physical activity and deconditioning during cancer treatment can worsen fatigue[18]. When patients are diagnosed with cancer, their activity pattern changes and they become physically less active, possible leading to deconditioning[19]. This is the result of a negative spiral, because when patients become physically less active they become more easily fatigued, and when patients experience fatigue they react by becoming physically even less active. Exercise can break this cycle by improving tolerance for physical activity[11]. Therefore, increasing physical activity is an important element in reducing fatigue during cancer treatment. However, the mediating role of physical activity in interventions aimed at reducing fatigue during cancer treatment has never been demonstrated.

In the current RCT, two interventions for fatigue during cancer treatment were compared with usual care (UC). The first intervention was a minimal intervention performed by nurses. The brief nursing intervention (BNI) was aimed at advising patients how to avoid deconditioning. There is evidence that such brief interventions for fatigue given by nurses are effective[15-17]. Furthermore, it is recognized that oncology nurses can play significant roles in the translation of cancer-related fatigue guidelines by teaching patients and decreasing barriers[19]. The second intervention was an extensive intervention

aimed at fatigue based on cognitive behavior therapy (CBT). This CBT intervention was, in addition to avoiding deconditioning, based on elements such as changing dysfunctional cognitions about fatigue, changing a distorted sleep–wake rhythm, and coping with the consequences of having cancer.

The first aim of this RCT was to determine the efficacy of these two interventions compared with UC. The moment of postintervention assessment (T2) was chosen at a clinically relevant point. T2 was chosen postintervention and also after a recovery period from the direct effects of cancer treatment. A previous study found that the immediate effects of surgery, chemotherapy, or radiotherapy on fatigue disappear after six weeks[20]. Therefore, the postintervention assessment was completed at least two months after cancer treatment finished. It was expected that patients in these two intervention groups would be less fatigued at least two months after cancer treatment than patients given UC. In addition, it was expected that patients in the intervention groups would have higher levels of functioning, less psychological distress, and a better quality of life.

Our second aim was to determine the role of physical activity in reducing fatigue during cancer treatment. It was expected that a reduction in fatigue was mediated by enhanced physical activity.

METHODS

Patients and procedure

Sample

Patients were recruited from the Radboud University Nijmegen Medical Centre and six regional hospitals from November 2005 until August 2007. Patients were included after being diagnosed with a primary tumor and scheduled to receive treatment with curative intent. Patients had to be 18–75 years of age and able to speak, read, and write Dutch. To minimize dropout and exclusion during the study, patients with lung cancer and with head and neck cancer were excluded. Exclusion criteria were: comorbidities causing fatigue, seeking treatment for pre-

existing chronic fatigue, and receiving psychiatric or psychological treatment in the preceding three months. The ethics committees from all seven hospitals approved the study. Informed consent was obtained from all participants.

Design and procedure

Eligible patients were approached by their physician or specialized nurse at the time they were informed about their diagnosis and treatment plan. The recruitment procedure is described in detail elsewhere[21]. Patients with initial interest received written information and supplementary information by telephone. Subsequently, patients who consented completed the baseline assessment (T1) by computer or paper and pencil depending on their preference. T1 was completed before the start of cancer treatment. Subsequently, participants were randomly allocated to one of the three groups: BNI, CBT, or UC. Randomization was performed in blocks separately for each hospital, using labeled cards in numbered closed envelopes prepared by a statistician not involved in the study. Test assistants blinded to the randomization sequence opened the envelopes and informed the participants. The follow-up assessment (T2) was initially planned for six months after T1. If patients received surgery, chemotherapy, or radiotherapy in the fifth or sixth month, they were assessed two months after these treatments were finished.

Interventions

The UC group received treatment for cancer as proposed by the multidisciplinary working party for their specific tumor group, conforming to the guidelines of the comprehensive cancer center. None of the hospitals already offered supportive care for fatigue during cancer treatment.

BNI

The BNI consisted of two one-hour sessions and a booklet. In the first session, the nurse explained how to break the negative spiral of low physical activity and fatigue. To demonstrate this, the patient's level of physical activity was determined before diagnosis and in the previous week. These levels were

estimated with the questionnaire physical activity (QPA). Consequently, patients were advised to increase their physical activity level stepwise (five minutes per week, up to one hour per day, for five days a week, by walking or cycling) up to 300 minutes per week. Patients who were physically active at this level were encouraged to maintain it. Additionally, how to remain physically active during cancer treatment was discussed, and what to do if complications occurred. The second session was planned for three months later. During that session, the level of physical activity was determined again and difficulties and solutions for becoming active or maintaining activity were discussed. Information and recommendations on physical activity could be reread in the booklet. All nurses received a protocol. To improve integrity, nurses were trained and supervised by G.B. and C.V. about every two months, and they were requested to send a checklist to the researcher after each session. The checklist contained questions on how much time was spent at the current level of physical activity and on discussing difficulties.

CBT

Participants in the CBT group received up to ten one-hour sessions during six months. The number of sessions and the time spend on each element varied among individual patients, depending on problems encountered. The methods used were: restructuring of cognitions and beliefs, education and behavioral instructions, and providing emotional support. The intervention focused on six elements. (a) Physical activity: patients received the same information and booklet as provided in the BNI; in addition, activity-related cognitions were disputed. (b) Fatigue-related cognitions: dysfunctional cognitions were changed to more helpful ones. (c) Sleep–wake rhythm: patients were motivated to maintain fixed bedtimes, taking the phase of cancer treatment into account; napping during the day was discouraged. (d) Effects of cancer and treatment: the consequences of having cancer and the side effects of cancer were discussed, aimed at helping patients to cope and accept these (e.g., stoma, amputation). (e) Cancer in contact with others: unhelpful cognitions were changed and coping strategies for dealing with having cancer in contact with others, such as family or

colleagues, were discussed; for example, "With whom do you want to share your emotions?" or "How do I tell the kids?" (f) Plans for the future: patients were asked to think about the future, and to make a plan; for example, a concrete plan for returning to work. Obstacles, fears, and solutions were discussed. Therapists with previous CBT experience in treating chronically fatigued cancer survivors gave the CBT[22]. A protocol was developed and the therapists received training and supervision every two weeks by G.B., during which each case was discussed.

INSTRUMENTS

Demographic characteristics were gathered by self-report using questionnaires. Information on diagnosis was obtained from the patient's physician.

Fatigue severity was the primary outcome and was assessed using the fatigue subscale of the Checklist Individual Strength (CIS)[23, 24]. The CIS is a well-validated instrument[25, 26]. The fatigue subscale (CIS-fat) consists of eight items with scores in the range of 8–56. A cutoff score ≥ 35 indicates severe fatigue[24]. It has been used in previous research investigating fatigue in cancer survivors and has shown sensitivity to detect change[3, 22, 27, 28].

As a secondary outcome, functioning was assessed using the Health Survey Short Form-36 (SF-36). The Dutch language version of the SF-36 has been proven to be a reliable and valid instrument in the general population and in chronic disease populations[29]. The Symptom Checklist-90 (SCL-90) was used to measure psychological distress. The SCL-90 has good reliability and discriminating validity[30]. Quality of life was assessed using the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30), version 3.0. The EORTC-QLQ C30 is an internationally validated questionnaire[31, 32].

To test for mediation, physical activity was assessed using three different instruments. For all instruments, higher scores indicate higher levels of physical activity. Physical activity was measured with actigraphy using an actometer, which has been used in cancer survivors[33]. An actometer is a motion-sensing device based on a piezoelectric sensor, with highly reproducible readings[34]. It

records the number of movements in five-minute intervals. At baseline, participants wore an actometer from the assessment to the start of cancer treatment, for up to 12 days and nights. At T2, the actometer was worn for 12 consecutive days and nights. The mean daily physical activity score across all worn days and nights was the parameter used to assess the level of physical activity.

During the same period, participants were asked to complete the Daily Observed Activity (DOA), scoring their level of physical activity four times a day. A mean daily score was calculated, varying in the range of 0 –16. The DOA has previously been used in cancer survivors[35].

To measure whether patients complied with advice concerning physical activity, the QPA was developed. Patients were asked whether they had practiced sports, walked, or cycled in the past week for at least 30 minutes. They were asked how many days and for how long they had performed these activities. The total duration was calculated in minutes. Criterion validity with the actometer was moderate (Spearman's ρ =.31); however, it was similar to the International Physical Activity Questionnaire with the actometer[36].

Statistical methods

The data analysis was performed with SPSS, version 16.0 (SPSS Inc, Chicago, IL). Data were used from participants who met the eligibility criteria at both T1 and T2. According to Fergusson et al.[37], patient data can be excluded from analysis without risking bias when ineligible patients are mistakenly randomized into a trial.

An a priori power analysis indicated that 48 patients would be required in each group, based on the following assumptions. A change of 8 points was expected on the CIS-fat[22]. An α of .017 (.05/3) and two-sided significance level were used to yield an 80% power. This study was overpowered as a result of the fact that fewer patients were excluded during the study than expected.

Baseline differences among the three conditions were tested with a *t*-test or χ^2 test for independent samples. Significant differences were entered as covariates in all further analyses. To test for an overall significant difference

among mean scores for the three conditions, analyses of covariance (ANCOVA) were performed for the outcome measures, with baseline scores entered as covariates and condition as a fixed factor. When an overall effect was significant, a contrast analysis was performed to compare the intervention groups (level 2 and 3) with the UC group (level 1). To test whether there was a clinically significant difference, the differences among the proportions of severely fatigued participants in the three groups were tested with a logistic regression analysis using the enter method. A two-sided $p < .05$ was considered significant.

Primary outcome data were missing from two participants at T2. To avoid overestimation of the effects of the interventions, missing data were substituted with the mean score of the UC group. A sensitivity analysis showed that entering the missing data with the mean score of the UC group added with one or two standard deviations (SDs) did not influence the results.

An intention-to-treat analysis was performed for all outcomes except for the actometer and the DOA. Completers were used for these measures, because less than half the participants wore the actometer and completed the DOA at both assessments.

The mediation hypothesis was tested with a nonparametric bootstrap approach. This approach was chosen because it gives more power to detect significant differences in small, non-normally distributed samples. A macro expansion, consisting of a syntax file for SPSS, was introduced by Preacher and Hayes[38] to test for mediation according to the guidelines of Baron and Kenney[39]. The macro generates a mean mediation effect with a 95% confidence interval (CI) by randomly resampling the observed dataset 5.000 times with replacement. The mediation hypothesis was accepted when the 95% CI included zero[38].

RESULTS

Figure 1 illustrates the flow of participants. A total of 395 eligible cancer patients were approached, and 155 refused to participate. "Participating would take too much time" was the most common reason. Nonparticipants were older than participants, but no significant difference was found for sex or type of malignancy[21]. Because of the short time span between the diagnosis and start of treatment, not all participants could be assessed before the start of treatment. Twenty six percent of the participants were assessed after surgery or the start of hormone therapy, but always before adjuvant chemotherapy or radiotherapy. Of the 240 participants, 77 were assigned to the BNI group, 82 were assigned to the CBT group, and 81 were assigned to the UC group. The majority were recruited from the university hospital (n = 158). Twenty patients were excluded postrandomization. Intention-to-treat analyses were based on 220 participants—72 in the BNI group, 76 in the CBT group, and 72 in the UC group. Two participants dropped out. T2 was completed by 162 participants six months after T1. Fifty six participants who received cancer treatment for a longer period completed T2 two months after their cancer treatment was finished.

Interventions

BNI

Of the 68 patients who started the BNI, 66 attended both sessions. Most sessions were face to face; 10% were telephone sessions. All but two of the checklists were returned by the nurses. The mean time between the two sessions was 4.5 months (SD, 2.5 months). In total, 12 nurses gave the BNI. The mean hours of training and supervision were 7.8 (SD, 4.9 hours), varying in the range of 2–12 hours. In the university hospital, two nurses administered the BNI to 20 and 26 participants each. In the regional hospitals, nurses gave the BNI to one to seven participants. There was no significant difference between participants treated in the university hospital by the more experienced nurses and those treated in the regional hospitals for level of fatigue and physical activity at T2 (data not shown).

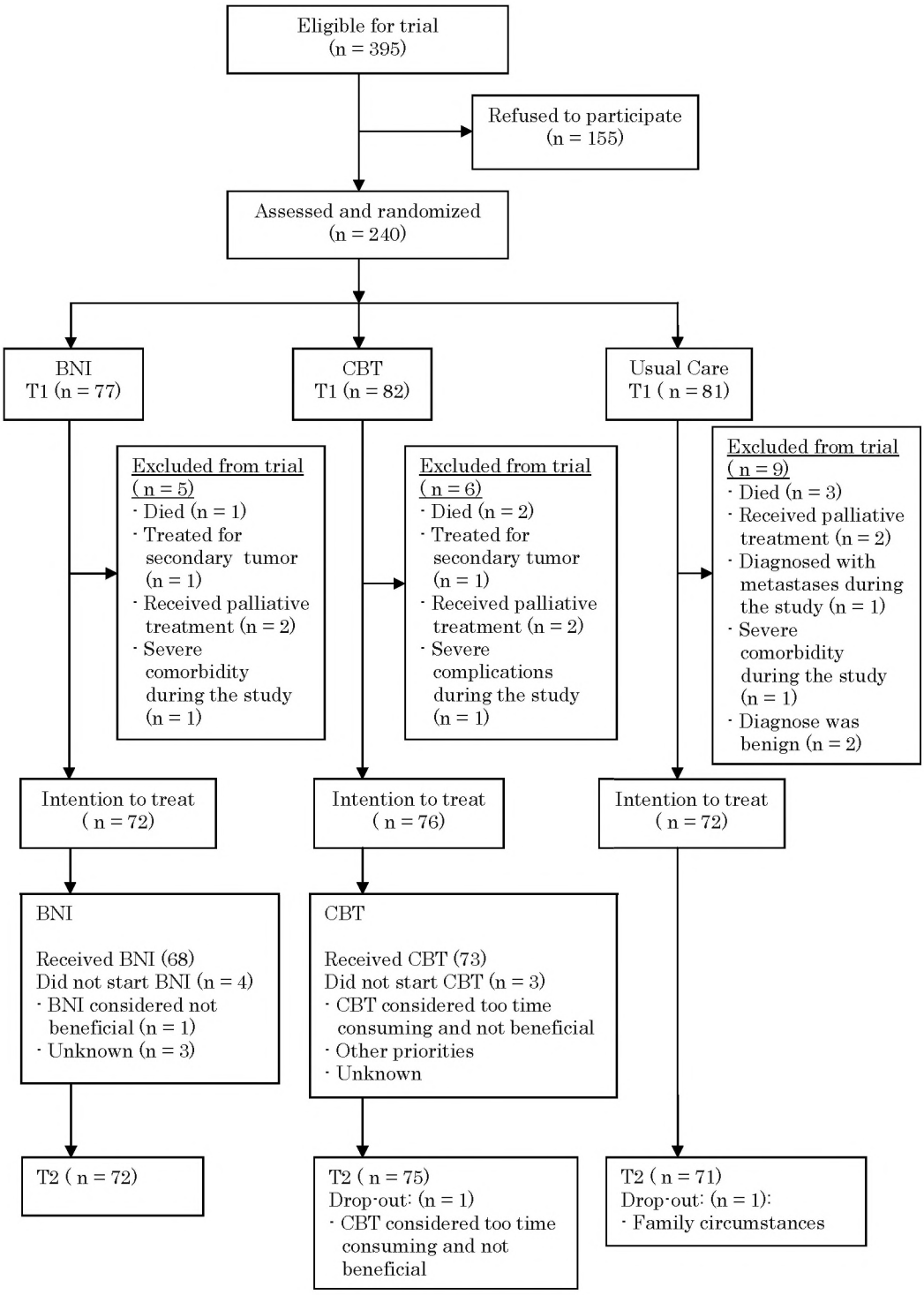

Figure 1: Participant flow diagram.

Table 1: Baseline characteristics for the three groups

Characteristics		Total (n= 220)		BNI (n=72)		CBT(n=76)		UC(n=72)		P-value
		n	%	n	%	n	%	n	%	
Sex	Male	81	37	28	39	28	37	25	35	.874
	Female	139	63	44	61	48	63	47	65	
Age (years)	Mean	56.7		57.1		55.6		57.3		.562
	(s.d.)	(10.8)		(10.0)		(11.3)		(11.1)		
Education	Mean	3.99		4.31		3.93		3.74		.127
(1=low – 7 high)	(s.d.)	(1.71)		(1.87)		(1.59)		(1.63)		
Marital status										
Married / cohabiting		178	81	65	90	61	80	52	72	**.022**
Other status		42	19	7	10	15	20	20	28	
Diagnosis (*)										
Breast cancer		105	48	35	49	36	47	34	47	.822
Prostate cancer		51	23	19	26	15	20	17	24	
Other tumors		64	29	18	25	25	33	21	29	
Gastrointestinal		27		7		10		8		
Urogenital		15		3		7		5		
Gynecological		12		6		3		3		
Lymphomas		6		1		3		2		
Sarcoma		3		1		1		1		
Melanoma		1		-		-		1		
Thyroid carcinoma		2		-		1		1		
Treatment type (**)										
Surgery		201	93	66	92	71	97	64	90	.207
Chemotherapy		67	31	22	31	28	38	17	24	.173
Radiotherapy		128	59	42	58	44	60	42	59	.972
Hormone therapy		65	30	22	31	20	28	23	32	.833
Treatment before	no	164	74	49	68	57	79	58	76	.282
assessment	yes	56	26	23	32	15	21	18	24	
Time between T1	Mean	7.42		7.40		7.52		7.35		.787
and T2 (months)	(s.d.)	(1.56)		(1.54)		(1.52)		(1.64)		

BNI: brief nursing intervention, CBT: Cognitive Behavior Therapy, UC: usual care, T1: baseline assessment, T2: follow-up assessment. (*) Two patients were diagnosed with both bladder and prostate cancer and were categorized as other tumors. One was allocated to the control group, the other to CBT. (**) The total is more than 100%, as several combinations of treatment regimes were given to patients.

CBT

Seventy three patients started with CBT. The mean duration was 7 months (SD, 2.6 months). The mean number of sessions was 6.2 (SD, 1.9; range, 2–11). One person received 11 sessions. Fifty nine percent of the participants had only face-to-face sessions; 41% combined face-to-face sessions with telephone sessions. Most of the sessions (80%) were given face to face. No relationship was found between change in fatigue severity, and the number of sessions and type of contact. Two therapists treated 34 and 39 patients each. No therapist effect was found on fatigue at T1 (p = .937) or at T2 (p = .991), or on other outcome measures (data not shown).

Baseline comparison

No baseline significant differences were found among the three groups in terms of diagnosis, cancer treatment, or fatigue (Tables 1, 2, and 3). Significantly more participants in the BNI group than in the UC group were married. For the secondary outcomes, a significant difference (p = .029) was found on the cognitive functioning subscale of the EORTC-QLQ C30 between the CBT group (mean, 86.0; SD, 19.5) and the UC group (mean, 92.8; SD, 12.5). In addition, a significant difference was found for the QPA between the BNI group and the UC group (Table 4). These three significant differences were entered as covariates in further analyses.

Effect of the interventions

The results of the ANCOVA on fatigue are shown in Table 2. Participants in the CBT group were significantly less fatigued than those in the UC group. From T1 to T2, fatigue increased in the UC group, whereas fatigue decreased in the CBT group. This resulted in a mean difference between the two conditions of 5.6 points on the CIS-fat. There was no significant difference in fatigue between the BNI group and the UC group (p = 1.000). The proportion of severely fatigued cancer patients was significantly lower in the CBT group than in the UC group (p = .019) (Table 3). No significant differences were found for the secondary outcomes (data available upon request).

Table 2: Means and standard deviation of fatigue at T1 and T2 and results of the ANCOVA showing the overall effects and contrast analysis of the interventions on fatigue

Overall effect		**BNI**	**CBT**	**UC**	**F**	**P-value**
n		72	76	72		
CIS- fat	T1 mean (s.d.)	21.5 (12.7)	25.3 (14.0)	23.4 (12.4)	1.568	.211
	T2 mean (s.d.)	23.3 (14.6)	21.0 (11.6)	25.9 (13.5)	4.255	**.015**
Contrast analysis		Covariate adjusted Mean difference		95% CI		P-value
CIS- fat T2	UC - BNI	1.30		-3.74 – 6.34		1.000
	UC - CBT	5.60		0.69 – 10.5		**.019**

BNI: Brief Nursing Intervention, CBT: Cognitive Behavior Therapy, UC: Usual Care, CIS-fat: Checklist Individual Strength subscale fatigue, T1: baseline assessment, T2: follow-up assessment, CI: Confidence Interval.

Table 3: Percentages severe fatigue in the three conditions at T1 and T2 and results of the logistic regression analysis.

Percentage severely fatigued cancer patients							
	n	**T1**	**T2**	**B (SE)**	**Exp b**	**P-value**	**95% CI**
UC	72	19%	31%			**0.020**	
BNI	72	19%	22%	-.393 (.418)	.675	0.348	.297– 1.53
CBT	76	26%	15%	-1.30 (.467)	.272	**0.005**	.109 – .680
Constant				1.94 (1.03)	6.93	0.061	

(R2 was 0.127 (Cox & Snell) and 0.195 (Nagelkerke)). A two-sided $P < 0.05$ was considered significant. BNI: Brief Nursing Intervention, CBT: Cognitive Behavior Therapy, UC: Usual Care, CI confidence interval, T1: baseline assessment, T2: follow-up assessment

Results of ANCOVA showed no significant differences in physical activity between the two intervention groups compared with the UC group (Table 4). The bootstrap approach showed that, at most, 3.4% of the effect of CBT on fatigue

could be explained by physical activity (Table 5). The 95% CI of the mean mediation effect included zero, rejecting the mediation hypothesis.

Table 4: Means and standard deviation of physical activity at T1 and T2 and results of the ANCOVA showing the overall effects and contrast analysis of the interventions on physical activity.

Outcome		**BNI**	**CBT**	**UC**	**F**	**P-value**
	n	35	30	25		
Actometer	T1 mean (s.d.)	68.4 (17.4)	69.4 (31.1)	69.1 (24.1)	0.015	.986
	T2 mean (s.d.)	65.9 (21.3)	71.6 (25.0)	69.1 (22.9)	0.825	.442
DOA	n	34	29	31		
	T1 mean (s.d.)	4.4 (2.2)	4.5 (1.5)	4.8 (2.0)	0.251	.779
	T2 mean (s.d.)	4.8 (1.9)	4.9 (1.5)	4.6 (1.9)	0.405	.668
QPA	n	72	76	72		
	T1 mean (s.d.)	248 (270)	203 (197)	140 (174)	4.527	**.012**
	T2 mean (s.d.)	273 (303)	322 (277)	211 (223)	2.830	.061
Contrast analysis		Covariate adjusted Mean difference		95% CI		P-value
QPA T1	UC - BNI	-108		-196 – -21.0		**.009**
	UC - CBT	-63.5		-150 – 22.6		.229

BNI: Brief Nursing Intervention, CBT: Cognitive Behavior Therapy, UC: Usual Care, DOA: Daily Observed Activity, QPA: Questionnaire Physical Activity, T1: baseline assessment, T2: follow-up assessment, CI: Confidence Interval.

Table 5: Results of the mediation effect of physical activity in the CBT group compared to UC, according to the Bootstrap approach

	Actometer	**DOA**	**QPA**
mean mediation effect	-0.006	0.015	0.058
CI (95%)	-0.250 - 0.215	-0.322 - 0.430	-0.067 - 0.212
Percentage of total treatment effect	-0.29%	0.92%	3.40%

CBT: Cognitive Behavior Therapy, UC: Usual Care, DOA: Daily Observed Activity, QPA: Questionnaire Physical Activity, CI: Confidence Interval.

DISCUSSION

The first aim of this study was to evaluate two interventions for fatigue during curative cancer treatment—CBT and the BNI. Our results showed that CBT was effective. CBT significantly reduced fatigue shortly after cancer treatment. Also, significantly fewer participants were severely fatigued at least two months after cancer treatment, demonstrating its clinical relevance. The BNI did not reduce fatigue compared with UC. The uniqueness of this study was that the CBT intervention proved to be effective at a clinically relevant time, that is, after a recovery period from the direct effects of cancer treatment.

Contrary to our expectations, physical activity did not mediate the reduction in fatigue realized by CBT, whether physical activity was measured with actigraphy or questionnaires. The finding that there was no effect of the interventions on physical activity already showed that mediation was absent, but because mediation analyses require a large power, a bootstrap analysis was performed. The lack of mediation was a surprising finding because increasing physical activity is an important therapeutic component. Our findings indicate that, with CBT, it was possible to realize a significant reduction in fatigue without a lasting increase in physical activity.

A number of limitations should be considered. The majority of the participants were recruited from the university hospital. This could have raised the question of sample bias, but we found no difference between the university hospital and the regional hospitals for fatigue. The fact that this was a multicenter trial increases the generalizability of the findings.

Contamination could have occurred, although preventive actions were taken. The therapists and nurses who gave the interventions were not involved in recruiting participants or in UC.

No effect on secondary outcomes was found. This could be explained by the fact that the mean and SD for the SCL-90 and SF-36 were similar to those in the general Dutch population at baseline[29, 30]. Therefore, it was difficult to realize an improvement.

One could argue that an effect of the BNI failed to occur for several reasons,— because it consisted of only two sessions, because the time between the last session and T2 was longer than in the CBT condition, or because the nurses were less experienced than the therapists. However, the more intensive CBT also failed to show an increased level of physical activity.

A formal integrity check, such as recording of sessions, did not take place. Several actions were taken to ensure that nurses and therapists worked according to protocol, such as training and supervision. Almost all checklists were returned by the nurses, demonstrating good adherence.

We did not control for level of attention. It could be that part of the effect of CBT on fatigue can be explained by attention, but it is improbable that the effect is caused by attention alone. For example, we could not find a dose-response effect for CBT. Furthermore, no effect of an attention placebo group on fatigue was found in patients with chronic fatigue syndrome (CFS)[40, 41].

Actometer and daily self-observation data were not obtained from all participants. This could raise concerns about possible differences between those who did and those who did not complete these evaluations. However, no difference in fatigue at T1 and T2 or condition was found between completers and noncompleters.

The assumption that increasing physical activity reduces fatigue is widespread, but not always empirically supported. Some reviews found no effect of exercise on reducing fatigue[42, 43]. In addition, some exercise studies did not find an effect on fatigue, even though physical fitness increased[44-46]. Other intervention studies with mediation analyses support our findings, demonstrating that increasing physical activity is not necessary to reduce fatigue in CFS patients[47].

Because no intermediate assessments were performed, it could not be ruled out if a temporary increase in physical activity contributed to lower fatigue. However, it is more likely that other factors, such as fatigue- and cancer-related cognitions or stress reduction, and not physical condition, mediated the fatigue reduction. Results of a graded exercise RCT for CFS also demonstrated that

symptom focusing, not physical condition, mediated the improvement in fatigue[48].

As expected, the number of patients with severe fatigue increased in the UC group. However, a finding not expected beforehand was that at T1 more participants than expected were already severely fatigued. This cannot be attributed to preceding cancer treatment, because no difference was found in fatigue between cancer treatment–naïve patients and patients assessed before adjuvant therapy. Type of malignancy was also not found to be a contributing factor to severe fatigue before the initiation of cancer treatment[21].

Although fatigue was not assessed during active cancer treatment, many patients in the UC group were not severely fatigued after cancer treatment finished. Apparently, the group of patients without severe fatigue managed without a specific intervention for fatigue, implying that not all cancer patients need CBT for fatigue during curative cancer treatment. Future studies should identify patients at risk for severe fatigue shortly after cancer treatment, and interventions should focus on these risk groups.

SUMMARY

Until now, there was no interventional RCT for fatigue during curative cancer treatment that assessed patients before the start of cancer treatment and shortly after cancer treatment, after patients recovered from acute effects. Our RCT showed that participants who received CBT for fatigue during cancer treatment were less fatigued than patients who received UC at least two months after cancer treatment. The BNI was not effective.

Unexpectedly, physical activity did not mediate the reduction in fatigue. Thus, with CBT it was possible to realize an improvement in fatigue without a lasting increase in physical activity.

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Chapter 5

Moderators and long-term effectiveness of cognitive behaviour therapy for fatigue during cancer treatment

Psycho-Oncology (in press)

Martine Goedendorp, Marieke Gielissen,
Marlies Peters, Stans Verhagen, Gijs Bleijenberg.

ABSTRACT

Objective. A randomised controlled trial (RCT) demonstrated that cognitive behaviour therapy (CBT) for fatigue during curative cancer treatment was effective shortly after cancer treatment. This study aimed to identify which patient characteristics predict fatigue improvement after CBT. Additionally the long term effectiveness was investigated.

Methods. Patients with various malignancies participated in the RCT (n=210). Participants were assessed before cancer treatment (T1), post-intervention (T2), which was at least two months after cancer treatment and after one year follow-up (T3). Monthly fatigue assessments were completed between T2 and T3. A regression analysis with interactions was performed to determine if domains of quality of life (EORCT-QLQ-C30) functioning (SF-36) or psychological distress (SCL-90) moderated the effect of CBT on fatigue. ANCOVAs were used to study the long term effectiveness of CBT.

Results. Fatigue at T2 was predicted by a significant interaction between self-reported cognitive functioning and CBT. No interactions were found between other domains of quality of life, functioning, psychological distress and CBT. At T3 no significant difference on fatigue was found between CBT and usual care. Exploratory analyses showed that the difference nearly reached significance until seven months post-intervention.

Conclusions. Patients who experienced more concentration and memory problems at T1 benefited more from CBT for fatigue and are indicators. After a year follow-up the effect of CBT for fatigue was no longer observed, the effect on fatigue seemed to be diminished seven months post-intervention. The implication is that CBT for fatigue should be offered to cancer patients with the highest chance to benefit.

INTRODUCTION

Fatigue is one of the most frequently reported symptoms during cancer treatment[1, 2]. Unfortunately not all cancer patients recover from fatigue after cancer treatment is finished. Many cancer survivors remain severely fatigued for years after finishing cancer treatment with profound effects on daily functioning and quality of life[1-3].

There are strong indications that psychosocial interventions specifically aimed at fatigue during cancer treatment have a high probability of being effective in reducing fatigue[4]. Five[5-9] of the six interventions[5-10] (83%) reported in the literature specifically designed to reduce fatigue were effective. Three [11-13] out of 22 (14%) psychosocial interventions with a general approach, aimed at improving psychological distress, mood and physical symptoms have shown efficacy for fatigue. Most interventions specifically aimed at reducing fatigue were brief, consisting of three individual sessions, provided by (oncology) nurses[5, 6, 8, 9]. One intervention was more intensive. Patients received 12 sessions of cognitive behaviour therapy and hypnosis for six weeks supported by a therapist[7]. Long term effectiveness of these interventions was seldom investigated and none of these studies tested which factors moderated the effectiveness of the interventions.

Recently we performed a randomised controlled trial (RCT) in which two interventions specifically aimed at fatigue during curative cancer treatment were compared to usual care (UC)[14]. The strength of this RCT was the timing of the assessments, as these took place at clinically relevant moments. First, the baseline assessments (T1) were completed before the start of cancer treatment. This is a clinically relevant moment, because at this stage fatigue can't be

attributed to oncological treatment. Second, the post-intervention assessment (T2) took place at least two months after cancer treatment was finished. A previous study found that the immediate effects of surgery, chemotherapy or radiotherapy on the presence of fatigue disappeared within six weeks[15]. T2 was thus chosen at a clinically relevant moment, after a recovery period from the direct effects of cancer treatment.

The interventions evaluated in our recent RCT were a brief nursing intervention (BNI) and cognitive behaviour therapy (CBT) for fatigue[14]. The BNI consisted of two one-hour sessions with a nurse and a booklet aimed at increasing and maintaining physical activity. Results showed that compared to UC the BNI had no effect on fatigue.

The CBT intervention consisted of, on average, six one-hour individual sessions with a cognitive behavioural therapist in about seven months during cancer treatment. In addition to increasing and maintaining physical activity the CBT intervention was directed toward changing several dysfunctional cognitions about fatigue, cancer, cancer treatment, the future, and about relations with other people (self efficacy, catastrophic cognitions, unhelpful attributions and expectations). Methods used included cognitive restructuring, education and behavioural instructions, with homework assignments, and exposure. The intervention focused on six elements. 1) Physical activity: Patients received the same information and booklet as provided in the BNI. In addition, dysfunctional activity-related cognitions were challenged. 2) Fatigue related cognitions: dysfunctional cognitions were changed to more helpful ones and excessive focusing on fatigue was minimized. 3) Sleep-wake rhythm: Patients were encouraged to maintain regular bed and wake up times and napping during the day was discouraged, taking the phase of cancer treatment into account. 4) Effects of cancer and treatment: The consequences and side effects of having cancer were discussed (e.g. stoma, amputation), with the aim to help patients to cope and accept them. 5) Cancer and fatigue in contact with others: dysfunctional cognitions were changed and more helpful coping strategies to use in interacting with others (family, colleagues) concerning having cancer were discussed. 6) Plans for the future: Patients were asked to

allow themselves to think about the future, and to make future plans; obstacles and fears regarding doing so, and ways to overcome them, were discussed. Results of the RCT showed that at least two months after cancer treatment, significantly fewer participants were severely fatigued in the CBT group compared to UC[14].

Despite finding that the CBT intervention proved to be effective in reducing fatigue, the results of our study also implied that some participants in the UC group managed fatigue very well without a specific intervention for fatigue. Based on the finding that 65% of the patients in the UC group were not severely fatigued both before the start of cancer treatment (T1) and two months after cancer treatment was finished (T2), we conclude that these patients may not need a fatigue intervention. Therefore, it is not unreasonable to assume that about the same percentage of the CBT group could have recovered spontaneously from fatigue and may thus have been overtreated. Therefore an important question is who would benefit most from our CBT intervention? In other words what are the indicators for CBT for fatigue during cancer treatment? To answer these questions it is important to identify factors that moderated the effectiveness of CBT.

Although several RCTs demonstrated the effectiveness of a psychosocial intervention for fatigue during cancer treatment, there is a lack of interaction models of fatigue in controlled intervention studies. Using linear regression analysis, Armes et al., (2007) identified mood disturbance and comorbid disorders as confounders of fatigue[5]. Cohen et al., (2009) found treatment with chemotherapy predicted less change in fatigue[11].

The first aim of this study was to explore which baseline factors moderated the effect of our CBT intervention on fatigue measured two months after cancer treatment. Besides baseline characteristics such as age, gender, and type of cancer treatment, we explored whether any of the secondary outcomes of our RCT, such as functional impairments, psychological distress and quality of life before the start of cancer treatment moderated the effect of CBT on fatigue.

Long term effects of psychosocial interventions specifically for fatigue during cancer treatment are seldom demonstrated[4]. Of the eight psychosocial

intervention studies demonstrating effectiveness for fatigue during cancer treatment, only two RCTs demonstrated long term effectiveness at four and seven months follow-up[5, 11]. The other six studies had no follow-up assessment at all, or only a short follow-up period of about 4 weeks post-intervention. To our knowledge there is no RCT that examined the effect of a psychosocial intervention for fatigue during cancer treatment beyond seven months follow-up. Therefore the second aim of this study was to determine if the effect of CBT for fatigue during curative cancer treatment would be maintained after a year follow up. It was hypothesized that at one year follow up participants in the CBT group would be significantly less fatigued compared to the UC group.

MATERIALS AND METHODS

Patients and Procedure

Sample

Patients were recruited after being diagnosed with a primary tumour and scheduled to receive treatment with curative intent. Participants had to be between 18 and 75 years of age. Exclusion criteria were: comorbidity that could cause fatigue; receipt of psychiatric or psychological treatment in the preceding three months; and unable to speak, read or write Dutch. Patients were not included in the study if they reported severe fatigue for several years or indicated seeking treatment for pre-existing chronic fatigue. As this intervention study was aimed at fatigue in patients who would receive treatment with curative intent patients exhibiting disease progression or recurrence during the study were excluded. To minimize exclusion and drop-out during the study, patients with lung or head and neck cancers were not included.

Patients were recruited from the Radboud University Nijmegen Medical Centre and six regional hospitals from November 2005 thru August 2007. The ethics committees from all seven hospitals gave their approval for the study. Informed consent was obtained from all participating patients.

Design and Procedure

Eligible patients who agreed to participate completed the baseline assessment (T1) before the start of cancer treatment and were subsequently randomized to one of the three conditions: BNI, CBT or UC. The procedures for recruitment[16] and randomization[14] are described in detail elsewhere. The short term follow-up assessment (T2) took place six months after T1 and at least two months after cancer treatment was finished. Thus, participants who received surgery, chemotherapy or radiotherapy more than four months after T1 were assessed two months after these treatments were finished. The long term follow-up assessment (T3) was completed one year after T2. Between T2 and T3 participants were asked to complete the Checklist Individual Strength (CIS) at home each month.

INSTRUMENTS

Demographic, medical, and cancer treatment characteristics were gathered from all participating patients by self-report questionnaire. Information on the type of malignancy was provided by the patient's physician. The instruments used to assess the secondary outcomes in our RCT were used in this study for the exploratory moderator analyses.

Checklist Individual Strength[17, 18]. The Checklist Individual Strength (CIS) consists of four subscales: fatigue severity (8 items), concentration problems (5 items), decreased motivation (4 items) and decreased activity (3 items). Each item on the fatigue severity subscale is scored on a seven-point Likert scale. The CIS was completed at T1, T2, T3 and eleven times (monthly) between T2 and T3. The CIS is a well-validated instrument,[19, 20] sensitive to detect change and was used in previous research investigating fatigue in cancer patients[21-24]. Scores on the fatigue severity subscale (CIS-fat) range from 8 to 56. A score of 35 or higher indicates severe fatigue and a score between 27 and 34 indicates heightened fatigue.

The *Health Survey Short Form-36 (SF-36)* was used to assess functional impairment in different domains with eight multi-item scales: physical functioning, social functioning, role limitations due to physical health problems,

role limitations due to emotional problems, bodily pain, vitality, general health perceptions, and general mental health. The Dutch language version of the SF-36 has proven to be a practical, reliable, and valid instrument in the general population and in chronic disease populations[25].

The *Quality of Life Questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) version 3.0* contains five functioning scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), three symptom scales (fatigue, pain, nausea and vomiting) and one scale assessing global quality of life. The EORTC-QLQ C30 is an internationally validated questionnaire[26, 27].

The *Symptom Checklist-90* (SCL-90)[28] is a 90 item questionnaire consisting of eight subscales, anxiety, agoraphobia, depression, somatisation, obsessive-compulsive behaviour, interpersonal sensitivity, hostility and sleeping problems. The total score on the SCL-90 was used to measure psychological distress. The SCL-90 has good reliability and discriminant validity.

Statistical method

SPSS, version 16.0 (SPSS Inc, Chicago, IL) was used for all data analyses.

One significant difference (marital status) was found between the three study groups at baseline. Marital status was thus used as a covariate in all analyses.

This study was powered to demonstrate effectiveness of interventions[14], but not powered for moderator analyses. Powering for moderator analyses was not possible, as no moderators could be hypothesized beforehand. The moderator analyses were exploratory.

Moderator analysis

Two steps were taken to investigate which factors moderated the effect of CBT on fatigue. First, using Pearson correlations, it was tested if fatigue, quality of life, functional impairments and psychological distress in several domains at T1 significantly correlated with fatigue severity at T2. Second, linear regression analysis was performed to test for significant interactions. The method of Aiken and West (1991) was chosen to test for interactions. With this method potential

multicollinearity can be greatly reduced by centering variables[29]. Two dummy variables representing the intervention variable were entered in the first block. In addition, Z-scores for significantly correlated factors at T1 were entered in the first block. Z-scores of these factors at T1 multiplied by study condition were entered in the second block. Fatigue severity at T2 was the dependent variable.

Long term effect of CBT

To examine the long term effect of CBT, analysis of covariance (ANCOVA) was performed with fatigue severity as the dependent variable. Baseline scores were entered as covariates and study condition was used as a fixed factor. Contrast analyses were performed to compare the intervention groups (level 2 and 3) against usual care (level 1). Intention-to-treat analysis was used. A two-sided $p < .05$ was considered significant. To avoid overestimation of intervention effects, missing data on fatigue were replaced by the mean fatigue score of the UC group.

RESULTS

In total 395 eligible cancer patients were approached, and 155 refused to participate. The flow of participants through each stage of the study is illustrated in Figure 1. The recruitment procedure and the flow of participants through the study until T2 are described in more detail elsewhere[16]. After T2, 10 ineligible participants were excluded. When ineligible patients are randomized mistakenly into a trial, their data can be excluded post-randomization without risking bias[30]. These participants no longer met eligibility criteria because of, for example, disease progression or cancer recurrence during the study (see Figure 1).

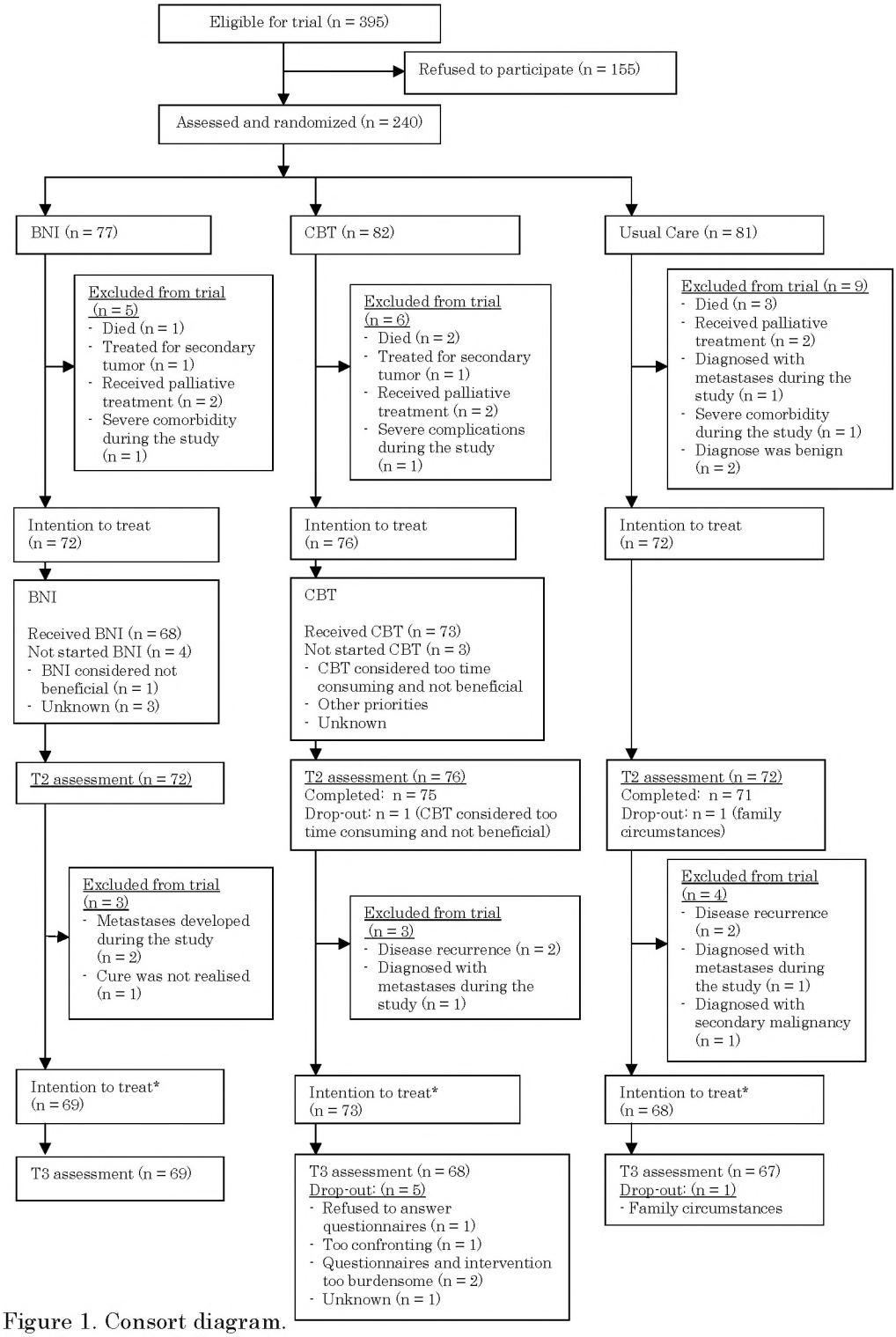

Figure 1. Consort diagram.
*intention to treat including drop-out

In total, the number of participants in this study was 210; 69 in the BNI group, 73 in the CBT group, and 68 in the UC group. Baseline characteristics are described in Table 1. There were no significant baseline differences between the three study groups except for marital status. More participants in the BNI group were married compared to the UC (p=.008).

Not all participants could be assessed before the start of cancer treatment because of the short time span between the diagnosis and start of treatment. Thus, 27% of the participants were assessed after surgery or start of hormone therapy, but always before beginning adjuvant chemotherapy or radiotherapy. T2 was completed by 156 participants 6 months after T1. Fifty-two participants, who received cancer treatment for a longer period completed T2 two months after cancer treatment was finished. Drop-out in this study was low. Two participants did not complete both T2 and T3, and an additional four participants did not complete T3.

Most participants (88%, n=185) completed all monthly fatigue assessments between T2 and T3 or missed one assessment at most. The median number of monthly assessments completed was 11. Eight percent of participants (n=17) did not complete any of the monthly fatigue assessments.

Table 1: Baseline characteristics for the three study groups

Characteristics		**Total (n= 210)**		**BNI (n=69)**		**CBT (n=73)**		**UC (n=68)**		**P-value**
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Sex	Male	74	35	26	38	26	36	22	32	.805
	Female	136	65	43	62	47	64	46	68	
Age (years)	Mean	56.5		57.2		55.6		56.9		.629
	(s.d.)	(10.9)		(10.1)		(11.6)		(11.1)		
Education	Mean	3.99		4.30		3.97		3.69		.109
(1=low – 7 high)	(s.d.)	(1.71)		(1.87)		(1.61)		(1.61)		
Marital status										
Married / cohabiting		169	81	62	90	58	80	49	72	**.031**
Other status		41	19	7	10	15	20	19	28	
Diagnosis (*)										
Breast cancer		102	49	34	49	35	48	33	49	.780
Prostate cancer		49	23	19	28	15	21	15	22	
Other tumors		59	28	16	23	23	31	20	29	
Gastrointestinal		27		7		8		7		
Urogenital		15		2		7		5		
Gynecological		12		6		3		3		
Lymphomas		6		1		3		2		
Sarcoma		3		0		1		1		
Melanoma		1		-		-		1		
Thyroid carcinoma		2		-		1		1		
Treatment type (**)										
Surgery		193	94	63	91	70	97	63	93	.311
Chemotherapy		62	30	20	29	25	35	17	25	.414
Radiotherapy		123	59	40	58	44	60	39	57	.933
Hormone therapy		64	31	22	32	20	29	22	32	.871

BNI: brief nursing intervention, CBT: Cognitive Behaviour Therapy, UC: usual care, T1: baseline assessment, T3: follow-up assessment.

(*) Two patients were diagnosed with both bladder and prostate cancer and were categorized as other tumors. One was assigned to the control group, the other to CBT.

(**) The total is more than 100%, as several combinations of treatment regimes were given to patients.

Moderator analysis

Results of the linear regression analysis showed that the interaction between CBT the EORTC-QLQ-C30 cognitive functioning subscale score was significant (Table 2). Specifically, patients in the CBT group who reported more impaired cognitive functioning at T1 had less fatigue at T2 compared to the UC group. CIS-fat scores (p=.810), SCL-90 total or subscale score (all p≥.194), and SF-36 subscale score (all p≥.139) at baseline did not significantly interact with CBT on fatigue at T2.

Table 2: Results of linear regression analyses, with significant moderators for the effect of CBT on fatigue.

Independent variables	B	Std. error	ß	P-value
Step 1				
(Constant)	21.99	1.02		**.000**
Condition CBT	-6.48	2.07	-.228	**.002**
Condition BNI	-2.48	2.07	-.087	.234
z-score CIS-fat	5.93	0.95	.433	**.000**
z-score EORTC-QLQ C30 CF	-.41	0.94	-.030	.666
Step 2				
(Constant)	22.27	1.01		**.000**
Condition CBT	-6.46	2.06	-.228	**.002**
Condition BNI	-2.92	2.08	-.102	.161
z-score CIS-fat	5.53	.952	.404	**.000**
z-score EORTC-QLQ C30 CF	-.55	1.08	-.041	.611
z-score EORTC-QLQ C30 CF x CBT	4.77	2.20	.175	**.031**

R^2 = .026 for Step 1; ΔR^2 = .251 for Step 2. A two-sided P-value < 0.1 was considered significant.

BNI: Brief Nursing Intervention, CBT: Cognitive Behaviour Therapy, CIS-fat: subscale fatigue severity of the Checklist Individual Strength, EORTC-QLQ C30 CF: Quality of life questionnaire subscale cognitive functioning

Long term effect of CBT

Results of the ANCOVA showed no significant differences between the CBT and UC groups on fatigue at T3 (see Table 3). Thus, the effect of CBT on fatigue was not maintained at one year follow-up.

Table 3: Means and standard deviation for fatigue at the monthly and T3 assessments, mean differences between the intervention and usual care groups, and p-values for the ANCOVA's

Assessment	Groups	N	Mean (s.d.)	F	Overall p-value	Mean difference	p-value*
CIS-fat 1	UC	62	25.0 (14.3)	2.677	.071		
	CBT	64	21.6 (12.6)			4.6	*.080*
CIS-fat 2	UC	62	25.0 (13.8)	1.443	.239		
	CBT	64	22.5 (13.3)			3.7	.274
CIS-fat 3	UC	59	27.3 (13.0)	2.441	.090		
	CBT	63	23.1 (13.4)			4.8	*.088*
CIS-fat 4	UC	61	26.4 (13.0)	2.730	.068		
	CBT	63	22.3 (13.1)			4.8	*.065*
CIS-fat 5	UC	61	25.6 (12.9)	2.148	.120		
	CBT	63	22.2 (13.0)			4.1	.162
CIS-fat 6	UC	60	24.4 (13.1)	4.627	**.011**		
	CBT	62	20.0 (12.8)			5.0	*.069*
CIS-fat 7	UC	60	24.0 (12.6)	4.266	**.015**		
	CBT	62	20.1 (13.4)			4.7	*.096*
CIS-fat 8	UC	60	23.9 (13.4)	1.616	.202		
	CBT	62	21.2 (13.3)			3.4	.378
CIS-fat 9	UC	60	23.6 (13.2)	0.456	.635		
	CBT	61	22.1 (13.7)			2.0	1.000
CIS-fat 10	UC	60	23.7 (13.7)	0.228	.797		
	CBT	61	23.3 (14.9)			0.9	1.000
CIS-fat 11	UC	58	23.0 (13.4)	1.290	.278		
	CBT	60	20.6 (12.7)			3.1	.476
T3	UC	67	24.2 (14.7)	1.273	.282		
	CBT	68	22.0 (13.5)			3.0	.472

BNI: Brief Nursing Intervention, CBT: Cognitive Behaviour Therapy, UC: Usual Care, CIS: Checklist Individual Strength, T1: baseline assessment, T2: follow-up assessment, CI: Confidence Interval.

*p-values of contrast analyses: first p-value is the difference between the BNI and UC, the second p-value is the difference between the CBT and UC. P-values <.100 in italics indicated a trend.

As fatigue was assessed monthly, exploratory analyses were performed to investigate how long the effect of CBT was maintained after T2. Results of these ANCOVA analyses and the differences between the UC group and the CBT intervention are shown in Table 3. At the sixth and seventh month post-T2 assessments a significant overall effect was found on fatigue. Until the seventh month the difference between the CBT and the UC groups had a p-value smaller than 0.100, indicating a trend. The mean monthly fatigue scores for the CBT and UC groups are also illustrated in Figure 2. This figure demonstrates that throughout the year between the T2 and T3 assessments fatigue in the CBT group remained lower than the UC group. Although fatigue had roughly a parallel course until the seventh month, after this point the differences between the CBT and the UC group disappeared. The difference between the BNI and the UC group on fatigue was not significant at T3 or any of the monthly assessments (all p=1.000).

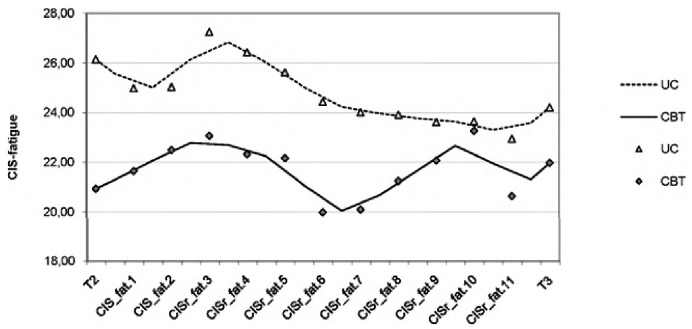

Figure 2. Mean fatigue scores from T2 to T3.

CIS-fatigue: fatigue severity, UC: usual care, CBT: cognitive behavior therapy, T2: post-intervention assessment, T3: one year follow-up assessment.

DISCUSSION

The first aim of this study was to determine who would benefit the most from cognitive behaviour therapy (CBT) for fatigue during curative cancer treatment, i.e., identify moderating factors. Our results showed that self-reported impairments in cognitive functioning before the start of cancer treatment moderated the effect of CBT on fatigue. Thus, participants who experienced more concentration and memory problems benefited more from CBT for fatigue. No other moderators of CBT including psychological distress, global quality of life, fatigue, pain, nausea and vomiting, or status in other domains of functioning could be identified in this study.

This exploratory study was a first step to determine clinical indications for CBT specifically aimed at fatigue during curative cancer treatment. Currently there are no other studies that determined which factors moderated the effect of a specific intervention for fatigue during cancer treatment. Although some intervention studies identified some factors influencing fatigue, such as receipt of chemotherapy, these factors were not moderators of CBT for fatigue. There could be other moderators for CBT for fatigue that weren't found in this exploratory study. Severe fatigue before the start of cancer treatment could be the first indicator for CBT, because fatigue at T1 correlated significantly with fatigue at T2. As there is also a group of participants who were severely fatigued at T2 but not at T1, we subsequently compared this group with participants who were not severely fatigued at T1 and T2. Making this comparison with patients for the UC and the BNI groups revealed that poorer general mental health and somatisation before the start of cancer treatment might be indicators for CBT.

In this study the long term effect of CBT for fatigue during curative cancer treatment was also investigated. Results showed that after one year follow-up (T3) no significant difference was found between the CBT and UC groups on fatigue. This result raised the question of how long the effect of CBT intervention on fatigue was maintained.

Subsequently the monthly fatigue assessments were studied. These analyses demonstrated a trend until 7 months post-intervention, but thereafter the positive effect of CBT on fatigue disappeared totally.

One reason why the effect of CBT for fatigue could not be maintained for longer than seven months post-intervention could be explained by the fact that fatigue may decline naturally after cancer treatment is finished[31]. Secondly, it was probably more difficult to demonstrate a long term effect because we overtreated our patients and this weakened the effects of our intervention. With a larger sample size the long term effect of CBT on fatigue might become significant. Clinically, it is probably more important that CBT should be offered to the patients who have the highest chance to benefit from CBT for fatigue. To our knowledge there is only one intervention RCT that has demonstrated a long term effect on fatigue at seven months follow-up[5]. An important difference between this study and our RCT is that in this study patients were only included when they reported significant fatigue. These results support our idea that severe fatigue might be a potential indication for CBT.

Our study had some limitations. First, the study was not powered for a moderator analysis, or powered to determine how long the effect of the CBT intervention was maintained. To power for these types of analyses many more patients would be required to participate. Therefore concentration and memory problems shouldn't be taken as firm indications for CBT for fatigue, because our analyses could only be exploratory.

Second, it should be noted that cognitive functioning was assessed using a questionnaire, the EORTC-QLQ C30. The subscale consists of two items in which patients are asked if they experience difficulties with concentrating and remembering. Scores on questionnaires assessing cognitive impairments are often inconsistent with neuropsychological test scores. Furthermore, it has been demonstrated that fatigued breast cancer survivors also have higher self reported concentration and memory problems[32].

So an interpretation of our finding could be that patients with more concentration and memory problems benefit more from CBT because they are more severely fatigued. The correlation between fatigue and both of these self reported complaints measured at baseline (T1) was rather high (r=.448).

Because of the short time span between diagnosis and treatment, 27% of the patients were not treatment naïve at the T1 assessment. However, 73% were treatment naïve and all patients were assessed before beginning adjuvant cancer treatment. The fact that about a quarter of our sample were not treatment naive at T1 most likely did not influence our results, because no significant difference was found between cancer treatment naïve patients and patients assessed before adjuvant therapy on fatigue.

Finally, not all participants volunteered to complete the monthly fatigue assessments between T2 and T3. This might raise the question of whether participants who completed the monthly assessments differed in their level of fatigue compared to participants who did not complete the monthly fatigue assessments. However, no significant difference on fatigue was found at T2 and T3 between participants who completed the monthly fatigue assessments and participants who completed none of the monthly assessments.

Despite these limitations this exploratory study revealed some important insights, relevant for future studies and practice. Patients who reported more concentration and memory problems before the start of cancer treatment benefited the most from CBT for fatigue. In the future it is important to avoid overtreatment with CBT for fatigue. If CBT for fatigue during cancer treatment can be indicated for a specific risk group the intervention will have a better chance to demonstrate solid long term effectiveness.

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Chapter 6

Development of fatigue in cancer survivors; a prospective follow-up study from diagnosis into the year after successful cancer treatment

Martine Goedendorp, Marieke Gielissen, Stans Verhagen, Gijs Bleijenberg.

ABSTRACT

Background. There is a lack of longitudinal studies investigating fatigue from prior to cancer treatment to long after successful cancer treatment. The aim of this prospective follow-up study was to determine the prevalence and predictors of persistent fatigue in cancer survivors in the first year after finishing cancer treatment.

Methods. One-hundred-thirty-six patients with various malignancies were assessed before (T1), shortly after curative cancer treatment (T2) and one year later (T3). Fatigue was assessed monthly between T2 and T3. Fatigue severity was measured using the subscale of the Checklist Individual Strength. Questionnaires were used to measure impaired sleep and rest, physical activity, social support, fatigue catastrophising, somatic related attributions regarding fatigue. Linear regression analyses were performed to identify predictors of persistent fatigue.

Results. In total 21% survivors had *severe* persistent fatigue over the last 6 months in the first year after cancer treatment (prostate cancer 3%, breast cancer 23%, and 34% in other malignancies). Fatigue at T1 or T2 predicted the severity of persistent fatigue. Analyses without fatigue showed that lower self-reported physical activity, impaired sleep and rest, fatigue catastrophising and somatic fatigue related attributions at T2, were associated with higher levels of persistent fatigue.

Discussion. Twenty-one percent of the survivors had severe persistent fatigue in the year after successful cancer treatment. Fatigue and cognitive behavioural factors predicted persistent fatigue in the year after cancer treatment. The implication is that cognitive behaviour therapy for postcancer fatigue, aimed at these perpetuating factors, could be offered from two months after successful cancer treatment.

INTRODUCTION

Almost all cancer patients experience fatigue during active treatment. Percentages of 90% or higher were found in several studies[1-4]. Unfortunately not all cancer survivors recover from fatigue, but 16-38% remain severely fatigued[5-11]. Fatigue in cancer survivors can become persistent for years with a major impact on daily functioning and quality of life[11-13]. Cancer patients experience significantly more fatigue compared to individuals without a history of cancer; before, during and also after cancer treatment[14, 15]. Data on the occurrence of fatigue in cancer patients are often based on cross-sectional studies. Longitudinal studies investigating the course of fatigue in cancer patients from end of cancer treatment are scarce. We do not know which patients are at risk for developing persistent fatigue after successful cancer treatment.

There are longitudinal studies that demonstrated that the level of fatigue decreases after successful cancer treatment[14, 16, 17], but there are also studies that found no change in fatigue over time[18, 19]. This inconsistency could be the result of methodological flaws, such as fatigue not being assessed frequently enough to detect fluctuations[15]. It is reasonable to assume that fatigue increases from pre-treatment to the post-treatment period[15, 20, 21]. However, to our knowledge there are no longitudinal studies that assessed cancer patients prior to treatment, when they were still treatment naïve, and continue to assess fatigue frequently after cancer treatment was finished.

Therefore in this prospective longitudinal study we assessed fatigue prior to the oncological treatment for cancer, assessed them again at least two months after the end of cancer treatment and followed these patients up during the next 12 months. There are only a few studies in treatment naïve cancer patients that

give clues to hypothesize which pre-treatment factors might predict persistent fatigue. One could speculate that depressive mood[22, 23], less physical activity[20, 23], impaired sleep and rest[23], and fatigue before initiation[22, 23] of cancer treatment might candidate predictors.

In long term cancer survivors, who finished cancer treatment longer than a year previously, there are at least six fatigue perpetuating factors[24, 25]; poor coping with cancer and treatment, excessive fear of disease recurrence, dysfunctional cognitions regarding fatigue, dysregulation of sleep, dysregulation of activity, low social support and negative social interactions. CBT for postcancer fatigue is directed at changing these fatigue perpetuating factors. It is not known if these six factors already assessed shortly after cancer treatment can also predict persistent fatigue. This has never been tested. If this is the case it is a plea that CBT for postcancer fatigue can be offered to fatigued cancer survivors shortly after cancer treatment.

Therefore we had three research questions: First, how many cancer survivors suffer from severe persistent fatigue in the year after finishing treatment? Secondly, which pre-treatment variables might predict persistent fatigue in the year after cancer treatment? Thirdly, do the known perpetuating factors of fatigue in long term cancer survivors also have a predictive value for persistent fatigue in the year after cancer treatment? More specifically, can the six fatigue perpetuating factors assessed shortly after cancer treatment predict persistent fatigue?

METHODS

Patients and Procedure

Sample

Patients were recruited after being diagnosed with a primary tumour and scheduled to receive treatment with curative intent. Participants had to be between 18 and 75 years. To minimize drop-out and exclusion during the study, patients with lung cancer, and head and neck cancer were not included. Patients were not included in the study when they indicated to be severely fatigued for

several years or indicated to seek treatment for chronic fatigue before cancer manifested. Other exclusion criteria were: co-morbidity that could cause fatigue; receiving psychiatric or psychological treatment in the preceding three months; not being able to speak, read or write Dutch.

Patients were recruited from the Radboud University Nijmegen Medical Centre and six regional hospitals from November 2005 until August 2007. The ethics committees from all seven hospitals gave their approval for the study. Informed consent was obtained from all participating patients.

Design and Procedure

Data of the current study were drawn from a larger intervention RCT. In the RCT cognitive behaviour therapy and a brief nursing intervention (BNI) for fatigue during curative cancer treatment were compared with usual care. For this study data were used of participants not influenced by the active arm of the RCT, thus data of participants assigned to the usual care group. In addition, data of participants assigned to the BNI were also used in the current study, because the BNI had no significant effect on fatigue compared to usual care[21].

Eligible patients were approached for the study by their physician or specialized nurse. Patients with initial interest received written information and supplementary information by telephone (by the researcher (MMG) or a test-assistant). Patients who agreed to participate completed the baseline assessment (T1) before the start of cancer treatment and were subsequently randomly assigned to one of the three conditions. The procedures for recruitment[23] and randomization[21] was described in detail elsewhere. The short-term follow-up assessment (T2) took place at least 2 months after cancer treatment, when patients recovered from the direct effects of cancer treatment. At the end of the T2 assessment participants received a folder with 11 fatigue questionnaires and 11 envelopes to cover the whole period of extended follow-up. Participants were requested to complete a fatigue questionnaire (the Checklist Individual Strength) each month and return it by mail. When participants forgot to send the questionnaire, they received reminding letters and when necessary a telephone call. One year after T2 the final follow-up assessment (T3) took place. Thus,

fatigue was assessed monthly for 12 times, from 2 months until 14 months after cancer treatment was finished.

INSTRUMENTS

Persistent fatigue

The last six monthly fatigue assessments were used to determine persistent fatigue. A period of 6 months was chosen in accordance with the definition of chronic fatigue[26]. Fatigue severity was measured with the subscale of the Checklist Individual Strength (CIS-fat)[27, 28]. The CIS-fat consists of eight items scored on a seven-point Likert scale. Scores range from 8 to 56. The CIS is a well-validated instrument[29, 30], was used in several studies investigating fatigue in cancer patients and is sensitive to detect change[25, 31-33]. The same operationalisation as used by Servaes et al., (2007) was used to determine the prevalence of severe persistent fatigue and the severity of persistent fatigue[34]. The severity of persistent fatigue was determined by calculating a mean CIS-fat score over the last 6 monthly fatigue assessments. When patients only had completed five fatigue assessments the mean of the 5 assessments was calculated. A mean score of 35 or higher over all 6 fatigue assessments indicated severe persistent fatigue.

Predictors of persistent fatigue

Demographic, medical, and cancer treatment related characteristics were gathered by self-report using questionnaires. Information on the type of malignancy was provided by the patient's physician. To assess the pre-treatment factors the same instruments were used as in our earlier study[23] being the following:

Depressive mood was measured with the subscale depression of the Symptom Checklist-90 (SCL-90). The SCL-90 is sensitive to change, has good internal consistency and the stability is high. In addition, the convergent, discriminant and predictive validity of the SCL-90 were demonstrated[35].

Impaired sleep and rest was measured with the subscale sleep/rest of the Sickness Impact Profile –8 (SIP). The SIP has a high reliability, good construct,

convergent and discriminant validity and was validated in the Dutch population[36, 37].

The level of physical activity before cancer treatment and fatigue one year before diagnosis (retrospective) were measured with 11-point numeric rating scales (NRS) ranging from zero to ten.

The following questionnaires were used to assess the six aforementioned perpetuating factors of fatigue. These instruments were also used in previous studies with long term cancer survivors[24, 25, 34, 38]. Coping with the cancer and treatment was measured with the Dutch version of the Impact of Event Scale (IES)[39-41]. Fear of disease recurrence was measured by two items of the cancer acceptance scale (CAS)[33]. Impaired sleep and rest shortly after cancer treatment was measured with the subscale sleep/rest of the Sickness Impact Profile –8 (SIP). The level of physical activity shortly after cancer treatment was measured with a NRS. Several dysfunctional cognitions regarding fatigue were measured. Somatic related attributions regarding fatigue were measured using the Causal Attribution List (CAL)[32], Self-efficacy regarding fatigue with the Self-Efficacy Scale (SES), and was based on the self-efficacy scale used in CFS patients[42], fatigue catastrophising with the Fatigue Catastrophising Scale (FCS)[43]. The Social Support Inventory was used to measure a discrepancy in social support (SSL-D) and, negative social interactions (SSL-NI)[44].

Statistical method

To determine if there were differences on demographic and cancer-related characteristics between participants with severe persistent fatigue and participants without severe persistent fatigue an independent sample *t*-test or a chi-square were performed. ANCOVA was used to determine if there was a significant difference on the severity of persistent fatigue between the types of malignancy. To explore which pre-cancer treatment factors predicted the severity of persistent fatigue correlations between above mentioned factors and the severity of persistent fatigue were calculated with Pearson. These tests were also performed for demographic factors. Subsequently significant factors were entered in a linear regression using enter method.

A linear regression analysis was performed to determine if the model of precipitating and perpetuating factors for fatigue in long term cancer survivors was applicable to cancer survivors in the year after cancer treatment. The aforementioned six perpetuating factors were entered in a linear regression using enter method, with the severity of persistent fatigue as dependent variable. A two-sided $p < 0.05$ was considered significant. SPSS version 16.0 (SPSS Inc, Chicago, IL) was used for all data analyses.

RESULTS

For the current study data from patients assigned to the BNI and UC from the larger RCT were used for analyses. Data from the active intervention arm (CBT) were not used. In total 158 participants completed the baseline assessment (T1), from which 81 were consequently assigned to the UC and 77 to the BNI. No significant differences were found between the UC and the BNI group on the baseline characteristics and fatigue at T1, T2, T3 or any of the 11 monthly fatigue assessments (all p>.154). Twenty-one ineligible participants were excluded after T1 (fourteen between T1 and T2, and seven between T2 and T3). The most frequent reason why these participants no longer met the eligibility criteria was because of disease progression. When ineligible patients are mistakenly randomized into a trial, their data can be excluded post-randomization without risking bias[45]. In total 137 participants curatively treated for cancer were followed.

Twelve of the 137 participants completed less than 5 of the 12 monthly fatigue assessments (T3 and the 11 monthly fatigue assessments) and were not used for data analyses. Of the 125 participant whose data were used for analyses 91% completed all last 6 fatigue assessments (n=117) or missed only one (n=8).

Baseline demographic and treatment related characteristics of the total group are described in Table 1. Most patients in our sample were diagnosed with breast cancer (48%) or prostate cancer (26%) and most patients received surgery (92%) and/or radiotherapy (59%). The mean age was 57 years.

Table 1: Data of demographic variables, diagnosis and presence of severe persistent fatigue.

Characteristics	**Total sample** n (%)	**Survivors without severe persistent fatigue** n (%)	**Survivors with severe persistent fatigue** n (%)	**Difference[1]** P
Total	125	99 (79)	26 (21)	
Sex				**.011**
Male	46 (37)	42 (91)	4 (9)	
Female	79 (63)	57 (72)	22 (28)	
Age (years)				.205
Mean	57.1	57.7	54.8	
s.d.	10.4	10.1	11.2	
Education level				.146
Lower education (≤ 4)	81 (65)	61 (75)	20 (25)	
Higher education (>4)	44 (35)	36 (86)	6 (14)	
Marital				.208
Married / cohabiting	102 (82)	83 (81)	19 (19)	
Other status (unmarried/divorced/ widowed)	23 (18)	16 (70)	7 (30)	
Diagnosis *				**.007**
Breast cancer	61 (48)	47 (77)	14 (23)	
Prostate cancer	32 (26)	31 (97)	1 (3)	
Other tumours	32 (26)	21 (66)	11 (34)	
Gastrointestinal	14 (11)		3	
Urogenital	5 (4)		2	
Gynaecological	7 (6)		3	
Lymphomas	3 (2)		1	
Sarcoma	1		1	
Melanoma	1		1	
Thyroid carcinoma	1		0	
Cancer treatment **				
Surgery	115 (92)	90 (78)	25 (22)	.380
Radiotherapy	74 (59)	62 (84)	12 (16)	.128
Chemotherapy	32 (26)	22 (69)	10 (31)	.091
Hormone therapy	41 (33)	32 (78)	9 (22)	.825

* One patient was diagnosed with both bladder and prostate cancer and was categorized as urogenital tumours of the other tumours.

** The total is more than 100%, as several combinations of treatment regimes were given to patients.

Severe persistent fatigue

How many cancer survivors suffer from severe persistent fatigue in the year after finishing treatment?

Results showed that 21% of the total sample had severe persistent fatigue during the last 6 months of the first year after finishing cancer treatment. The prevalence of severe persistent fatigue was 3% in prostate cancer survivors, 23% in breast cancer survivors, and 34% in participants who were successfully treated for other malignancies. Two significant differences were found on demographic and cancer related characteristics between cancer survivors with or without severe persistent fatigue: diagnosis and sex. Participants who were male and participants who were curatively treated for prostate cancer had significantly less often severe persistent fatigue, compared to women and participants treated for other malignancies (see Table 1).

Predictors of persistent fatigue in the year after successful cancer treatment.

Which pre-treatment factors predict persistent fatigue?

Five factors assessed before the start of cancer treatment correlated significantly with persistent fatigue in cancer survivors: depressive mood ($r=.470$, $p=.000$), impaired sleep and rest ($r=.218$, $p=.015$), higher levels of retrospectively reported fatigue one year before the diagnosis ($r=.560$, $p=.000$), higher levels of fatigue at T1 ($r=.562$, $p=.000$) and lower levels of self-reported physical activity before the start of cancer treatment ($r=-.187$, $p=.037$). The linear regression analysis with pre-treatment factors and cancer-related factors entered as independent factors showed that higher levels of fatigue at T1 and higher levels of fatigue reported one year before diagnosis predicted significantly higher levels of persistent fatigue in cancer survivors (Table 2).

Table 2: Results of linear regression analysis of pre-treatment and cancer-related factors on persistent fatigue

Persistent fatigue	Unstandardized Coefficients			t	p	95% CI	
	B	SE	Beta			Lower bound	Upper bound
(Constant)	6.98	4.54		1.54	.127	-2.01	16.0
sex	-.820	3.51	-.031	-.233	.816	-7.78	6.14
Prostate cancer (dummy)	-3.35	3.19	-.115	-1.05	.296	-9.66	2.97
Breast cancer (dummy)	.630	2.76	.025	.228	.820	-4.84	6.10
NRS – physical activity one year before diagnosis	.240	.372	.050	.644	.521	-.497	.977
NRS - fatigue one year before diagnosis	2.08	.453	.366	4.59	**.000**	1.18	2.97
CIS-fatigue T1	.321	.122	.320	2.62	**.010**	.079	.564
SCL-90 depression T1	.254	.147	.155	1.74	.085	-.036	.545
SIP- sleep/rest T1	-.011	.019	-.049	-.558	.578	-.049	.028

Note R2=.460

NRS: Numeric Rating Scale, CIS: Checklist Individual Strength, SCL-90: symptom checklist 90, SIP: Sickness Impact Profile, T1: baseline assessment before the start of cancer treatment.

Do the known perpetuating factors of fatigue now assessed shortly after cancer treatment predict persistent fatigue?

The linear regression analysis with the six aforementioned perpetuating factors assessed shortly after cancer treatment (at T2) entered as independent variables showed that stronger somatic attributions regarding fatigue, more fatigue catastrophising, a lower level of self-reported physical activity and more impaired sleep, were factors significantly predicting higher levels of persistent fatigue (Table 3). This linear regression analysis was performed without fatigue at T2 as a predictor, because the level of fatigue at T2 significantly predicted persistent fatigue (beta= .484, p=.000).

Table 3: Results of linear regression analysis of perpetuating factors at T2 on persistent fatigue

Persistent fatigue	Unstandardized Coefficients			t	p	95% CI	
	B	SE	Beta			Lower bound	Upper bound
(Constant)	7.81	9.34		.836	.405	-10.7	26.3
Social support (SSL-I)	-.020	.060	-.023	-.334	.739	-.140	.100
Discrepancy social support (SSL-D)	.019	.120	.012	-.158	.875	-.219	.257
Negative interactions SSL-NI	.541	.364	.103	1.49	.140	-.179	1.26
Physical activity (NRS)	-1.15	.394	-.214	-2.91	**.004**	-1.93	-.366
Impaired sleep and rest (SIP-SR)	.035	.016	.167	2.20	**.030**	.003	.066
Somatic attributions (CAL)	.915	.443	.170	2.07	**.041**	.037	1.79
Fear of disease recurrence (CAS)	-.210	.684	-.027	-.307	.759	-1.57	1.14
Coping with cancer (IES)	.111	.081	.123	1.36	.177	-.051	.272
Self-efficacy (SES)	-.057	.189	-.021	-.301	.764	-4.31	.318
Fatigue catastrophising (FCS)	8.11	2.59	.294	3.13	**.002**	2.97	13.2

Note R2=.580.

SSL-I: Sonderen Social Support Inventory, SSL-D: discrepancy in social support, SSL-NI negative social interactions, NRS-PA: Numeric Rating Scale-physical activity, SIP-SR; Impaired sleep & rest, CAL: Causal Attribution List, CAS: cancer acceptance scale, IES: Impact of Event Scale, SES: Self-Efficacy Scale, FCS: Fatigue Catastrophising Scale.

DISCUSSION

Persistent fatigue, established with monthly assessments was previously not investigated in the first year after successful cancer treatment. To our knowledge this is the first prospective longitudinal study that assessed patients treated for various malignancies before and shortly after cancer treatment and followed the course of fatigue monthly for a year after successful cancer treatment. Our study revealed three important issues. First, 21% of the cancer survivors were severely persistent fatigued in the year after cancer treatment. Second, fatigue before the start of the oncological treatment was the only risk factor found for persistent fatigue. Third, the known perpetuating factors for fatigue assessed shortly after cancer treatment had predictive value for persistent fatigue in the year after successful cancer treatment.

First, our results showed that 3% of the survivors of prostate cancer, 23% of the breast cancer survivors, and 34% of the participants successfully treated for other tumours were severely persistent fatigued. The finding that prostate cancer patients had less fatigue than breast cancer patients was also found in elderly cancer patients who were followed for a year[46]. There are indications that the factors sex and age can be relevant. Within a large sample of survivors of Hodgkin lymphoma's an effect of sex and age was found on fatigue[47]. There is also evidence that patients who receive an intensive oncological treatment are more likely to remain persistently fatigued[48, 49]. For example, it has been found that fatigued breast cancer survivors were more likely to have been treated with a combination of chemotherapy and radiation therapy or with chemotherapy alone as adjuvant treatment than non-fatigued breast cancer survivors who received only radiation therapy[48]. There is also evidence that patients who did not have to undergo adjuvant treatment at all, and for whom surgery was without complications experienced less often persistent fatigue[49]. However, in our study it was not possible to draw separate conclusions about the effect of cancer treatment, diagnosis, age or sex on severe persistent fatigue, because further subgroup analyses were not possible due to the small numbers. The diagnosis groups were inherently related to the malignancy and consequently on types of

treatment, sex and age. For example, prostate cancer is confined to older men, who don't receive chemotherapy as curative cancer treatment.

Another limitation of our study is that the sample did not reflect the incidence of malignancies in the Dutch population. In the Dutch population breast cancer is the most common type of cancer, followed by colorectal cancer, lung cancer, skin cancer and prostate cancer, but in our sample patients with breast cancer and prostate cancer were the largest groups. Thus the finding that 21% of our sample had severe persistent fatigue can't be generalized to the population of all cancer survivors in the Netherlands. As it was not a population study the results on the prevalence of severe persistent fatigue are difficult to generalize to other cancer survivors. However, our percentage of persistent fatigue in the breast cancer survivors is surprisingly similar to percentages found in other studies. We found that 23% of the breast cancer survivors had severe persistent fatigue. This percentage is within the same range as reported in longitudinal studies in breast cancer survivors long after cancer treatment (21-24%)[34, 50].

Our exploratory analysis of predictors showed that fatigue before the start of oncological treatment was the strongest predictor for persistent fatigue in the year after cancer treatment. This strong association between fatigue during several phases of cancer treatment and thereafter was also found in other studies[47, 51, 52]. The current study suggests that cancer-related factors are no strong risk factors in developing persistent fatigue. This was also found in other studies with long term cancer survivors[16, 34]. Although other studies found that depression was related to persistent fatigue long after cancer treatment [5, 7] we did not find that depressive mood was a predictor of persistent fatigue in our multivariate analysis.

This study showed that the known perpetuating factors for fatigue in long term cancer survivors also predict persistent fatigue in the year after successful cancer treatment when assessed shortly after cancer treatment. Stronger somatic attributions regarding fatigue, more fatigue catastrophising, a lower level of self-reported physical activity and more impaired sleep (more specifically, difficulties sleeping at night, sleeping and resting more during the day) could be identified

prospectively as factors related to persistent fatigue. Several other studies also found these fatigue perpetuating factors in long term cancer survivors[11, 12, 32, 53, 54]. In the current study these factors were already identified shortly after cancer treatment, when the acute effects of cancer treatment had subsided. The fact that not all six factors significantly predicted persistent fatigue in our study might be explained by the fact that the number of patients with severe persistent fatigue was rather low.

Other limitation of this study should also be acknowledged. The data were used from participants who received usual care only and from participants who received a brief nursing intervention (BNI) aimed at fatigue. Using the data both conditions was justified to our opinion, as the BNI had no effect on fatigue compared to usual care[21] and no significant differences were found between the two groups on the baseline characteristics and fatigue at any of the other assessments.

Furthermore, not all participants completed all monthly fatigue assessments between T2 and T3. This might raise the question if participants who adhered to completing the monthly assessments differed in the level of persistent fatigue compared to participants who did not adhere. However, no significant difference on fatigue was found at T2 and T3 between participants who were included in the data analyses (n=125) and participants who were not included in the data analyses (n=12).

In our study we determined persistent fatigue over the last 6 months of our data collection. This period was chosen as the definition of chronic fatigue states that severe fatigue should be present for at least 6 months[26]. One could reason that the results might be different when a different time frame was chosen. However, we found the same results when persistent fatigue was determined over a longer period of time, suggesting that the results are stable.

The clinical implications of our findings are the following. It is important to identify patients at risk shortly after cancer treatment is finished. Based on our results, patients with severe fatigue before and shortly after cancer treatment are probably the patients at risk to develop severe persistent fatigue. CBT for postcancer fatigue proved to be an effective treatment for severely fatigued long

term cancer survivors[24, 25]. The current study found that the perpetuating factors of fatigue assessed shortly after cancer treatment had predictive value for persistent fatigue. So it would be advisable to offer CBT for postcancer fatigue to cancer patients suffering from severe fatigue shortly after cancer treatment is finished.

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Chapter 7

General discussion: learning points

In the studies of this dissertation patients who just received the diagnosis cancer were followed until fourteen months after successful cancer treatment for various malignancies. Patients were assessed before start of the oncological treatment, shortly after the oncological treatment and one year later. In the year after cancer treatment fatigue was assessed monthly for a year. During the curative cancer treatment patients participated in a randomized controlled trial (RCT) to evaluate two interventions for fatigue and compare these with usual care. Our studies revealed new and even some unexpected insights. In this chapter we will start with briefly repeating the results of the intervention RCT, because several new questions rose as a consequence of this RCT. Thereafter we will describe the new findings in each paragraph. We will describe why a particular research question rose, we will present the findings, and we will place the results in view of the current literature. We will finish each paragraph with the conclusions and clinical implications. In this chapter we will inevitably repeat some findings from the previous chapters, but we will try to place the findings in a broader perspective and will use updated literature. We will not describe the used methods in detail here.

EVALUATING STRATEGIES TO MANAGE FATIGUE DURING ACTIVE TREATMENT AND TO PREVENT PERSISTENT FATIGUE AFTER CURATIVE TREATMENT FOR CANCER.

Fatigue is one of the most common and distressing symptoms in cancer patients, and when severe it has a large impact on daily functioning and quality of life[1-3]. Almost all cancer patients experience fatigue during active cancer treatment. Prevalences of 90% or higher were even reported[4-8]. Fatigue continues to be problematic for many patients after cancer treatment is finished. To reduce fatigue after cancer treatment it might be important to intervene as early as

possible. Therefore we wanted to intervene already during active cancer treatment. There are several psychosocial interventions given to patients during cancer treatment (see a systematic review in chapter two). However, the assessments of these RCTS were seldom performed at clinically relevant moments, but incongruent with the phase of the oncological treatment. For example, in several intervention studies for fatigue part of the patients still continued receiving treatment for cancer after the post-intervention assessment[9-12]. This design is suitable to investigate the efficacy of an intervention, but is unsuitable to evaluate whether the intervention had effect at the moment when the oncological treatment is finished. To our best knowledge there is no fatigue intervention RCT during cancer treatment that assessed patients at clinical relevant moments; before the start of cancer treatment and shortly after finishing cancer treatment.

In the current RCT two interventions for fatigue during cancer treatment were compared to usual care (UC). The first intervention was a minimal intervention performed by nurses. The brief nursing intervention (BNI) focused only on regulating and increasing physical activity. The second intervention was cognitive behaviour therapy (CBT). This intervention was also focused on physical activity, but additionally changed fatigue related cognitions and behaviours, such as dysfunctional cognitions about fatigue, a distorted sleep-wake rhythm, and dysfunctional coping with the consequences of having cancer. The main aim of this intervention RCT was, first to reduce fatigue shortly after successful cancer treatment and, secondly to prevent patients from becoming chronically fatigued long after cancer treatment.

Patients were recruited shortly after the diagnosis cancer and assessed before the start of cancer treatment with curative intent (see chapter three). In total 240 patients were assessed at baseline (T1) and consequently they were randomly assigned to one of the three conditions. The post-intervention assessment (T2) was initially planned six months after T1. If patients received surgery, chemotherapy or radiotherapy in the fifth or sixth month, they were assessed two months after these treatments were finished. Thus T2 took place at least two months after cancer treatment was finished. The follow-up assessment

(T3) took place one year after T2, and between T2 and T3 fatigue was assessed monthly with the Checklist Individual Strength[13, 14], a well validated instrument[15, 16]. Thirty patients were excluded post-randomization because of disease progression or other reasons.

Our results showed that CBT significantly reduced fatigue assessed shortly after cancer treatment was finished. Also significantly fewer participants were severely fatigued from two months after cancer treatment, demonstrating the clinical relevance of this outcome. The BNI did not reduce fatigue compared to UC. After one year follow-up the effect of CBT were not significant anymore. Further analyses showed that the CBT nearly had a significant effect on fatigue until seven months post-intervention, but thereafter the effect diminished. Overtreatment is probably one of the main reasons why we could not find an effect anymore of CBT at one year follow-up. This will be explained in the following paragraphs.

The current RCT did demonstrate the effectiveness of CBT for fatigue during curative cancer treatment. Other important findings, the clinical implications of our findings, and comparisons of our RCT with other intervention studies are described in the following paragraphs.

SURPRISINGLY LARGE NUMBERS OF CANCER PATIENTS ARE ALREADY SEVERELY FATIGUED BEFORE INITIATION OF CANCER TREATMENT.

Almost all patients experience fatigue during active cancer treatment[17]. Generally it is thought that there are probably three factors contributing to fatigue during this period; 1) the cancer itself, 2) the oncological treatment against cancer and side-effects, 3) the associated distress, such as regular visits to the hospital or concerns about the future. Therefore it was expected that the level of fatigue in cancer patients before the start of cancer treatment would be low. However, there was no scientific evidence for these assumptions. Before the current study was performed there were three studies that indicated that fatigue could be a relevant issue prior to cancer treatment[18-20]. One study found that lung cancer patients before surgery reported significantly more fatigue compared with age-matched control subjects[19]. Two other studies concluded that fatigue

contributed to increased distress and impaired quality of life in newly diagnosed cancer patients[18, 20]. There were no studies that focused on the occurrence and related factors of fatigue in treatment naïve cancer patients. Our first aim was to determine how many cancer patients reported severe fatigue after being diagnosed, but before initiation of any medical treatment for cancer.

Patients were included in this study after being diagnosed with a primary tumour and before initiation of treatment with curative intention. Treatment could be surgery, radiotherapy, chemotherapy, or a combination of these. Patients could additionally receive hormone therapy. Detailed information about inclusion criteria and recruitment procedure is described in chapter three.

In total 24% patients appeared to be severely fatigued prior to cancer treatment, varying between diagnoses. The presence of severe fatigue was the lowest in patients with prostate cancer (14%), but higher in breast cancer patients (20%), and the highest in gastrointestinal cancer patients (28%)[21].

Our study sample did not reflect the incidence and types of cancer in the Dutch population. In the Netherlands breast cancer is the most common type of cancer, followed by colorectal cancer, lung cancer and prostate cancer. In our sample more participants were diagnosed with prostate cancer, with low levels of fatigue, and fewer participants were diagnosed with gastro-intestinal cancer, with high levels of fatigue. So the found prevalence of 24% severe fatigue could be an underestimation. A recently published study in a group of older cancer patients prior to surgery for various malignancies confirmed our findings[22]. In this study 28% of the cancer patients had moderate to severe fatigue (a score between 4 and 10 on the brief fatigue inventory[23]) two weeks before planned surgery for mostly breast cancer, gastrointestinal cancer and genitourinary cancers. Furthermore this study found that moderate to severe fatigue prior to surgery increased the likelihood of having a post-surgical complication[22]. This indicates that fatigued cancer patients starting with oncological treatment might be a vulnerable group for ongoing problems. Unfortunately in our study we did not measure complications of surgery or adjuvant treatment.

In the literature no indication can be found that postcancer fatigue is associated with type of malignancy[17]. However, in the current study, in

treatment naïve cancer patients, there is evidence that fatigue differs between diagnosis groups. The number of severely fatigue treatment naïve cancer patients was the lowest in patients diagnosed with prostate cancer. A more recent study even found no significant difference in fatigue between men with prostate cancer compared to a non-cancer matched control group[24]. Prostate cancer is often diagnosed after a screening test, and less often because patients seek treatment for symptoms. Consequently patients probably don't have symptoms of fatigue at this stage. Fatigue appears to be higher in patients who are diagnosed after presenting symptoms. For example, many patients get diagnosed with colon cancer after consulting with their physician when having symptoms, such as constipation or blood in their stools. Our study showed that 28% of patients with gastrointestinal cancer were severely fatigued.

To conclude; it is generally thought that fatigue arises when cancer patients start with oncological treatment. Consequently, we expected that fatigue levels would be low before initiation of treatment, but there were hardly any studies that investigated fatigue in treatment naïve cancer patients. Contrary to what was expected our study revealed that rather large numbers of cancer patients were already severely fatigued before the start of cancer treatment. The presence of severe fatigue varied between the diagnosis groups, the lowest in patients with prostate cancer.

NOT TYPE OF MALIGNANCY BUT PSYCHOLOGICAL AND BEHAVIOURAL FACTORS CONTRIBUTE TO SEVERE FATIGUE BEFORE INITIATION OF CANCER TREATMENT.

As the first study showed that about a quarter of the participants had severe fatigue before initiation of cancer treatment we subsequently investigated which factors were associated with severe fatigue at this stage. To our knowledge this has never been done before. We explored if type of malignancy, depressive mood and anxiety, sleep disturbances, pain, self reported physical activity and pre-existing fatigue were associated with severe fatigue in treatment naïve cancer patients.

Although statistically significant differences were found in the prevalence of severe fatigue between various malignancies in univariate analysis, results of multivariate analyses showed that four other factors were more strongly related to severe fatigue prior to cancer treatment. These factors were higher levels of fatigue one year before diagnosis, currently lower levels of self reported physical activity, depressive mood and more impaired sleep and rest[21]. Thus, our findings demonstrated that psychological and behavioural aspects were more strongly related to severe fatigue before cancer treatment, than type of malignancy.

THERE IS NO SOLID EVIDENCE FOR THE EFFECTIVENESS OF INTERVENTIONS NOT SPECIFIC FOR FATIGUE DURING CANCER TREATMENT.

Efforts to manage fatigue in cancer patients should first focus on treating somatic causes for fatigue, such as anaemia. Treating somatic causes of fatigue is a discussion in itself, but lies beyond the scope of this thesis. Often no other somatic causes can be identified other than the disease itself and the oncological treatments. Psychosocial interventions have been regarded as one of the most promising interventions to manage fatigue in cancer patients, but there was no systematic review evaluating the effectiveness of psychosocial interventions for fatigue during active cancer treatment. We investigated if psychosocial intervention in general were effective in reducing fatigue, and if specific types of interventions were the most effective in reducing fatigue during cancer treatment.

The systematic review, performed until September 2008, identified 27 RCTs of which only seven studies reported significant effects of the psychosocial intervention on fatigue. Thus, in general there was limited evidence that psychosocial interventions during cancer treatment were effective in reducing fatigue. More specifically, we found no solid evidence for the effectiveness of interventions not specific for fatigue. These are interventions aimed at improving psychological distress, mood and physical symptoms. Contrary to this, psychosocial interventions specifically for fatigue can be seen as a promising type of intervention. The phrase 'promising intervention' was chosen because the

number of RCTs is still limited. The effectiveness of interventions specific for fatigue was significantly higher (80%) compared to interventions not specific for fatigue (14%). In five studies the interventions were specifically focused on fatigue, with four being effective. The five interventions, of which four were effective, were brief, consisting of three individual sessions, provided by (oncology) nurses. In general, during these interventions participants were educated about fatigue, were taught in self-care or coping techniques, and learned activity management.

A literature update of psychosocial interventions for fatigue during cancer treatment.

In the following paragraphs we will update the review on psychosocial interventions for fatigue during active cancer treatment. We would like to confirm if psychosocial interventions specifically for fatigue are the most effective type of intervention in reducing fatigue. Our aim is also to confirm that psychosocial interventions not specifically aimed at fatigue are rarely effective in reducing fatigue.

Between September 2008 and December 2010 five new RCT studies, including our own, were published evaluating psychosocial interventions during cancer treatment[9, 10, 25-27]. Two RCTs demonstrated the effectiveness of interventions specifically aimed at fatigue. The other three RCTs evaluated interventions not specifically aimed at fatigue, but these interventions were not effective in reducing fatigue.

We describe each of the five intervention studies in brief below. First, we discuss the intervention RCTs *specifically* aimed at fatigue. One of the two intervention studies *specifically* aimed at fatigue during cancer treatment was our own intervention study. This study is described in detail in chapter four.

In the second RCT a psychological intervention combining cognitive–behavioural therapy and hypnosis (CBTH) for fatigue was evaluated in breast cancer patients who received radiotherapy (n=42)[27]. The CBTH intervention consisted of a hypnosis session and a session teaching participants CBT skills on the pre-radiotherapy planning session. Participants received a CD with hypnosis

intervention, a CBT workbook to review and worksheets. During radiotherapy the therapist met twice a week for a total of 12 sessions to go over the worksheets. Assessment took place weekly during the intervention and radiotherapy. A significant effect of the CBTH intervention on the rate of change in fatigue was found, such that on average, CBTH participants' fatigue did not increase over the course of treatment, whereas control group participants' fatigue increased linearly[28]. Cohen's d of .82 was reported, which indicates a large effect size.

The following three RCTs of Molassiotis et at., (2009), Berger et al. (2009), and Barsevick et al., (2010) evaluated psychosocial interventions *not specifically* aimed at reducing fatigue during cancer treatment. Molassiotis et at., (2009)[26] assessed the effectiveness of a symptom-focused home care program by a nurse compared with standard care. The intervention was given during the six cycles of chemotherapy in patients with a diagnosis of colorectal (n = 110) and breast (n = 54) cancer who were receiving oral chemotherapy (capecitabine). Significant improvements in symptoms of oral mucositis, diarrhea, constipation, nausea, pain, fatigue, and insomnia were observed in the home care group in comparison with the control group. However, the improvement on fatigue was only significant during the initial two cycles, but not thereafter. Thus the intervention only had a temporarily effect on fatigue. The effect size of this study could not be calculated, because only means were reported.

Berger et al. (2009) evaluated a behavioural therapy consisting of an individualized Sleep Promotion Plan, including modified stimulus control, modified sleep restriction, relaxation therapy, and sleep hygiene. This intervention was given to breast cancer patients receiving adjuvant chemotherapy treatments (n=219). Results showed that sleep quality improved shortly after the intervention[10] and after one year follow-up[29] compared to controls who received healthy eating information and attention. There were no differences between the two groups on any of the fatigue assessments. Thus, there were no short term or long term effects on fatigue.

The RCT of Barsevick et al., (2010)[9] evaluated the efficacy of an energy and sleep enhancement intervention to relieve sleep disturbance and fatigue and

improve health-related functional status in cancer patients receiving chemotherapy (n=153). The intervention had no effect on any of the outcomes including fatigue.

To summarize, after September 2008 five new RCTs were published that evaluated psychosocial interventions for fatigue during cancer treatment. The three interventions *not* specifically aimed at fatigue did not have an effect on fatigue, although one intervention reduced fatigue temporarily. Both interventions specifically aimed at fatigue were effective. These RCTs confirm our previous conclusions that the psychosocial interventions specifically aimed at reducing fatigue during cancer treatment have the highest probability of being effective. There is no solid evidence for the effectiveness of interventions not specific for fatigue.

NOT ALL CANCER PATIENTS NEED AN INTERVENTION FOR FATIGUE DURING ACTIVE CANCER TREATMENT.

As nearly all cancer patients will experience fatigue during active cancer treatment[17], we assumed that most patients could benefit from an intervention for fatigue. Therefore in the design of the RCT it was decided to offer the interventions to all recently diagnosed cancer patients who were going to receive treatment with curative intent. Although fatigue was not assessed during active cancer treatment, results of the RCT showed that the number of patients with severe fatigue increased in the UC group as expected. The frequency of severe fatigue was 19% before the start of cancer treatment in the UC group, and increased to 31% at two months after cancer treatment was finished (see chapter four). Furthermore we found that in the UC group 65% were not severely fatigued at T1 or T2. Thus these patients managed fatigue themselves without a specific intervention. It is reasonable to assume that about the same percentage in our CBT condition also didn't need this intervention[25]. Although we demonstrated the effectiveness of CBT for fatigue during cancer treatment, offering all cancer patients CBT intervention did probably lead to overtreatment.

WHICH INDICATIONS CAN BE FOUND FOR CBT FOR FATIGUE DURING CURATIVE CANCER TREATMENT?

Because we probably over treated cancer patients with CBT for fatigue during cancer treatment this raised the question who would benefit the most from CBT, or in other words what are the indicators for CBT for fatigue during cancer treatment? Therefore we explored which factors moderated the CBT intervention, using interaction models. Our results showed that participants who experienced more concentration and memory problems benefited more from CBT for fatigue. It should be noted that this exploratory study and that it is possible that there could be other moderators that weren't found in this study because of a lack of power. In a previous study it was demonstrated that fatigued cancer survivors also have higher scores on self reported concentration and memory problems[30]. So an interpretation of our findings could be that patients with more concentration and memory problems benefit more by CBT because they are more severely fatigued.

INCREASING PHYSICAL ACTIVITY IS NOT A MEDIATOR IN REDUCING FATIGUE DURING ACTIVE CANCER TREATMENT.

It is generally assumed that exercise is beneficial for cancer patients, but the effect on fatigue is not clear-cut. Some reviews found no effect of exercise on reducing fatigue[31, 32]. In addition, some exercise studies did not find an effect on fatigue, even though physical fitness increased[33-35].

Exercise interventions aiming to reduce fatigue are based on the assumption that a lack of physical activity and deconditioning during cancer treatment can worsen fatigue[36]. When patients are diagnosed and treated for cancer, their activity pattern changes and they become physically less active, possibly leading to deconditioning[37]. This can result in a downward spiral. Patients with decreased physical condition become more easily fatigued, and when patients experience fatigue they react by becoming physically even less active. Exercise can break this cycle by increasing physical condition and physical activity.

Physical activity was an important part of both interventions of our RCT. The BNI focused only on physical activity and it was one of the elements in the CBT for fatigue during cancer treatment. Patients were advised to be as active as possible and subsequently to increase their physical activity level stepwise; they were encouraged to maintain it. The assumption that increasing physical activity reduces fatigue is widespread, but the mediating role of physical activity in interventions aiming to reduce fatigue during cancer treatment had never been demonstrated. We investigated if the reduction in fatigue induced by the CBT was mediated by increased physical activity.

To test for mediation, physical activity was assessed with actigraphy (actometer) and questionnaires. We found that there was no effect of the interventions on physical activity. This already showed that mediation was absent. Further analyses showed that the reduction in fatigue realized by CBT could not be explained by an increase in physical activity. Contrary to our initial expectations increased physical activity did not mediate the reduction in fatigue realized by CBT, whether physical activity was measured with actigraphy or with self report measures.

One could reason that the mediating role of physical on fatigue could not be demonstrated, because the interventions were not successful in increasing physical activity. It could be that physical activity increased temporarily during the interventions, but this was not assessed in our study. More importantly our study did show that without a lasting increase in physical activity the CBT significantly reduced fatigue.

Increasing and regulating physical activity is also one of the elements of CBT for postcancer fatigue and chronic fatigue syndrome. The mediating role of physical activity was also investigated in these types of CBT. These studies also demonstrated that a lasting increase in physical activity was not necessary to reduce fatigue in patients with postcancer fatigue and chronic fatigue syndrome[38] (Gielissen et al., submitted).

The results of two recent meta-analyses on exercise studies can be seen as support of our finding that increasing physical activity is not a necessity to reduce fatigue during cancer treatment. Speck et al., (2009) investigated the

effects of physical activity trials during and post cancer treatment on various health outcomes. They found that 15 trials assessed the effect of exercise on fatigue, of which six trials found a significant effect. The strength of the effect sizes were highly heterogeneous probably because the physical activity interventions have not targeted participants on a needs-based approach. The meta-analysis demonstrated no significant effect on fatigue of exercise during cancer treatment[39]. Another meta-analysis identified 18 RCTS, 12 in patients with breast cancer, four in prostate cancer patients and two in other cancer patients. They found a significant reduction on fatigue of exercise during breast cancer treatment, compared with no exercise, but in general the effect sizes were small. Subgroup analyses even showed that home-based exercise did not lead to a significant reduction in fatigue[40]. If increasing physical activity would be the mediator for reducing fatigue one would expect much more effective exercise studies than found.

It could be that physical activity has an indirect effect on fatigue rather than a direct effect. This indirect association was demonstrated in a recent study in breast cancer survivors. They found that physical activity had a direct effect on self-efficacy and, in turn, self-efficacy had a direct effect on fatigue[41].

It is probably not the physical activity itself leading to a reducing in fatigue. It is more likely that during exercise certain cognitions are changed that have a positive effect on fatigue. Young and White (2006) found that self-reported activity level bore no relationship to fatigue, but beliefs about activity appeared to predict fatigue directly in breast cancer survivors[42]. Results of a graded exercise RCT for CFS also demonstrated that not physical condition, but symptom focusing mediated the improvement in fatigue[43]. To conclude, it could be that physical activity has an indirect effect on fatigue, but cognitions are probably more important factors for reducing fatigue during cancer treatment.

THE COURSE OF FATIGUE IS ALREADY STABLE FROM TWO MONTHS AFTER THE END OF CANCER TREATMENT.

Many patients recover spontaneously from the direct effects of cancer treatment, but unfortunately part of the cancer survivors remain severely fatigued. Between

20 - 40% of the survivors don't recover, but continue to be severely fatigued[44-48]. Persistent fatigue can continue for years with a major impact on daily functioning and quality of life[17, 49, 50].

A review in disease free breast cancer survivors found support for the existence of ongoing postcancer fatigue, but found an improvement over time[51]. In the study of Servaes et al., (2007) fatigue was investigated monthly for two years in breast cancer survivors who were treated at least 6 months previously. The percentage of severe fatigue was 39% at baseline and 23% at two years follow-up, suggesting that some recovery of fatigue takes place within the first 3-4 years after breast cancer treatment and thereafter stabilizes[52]. The percentages of severe fatigue after treatment for malignant and benign bone and soft tissue tumours was 43% between the first and second year, 34% between the second and the third year, and thereafter stabilized between 18 to 26%[53]. Based on this study it was assumed that the level of fatigue would be even higher shortly after cancer treatment was finished, estimated between 40 - 50%, would decrease significantly during the first six to twelve months after cancer treatment to 30% - 40%, and stabilizing thereafter to about 25%. This was only a presumption, because studies testing this assumption were lacking. Studies providing insight into the course of fatigue in first year after cancer treatment were absent. Therefore, as part of our study design, fatigue was assessed monthly for a year in patients successfully finished treatment treated for various malignancies.

Studying the course of fatigue in various diagnosis groups revealed that the level of fatigue did not decrease during the year after successful cancer treatment as initially expected, but remained stable.

One could reason that patients recovered from fatigue in the first two months after cancer treatment finished. For example Given et al., (2001) assessed older cancer patients who were newly diagnosed with breast, colon, lung, or prostate cancer and additional assessments took place at 6–8, 12–16, 24–30, and 52 weeks. They found that after 40 days no extended effects cancer treatment could be found on fatigue[54]. So it is possible that levels of fatigue were

higher immediately after cancer treatment was finished and decreased to 21% at time of T2.

The prevalence of severe persistent fatigue was lower than presumed. In our study the occurrence of severe persistent fatigue was 21%, and not about 40% to 50%. The occurrence of severe persistent fatigue varied significantly between the type of cancer in an univariate analysis. Patients successfully treated for prostate cancer had significantly less often severe persistent fatigue (3%) compared to patients treated for breast cancer (23%), or for other malignancies (34%). The differences in fatigue between the diagnosis groups that was already present from two months after cancer treatment, remained stable through the year thereafter. This is illustrated in Figure 1.

To conclude, fatigue remains problematic for a part, between 3 and 34 percent, of the patients after successful cancer treatment and the level of fatigue is already stable from two months after the oncological treatment.

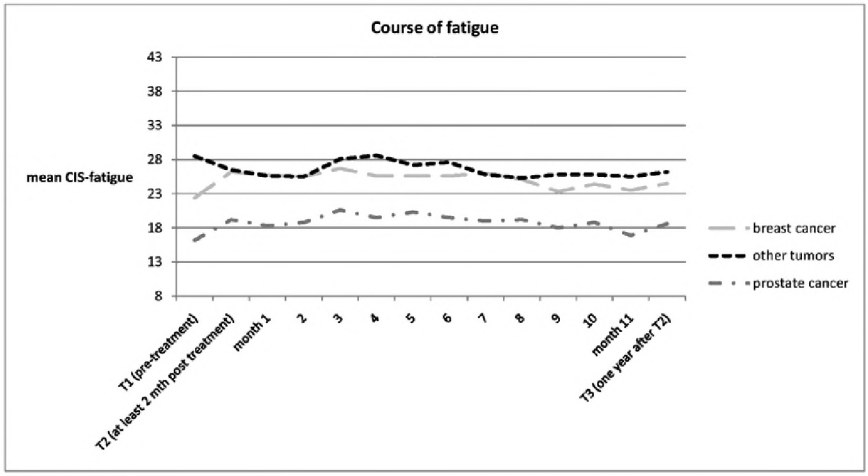

Figure 1: Course of fatigue in patients with various malignancies.

WHO ARE AT RISK FOR REMAINING PERSISTENTLY FATIGUED AFTER SUCCESSFUL CANCER TREATMENT?

In chapter six we performed a prospective longitudinal study aiming to identify which pre-treatment factors, post-treatment factors and cancer-related factors could predict persistent fatigue in the year after cancer treatment.

The occurrence of severe persistent fatigue in the natural course varied significantly between the type of cancer patients were treated for. There is evidence that patients who receive an intensive oncological treatment are more likely to remain persistently fatigued[55, 56]. For example, it has been found that fatigued breast cancer survivors were more likely to have been treated with a combination of chemotherapy and radiation therapy or with chemotherapy alone as adjuvant treatment than non-fatigued breast cancer survivors who received only radiation therapy[55]. There was also found that patients who did not have to undergo adjuvant treatment at all, and for whom surgery was without complications experienced less often persistent fatigue[56]. In our study it was not possible to draw separate conclusions about the effect of cancer treatment, diagnosis, age or sex on persistent fatigue, because the diagnosis groups were inherently related to the malignancy and consequently on types of treatment, sex and age. For example, prostate cancer is confined to older men, who don't receive chemotherapy as curative cancer treatment.

Although we did found differences in persistent fatigue between the various malignancies the results of the multi-variate analysis showed that cancer-related characteristics were not predictive of persistent fatigue. Our analysis with pre-treatment related factors and cancer and treatment related factors showed that fatigue before the start of cancer (at T1), and fatigue one year before the diagnosis (retrospectively) were the strongest predictors of persistent fatigue. Our analysis with post-treatment related factors showed that post-treatment fatigue was the only predictor of persistent fatigue. This strong association between fatigue during several phases of cancer treatment and thereafter was also found in other studies[57-59].

Thus, cancer patients who are fatigued prior to cancer treatment and patients who become fatigued shortly after cancer treatment is finished are at risk for persistent fatigue after successful cancer treatment.

THE PERPETUATING FACTORS OF SEVERE FATIGUE IN LONG TERM CANCER SURVIVORS CAN ALREADY BE IDENTIFIED SHORTLY AFTER CANCER TREATMENT IS FINISHED.

The finding that severe fatigue is already present from two months after cancer treatment is finished and that the level of fatigue did not change thereafter, raised the question if CBT for postcancer fatigue, aimed at the fatigue perpetuating factors, that proved to be effective in severely fatigued long term cancer survivors, could be offered at an earlier stage, as early as two months after successful cancer treatment.

First, a short explanation of perpetuating factors of fatigue. To understand fatigue in long term cancer survivors a model of precipitating and perpetuating factors was developed by our group[60]. According to this model the cancer itself, the consequences of the illness and/or the treatment for cancer triggered fatigue (precipitating factors). After the direct effects of cancer treatment disappear, other factors cause severe fatigue to persist (perpetuating factors). Poor coping with cancer and treatment, excessive fear of disease recurrence, dysfunctional cognitions regarding fatigue, dysregulation of sleep, dysregulation of activity, low social support and negative social interactions were identified as perpetuating factors for persistent fatigue in long term cancer survivors[61, 62]. CBT for postcancer fatigue clinically and significantly reduced fatigue and functional impairments in severely fatigued long term cancer survivors (on average five years after successful cancer treatment) and the effects were maintained for at least 2 years[61, 62]. Currently CBT for postcancer fatigue is offered as a regular treatment for severely fatigued cancer survivors who finished cancer treatment at least one year previously.

As it is unknown if CBT for postcancer fatigue can be offered shortly after cancer treatment, we investigated if the known perpetuating factors of fatigue in long term cancer survivors had a predictive value in the year after cancer

treatment. We tested if the six fatigue perpetuating factors assessed shortly after cancer treatment (T2) predicted persistent fatigue.

Our results showed that four of the six known fatigue perpetuating factors assessed shortly after cancer treatment predicted persistent fatigue in the year after cancer treatment. These factors were: stronger somatic attributions regarding fatigue, more fatigue catastrophising, a lower level of self-reported physical activity and more impaired sleep. The clinical implication of these findings is that it is useful and possible to treat severely fatigue cancer survivors with CBT for postcancer fatigue as early as two months after cancer treatment is successfully finished.

SUMMARY OF THE NEW FINDINGS

- CBT for fatigue during curative cancer treatment proved to be an effective intervention.
- Surprisingly large numbers (24%) of cancer patients are already severely fatigued prior to the oncological treatment. Although the occurrence of severe fatigue varied between the types of malignancies (14% - 28%) psychosocial factors contributed more strongly to severe fatigue before initiation of cancer treatment.
- Psychosocial interventions specifically aimed at reducing fatigue during cancer treatment have the highest probability of being effective. There is no solid evidence for the effectiveness of interventions not specific for fatigue.
- Not all cancer patients need CBT for fatigue during curative cancer treatment. Offering CBT to all cancer treatment during cancer treatment lead to overtreatment.
- Concentration and memory problems prior to cancer treatment are indications for CBT for fatigue during curative cancer treatment.
- Increasing physical activity is not a mediator in reducing fatigue during active cancer treatment. CBT for fatigue during curative cancer treatment was effective in reducing fatigue. This reduction was realised without an increase in physical activity. The reduction was most likely realised by changing cognitions.

- The course of fatigue is already stable from two months after the end of cancer treatment and does not decrease thereafter.
- Patients experiencing fatigue before cancer treatment and becoming fatigued shortly after cancer treatment are patients at risk for remaining persistently fatigued after cancer treatment is successfully finished.
- The known perpetuating factors for persistent fatigue in long term cancer survivors already had predictive value from two months after successful cancer treatment. These findings implicate that it advisable to offer CBT for postcancer fatigue to severely fatigued cancer survivors from two months after successful cancer treatment.

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Summary

Cancer is potentially a deadly disease, but with early detection and modern available treatments many cancer patients survive these days. As the number of cancer survivors increases concerns were raised about the long term well being of cancer survivors. One of the long term complications of cancer treatment is chronic fatigue. Fatigue is one of the most common symptoms experienced by patients during cancer treatment. Unfortunately not all cancer survivors recover spontaneously from fatigue. About 20 - 40% of the survivors remain persistent severely fatigued, even for years. Persistent fatigue impairs their daily activities and diminishes their quality of life substantially. Cognitive behaviour therapy for postcancer fatigue proved to be an effective therapy. This was demonstrated in a randomised controlled trial (RCT) with long term cancer survivors. It would be in survivors' best interest if postcancer can be treated at an earlier stage and ideally if postcancer fatigue could be prevented. The goal of the studies described in this thesis was to evaluate two intervention strategies for fatigue during curative cancer treatment. These interventions were aimed at reducing fatigue shortly after cancer treatment and preventing patients from becoming chronically fatigued. It was also investigated if persistent fatigue could be predicted and if risk factors or groups could be identified.

The *first chapter* starts with a brief description on the history of cancer, the treatment and the prevalence. In the last decennia fatigue in cancer survivors has been recognized as a serious problem. The Expert Centre Chronic Fatigue of the Radboud University Nijmegen Medical Centre was one of the first performing scientific research on postcancer fatigue and developing a treatment. In this chapter the performed studies on the prevalence of postcancer fatigue and the model of precipitating and perpetuating factors of fatigue are briefly described. Furthermore the content of the thesis has been outlined.

Studying the literature we noticed that there was a limited number of reviews evaluating interventions for fatigue, moreover the reviews did not distinguish interventions provided during active cancer treatment from interventions given to cancer survivors. Based on this finding we systematically studied the literature and wrote a review.

In the *second chapter* this Cochrane review is described. We evaluated if psychosocial interventions were effective in reducing fatigue in cancer patients receiving active treatment for cancer, and which types of psychosocial interventions showed to be the most effective. Until September 2008 we systematically searched for RCTs that evaluated psychosocial interventions in adult cancer patients during active treatment, with fatigue as an outcome measure. The search was not restricted to type of malignancy, stage, or cancer treatment. The psychosocial intervention needed to be a systematic treatment consisting of a process between the patient and the person giving the intervention. The intervention consisted of at least two contacts in which a care provider gave the patient some kind of personal feedback concerning the changes they were trying to achieve. Providing only information was not considered a psychosocial intervention in this review. The search yielded 27 studies.

This review demonstrated that there was no solid evidence for the effectiveness of psychosocial interventions with a general approach. Only 3 of the 22 studies (14%) were effective in reducing fatigue. These interventions were not specifically aimed at fatigue, but at psychological distress, mood and physical symptoms in general.

Psychosocial interventions specifically aimed at fatigue were found to be a promising type of intervention. Four of the five RCTs (80%) were effective in reducing fatigue. The five interventions were brief, consisting of three individual sessions, provided by (oncology) nurses. During these interventions participants were educated about fatigue, were taught in coping techniques or self-care, and learned to balance their periods of activities and rest.

The RCTs were very heterogeneous, on patient and treatment characteristics, types of interventions, and outcome measures. This made it difficult to establish which elements could be essential in an intervention that

aims to reduce fatigue in cancer patients. Long term follow-up assessments were often lacking.

Most cancer patients experience fatigue during active treatment. It is generally thought, symptoms of fatigue arise as a consequence of the cancer itself, the treatments patients receive, and associated distress. Although several studies that investigated the quality of life in cancer patients prior to the oncological treatment indicated that fatigue might be problematic at this stage, fatigue was never the primary focus of study.

The study described in the *third chapter* investigated the prevalence of severe fatigue and related factors, in cancer patients before the initiation of treatment. This cross-sectional study was based on 179 patients with various malignancies who were assessed before start of the oncological treatment with curative intention. All participants completed the Checklist Individual Strength to assess fatigue.

Contrary to what was expected relatively many cancer patients already experienced severe fatigue before initiation of treatment. In total 24% patients were severely fatigued. The presence of severe fatigue prior to treatment was the lowest in patients with prostate cancer (14%), higher in breast cancer patients (20%) and the highest in the remaining group of patients diagnosed with for example lymphomas, colon cancer or gynaecological cancer (33%). When patients with gastrointestinal cancer were considered as a separate group, severe fatigue was 28%. The prevalence of severe fatigue might even be underestimated as fewer patients with colorectal cancer (who are more often severely fatigued) were present in this study, compared with the prevalence in the Dutch population.

Results of this study showed that four independent factors contributed to severe fatigue in treatment naïve cancer patients; self-reported physical activity, depressive mood, impaired sleep and rest, and fatigue one year before the diagnosis. Psychological and behavioural factors contributed more strongly to severe fatigue before initiation of cancer treatment than the type of malignancy itself.

One of the main aims of this thesis was to evaluate two interventions for fatigue during curative cancer treatment, comparing these with usual care. In *chapter four* this multicentre RCT is described in which seven hospitals participated. In total 220 patients with various malignancies were assessed before the start of cancer treatment (T1) and consequently they were randomized to one of the three conditions. Patients assigned to the brief nursing intervention (BNI) received two one-hour sessions, three months apart. The intervention focused on increasing and maintaining physical activity only, and what to do if complications during the oncological treatment occurred. Participants also received a booklet with the same recommendations, explanations and advises as received during the sessions. Patients assigned to the cognitive behaviour therapy (CBT) received of up to ten one-hour sessions, within six months, and the same booklet. The CBT focused besides physical activity on psychosocial elements, such as changing dysfunctional cognitions about fatigue and maintaining a fixed sleep-wake rhythm. The third condition was the control group and received only usual care (UC). The post-intervention assessment (T2) took place at least two months after cancer treatment, a period in which patients could recover from the direct effects of the oncological treatment. Results showed that the CBT group was significantly less fatigued at T2 compared to the UC group, however no significant difference was found between the BNI and the UC. To conclude, this RCT demonstrated that CBT given during curative cancer treatment proved to be an effective intervention, reducing fatigue at a clinical relevant moment; shortly after cancer treatment. Because the BNI had no effect on fatigue also doubts were raised about the role of physical activity on fatigue.

The assumption that increasing physical activity reduces fatigue is widespread but the mediating role of physical activity in interventions aiming to reduce fatigue during cancer treatment has never been demonstrated. A non-parametric bootstrap approach was used to test if the effect of CBT on fatigue was mediated by physical activity, but contrary to what was expected the mediating effect was not confirmed. Thus, the reduction on fatigue elicited by CBT was realized without an increase in physical activity.

This RCT also showed that a large group of the UC condition was not severely fatigued shortly after cancer treatment was finished. Apparently this group of patients managed fatigue during curative cancer treatment without a specific intervention, such as CBT.

The study described in *chapter five* aimed to identify the patient characteristics predicting an improvement in fatigue after CBT. A regression analysis with interactions was performed to determine if functional impairments quality of life and psychological distress on several domains moderated the effect of CBT on fatigue. Results showed that there was significant interaction with self reported cognitive functioning and CBT. This interaction showed that patients who reported more concentration and memory problems prior to the oncological treatment benefited more from CBT for fatigue. These factors are indicators for CBT. As this was an exploratory study there could be other moderators for CBT for fatigue that weren't found due to a lack of power.

This chapter also describes the long term effect of CBT on fatigue. Two-hundred-ten participants in the RCT were additionally assessed one year after the second assessment (T3). Monthly fatigue assessments were completed during that year. Results showed that at T3 no significant difference on fatigue could be found anymore between CBT and the UC group. Further analysis showed that the difference on fatigue between the CBT and the UC was observable until seven months after T2, but thereafter the difference diminished. Overtreatment, treating patients with CBT who could manage fatigue themselves, is probably one of the main reasons why we could not find an effect anymore of CBT at one year follow-up. Clinically it is important that CBT should not be offered to all cancer patients, but to the patients at risk for becoming chronically fatigued after cancer treatment.

As the course of fatigue was followed monthly in the year after successful cancer treatment persistent fatigue in cancer survivors could be investigated. In *chapter six* this prospective study is described. The BNI had no effect on fatigue compared to the UC and therefore data of patients in these two groups could be

combined for studying the natural course on fatigue. First, the prevalence of severe persistent fatigue was investigated. Results showed that in total 24% of the 169 patients had severe persistent fatigue during the period of the last 6 months of that year. The percentage severe persistent fatigue was low in patients treated for prostate cancer (3%), but patients treated for breast cancer (23%) and other malignancies (34%) remained more often severely fatigued.

Secondly, the risk factors for persistent fatigue after successful cancer treatment was investigated. Results showed that (1) fatigue before the start of the oncological treatment, (2) fatigue one year before diagnosis, and (3) fatigue shortly after the treatment were the strongest predictors of persistent fatigue. Not former diagnosis and cancer treatment seems to be parameters for developing persistent fatigue, but fatigue experienced before or shortly after cancer treatment proved to be risk factors.

CBT for postcancer fatigue is aimed at changing the fatigue perpetuating factors proved to be a highly effective intervention in severely fatigued long term cancer survivors. Early treatment with CBT for postcancer fatigue, shortly after cancer treatment, would be possible when the fatigue perpetuating factors have a predictive value for persistent fatigue. In this study it was tested if the six known fatigue perpetuating factors assessed shortly after cancer treatment predict persistent fatigue in the year after cancer treatment. We found that four of the six perpetuating factors assessed shortly after cancer treatment (T2) predicted persistent fatigue. These factors were strong somatic related attributions regarding fatigue, fatigue catastrophising, a low level of self-reported physical activity and impaired sleep and rest. The clinical implication is that CBT for postcancer can already offered to severely fatigued cancer survivors as early as two months after cancer treatment is successfully finished.

The final discussion is held in *chapter seven*. In this chapter new and unexpected findings are discussed and put in broader perspective in view of the most recent literature. In the first paragraph we summarize our findings of the main study aim; evaluating strategies to manage fatigue during active cancer treatment and to prevent persistent fatigue. In the next paragraphs the following

new findings and questions are discussed: 1) Surprisingly large numbers of cancer patients are already severely fatigued before initiation of cancer treatment. 2) Not type of malignancy but psychological and behavioural factors contribute to severe fatigue before initiation of cancer treatment. 3) There is no solid evidence for the effectiveness of interventions not specific for fatigue during cancer treatment. 4) Not all cancer patients need an intervention for fatigue during active cancer treatment. 5) Which indications can be found for CBT for fatigue during curative cancer treatment? 6) Increasing physical activity is not a mediator in reducing fatigue during active cancer treatment. 7) The course of fatigue is already stable from two months after the end of cancer treatment. 8) Who are at risk for remaining persistently fatigued after successful cancer treatment? 9) The perpetuating factors of severe fatigue in long term cancer survivors can already be identified shortly after cancer treatment is finished.

Samenvatting

Kanker is potentieel een dodelijke ziekte, maar door vroege detectie en moderne beschikbare behandelingen overleven veel patiënten de ziekte. Door het toenemende aantal patiënten die de ziekte overleefden is er meer aandacht gekomen voor hun welzijn. Eén van de lange termijn effecten van de behandeling van kanker is chronische vermoeidheid. Tijdens de behandeling van kanker is vermoeidheid één van de meest voorkomende symptomen. Helaas herstellen niet alle patiënten van vermoeidheid. Ongeveer 20 tot 40% van de ziektevrije oncologie patiënten blijft chronisch vermoeid, soms zelfs jaren lang. Chronische vermoeidheid leidt tot beperkingen in het dagelijkse leven en tast de kwaliteit van leven ernstig aan. Cognitieve gedragstherapie voor "vermoeidheid na kanker" is een bewezen effectieve therapie. Dit is aangetoond in een gerandomiseerde gecontroleerde studie (RCT) met patiënten die lang ziektevrij waren. In het belang van de patiënten is het wenselijk dat vermoeidheid in een eerder stadium zou kunnen worden behandeld en chronische vermoeidheid na kanker idealiter zou kunnen worden voorkomen. Het doel van de studie in dit proefschrift was om twee interventiestrategieën voor vermoeidheid tijdens curatieve behandeling van kanker te evalueren. Deze interventies waren erop gericht om vermoeidheid kort na de behandeling van kanker te verminderen en om chronische vermoeidheid na behandeling van kanker te voorkomen. Het is ook onderzocht of chronische vermoeidheid te voorspellen was en of risicofactoren of –groepen geïdentificeerd konden worden.

Het *eerste hoofdstuk* begint met een korte beschrijving van de geschiedenis over kanker, de behandeling, en de prevalentie. In de laatste decennia is vermoeidheid bij ziektevrije oncologie patiënten erkend als een ernstig probleem. Het Nijmeegs Kenniscentrum Chronische Vermoeidheid van het Universitair Medische Centrum St Raboud was één van de eersten die onderzoek deed naar vermoeidheid na kanker en een therapie hier tegen ontwikkelde. In dit hoofdstuk worden de uitgevoerde onderzoeken naar de prevalentie van vermoeidheid na kanker beschreven en wordt het model van uitlokkende en instandhoudende

factoren van vermoeidheid kort uitgelegd. Verder wordt de inhoud van dit proefschrift geschetst.

Bij het bestuderen van de literatuur was het opvallend dat er een beperkt aantal overzichtsartikelen waren die interventies voor vermoeidheid evalueerden, en dat deze overzichtsartikelen geen onderscheid maakten tussen interventies tijdens actieve behandeling van kanker en interventies na behandeling van kanker. Naar aanleiding van deze constatering hebben we een systematisch de literatuur onderzocht en een overzichtsartikel geschreven.

In het *tweede hoofdstuk* staat dit overzichtsartikel van Cochrane beschreven. We hebben geëvalueerd of psychosociale interventies effectief waren in het reduceren van vermoeidheid bij patiënten met kanker die actief behandeld werden en welke typen psychosociale interventies het meest effectief waren. Tot september 2008 hebben we systematisch gezocht naar RCTs die psychosociale interventies evalueerden in volwassenen met kanker tijdens actieve behandeling, waarin vermoeidheid een uitkomstmaat was. De zoekopdracht was niet beperkt tot een type maligniteit, stadium van de ziekte, of behandeling. De psychosociale interventie moest een systematische behandeling zijn, die bestond uit een proces tussen de patiënt en de persoon die de interventie gaf. De interventie moest tenminste uit twee contact momenten bestaan waarin de zorgverlener een vorm van persoonlijke feedback gaf over de veranderingen die de patiënt probeerde te realiseren. Het geven van informatie alleen werd niet beschouwd als een psychosociale interventie in dit overzichtsartikel. De zoekopdracht leverde 27 studies op.

Dit overzichtsartikel toonde aan dat er geen sterk bewijs is voor de effectiviteit voor psychosociale interventies met een algemene benadering. Slechts 3 van de 22 studies (14%) waren effectief in het verminderen van vermoeidheid. Deze interventies waren niet specifiek gericht op vermoeidheid, maar op psychologische stress, stemming en fysieke symptomen in het algemeen.

Psychosociale interventies specifiek gericht op vermoeidheid bleek een veelbelovend type interventie. Vier van de vijf RCTs (80%)bleken effectief te zijn in het reduceren van vermoeidheid. De vijf interventies waren kort, bestonden uit

3 individuele sessies, die gegeven werden door (oncologie)verpleegkundigen. Tijdens deze interventies werden deelnemers geïnformeerd over vermoeidheid, werd hen geleerd over copingstechnieken of zelfzorg en leerden ze een balans te vinden tussen perioden van activiteit en rust.

De RCTs waren zeer heterogeen, wat betreft patiënt- en behandelingskarakteristieken, typen interventies en uitkomstmaten. Dit maakte het moeilijk om vast te stellen welke elementen essentieel zijn in een interventie gericht om vermoeidheid in patiënten met kanker te verminderen. Vaak ontbraken follow-up metingen.

De meeste patiënten ervaren vermoeidheid tijdens actieve behandeling van kanker. In het algemeen wordt gedacht dat vermoeidheidsklachten ontstaan als gevolg van de kanker zelf, de behandeling die patiënten ondergaan en de stress die hiermee gepaard gaat. Ondanks dat verschillende studies naar kwaliteit van leven aangeven dat vermoeidheid problematisch is bij patiënten met kanker voorafgaand aan de oncologische behandeling, was vermoeidheid zelf niet eerder onderwerp van studie geweest.

In de studie die in het *derde hoofdstuk* wordt beschreven is onderzocht wat de prevalentie is van ernstige vermoeidheid en daaraan gerelateerde factoren in patiënten met kanker vóór aanvang van de oncologische behandeling. Deze cross-sectionele studie is gebaseerd op 179 patiënten met verschillende maligniteiten die werden gemeten voor de start van de behandeling met curatieve intentie. Alle deelnemers vulden de Checklist Individuele Spankracht in, om vermoeidheid in kaart te brengen.

Anders dan we hadden verwacht ervoeren relatief veel patiënten met kanker al ernstige vermoeidheid voor aanvang van de behandeling. In totaal waren 24% van de patiënten al ernstig vermoeid. Ernstige vermoeidheid was het minst vaak aanwezig bij patiënten met prostaatkanker (14%), vaker bij patiënten met borstkanker (20%) en het vaakst bij de overige groep, bijvoorbeeld patiënten met lymfomen, darmkanker en gynaecologische kanker (33%). Als patiënten met gastro-intestinale kanker als een aparte groep bekeken werd was het percentage ernstige vermoeidheid 28%. De prevalentie van ernstige vermoeidheid kan zelfs

een onderschatting zijn, omdat minder mensen met colorectale kanker (die vaker ernstig vermoeid zijn) in de studie aanwezig waren vergeleken met de prevalentie in de Nederlandse bevolking.

Resultaten van deze studie lieten zien dat er vier factoren gerelateerd waren aan ernstige vermoeidheid bij patiënten voorafgaand aan de behandeling van kanker: zelfgerapporteerde lichamelijke activiteit, depressieve stemming, gestoorde slaap en rust, en retrospectief vermoeidheid één jaar voor de diagnose. Psychologische en gedragsaspecten waren sterker gerelateerd aan vermoeidheid voor aanvang van de behandeling van kanker, dan het soort maligniteit.

Eén van de hoofddoelen van dit onderzoek was om twee interventies voor vermoeidheid tijdens curatieve behandeling van kanker te evalueren, door deze te vergelijken met de gebruikelijke zorg. In *hoofdstuk vier* is deze multicenter RCT beschreven waaraan zeven ziekenhuizen deelnamen. In totaal werden 220 patiënten met verschillende maligniteiten gemeten voor de start van de behandeling van kanker (T1) en vervolgens werden ze random toegewezen aan één van de drie condities. Patiënten die toegewezen waren aan de korte verpleegkundige interventie (VPI) kregen twee sessies van een uur, drie maanden na elkaar. Tijdens de interventie stond het opbouwen en behouden van lichamelijke activiteiten centraal. Daarnaast kregen ze adviezen over wat ze konden doen als er complicaties van de oncologische behandeling voor zouden doen. Tevens kregen patiënten een boekje met daarin dezelfde aanbevelingen, verklaringen en adviezen die ook tijdens de sessies werden gegeven. Patiënten die toegewezen waren aan de cognitieve gedragstherapie (CGT) kregen maximaal tien sessies van een uur gedurende zes maanden en hetzelfde patiëntenboekje als bij de VPI. De CGT richtte zicht naast lichamelijke activiteit op psychosociale elementen, zoals het veranderen van disfunctionele cognities over vermoeidheid en het behouden van een vast slaap- waakritme. De derde conditie was de controle groep, waarin patiënten de zorg kregen die gebruikelijk is binnen het ziekenhuis (ZG). De meting na de interventie (T2) vond tenminste twee maanden na afronding van de oncologische behandeling plaats, een periode waarin patiënten konden herstellen van de directe gevolgen van de behandeling van

kanker. Resultaten lieten zien dat op T2 de CGT groep significant minder vermoeid was vergeleken met de ZG groep. Er werd geen significant verschil gevonden tussen de VPI en de ZG. Concluderend kan gezegd worden dat deze RCT aantoonde dat CGT, gegeven tijdens curatieve behandeling van kanker, een bewezen effectieve interventie is die vermoeidheid reduceert op een klinisch relevant moment; kort na de behandeling van kanker. Doordat de VPI geen effect had op vermoeidheid ontstond er ook twijfel over de rol van lichamelijke activiteit op vermoeidheid.

De aanname dat een toename van lichamelijke activiteit vermoeidheid vermindert is wijdverspreid, maar de medierende rol van lichamelijke activiteit in interventies gericht op het verminderen van vermoeidheid gedurende de behandeling van kanker is nooit aangetoond. Een non-parametrische bootstrap analyse werd gebruikt om te testen of het effect van CGT op vermoeidheid gemedieerd werd door lichamelijke activiteit, maar tegenovergesteld wat werd verwacht, kon dit mediërende effect niet worden bevestigd. Een afname van vermoeidheid, bewerkstelligd door CGT, was gerealiseerd zonder een toename van lichamelijke activiteit.

Deze RCT liet ook zien dat een groot deel van de ZG groep niet ernstig vermoeid was kort na dat de behandeling van kanker was afgerond. Waarschijnlijk is deze groep patiënten in staat om met vermoeidheid om te gaan tijdens curatieve behandeling van kanker zonder een specifieke interventie, zoals CGT.

De studie beschreven in *hoofdstuk vijf* had tot doel om de karakteristieken van patiënten te identificeren die de verbetering in vermoeidheid na CGT voorspelden. Een regressie analyse met interacties werd uitgevoerd om te bepalen of verschillende domeinen van functionele beperkingen, kwaliteit van leven en psychologische stress het effect van CGT op vermoeidheid modereerden. Resultaten lieten zien dat er een significante interactie was tussen zelfgerapporteerd cognitief functioneren en CGT. Deze interactie liet zien dat patiënten die meer concentratie en geheugen problemen rapporteerden voorafgaand aan de oncologische behandeling profiteerden meer van CGT voor

vermoeidheid Deze factoren zijn dan ook indicaties voor CGT. Omdat dit een exploratieve studie was, is het mogelijk dat we andere moderatoren voor CGT voor vermoeidheid hebben gemist door een gebrek aan power.

Dit hoofdstuk beschrijft ook het lange termijn effect van CGT op vermoeidheid. Tweehonderd tien deelnemers van de RCT werden één jaar na de tweede meting nogmaals gemeten (T3). Maandelijkse vermoeidheidsmetingen werden gedurende dat jaar verzameld. Resultaten lieten zien dat er tijdens T3 geen significante verschil op vermoeidheid werd gevonden tussen de CGT en de ZG groep. Verdere analyse liet zien dat het verschil op vermoeidheid tussen CGT en de ZG zichtbaar bleef tot zeven maanden na T2, hierna werd het verschil kleiner. Overbehandeling, behandeling van patiënten met CGT die vermoeidheid zelf konden hanteren, is waarschijnlijk de belangrijkste reden waarom er na een jaar geen effect van CGT meer gevonden kon worden. Klinisch is het van belang dat CGT niet aan alle patiënten met kanker moet worden aangeboden, maar aan de patiënten die het risico lopen om chronisch vermoeid te worden na behandeling van kanker.

Omdat het verloop van vermoeidheid maandelijks gevolgd werd in het jaar na succesvolle behandeling van kanker, kon persisterende vermoeidheid worden onderzocht in ziektevrije oncologie patiënten. In *hoofdstuk zes* is deze prospectieve studie beschreven. De VPI had geen effect op vermoeidheid vergeleken met ZG en daarom zijn de data van patiënten in deze twee groepen samengevoegd voor het bestuderen van het natuurlijk beloop van vermoeidheid. Eerst werd de prevalentie van ernstige persisterende vermoeidheid onderzocht. Resultaten lieten zien dat in totaal 24% van de 169 patiënten last had van ernstige persisterende vermoeidheid gedurende de laatste 6 maanden. Het percentage ernstige persisterende vermoeidheid was laag in patiënten die behandeld waren voor prostaatkanker (3%), maar patiënten die behandeld waren voor borstkanker (23%) of andere maligniteiten (34%) ervoeren veel vaker ernstige persisterende vermoeidheid.

Ten tweede, werden de risicofactoren voor persisterende vermoeidheid na succesvolle behandeling van kanker onderzocht. Resultaten lieten zien dat

vermoeidheid (1) voorafgaand aan de oncologische behandeling, (2) één jaar voor de diagnose en (3) kort na de behandeling voorspellers waren voor persisterende vermoeidheid. Niet de voormalige diagnose en de behandeling van kanker waren parameters voor het ontwikkelen van persisterende vermoeidheid, maar vermoeidheid voorafgaand en kort na de behandeling van kanker bleken risicofactoren.

CGT voor vermoeidheid na kanker, die gericht is op het veranderen van de instandhoudende factoren van vermoeidheid, is een zeer effectieve interventie voor mensen met ernstige vermoeidheid lang na succesvolle behandeling van kanker. Eerdere behandeling met CGT voor vermoeidheid, kort na de behandeling van kanker, zou mogelijk zijn als de instandhoudende factoren van vermoeidheid een voorspellende waarde hebben voor het persisteren van vermoeidheid. In dit onderzoek werd getest of de zes bekende instandhoudende factoren van vermoeidheid persisterende vermoeidheid voorspelden in het jaar na behandeling van kanker. We vonden dat vier van de zes instandhoudende factoren gemeten kort na behandeling van kanker (T2) persisterende vermoeidheid voorspelden. Deze factoren waren: sterke somatisch gerelateerde attributies, catastroferen van vermoeidheid, een laag niveau van zelfgerapporteerde lichamelijke activiteit, en gestoorde slaap en rust. De klinische implicatie is dat CGT voor vermoeidheid na kanker twee maanden na succesvolle behandeling van kanker al aangeboden kan worden aan ernstig vermoeide patiënten.

De afsluitende discussie wordt gevoerd in *hoofdstuk zeven*. In dit hoofdstuk worden nieuwe en onverwachte bevindingen bediscussieerd en in een breder perspectief geplaatst in het licht van de meest recente literatuur. In de eerste paragraaf vatten we onze bevindingen omtrent de belangrijkste doelstelling samen: evaluatie van managementstrategieën voor vermoeidheid tijdens curatieve behandeling van kanker en ter preventie van persisterende vermoeidheid. In de paragrafen daarna worden de volgende nieuwe bevindingen en vragen bediscussieerd: 1) Verrassend veel patiënten met kanker zijn al ernstig vermoeid voorafgaand aan de behandeling van kanker. 2) Niet het soort

maligniteit, maar psychologische en gedragsfactoren dragen bij aan ernstige vermoeidheid voorafgaand aan de behandeling van kanker. 3) Er is geen sterk bewijs voor de effectiviteit van interventies die niet specifiek gericht zijn op vermoeidheid tijdens actieve behandeling van kanker. 4) Niet alle patiënten met kanker hebben een interventie voor vermoeidheid tijdens behandeling van kanker nodig. 5) Welke indicaties voor CGT voor vermoeidheid tijdens behandeling van kanker konden worden aangetoond? 6) Een toename in lichamelijke activiteit is geen mediator voor een afname in vermoeidheid tijdens actieve behandeling van kanker. 7) Het verloop van vermoeidheid is al stabiel vanaf twee maanden na afronding van de behandeling van kanker. 8) Wie lopen het risico om persisterend vermoeid te blijven na afronding van succesvolle behandeling van kanker? 9) De instandhoudende factoren van ernstige vermoeidheid bij ziektevrije oncologie patiënten die de behandeling lang geleden hebben afgerond zijn al kort na behandeling van kanker aanwezig.

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Over de auteur

Martine Margaretha Goedendorp is op 13 mei 1976 geboren te Drachten. In 1993 heeft ze haar HAVO diploma behaald, waarna ze in Bolsward HBO levensmiddelentechnologie is gaan studeren aan de "Suvelschool". Vier jaar later nam ze haar diploma in ontvangst aan het Van Hall Instituut te Leeuwarden. In de periode tussen 1997 en 2001 heeft ze in de zuivelindustrie gewerkt op het gebied van kwaliteit en productontwikkeling.

Na terugkomst van een jaar durende wereldreis in 2002 heeft ze een switch gemaakt en is fulltime psychologie gaan studeren. Drie jaar later studeerde ze af aan de Rijksuniversiteit van Groningen, met als afstudeerrichting sociale psychologie met nevenrichting gezondheidspsychologie. Haar afstudeerproject voerde ze uit bij het Nijmeegs Kenniscentrum Chronische Vermoeidheid (NKCV) van het UMC St Radboud. Daar is ze gevraagd om als promovendus te komen werken aan een interventieonderzoek naar vermoeidheid tijdens curatieve behandeling van kanker. Het wetenschappelijk onderzoek is in september 2005 van start gegaan en hierop is dit proefschrift gebaseerd.

In april en mei 2010 heeft ze bij het H. Lee Moffitt Center en de Kentucky University in de Verenigde Staten onderleiding van Paul Jacobsen en Michael Andrykowski onderzoek gedaan naar vermoeidheid bij vrouwen met borstkanker en een gezonde controle groep, waarvoor ze een academische stagebeurs had gekregen van de KWF Kankerbestrijding. Na terugkomst uit de VS heeft ze haar werk bij het NKCV voorgezet en gefocused op het verkrijgen van subsidies voor nieuw onderzoeken. Op basis van verkregen subsidie van het diabetesfonds werkt ze nu als parttime onderzoeker aan een project over vermoeidheid bij patiënten met diabetes type 1.