Advancing knowledge and treatment of severe fatigue in breast cancer survivors

with a focus on cognitive behavioral therapy

Harriët Abrahams

Over de cover | ***About the cover***

De schildering symboliseert een weg vooruit - op weg naar herstel

The painting represents a road ahead – on the road to recovery.

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General introduction

Severe fatigue in breast cancer survivors

Worldwide, breast cancer is the most frequently diagnosed type of cancer among women (1). As the general population is growing and aging, the number of women diagnosed with breast cancer continues to increase. In the Netherlands, there were approximately 14,600 new breast cancer diagnoses in 2016 (2). At the same time, survival rates have been improved due to early detection of breast cancer in screening programs and advances in the treatment of breast cancer (3). Nowadays about 77% of Dutch breast cancer patients survive cancer up to ten years after diagnosis (2).

In the literature, the term "cancer survivor" has been defined in various ways (4). In this thesis, the definition from the practice guidelines for fatigue in cancer survivors will be followed: "individuals diagnosed at age of at least 18 years who have completed primary cancer treatment with curative intent, are in clinical remission and off therapy, as well as patients who are disease free and have transitioned to maintenance or adjuvant therapy (5)."

Given the increasing number of breast cancer survivors, awareness of cancer- or treatment-related side-effects that persist after cancer treatment is important. Studies have shown that most breast cancer survivors report a good overall quality of life (QOL). However, a substantial subgroup suffers from debilitating symptoms after completion of curative cancer treatment (6). Fatigue, pain, arm lymphedema, postmenopausal symptoms, anxiety and depressive symptoms are frequently reported (7).

Fatigue is reported as one of the most troublesome symptoms after cancer treatment (8). The definition used in the guidelines for fatigue in cancer survivors is "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness, related to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning (5)."

Cancer-related fatigue can persist for many years after cancer treatment and usually differs from fatigue that everyone experiences from time to time: it is continuously present, unpredictable, and not relieved by rest (9, 10). Cancer-related fatigue often limits the resumption of work and other activities, and has substantial negative impact on patients' quality of life (5).

Need for further progress

In the past decades, substantial progress has been made in the field of cancer-related fatigue. A large number of studies has been conducted and provided more insight in the symptom. In 2015, a group of leading American researchers in the field released a joint guideline for cancer-related fatigue (5). This provides evidence-based recommendations for the definition, screening, assessment, and management of the symptom.

Moreover, multiple interventions have been developed to treat cancer-related fatigue effectively, including educational, physical, and psychosocial interventions (5).

Despite of this progress achieved, we are not there yet. The current thesis was aimed at advancing the knowledge (part I) and treatment (part II) of severe fatigue in breast cancer survivors and DCIS, with a focus on cognitive behavioral therapy.

PART I: ADVANCING KNOWLEDGE OF SEVERE FATIGUE IN BREAST CANCER SURVIVORS

This section will address four important, unresolved issues in the current literature on severe fatigue in breast cancer survivors.

Prevalence and course

Fatigue after breast cancer treatment is common, but prevalence rates vary substantially between studies. In a systematic review of Minton et al, it was concluded that fatigue is a problem for a significant percentage of breast cancer survivors, ascending to 50% in some studies (11). In a narrative review of Ganz et al., it was estimated that about one in three patients are fatigued after breast cancer treatment (12). More detailed conclusions on the prevalence rate and the course of severe fatigue after completion of breast cancer treatment could not be drawn. Thus, although a large body of research has focused on cancer-related fatigue, prevalence and course of this symptom in breast cancer survivors are still unclear.

Fatigue-related factors

Servaes et al. and Prue et al. (13, 14) provided an overview of fatigue-related factors in a systematic review on survivors of various cancer diagnosis. Both reported mixed findings regarding demographic factors, like age, marital status and education. No relationship was found between fatigue and disease- and treatment-related factors, but fatigue was found to be related to multiple psychological and behavioral factors (13, 14).

However, these reviews did not specifically focus on breast cancer survivors and are outdated as the literature searches were conducted at least 10 years ago. The levels of evidence for the relationship between fatigue and relevant factors are still unclear. Besides, some relevant fatigue-related factors could be missed, because sample sizes of included individual studies were too small and there possibly was a lack of power to detect these relationships. A meta-analysis has not been conducted yet, but could provide insight in two clinically relevant types of fatigue-related factors: (i) risk factors to identify patients at increased risk for developing severe fatigue after cancer

treatment, and (ii) fatigue-perpetuating factors (involved in the maintenance of fatigue over time) to identify potential target factors for fatigue-oriented interventions.

Fatigue in patients treated for DCIS

In the nineties, breast cancer screening programs were introduced. These screening programs have improved the early detection of breast cancer, but also led to a large increase in the number of detected benign breast conditions. The most commonly diagnosed benign condition is ductal carcinoma in situ (DCIS), a non-invasive condition confined to the ducts of the breasts (15, 16).

The incidence of detected DCIS in the Netherlands has increased from 338 new cases in 1990 to 2057 new cases in 2016 (2). It is estimated that if left untreated, DCIS would develop into invasive breast cancer in about 20 to 30% of cases (17). DCIS is generally treated with surgery and/or radiotherapy to prevent this potential progression (18).

Being treated with anti-cancer interventions can be confusing for patients with DCIS. Although DCIS is non-invasive, patients often wonder whether they have cancer or not (18). Besides, patients may suffer from debilitating symptoms after completion of treatment, just like cancer survivors. Fatigue could be one of the symptoms induced by cancer treatment.

Given the rising number of DCIS patients, it needs to be explored if fatigue is a problem in this specific patient group. Prevalence and related factors of fatigue have not specifically been examined in DCIS patients yet.

Detecting severe fatigue in oncology practice

The NCCN guideline for cancer-related fatigue (9) recommends that "patients should be screened for the presence and severity of fatigue at their initial clinical visit, at appropriate intervals during and after cancer treatment, and as clinically indicated." Health care professional are advised to assess the presence and severity of fatigue using a (semi)quantitative measure.

Despite of the recommendations in the guideline, patients are often not screened in routine clinical practice. Time limitations are an important barrier. Patients do also not always communicate with their clinicians about fatigue and clinicians may not recognize it as a problem (19). To prevent severe, clinically relevant levels of fatigue from being overlooked in routine clinical practice, a quick screening tool would be helpful. In the Netherlands, a standard screening tool to detect severe fatigue is not implemented in routine clinical care yet. However, the Distress Thermometer has been recommended as screening tool for psychological distress and was implemented in several hospitals (20). This screening tool also includes a problem list with a fatigue

item. So far, the usability of the fatigue item of this screening tool to detect severe fatigue has not been explored.

PART II: ADVANCING COGNITIVE BEHAVIORAL THERAPY

Internet-based cognitive behavioral therapy

According to the cognitive behavioral model of cancer-related fatigue, fatigue has been triggered by cancer and/or cancer treatment. Cognitive and behavioral factors are responsible for the persistence of fatigue (21). Cognitive behavioral therapy (CBT) for severely fatigued cancer survivors targets the following perpetuating factors of cancer-related fatigue: severe fear of cancer recurrence, poor coping with cancer and cancer treatment, a deregulated sleep-wake cycle, deregulation of activity, dysfunctional cognitions regarding fatigue and a perceived lack of social support. The intervention is tailored to the individual patient. Patients follow those treatment modules that are relevant for them. The intervention consists of 12-14 sessions with a therapist at a specialist treatment facility and takes about six months to complete (21).

An RCT was conducted to determine the efficacy of CBT on severe fatigue in cancer survivors compared to a waiting list control condition. Patients reported a significantly larger decrease in fatigue severity and functional impairment following CBT than patients in the control condition (21). These findings have been replicated (22). A follow-up study showed that the positive effects of CBT on fatigue severity were maintained at a two-year follow-up period (23).

Although CBT is effective, the availability of the intervention is limited. Therapists need training and supervision before they can provide CBT. There are a limited number of trained therapists and treatment centers. These treatment locations do not cover the Netherlands and treatment capacity is limited. Besides, CBT is an intensive intervention for which patients need to travel to a treatment center. This is quite burdensome, especially for severely fatigued patients.

The field of e-health is growing rapidly and creates new possibilities in the development of fatigue-oriented interventions for breast cancer survivors. Internet-based interventions are easier accessible for patients in comparison with face-to-face interventions: patients do not need to travel to a treatment center and can decide for themselves when and where they work on the intervention. Economic evaluations have also shown that internet-based interventions can reduce treatment time and costs, which may help to increase treatment capacity (24).

As shown in a theoretical framework for internet interventions of Ritterband et al. (25), different factors come into play in internet-based interventions compared with face-to-face interventions. Examples of these factors are the appearance and content

of a website, the way in which content is delivered, and the program's ability to engage users. These factors are likely to contribute to the effects of the intervention (e.g., by increasing patients' motivation and knowledge) and need to be considered when developing a new internet-based intervention (25).

Internet-based interventions are a viable option for fatigued breast cancer survivors. Generally, 94% of the Dutch inhabitants have internet access, of which 88% use the internet regularly (i.e., ≥once a week) (26). Research has shown that about half of patients, in particular younger patients with a higher income, use the internet to gather breast cancer-related information (27, 28).

According to a recent systematic review and meta-analysis (29), there is an increasing number of eHealth interventions for fatigued cancer survivors. Results of this meta-analysis showed that the current eHealth interventions are effective in improving fatigue in cancer survivors, with small to moderate effect sizes (29). Higher effect sizes appeared for therapist-guided interventions compared with self-management interventions, and effects were maintained at a 3- and 6-month follow-up (29). An internet-based CBT intervention, specifically aimed at fatigue in breast cancer survivors and tested in an RCT, is not available yet.

Determining the long-term efficacy of CBT

In CBT, cancer survivors learn how to cope with severe fatigue. In the majority of patients, this leads to clinically significant improvement of fatigue levels which persisted up to a mean of two years after face-to-face CBT (22-24). It is unclear if these positive effects are maintained in the long run. A recent long-term follow-up study of Janse et al. (30) has shown that long-term maintenance of benefits of CBT for chronic fatigue is not self-evident. In patients who were successfully treated with CBT for chronic fatigue syndrome, levels of fatigue were deteriorated at long-term follow-up (up to 10 years after CBT) (30). It is unknown whether positive effects of face-to-face CBT on fatigue severity of cancer survivors will be retained in the long-term, over two years of follow-up.

OUTLINE OF THE DISSERTATION

To summarize, this thesis aims to advance the current knowledge and treatment of severe fatigue in breast cancer survivors, with a focus on cognitive behavioral therapy.

In part I (advancing knowledge), we present a meta-analysis to examine the prevalence, course, and risk factors of severe fatigue after breast cancer treatment **(Chapter 2)**. Additionally, we provide a systematic review to assess the relationship of fatigue with quality of life and psychological factors in breast cancer survivors

(chapter 3). Next, we show a study on the prevalence and related factors of severe fatigue in patients treated for DCIS **(chapter 4)** and a study on the usability of the fatigue item of the Distress Thermometer as screening tool for severe fatigue in cancer patients **(chapter 5)**.

In part II (advancing cognitive behavioral therapy), we first provide a study protocol, describing the development of internet-based cognitive behavioral therapy (ICBT) for severe fatigue in breast cancer survivors, and the design of an RCT to examine its efficacy **(chapter 6)**. Then, we present results of a randomized controlled trial on the efficacy of ICBT for severely fatigued breast cancer survivors, compared with care as usual **(chapter 7)**. Last, we show a long-term follow-up study that examined if effects of face-to-face CBT on fatigue severity are maintained after two years of follow-up **(chapter 8)**.

We conclude this thesis with a summary and general discussion of the dissertation including future directions for CBT in research and clinical practice **(chapter 9)**.

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Part I

Advancing knowledge of severe fatigue in breast cancer survivors

2

Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors

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ABSTRACT

Background: This meta-analysis aimed to (i) examine demographic, disease-related, and treatment-related risk factors, (ii) estimate the prevalence, and (iii) describe the course of severe fatigue following breast cancer (BC) treatment.

Methods: PubMed, PsycINFO, Cochrane, CINAHL, and Web of Science were systematically searched from inception up to 23 November 2015. Risk factors and prevalence rates were analyzed with inverse variance random-effects analyses. Heterogeneity was studied with sensitivity analyses.

Results: Twenty-seven studies were included (*N* = 12,327). Breast cancer survivors (BCS) with a partner were at lower risk for severe fatigue than survivors without a partner (RR 0.96, 95% CI 0.93-0.98). Survivors with stage II or III cancer, and survivors treated with chemotherapy were at higher risk for severe fatigue than survivors with stage 0 or I cancer and without chemotherapy (RR respectively 1.18, 95% CI 1.08-1.28; 1.12, 95% CI 1.06-1.19). Survivors treated with surgery, radiotherapy, and chemotherapy, and survivors with this combination plus hormone therapy were at higher risk than survivors with other treatment combinations (RR respectively 1.18, 95% CI 1.05-1.33; 1.38, 95% CI 1.15-1.66). Survivors treated with surgery and surgery plus radiotherapy were at lower risk than survivors with additional treatments (RR respectively 0.83, 95% CI 0.70-0.98; 0.87, 95% CI 0.78-0.96). Hormone and targeted therapy were no significant risk factors. The pooled prevalence of severe fatigue was 26.9% (95% CI 23.2-31.0), but this should be interpreted with caution because of high heterogeneity. A relatively large decrease in the prevalence of severe fatigue seemed to occur in the first half year after treatment completion.

Conclusions: Approximately one in four breast cancer survivors suffer from severe fatigue. Risk factors of severe fatigue were higher disease stages, chemotherapy and receiving the combination of surgery, radiotherapy and chemotherapy, both with and without hormone therapy. Having a partner, receiving only surgery, and surgery plus radiotherapy decreased the risk.

INTRODUCTION

Breast cancer (BC) represents one fourth of all cancer cases and is the most common tumor type in women worldwide (1). As survival rates have improved due to advances in BC treatment, an increased number of women are faced with persistent symptoms that are related to the diagnosis and treatment (2,3). Cancer-related fatigue is among the most troublesome symptoms, defined by the National Comprehensive Cancer Network (NCCN) as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness, related to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning (4)."

The prevalence of fatigue in breast cancer survivors (BCS) was examined in two reviews (5,6). Minton et al. reported in a systematic review of 18 studies that fatigue is a problem for a significant percentage of BCS (up to 50% in some studies) (5). The overall prevalence in this review was not estimated with a meta-analysis. Ganz et al. reported in a narrative review that, based on three studies, approximately one in three BCS experience fatigue symptoms (6). This prevalence rate was not based on a systematic search of the literature. Both reviews did not describe how prevalence rates of fatigue after treatment develop over time. Therefore, the prevalence rate and course of fatigue in BCS are still unclear.

To identify which BCS are more likely to develop severe fatigue following treatment, it is important to know which demographic, disease and treatment characteristics are risk factors. Previous reviews on risk factors for fatigue in cancer survivors did not specifically examine these factors in BCS. Prue et al. and Servaes et al. performed a systematic review in survivors with various tumor types and included respectively 24 and 22 studies (7,8). Findings regarding demographic variables and fatigue were mixed. About half of studies found no association between the age of BCS and fatigue, whereas the other half reported that being younger was associated with fatigue. A few studies found that fatigue was associated with marital status and education (7,8). Almost all disease characteristics, including stage of disease and lymph node status, were not found to be related to fatigue after treatment of various tumor types. In addition, almost all treatment characteristics, including type of cancer treatment and time since cancer treatment, were not significantly related to fatigue (7,8).

It is uncertain if these findings can be generalized to BCS, because at least half of the study populations in both reviews were survivors with other tumor types (7,8). Besides, the literature was searched up to September 2005, while BC treatment has evolved during the past decade. The understanding of tumor biology has rapidly

developed, generating a range of molecularly targeted drugs of which fatigue is a well-known side-effect (9,10). These kinds of changes in BC treatment over time should be considered when examining treatment-related risk factors for fatigue. Moreover, no meta-analysis was performed before, and sample sizes of individual studies were possibly too small to detect significant associations between the prementioned characteristics and fatigue.

Our meta-analysis focused on clinically relevant severe fatigue, because this level of fatigue often has profound negative effects on patients' daily life, work ability and quality of life (11). The aims of this meta-analysis were to (i) determine which demographic characteristics (i.e., age, ethnicity, partner status, and education level), disease characteristics (i.e., lymph node status, stage of disease and menopausal status), and treatment characteristics (i.e., type of cancer treatment, type of surgery, breast reconstruction, treatment combinations, and time since cancer treatment) were risk factors, (ii) to estimate the prevalence rate and (iii) to describe the course of severe fatigue following BC treatment.

METHODS

Protocol and registration

This section is written in accordance with the PRISMA statement for systematic reviews and meta-analyses (12). A detailed protocol is published in the International Prospective Register of Systemic Reviews (PROSPERO, reference no. CRD42015015768) (13).

Search strategy

PubMed, PsycINFO, Cochrane, CINAHL, and Web of Science were systematically searched from inception up to 23 November 2015 for studies on fatigue in disease-free BCS. The search strategy existed of three components, used as MeSH-headings and free text words: breast cancer, fatigue, and survivors (complete search strategy: Appendix).

Study selection

Two reviewers (HA and IS) independently assessed the eligibility of articles based on title and abstract. If necessary, full text versions were retrieved. In case of disagreement about eligibility, consensus was reached by consulting a third reviewer (MG). The eligibility criteria were: (i) quantitative data were reported on the prevalence, course, or related factors of fatigue in BCS; (ii) only disease-free BCS were examined, defined

as patients who had completed curative cancer treatment, except for ongoing adjuvant hormone therapy; (iii) sample size was ≥50; (iv) a full-report in English, Dutch, or German was provided.

Data extraction and quality assessment

All corresponding authors who used a fatigue instrument with published cut-off score for severe fatigue were contacted for primary data by e-mail. We asked the authors to distinguish between severely fatigued and non-severely fatigued survivors in their study. All cut-off scores including its references are reported in Tables 1 and 2. We asked the authors to provide us with information on age (continuous), partner status (having a partner: yes/no), ethnicity (Caucasian/not Caucasian), and education level (≤primary school/>primary school). Three disease characteristics were included: lymph node status (positive/negative), menopausal status (premenopausal/postmenopausal), and stage of disease (0 or I/ II or III). Guidelines differ with regard to the latter variable (14,15). We followed the NCCN guidelines, in which stage 0 was described as early-stage BC (15). Eight treatment characteristics were included: treated with chemotherapy (yes/no), radiotherapy (yes/no), hormone therapy (yes/no), targeted therapy (yes/no), type of surgery (lumpectomy/mastectomy), having had breast reconstruction (yes/no), time since cancer treatment (continuous), and treatment modalities (combinations of surgery, chemotherapy, radiotherapy, hormone therapy and/or targeted therapy). If the corresponding author did not respond within two weeks, one reminder was e-mailed to the corresponding author and all co-authors.

Two reviewers (HA and MG) assessed the methodological quality of the included studies using a checklist (16,17), especially designed for studies in psychosocial oncology (Table 2). One point was assigned for each criterion that was fulfilled, with a maximum score of 14 points. Studies attaining ≥75% of the maximum score (≥11 points) were considered high-quality studies. Studies with a score of 50-75% (7-11 points) were considered moderate-quality studies, and studies with a score of <50% (<7 points) low-quality studies (16,17).

Data synthesis and analyses

Data of both cross-sectional and longitudinal studies were used to plot individual study estimates of incidences and proportions. From longitudinal studies, the first reported prevalence rate after the period of early survivorship (≥6 months after BC treatment (18)) was used to prevent a confounding influence of direct consequences of cancer treatment. We used the inverse variance method for pooling the incidences and to calculate the corresponding 95% confidence intervals (CIs). As recommended in

the Cochrane handbook, we used I^2 tests to measure heterogeneity. We defined an I^2 value of 50-75% as substantial heterogeneity and an I^2 value of ≥75% as considerable heterogeneity. As we expected heterogeneity between studies, we used random effects meta-analyses for the primary analyses. Random effects meta-analysis models assume that the estimated effects of the different studies are not identical, but follow some distribution. In case of heterogeneity, sensitivity analyses were performed to study whether specific groups of patients would provide more homogeneous results. Specific groups of patients were composed based on type of study (cross-sectional/longitudinal), primary study outcome (fatigue/other outcomes), type of fatigue measure (clinical interview/questionnaire/single item), study population (selected with eligibility criteria/consecutively screened patient samples), study quality (high/moderate/low), and study period (before/after 2007). The latter division was applied, because we know from clinical practice that treatment regimens became more intensive since ~ 2007.

The associations of demographic, disease and treatment characteristics with severe fatigue were analyzed with inverse variance analyses, using Review Manager 5 statistical software (version 5.3). Risk ratios and their corresponding 95% CIs were calculated for dichotomous variables and standardized mean differences for continuous variables. A separate meta-analysis was performed for each risk factor.

RESULTS

Study selection and data request

The literature search resulted in 5003 hits (flow chart: Figure 1). Duplicates were removed (N=1611) and titles were screened (2145 records excluded). The abstracts and/or full-texts of the remaining 1247 studies were reviewed for eligibility. Studies were excluded because: (i) no quantitative data were provided on prevalence, course and/or related characteristics of fatigue (N=777); (ii) disease-free BCS were not examined (N=248); (iii) no full report in English, Dutch, or German was provided (N=96), and (iv) sample size was <50 (N=58).

Altogether, 68 studies were eligible. Useful data for the meta-analysis were reported in 15 eligible studies. The other 53 studies were considered for a data request. Twenty studies were excluded because: (i) a measure without cut-off point for severe fatigue was used (N=16); (ii) study populations were duplicate (N=4), and (iii) authors could not be located (N=3) (see also Figure 1). A data request was sent to authors of the remaining 30 studies. Authors of 21 studies were willing to provide data (70%). However, the authors of nine studies had no access to the raw data. Data were provided for the remaining 12

studies. Finally, 27 studies (12 327 patients) were included in the meta-analysis.

Study characteristics

Sample sizes ranged from 67 to 3088 patients per study. Fourteen different fatigue instruments were used. A multi-item questionnaire was used in 14 studies, a diagnostic interview in four studies and a single item in nine studies. An unselected population (i.e., consecutive patients screened for fatigue) was included in five studies. The other 22 studies used eligibility criteria to select their study population. Eight studies had a longitudinal design (Tables 1 and 2).

Methodological quality

Ten studies were of high-quality, 13 of moderate-quality and four of low-quality. The mean quality score was 9.2 out of 14 (range 4-13; standard deviation=2.33). The most common methodological shortcomings were not explaining how the sample size was determined (78%) and a lack of a validated questionnaire to measure fatigue (63%) (Appendix, Table S1)

Risk factors

BCS with a partner had a lower risk of severe fatigue than BCS without a partner (RR 0.96, 95% CI 0.93-0.98; supplementary Figure S1a, Appendix). BCS with stage II or III cancer had a higher risk than BCS with stage 0 or I cancer (RR 1.18, 95% CI 1.08-1.28; supplementary Figure S1b). The risk was higher in BCS treated with chemotherapy than BCS without chemotherapy (RR 1.12, 95% CI 1.06-1.19; supplementary Figure S1c). Radiotherapy, hormone therapy and targeted therapy were no significant risk factors. Survivors treated with the combination surgery, chemotherapy and radiotherapy were at higher risk than other treatment combinations (RR 1.18, 95% CI 1.05-1.33; supplementary Figure S1d). If hormone therapy was added to these three treatment modalities, the risk was 38% higher than in other treatment combinations (RR 1.38, 95%, CI 1.15-1.66; supplementary Figure S1e). The risk was decreased in survivors who only had received surgery and surgery plus radiotherapy compared to survivors who had received additional treatment modalities (RR respectively 0.83, 95% CI 0.70-0.98 and 0.87, 95% CI 0.78-0.96; supplementary Figures S1f and S1g). All other examined risk factors were not significant (Table 3).

Prevalence of severe fatigue

Prevalence rates of severe fatigue in cross-sectional studies ranged from 7% to 52%. The pooled prevalence was 26.9% (95% CI 23.2-31.0; Figure 2) in a sample of 12 125 BCS.

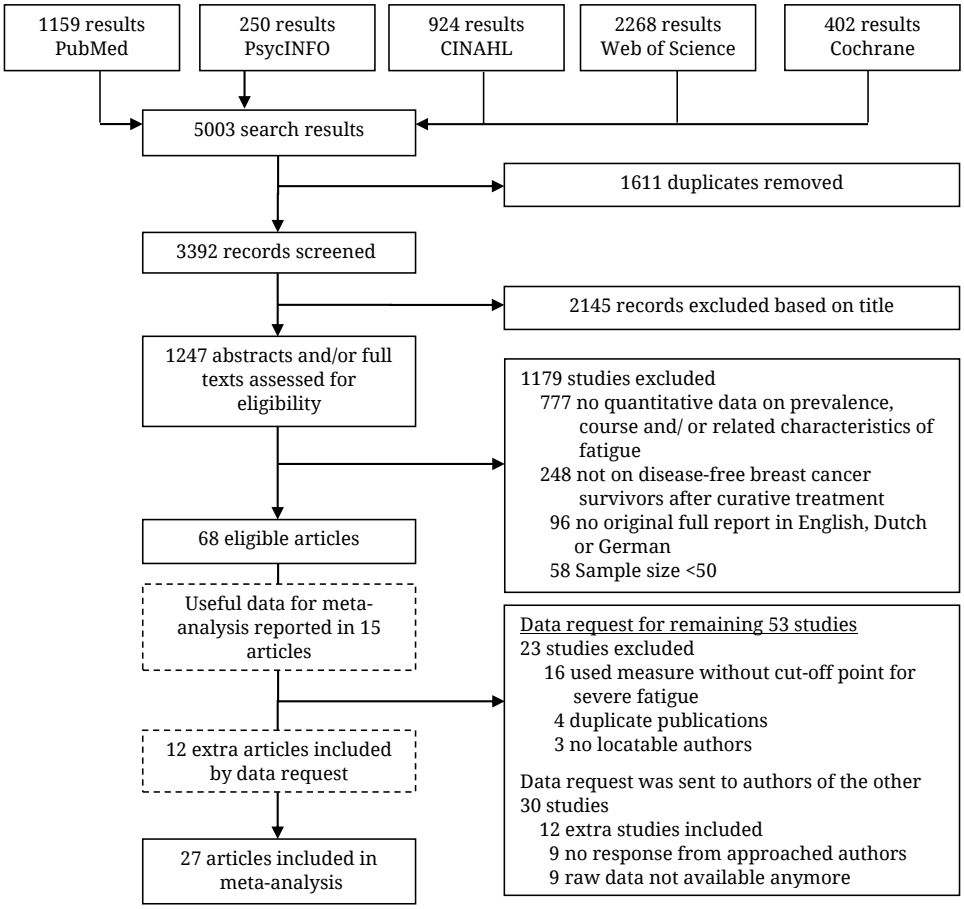


Figure 1. Selection of descriptive studies.

The heterogeneity in prevalence rates was high (I^2 = 95). Sensitivity analyses on study selection showed a fatigue prevalence of 27.7% (95% CI 22.8-33.2) in studies examining consecutively screened patient samples, with a lower level of heterogeneity (I^2 = 67). Sensitivity analyses on type of study (longitudinal/cross-sectional), primary study outcome (fatigue/other outcomes), type of fatigue measure (diagnostic interviews/ multi-item questionnaires/single items) and study quality (high/moderate/low) did not reduce heterogeneity (supplementary Table S2, Appendix).

Course of severe fatigue

Given the high heterogeneity in prevalence rates, a meta-analysis on the course of severe fatigue after treatment could not be carried out. Visual inspection suggested

a relatively large decrease in the prevalence of severe fatigue in the first half year after treatment completion (Figure 3). Afterward, findings on prevalence rates were inconsistent and seemed relatively high when assessed approximately five years after cancer treatment.

DISCUSSION

In this meta-analysis on severe fatigue in BCS, data of 12 327 BCS were analyzed. Results demonstrated that BCS with a partner were at lower risk for severe fatigue. In addition, higher stages of BC and chemotherapy increased the risk for severe fatigue following cancer treatment. The risk was also increased in BCS treated with the combination surgery, chemotherapy, and radiotherapy, and in survivors treated with this combination plus hormone therapy. The risk was lower in survivors treated with surgery and surgery plus radiotherapy. Reported prevalence rates of severe fatigue ranged from 7% to 52%. The pooled prevalence was 27%, but this should be interpreted with caution because of high heterogeneity. A relatively large decrease in the prevalence of severe fatigue occurred in the first half year after BC treatment. Afterwards, findings on prevalence rates were inconsistent.

In contrast to our findings, the majority of included studies in previous reviews on cancer survivors did not find a significant association between fatigue, and having a partner, stage of disease, chemotherapy and cancer treatment modalities. It is likely that sample sizes of individual studies in these reviews were too small to detect a significant association. However, our finding on having a partner is in line with several community-based studies, in which having a partner was also significantly associated with being less fatigued (19-21). Notably, hormone therapy was only was a significant risk factor if received in addition to surgery, radiotherapy and chemotherapy, in spite of the fact that fatigue is often seen as a side-effect of hormone therapy (22). Limited data were available on targeted therapy. More studies are needed to determine if targeted therapy is associated with severe fatigue after cancer treatment. Clear conclusions on the prevalence rate and course of severe fatigue in BCS were not drawn in previous reviews. However, our finding that the prevalence of severe fatigue especially decreased in the first half year after cancer treatment corresponds with the current literature on early survivorship. This time period is known as the re-entry phase, in which patients need to adapt to multiple adaptive challenges (18). After this phase, only a subgroup of patients experiences persistent symptoms like severe fatigue (23).

The major strengths of our study are the large sample size of over 12 000 BCS, the

Study (ref)	Fatigue primary outcome	Sample size (N)	Fatigue measure			Prevalence severe fatigue	Time since BC treatment [a] (months)			Population	Quality rating
			Category	Instrument	Cut-off (ref)		Mean (SD)	Min	Max		
Alexander (2009) (26)	Yes	200	Diagnostic interview	-	-	30%	10 (6)	3	24	Selected	High
Berger (2012) (27)	No	162	Single item	BCSSS, item fatigue worst	≥7 (27)	24%	-	-	-	Unselected	Moderate
Crosswell (2014) (28)	Yes	84	Single item	FSI, item average fatigue	≥5 (29)	46%[b]	44 (26)[c]	-	-	Selected	Low
Dupont (2014) (30)	No	558	Single item	FSI, item average fatigue	≥5 (29)	35%[b]	6 (3)[c]	-	-	Selected	Moderate
Fu (2009) (31)	No	139	Single item	MSAS-SF item fatigue	≥4 (31)	22%	-	≥3	-	Unselected	Moderate
Goldstein (2006) (32)	Yes	176	Multi-item	SPHERE, subscale SOMA	Not reported	49%	10[d]	-	-	Selected	Moderate
Hall (2014) (33)	Yes	313	Multi-item	PFS-R	≥7 (34)	13%[b]	36	24	48	Selected	Moderate
Hall (2015) (35)	Yes	67	Single item	FSI, item average fatigue	≥5 (29)	21%[b]	63 (1)[c]	-	-	Selected	Moderate
Hong (2007) (36)	No	3088	Multi-item	RAND SF-36, subscale vitality	≤50 (37)	36%[b]	23 (12)[c]	-	48	Selected	Low
Jones (2015) (38)	Yes	1294	Single item	FACT-F	≤36 (39)	43%[b]	-	6	78	Selected	High
Karakoyun-Celik (2010) (40)	No	120	Multi-item	EORTC-QLQ-C30 subscale fatigue	≥40 (41)	30%[b]	49	12	168	Unselected	Low
Kim (2008) (42)	Yes	1884	Single item	BFI, item fatigue worst	Not reported	32%	55 (29)[e]	-	-	Unselected	High

Kluthcovsky (2012) (43)	Yes	202	Multi-item	PFS-R	≥4 (43)	38%[f]	59 (56)[g]	-	-	Unselected	High
Meeske (2007) (44)	Yes	800	Multi-item	PFS-R	≥7 (44)	7%	35	24	60	Selected	High
Minton (2012) (45)	Yes	114	Diagnostic interview	-	-	39%	13	3	24	Selected	Moderate
Reidunsdatter (2013) (46)	Yes	221	Multi-item	EORTC-QLQ-C30 subscale fatigue	≥40 (41)	30%[b]	3	-	-	Selected	Moderate
Ventura (2013) (47)	No	163	Single item	FSI, item average fatigue	≥5 (29)	55%[b]	41 (18)[c]	≥6	-	Selected	Moderate
Versmessen (2012) (48)	No	121	Multi-item	EORTC-QLQ-C30 subscale fatigue	≥40 (41)	31%[b]	3[d]	-	-	Selected	Moderate
Young (2006) (49)	Yes	69	Diagnostic interview	-		19%	-	≥6	-	Selected	High

[a] Time since completion of BC treatment (surgery, chemotherapy, and/or radiotherapy), unless stated otherwise.
[b] Prevalence rate was obtained through a data request.
[c] Time since diagnosis.
[d] This concerns a fixed measurement point.
[e] Time since surgery.
[f] This concerns the prevalence of moderate instead of severe fatigue after BC treatment.
[g] Mean time since the diagnosis of fatigued BCS only.
BCS, breast cancer survivor; BCSSS, BC Survivor Symptom Survey; BFI, Brief Fatigue Inventory; CFS, Chronic Fatigue Syndrome; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer–Quality-of-Life Questionnaire-C30; FSI, Fatigue Symptom Inventory; MSASF, Memorial Symptoms Assessment Scale Short Form; PA, physical activity; PFS-R, Piper Fatigue Scale-revised; SPHERE, Somatic and Psychological Health Report.

Table 1. Cross-sectional studies on prevalence and/or determinants of severe fatigue in breast cancer survivors

Study (ref)	Fatigue primary outcome	Measurement point	Sample size (N)	Time since BC treatment[a] (months)	Prevalence severe fatigue	Fatigue measure			Study population	Quality rating
						Category	Instrument	Cut-off		
Andrykowski (2010) (50)	Yes	T1	304	0	22%	Diagnostic interview	-	-	Selected	High
		T2	282	6	9%					
		T3	222	42	13%					
Bower (2006) (51)	Yes	T1	1953	12-60[b]	35%	Multi-item	RAND SF-36, subscale vitality	≤50 (37)	Selected	Moderate
		T2	763	60-120[b]	34%					
Goldstein (2012) (52)	Yes	T1	218	0	41%	Multi-item	SPHERE, subscale SOMA	Not reported	Selected	Moderate
		T2	218	1	28%					
		T3	218	3	23%					
		T4	218	6	18%					
		T5	218	9	15%					
		T6	218	12	14%					
		T7	218	60	21%					
Jacobsen (2007) (29)	Yes	T1	221	0	28%	Multi-item	POMS, subscale fatigue		Selected	High
		T2	221	2	18%					
		T3	221	4	17%					
		T4	221	6	16%					
		T1	221	0	28%	Single item	FSI, item average fatigue			
		T2	221	2	18%					
		T3	221	4	19%					
		T4	221	6	18%					

Nieboer (2005) (53)	Yes	High dose CT:				Multi-item	RAND SF-36, subscale vitality	≤46 (53)	Selected	Low
		T1	186	12[c]	19%					
		T2	181	24[c]	17%					
		T3	170	36[c]	19%					
		Standard CT:								
		T1	206	12[d]	21%					
		T2	207	24[d]	21%					
		T3	195	36[d]	22%					
Reinertsen (2010) (54)	Yes	T1	249	30-84[b]	33%[e]	Multi-item	CFS	≥4 (54)	Selected	High
		T2	249	30-36 thereafter[b]	39%[e]					
Schmitz (2012) (55)	No	T1	275	12[b]	16%	Single item	FACT-B fatigue item	≥4 (55)	Selected	High
		T2	272	18[b]	12%					
		T3	182	72[b]	16%					
Servaes (2007) (56)	Yes	T1	150	29 (mean)	38%	Multi-item	CIS, subscale fatigue severity	≥35 (56)	Selected	Moderate
		T2	121	24 thereafter	23%					

[a] Time since completion of BC treatment (surgery, chemotherapy, and/or radiotherapy), unless stated otherwise.
[b] Time since diagnosis.
[c] After standard dose chemotherapy.
[d] After high-dose chemotherapy.
[e] This concerns the prevalence of moderate instead of severe fatigue after BC treatment.
BCS, breast cancer survivor; CT, chemotherapy; RAND SF-36, RAND Short Form-36; CIS, checklist individual strength; CFS, Chalder Fatigue Scale; FACT-B + 4, Functional Assessment of Cancer Therapy-Breast.

Table 2. Longitudinal studies on course and/or determinants of severe fatigue in breast cancer survivors

Variables (REF)	References	Number of studies	Sample size (N)	Risk ratio (CI)
Demographic characteristics				
Age (SMD (CI))	(28, 30, 32, 33, 35, 36, 38, 40, 43, 45-48, 50, 54-57)	19	8 678	-.06 (-.14-.03)[a]
Having a partner	(28, 30, 33, 35, 36, 38, 40, 42, 43, 46, 47, 50, 54-57)	16	9 991	.96 (.93-.98)*
Ethnicity (Caucasian)	(26, 28, 30, 33, 35, 36, 43, 45, 47, 50)	10	4 877	1.00 (.97-1.04)
Education level (≤primary school)	(36, 38, 40, 42, 46, 47, 50, 54, 55)	8	6 456	1.09 (.99-1.20)
Disease characteristics				
Stage of disease (II or III)	(26, 35, 38, 42, 43, 45-48, 50, 54, 55)	11	4 093	1.18 (1.08-1.28)*
Negative lymph node status	(26, 43, 45, 46, 48, 54)	6	1 068	.89 (.77-1.03)
Menopausal status (pre-/ perimenopausal)	(26, 33, 36, 43, 45, 47, 50)	9	6 269	.98 (.94-1.02)
Treatment characteristics				
Chemotherapy	(26, 28, 30, 32, 36, 38, 42, 43, 45-48, 50, 54-57)	17	10 100	1.12 (1.06-1.19)*
Radiotherapy	(26, 28, 30, 32, 36, 38, 43, 45, 47, 55-57)	12	7 342	1.01 (0.98-1.05)
Hormone therapy	(26, 30, 36, 38, 42, 43, 45-48, 51, 54, 55)	13	9 412	.98 (.93-1.03)
Targeted therapy	(46-48)	4	611	.66 (.43-1.00)
Mastectomy	(26, 28, 30, 32, 35, 36, 42, 43, 45-48, 50, 54-56)	16	7 784	1.01 (.96-1.07)
Breast reconstruction	(30, 43, 45, 47, 54, 56)	7	1 587	1.02 (.94-1.12)
Time since cancer treatment (SMD (CI))	(26, 35, 45, 50, 54, 56)	7	1 260	-.01 (-.14-.11)
Treatment combinations				
SU	(26,38,42,45,47,56,57)	6	3 028	.83 (.70-.98)*
SU+CT	(32,38,42,47,55-57)	7	3 379	1.33 (.97-1.82)
SU+RT	(26,32,38,45-48,50,55-57)	11	4 164	.87 (.78-.96)*
SU+HT	(38,42,45-47)	4	981	.83 (.57-1.20)
SU+CT+RT	(26,32,38,45-48,55-57)	10	3 882	1.18 (1.05-1.33)*
SU+CT+HT	(38,42,45-47)	4	981	.99 (.66-1.49)
SU+RT+HT	(26,38,45-48)	6	1 264	.89 (.74-1.07)
SU+CT+RT+HT	(26,38,45-48)	6	1 264	1.38 (1.15-1.66)*

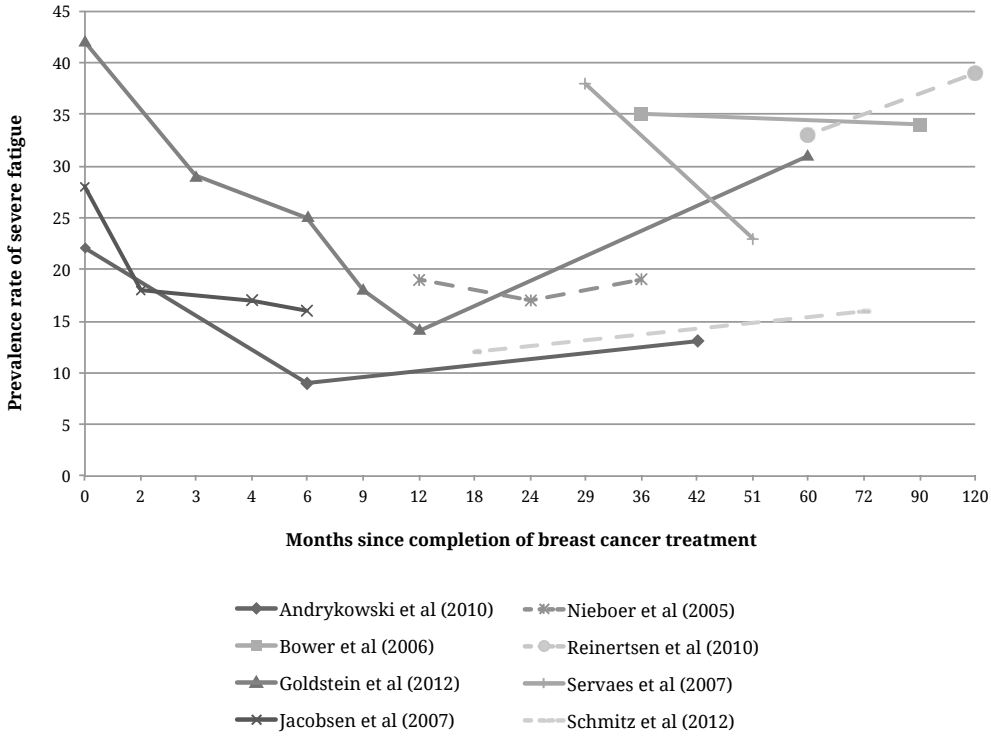
I^2 was <50% in all analyses, unless indicated otherwise. Results are reported as risk ratio (CI), unless indicated otherwise; * $P < 0.05$; [a] $I^2 = 55\%$; SU, surgery; CT, chemotherapy; RT, radiotherapy; HT, hormone therapy; SMD, standardized mean difference; SD, standard deviation.

Table 3. Risk factors of severe fatigue in breast cancer survivors

	Event rate	Lower limit	Upper limit	–1.00	–0.50	–0.00	0.50	1.00
Alexander et al (2009)	0.300	0.241	0.367					
Andrykowski et al (2010)	0.092	0.064	0.132					
Berger et al (2012)	0.241	0.181	0.313					
Bower et al (2000)	0.350	0.329	0.372					
Crosswell et al (2014)	0.457	0.352	0.566					
Dupont et al (2014)	0.352	0.313	0.393					
Fu et al (2009)	0.223	0.161	0.300					
Goldstein et al (2006)	0.489	0.416	0.562					
Goldstein et al (2014)	0.183	0.138	0.240					
Hall et al (2014)	0.127	0.089	0.177					
Hall et al (2015)	0.214	0.151	0.294					
Hong et al (2014)	0.359	0.342	0.377					
Jacobsen et al (2007)	0.181	0.136	0.237					
Jones et al (2015)	0.426	0.382	0.470					
Karakoyun-celik (2010)	0.302	0.225	0.391					
Kim et al (2008)	0.320	0.299	0.341					
Meeske et al (2007)	0.070	0.054	0.090					
Minton et al (2012)	0.395	0.309	0.487					
Nieboer et al (2005)	0.171	0.123	0.233					
Reidunsdatter et al (2012)	0.300	0.243	0.364					
Reinertsen et al (2010)	0.329	0.274	0.390					
Schmitz et al (2012)	0.118	0.084	0.162					
Servaes et al (2007)	0.380	0.306	0.460					
Ventura et al (2013)	0.552	0.475	0.627					
Versmessen et al (2012)	0.311	0.234	0.399					
Young et al (2006)	0.188	0.113	0.298					
Total (random)	**0.269**	**0.232**	**0.310**					

Statistices are reported as risk (CI), unless indicated otherwise. I^2= 95.13

Figure 2. Prevalence of severe fatigue in breast cancer survivors.



Note. Studies that only reported time since diagnosis are shown as dotted lines.

Figure 3. Course of severe fatigue in breast cancer survivors after completion of cancer treatment.

wide range of examined risk factors and the specification of our target population (i.e., preventing any confounding influence of active, noncurative cancer treatment and tumor type on the results). Some potential limitations should also be discussed. To start with, cutoff scores of fatigue questionnaires were used to divide BCS in severely fatigued and nonseverely fatigued groups. The criteria for severe fatigue differ between questionnaires, which probably led to variability between studies and could have distorted our results. Second, data of 18 eligible studies could not be included in our meta-analysis, mostly because the authors had no access to the raw data. Especially, our results on risk factors with small subsets of studies, like targeted therapy and time since cancer treatment, might have been different if more eligible studies were included. Third, our meta-analysis on the prevalence of severe fatigue was limited because of high heterogeneity. Sensitivity analyses showed that the level of heterogeneity was only reduced, though still substantial, in studies that screened patients consecutively in clinical practice. It is disappointing that no firm conclusions

can be drawn about the prevalence of severe fatigue in BCS after more than 20 years of research. Not knowing the scope of the problem makes it unclear what sources have to be allocated to follow guidelines for screening and management of severe fatigue (24). Fourth, fatigue was described as one unified concept, while fatigue actually consists of multiple dimensions like mental fatigue, physical fatigue and the impact of fatigue (25). We only had access to the total scores of questionnaires and were not able to select specific items that distinguish different dimensions of fatigue. Finally, the patients in the included studies were recruited over a period of more than 20 years. It is important to note that treatments and diagnostic criteria of cancer have changed in this time period. However, a sensitivity analyses on study period (before and after 2007) did not show substantial differences in prevalence rates of severe fatigue between both study periods.

This meta-analysis involves several implications for future research and clinical practice. To start with, extra attention should be paid to BCS at increased risk for severe fatigue. Our results showed that the risk for severe fatigue is relatively highest in BCS treated with a combination of surgery, chemotherapy, radiotherapy, and hormone therapy. These patients should especially be monitored closely during follow-up examinations. Second, the included studies in our meta-analysis used 14 different instruments to measure fatigue, which reflects that a generally accepted definition for fatigue in cancer survivors is lacking. Future studies should agree on one definition or at least describe which definition is used in their assessment. Besides, future studies should acknowledge that fatigue is a multidimensional concept, distinguish different domains of fatigue in their assessment, and make more explicit which dimensions are studied. This might also help to reduce heterogeneity when estimating the prevalence of severe fatigue. Third, insight should be gained in the course of severe fatigue after BC treatment. More longitudinal studies that measure severe fatigue frequently over longer time periods are needed. This would clarify which patients recover spontaneously from fatigue, and which patients remain fatigued and may need fatigue-oriented interventions. According to a recent practice guideline of the American Society of Clinical Oncology, available evidence-based interventions for fatigue in cancer survivors are exercise and psychosocial interventions (i.e. cognitive behavioral therapy and psycho-educational therapies). Evidence for the efficacy of mind-body interventions (i.e. mindfulness-based approaches, yoga, and acupuncture) is limited, and evidence for pharmacologic interventions (i.e. psychostimulants and supplements like vitamin D) is lacking (11). Finally, next to demographic, disease, and treatment characteristics, other categories of risk factors for severe fatigue in BCS should be examined in future studies. For instance, behavioral risk factors should be

further examined as there is evidence for behavioral characteristics that maintain severe fatigue in cancer survivors (e.g., physical inactivity and deregulated sleep patterns) (8,11).

In conclusion, approximately one in four breast cancer survivors suffer from severe fatigue. Risk factors of severe fatigue were higher disease stages, chemotherapy and receiving the combination of surgery, radiotherapy and chemotherapy, both with and without hormone therapy. Having a partner, receiving only surgery, and surgery plus radiotherapy decreased the risk.

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APPENDICES

Search strategy systematic review

A. Search strategy Pubmed

("Breast Neoplasms"[Mesh] OR ((breast[tiab] OR mammary[tiab] OR mamma[tiab]) AND (cancer[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR maligne[tiab] OR malignant[tiab] OR malignanc*[tiab] OR neoplasm*[tiab])))

AND

(("Fatigue"[Mesh] OR fatigue*[tiab] OR asthenia[tiab] OR asthenic[tiab] OR astheni*[tiab] OR exhaustion[tiab] OR exhausted[tiab] OR loss of energy[tiab] OR loss of vitality[tiab] OR weary[tiab] OR weariness[tiab] OR weakness[tiab] OR apathy[tiab] OR apathetic[tiab] OR lassitude[tiab] OR lethargic[tiab] OR lethargy[tiab] OR sleepy[tiab] OR sleepiness[tiab] OR drowsy[tiab] OR drowsiness[tiab] OR tired[tiab] OR tiredness[tiab] OR energy loss[tiab] OR vitality loss[tiab])

AND

("Survivors"[Mesh] OR "Disease-Free Survival"[Mesh] OR survivor*[tiab] OR disease free[tiab] OR survival[tiab] OR postcancer[tiab] OR post cancer[tiab] OR posttreatment[tiab] OR post treatment[tiab])

B. Search strategy PsycINFO

(Breast neoplasms/ OR ((breast.ti,ab. OR mammary.ti,ab. OR mamma.ti,ab.) AND (cancer.ti,ab. OR carcinoma*.ti,ab. OR adenocarcinoma*.ti,ab. OR tumor.ti,ab. OR tumors.ti,ab. OR tumour*.ti,ab. OR maligne.ti,ab. OR malignant.ti,ab. OR malignanc*.ti,ab. OR neoplasm*.ti,ab.)))

AND

(Fatigue/ OR (fatigue*.ti,ab. OR asthenia.ti,ab. OR asthenic.ti,ab. OR astheni*.ti,ab. OR exhaustion.ti,ab. OR exhausted.ti,ab. OR loss of energy.ti,ab. OR loss of vitality.ti,ab. OR weary.ti,ab. OR weariness.ti,ab. OR weakness.ti,ab. OR apathy.ti,ab. OR apathetic.ti,ab. OR lassitude.ti,ab. OR lethargic.ti,ab. OR lethargy.ti,ab. OR sleepy.ti,ab. OR sleepiness.ti,ab. OR drowsy.ti,ab. OR drowsiness.ti,ab. OR tired.ti,ab. OR tiredness.ti,ab. OR energy loss.ti,ab. OR vitality loss.ti,ab.))

AND

(Survivors/ OR survivor*.ti,ab. OR disease free.ti,ab. OR survival.ti,ab. OR postcancer.ti,ab. OR post cancer.ti,ab. OR posttreatment.ti,ab. OR post treatment.ti,ab.)

C. Search strategy Cochrane

#1 MeSH descriptor: [Breast Neoplasms] explode all trees

#2 ((breast or mammary or mamma) and (cancer or carcinoma* or adenocarcinoma* or tumor or tumors or tumour* or maligne or malignant or malignanc* or neoplasm*)):ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Fatigue] explode all trees

#5 fatigue* or asthenia or asthenic or astheni* or exhaustion or exhausted or loss of energy or loss of vitality or weary or weariness or weakness or apathy or apathetic or lassitude or lethargic or lethargy or sleepy or sleepiness or drowsy or drowsiness or tired or tiredness or energy loss or vitality loss:ti,ab,kw (Word variations have been searched)

#6 #4 or #5

#7 #3 and #6

#8 MeSH descriptor: [Survivors] explode all trees

#9 MeSH descriptor: [Disease-Free Survival] explode all trees

#10 survivor* or disease free or survival or postcancer or post cancer or posttreatment or post treatment:ti,ab,kw (Word variations have been searched)

#11 #8 or #9 or #10

#12 #7 AND #11

D. Search strategy Cinahl

(MH "Breast Neoplasms+") OR (TI (breast OR mammary OR mamma) OR AB (breast OR mammary OR mamma) AND TI (cancer OR carcinoma* OR adenocarcinoma* OR tumor OR tumors OR tumour* OR maligne OR malignant OR malignanc* OR neoplasm*) OR AB (cancer OR carcinoma* OR adenocarcinoma* OR tumor OR tumors OR tumour* OR maligne OR malignant OR malignanc* OR neoplasm*))

AND

(MH "Fatigue+") OR TI(fatigue* OR asthenia OR asthenic OR astheni* OR exhaustion OR exhausted OR loss of energy OR loss of vitality OR weary OR weariness OR weakness OR apathy OR apathetic OR lassitude OR lethargic OR lethargy OR sleepy OR sleepiness OR drowsy OR drowsiness OR tired OR tiredness OR energy loss OR vitality loss) OR AB(fatigue* OR asthenia OR asthenic OR astheni* OR exhaustion OR exhausted OR loss of energy OR loss of vitality OR weary OR weariness OR weakness OR apathy OR apathetic OR lassitude OR lethargic OR lethargy OR sleepy OR sleepiness OR drowsy OR drowsiness OR tired OR tiredness OR energy loss OR vitality loss)

AND

(MH "Survivors+") OR TI (survivor* OR disease free OR survival OR postcancer OR post cancer OR posttreatment OR post treatment) OR AB (survivor* OR disease free OR survival OR postcancer OR post cancer OR posttreatment OR post treatment)

E. Search strategy Web of Science

((breast OR mammary OR mamma) AND (cancer OR carcinoma* OR adenocarcinoma* OR tumor OR tumors OR tumour* OR maligne OR malignant OR malignanc* OR neoplasm*))

AND

(fatigue* OR asthenia OR asthenic OR astheni* OR exhaustion OR exhausted OR loss of energy OR loss of vitality OR weary OR weariness OR weakness OR apathy OR apathetic OR lassitude OR lethargic OR lethargy OR sleepy OR sleepiness OR drowsy OR drowsiness OR tired OR tiredness OR energy loss OR vitality loss)

AND

(survivor* OR disease free OR survival OR postcancer OR post cancer OR posttreatment OR post treatment)

Positive if:		% of studies that met this criterion
1.	A validated, complete questionnaire measuring fatigue was used (not only subscales)	34%
2.	A description was given of at least three socio-demographic variables	83%
3.	In- and exclusion criteria were described	90%
4.	Response rate to the fatigue questionnaire was ≥65 %	41%
5.	Information was provided on differences of characteristics between responders and non-responders	55%
6.	Time since completion of cancer treatment was provided	55%
7.	Type of cancer treatment and stage of disease were described	41%
8.	Data were prospectively gathered	100%
9.	The process of data collection was described	92%
10.	The sample size determination was explained	21%
11.	Missing data were described	55%
12.	The results were compared between two groups or more (e.g., healthy population, groups with different treatment or age and/or compared with at least two time points)	76%
13.	Mean, median, standard deviations or percentages were reported for the most important clinical outcome measure	93%
14.	Limitations of the study were discussed	83%

Table S1. Criteria list for assessing the methodological quality of studies on fatigue in breast cancer survivors

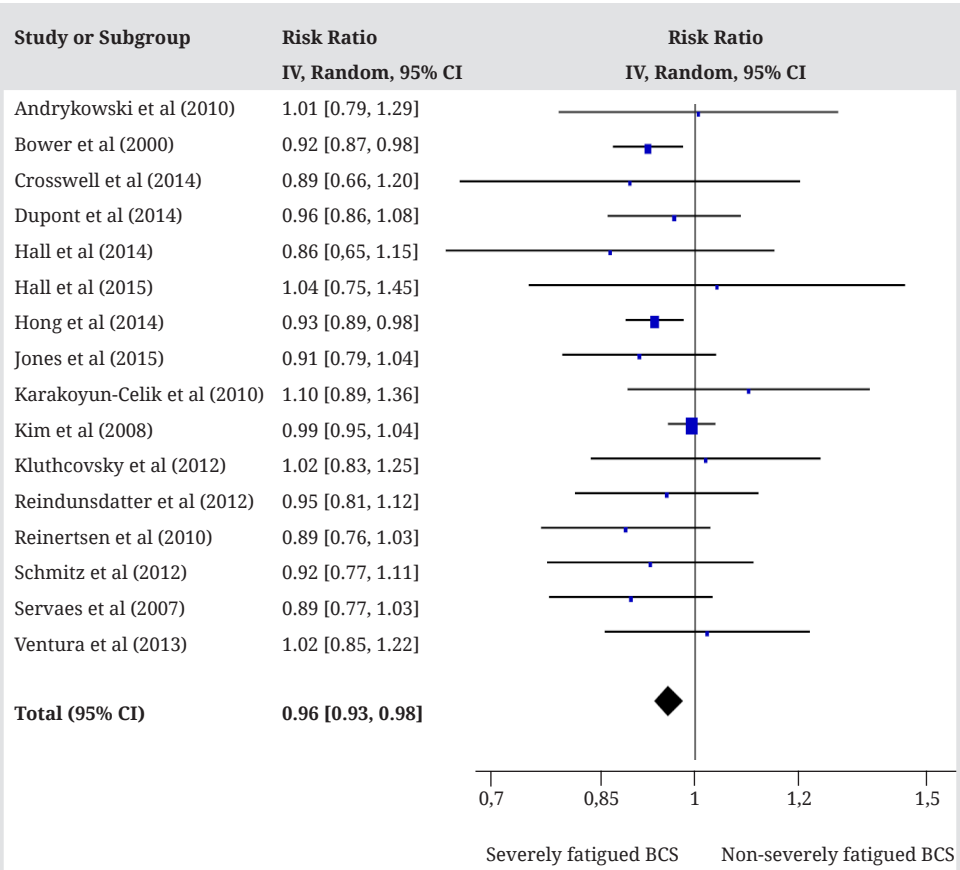
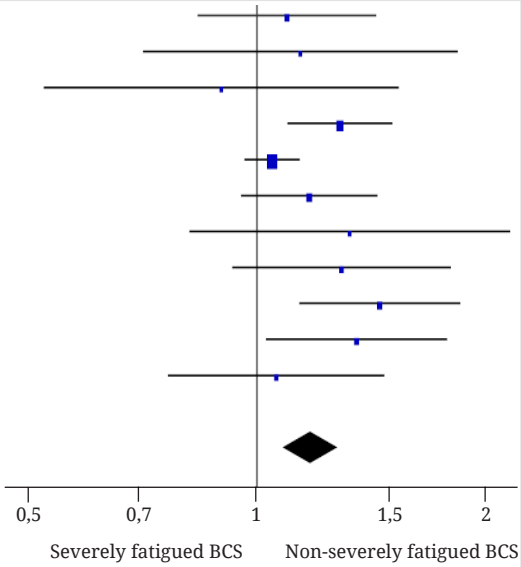


Figure S1a. Having a partner

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Alexander et al (2009)	1.09 [0.84, 1.43]	
Andrykowski et al (2010)	1.14 [0.71, 1.84]	
Hall et al (2015)	0.90 [0.52, 1.54]	
Jones et al (2015)	1.29 [1.10, 1.51]	
Kim et al (2008)	1.05 [0.96, 1.14]	
Kluthcovsky et al (2012)	1.17 [0.95, 1.44]	
Minton et al (2012)	1.32 [0.81, 2.15]	
Reindunsdatter et al (2012)	1.29 [0.93, 1.80]	
Schmitz et al (2012)	1.45 [1.14, 1.85]	
Ventura et al (2013)	1.35 [1.03, 1.78]	
Versmessen et al (2012)	1.06 [0.76, 1.47]	
Total (95% CI)	**1.18 [1.08, 1.28]**	



Total events

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.43$, df = 10 (P = 0.20); $I^2 = 26\%$
Test for overall effect Z = 3.81 (P = 0.0001)

Figure S1b. Stage of disease: II or III

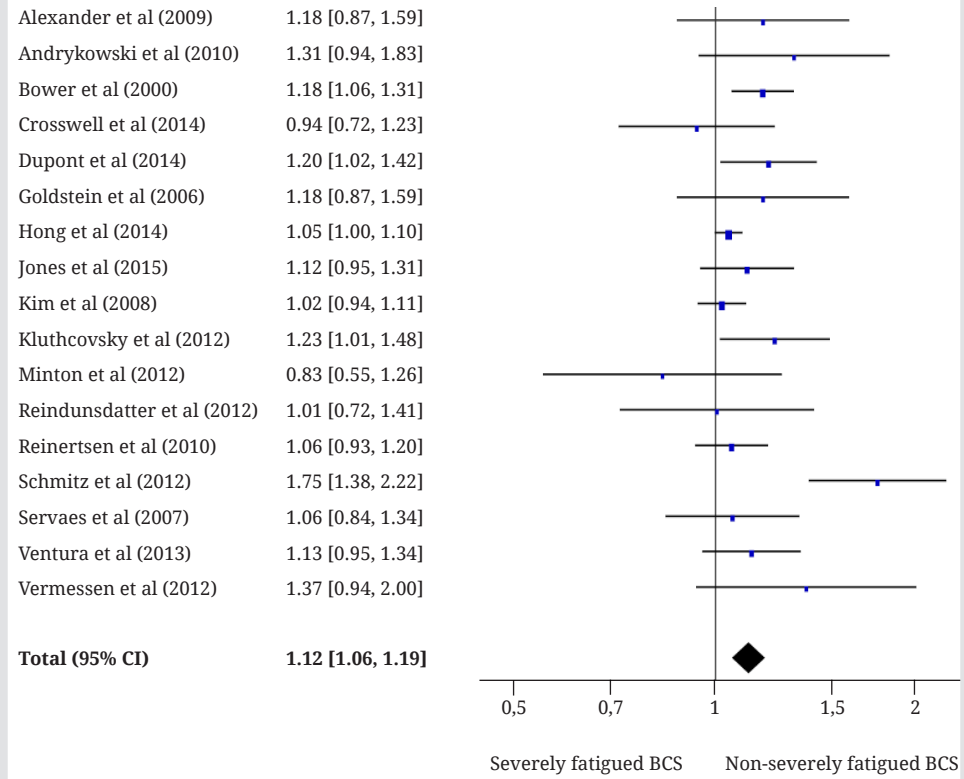
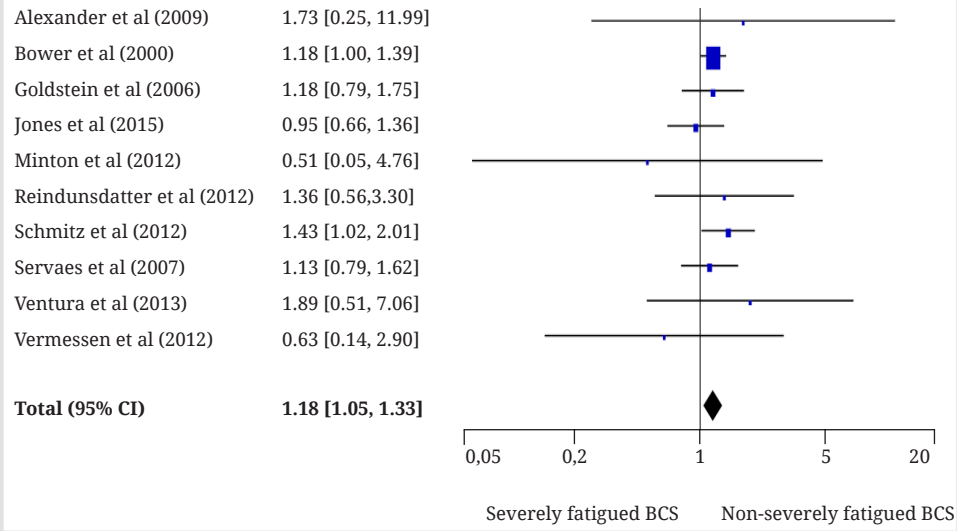


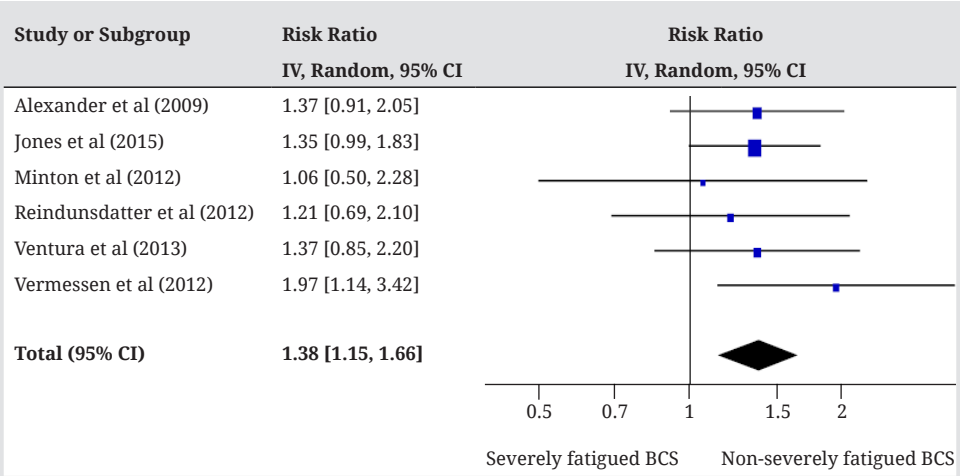
Figure S1c. Chemotherapy



Total events

Heterogeneity: Tau² = 0.00; Chi² = 4.64, df = 9 (P = 0.86); I² = 0%
Test for overall effect Z = 2.69 (P = 0.007)

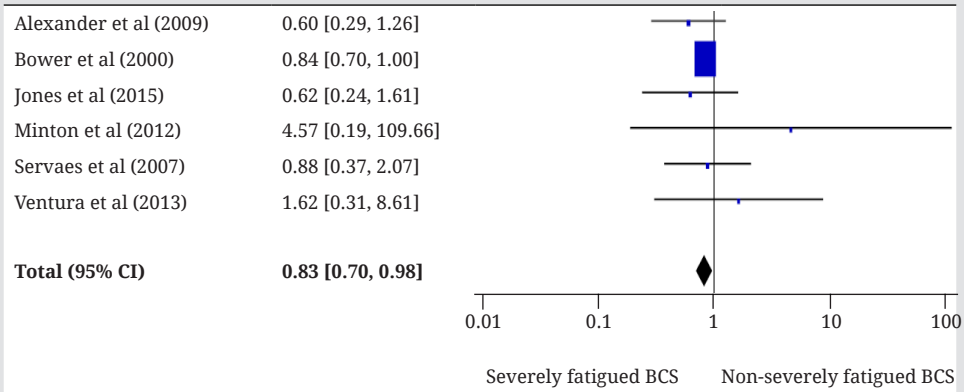
Figure S1d. Treatment combination: surgery, chemotherapy and radiotherapy



Total events

Heterogeneity: Tau² = 0.00; Chi² = 2.31, df = 5 (P = 0.80); I² = 0%
Test for overall effect Z = 3.41 (P = 0.0007)

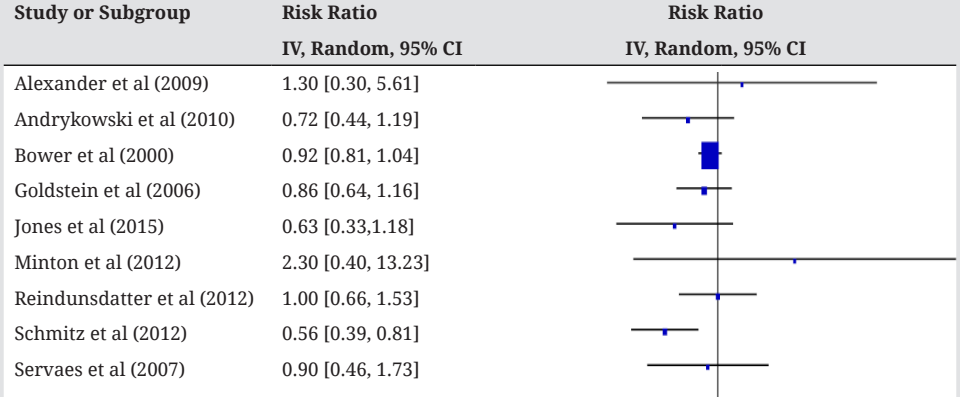
Figure S1e. Treatment combination: surgery, chemotherapy, radiotherapy and hormone therapy



Total events

Heterogeneity: Tau² = 0.00; Chi² = 2.82, df = 5 (P = 0.73); I² = 0%
Test for overall effect Z = 2.25 (P = 0.02)

Figure S1f. Treatment combination: surgery only



Total events

Heterogeneity: Tau² = 0.00; Chi² = 9.96, df = 10 (P = 0.44); I² = 0%
Test for overall effect Z = 2.74 (P = 0.006)

Figure S1g. Treatment combination: surgery and radiotherapy

	Relative risk of severe fatigue RR (95% CI)	Level of heterogeneity (I^2)
Type of study		
Cross-sectional	29.8 (25.0-35.0)	95.04
Longitudinal	21.0 (14.4-29.6)	95.57
Primary study outcome		
Fatigue	25.7 (20.8-31.2)	95.67
Other outcomes	29.7 (23.3-37.0)	93.22
Type of fatigue measurement		
Diagnostic interview	22.3 (11.3-39.3)	93.95
Multi-item questionnaire	27.5 (22.2-33.4)	92.11
Single item	27.9 (21.9-34.8)	92.11
Study population		
Selected with eligibility criteria	26.8 (22.4-31.8)	95.81
Consecutively screened patient sample	27.7 (22.8-33.2)	67.52
Study quality		
High	22.1 (16.0-29.6)	96.49
Moderate	32.6 (26.9-38.9)	91.46
Low	31.2 (22.0-42.2)	89.92
Study period		
≥ 2007	30.4 (28.8-32.1)	97.56
< 2007	33.0 (32.0-34.0)	93.11

Table S2. Sensitivity analyses of prevalence rates of severe fatigue in breast cancer survivors

3

The relationship of fatigue with quality of life and psychological factors in breast cancer survivors: a systematic review.

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Marieke Gielissen
Stans Verhagen
Hans Knoop

Submitted for publication

ABSTRACT

Severe fatigue occurs in one in four breast cancer survivors (BCS). Quality of life (QOL) and psychological factors are important in fatigue-oriented interventions for BCS, but an up-to-date overview is lacking. The aims of this review were to (i) provide a comprehensive overview of the relationship of fatigue with QOL and psychological factors in BCS and (ii) determine the strength of evidence for these relationships. A systematic literature search was conducted to find studies on fatigue after curative breast cancer treatment. Fatigue-related factors of 57 eligible studies were extracted and the level of evidence was determined. Factors regarding QOL (ie, general QOL, functioning, work ability, pain, and mental health) had a negative relationship with fatigue (moderate to strong evidence). This underlines the severity of cancer-related fatigue and its negative consequences on patients' lives. Psychological factors were divided into the subcategories emotional problems, sleep, activity regulation, coping with cancer, dysfunctional cognitions, and social support. Moderate to strong evidence appeared for a relationship of fatigue with depressive symptoms, anxiety, distress, sleep disturbances, lower physical activity levels, difficulties with coping with cancer, and catastrophizing about symptoms. These factors are points of attention for existing and future psychological interventions for fatigue in BCS.

INTRODUCTION

Breast cancer is by far the most prevalent type of cancer among women, affecting one in eight women during their lifetime (1, 2). As populations throughout the world are growing and aging, the number of new breast cancer diagnoses is rising. Meanwhile, survival rates have been improved due to advances in the detection and treatment of breast cancer, resulting in an increasing number of breast cancer survivors (BCS) (3).

A subgroup of BCS experience troublesome and debilitating symptoms after curative cancer treatment. Cancer-related fatigue is one of the most common sequelae of cancer treatment, defined by the National Comprehensive Cancer Network as 'a distressing, persistent, subjective sense of physical, emotional and/ or cognitive tiredness, related to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning' (4, 5).

A recent meta-analysis of our research group on severe fatigue in BCS showed a pooled prevalence rate of severe fatigue of 27%. Regarding the course of severe fatigue over time, there seemed to be a relatively large decrease in the prevalence in the first six months after breast cancer treatment. Higher disease stages, chemotherapy and certain combinations of cancer treatment modalities were identified as potential risk factors for fatigue in BCS, whereas having a partner and receiving surgery with or without radiotherapy decreased this risk (6).

If fatigue in cancer survivors is caused by an underlying somatic condition (eg, anemia), treatment can be directed at this cause. However, this is only the case in a minority of patients. Mostly, a somatic etiology cannot be found and non-medical interventions are indicated (7, 8). In the current guidelines for fatigue in cancer survivors, a main category of recommended interventions concerns psychological interventions (eg, psycho-education and cognitive (behavioral) therapy), focusing on behavioral and psychosocial factors that contribute to the maintenance of fatigue over time (9-11).

Insight in the relationship of fatigue with quality of life (QOL) and psychological factors in BCS would help us to identify target factors and outcomes for existing and future psychological interventions. There is a growing body of literature on cancer-related fatigue (8), but to the best of the authors' knowledge, no systematic review has specifically focused on fatigue-related QOL and psychological factors in BCS yet. Two systematic reviews summarized the psychosocial and behavioral correlates of fatigue in cancer survivors with mixed cancer diagnoses. Fatigue-related QOL of life and psychological factors that appeared from this review concerned depression, anxiety,

distress, pain, poorer sleep quality, lower physical activity, catastrophizing, and worse physical functioning (12, 13). However, besides a lack of a specific focus on BCS, these reviews date from 10 to 15 years ago, and did not determine a level of evidence for the relationships of fatigue with QOL and psychological factors.

In this systematic review, we aimed to (i) provide a comprehensive overview of the relationship of fatigue with QOL and psychological factors in BCS and (ii) determine the strength of evidence for these relationships, in order to detect target factors for fatigue-oriented interventions. This knowledge could be used to guide the development of new interventions, or to optimize the efficacy of existing interventions aimed at fatigue in BCS.

METHOD

A systematic review protocol has been published in the International Prospective Register of Systemic Reviews (PROSPERO, reference no. CRD42015015768). Review methods are in accordance with the PRISMA statement for systematic reviews and meta-analyses (14).

Search strategy and selection criteria

A systematic search of the databases Pubmed, PsycINFO, Cochrane, CINAHL and Web of Science was conducted. The search strategy consisted of the main components 'breast cancer', 'fatigue', and 'survivors', included as MeSH-headings and free text words. The complete search strategy is provided in Appendix A.

The literature search consisted of two parts. The first part were the results of an original search, which were reported in a recent meta-analysis of our research group, described in the Introduction section (6). This search included all studies from inception up to November 23, 2015 that had reported the prevalence, socio-demographic, and/or medical related factors of fatigue in BCCS. The eligibility of the 1247 full texts that had resulted from this search were re-evaluated for the purpose of the current systematic review (ie, fatigue-related QOL and psychological factors in BCS). The second part of the literature search was a full-update search from November 23, 2015 up to April 5, 2017.

In both parts of the search, studies were eligible if: (a) only included BCS who had completed curative cancer treatment (except for ongoing adjuvant hormone therapy) were included; (b) quantitative data (obtained through questionnaires) were reported on fatigue-related QOL and/or psychological factors; (c) the study consisted of at least

50 participants, and (d) a full-report in English, Dutch or German was provided.

We used the definition of the World Health Organization for QOL: "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." This is a broad ranging concept, which also incorporates individuals' physical health and mental health (15). We defined psychological factors as "variables which relate to behaviors, feelings, thoughts and attitudes which would be modifiable for the purposes of intervention, or which may moderate the effects of treatment" (16).

Data extraction and synthesis

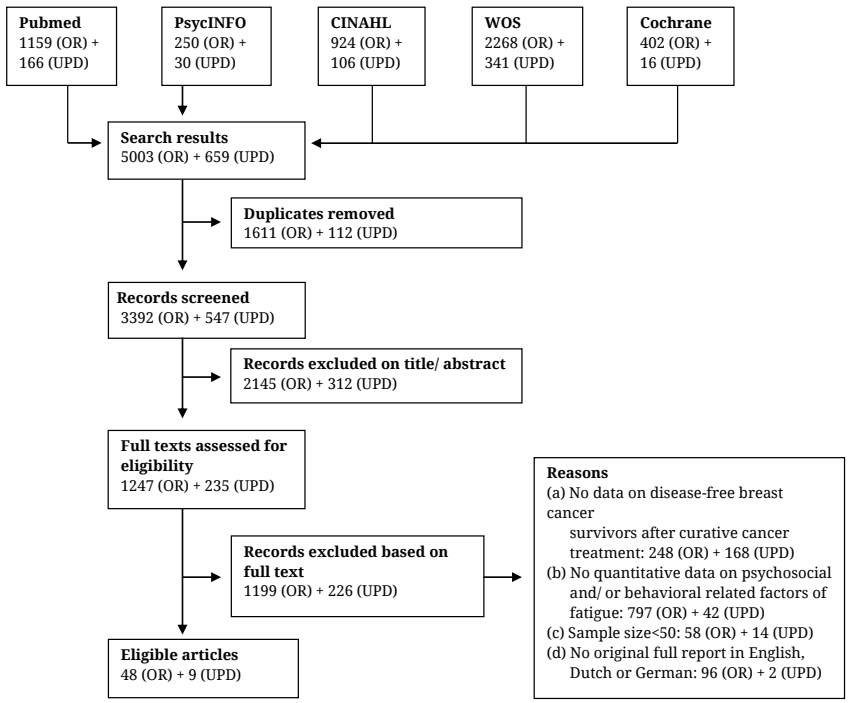
Study titles and abstracts were screened for eligibility independently by two reviewers. Full text versions were retrieved if necessary. Only fatigue-related factors that were examined in at least two unique study populations, or at least two time points in one study population, were reported. Findings must be based on univariate analyses (mean or frequency comparisons, correlations, univariate regression analyses) and/or multivariate analyses (multivariate regression and modeling analyses). If univariate and multivariate analyses were both conducted for a certain variable in one study population, only the multivariate results were reported. Related factors of fatigue were categorized based on conceptual similarity, determined by consensus between all authors.

Study quality

The methodological quality of the included studies was assessed by two reviewers (H.A. and M.G.) with a checklist for psychosocial oncology studies, consisting of 14 criteria (Table A.1, Appendix). One point was assigned to each fulfilled criterion, after which studies were divided into high (≥11 points), moderate (7-11 points), and low (<7 points) quality studies (6, 17, 18).

Level of evidence

The criteria of a previous review that summarized determinants of fear of cancer recurrence (19) were used to assess the level of evidence: (a) strong evidence: consistent finding in at least five studies, with a non-significant finding in less than half of the selected studies; (b) moderate evidence: consistent finding in the same direction in at least three studies or at least half of studies reporting a non-significant relationship; (c) insufficient evidence: a significant relationship was only found in one or two studies (19). Findings of low quality studies were not included in the determination of the level of evidence.



Notes. Number of records from original search (OR) plus full-update search (UPD) are reported.
WOS=Web of Science.

Figure 1 Selection of descriptive studies

RESULTS

Search results

The records that resulted from the original and full-update search are described separately in the flow-chart of study selection (Figure 1). The search strategy resulted in a total number of 5.662 hits. After removing 1.723 duplicates and excluding 2.457 records based on title and/or abstract, the full texts of 1.482 studies were assessed for eligibility. A total of 1.424 studies were excluded, because: (a) the analyses contained survivors with other tumor types or survivors who were not disease-free (n=416); (b) no quantitative data were reported on fatigue-related QOL and/or psychological factors (n=839); (c) the sample size was below 50 participants (n=72), and (d) a full-report in English, Dutch or German was lacking (n=98). Finally, 57 eligible studies remained.

Study characteristics

The design of 40 of 57 included studies was cross-sectional, whereas the 17 other studies were longitudinal with a mean of 3 (range 2 to 6) measurement points. Sample

sizes at start of the studies ranged from 59 to 3088 BCS. Four studies used a diagnostic interview, whereas the other 53 studies used questionnaires to measure fatigue. Twenty-one different questionnaires were used to measure fatigue in BCS. The most frequently used questionnaires to assess fatigue were the Fatigue subscale of the EORTC QOL questionnaire-C30 (n=6), the Vitality subscale of the RAND SF-36 (n=6) and the Fatigue subscale of the Profile of Mood States (POMS) (n=6). The mean time since cancer treatment was reported in 21 studies and was 20 months (SD=21; range=0-64 months), while 21 studies only reported the mean time since diagnosis (42 months; SD=25; range=10 to 90 months). Study quality was high in 18 studies, moderate in 33 studies, and low in six studies (Table 1).

The relationship between fatigue and QOL in BCS

There was strong evidence for a negative relationship between patients' level of fatigue and their QOL in general (11 studies). Twelve other factors with regard to QOL of BCS have been examined. These factors were divided into the subcategories functioning and mental health. The evidence on each included factor (none, insufficient, moderate, or strong) is described in Table 2. Only the factors with moderate to strong evidence will be discussed in the text.

Functioning

Evidence was strong for a relationship between fatigue and physical functioning (9 out of 11 studies), role functioning (8 out of 10 studies), cognitive functioning (7 out of 9 studies), emotional functioning (10 studies), social functioning (9 out of 11 studies), and pain (7 out of 10 studies). Moderate evidence appeared for a relationship of fatigue with sexual functioning (3 out of 4 studies) and work ability (3 out of 4 studies). Higher levels of fatigue were found to be related to more pain, lower levels of functioning and a lower work ability.

Mental health

There was moderate evidence for a relationship of higher fatigue levels with lower mental health (3 studies), and for the absence of a relationship with a history of a DSM-IV axis I diagnosis (not significant in 4 studies).

The relationship between fatigue and psychological factors in BCS

In total, 16 psychological factors were examined and divided into the subcategories emotional problems, sleep, activity regulation, coping with cancer diagnosis, dysfunctional cognitions, and social support. The evidence on the included factors

is described in Table 3. Only the factors with moderate to strong evidence will be discussed in the text.

Emotional problems

Higher levels of fatigue were related with more emotional problems (moderate to strong evidence), which concerned symptoms (not psychiatric disorders). The identified problems were depressive symptoms (22 out of 25 studies), anxiety (7 out of 10 studies), and distress (4 out of 5 studies).

Sleep

There was strong evidence for a relationship between higher fatigue levels and sleep disturbances (9 out of 14 studies). Mostly, this concerned a relationship between fatigue and insomnia (5 out of 9 studies). Insufficient data were available for a further specification of the types of sleep disturbances. Moderate evidence appeared for the relationship between higher fatigue levels and a lower sleep quality (4 out of 5 studies).

Activity regulation

Lower activity levels were found to be related to higher fatigue levels, with a strong level of evidence (7 out of 11 studies).

Coping with cancer diagnosis

Moderate evidence was found for a relationship between a higher level of fatigue and a more negative body image (4 studies), and a more negative future perspective (ie, more worries about future health) (3 studies).

Dysfunctional cognitions

There was strong evidence (5 out of 6 studies) for a positive relationship between fatigue and catastrophizing about symptoms, which reflects a tendency to engage in negative self-statements and overly negative thoughts about the future regarding fatigue.

Study quality

Findings of the six low quality studies were not included in the determination of the levels of evidence. If these studies would be included, the level of evidence would remain unchanged for all factors except mental health. The level of evidence of both factors for a relationship with fatigue would change from moderate into strong.

Study (Authors, year (ref))	Design	N at baseline	Fatigue measurement	Timeframe	Study quality
Abrahams e.a., 2017 (41)	CS	67	CIS, subscale fatigue severity	49 (10) months after cancer diagnosis	High
Alexander e.a., 2009 (29)	CS	200	Diagnostic interview	10 (6); 3-24 months after cancer treatment	High
Alfonsson e.a., 2016 (42)	L	833	EORTC-QLQ-C30 subscale fatigue	Directly and 36 months (range 35-42 months) after cancer diagnosis	Moderate
Andrykowski e.a., 2005 (10)	L	288	Diagnostic interview	Before adjuvant therapy and (a) directly after cancer treatment	High
Andrykowski e.a., 2010 (43)	L	304	Diagnostic interview	(b) 6 and (c) 24 months after cancer treatment	High
Ariza-García e.a., 2013 (44)	CS	108	POMS, subscale fatigue	10 (9) months after cancer diagnosis	Moderate
Arraras, et al., 2016 (45)	CS	243	EORTC-QLQ-C30 subscale fatigue	10 (4) years after surgery (range 5-20 years)	Low
Berger e.a., 2012 (46)	CS	162	BCSSS, item fatigue worst	<5 to ≥10 years after cancer diagnosis	Moderate
Bower e.a., 2000 (47)	CS	1957	RAND SF-36, subscale vitality	(a) 3; 1-5 years after cancer diagnosis	Moderate
Bower e.a., 2006 (48)	L	763	RAND SF-36, subscale vitality	(a) 3; 1-5 years and 6 (1) and (b) 5-10 years after cancer diagnosis	Moderate
Broeckel e.a., 1998 (49)	CS	61	POMS, subscale fatigue	673 (221); 325-1063 days after chemotherapy	High
Calvio e.a., 2010 (50)	CS	122	MFSI-SF	3.1 (2.4) years after cancer treatment	High
Cantarero-Villanueva et al., 2011 (51)	CS	59	PFS	12 (5); 6-35 months after cancer diagnosis	Moderate
Carlsen e.a., 2013 (52)	CS	170	Single item: “How often have you felt unusual tiredness?”	N/A	Moderate
Charlier e.a., 2012 (53)	CS	464	FACIT-Fatigue scale	14.7 (7.1) weeks after cancer treatment	Moderate
Dirksen e.a., 2009 (54)	CS	464	POMS, subscale fatigue	57.9 (68.6); 3-369 months after diagnosis	Moderate
Donovan e.a., 2007 (55)	L	261	FSI	End of treatment, 2, 4 and 6a months after cancer treatment	High
Evangelista e.a., 2012 (56)	CS	354	POMS, subscale fatigue	N/A	Moderate

Table 1 Overview of studies on psychosocial related factors of fatigue in breast cancer survivors

Fagundes e.a., 2011 (57)	CS	109	RAND SF-36, subscale vitality	11 (8); 2-24 months after cancer treatment	Moderate
Galiano-Castillo e.a., 2014 (58)	CS	108	PFS-R	14 (13); 6-38 months after cancer diagnosis	Moderate
Goldstein e.a., 2006 (59)	L	176	SPHERE, subscale SOMA	11 (6) months after cancer treatment	Moderate
Goldstein e.a., 2012 (60)	L	218	SPHERE subscale SOMA	1, 3, 6a, 9, 12, 60 months after cancer treatment	Moderate
Hall e.a., 2014 (61)	L	313	PFS-R	3 (2-4) years after cancer treatment	Moderate
Ho e.a., 2015 (62)	L	134	MFSI-SF	Baseline (≥2 weeks after surgery, before CT), 1-6 months (<1 months after CT) and 8-10 after baselinea	Moderate
Hong e.a., 2007 (63)	CS	3088	RAND SF-36, subscale vitality	2 (1) years after diagnosis	Low
Karakoyun-Celik e.a., 2010 (64)	CS	120	EORTC-QLQ-C30 subscale fatigue	49; 12-168 months after cancer treatment	Low
Kim e.a., 2008 (65)	CS	1993	BFI	4.6 (2.4) years after surgery	High
Kluthcovsky e.a., 2012 (66)	CS	202	PFS-R	5.4 (4.5); >1 years after cancer diagnosis	High
Lavigne e.a., 2008 (67)	CS	83	RAND SF-36, subscale vitality	3 (2); ≥ 1 years after cancer treatment	High
Lee e.a., 2008 (68)	L	61	EORTC-QLQ-C30 subscale fatigue	Baseline, directly after radiotherapy, and 6 months thereafter	Low
Lockefeer e.a., 2013 (69)	L	163	FAS	Pre-diagnosis, 1, 3, 6, 12, and 24a months after surgery	High
Mast e.a., 1998 (70)	CS	109	SDS, item fatigue	35 (17); 12-68 months after cancer treatment	Moderate
Meeske e.a., 2007 (71)	L	800	PFS-R	Baseline and 24 months after cancer diagnosis	High
Minton e.a., 2012 (72)	CS	114	Diagnostic interview	13 (3-24) months after cancer treatment	High
Nieboer e.a., 2005 (73)	L	430	RAND SF-36, subscale vitality	Before, (a) 1, (b) 2, and (c) 3 years after chemotherapy	Low
Okuyama e.a., 2000 (74)	CS	134	CFS	537 (458) days after chemotherapy; 516 (364) days after radiotherapy	High
Paiva e.a., 2016 (31)	CS	216	EORTC-QLQ-C30 subscale fatigue	60.7 (14.5) months after chemotherapy	Moderate
Paquet e.a., 2017 (75)	CS	80	FACT-F	3 (3.5); 1-12 months after cancer treatment	Moderate
Paxton e.a., 2012 (76)	CS	3013	SF-36, subscale vitality	Median 2 years after cancer diagnosis	Low

Pinto e.a., 2004 (78)	CS	129	POMS-F	2 (1) years after cancer diagnosis	Moderate
Phillips e.a., 2013 (25)	CS	202	FSI	4.1 (0.3); 2.6-5.2 years after cancer diagnosis	High
Reinertsen e.a., 2010 (79)	L	249	FQ	2.5-7 years after cancer diagnosis, and 2.5-3 years thereafter	High
Reinertsen e.a., 2017 (80)	L	84	FQ	Before cancer treatment (baseline), during treatment, and 2 years after baseline	Moderate
Rosenberg e.a., 2014 (32)	CS	461	BCPT, fatigue item	13 (2); range 8-22 months after cancer diagnosis	Moderate
Schmidt e.a., 2014 (81)	CS	1928	FAQ	Median 6.3 years post-diagnosis; Q1, Q3=5.4, 7.1)	Moderate
Schultz e.a., 2011 (82)	L	775	EORTC-QLQ-C30 subscale fatigue	1.38 years after surgery (5-95%: 0.34-4.47), and 12 months thereafter	Moderate
Servaes e.a., 2002 (27)	CS	150	CIS, subscale fatigue severity	29 (17) months after cancer treatment	Moderate
Servaes e.a., 2007 (83)	L	121	CIS, subscale fatigue severity	2 years thereafter	Moderate
Sugawara e.a., 2005 (84)	CS	79	CFS	≥3 years after surgery	Moderate
Taylor e.a., 2011 (85)	CS	260	MFSI-SF	5 (3.2); 0-18 years after cancer diagnosis	Moderate
Trinh e.a., 2015 (86)	CS	195	POMS, abbreviated version	3.5 (2.4) months after cancer treatment	Moderate
Vallance, e.a., 2012 (87)	CS	524	TOI-F	76.4 (36.5) months after cancer diagnosis	Moderate
Von Ah e.a., 2015 (88)	CS	88	FACT-F	5.3 (4.1) years after cancer treatment	Moderate
Von Ah e.a., 2016 (89)	CS	68	AFI	5 (3); ≥1 year after cancer treatment	Moderate
Xiao, e.a., 2017 (90)	CS	111	MFI-20	1 year after radiotherapy	Moderate
Young e.a., 2006 (26)	CS	69	MFSI global fatigue	≥6 months after cancer treatment	High

Table 1 Continued

	Significant	Not significant	Level of evidence
Quality of life			
Global health status/ quality of life in general	N=11 (29)[a-], (41)[a-], (43a)[a-], (43b)[a-], (54)[a-], (56)[b-], (65)[a-], (66)[a-], (71)[b-], (72)[a-], (77)[e-]	N=0	Strong
Functioning			
Physical functioning	N=9 (29)[a-], (41)[a-], (43a)[a-], (43b)[a-], (65)[a-], (66)[a-], (71)[ab-], (72)[a-], (77)[a-]	N=2 (27)[c], (83)[c]	Strong
Role functioning	N=8 (29)[a-], (41)[a-], (43a)[a-], (43b)[a-], (66)[a-], (65)[a-], (71)[ab-], (77)[a-]	N=2 (27)[c], (83)[c]	Strong
Cognitive functioning	N=7 (27)[a-], (41)[a-], (65)[a-], (66)[a-], (71)[d-], (72)[a-], (77)[a-]	N=2 (29)[a], (83)[c]	Strong
Emotional functioning	N=10 (27)[a-], (29)[a-], (41)[a-], (65)[a-], (66)[a-], (71)[ab-], (72)[a-], (77)[a-], (80)[d-], (82)[d-]	N=0	Strong
Social functioning	N=9 (29)[a-], (41)[a-], (43a)[a-], (43b)[a-], (65)[a-], (66)[a-], (71)[ab-], (72)[a-], (77)[a-]	N=2 (27)[c], (83)[c]	Strong
Sexual functioning	N=3 (29)[a-], (31)[a-], (32)[e-]	N=1 (65)[a]	Moderate
Sexual satisfaction	N=2 (29)[a-], (65)[a-]	N=0	Insufficient
Pain	N=7 (46)[d+], (47)[d+], (65)[d+], (66)[d+], (71)[d+], (72)[a+], (86)[b+]	N=3 (29)[a], (48)[c], (80)[d]	Strong
Work ability	N=3 (53)[a-], (67)[e-], (89)[e-*]	N=1 (50)[e]	Moderate
Mental health			
History of a DSM IV axis I diagnosis	N=0	N=4 (10)[d**], (43a)[a**], (43b)[a**], (49)[b]	Moderate
Mental health	N=3 (43a)[a-], (43b)[a-], (71)[b-]		Moderate

Notes. Findings of low quality studies are not included in the determination of the level of evidence. [a]Mean or frequency comparison analysis. [b]Correlations. [c]Univariate regression analysis. [d]Multivariate regression analysis with fatigue as dependent variable. [e]Multivariate regression analysis with fatigue as independent variable. [-]Negative relationship; [+]Positive relationship; *Attentional fatigue; **History of a major depressive disorder.

Table 2 Relationship of fatigue with quality of life in breast cancer survivors

	Significant	Not significant	Level of evidence
Emotional problems			
Depressive symptoms	N=22 (10)[a+], (26)[b+], (27)[d+], (29)[a+], (42)[e+], (43a)[a+], (47)[d+], (48)[d+], (50)[d+], (54)[a+], (57)[a+], (58)[e+], (59)[d+], (62)[f+], (65)[b+], (74)[d+], (75)[b+], (77)[b+] (85)[b+], (86)[b+], (88)[b+], (90)[d+]	N=3 (60)[d], (69)[d], (84)[d]	Strong
Anxiety	N=8 (26)[b+], (27)[a+], (29)[a+], (42)[e+], (54)[a+], (74)[b+], (84)[d+], (88)[b+]	N=2 (69)[d], (83)[d]	Strong
Distress	N=4 (26)[d+], (29)[a+], (72)[a+], (79)[d+]	N=1 (46)[d]	Moderate
Sleep-wake pattern			
Sleep disturbances	N=9 (27)[d+],(29)[a+*], (46)[d+], (54)[a+], (62)[b+], (65)[d+*], (66)[d+*], (72)[a+*], (82)[d+*]	N=5 (60)[d], (80)[d], (83)[d], (84)[b], (90)[d]	Strong
Sleep quality	N=4 (27)[a-], (49)[b-], (74)[d-], (88)[b-]	N=1 (69)[d]	Moderate
Activity regulation			
Level of physical activity	N=7 (10)[a-], (27)[d-], (44)[a-], (52)[e-], (58)[b-], (86)[d-], (87)[a-]	N=4 (26)[b], (57)[a], (77)[b], (85)[d]	Moderate
Exercise activity	N=2 (71)[d-], (78)[a-]	N=2 (55)[f], (84)[b]	Insufficient
Coping with cancer diagnosis			
Body image	N=4 (29)[a-], (50)[d-], (58)[b-], (65)[a-]	N=0	Moderate
Future perspective	N=3 (29)[a-], (58)[b-], (65)[a-]	N=0	Moderate
Fear of cancer recurrence	N=2 (25)[e+], (48)[a+]	N=1 (26)[d]	Insufficient
Cancer-related uncertainty	N=2 (61)[d+], (70)[e+]	N=0	Insufficient

Table 3 Relationship of fatigue in breast cancer survivors with psychological factors

Dysfunctional cognitions			
Catastrophizing about symptoms	N=5 (10)[d+], (29)[a+], (43b)[a+], (49)[d+], (55)[f+]	N=1 (43a)[a]	Strong
Self-efficacy	N=1 (83)[d+]	N=1 (27)[d]	Insufficient
Focusing on illness	N=1 (43b)[a+]	N=2 (10)[d], (43a)[a]	Insufficient
Accommodating to illness	N=1 (43b)[a+]	N=2 (10)[d], (43a)[a]	Insufficient
Causal psychological attributions of fatigue	N=1 (27)[a+]	N=1 (83)[d]	Insufficient
Social support			
Satisfaction with social support	N=2 (27)[a-], (74)[b-]	N=0	Insufficient

Notes. Findings of low quality studies are not included in the determination of the level of evidence.
[a]Mean or frequency comparison analysis. [b]Correlations. [c]Univariate regression analysis. [d]Multivariate regression analysis with fatigue as dependent variable. [e]Multivariate regression analysis with fatigue as independent variable. [f]Modeling analysis (path and growth curve analysis).
[-]Negative relationship; [+]Positive relationship; *Insomnia.

Table 3 Continued

DISCUSSION

Summary of findings

The aims of this systematic review were to provide a comprehensive overview of fatigue-related QOL and psychological factors in BCS and to determine the strength of evidence for these relationships. There was moderate to strong evidence for the conclusion that higher levels of fatigue in BCS go together with a lower QOL, a lower level of functioning (in the physical, role, cognitive, emotional, social, and sexual domain), a lower work ability, more pain, and lower mental health. Looking at psychological factors, moderate to strong evidence appeared for the relationship of fatigue in BCS with depressive symptoms, anxiety, distress, sleep disturbances, a lower sleep quality, lower levels of physical activity, components of coping with cancer (ie, body image and worries about future health), and catastrophizing about symptoms.

Strengths and limitations

This is the first systematic review that provides a comprehensive overview of fatigue-related QOL and psychological factors in BCS. Strengths include the structured and thorough search of the literature and the determination of the level of evidence. Our choice to limit our review to breast cancer survivors removes a potentially confounding influence of tumor type and active cancer treatment. Thus far, research on fatigue in cancer survivors has predominantly been focused on BCS (20). This means that our findings represent the majority of the current literature on fatigue in cancer survivors.

A limitation of this review is the lack of sufficient data from longitudinal studies to distinguish causes and consequences of fatigue. It should also be mentioned that we could only draw broad conclusions from group data. Individual patient data would have enabled us to provide more detailed insights, for instance by analyzing if related factors of fatigue differ between certain subgroups of patients (ie, regarding age or type of cancer treatment) (21). Another limitation concerns the heterogeneity of the measurements in the included studies. Questionnaires that measured fatigue and related psychological factors differed, and may (partly) have involved different concepts. The use of 21 different questionnaires in the 57 included studies reflects a lack of consensus on the measurement and definition of fatigue in BCS. Achieving more consensus is required to be able to integrate research results and optimize the scientific knowledge on cancer-related fatigue.

Recommendations for future research

Our findings are in accord with previous systematic reviews on fatigue in cancer survivors with mixed diagnoses. The fatigue-related QOL and psychological factors that were reported in these reviews were also identified in our review on BCS: depression, anxiety, distress, pain, poorer sleep quality, lower physical activity, catastrophizing about symptoms, and worse physical functioning (12, 13). Future reviews should verify if the strength of evidence for these factors and the other fatigue-related factors (ie, components of coping with cancer, different domains of functioning, and work ability) can also be extrapolated to cancer survivors with other tumor types.

The identified fatigue-related psychological factors from our review may influence effects of interventions aimed at fatigue in BCS. It would be valuable to explore the potentially mediating role of these factors. To date, the mechanisms behind cancer-related fatigue are not fully understood, which is seen as a major barrier to enhance symptom control (8). Identifying potential mediators of effects of fatigue-oriented interventions could help to clarify which intervention elements work for whom. In turn, this could improve the tailoring of interventions to individual patients, which could (further) improve its efficacy. Integration of different types of interventions might be beneficial, like combining exercise interventions with elements of cognitive behavioral therapy or mindfulness.

Our review revealed some important gaps in the knowledge on fatigue in BCS. Factors with insufficient evidence require further research. This is the case for four types of dysfunctional cognitions (other than catastrophizing about symptoms) that were only assessed in one population of BCS at multiple time points: (i) self-efficacy (ie, patients' sense of control regarding fatigue), (ii) psychological attributions regarding fatigue (ie, patients' tendency to attribute fatigue complaints to ruminating or sleep disturbances), (iii) focusing on symptoms (ie, preoccupation with symptoms), and (iv) accommodating to illness (ie, patients' tendency to organize their lives to avoid overexertion and control stress). Research has shown that changing dysfunctional cognitions helped to decrease fatigue severity in other patient populations: a decrease in focusing on symptoms and an increase in self-efficacy partly mediated effect of cognitive behavioral therapy on fatigue in patients with chronic fatigue syndrome and type 1 diabetes (22, 23).

Strong evidence appeared for the relationship between higher levels of fatigue with higher levels of anxiety, but fear of cancer recurrence was only examined in three studies (24-26). Future studies should examine the relationship of fatigue with anxiety in BCS, and particularly fear of cancer recurrence, in further detail. It also needs to be examined how to integrate fear of cancer recurrence in interventions for fatigue

in BCS. For instance, our research group has developed an evidence-based cognitive behavioral therapy for fatigue in cancer survivors, in which decreasing high levels of fear of cancer recurrence is seen as a perpetuating factor of fatigue and included as one of the treatment modules (9).

Only two studies took patients' social environment into account and concluded that dissatisfaction with social support was related to a higher level of fatigue (27, 28). Together with the strong and consistent evidence on the negative relationship of fatigue with social functioning, this shows an area of interest for future research on fatigue in BCS.

Few studies focused on sexual functioning and fatigue in BCS (29-32). Sexual dysfunctions resulting from cancer treatment are common and occur in 37 to 51% of BCS (33). Given the high prevalence of both fatigue and sexual dysfunctions, the interrelatedness between these two sequelae of cancer treatment should be examined in further detail. It is likely to hypothesize that a decrease in fatigue severity may improve sexual dysfunctions, which makes it worthwhile to explore the influence of fatigue-oriented interventions on sexual functioning.

Finally, attention should be paid to the relationship of fatigue in BCS with protective psychological factors, like optimism and mindfulness. So far, the main focus has been on factors that are likely to have a negative influence on fatigue. However, it would be valuable to know which skills are helpful to cope with cancer-related fatigue and may prevent it from becoming chronic. Protective psychological factors may also mediate effects of fatigue-oriented interventions. An example was shown in a study on a stress reduction intervention for cancer patients, in which self-reported mindfulness (ie, self-regulation of awareness towards present mental states, and a non-evaluative acceptance towards moment-to-moment experiences) mediated the positive effect on psychological well-being (34).

Clinical implications

The consistent evidence for the relationship of fatigue in BCS with lower scores regarding QOL, all functioning domains, work ability, and mental health reflects the severity of the symptom and its negative consequences on patients' lives. This underlines the importance of interventions that target fatigue in BCS. Our systematic review highlights important areas of attention for existing and future fatigue-oriented interventions: depressive symptoms, anxiety, distress, sleep disturbances, lower physical activity levels, difficulties with coping with cancer, and catastrophizing about symptoms.

Findings of this review showed that fatigue and depressive symptoms go

hand-in-hand. As depressive symptoms were by far the most frequently studied psychological variable, the evidence for its positive relationship with fatigue was the strongest of all variables. It is important to screen for a depressive disorder in fatigued BCS. In that case, fatigue is one of the symptoms (35), and the depressive disorder should be treated first. Once the depressive disorder has been treated successfully, levels of fatigue may decrease at the same time. If not, a fatigue-oriented intervention can be provided afterwards.

Fatigue and depressive symptoms seem to be interdependent: depressive symptoms were shown to be a predictor of fatigue and vice versa. A consistent correlation between depression and fatigue was also found in another systematic review that focused on cancer patients in all phases of the curative and palliative trajectory of cancer treatment (36). Recently, it was shown that a decrease in depressive symptoms influenced the effect of CBT on fatigue in patients with type 1 diabetes. Although patients with a depressive disorder were excluded from this study, depressive symptoms were still identified as one of the mediators of the reduction in fatigue (Menting, Tack, et al., submitted; (37). Elements of psychological interventions like changing dysfunctional cognitions and improving sleep patterns might decrease fatigue and depressive symptoms simultaneously. Directly addressing depressive symptoms may contribute to a further reduction of fatigue. The role and place of depressive symptoms in fatigue-oriented interventions for BCS should be further examined.

Two factors regarding patients' functioning that need attention in treatment of cancer-related fatigue are return to work and pain. Findings of our review showed moderate evidence for a relationship of fatigue and patients' work ability. This relationship was also found in a systematic review of Duijts e.a. on survivors with mixed cancer diagnoses. As the group of occupationally active BCS is expanding and work is important for social integration and participation (38), return to work should be addressed in interventions aimed at fatigue. Besides, future studies should investigate the effects of fatigue-oriented interventions on the work ability of BCS.

Strong evidence emerged from our review regarding a positive relationship between pain and fatigue. More detailed conclusions (eg, on the influence of different locations and causes of pain) cannot be drawn but should be examined future research. Pain resulting from cancer treatment is often complex and difficult to diagnose (39). There is a diversity of pain syndromes in cancer survivors, and a consistently effective pharmacological treatment is lacking (40). Studies have shown a positive relationship of pain with a passive coping style and catastrophizing, which shows potential for psychological coping interventions to improve pain control (39). Integrating coping interventions for pain into interventions for cancer-related fatigue has potential

benefit that needs to be explored in future research.

CONCLUSIONS

Higher levels of fatigue go together with a worse QOL, lower functioning and work ability, more pain, and lower mental health of BCS. This underlines the importance of interventions that decrease this debilitating symptom. The moderate to strong evidence for the relationship of fatigue with depressive symptoms, anxiety, distress, sleep disturbances, lower physical activity levels, difficulties with coping with cancer, and catastrophizing about symptoms reflects important points of attention for interventions aimed at fatigue in BCS. Future research is needed to identify mediators of treatment effects, which could help to explore what intervention elements work for which patients. It also needs to be examined how to integrate pain and return to work into fatigue-oriented interventions. This could guide the development of new interventions, or help to optimize the efficacy of existing interventions aimed at fatigue in BCS.

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APPENDIX

Positive if:	
1.	A validated, complete questionnaire measuring fatigue was used (not only subscales)
2.	A description was given of at least three socio-demographic variables
3.	In- and exclusion criteria were described
4.	Response rate to the fatigue questionnaire was reported and ≥65 %
5.	Information was provided on differences of characteristics between responders and nonresponders
6.	Time since completion of cancer treatment was provided
7.	Type of cancer treatment and stage of disease were described
8.	Data were prospectively gathered
9.	The process of data collection was described
10.	The sample size determination was explained
11.	Missing data were described
12.	The results were compared between two groups or more (e.g., healthy population, groups with different treatment or age and/or compared with at least two time points)
13.	Mean, median, standard deviations or percentages were reported for the most important clinical outcome measure
14.	Limitations of the study were discussed

Supplementary Table 1. Criteria list for assessing the methodological quality of studies on fatigue in breast cancer survivors

4

Severe fatigue after treatment of ductal carcinoma in situ: A comparison with age-matched breast cancer survivors and healthy controls.

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ABSTRACT

Purpose: Severe fatigue after treatment of ductal carcinoma in situ (DCIS) has not been studied before. The current study examined (i) the prevalence of severe fatigue in DCIS patients versus breast cancer survivors (BCS) and healthy controls (HC), (ii) quality of life and functioning of severely versus non-severely fatigued DCIS patients and BCS, and (iii) the association of fatigue with psychosocial and behavioral factors in DCIS patients.

Methods: 89 patients treated for DCIS were matched on age and gender to 67 BCS and 178 HC (ratio 1:1:2). Fatigue was measured with the Fatigue Severity subscale of the Checklist Individual Strength.

Results: 23% of DCIS patients, 25% of BCS, and 6% of HC were severely fatigued (DCIS versus HC: $P < .001$). Severely fatigued DCIS patients had a lower quality of life and were more impaired in all domains of functioning than non-severely fatigued DCIS patients. Sleep problems, dysfunctional cognitions regarding fatigue, avoidance of activities, all-or-nothing behavior, perceived lack of social support, DCIS-related coping problems, and fear of future cancer occurrence were related to fatigue.

Conclusions: The prevalence of severe fatigue in DCIS patients was similar to BCS, but higher than in HC. Severely fatigued DCIS patients had a lower quality of life and more functional impairments. The psychosocial and behavioral fatigue-related factors in DCIS patients are known to perpetuate fatigue in BCS. These factors can be targeted in interventions for cancer-related fatigue. Our findings suggest that the same treatment elements might be applicable to severely fatigued DCIS patients.

INTRODUCTION

Since the introduction of breast cancer screening programs in western countries in the nineties, the number of detected cases of ductal carcinoma in situ (DCIS) has increased rapidly (1). Nowadays, an estimated proportion of 1 in 33 women will be diagnosed with DCIS in her lifetime (2). It cannot be predicted in which cases DCIS will be harmless, and in which cases it will develop into breast cancer (3). To prevent any progression, DCIS is generally treated with a mastectomy or breast-conserving surgery followed by radiotherapy (4).

This means that although DCIS is non-invasive, it is treated with the same treatment modalities as breast cancer. This paradox can make DCIS a confusing diagnosis for patients (5). So far, the influence of DCIS on patients' lives has been examined in a limited number of studies. A recent large study showed that the overall quality of life does not differ between DCIS patients and age-matched women without a history of a breast disease (6). Nevertheless, the diagnosis and treatment of DCIS can have significant impact on psychosocial functioning.

A subgroup of DCIS patients has increased distress levels and poor mental health during and after treatment completion, and coping problems frequently occur (7-9). Patients are often unsure about their diagnosis, for example about whether DCIS is cancer (9). Despite the favorable prognosis of DCIS, many patients overestimate their actual risk on the occurrence of breast cancer or metastases (8, 10, 11). Anxiety plays a main role in this overestimation (8).

In contrast to the limited number of studies on sequelae of DCIS treatment, numerous studies examined this subject in breast cancer survivors (BCS). In these studies, severe fatigue emerged as one of the most troublesome cancer-related symptoms, occurring in approximately one in four BCS and diminishing patients' quality of life (12, 13). Thus far, the prevalence of severe fatigue and its consequences have not been studied in DCIS patients.

Guidelines on cancer-related fatigue assume that fatigue is related to cancer and its treatment (13). However, these triggers are no longer present after treatment completion. At that point, factors that maintain fatigue come into play (14). There is evidence for multiple psychosocial and behavioral factors that can perpetuate fatigue in cancer survivors: sleep problems, perceived lack of social support, low physical activity levels, dysfunctional cognitions regarding fatigue, heightened fear of cancer recurrence, and poor coping with the diagnosis cancer and being treated for cancer (14, 15). Though DCIS-related coping problems and worries about future cancer occurrence

are also common in DCIS patients (8, 10, 11), it is unknown if these factors are related to fatigue. The other factors and their association with fatigue have not been explored in DCIS patients yet.

In this study, we examined (i) the prevalence of severe fatigue in DCIS patients compared to BCS and healthy controls (HC), (ii) quality of life and functioning of severely versus non-severely fatigued DCIS patients and BCS, and (iii) the association of fatigue with psychosocial and behavioral factors in DCIS patients.

METHODS

Participants and procedure

A cross-sectional study was conducted in two general hospitals in the Netherlands: hospital Gelderse Vallei (Ede) and hospital Pantein (Boxmeer). All patients who were treated for DCIS or breast cancer between January 2010 and September 2015 were registered in anonymous patient registries. DCIS patients and BCS were selected from these registries. Ethical approval was obtained from the medical ethic committees of both hospitals.

DCIS patients were eligible if treatment for DCIS was completed up to five years ago. DCIS patients were excluded if (i) a current or former malignant tumor, or (ii) a somatic comorbidity that can cause severe fatigue was reported in their medical records. All eligible DCIS patients were selected from the patient registries, and invited to participate by mail. If they were willing to participate, they were asked to return a participation form and to indicate if they preferred to complete the questionnaires by e-mail or by mail. Subsequently, participants received the questionnaires in the preferred way, as well as an informed consent with a self-addressed envelope by mail.

To determine if the prevalence of fatigue in DCIS patients differed from women who have had a malignant breast tumor and healthy women, two control groups were selected. Each DCIS patient was matched to one BCS and two HC (ratio 1:1:2) with respect to gender and age, based on categories of 5-year strata. Matched BCS were selected from the patient registries of the participating hospitals. All matched BCS (i) had completed breast cancer treatment up to five years ago (except for hormone therapy), (ii) were disease-free, and (iii) had no somatic comorbidities that could cause severe fatigue according to their medical records. To equalize type of treatment, DCIS patients were only matched to BCS who had not received chemotherapy. A recent meta-analysis of our research group indicated chemotherapy as a potential risk factor for severe fatigue in BCS (12). For this reason, BCS who had received chemotherapy

were excluded. Matched BCS received questionnaires by mail. They were asked to return the questionnaires and an informed consent if they were willing to participate.

Matched HC were derived from CentERdata, a cohort of over 2000 Dutch adults who represent the general Dutch population (16). Precision matching on age and gender was performed with the procedure Coarsened Exact Matching (CEM) using STATA/SE 12.1. Being healthy was defined as zero days of sick leave in the past month, and no self-reported limitations in daily activities, social activities and work due to health problems.

Measures

Data on the clinical variables stage of DCIS, type of surgery, radiotherapy, and date of diagnosis were retrieved from medical records. Data on the latter two variables were also available in BCS. Data on the socio-demographic variables partner and work status, educational level, medical problems, and recent significant life events were gathered with self-report questionnaires. Educational level was also available in HC and categorized into low, medium and high, according to the Dutch national public health compass (17).

The level of fatigue was measured in DCIS patients, BCS and HC with the subscale Fatigue Severity of the Checklist Individual Strength (CIS-fatigue; 8 items, 7-point scale, range 8-56) (18, 19). Higher score indicate higher levels of fatigue. The established cut-off score for severe fatigue is 35 or higher, which is two standard deviations above the mean score in HC (18, 19). The CIS-fatigue has good psychometric properties (20, 21), and was used in previous research on cancer patients and survivors (14, 15, 22).

Quality of life and functioning were measured in DCIS patients and BCS with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30; 30 items, 4-point scale) (23). This questionnaire consists of function scales (physical, social, cognitive, emotional, and role functioning) and a global quality of life scale. Higher scores indicate better functioning. The EORTC-QLQ-C30 has adequate validity and reliability (24).

Questionnaires on behavioral and psychosocial factors were only administered in DCIS patients. Sleep quality was measured with the Sleep/Rest subscale of the Sickness Impact Profile-8 (SIP-8). Higher scores indicate more sleep problems (25).

Activity patterns were assessed with the two subscales of the Cognitive and Behavioral Responses to Symptoms Questionnaire (CBRSQ): avoidance of activities and fluctuating activity patterns (i.e., all-or-nothing behavior). Higher scores indicate a more dysfunctional activity pattern (26).

Cognitions regarding fatigue were measured with the Self-Efficacy Scale (SES).

Higher scores indicate a lower sense of control with regard to fatigue (27). Focusing on fatigue was measured with the Illness Management Questionnaire (IMQ). Higher scores indicate a higher tendency to focus on fatigue (28).

Fear of cancer occurrence was measured with an adapted version of the Cancer Worry Scale (CWS). The word 'again' was removed from all items to adapt this questionnaire for DCIS patients. Higher scores indicate more worries about cancer (29).

Coping with DCIS was assessed with the Impact of Event Scale (IES), which measures patients' responses to having had DCIS and being treated for DCIS with the two dimensions intrusion and avoidance. Higher scores indicate more coping problems (30).

Discrepancies in social support were measured with the shortened version of the Social Support List Discrepancy (SSL-D). Lower scores indicate more discrepancies between the level of desired and actual social support (31).

Statistic analyses

Descriptive statistics were used to report socio-demographic and clinical characteristics of study participants. Available characteristics of the control groups were compared to DCIS patients using chi-square tests for independence and independent samples T-tests. These methods were also used to compare characteristics of severely and non-severely fatigued DCIS-patients.

DCIS patients, BCS and HC were divided in severely versus non-severely fatigued patients, using the cut-off score of 35 of the CIS-fatigue. Chi-square tests for independence and independent samples T-tests were used to compare fatigue prevalence rates and mean fatigue scores between DCIS patients and BCS, and DCIS patients and HC. Independent samples T-tests were used to compare quality of life and functioning between severely and non-severely fatigued DCIS patients, and between severely and non-severely fatigued BCS. Differences on the EORTC-QLQ-C30 subscales of at least 10 points were considered to be clinically relevant (32).

Pearson correlations were used to assess if fatigue severity was related to psychosocial and behavioral factors. Spearman's rank correlation coefficients were used for ordinal variables. Correlations were interpreted following of Cohen's guidelines (0.1-0.29 = weak, 0.3 - 0.49 = moderate, ≥0.5 = strong (33)). P-values of .05 were considered as statistically significant, and SPSS version 22 was used for all analyses.

RESULTS

Sample characteristics

Figure 1 illustrates the flow chart of patient inclusion. Between January 2010 and September 2015, 156 patients were diagnosed with DCIS in the two participating hospitals. Twenty-eight patients were excluded, because they had a somatic comorbidity that could cause severe fatigue (*N* = 11), a current or former malignant tumor (n=6), were deceased (*N* = 5), not locatable (*N* = 4), or had cognitive impairments (*N* = 2).

In total, 128 DCIS patients were eligible. Thirty-nine patients did not participate in the study, of which 11 patients actively declined to participate. Questionnaires were completed by 89 patients (response rate of 70%). Non-participants did not differ significantly from participants regarding age at diagnosis, stage of DCIS, and type of DCIS treatment. Socio-demographic and clinical characteristics of study participants, and severely versus non-severely fatigued DCIS-patients are reported in Table 1. None of the characteristics differed significantly between these two groups.

Regarding the control groups, 67 of 89 BCS completed the questionnaires on fatigue and QOL (response rate of 75%), and 178 HC were retrieved from the CentERdata cohort. Mean time since diagnosis was significantly longer in BCS than in DCIS patients (respectively 49 months (SD = 10) and 35 months (SD = 19); *P* < .001). All BCS and

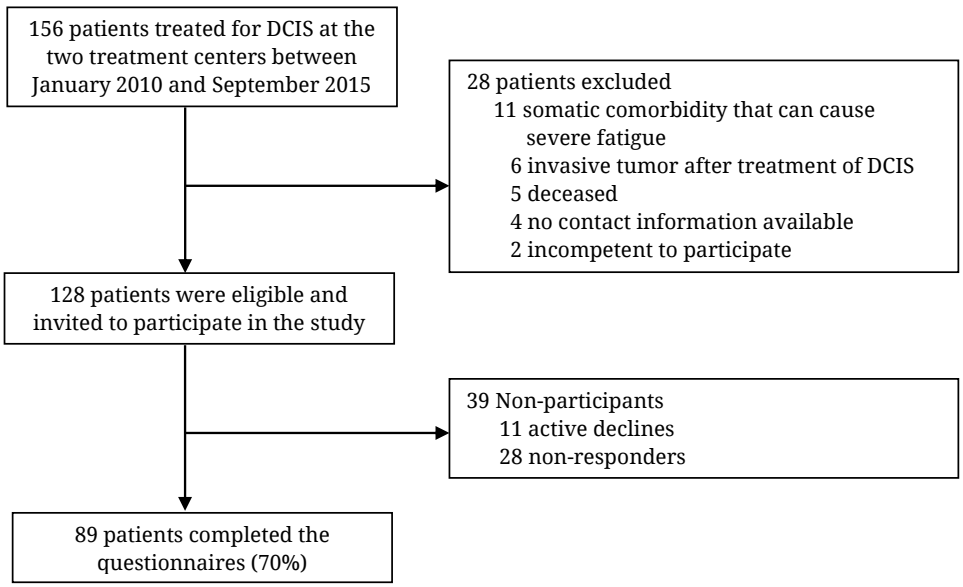

Figure 1. Flow chart of patient inclusion.

DCIS patients were treated with surgery. The number of patients who had received radiotherapy did not differ significantly between BCS and DCIS patients. Educational level did not differ significantly between DCIS patients and HC.

Prevalence of severe fatigue

In total, 20 of 88 DCIS patients (23%), 17 of 67 BCS (25%) and 11 of 178 HC (6%) were severely fatigued. One DCIS patient was excluded from the analyses because of missing values on the CIS-fatigue. The proportion of severely fatigued patients did not differ significantly between DCIS patients and BCS (P = 0.847), but was significantly higher in DCIS patients than in HC (P < 0.001). Mean fatigue severity scores were 24.7 (SD 13.2; range 8-56) in DCIS patients, 26.5 (SD 12.8; range 8-56) in BCS and 17.7 (SD 8.6; range 8-48) in HC. Mean fatigue severity scores did not differ significantly between DCIS patients and BCS (P = 0.397), but were significantly higher in DCIS patients than in HC (p< 0.001).

Quality of life and functioning in severely versus non-severely fatigued patients

Severely fatigued DCIS patients scored significantly lower on global quality of life, and physical, role, emotional, cognitive, and social functioning than non-severely fatigued DCIS patients. Mean differences were at least 10 points in all domains, which indicates that all differences were clinically relevant. This pattern of results was similar when comparing severely and non-severely fatigued BCS (Table 2).

Relationship of fatigue with psychosocial and behavioral factors

There were strong correlations between fatigue, and focusing on fatigue (IMQ; r = 0.62, P < 0.001) and avoidance of activities (CBRSQ; r = 0.52, P < 0.001). There were moderate correlations between fatigue and sleep problems (SIP; r=.45, p<.001), all-or-nothing behavior (CBRSQ; r = 0.42, P < 0.001), problems with coping with the diagnosis DCIS and its treatment (IES intrusion; r = 0.33, P = 0.002; IES avoidance; r = 0.32, P = 0.003), and perceived lack of social support (SSL-D; r = 0.33, P = 0.002). There was a weak correlation between fatigue, and sense of control regarding fatigue (SES; r = -0.26, P =0.015) and fear of future cancer occurrence (CWS; r = 0.24, P = 0.025).

	Total sample[a] (n=89)	Severely fatigued patients[a] (n=20)	Non-severely fatigued patients[a] (n=68)	Difference P-value[b]
Socio-demographic characteristics				
Age at diagnosis in years				
Mean ± SD, range	61.2 ± 9.0 (40-79)	58.7 ± 8.8 (42-72)	61.8 ± 9.0 (38-75)	0.18
Education level				
Low	37 (42)	7 (37)	29 (44)	0.72
Middle	25 (28)	7 (37)	18 (27)	
High	24 (27)	5 (26)	19 (29)	
Having a partner				
Yes	76 (85)	17 (90)	59 (87)	1.00[3]
No	11 (12)	2 (10)	9 (13)	
Having a paid job				
Yes	34 (38)	9 (47)	43 (63)	0.57
No	54 (61)	10 (53)	25 (37)	
Clinical characteristics				
Time since diagnosis in months				
Mean ± SD, range	35 ± 19 (5-100)	34 ± 17 (5-61)	36 ± 19 (5-100)	0.64
Stage of disease				
I	5 (6)	2 (10)	3 (4)	0.08
II	29 (33)	10 (50)	19 (28)	
III	55 (62)	8 (40)	45 (68)	
Type of surgery				
Lumpectomy	56 (63)	13 (65)	42 (62)	1.00[c]
Lumpectomy + breast reconstruction	3 (3)	0 (0)	3 (4)	1.00[c]
Mastectomy	13 (15)	3 (15)	10 (15)	1.00[c]
Mastectomy + breast reconstruction	17 (19)	4 (20)	13 (19)	1.00[c]
Type of adjuvant treatment				
Radiotherapy	57 (64)	12 (60)	44 (65)	0.90
Self-reported medical problems (≥1)				
	49 (55)	10 (53)	28 (41)	0.53

Notes. Total sample numbers differ because of missing data.
[a] Results are shown as *n* (%), unless indicated otherwise.
[b] Difference between severely and non-severely fatigued DCIS patients; **P* < .05.
[c] Fisher's exact test was used because of violation of the assumption of minimum expected cell frequency.

Table 1. Characteristics of DCIS patients.

EORTC-QLQ-C30 subscales	DCIS patients		P value	BCS		P value
	Severe fatigue (n=20)	No severe fatigue (n=68)		Severe fatigue (n=17)	No severe fatigue (n=50)	
Global quality of life	63.2 ± 16.3	84.1 ± 13.0	< 0.001*	53.9 ± 20.4	81.0 ± 14.0	< 0.001*
Physical functioning	80.0 ± 15.0	90.8 ± 11.6	0.001*	64.2 ± 19.0	87.8 ± 14.0	< 0.001*
Role functioning	64.8 ± 22.8	94.1 ± 13.4	< 0.001*	54.9 ± 28.7	90.0 ± 18.4	< 0.001*
Emotional functioning	64.9 ± 23.3	88.7 ± 14.1	< 0.001*	65.1 ± 21.1	82.0 ± 19.0	0.004*
Cognitive functioning	70.2 ± 21.2	91.4 ± 14.0	< 0.001*	69.6 ± 20.6	87.3 ± 17.4	0.001*
Social functioning	69.3 ± 25.0	93.9 ± 11.5	< 0.001*	79.2 ± 25.5	93.3 ± 13.0	0.047*

Notes. Scores are reported as mean ± SD. Higher scores indicate better functioning. *$P < 0.05$. Abbreviations: DCIS = ductal carcinoma in situ, BCS = breast cancer survivors.

Table 2. Mean scores on the EORTC-QLQ-C30

DISCUSSION

This was the first study that examined the prevalence of severe fatigue in DCIS patients with a validated fatigue measure. The prevalence of severe fatigue in DCIS patients of 23% was similar to BCS, but higher than in HC. Severely fatigued DCIS patients had a lower quality of life and were more impaired in all domains of functioning compared to non-severely fatigued DCIS patients. Differences in quality of life and functioning were similar between severely and non-severely fatigued BCS, which replicates previous research (34). Besides, fatigue was related to the psychosocial and behavioral factors known to perpetuate fatigue in BCS (15).

Severe fatigue is a common and troublesome symptom in DCIS patients, just as in BCS. Given its adverse consequences on quality of life and functioning, this symptom needs to be taken seriously. Clinicians should pay attention to fatigue in DCIS patients in daily practice, in the same manner as in cancer patients and survivors. In accordance with the NCCN guidelines for cancer-related fatigue, it seems appropriate to screen all DCIS patients for fatigue in clinical practice (35).

The similarities in DCIS patients and BCS concerning the prevalence, consequences and possible perpetuating factors of fatigue suggest that a breast disease does not need to be malignant to induce severe fatigue. Triggers of severe fatigue might be equal in DCIS patients and BCS (e.g., being diagnosed with a potentially serious medical condition, and being treated with surgery and/or radiotherapy). Once treatment of breast cancer of DCIS is completed, these triggers are no longer involved. After treatment completion, more generic factors are related to fatigue in both patient groups (e.g., sleep problems,

low physical activity levels, and dysfunctional cognitions regarding fatigue).

These factors are targeted in evidence-based interventions for fatigue in cancer survivors. For example, physical activity levels can be increased in exercise interventions, and adjustment of dysfunctional cognitions regarding fatigue is part of cognitive behavioral therapy (13). Our findings suggest that these interventions may also be applicable to DCIS patients. However, the interventional approach needs to be adapted to this patient group. In this case, attention should be paid to common DCIS-specific problems, like coping problems regarding the diagnosis (36). Further research is needed to adapt current interventions for fatigue in cancer survivors to DCIS patients, and to examine the efficacy of these interventions.

Only 6% of our HC were severely fatigued, which is a low prevalence rate compared to other studies that retrieved HC from the CentER dataset. These studies found prevalence rates ranging from 7 to 22% using different criteria for health (37-39). Our criteria for being healthy were relatively strict, as all women with any limitations caused by health problems were excluded. Therefore, the prevalence of fatigue in our HC sample possibly is an underestimation. Moreover, some baseline characteristics of the two control groups are unknown (e.g., partner and work status). However, due to the applied matching procedure, the three research groups were comparable with regard to gender and age. Besides, the fact that recruitment procedures were identical for DCIS patients and BCS enhances the comparability of these two groups. Another limitation of this study is a lack of information on when patients became fatigued and how long they were fatigued. Therefore, the diagnosis and treatment of DCIS have not necessarily been the only triggers of fatigue. Future studies should take the length and starting point of fatigue symptoms into account.

Participants in this study were diagnosed between 2010 and 2015. In this five-year period, Dutch breast cancer guidelines had been revised once (40). It is possible that cancer treatment has changed after this guideline revision. A sensitivity analysis was conducted to compare fatigue levels between DCIS patients treated before and after the guideline change in 2012. The same analysis was conducted for BCS. Fatigue levels did not differ significantly between the two treatment periods in both patient groups (p-values respectively 0.187 and 0.732). This suggests that our results were not influenced by changes in cancer treatment during the five-year study period.

This study was a first attempt to identify factors that were associated with fatigue in DCIS patients. However, the related factors of fatigue will probably be interrelated, and causality could not be determined. The sample size of our study was too small to conduct more advanced analyses like a multiple regression or a cluster analysis. Future studies with larger sample sizes are needed to further examine related factors

of fatigue in DCIS patients.

In conclusion, this study showed that severe fatigue is a common symptom that occurs in almost a quarter of DCIS patients, and influences quality of life and functioning adversely. Fatigue was related to psychosocial and behavioral factors that perpetuate fatigue in cancer survivors. Evidence-based interventions for fatigue in cancer survivors target these perpetuating factors, and might also be applicable to DCIS patients. However, it should be examined if the interventional approach needs to be adapted, taking DCIS-specific coping problems into account.

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5

The Distress Thermometer for screening for severe fatigue in newly diagnosed breast and colorectal cancer patients.

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ABSTRACT

Objective: Internationally, the Distress Thermometer and associated Problem List are increasingly used in oncology as screening tools for psychological distress. Cancer-related fatigue is common but often overlooked in clinical practice. We examined if severe fatigue in cancer patients can be identified with the fatigue item of the Problem List.

Methods: Newly diagnosed breast (*N* = 334) and colorectal (*N* = 179) cancer patients were screened for severe fatigue, which was defined as having a positive score on the fatigue item of the Problem List. The Fatigue Severity subscale of the Checklist Individual Strength was used as gold standard measure for severe fatigue.

Results: In total, 78% of breast cancer patients and 81% of colorectal cancer patients were correctly identified with the fatigue item. The sensitivity was 89% in breast cancer patients and 91% in colorectal cancer patients. The specificity was 75% in breast cancer patients and 77% in colorectal cancer patients. The positive predictive value was 53% in breast cancer patients and 64% in colorectal cancer patients, whereas the negative predictive value was 95% in both tumor types.

Conclusions: The fatigue item of the Problem List performs satisfactorily as a quick screening tool for severe fatigue. However, a positive screen should be followed up with a more thorough assessment of fatigue, i.e., a questionnaire with a validated cut-off point. Given time pressure of clinicians, this already implemented and brief screening tool may prevent severe fatigue from going undetected in clinical practice.

BACKGROUND

The Distress Thermometer (DT) and associated Problem List (PL) are increasingly used for routine screening in oncology practice, as recommended in the clinical practice guideline for distress management of the National Comprehensive Cancer Network (NCCN) (1, 2). The aim of this short self-report questionnaire is to detect psychological distress and related problems in cancer patients (3). As the time per patient in clinical visits is limited, screening tools like the DT can prevent important needs of patients from being overlooked. Given the emerging international implementation of the DT and associated PL, it is worthwhile to assess the potential of this screening tool for other screening purposes. For example, Hegel et al. already showed that a cut-off score of 7 on the DT has good sensitivity and specificity to detect depression in newly diagnosed breast cancer (BC) patients (4).

Another common and disabling symptom in cancer patients is cancer-related fatigue, defined by the NCCN as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness, related to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning" (5). Severe fatigue can cause impairments in daily functioning and diminish quality of life (6). According to current international guidelines (7), cancer patients should be screened routinely for the presence of fatigue in clinical practice using brief, quantitative self-report measures with empirically established cutoff scores. However, fatigue screening is not common in many clinical settings due to barriers of clinicians (eg, time limitations or not recognizing fatigue as a problem) or patients (eg, not wanting to complain or assuming that cancer-related fatigue is normal and permanent) (5).

The use of the already implemented DT and associated PL as a screening tool for severe fatigue might improve the detection of severe fatigue in cancer patients. The PL includes 1 fatigue item, in which patients are asked if fatigue is a problem for them. The aim of the current study was to examine the usability of this fatigue item of the PL to detect severe fatigue in newly diagnosed BC and colorectal cancer (CC) patients.

METHODS

Procedure

All patients who attended an intake session before the start of their cancer treatment filled out a psychosocial screening at the outpatient clinic of the oncological center of

hospital Gelderse Vallei (Ede, the Netherlands). This screening was administered by a nurse practitioner as part of routine clinical care for BC and CC patients, and consisted of a DT with associated PL and the subscale Fatigue Severity of the Checklist Individual Strength (CIS-fatigue). Administration of the DT is in accordance with the Dutch guideline "Detection of need for psychosocial care (8)." The CIS-fatigue was added to screen for severe fatigue because evidence-based cognitive behavioral therapy for severe fatigue (9) is part of routine care in hospital Gelderse Vallei. Data from screenings administered between December 2009 and January 2013 were available for the current study. Approval of a medical ethical committee was not required because all available patient data were deidentified and collected as part of routine clinical care.

Study population

Data from patients who (i) were newly diagnosed with breast or colorectal cancer, (ii) were scheduled for cancer treatment with curative intent, and (iii) filled out a psychosocial screening questionnaire prior to cancer treatment were included.

Measures

Distress Thermometer (DT)

The DT consists of a thermometer and a PL, in which patients are asked which problems or symptoms they experienced in the past week. The problems in this checklist are divided into 5 categories: practical problems, family problems, emotional problems, spiritual/ religious concerns, and physical problems (10). In the current study, only the fatigue item (yes/ no) of the category "Physical problems" of the PL was used.

Checklist Individual Strength (CIS)

The subscale Fatigue Severity (8 items, 7-point scale, range 8-56) of the CIS (CIS-fatigue) measures the level of fatigue over the past 2 weeks. The CIS-fatigue was originally developed to measure severe fatigue in patients with chronic fatigue syndrome (11,12). The established cutoff score for severe fatigue is 35 or higher (11). The CIS-fatigue has been shown to be sensitive to change in fatigue levels over time in previous studies on cancer patients during curative and palliative treatment, and in cancer survivors who had completed cancer treatment (9,13-16).

Previous studies have shown that the psychometric quality of the CIS-fatigue is adequate. In the current study, the reliability of the CIS-fatigue was excellent (Cronbach's α = .93). This was also the case in other studies in which this questionnaire was used

(11,12,17). In addition, previous research has demonstrated that the CIS-fatigue has good to excellent convergent, discriminative, and divergent validity (11,12,17). Besides, the CIS-fatigue has been found to be able to discriminate between severely and non-severely fatigued subjects in study populations of patients with chronic diseases (eg, chronic fatigue syndrome, rheumatoid arthritis, multiple sclerosis, neuromuscular diseases, and type 1 diabetes) and healthy populations (eg, healthy controls and different occupational groups) (17-21).

Analysis

The test variable was fatigue according to the fatigue item of the PL. The CIS-fatigue (cutoff ≥ 35) was used as gold standard measure for severe fatigue. Sensitivity analyses were performed to assess the usability of the fatigue item of the PL as screening tool for severe fatigue. Based on our gold standard measure, fatigue scores were defined as true positive (TP; correctly identified as case of severe fatigue), true negative (TN; correctly identified as noncase of severe fatigue), false positive (FP; incorrectly identified as case), and false negative (FN; incorrectly identified as noncase). The following psychometric properties of the fatigue item were calculated: (i) the number of severely fatigued cancer patients who were correctly identified with the fatigue item (overall test accuracy, [TP+TN]/[TP+TN+FP+FN]); (ii) the probability that the fatigue item will be positive when severe fatigue is present (true positive rate/sensitivity, TP/[TP+FN]); (iii) the probability that the fatigue item will be negative when severe fatigue is absent (true negative rate/specificity, TN/[TN+FP]); (iv) the probability that a patient is truly severely fatigued when the fatigue item is positive (positive predictive value, TP/[TP+FP]), and (v) the probability that a patient is not truly severely fatigued when the fatigue item is negative (negative predictive value, TN/[TN+FN]).

RESULTS

Patient characteristics

The eligibility of all patients who filled out a psychosocial screening (N = 592) was assessed. Seventy-nine patients were excluded because they were scheduled for cancer treatment with palliative intent

(N = 42), had a benign tumor (N = 18), were previously treated for cancer (N = 14), or had already received neo-adjuvant chemotherapy (N = 5). This resulted in a study sample of 513 patients: 334 BC and 179 CC patients. Demographic and clinical characteristics are shown in Table 1. The population of BC patients was primarily female (98%)

	Breast cancer patients (*N*=334) *N* (%)	Colorectal cancer patients (*N*=179) *N* (%)
Demographic characteristics		
Age		
(Mean ± SD, range)	59.7 ± 13.5, 29-92	69.3 ± 11.5, 29-92
Gender		
Female	328 (98)	78 (44)
Male	6 (2)	101 (56)
Clinical characteristics		
Stage of disease		
I	172 (51)	54 (30)
II	123 (37)	60 (34)
III	36 (11)	63 (35)
Unknown	3 (1)	2 (1)

Table 1 Patient characteristics

with a mean age of 60 years (SD = 14), and half of patients had early-stage BC. About half of the population of CC patients was male (56%), the mean age was 69 years (SD = 12), and the stage of cancer (I-III) was equally divided.

Screening for severe fatigue with the fatigue item

In total, 80 BC patients (24%) and 54 CC patients (30%) were severely fatigued according to the gold standard CIS-fatigue. The mean CIS-fatigue score at intake was 25 (SD = 13) in BC patients and 26

(SD = 15) in CC patients. The results of the sensitivity analyses are shown in Table 2. Five patients were excluded from these analyses due to missing data. The overall accuracy of the fatigue item of the PL to detect severe fatigue was 78% in BC survivors and 81% in CC survivors. There were 9 missed cases of severe fatigue (false negatives) in BC patients and 5 false negatives in CC patients. Given these false negatives, the probability that the fatigue item is positive when severe fatigue is present (sensitivity) was 89% in BC and 91% in CC patients. There was false alarm in 63 BC patients and in 28 CC patients because they were incorrectly identified as cases of severe fatigue (false positives). Given these false positives, the probability that the fatigue item is negative when severe fatigue is absent (specificity) was 75% in BC and 77% in CC patients. In addition, the probability that a patient is truly severely fatigued when the fatigue

	Breast cancer patients (*N*=330)	Colorectal cancer patients (*N*=178)
Outcomes, *N* (%)		
True positives	70 (21)	49 (27)
True negatives	188 (56)	96 (54)
False positives	63 (19)	28 (16)
False negatives	9 (3)	5 (3)
Psychometric properties		
Accuracy	0.782	0.815
Sensitivity	0.886	0.907
Specificity	0.749	0.774
Positive predictive value	0.526	0.636
Negative predictive value	0.954	0.950

Table 2. Detecting severe fatigue with the fatigue item of the Problem List

item is positive (positive predictive value) was 53% in BC and 64% in CC patients. The probability that non-cases of severe fatigue are indeed not severely fatigued when the fatigue item is negative (negative predictive value) was 95% in both tumor types.

CONCLUSIONS

This study showed that the fatigue item of the PL of the DT performs satisfactorily to screen quickly for severe fatigue in newly diagnosed cancer patients. However, a positive screen should be followed up with a more thorough assessment of fatigue (i.e., a questionnaire with a validated cutoff point) to confirm that the patient is severely fatigued. Given time pressure of clinicians, brief screening tools like the DT could prevent significant problems like severe fatigue from going unnoticed. As the DT and PL are increasingly used in daily clinical practice, this screening tool for severe fatigue can easily be integrated in regular care for cancer patients.

International guidelines recommend the use of brief self-report measures for routine screening of cancer-related fatigue in clinical practice (7). The current study showed that the fatigue item of the PL, with a mean sensitivity of 90% and a mean specificity

of 76%, can reliably be used for this purpose. This also applies to other single-item screening instruments for cancer-related fatigue. For instance, Butt et al. examined the usability of an eleven-point scale item "How would you rate your fatigue at its worst over the past three days?" This item was based on the NCCN Clinical Practice Guidelines for Supportive Care, and had an optimal cutoff score of 5 with a sensitivity of 69% and a specificity of 71% (22). Another examined single-item screening instrument concerns the four-point scale item "I get tired for no reason" of the Zung Self-Rating Depression Scale. Kirsh et al. showed that this item had an optimal cutoff score of 2, with a sensitivity of 79% and a specificity of 88% (23). These findings indicate that single-items can be quick and yet accurate screening tools for cancer-related fatigue.

It is important to detect severe fatigue as early as possible. A recent study of our research group showed that fatigue severity before start of cancer treatment strongly predicts the severity of persistent post-treatment fatigue (13). This indicates that screening for cancer-related fatigue may already start before initiation of cancer treatment. The current study showed that screening prior to treatment can quickly and reliably be performed with the Fatigue item of the PL.

Screening should continue during and after cancer treatment, as recommended by the NCCN guidelines for cancer-related fatigue (5). Previous studies with breast cancer survivors have identified different individual trajectories of fatigue symptoms, like (i) fatigue that is only present during cancer treatment, (ii) persistent fatigue that starts during cancer treatment and continues after cancer treatment, and (iii) delayed-onset fatigue that starts after conclusion of adjuvant therapy (16,24,25). In addition to these different trajectories of cancer-related fatigue, patients can value their levels of fatigue differently throughout treatment (16). These response shifts and individual variations in fatigue trajectories over time imply that fatigue is a dynamic symptom that warrants repeated screening throughout treatment.

Once patients have been identified as severely fatigued, it is warranted to monitor them. However, only detecting severe fatigue is not sufficient. In case of severe fatigue, a focused history and physical examination is needed, as recommended in the NCCN guidelines for cancer-related fatigue. For instance, the clinician should examine whether the fatigue is a symptom of recurrence of malignancy for cancer survivors who were assumed to be disease-free, or if the patient has non-cancer comorbidities that can explain severe fatigue (5).

Fatigue should also be discussed with patients. Previous research on cancer survivors has shown that severe fatigue, measured with the CIS-fatigue, often goes hand in hand with impairments in multiple domains of daily functioning (26,27). However, fatigue is a subjective experience that is experienced differently by each patient (5), and patients

can be severely fatigued but this does not necessarily mean that this is a problem to them. The Fatigue item of the PL is an easy way to detect severe fatigue quickly, but clinicians need to find out whether fatigue bothers patients and whether support is required to manage it.

Referral to fatigue-oriented interventions should be considered in case of persistent high levels of fatigue. Available evidence-based interventions during cancer treatment are physical exercise interventions (28,29). For patients with severe fatigue after cancer treatment, evidence-based psychosocial interventions (i.e., cognitive behavioral therapy and psycho-educational therapies) are also available in addition to physical exercise interventions. There is also, albeit limited, evidence for mind-body interventions for fatigue in cancer survivors (i.e., mindfulness-based approaches, yoga, and acupuncture) (7).

Strengths of the current study were the large sample size and the representativeness of the two samples of newly diagnosed cancer patients. In a previous study of Goedendorp et al, the prevalence of severe fatigue according to the CIS-fatigue was 20% in newly diagnosed BC and 28% in newly diagnosed gastrointestinal cancer patients, which is comparable to the prevalence rates in our two patient samples (30). A limitation was the assessment of the psychometric properties of the fatigue item prior to cancer treatment. As our study was cross-sectional, future research is needed to assess if the fatigue item of the Distress Thermometer can also be used to screen for severe fatigue during and after cancer treatment. However, there are no reasons to assume that the moment of screening influences the psychometric quality of the fatigue item. Additionally, although the psychometric properties of the CIS-fatigue have proven to be adequate and although the CIS-fatigue is sensitive to change in cancer patients, its cutoff score for severe fatigue has not specifically been validated in cancer patients yet.

In conclusion, the fatigue item of the Problem List performs satisfactorily as a quick screening tool for severe fatigue. However, a positive screen should be followed up with a questionnaire with a validated cutoff point. This tool can, in a time sensitive manner, prevent severe fatigue from being overlooked in clinical practice.

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Part II

Advancing cognitive behavioural therapy

6

A randomized controlled trial of internet-based cognitive behavioral therapy for severely fatigued breast cancer survivors (CHANGE-study): study protocol.

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ABSTRACT

Background: About one third of breast cancer survivors suffer from persistent severe fatigue after completion of curative cancer treatment. Face-to-face cognitive behavioral therapy (F2F CBT) especially designed for fatigue in cancer survivors was found effective in reducing fatigue. However, this intervention is intensive and treatment capacity is limited. To extend treatment options, a web-based version of CBT requiring less therapist time was developed. This intervention is aimed at changing fatigue-perpetuating cognitions and behaviors. The efficacy of web-based CBT will be examined in a multicenter randomized controlled trial.

Methods: In total, 132 severely fatigued breast cancer survivors will be recruited and randomized to either an intervention condition or care as usual (ratio 1:1). Participants will be assessed at baseline and six months thereafter. The intervention group will receive web-based CBT, consisting of three F2F sessions and maximally eight web-based modules over a period of six months. The care as usual group will be on a waiting list for regular F2F CBT. The total duration of the waiting list is six months. The primary outcome of the study is fatigue severity. Secondary outcomes are functional impairments, psychological distress and quality of life.

Discussion: If web-based CBT is effective, it will provide an additional treatment option for fatigue in breast cancer survivors. Web-based CBT is expected to be less time-consuming for therapists than regular F2F CBT, which would result in an increased treatment capacity. Moreover, the intervention would become more easily accessible for a larger number of patients, and patients can save travel time and costs.

BACKGROUND

Worldwide, breast cancer is the most common malignancy in women. About 1.7 million new cases were diagnosed in 2012 (1). In the last decades, survival rates have been improved due to early detection by screening programs and advances in oncological treatments (2, 3). Since the number of breast cancer survivors increases, concerns are raised about their long-term well-being. After completion of curative cancer treatment, side-effects can become chronic. One of these persistent side-effects is cancer-related fatigue (3). The National Comprehensive Cancer Network defined cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness, related to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning" (4). Once the malignancy is successfully treated, the fatigue is expected to decrease. Nevertheless, severe fatigue becomes a chronic condition in approximately one-third of breast cancer survivors (5-8).

Interventions for fatigue in cancer survivors

Since persisting severe fatigue interferes with daily functioning and has profound effects on quality of life, it should not be left untreated (5, 9). The evidence of available interventions was recently evaluated in a practice guideline of the American Society of Clinical Oncology (10). It was concluded that there is evidence for the efficacy of physical and psychosocial interventions. Initiating or maintaining adequate levels of physical activity (11-19), (cognitive) behavioral therapy (20-25), and (psycho) educational interventions (20, 25, 26) can reduce fatigue. In addition, there is some evidence for the efficacy of mindfulness-based approaches (21, 27, 28), yoga (29, 30), and acupuncture (31, 32).

The current study focuses on one of these evidence-based interventions: cognitive behavioral therapy (CBT). A CBT protocol for fatigue in cancer survivors with mixed diagnoses was developed and tested in a randomized controlled trial (RCT) at our treatment center, the Expert Center for Chronic Fatigue of the Radboud university medical center (Radboudumc) (22). This RCT showed that patients reported a clinically significant reduction in fatigue and functional impairments following CBT (22). These effects were maintained at a two-year follow-up (33). The efficacy of the CBT protocol was recently replicated in a RCT of Prinsen et al. (34). The CBT protocol is based on a model of precipitating and perpetuating factors of fatigue (22). According to this model, the malignancy and its treatment are the precipitating factors that induced fatigue.

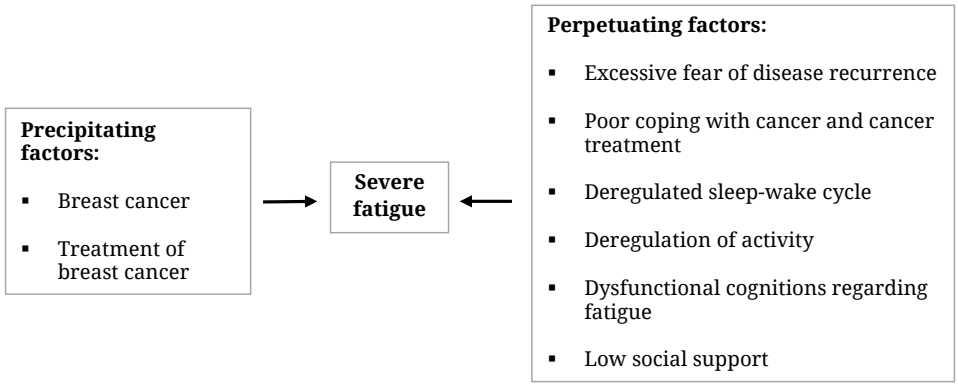


Figure 1. Explanatory model of the CBT protocol.

However, other factors are responsible for the persistence of severe fatigue after cancer treatment (22). These fatigue-perpetuating factors and the overall explanatory model are captured in Figure 1. Each fatigue-perpetuating factor is addressed in a module of the CBT protocol, offered as regular face-to-face (F2F) therapy. However, this F2F CBT is intensive for both therapists and patients, since it consists of twelve to fourteen F2F sessions over a period of six months. Therapists need to invest considerable time to deliver these sessions and a limited number of trained cognitive behavioral therapists provide this F2F therapy. Besides, patients need to travel to a treatment center to attend the sessions. The development of web-based CBT would reduce the therapist time needed to deliver the intervention and increase treatment accessibility for severely fatigued breast cancer survivors.

Web-based CBT

The fast-growing field of e-health has created new possibilities in the development of web-based interventions. Web-based CBT has been developed and examined for a wide range of mental health problems, and so far, results are promising. Multiple studies have shown that web-based CBT can be effective in reducing mental health problems (35). To extend treatment options for severely fatigued breast cancer survivors, we have developed a web-based version of our F2F CBT protocol for severely fatigued cancer survivors, named “On the road to recovery”. The efficacy of this intervention will be examined in a RCT, named “the CHANGE-study”.

The right time to intervene

In our previous RCT’s examining regular F2F CBT for severely fatigued cancer

survivors, the intervention was offered at least one year after completion of cancer treatment (22, 34). However, recent research has shown that fatigue does not decrease further after three months following curative cancer treatment (36), and fatigue-perpetuating factors can already be identified at three months following cancer treatment (37). Therefore, it might be possible to treat fatigue in cancer survivors at an earlier stage. To examine if this is the case, the web-based CBT will be offered at least three months after completion of cancer treatment.

Aims of the CHANGE study

1. To examine the efficacy of web-based CBT for severely fatigued breast cancer survivors on fatigue severity compared to care as usual.
2. To examine the efficacy of web-based CBT for severely fatigued breast cancer survivors on functional impairments, psychological distress, and quality of life compared to care as usual.
3. To examine if time since completion of cancer treatment moderates the efficacy of web-based CBT with respect to fatigue severity.

METHODS

The method section of this study protocol is written in accordance with the CONSORT statement for reporting parallel group randomized trials (38) and the CONSORT e-health criteria for reporting web-based interventions (39).

Design

A non-blinded multicenter RCT (the CHANGE study) will be conducted to evaluate the efficacy of web-based CBT compared to care as usual for severely fatigued breast cancer survivors.

Recruitment

1. Referrals by medical professionals

Patients will be recruited by medical professionals (physicians and nurses) at the outpatient clinic of the departments of surgery and/or oncology of eight hospitals in the Netherlands (Radboudumc, Nijmegen; Canisius Wilhelmina hospital, Nijmegen; hospital Gelderse Vallei, Ede; hospital Bernhoven, Uden; hospital Pantein, Boxmeer; VieCuri medical center, Venlo; Elkerliek hospital, Helmond; Slingeland hospital, Doetinchem). Physicians and nurses will inform eligible patients about the study

during regular medical follow-up consults and give them an information leaflet. If a patient agrees to be informed about the study by the researcher, the nurse practitioner will fill out a participation form and send it to the researcher (HA). Subsequently, the researcher will call the patient to give a detailed explanation about the study and to address questions.

As a second recruitment strategy, nurse practitioners from selected participating hospitals will identify cohorts of eligible patients through medical records. They will inform these cohorts by mail. Patients will receive an information leaflet with an accompanying letter. In this letter, patients are asked to contact the researcher if they want to participate in the study.

2. Self-referrals

Patients will also be informed about the study by leaflets and notifications on social media of patients' associations and the Radboudumc (e.g. Facebook and Twitter). Patients can complete a participation form, integrated in an informative website. Subsequently, the researcher will contact the patient by phone to inform her about the study and to address questions.

Participants

All patients who want to participate in the study will first be screened for eligibility. The in- and exclusion criteria are shown in Table 1. To verify the medical criteria (criterion 2, 3, and 4) of self-referrals, patients will send a copy of the most recent report of their medical follow-up examination to the researcher. The researcher will administer an online screening questionnaire to verify the other criteria. All patients will sign informed consent before filling out this online screening. The Checklist Individual Strength (40) will be used to screen for severe fatigue (criterion 6). The Beck Depression Inventory for Primary Care (BDI-PC) (41, 42) will be used to screen for a depressive disorder (criterion 9). If the score on the BDI-PC is ≥4, the researcher will administer the Depression module of the Mini-International Neuropsychiatric Interview (M.I.N.I.) (43) by phone to assess the presence of a major depression. If patients meet the criteria for major depression, they will be advised to contact their general practitioner for an appropriate referral.

Procedure

If patients are eligible and have signed written informed consent, they will start with a baseline assessment (T0). Following T0, participants will be randomized to either the intervention condition (web-based CBT) or the control condition (care as usual). After

Inclusion criteria	
1.	Women who are 18 years or older
2.	Treated for breast cancer with curative intent
3.	Breast cancer treatment (surgery, chemo- and/ or radiotherapy) must be finished at least three months previously. There is no upper limit for the time since completion of cancer treatment. Patients who currently receive hormone and/ or targeted therapy are eligible.
4.	Disease-free at entry of the study, defined by the absence of somatic disease activity parameters
5.	Able to speak, read, and write Dutch
6.	Severely fatigued, defined by a score of ≥35 on the fatigue severity subscale of the Checklist Individual Strength
7.	Having access to a computer with internet
Exclusion criteria	
8.	Presence of a co-morbidity that explains the presence of severe fatigue
9.	A depressive disorder, assessed with the BDI-PC and the M.I.N.I.
10.	Current psychological treatment for a psychiatric disorder
11.	Current CBT for fatigue

Table 1. In- and exclusion criteria

six months, all participants will be assessed again (T1). For participants assigned to the web-based CBT, this will be the post-intervention assessment. The overall study design is shown in Figure 2. A test assistant will perform T0, T1 and the randomization.

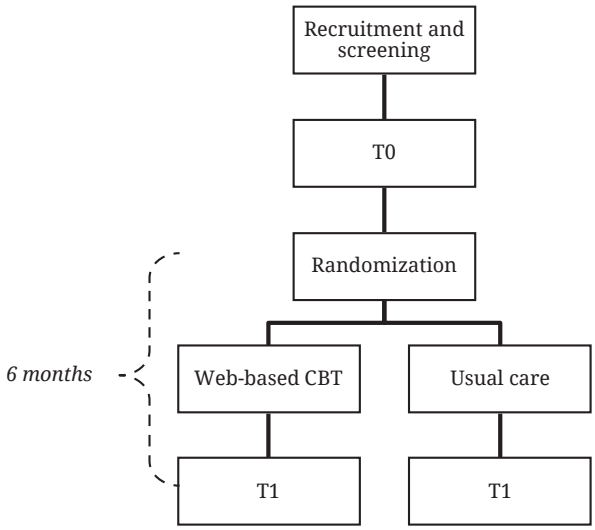
Randomization

Stratified randomization will be based on time since completion of cancer treatment (three months up to one year versus ≥ one year) and type of referral (referrals by medical professionals versus self-referrals). After T0, randomization will be performed by a test assistant in the presence of the patient. A computerized randomization tool, built by an independent statistical expert, will be used to randomly allocate patients to either intervention or control condition. The allocation ratio will be 1:1 and block-randomization will be used with a block size of six. The test assistant, the researcher and the participants will be blinded to the allocation sequence. They will not be blind for the randomization outcome, because this is not possible in psychological treatments.

Intervention

Development

On the road to recovery is built in a web portal, designed with technical guidance from the Psychological and Psychiatric Care Innovation (Utrecht, The Netherlands) (44). Experts in the field of fatigue in cancer survivors developed the content of this web



T0 = baseline assessment; T1 = second assessment

Figure 2. Overall study design.

portal. Trained, experienced cognitive behavioral therapists (HK, TB) and researchers (MGI, HA) wrote the texts and assignments. In total, the web portal consists of thirteen texts and twenty-six assignments. A graphic designer developed the lay-out of On the road to recovery, and a videographer made thirteen videos together with a therapist (HK) and the researcher (HA). These videos are integrated in the web portal. In the first video, a medical oncologist (SV) explains the rationale of the CBT. The other twelve videos are interviews of three cancer survivors. These patients are recovered from fatigue after receiving F2F CBT, and tell about their experiences with the CBT modules. A screenshot of the web portal is provided in Figure 3. For this occasion, the text is translated into English.

Usability testing

Five severely fatigued breast cancer survivors, who were following F2F CBT, participated in a test pilot. The usability of the web portal was tested by using a "think aloud procedure" (45). Participants were asked to think aloud while independently completing the modules. In the meanwhile, the researcher (HA) noted obstacles they encountered (i.e. usability problems and problems with text readability). Afterwards, all participants filled out a feedback form. They were asked about the sufficiency of information provided, text readability, and the lay-out and usability of the web portal. The findings of the usability testing were used to optimize the final version of the web portal.

Intervention condition: On the road to recovery

All participants in the intervention condition will follow On the road to recovery, a web-based version of the regular F2F CBT for severely fatigued cancer survivors. Participants will start with two F2F sessions with their therapist. In these sessions, the CBT model for fatigue in cancer survivors (Figure 1) will be explained and a treatment plan will be made. Thereafter, participants will follow On the road to recovery online. The web-based CBT consists of eight treatment modules. All participants will start with setting their treatment goals (module 1). Then, they will work on the fatigue-perpetuating factors that are applicable to them: (1) poor coping with breast cancer and breast cancer treatment; (2) high fear of cancer recurrence; (3) dysfunctional fatigue-related cognitions; (4) a deregulated sleep-wake rhythm; (5) a deregulated activity pattern; and/or (6) negative social interactions and low social support. Each of these six fatigue-perpetuating factors coincides with a treatment module (module 2-7). At baseline assessment, it is decided which modules are relevant for each participant. Finally, all participants will complete the therapy by realizing their treatment goals (module 8). On the road to recovery is tailor-made. Assessment tools are used to assess which fatigue-perpetuating factors are present and to determine which treatment modules patients need to follow (Table 2). All treatment modules consist of three parts: psycho-education ("READING"), assignments in which participants work on fatigue-perpetuating factors ("DOING") and a final assignment, in which participants evaluate their progress ("REVIEW"). The content of the eight treatment modules is described in more detail in Appendix 1.

Therapists will contact patients two-weekly by e-mail to give feedback on their progress and to answer questions. Therapists can also initiate video sessions with a secured video consultation system (Facetalk) (46). These video sessions are in particular recommended for the modules "Fear of cancer recurrence" and "Coping with cancer and cancer treatment". The guideline is to plan maximally two video sessions. The maximum duration of On the road to recovery is six months. Therapists will be blinded for the level of fatigue severity (primary outcome measure). Only after the post-treatment assessment (T1), they will be informed about the levels of fatigue severity on T0 and T1. The outcomes with respect to fatigue severity and other disabilities will be discussed with the participant in a final F2F session. In this session, the therapist and patient will determine if the patient is recovered from severe fatigue. If patients are not recovered from severe fatigue, F2F therapy will be offered outside the study context.

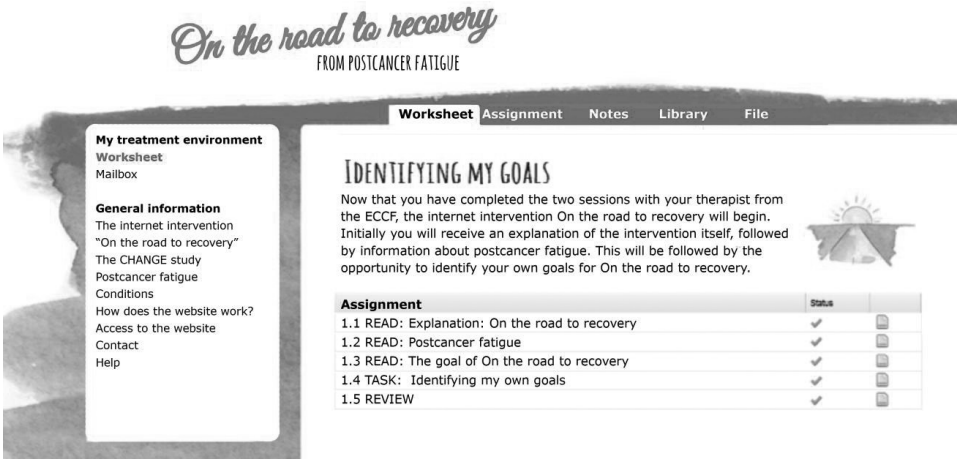


Figure 3. Screenshot of On the road to recovery

Treatment integrity

On the road to recovery will be given by licensed cognitive behavioral therapists. All therapists are experienced in working with the F2F CBT protocol for severe fatigue in cancer survivors. They will participate in a weekly supervision, in which cases are discussed in the presence of senior clinical psychologists (HK, TB). Changes in individual treatment plans will be made according to the study protocol and to the CBT principles for severely fatigued cancer survivors.

At the end of the study, a random five percent of the e-mail messages send to the patients will be evaluated. An experienced clinician (HK) and researcher (HA) will determine whether the web-based CBT was delivered according to the predefined treatment protocol. To determine if web-based CBT is less time consuming than F2F CBT, therapists will register the invested time for each patient.

Control condition: care as usual

Participants in the control condition will be on a waiting list for regular F2F CBT for fatigue in cancer survivors. The total duration of the waiting list is six months. In this period, patients will receive care as usual. The usual care for breast cancer survivors in the Netherlands consists of follow-up examinations conform the Dutch guidelines for oncology care (47). The frequency of these follow-up examinations depends on age, time since diagnosis and a possible BRCA1/2 mutation. In general, there will be a three-month follow-up in the first year, a biannual follow-up in the second year, and an annual follow-up in the following years up to five years after diagnosis.

Recently, a guideline for the management of psychosocial distress in breast cancer survivors is implemented (48). According to this guideline, psychosocial problems are identified and patients should be referred to specialized care providers. Participants may therefore be referred to other fatigue-oriented interventions during the study (e.g. psychosocial interventions, a rehabilitation trajectory, or physical therapy). At T1, all participants will be asked if they have received any treatment for fatigue during the study, and if so, they are asked to describe this treatment.

Outcomes

Primary outcome

Fatigue severity, measured by the subscale Fatigue Severity (8 items, 7-point Likert Scale) of the Checklist Individual Strength (CIS) (49). This subscale consists of eight items, scored on a 7-point Likert scale. The range of scores is 8 to 56, with a higher score indicating a higher level of fatigue. The cut-off score for severe fatigue is ≥35 (49). The CIS has been established as a valid and reliable measure (50, 51), which showed sensitivity to detect change in previous studies investigating fatigue in cancer survivors [22,33,52,53].

Secondary outcomes

Functional impairments, measured by the Sickness Impact Profile 8 (SIP) (54,55). This questionnaire addresses the level of disability in eight domains: alertness behavior, sleep/ rest, homemaking, leisure activities, mobility, social interactions, ambulation, and work. The weighted total score on these eight domains will be used to assess functional disability, with higher scores indicating more disabilities. The SIP is a reliable measure with sufficient content validity (56).

Psychological distress, measured by the total score on the Brief Symptom Inventory 18 (BSI-18) (57). This multidimensional questionnaire consists of eighteen items, scored on a 5-point Likert scale. The range of scores is 0 to 72, with a higher score indicating more psychological distress. The BSI-18 is a shortened version of the Symptom Checklist 90 (SCL-90) (58). The BSI-18 has high levels of sensitivity and specificity (59).

Quality of life, measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) (60). This questionnaire consists of thirty items that cover five function scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality of life scale. All scales are scored on a 4-point Likert scale. The EORTC-QLQ-C30 has been established as a valid and reliable measure (61).

Other variables

Demographic variables will be assessed by using a self-report questionnaire at T0. The instruments used to determine the relevant fatigue-perpetuating factors are shown in Table 2.

Power

The sample size calculation is based on the guidelines of Borm et al. (2007) for analysis of covariance (ANCOVA) in RCT's (72). A clinically relevant difference of six points is expected for the primary outcome (fatigue severity subscale of the CIS) between the intervention and control condition. This difference is based on a study of Knoop et al. (73), in which the efficacy of a minimal intervention for patients with chronic fatigue syndrome was examined (73). A minimum number of 60 patients per condition would be needed for a t-test with an alpha of .05, a two-sided significance level and a power of .85. According to Borm et al. (72), this number of patients needs to be multiplied by a "design factor" to calculate the needed sample size for an ANCOVA (60). This factor is one minus the squared correlation coefficient between the baseline and outcome measure of fatigue severity. In our previous study examining the efficacy of F2F CBT for fatigue in cancer survivors, the correlation of the baseline and outcome measure was .36 (22, 33). This leads to a factor of .87 (1 - .362 = .87). Thus, the minimal number of patients in each condition is 53 (60*.87=52.2). The drop-out rate in our first RCT examining F2F CBT for fatigue in cancer survivors was 13% (22, 33). In the current study, patients might experience less support from their therapist in the web-based CBT. Therefore, the drop-out in the current RCT is estimated to be 50% higher than in the first RCT (1,5*13=19,5%) Therefore, a margin of 19,5% for drop-out is added to the minimal number of 53 patients per condition. This results in a sample size of 132 severely fatigued breast cancer survivors.

Intended statistical analyses

The primary objective of the study is to examine the effects of web-based CBT on reducing fatigue severity compared to care as usual. Therefore, an analysis of covariance (ANCOVA) will be used with the CIS-fatigue score at T1 as dependent variable, the CIS-fatigue score at T0 as covariate and condition as fixed factor (39). The clinical importance of the treatment effect will be determined. Differences between the intervention and control condition on the amount of change in fatigue severity will be calculated on T0 and T1. Clinically meaningful change will be defined as a reliable change index of more than 1.96 and a decrease of the fatigue level to a normal

Treatment module	Instrument (REF)	Outcome	Response format	Psychometric properties	Cut-off value
1. Coping with cancer and cancer treatment	Impact of Event Scale (62)	Intrusion and avoidance	4-point Likert scale, range 0-60	Cronbach's α ranges between .87 and .96; adequate convergent validity (63)	Score ≥10 for each separate scale
2. Fear of cancer recurrence	Modified Cancer Acceptance Scale (53)	Fear of disease recurrence	4-point Likert scale, range 3-12	N/A	Score ≥7
	Cancer Worry Scale (64)	Worries about the risk of developing cancer (again)	4-point Likert scale, range 8-32	Cronbach's α = .87; good convergent and divergent validity (64)	Score ≥14 (64)
3. Helpful thinking	Modified Causal Attribution List (52,65)	Somatic and non-somatic attributions	4-point Likert scale	Cronbach's α ranges between .71 and .77 (65)	N/A
	Illness Management Questionnaire (65-67)	Focusing on symptoms	6-point Likert-scale, range 9-54	Cronbach's α ranges between .85 and .93 (66)	Score ≥30
	Fatigue Catastrophizing Scale (68)	Catastrophizing in response to fatigue	5-point Likert scale, range 1-5	Cronbach's α = .85 (68)	Score ≥2 (magnifying); score ≥7 (ruminating).
	Self-Efficacy Scale (33,65)	Self-efficacy with respect to fatigue	4 point Likert scale, range 7-28	N/A	Score ≤19
4. Sleep-wake rhythm	Sleep-wake diary	Sleep-wake rhythm	Bedtimes and wake-up times of twelve consecutive days and nights	N/A	N/A
5. Activity regulation	An actometer, a motion-sensing device, worn to the ankle for twelve consecutive days and nights	Activity pattern (relatively active versus low active)	Average physical activity level (number of accelerations per five minute period) (69)	Adequate reliability and validity (73)	N/A
6. Social support	Van Sonderen Social Support Inventory, subscales Interactions (SSLI) and Discrepancies (SSLD) (70)	Discrepancy between actual and desired social support	4-point Likert Scale, range 34-136	Cronbach's α=.93 (SSLI); α=.95 (SSLD); good content validity (71)	Score ≥14 (SSLI); score ≥50 (SSLD)

Table 2. Tools to assess which treatment modules are indicated

range (i.e. a score of <35 on the fatigue severity subscale of the Checklist Individual Strength). The effects of web-based CBT on the secondary outcomes of the study (functional impairments, psychological distress and quality of life) compared to care as usual will be determined with ANCOVA's. For each secondary outcome measure, an ANCOVA will be performed with the score of the outcome measure at T1 as dependent variable, the score at T0 as covariate and condition as fixed factor. The third objective of the study is to examine if time since completion of cancer treatment moderates the effects of web-based CBT. This will be analyzed with an ANCOVA with time since completion of cancer treatment (3 months-1 year versus ≥1 year) as covariate. The CIS-fatigue score at T1 will be the dependent variable, and the fatigue score at T0 will be the second covariate. All data analyses will be based on intention to treat. Missing values on primary and secondary outcome measures will be replaced with multiple imputation using fully conditional specification with at least five imputations. In case of statistically significant differences, a sensitivity analysis will be performed, based on different assumptions about the values of missing data.

Ethical approval

This study has been reviewed and approved by the Medical Ethical Committee of the Radboudumc (reference no. 2013/167). The study has also been approved by the local ethical committees of each participating hospital (Radboudumc, Canisius Wilhelmina hospital, hospital Gelderse Vallei, hospital Bernhoven, hospital Pantein, VieCuri medical center, Elkerliek hospital and Slingeland hospital). The study is registered in the Dutch Trial Registry (reference no. NTR4309, date registered: December 6, 2013).

DISCUSSION

The CHANGE study will examine the efficacy of a web-based version of an evidence-based CBT protocol for severe fatigue in breast cancer survivors. The efficacy of the intervention on fatigue, functional impairments, psychological distress and quality of life will be examined as well. Web-based CBT has several advantages over F2F CBT; (i) e-mail contacts are expected to be less time consuming for therapists than F2F contacts, which would result in an increased treatment capacity; (ii) the intervention becomes more easily accessible for a larger number of patients, and (iii) the burden for patients can be reduced, because they can save travel time and costs to the treatment center. Besides, patients can work on the intervention at their own pace, at any preferred time.

After completion of the patient inclusion, the CHANGE study will be extended to

form a non-inferiority trial. In this trial, stepped care will be compared to F2F CBT for severely fatigued breast cancer survivors. The first step in the stepped care condition will be web-based CBT. If patients are not recovered from severe fatigue after completion of web-based CBT, additional F2F CBT sessions will be offered. We will examine whether the effects of stepped care on fatigue severity are noninferior to regular F2F CBT after a waiting period. We will also determine whether stepped care requires less therapist time than regular F2F CBT. The non-inferiority trial is registered in the Dutch Trial Registry (reference no. NTR5179).

In conclusion, if web-based CBT is effective, it would provide an additional treatment option that is easily accessible for breast cancer survivors suffering from severe fatigue.

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APPENDIX

Overview of the treatment modules of On the road to recovery

The CBT protocol for fatigue in cancer survivors is aimed at changing fatigue-related cognitions and behaviors. On the road to recovery consists of eight treatment modules. All patients will start with module 1 (goal setting) and finish with module 8 (realizing of goals). The intermediate six modules coincide with six fatigue-perpetuating factors, and can differ between patients depending on their baseline assessment. Assessment tools are used to determine which factors are applicable (Table 2). Each patient will work on at least one fatigue-perpetuating factor. All treatment modules are illustrated in Figure 4. In total, patients will follow from three up to eight treatment modules:

Module 1: Goal setting

This module starts with an explanation of the web portal and the rationale of On the road to recovery. The cognitive behavioral model of fatigue in cancer survivors (Figure 1) is explained to patients. This model assumes that the fatigue is induced by the cancer and cancer treatment, but other factors cause the fatigue to persist. Subsequently, patients are asked to set concrete treatment goals. The overall goal of the intervention is no longer being severely fatigued and no longer being disabled by fatigue. Concrete goals are the activities patients would do (and do not do now), if they were no longer limited by severe fatigue.

Module 2: Coping with cancer and cancer treatment

Being treated for cancer can be a traumatic event. If patients keep reliving or actively avoiding memories of this period in their life, they might suffer from posttraumatic symptoms that can perpetuate fatigue. The aim of this module is to help patients with the processing of their experiences. To this end, patients will first complete a targeted writing assignment. They will write about the events, their experiences and its impact from breast cancer diagnosis up to now [74]. After writing it down, patients will repeat reading their story until they no longer feel distressed when thinking of the cancer and cancer treatment. Talking about their story with their therapist (using Facetalk), their spouses or with significant others can be part of this process as well.

Module 3: Fear of cancer recurrence

Fear of disease recurrence is normal after completion of cancer treatment. It is also normal that anxious thoughts increase in particular situations, like upcoming medical

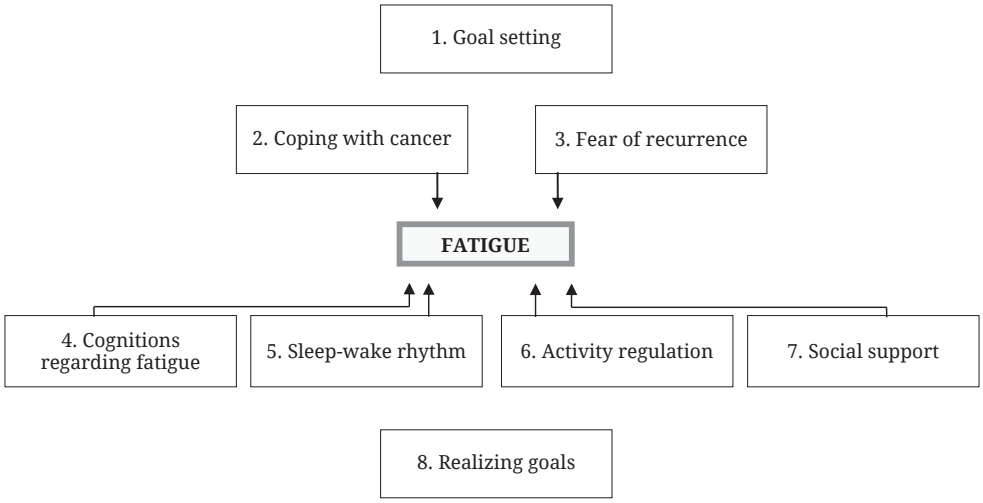

Figure S1. Overview of the treatment modules of *On the road to recovery*.

follow-up examinations. However, in some patients, fear of cancer recurrence is continuously and excessively elevated. These heightened levels of fear can perpetuate severe fatigue. In this module, patients will first get insight in the triggers of their anxiety. They will rank several situations that can provoke anxiety, and define their coping strategies in these situations. Then, patients will be helped to identify the cognitions underlying their fear. They will define what they are scared of, and the extent to which this corresponds with reality. If needed, patients are advised to talk with their physician to get insight in their actual risk of cancer recurrence. Finally, patients will learn to adopt helpful cognitions that can decrease their worrying. An example of a helpful cognition is: "It makes no sense to worry about the cancer coming back. This does not help me and only makes me feel bad".

Module 4: Helpful thinking

Dysfunctional fatigue-related cognitions can perpetuate severe fatigue. Examples are catastrophizing (i.e. having a highly negative orientation towards fatigue), a low self-efficacy (i.e. not feeling able to influence fatigue) and somatic attributions (i.e. attributing the fatigue mainly to the cancer and cancer treatment). These cognitions make patients feel like they have no control over their fatigue. In this module, patients will first assess their thoughts when feeling tired, and identify the subsequent feelings, behaviors and its consequences. Then, they will learn to replace dysfunctional thoughts with more realistic, helpful cognitions that can increase their self-efficacy. An example

is: “I accept that I am tired, that is just how it is NOW. It does not have to stay like this, I am able to do something about the fatigue.”

Another part of this module is learning to focus less on fatigue. Patients will learn how to shift their attention, for example by focusing on other activities or on the environment. Patients are advised to stop using fatigue as an indicator for what they can and cannot do, and no longer talk about their fatigue.

Module 5: Sleep-wake rhythm

Irregular sleep patterns are common in fatigued cancer survivors and can perpetuate severe fatigue. Keeping irregular bedtimes and wake-up times, and lying down or sleeping during the day can lead to a disrupted circadian pattern. In this module, a consistent sleep-wake pattern will be established. Patients will be temporarily asked to get up and go to bed at fixed times each day. They will also be asked not to sleep or lie down during the day. In this way, patients can (re)set their “biological clock”. Advices for adequate sleep-hygiene practices are given (i.e. adopt a regular going-to-bed ritual and avoid drinking any caffeinated drinks or alcohol before going to sleep).

Module 6: Activity regulation

After completion of cancer treatment, activity patterns can be deregulated. The activity patterns of all participants will be measured and divided in one of two categories:

1. Relatively active: these patients have fluctuating activity levels with bursts of activities followed by periods of inactivity (“all-or-nothing behavior”).
2. Low active: these patients have a continuous low level of physical activity. This may be habit, or patients may avoid activities out of fear of getting tired.

Both activity patterns can perpetuate severe fatigue. Relatively active patients will first learn to evenly distribute their activities, leaving sufficient space for unforeseen circumstances. Subsequently, they will gradually increase their (physical) activity level. Patients choose a physical activity that they can perform daily (walking or cycling). They gradually and systematically build up the duration of this physical activity. Low active patients will immediately start with this graded activity program. When patients are able to increase their physical activity level, their self-efficacy with respect to fatigue and being active often increases as well. This module finishes with optional assignments for building up mental and social activities, and resumption of work (if applicable).

Module 7: Social support

Severely fatigued breast cancer survivors can experience negative social interactions regarding their fatigue, like overly concerned responses or a lack of understanding of significant others. In this module, patients will learn how to communicate about their fatigue with significant others. They will also learn how to be more assertive, for example by setting clear limits concerning the information they want to share. Some patients might still expect the same amount of support from their environment as during their illness. When the expectations of patients with regard to social support are unrealistic, patients will learn to adopt a different attitude towards their environment and to modify their expectations.

Module 8: Realizing goals

When patients have finished building up their physical activity level, they are advised to start realizing the treatment goals they set in the first module. They will make an action plan and realize their pre-set goals step-by-step. Another part of this module is letting go of the regular sleep-wake rhythm and even distribution of activities. In this way, patients learn how to cope with disruptions in their sleep-wake rhythm and activity pattern. Finally, patients will evaluate the overall progress they have made during the treatment program On the road to recovery. Part of this evaluation is to determine if they consider themselves as recovered from severe fatigue.

7

The efficacy of internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: a randomized controlled trial.

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ABSTRACT

Background: Severe fatigue is a common and distressing symptom affecting approximately one in four survivors of breast cancer. The current study examined the efficacy of Internet-based cognitive behavioral therapy (ICBT) for severe fatigue in survivors of breast cancer compared with care as usual (CAU).

Methods: The authors conducted a parallel-group randomized controlled trial. Severely fatigued, disease-free survivors of breast cancer who had completed cancer treatment at least 3 months previously were eligible. Participants were randomly allocated to ICBT or CAU using computer-generated stratified block randomization. The primary outcome of fatigue severity was assessed at baseline and after 6 months, as were the secondary outcomes of functional impairment, psychological distress, and quality of life. Statistical effects were tested with analyses of covariance (intention-to-treat analysis).

Results: Participants were recruited between January 2014 and March 2016 and assigned to ICBT (66 patients) or CAU (66 patients). Compared with the participants who had received CAU, those who had received ICBT reported lower fatigue scores at 6 months (mean difference [D], 11.5; 95% confidence interval [95% CI], 7.7-15.3) and a large effect size (Cohen d = 1.0), with the majority of patients (73%) demonstrating clinically significant improvement. ICBT also was found to lead to lower functional impairment (D, 297.8; 95% CI, 145.5-450.1) and psychological distress scores (D, 5.7; 95% CI, 3.4-7.9) and higher quality-of-life scores (D, 11.7; 95% CI, 5.8-17.7) compared with CAU, with medium to large effect sizes (Cohen d = 0.6-0.8).

Conclusions: ICBT appears to be effective in reducing severe fatigue and related symptoms and meets the current need for easy accessible and more efficient evidence-based treatment options for severely fatigued survivors of breast cancer.

BACKGROUND

Severe fatigue is a common and distressing symptom that is reported by approximately one in four of survivors of breast cancer (1). Severely fatigued survivors report a lower quality of life (QOL) and more functional impairment compared with survivors without severe fatigue (2). Given these serious consequences, it is important to treat severe fatigue effectively. However, having evaluated the current management of cancer-related fatigue, experts recently concluded that the availability of evidence-based interventions such as graded exercise and cognitive behavioral therapy (CBT) is too limited. E-Health approaches could improve their accessibility (3).

The results of an integrative review by Post and Flanagan (4) support the feasibility and acceptability of Web-based platforms for survivors of breast cancer. The authors also evaluated the efficacy of Internet-based interventions in this patient population, and concluded that the strongest data have been provided by studies on Internet-based CBT (ICBT) interventions (4).

To our knowledge to date, the ICBT interventions that have been evaluated for survivors of breast cancer have not specifically been aimed at fatigue. However, the effects of other types of Web-based interventions aimed at fatigue in cancer survivors are promising. A randomized controlled trial (RCT) by Yun et al (5) demonstrated that a Web-based self-management education program led to greater improvements in fatigue in cancer survivors compared with care as usual (CAU) (5). In addition, explorative analyses of a feasibility RCT by Foster et al (6) demonstrated that a Web-based self-management intervention enhanced the self-efficacy of cancer survivors in managing fatigue compared with a patients with a control condition who only received an information leaflet. However, this effect was not sustained at a follow-up of 12 weeks, and no positive effect on fatigue severity was found (6).

Another type of intervention for fatigue in cancer survivors is a Web-based, mindfulness-based cognitive therapy intervention developed by Bruggeman-Everts et al (7). The results of an uncontrolled pilot study indicated that this intervention was effective in reducing fatigue severity (7). This intervention currently is being tested in an RCT, but to our knowledge the results have not been published to date (8). Another relevant, ongoing RCT concerns a pilot study by Corbett et al examining an online self-management intervention with CBT elements (9). Finally, 2 RCTs by Willems et al (10) and van den Berg et al (11) demonstrated that a general Web-based self-management intervention for psychosocial adjustment in cancer survivors (without a specific focus on fatigue) led to improvements in fatigue compared with a nonactive control group,

with small effect sizes (Cohen's d of 0.2 and 0.3, respectively) (10,11).

Because to the best of our knowledge an evidence-based ICBT intervention for severe fatigue in survivors of breast cancer was lacking, we translated an evidence-based, face-to-face CBT intervention into a Web-based format. A previous review of Andersson et al (12) demonstrated the potential of this translation by concluding that, if guided by a therapist, the effects of ICBT and face-to-face CBT were equivalent for a range of psychiatric and somatic disorders (12).

The efficacy of the face-to-face intervention was shown in 2 trials aimed at severe fatigue in cancer survivors with various diagnoses, with effects being maintained at a follow-up of 2 years (13-15). Generally, the delivery of face-to-face CBT is challenging. It is an intensive intervention with a mean of 13 face-to-face sessions (13), thereby limiting treatment capacity while being demanding for patients. ICBT makes treatment accessible to more patients because it reduces travel time and dependence on scheduled appointments with a therapist. A Web portal with information and assignments, supported by E-mail contact with a therapist, enables patients to complete the intervention online and might reduce therapist time.

The main objective of the current study was to examine whether ICBT is superior to CAU in reducing severe fatigue in survivors of breast cancer. Secondary outcomes were functional impairment, psychological distress, and quality of life (QOL). We hypothesized that ICBT would be more effective than CAU in reducing fatigue, functional impairment, and psychological distress and in improving QOL.

METHODS AND MATERIALS

Study design and participants

In a parallel-group multicenter RCT, we compared the efficacy of ICBT for severely fatigued survivors of breast cancer with CAU at the Radboud University Medical Center in Nijmegen, the Netherlands.

Eligible survivors of breast cancer were recruited from 8 hospitals located in the eastern and southern parts of the Netherlands using various recruitment strategies: physicians and nurses introduced the study to eligible patients during a regular follow-up consultation, nurse practitioners informed cohorts of eligible patients about the study by mail (ie, clinician-referred participants), or patients were approached by patients' associations and participating hospitals via social media such as Facebook and Twitter (ie, self-referrals). If interested, patients were invited to sign up for the study on a dedicated Web site.

All participants were enrolled by the primary researcher (H.J.G.A.). Patients who signed up for participation received verbal and written information regarding the study and patient questions were addressed, after which interested patients were screened for eligibility.

Female patients were eligible if they were aged ≥18 years, free of disease, and had completed treatment for breast cancer with curative intent at least 3 months previously (barring hormone and targeted therapy) as verified by their general practitioner, oncologist, or surgeon. If potential participants were able to speak, read, and write Dutch and had access to a computer and the Internet, they were screened online for being severely fatigued (defined as a score of ≥35 on the Fatigue Severity subscale of the Checklist Individual Strength [CIS-Fatigue Severity]) and having basic Internet skills (eg, having an E-mail address and being able find information online).

Exclusion criteria were: 1) comorbidity that could explain the severe fatigue (as assessed by a medical oncologist [C.V.]); 2) a depressive disorder (as assessed with the Beck Depression Inventory for Primary Care and, in the case of a score of ≥4, the Depression module of the Mini-International Neuropsychiatric Interview); 3) undergoing current psychological treatment for a psychiatric disorder; and 4) undergoing current CBT for fatigue. At the start of the study, patients aged ≥65 years also were excluded. However, to increase the number of eligible patients, this maximum age restriction was lifted during the study.

After providing written informed consent, the survivors of breast cancer who were enrolled in the trial completed a baseline assessment at the study treatment center, after which they were randomized (allocation ratio of 1:1) to either the intervention condition comprising ICBT or the control condition consisting of CAU. After 6 months, participants completed the second assessment online. Further details regarding the study design have been published in a protocol article (16).

The RCT was reviewed and approved by the Arnhem-Nijmegen Medical Research Ethics Committee (NL43781.091.13) and the ethics committees of the participating hospitals. The study was recorded in the Netherlands Trial Registry (no. NTR4309).

Randomization

Randomization was in blocks of 6 and stratified based on time since cancer treatment (3-12 months vs ≥12 months) and type of referral (clinician-referred participants vs self-referrals). The computer-generated allocation sequence was prepared by an independent statistician, whereas a test assistant who performed the randomization informed individual participants about the allocation by telephone. The primary researcher and the test assistant were not blinded for allocation after randomization

because of practical constraints. Statistical analyses were conducted by an independent researcher who was blinded for the allocation.

Intervention Condition

ICBT for severely fatigued survivors of breast cancer was developed from an evidence-based, face-to-face CBT protocol for severely fatigued cancer survivors with mixed cancer diagnoses (13-15). The protocol is based on a cognitive behavioral model of precipitating and perpetuating factors of fatigue, in which it is assumed that the malignancy and its treatment induce the fatigue whereas cognitive behavioral factors (eg, a deregulated sleep-wake cycle or dysfunctional cognitions regarding fatigue) maintain the fatigue (13).

ICBT consisted of a total of 3 face-to-face sessions and a maximum of 8 Web-based modules. Participants initiated ICBT with 2 face-to-face sessions, after which they followed their treatment online, in which they were guided by licensed cognitive behavioral therapists through electronic consultations (ie, E-mail contacts and a maximum of 2 telephone or video consultations). Six therapists delivered the intervention, which was tailored to the individual patient. The intended duration of ICBT was 6 months and the intervention was completed with a face-to-face evaluation session. All participants first set their treatment goals (module 1). They then worked on the fatigue-perpetuating factors that were applicable to them: 1) poor coping with breast cancer (treatment); 2) high fear of cancer recurrence; 3) dysfunctional fatigue-related cognitions; 4) a deregulated sleep-wake rhythm; 5) a deregulated activity pattern; and/or 6) negative social interactions and low social support. Each of these 6 fatigue-perpetuating factors corresponded with a treatment module (modules 2- 7). Finally, participants realized their treatment goals (module 8).

The intervention was tailored to the individual patients. At baseline, it was decided which modules were relevant to them. Assessment tools were used to assess which fatigue-perpetuating factors were present and which treatment modules patients needed to follow. A detailed description of these assessment tools and cutoff scores has been provided in the protocol article (16).

Control Condition

Participants in the control condition received CAU, which meant that they were placed on a 6-month waiting list for face-to-face CBT, which was the regular waiting time at the treatment center because of limited treatment capacity. CAU also comprised oncological follow-up examinations and a referral for psychosocial care, if pertinent. There were no restrictions regarding the use of fatigue interventions for the duration

of the study, but all participants were requested to report these at 6 months.

Outcome Measures

Primary outcome

The primary outcome was fatigue severity as assessed with the 8-item CIS-Fatigue Severity (7-point Likert scale [range, 8-56]). The CIS-Fatigue Severity measures the patient's fatigue levels over the past 2 weeks, with higher scores indicating higher levels of fatigue. The cutoff score for severe fatigue is ≥35 (17). Previous studies have shown the reliability and validity of the subscale to be good to excellent (17-19). It has been used before in intervention studies with cancer survivors (7,11,13,14).

Secondary outcomes

Secondary outcomes were: 1) functional impairment, as assessed with the Sickness Impact Profile 8 (8 subscales [range, 0-5799]), with higher scores indicating more disabilities (20); 2) psychological distress, as assessed with the Brief Symptom Inventory 18 (18 items on 5-point Likert scale [range, 0-72]), with higher scores indicating more psychological distress (21); and 3) QOL, as assessed with the global QOL scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30; 2 items on a 7-point Likert scale [range, 0-100]) (22). All 3 questionnaires have been established as reliable and valid measures (23-25).

Evaluation of ICBT

Two raters (H.J.G.A. and an independent researcher) screened a random selection of 5% of all E-mails sent by the therapists to determine treatment integrity in terms of the percentage of intervention elements that were in accordance with the treatment protocol. The percentage of scores that were rated equally by the 2 raters (interrater agreement) also was calculated. Participants were defined as ICBT starters if they had filled in their treatment goals on the Internet portal, which was a prerequisite to gain access to the other modules.

Participants were defined as treatment dropouts if they had agreed with their therapist to discontinue ICBT prematurely. Criteria to determine which modules were indicated for each patient have been reported in the protocol article (16). The percentages of indicated modules were calculated, as well as the percentages of patients who had opened these modules.

Therapists recorded the time they spent on each patient during ICBT. At 6 months, all ICBT completers rated their satisfaction with ICBT on a scale of 1 to 10, with 10 being the most positive score.

Statistical Analysis

Sample size calculation

A sample of 120 participants was needed for a Student t test with an α of .05, a 2-sided significance level, and a power of 0.85 (16). Based on a study that examined the efficacy of a minimal intervention for patients with medically unexplained chronic fatigue, we assumed a clinically relevant difference in fatigue severity between the intervention and control condition of 6 points (26). To calculate the required sample size for an analysis of covariance, this sample size wasmultiplied with the factor $(1- r^2)$, in which r was 0.36 (27). This resulted in a minimal number of 53 patients in each condition. Because we expected treatment dropout to be 50% higher than the rate recorded in the 2006 RCT examining the efficacy of face-to-face CBT (13%) because of decreased therapist involvement, we included a dropout margin of 19.5% in the sample size calculation (13,16). This resulted in a sample size of 132 participants.

Statistical effects

Descriptive statistics, chi-square tests, and independent-sample Student t tests were used to confirm the comparability of the baseline characteristics of the intervention and control groups. Analyses of covariance were conducted to assess the efficacy of ICBT on fatigue severity, functional impairment, psychological distress, and QOL compared with CAU. Condition was entered as the fixed factor and baseline scores on the corresponding questionnaires as the covariates. Standardized effect sizes (Cohen d) were calculated by subtracting the unadjusted mean scores of the intervention and control condition at 6 months, divided by the pooled standard deviation (SD) of both groups at 6 months. Effect sizes of 0.2 to 0.5 were considered small, those of 0.5 to 0.8 as moderate, and those ≥0.8 as large (28). All analyses were based on intention to treat for all participants. SPSS statistical software (version 22; IBM Corporation, Armonk, NY) was used for all analyses.

Sensitivity analyses

We conducted multiple imputation for missing values for the primary and secondary outcomes at 6 months based on the assumption that data were missing at random, using fully conditional specification with 20 imputations (29). A sensitivity analysis was conducted to assess the robustness of our findings for missing data. We computed whether findings would be maintained in the case of no change in missing values in the intervention condition at 6 months using the last observation carried forward. We assumed improvement in the control condition because regression toward the mean is

likely to occur (30). Because lower scores indicate more improvement, we subtracted the mean change score of the controls (ie, baseline score minus score at 6 months) from the baseline score for missing values in the CAU condition. With regard to QOL, for which higher scores indicate better functioning, we added the mean change score of the controls to the score at 6 months. In addition, we conducted a post hoc per-protocol analysis including all ICBT completers and all participants who had not received any additional treatment for their fatigue during the trial.

Clinical significance

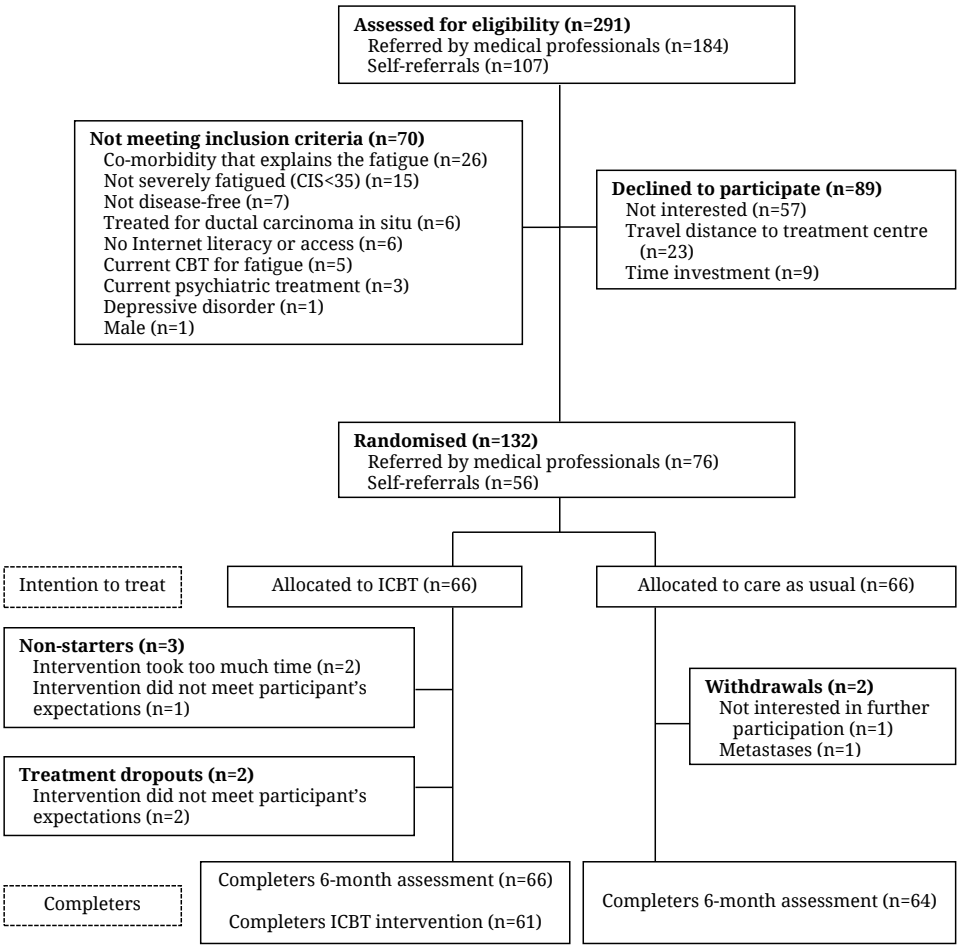
A clinically significant improvement was defined as a reliable change index of at least -1.96 and a fatigue level within the normal range (CIS-Fatigue Severity <35) (17,31). In addition, participants rated improvement at 6 months using a single question to which they could respond with "I am no longer bothered by fatigue," "I feel much better," "I experience the same level of fatigue," or "the fatigue has worsened in the past 6 months," in which the first 2 response options were considered to indicate self-rated improvement (13). We used chi-square tests to compare the percentages of clinically significant and self-rated improvement in the ICBT group with the percentages in the control group.

RESULTS

Sample Characteristics

Between January 2014 and March 2016, a total of 291 survivors of breast cancer indicated they wished to be informed about the study, of whom the primary researcher excluded 70 (24%) women, whereas 89 women (31%) declined participation. In total, 132 patients (45%) were included and randomized to ICBT (66 patients) and CAU (66 patients). Figure 1 shows the flow chart of patient inclusion, with reasons for ineligibility and nonparticipation.

The baseline characteristics of the participants are shown in Table 1. None of these characteristics differed significantly between the 2 conditions. We recorded 2 serious adverse events during the trial. Both concerned cancer recurrence in 2 participants in the CAU condition, 1 of whom withdrew from the study. Of the 66 women assigned to ICBT, 3 (5%) did not initiate the intervention and 2 (3%) discontinued treatment prematurely (see Fig. 1 for further details).



CBT indicates cognitive behavioral therapy; CIS, Checklist Individual Strength (Fatigue Severity subscale); ICBT, Internet-based cognitive behavioral therapy.

Figure 1. Flow chart of patient selection and participation.

Characteristic	ICBT (n=66)	CAU (n=66)
Sociodemographic characteristics		
Mean age at entry (SD), y	52.5 (8.2)	50.5 (7.6)
Education level[a]		
Low	17 (26%)	14 (21%)
Middle	24 (36%)	31 (47%)
High	25 (38%)	21 (32%)
Having a partner (yes)	57 (86%)	54 (82%)
Having children (yes)	52 (79%)	56 (85%)
Having a paid job (yes)	37 (56%)	40 (61%)
Medical characteristics		
Stage of disease at diagnosis[b]		
I	32 (49%)	31 (47%)
II	25 (38%)	26 (39%)
III	9 (14%)	9 (14%)
Type of cancer treatment		
Surgery	5 (8%)	3 (5%)
Surgery and radiotherapy	7 (11%)	10 (15%)
Surgery and chemotherapy	15 (23%)	14 (21%)
Surgery and radiotherapy and chemotherapy	39 (59%)	39 (59%)
Hormone therapy		
During study participation	38 (58%)	44 (67%)
Prior to study participation	11 (17%)	5 (8%)
Targeted therapy		
During study participation	2 (3%)	2 (3%)
Prior to study participation	9 (14%)	9 (14%)
Mean time since diagnosis (SD), mo	43.7 (31.0)	39.0 (25.5)
Time since completion of cancer treatment, mo	37.1 (30.8)	32.5 (25.1)
3-12	16 (24%)	14 (21%)
>12	50 (76%)	52 (79%)

Abbreviations: CAU, care as usual; ICBT, Internet-based cognitive behavioral therapy; mo, months; SD, standard deviation; y, years.
Data are shown as the number (%) unless otherwise indicated. Baseline characteristics did not differ significantly between the 2 groups (P >.05).
[a] Level of education was categorized as low, middle, or high according to the Dutch National Public Health Compass.
[b] Stage of disease was determined according to the 6th edition of the TNM classification of malignant tumors.

Table 1. Baseline characteristics of the study participants

Efficacy of ICBT

Primary outcome

The results of the intention-to-treat analyses of the primary and secondary outcomes at 6 months are shown in Table 2. Participants randomized to ICBT reported significantly lower fatigue scores compared with those who received CAU. The effect size was large (Cohen = 1.0; 95% confidence interval [95% CI], 0.6-1.3).

Secondary outcomes

Compared with the CAU patients, participants in the ICBT condition reported less functional impairment and psychological distress, and a better QOL at the 6-month assessment. Effect sizes were moderate (Cohen d of 0.6, 0.8, and 0.7, respectively).

Clinical significance

The percentage of survivors of breast cancer with clinical improvement of fatigue severity was significantly higher after ICBT (73%) than after CAU (27%), as was the case with self-rated improvement (85% in the ICBT group vs 31% in the CAU condition) (Table 2). The change in fatigue scores for each individual participant is depicted in Figure 2 (32); the figure also shows whether the change between baseline and the 6-month assessment was clinically significant and reliable or reliable only, and whether there was no change or a deterioration in fatigue. There was more often clinically significant and reliable change noted in the ICBT condition, and more often no change observed in the control condition.

Sensitivity Analyses

Scores of 2 participants (2%) in the CAU condition were missing for all outcome measures at the 6-month assessment, whereas 4 of the 132 survivors of breast cancer (3%) had only completed the primary outcome measure at 6 months. The results of the sensitivity analyses demonstrated the robustness of the findings of the current study for missing data (see Supporting Information Table S1).

In the per-protocol analysis, 3 ICBT nonstarters, 2 treatment dropouts, and 12 participants who received treatment for their fatigue other than ICBT during the study were excluded. The effect sizes computed for the remaining participants were higher (fatigue severity: d = 1.2; functional impairment: d = 0.7; psychological distress: d = 0.9; and QOL: d = 0.9) (see Supporting Information Table S2).

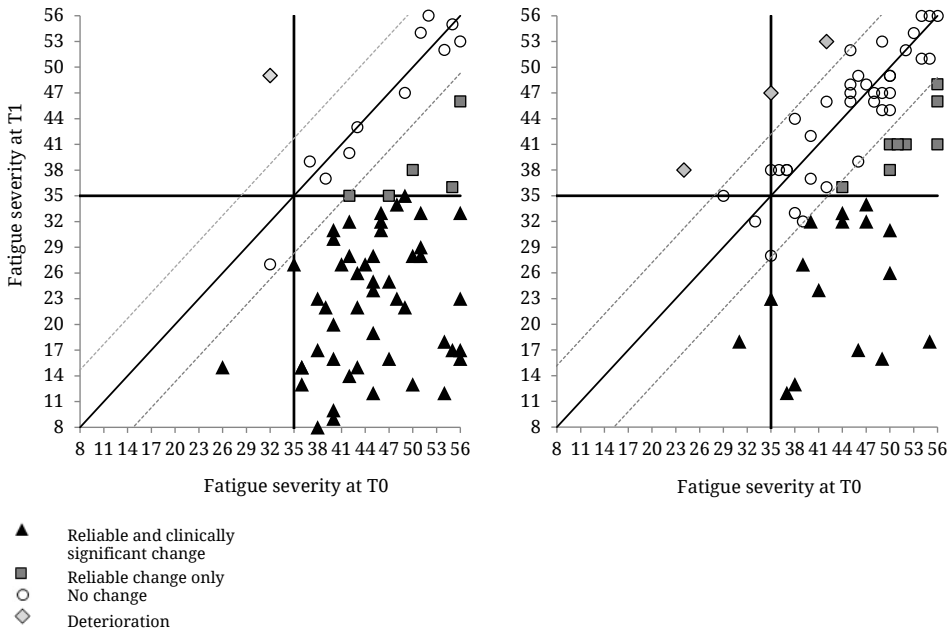
	ICBT (n=66)	CAU (n=66)	Mean difference (95% CI)	P-value	Effect size (95% CI)[a]
Primary outcome					
Fatigue severity (CIS-fatigue, range 8-56)[b]					
Baseline	45.2 (7.0)	44.9 (7.5)			
6 mo	27.7 (12.2)	39.1 (11.3)	11.5 (7.7 to 15.3)	<0.0001[c]	1.0 (0.6 to 1.3)
Clinically significant improvement (no., %)[d]					
	48 (73%)	18 (28%)		<0.0001[c]	
Self-rated improvement (no., %)[e]					
	50 (85%)	18 (31%)		<0.0001[c]	
Secondary outcomes					
Functional impairment (SIP-8, range 0-5799)[b]					
Baseline	1039.0 (617.6)	1127.5 (598.5)			
6 mo	490.2 (552.3)	841.8 (592.1)	297.8 (145.5 to 450.1)	<0.0001[c]	0.6 (0.3 to 1.0)
Psychological distress (BSI-18, range 0-72)[b]					
Baseline	11.5 (9.2)	12.4 (8.2)			
6 mo	6.9 (6.9)	13.1 (8.8)	5.7 (3.4 to 7.9)	<0.0001[c]	0.8 (0.4 to 1.1)
Quality of life (EORTC-QOL-C30, range 0-100)[f]					
Baseline	60.1 (17.7)	56.6 (18.3)			
6 mo	77.1 (16.5)	63.9 (20.1)	11.7 (5.8 to 17.7)	<0.0001[c]	0.7 (0.4 to 1.1)

Abbreviations: 95% CI, 95% confidence interval; BSI-18, Brief Symptom Inventory 18; CAU, care as usual; CIS-Fatigue Severity, Checklist Individual Strength-Fatigue Severity subscale; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ICBT, Internet-based cognitive behavioral therapy; Mo, months; QOL, quality of life; SIP-8, Sickness Impact Profile 8.
Data are shown as the mean (standard deviation), unless otherwise indicated. P values were calculated using analyses of covariance with adjustment for baseline scores.
[a] Cohen d.
[b] Higher scores indicate more symptoms or impairment.
[c] P<.05.
[d] Reliable change index >1.96 and cutoff value for CIS-Fatigue Severity <35; the data regarding 2 patients (2%) were missing.
[e] Based on the responses "I have completely recovered" or "I feel much better but still experience some symptoms"; the data regarding 15 patients (11%) were missing.
[f] Higher scores indicate a better QOL.

Table 2. Results of the intention-to-treat analysis for all outcomes from baseline to the 6-month assessment

Evaluation of ICBT

With regard to treatment integrity, a mean of 95% of the interventions in the E-mails sent by therapists were delivered in accordance with the ICBT protocol, with an interrater agreement of 99%. The mean self-reported therapist time for ICBT completers (face-to-face sessions and electronic consultations) was 7.1 hours (SD, 2.5 hours; range, 3.6-16.6 hours). The mean duration of ICBT was 25 weeks (SD, 4 weeks). The mean number of electronic consultations was 11, with an average of 10 E-mails and 1 telephone/video consultation. Supporting Information Table S3 shows the percentages of modules that were indicated and opened during ICBT, which ranged from 63% to 100%. The vast majority of ICBT completers (85%) gave their overall satisfaction with ICBT a score of ≥7 of 10, with a mean score of 7.6.



The horizontal and vertical lines indicate the Checklist Individual Strength (CIS)-Fatigue Severity subscale cutoff score for severe fatigue (35). The diagonal line indicates no change in fatigue severity between baseline and the 6-month assessment. The dashed parallel lines indicate the 95% confidence intervals for the Reliable Change Index. Figures were created using the Leeds Reliable Change Index calculator.32 Two patients were not included due to missing data on the CIS-Fatigue Severity subscale at baseline. The CIS-Fatigue Severity score already dropped below the cutoff score for severe fatigue (CIS-Fatigue Severity <35) between screening and baseline in 5% of participants.

CAU, care as usual; ICBT, Internet-based cognitive behavioral therapy.

Figure 2. Changes in fatigue scores from baseline to the 6-month assessment.

DISCUSSION

To our knowledge, the current study is the first RCT to examine the efficacy of an ICBT intervention specifically aimed at decreasing severe fatigue in survivors of breast cancer. Compared with participants who had received CAU, participants in the ICBT condition reported significantly less fatigue, with a large effect size and the majority demonstrating clinically significant and self-rated improvement. ICBT also was found to lead to significantly less functional impairment and psychological distress and a better QOL compared with CAU.

The Web-based intervention was based on our center's treatment protocol for face-to-face CBT for severe fatigue, the efficacy of which was demonstrated in 2 previous RCTs (13,14). Comparing the effect sizes, we found that both treatment formats appeared to be equally effective in reducing severe fatigue (effect size for ICBT: 1.0 [95% CI, 0.6-1.3] vs effect size for face-to-face CBT: 1.0 [95% CI, 0.6-1.5]) (13). This is in keeping with a previous meta-analysis that demonstrated that the effects of face-to-face CBT and therapist-guided ICBT also were equivalent in patients with various psychiatric and somatic disorders (12).

The effects of the current ICBT intervention on fatigue were found to be large compared with other Webbased interventions for fatigue in cancer survivors. The results of the RCT by Yun et al (5) on a Web-based selfmanagement education program demonstrated rates of clinically relevant improvement for fatigue outcomes ranging from 47% to 56% in the intervention condition and from 33% to 45% in the control condition (5). In addition, the pilot study by Bruggeman-Everts et al (7) demonstrated that Web-based, mindfulness-based cognitive therapy led to a clinically relevant improvement in 35% of participants (7). The effects of general self-management interventions on fatigue in the RCTs of Willems et al and van den Berg et al were small (Cohen's d of 0.2 and 0.3, respectively) compared with the current study (10,11).

In the current study, approximately 73% of patients demonstrated clinically significant improvement regarding fatigue compared with 28% of patients in the CAU condition, and the Cohen's d effect size of 1.0 was large. These positive findings may be explained in part by the fact that the intervention was based on an evidence-based face-to-face protocol, and guided by experienced therapists who worked at a specialized tertiary treatment center.

Although ICBT seems to be a relatively more effective intervention, it should be determined whether the efficiency of the intervention can be improved. The mean duration of the intervention of 24 weeks is long compared with other Web-based

interventions for fatigue. For example, the duration of the Web-based self-management education program of Yun et al was 9 weeks (5), and the Web-based, mindfulness-based cognitive therapy intervention of Bruggeman-Everts et al took 12 weeks (7). In future research, it should be examined whether the duration of ICBT can be shortened without losing efficacy. In addition, ways to decrease therapist involvement need to be examined to further improve treatment capacity. Integration of computerized automated feedback into the intervention could be useful to realize this objective.

Not all indicated modules were opened by patients who followed ICBT. Therapists guided patients through the Web site by E-mail, and suggested which modules patients should read. However, this was only suggested as advice, and none of the modules were stated to be mandatory to follow. In addition, patients had access to optional modules that were not indicated for them. This made it difficult to define proper adherence criteria. We had predicted that minimal therapist involvement would lead to more participants dropping out of ICBT (an estimated 20%) than generally is the case for face-to-face interventions. Surprisingly, only 8% of patients discontinued ICBT prematurely.

The expectation that less therapist involvement is required for ICBT appears to be confirmed by the results of the current study: the mean therapist time per participant was 7.1 hours (range, 3.6-16.6 hours) for ICBT compared with 12.5 hours (range, 5-26 hours)(13) in face-to-face CBT. Although the results of the current study suggest that ICBT is more time-efficient, a note of caution is in order because the 2 treatment formats, although based on the same protocol, were studied in different patient samples.

In the current study protocol, we planned to determine whether ICBT already could be provided from 3 months (instead of the regular 12 months) after cancer treatment. We wanted to compare the efficacy of ICBT between patients who had completed cancer treatment 3 to 12 months previously with those who had completed treatment >12 months previously. However, conclusions could not be drawn because the current analysis was underpowered (only 23% of participants fell into the first category).

Limitations of the current study are a lack of blinding of the outcome assessors (due to practical constraints) and a lack of an active control condition. The clinically significant improvement in fatigue noted in 28% of the survivors in the control condition is remarkable because cancer-related fatigue generally is considered to be a persistent symptom. Assuming that in some of these survivors the fatigue had been transitory, it would be better to offer the intervention only to those patients with chronic fatigue symptoms (ie, those indicating a duration of persistent fatigue of at least 6 months) to avoid patients being treated unnecessarily. Another limitation of the current study concerns the fact that we could not determine the long-term effect

of ICBT. Controlled follow-up assessments could not be incorporated into the design of the current study because patients in the CAU condition were placed on a waiting list to receive face-to-face CBT directly after the 6-month assessment.

Given the limited budgets in mental health care, future studies need to determine the cost-effectiveness of ICBT (33). We propose that combining our ICBT program for cancer-related fatigue with a stepped-care model is likely to further increase treatment efficiency. Toward this end, we will extend the current study to a noninferiority trial (Dutch Trial Registry trial no. NTR5179), in which survivors of breast cancer will be offered face-to-face sessions in addition to ICBT, if possible. Outcomes again will be compared with usual care (ie, face-to-face CBT after a 6-month waiting period). If the Web-based, stepped-care intervention is not found to be inferior to usual care, broader implementation will be considered.

It also should be noted that with a mean age of 51.5 years, the participants in the current study were relatively young, whereas breast cancer is most prevalent among women aged 60 to 75 years (34). This limits the generalizability of the current study results and may indicate that ICBT in particular attracts younger women, but we must not overlook those severely fatigued survivors of breast cancer whose Internet literacy skills are deficient or who reject online interventions. It is important that face-to-face CBT remains available for these women. Moreover, the current study should be replicated among cancer survivors with different tumor types because we are unsure whether the results of the current study can be generalized to these patient populations.

Requiring less therapist involvement than face-to-face CBT without losing efficacy, ICBT appears to be a logical next step in the development of more accessible, minimally intensive psychological interventions for severely fatigued survivors of breast cancer.

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	ICBT (n=66)	CAU (n=66)	Mean difference (95% CI)	P-value	Effect size (95% CI)[a]
Primary outcome					
Fatigue severity (CIS-fatigue, range 8-56)[b]					
Baseline	45.2 (7.0)	44.9 (7.5)			
6 months	27.7 (12.2)	39.3 (11.2)	11.7 (7.9 to 15.5)	<0.0001[c]	1.0 (0.6 to 1.4)
Secondary outcomes					
Functional impairment (SIP-8, range 0-5799)[b]					
Baseline	1039.0 (617.6)	1127.5 (598.5)			
6 months	494.9 (554.5)	856.4 (596.9)	306.2 (156.2 to 456.2)	<0.0001[c]	0.6 (0.3 to 1.0)
Psychological distress (BSI-18, range 0-72)[b]					
Baseline	11.5 (9.2)	12.4 (8.2)			
6 months	6.9 (6.8)	13.1 (8.8)	5.7 (3.5 to 7.8)	<0.0001[c]	0.8 (0.4 to 1.1)
Quality of life (EORTC-QOL-C30, range 0-100)[d]					
Baseline	60.1 (17.7)	56.7 (18.3)			
6 months	76.0 (17.5)	63.4 (20.0)	10.9 (5.1 to 16.8)	<0.0001[c]	0.7 (0.3 to 1.0)

Data are mean (SD), unless otherwise indicated. P-values were calculated using analyses of covariance with adjustment for baseline scores.
Abbreviations: CAU=Care as usual; ICBT=internet-based cognitive-behavioural therapy; CIS-fatigue=Checklist Individual Strength, Fatigue Severity subscale; SIP=Sickness Impact Profile; BSI-18=Brief Symptom Inventory-18; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.
[a] Cohen's d.
[b] Higher scores indicate more symptoms or impairment.
[c] P<0.05
[d] Higher scores indicate a better quality of life

Table S1. Results of the sensitivity analysis of missing values for all outcomes at the 6-month assessment

	ICBT (n=58)	CAU (n=56)	Mean difference (95% CI)	P-value	Effect size (95% CI)[a]
Primary outcome					
Fatigue severity (CIS-fatigue, range 8-56)[b]					
Baseline	45.2 (7.0)	44.9 (7.5)			
6 months	25.6 (10.8)	38.8 (11.2)	13.4 (9.5 to 17.3)	<.0001[c]	1.2 (0.8 to 1.6)
Secondary outcomes					
Functional impairment (SIP-8, range 0-5799)[b]					
Baseline	1039.0 (617.6)	1127.5 (598.5)			
6 months	459.3 (551.4)	829.6 (554.5)	360.9 (211.7 to 510.2)	<.0001[c]	0.7 (0.3 to 1.1)
Psychological distress (BSI-18, range 0-72)[b]					
Baseline	11.5 (9.2)	12.4 (8.2)			
6 months	6.1 (6.3)	13.3 (8.8)	6.6 (4.3 to 8.8)	<.0001[c]	0.9 (0.5 to 1.3)
Quality of life (EORTC-QOL-C30, range 0-100)[d]					
Baseline	60.1 (17.7)	56.7 (18.3)			
6 months	79.8 (13.3)	63.9 (20.4)	14.6 (8.5 to 20.7)	<.0001[c]	0.9 (0.5 to 1.3)

Data are mean (SD), unless otherwise indicated. Values of one participant in the ICBT and one participant in the CAU condition were missing on all secondary outcomes. P-values were calculated using analyses of covariance with adjustment for baseline scores.
Abbreviations: CAU=Care as usual; ICBT=internet-based cognitive-behavioural therapy; CIS-fatigue=Checklist Individual Strength, Fatigue Severity subscale; SIP=Sickness Impact Profile; BSI-18=Brief Symptom Inventory-18; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.
[a] Cohen's d.
[b] Higher scores indicate more symptoms or impairment.
[c] P<0.05
[d] Higher scores indicate a better quality of life

Table S2. Results of per protocol analysis for all outcomes at the 6-month assessment

Treatment module	% patients for whom the module was indicated	% patients that opened the indicated module
Sleep-wake rhythm	All participants	60/61 (98%)
Fatigue-related cognitions	All participants	57/61 (93%)
Activity pattern	All participants	57/61 (93%)
Fear of cancer recurrence	46/61 (75%)	27/46 (59%)
Coping with cancer	24/61 (39%)	15/24 (63%)
Social environment	24/61 (40%)	15/24 (63%)

Table S3. Usage of the web-portal

8

Are the effects of cognitive behavioral therapy for severe fatigue in cancer survivors sustained up to 14 years after therapy?

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ABSTRACT

Purpose: Cognitive behaviour therapy (CBT) reduces cancer-related fatigue (CRF) in cancer survivors in the short-term. We examined fatigue levels up to 14 years after CBT.

Methods: Eligible participants of two randomized controlled trials who had completed CBT for CRF and a post-treatment assessment were contacted (n=81). Fatigue was assessed with the subscale 'fatigue severity' of the Checklist Individual Strength (CIS-fatigue). The course of fatigue over time was examined with linear mixed model analyses. Fatigue levels of participants were compared to matched population controls at long-term follow-up. We tested with multiple regression analysis if fatigue at follow-up was predicted by patients' fatigue level and fatigue perpetuating factors directly after CBT (post-CBT).

Results: Seventy-eight persons completed a follow-up assessment (response-rate=96%, mean time after CBT=10 years). The mean level of fatigue increased from 23.7 (SD=11.1) at post-CBT, to 34.4 (SD=12.4) at follow-up (p<0.001). Population controls (M=23,9, SD=11.4) reported lower fatigue levels than participants. Half of patients (52%) who were recovered from severe fatigue at post-CBT (CIS-fatigue<35) were still recovered at long-term follow-up. Patients with lower fatigue levels at post-CBT were less likely to show relapse.

Conclusion: Despite initial improvement after CBT, levels of fatigue deteriorated over time. Half of patients who were recovered from severe fatigue after CBT still scored within normal ranges of fatigue at long-term follow-up.

Implications for cancer survivors: It should be explored how to help patients with a relapse of severe fatigue following an initially successful CBT. They may profit from CBT again, or another evidence-based intervention for fatigue could be more beneficial (like mindfulness or exercise therapy). Future research to gain insight into reasons for relapse is warranted.

INTRODUCTION

Fatigue is one of the most common and distressing consequences of cancer and cancer treatment. Cancer-related fatigue (CRF), defined by the National Comprehensive Cancer network (NCCN) as 'a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning, arises over a continuum, ranging from tiredness to exhaustion. When compared to the tiredness felt by a healthy individual, cancer-related fatigue is perceived of greater magnitude, disproportionate to activity and exertion, and not completely relieved by rest (1).' CRF has negative effects on patients' quality of life. Prevalence rates of CRF vary, approximately 25-30% of cancer survivors report persistent fatigue after cancer treatment (2,3).

The cognitive-behavioural model of CRF makes a distinction between precipitating and perpetuating factors of fatigue. It is assumed that cancer and its treatment trigger fatigue, but that cognitive and behavioural factors perpetuate it. Six perpetuating factors are distinguished: 1) Insufficient coping with the experience of cancer, 2) excessive fear of disease recurrence, 3) dysfunctional cognitions concerning fatigue, 4) deregulation of sleep-wake pattern, 5) deregulation of activity or low activity, 6) perceived lack of social support and negative social interactions (4).

Cognitive behaviour therapy (CBT) for CRF is aimed at these fatigue perpetuating cognitions and behaviours. The efficacy of CBT for CRF has been tested in several randomized controlled trials (RCT's) (4-6). It was found that CBT led to significant reduction of fatigue and functional impairment in severely fatigued cancer survivors. Positive effects of CBT were maintained up to 2 years after completion of CBT (7), with the majority of patients reporting a level of fatigue within normal range following treatment.

It is unclear if treatment effects are maintained in the long-term; there are no studies on CBT in cancer survivors that expanded the scope of the follow-up beyond the aforementioned period of two years. Studies on the long-term effect of CBT for fatigue in other patient populations have shown that sustainment of treatment effect is not self-evident. For example, Janse et al. (8) recently reported on the long-term effect of CBT for chronic fatigue syndrome (CFS). Patients with CFS suffer from medically unexplained, severe fatigue leading to substantial disability. The 583 participants of previously published studies on the effects of CBT for CFS were contacted for a long-term follow-up assessment. Positive effects of CBT for CFS were sustained up to 18 months after CBT,64% of the patients had fatigue scores in the normal range. At long-term follow-up, up to 10 years after end of treatment, fatigue severity had again

increased significantly, and at long-term follow-up 37% of the participants had a fatigue score in the normal range. Similar results were found by Van Akker et al. (9), their study showed a positive effect of CBT on fatigue in patients with multiple sclerosis directly following treatment, which was also not sustained at follow-up.

The main objective of this study was to determine whether the positive effects of CBT on fatigue severity in cancer survivors were sustained at long-term follow-up. We defined long-term follow-up as more than 2 years after finishing CBT for CRF. The second objective of this study was to determine predictors of fatigue at long-term follow-up. More specifically, we examined whether the level of fatigue at long-term follow-up could be predicted by the fatigue perpetuating factors and patients' level of fatigue directly after CBT.

MATERIAL AND METHODS

Study design and participants

A total of 93 patients derived from two previous RCT's of Gielissen et al. (4) and Prinsen et al. (5) were invited to participate in our long-term follow-up study:

- In the RCT of Gielissen et al. (4), a total of 112 patients were randomized to either CBT or waiting list condition. . Patients from both conditions received CBT, either directly after randomization or after the waiting list period. Of the 112 patients, 98 started CBT and 70 completed the post-treatment assessment. These 70 patients were invited to participate in the current follow-up study.
- In the RCT of Prinsen et al. (5), 50 patients were randomized in the study. Follow-up measurements of the patients still undergoing CBT were incomplete because of logistic reasons. Therefore, the study was stopped prematurely, and only 23 randomized patients from the intervention condition were included in the analyses to determine the efficacy of CBT (5). We only invited these 23 patients for the current follow-up study.

The initial RCT's had the following inclusion criteria: (1) being severely fatigued at baseline (operationalized as a score of 35 or higher on the fatigue subscale of the Checklist Individual Strength (CIS); (2) no known somatic cause for the fatigue; (3) completion of curative treatment for cancer at least 1 year ago; (4) a minimal age at disease onset of 18 years; (5) no evidence of disease recurrence and (6) not being older than 65 years (4,5). In the current follow-up study, we excluded patients who had metastatic cancer and/or received treatment for cancer in the six months prior to the follow-up assessment.

Because general populations surveys have shown that fatigue increases with advancing age (10), we examined if fatigue levels of our participants at long term follow-up differed from the level of fatigue in an age-matched control group that represented the general Dutch population. A sample of general population controls was derived from a research panel of CentERdata, a research institute at Tilburg University. CentERdata has access to a large panel of participants for surveys. The panel reflects the distribution of the Dutch population with respect to age, sex, education level and socio-economic status. For each participant in our study, three controls were derived from the research panel. The control group was matched to our study population based on age and gender with the procedure Coarsened Exact Matching (CEM) using STATA/SE12.1.

Intervention

Participants in our study originated from two RCT's testing the efficacy of CBT for CRF in cancer survivors with mixed cancer diagnoses (4,5). In both RCT's, patients were significantly less fatigued and functionally impaired following CBT compared to a waiting list control group (4,5). In the study from Gielissen et al. (7), patients from the waiting list also received CBT after the waiting period with similar treatment effects.

CBT for CRF is protocolized and aimed at the aforementioned fatigue perpetuating factors (4). CBT starts with educating patients about the cognitive behavioural model of CRF. Treatment is tailored: the relevant perpetuating factors are assessed through use of specific questionnaires. The patient formulates treatment goals and then starts with regulating the sleep-wake pattern. This is followed by reformulating fatigue related beliefs and a graded activity program. Low active patients gradually increase their level of physical activity; relatively active patients first learn to divide their activities more evenly before the start of the graded activity program. If indicated, excessive fear of cancer recurrence, insufficient coping with cancer and cancer treatment are addressed. It is also discussed how to deal with a perceived lack of support with respect to fatigue and how to reduce negative interactions. During therapy, patients realize their goals step by step followed by an evaluation of the treatment. The mean number of therapy sessions during the 6-month period was 12.5 (S.D. 4.7) in the intervention condition and 12.4 (S.D. 4.6) in the waiting list condition in the Gielissen study (4), and 12.0 (S.D. 5.0) in the Prinsen study (5). A detailed description of the conditions and followed procedures concerning both studies can be found in the original published papers (4,5).

Procedures

The municipal registration was consulted in case of unknown address and for the purpose of preventing approaching the family of deceased participants. An invitation letter and follow-up questionnaires were sent by mail. Patients who did not respond within a timeframe of two weeks received the questionnaires again and were contacted by phone simultaneously. Non-responders that could not be reached by phone were sent a reminder by mail up to 5 times. When patients did not want to fill in questionnaires, they were asked to complete only the primary outcome measure, the subscale Fatigue Severity of the Checklist Individual Strength (CIS-fatigue) by phone. The local medical ethical committee Arnhem-Nijmegen approved the study (registration number: 2015-2048).

Assessment

With regard to patient characteristics, data on partner status, work status and recent life-events were gathered. Patients were asked if they were currently treated for fatigue, received treatment by a psychologist or psychiatrist, had seen a specialist for a somatic co-morbidity other than cancer, had a recurrence of cancer since their treatment with CBT for CRF and/or were treated for cancer in the past six months.

Fatigue severity was assessed with the subscale Fatigue Severity of the Checklist Individual Strength (CIS-fatigue), indicating the level of fatigue in the previous two weeks, measured with eight items on a seven-point scale (range 8-56). A score of 35 or higher indicates severe fatigue. The CIS is found to be a reliable and valid instrument with a high internal consistency: Cronbach's alpha ranges from .92 to .95 in cancer survivors (11).

Physical functioning, mental health and bodily pain were assessed with the respective subscales of the Short Form-36 (SF-36) (12). Physical functioning at follow-up was measured because the negative effect of fatigue on physical functioning is well known and CBT had a positive effect on physical functioning in the two RCT's (4,5). Mental health and pain were measured as potential confounders of the long-term effect of CBT on fatigue severity. Weighted subscale scores range from 0 to 100, with higher scores indicating a better health status. The SF-36 is a valid and reliable instrument for different patient populations (13).

Perpetuating factors of fatigue directly after CBT

The model of CBT for CRF comprises six perpetuating factors. During CBT, each of the

relevant perpetuating factors is targeted with a specific treatment module. Knowledge on which patients are vulnerable for a relapse of severe fatigue and whether relapse is related to these perpetuating factors would be valuable to optimize our CBT and other interventions aimed at fatigue in cancer survivors. The dataset we used did not include a consistent useable measure of 'fear of cancer recurrence', one of the six perpetuating factors, from both studies. Therefore, this perpetuating factor was left out of our analyses. We included the other five perpetuating factors of fatigue, measured post-CBT, as potential predictors of fatigue at long-term follow-up:

- *Deregulated activities:* Self-reported activity level was measured with the activity subscale of the CIS.
- *Coping with the experience of cancer* (i.e., the extent to which a subject is currently occupied with the coping process after cancer and its treatment) was measured with the Dutch version of the Impact of Event Scale (IES) (14).
- *Dysfunctional cognitions:* Self-efficacy with respect to fatigue (i.e., confidence in one's own ability to cope with fatigue) was measured with the Self-Efficacy Scale (SES) (15).
- *Deregulated sleep-wake cycle:* Sleep disturbances were measured with the sleep/rest subscale of the Sickness Impact Profile-8 (SIP-8) (16).
- *A perceived lack of social support:* Discrepancies between amount of received and desired amount of social support were measured with the subscale 'discrepancies' (i.e., discrepancies between amount and desired amount of social support) of the van Sonderen Social Support Inventory (SSL-D) (17).

Statistical analyses

Data analyses were performed using SPSS (version 22). Threshold for significance was $p<0.05$ (two-tailed). Sample characteristics were analyzed using frequencies, percentages and mean scores.

Each participant had data of three measurement points: baseline, post-CBT and long-term follow-up. Analyses were conducted for both fatigue and physical functioning as continuous variables and for fatigue as a dichotomous variable (within normal range <35, outside normal range 35 or higher).

Because the three assessments were clustered within each participant, linear mixed model analyses were used to examine the course of fatigue and physical functioning over time. Time was included as a categorical variable (using dummy variables) to compare scores at long-term follow-up assessment with the scores at the baseline and post-CBT assessments. Because of the extensive span of the follow-up period, it was important to take into account that besides cancer and its treatment, many other

factors can cause and perpetuate fatigue. For both outcomes, additional analyses were conducted to assess the influence of the following covariates on the development of fatigue over time: somatic co-morbidities (yes/no), cancer recurrence (yes/no), significant life events (yes/no), pain (subscale SF-36) and mental health (subscale SF-36). A recent review by Abrahams et al. (18) has shown these factors to be of importance in CRF.

The same analyses (with and without covariates) were conducted with fatigue as a dichotomous outcome (i.e., within or outside normal ranges) using logistic generalized estimating equations (GEE). It was not possible to calculate the time effect between baseline and follow-up. Only severely fatigued patients (CISfatigue≥35) were eligible to participate in the randomized controlled trials of in this study. Therefore, there were only patients with severe fatigue at baseline (score of1 in all patients). This lack of variation makes it impossible to estimate proper regression coefficients. This impeded calculation of the time effect between baseline and follow-up.

A t-test for independent samples was performed to compare the mean CIS-fatigue scores of our participants at follow-up and general population controls.

We performed multiple regression analyses (method enter) to determine whether fatigue severity at long-term follow-up (dependent variable) was predicted by fatigue severity (block 1) and the fatigue-perpetuating factors measured at post-CBT (poor coping with cancer/ treatment, activity regulation, dysregulation of sleep, dysfunctional cognitions, a perceived lack of social support and fatigue severity) (block 2).

In a post-hoc analysis we used the mean CIS-fatigue score of the population control group (M=24, SD=11) as a reference point to divide our participants in the following two groups: a low fatigue group (CIS-fatigue <24) and a high fatigue group (CIS-fatigue≥24). By performing a chi-square test we determined if patients in the low fatigue group were less likely to relapse (CIS-fatigue ≥35 at long-term follow-up) than patients in the high fatigue group.

RESULTS

Of the 93 eligible patients, nine had died. We invited 84 patients to participate and excluded three participants: two patients were excluded because they reported to have received cancer treatment in the six months prior to follow-up and one patient was in the process of medical diagnostics because of possible cancer recurrence. In addition, three patients did not participate: one patient did not respond, and for two patients no contact details were available. A total of 78 patients participated in the study (78/81;

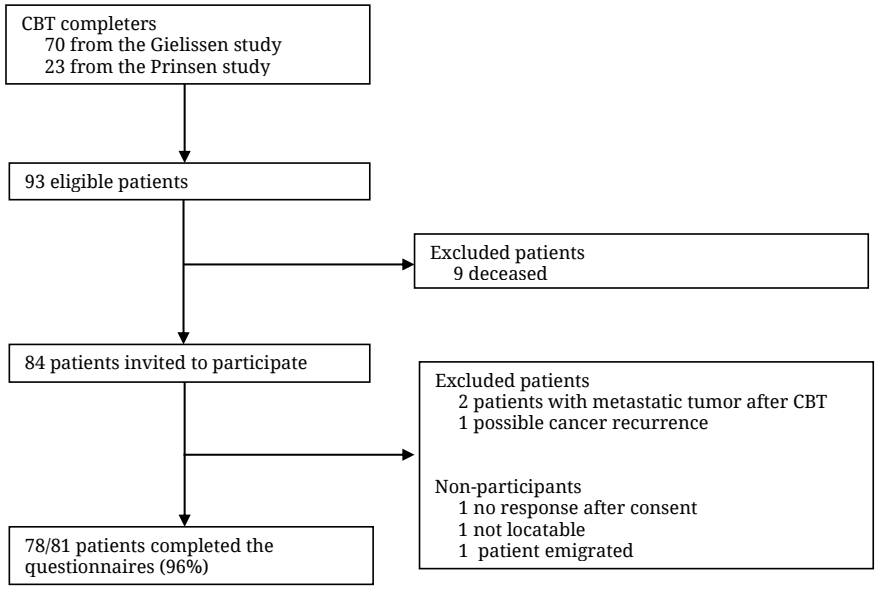

Figure 1. Flow chart of patient inclusion

response-rate 96%) (see figure 1 for flowchart of patient inclusion).

Mean age at long-term follow-up was 55.1 years (SD=10.1), 38 participants were female (49%) and the majority of our participants were married or living together (76%). Of the total group, 24 participants (31%) had experienced a significant life-event in the three months prior to the study and 32 participants (41%) reported the presence of a somatic co-morbidity (see also Table 1).

Linear mixed model analyses showed that fatigue levels had increased at long-term follow-up compared with the post-CBT assessment (mean change = 10.7 points, $p<0.001$). This time effect remained significant when the covariates were added. Lower mental health and higher pain scores predicted higher fatigue levels over time (Table 3). Fatigue levels at long-term follow-up were still lower compared with the baseline assessment (mean change = -12.5 points, $p<0.001$). Results were largely similar when comparing severely and non-severely fatigued patients in logistic GEE analyses. Time effects were comparable, but only pain was a significant covariate. Higher pain levels predicted higher levels of fatigue over time (supplementary table 1).

In the previous two RCTS's, 65 of 78 participants (83%) were recovered from severe fatigue (CIS-fatigue<35) directly after CBT. A total of 34 of these 65 participants (52%) were still recovered at long-term follow-up. Of the 13 participants (17%) that did not recover from severe fatigue directly after CBT, 11 participants were still severely fatigued at long-term follow-up whereas 2 participants (15%) were recovered.

	N (%)
Marital status	
Married, living together	59 (76%)
Divorced	11(14%)
Widowed	3 (4%)
Living alone	5 (6%)
Gender	
Female	38 (49%)
Male	40 (51%)
Having paid work	
Yes	32 (41%)
No	46 (59%)
Self-reported somatic co-morbidity	
Yes	32 (41%)
No	46 (59%)
Significant life events during past three months	
Yes	24 (31%)
No	54 (69%)
Treatment by psychologist/ psychiatrist during past six months	
Yes	11 (14%)
No	67 (86%)
Current treatment for fatigue complaints	
Yes	3 (4%)
No	74 (95%)
Unknown	1 (1%)
Cancer recurrence (currently no treatment, no metastatic cancer)	
Yes	9 (12%)
No	69 (88%)

Table 1: Patient characteristics at long-term follow-up assessment (N=78)

Physical functioning scores at long-term follow-up were improved compared to the baseline assessment (SF36 mean change = 9.1 points, $p<0.001$). However, the level of physical functioning (SF36) was decreased at long-term follow-up compared with post-CBT assessment (SF36 mean change = -9.7 points, $p<0.001$). After controlling for covariates, there was no significant reduction in levels of physical functioning between post-CBT assessment and follow-up anymore. Pain and somatic comorbidities predicted physical functioning over time (Table 3).

Participants' fatigue scores at long-term follow-up were significantly higher than fatigue scores in the matched general population control group (resp. CIS-fatigue

	Baseline assessment	Post-CBT assessment	Long-term follow-up
Fatigue severity			
Mean (SD)	46.9 (6.6)	23.7 (11.0)	34.4 (12.4)
Fatigue level within normal limits (CIS-fatigue<35)			
N (%)	N=0 (0)	N=65 (83.3)	N=33 (42.3)
Physical functioning			
Mean (SD)	66.0 (19.5)	84.7 (15.8)	75.4 (22.5)

Table 2. Fatigue and physical functioning at the three measurement points

	Level of fatigue			Level of physical functioning		
	ß	95% CI	p	ß	95% CI	p
Crude model						
Time baseline_FU	12.47	9.75 to 15.20	<0.001	-9.06	-14.05 to -4.08	<0.001
Time post_FU	-10.71	-13.43 to -7.98	<0.001	9.72	4.73 to 14.70	<0.001
Model with covariates						
Time baseline_FU	14.66	11.66 to 17.66	<0.001	-15.36	-21.22 to -9.51	<0.001
Time post_FU	-4.65	-7.70 to -1.60	0.003	0.42	-5.47 to 6.30	0.889
Mental health	-0.24	-0.31 to -0.16	<0.001	0.10	-0.04 to 0.24	0.168
Pain	-0.09	-0.15 to -0.03	0.004	0.34	0.23 to 0.45	<0.001
Cancer recurrence	3.73	-2.32 to 9.77	0.225	-0.61	-12.14 to 10.91	0.916
Self-reported comorbidities	2.58	-1.53 to 6.70	0.217	-9.99	-17.94 to -2.03	0.014
Significant life events	2.43	-1.81 to 6.66	0.260	-4.52	-12.68 to 3.65	0.277

Notes. Linear mixed model analyses. Time baseline_FU= time between baseline and follow-up assessment; time post_FU= time between post-CBT and follow-up assessment.

Table 3. Levels of fatigue and physical functioning over time

severity M=34.4 SD=12.4 vs. M=23,9, SD=11.4, p=0.01).

The blockwise linear regression analysis showed that fatigue at long-term follow-up was predicted by the level of fatigue directly after CBT (Supplementary table 2). None of the perpetuating factors at post CBT assessment predicted fatigue severity at long-term follow-up.

When comparing the low and high fatigue group at follow-up, patients in the low fatigue group at post-CBT assessment were less likely to be severely fatigued at follow up (p<0.05).

DISCUSSION

This study was the first to investigate the long term effects of CBT for CRF in cancer survivors. Although fatigue levels were improved up to two years after therapy, CBT could not avoid prevent that levels of fatigue increased over time. At long-term follow-up up to 14 years after therapy, fatigue levels had deteriorated and were higher than in general population controls. This deterioration was not explained by cancer recurrence, significant life events, somatic co-morbidities, pain, or a reduced mental health. Nevertheless, at long-term follow-up, positive effects of CBT on fatigue were sustained in a substantial subgroup. Half of patients (51%) who were recovered from severe fatigue at post-CBT were still recovered at long-term follow-up. Patients with a lower fatigue level at post-CBT were less likely to show relapse.

Just like the levels of fatigue, levels of physical functioning also showed deterioration between post-CBT assessment and follow-up. However, this time effect was not maintained after correction for covariates, with pain and comorbidities predicting physical functioning over time. We conclude from this that the positive effects of CBT for CRF on physical functioning are maintained at long term follow-up. As previous studies have shown that higher levels of fatigue are associated with a reduced physical functioning (18), it is remarkable that the deterioration of fatigue levels over time did not go together with worsening of patients' level of physical functioning.

The significant relationship between fatigue severity directly after CBT and fatigue levels at long-term follow-up needs to be replicated, but could have clinical implications. Reducing fatigue severity as much as possible during therapy may improve the long-term effectiveness of CBT. This suggests that it may be beneficial to continue treatment with CBT as long as the fatigue level decreases. A maximum reduction of the fatigue level is not a treatment goal in itself in the current treatment protocol for CBT for CRF.

The finding that there is relapse in a subgroup of patients at long-term follow-up of CBT has been previously found in several studies and in a variety of conditions. Our results show similarities with the study of Janse et al. (2017) on the long-term effects of CBT for patients with chronic fatigue syndrome (i.e., medically unexplained severe fatigue) (8).

Understanding factors and mechanisms that predict the long-term effect of CBT is crucial for the improvement of the existing treatment protocol and for identifying patients at risk for a relapse of CRF. After correction for covariates, fatigue still deteriorated over time. It is poorly understood why fatigue levels increased. To

understand the reasons for relapse, longitudinal studies incorporating qualitative research methods are needed to assess the course of fatigue, stressors and possible fatigue perpetuating factors.

There are several possible explanations for the deterioration after successful treatment of CRF: it is possible that patients who developed CRF after being treated for cancer had a pre-existent vulnerability for developing fatigue in response to a stressor, i.e. a serious somatic illness like cancer. According to the cognitive behavioural model of CRF, cancer and its treatment trigger the fatigue but the fatigue perpetuates due to cognitive-behavioural factors. Perhaps patients remain vulnerable for developing fatigue in response to stressors and the likelihood to encounter serious stressors will increase over time, hence the partial relapse at long-term follow-up. This vulnerability could also be caused by cancer and its treatment; up to date it is largely unclear how biological processes influence the mechanisms underlying CRF and its persistence. It could be that CBT for CRF addresses the fatigue but does not change an underlying somatic vulnerability which make cancer survivors prone to develop severe fatigue. An alternative explanation is that patients relapse into dysfunctional coping in response to 'everyday' fatigue, and dysfunctional behaviours and cognitions eventually lead to severe and persistent fatigue. To understand the reasons for relapse, longitudinal studies incorporating qualitative research methods are needed to assess the course of fatigue, stressors and possible fatigue perpetuating factors. Our outcome measure at long-term follow-up was restricted to fatigue severity. Measurement of scores on fatigue-perpetuating factors would have been valuable as well. Insight in these factors at long-term follow-up would enable us to test whether deterioration of fatigue scores is associated with changes in the perpetuating factors over time.

The strengths of this study are the long follow-up period and the high response rate. A limitation of our study is that the primary outcome variable, the level of fatigue, was measured only once at long-term follow-up. Patients were only asked about their level of fatigue in the previous two weeks. Therefore, it remains unclear whether severe fatigue at long-term follow-up was present longer than two weeks. A second limitation of our study is that our participants, derived from two RCT's of Gielissen et al.(4) and Prinsen et al. (5), all had completed CBT and the post-CBT assessment. The exclusion of patients who did not complete CBT and this assessment may bias our results, and could have caused an overestimation of long-term treatment effects.

In order to prevent relapse, various interventions have been developed: i.e., booster sessions of CBT, mindfulness or metacognitive therapy for depression (19). Our previous follow-up study has shown that effects of CBT on fatigue severity were maintained after a period of two years of follow-up. Therefore, relapse in CBT for CRF occurred

only after a period of two years post-CBT.

It seems more practical and efficient to develop interventions for patients who are again referred after relapse of fatigue, instead of applying interventions to prevent relapse directly following the end of CBT. It should be determined whether patients who have a relapse of severe fatigue following an initially successful CBT, can profit from CBT again or whether another evidence based interventions for fatigue (like mindfulness or exercise therapy) should be given.

In summary, we found that significant deterioration of fatigue over time occurred, but positive effects of CBT on fatigue severity were sustained in about half of the participants at long-term follow-up. Future research should study the underlying mechanisms of CRF and aim for optimizing the long-term treatment results of CBT for CRF.

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APPENDIX

	Severe fatigue		
	ß	**95% CI**	**p**
Crude model			
Time post_FU	-2.93	-3.53 to -2.32	<0.001
Model with covariates			
Time post_FU	-3.02	-3.80 to -2.23	<0.001
Mental health	-0.04	-0.06 to -0.02	0.001
Pain	-0.03	-0.05 to -0.01	0.002
Cancer recurrence	-0.10	-1.92 to 1.72	0.913
Self-reported co-morbidities	-1.06	-2.22 to 0.10	0.073
Significant life events	-0.84	-2.00 to 1.72	0.145

Notes. Logistic generalized estimating equations. Only severely fatigued patients were included at baseline, which impeded calculation of the time effect between baseline and follow-up.

Table S1: Severe fatigue over time

	Block 1			Block 2		
Predictors	**ß**	**SE ß**	**p**	**ß**	**SE ß**	**p**
Fatigue severity (CIS-fatigue)	.351	.123	.005	.103	.174	.557
Poor coping with cancer/ treatment (IES)	-	-	-	-.096	.143	.504
Activity regulation (CIS-activity)	-	-	-	.573	.410	.211
Dysregulation of sleep (SIP sleep/rest)	-	-	-	.029	.030	.333
Dysfunctional cognitions (SES)	-	-	-	-.149	.475	.755
Discrepancies in social support (SSL-D)	-	-	-	.387	.423	.363

Notes. Abbreviations: CIS-activity=Checklist Individual Strength, subscale Activity, CIS-fatigue=Checklist Individual Strength, subscale fatigue severity, IES=Impact of Events Scale; SES=Self-efficacy Scale, SIP=Sickness Impact Profile, SSL-D=van Sonderen Social Support-Discrepancies.

Table S2: Multiple regression analysis to predict changes in fatigue severity between post-CBT and long-term follow-up

9
Summary and general discussion

This chapter provides a summary and general discussion of the findings of the studies in this thesis, including future directions for research and development of cognitive behavioral therapy (CBT) for cancer-related fatigue.

SUMMARY

PART I: ADVANCING KNOWLEDGE OF SEVERE FATIGUE IN BREAST CANCER SURVIVORS

Prevalence and course

Findings on the prevalence rate of severe fatigue in breast cancer survivors were inconsistent, and the course of the symptom over time was still unclear. The meta-analysis in chapter 2 included 27 studies and 12,327 breast cancer survivors, and made it possible to explore prevalence rates in further detail. Prevalence rates in the included studies varied widely, ranging from 7% to 52%. The pooled prevalence of severe fatigue was 27%, but should be interpreted with caution because of high heterogeneity. Prevalence rates over time showed a relatively large decrease in the first half year after cancer treatment.

Fatigue-related factors

A large body of research has focused on cancer-related fatigue, but an up-to-date systematic review on fatigue-related factors in breast cancer survivors was lacking. The meta-analysis in chapter 2 focused on (i) demographic, (ii) disease-related, and (iii) treatment-related factors, and the systematic review in chapter 3 provided a comprehensive overview and level of evidence for the relationship of fatigue with (iv) quality of life and (v) psychological factors in breast cancer survivors:

(i) Demographic factors

Of the included demographic factors, having a partner was a significant protective factor: it slightly reduced the risk on having severe fatigue.

(ii) Disease-related factors

Stage of disease was a significant risk factor: breast cancer survivors with stage II or III breast cancer were at greater risk to develop severe fatigue than survivors with stage 0 or I breast cancer.

(iii) Treatment-related factors

The risk for severe fatigue was increased in patients who had received chemotherapy. Looking at treatment combinations, the risk for severe fatigue was higher in patients treated with surgery, chemotherapy and radiotherapy, with and without hormone therapy. The risk was lower in survivors treated with surgery with and without radiotherapy.

(iv) Quality of life

There was strong evidence for a negative relationship between patients' level of fatigue and quality of life. There was moderate to strong evidence for the relationship of fatigue with different domains of functioning (i.e., physical, role, cognitive, emotional, social, and sexual functioning), pain, work ability, and mental health.

(v) Psychological factors

There was moderate to strong evidence for a relationship of fatigue in breast cancer survivors with depressive symptoms, anxiety, distress, sleep disturbances, a lower sleep quality, lower levels of physical activity, less hours of exercise activities, coping with cancer (i.e., body image and worries about future health), and catastrophizing about symptoms.

Fatigue in patients treated for DCIS

In **chapter 4**, we examined fatigue in patients treated for ductal carcinoma in situ (DCIS). A total of 23% of DCIS patients reported severe fatigue. This prevalence rate was similar in age-matched breast cancer survivors, but higher than in age-matched healthy controls. DCIS patients with severe fatigue reported impaired functioning and a lower quality of life than DCIS patients without severe fatigue. Moreover, fatigue was correlated with the same psychosocial and behavioral factors as those assumed to perpetuate fatigue in breast cancer survivors.

Detecting severe fatigue in oncology practice

Management of severe fatigue starts with detecting this symptom in routine clinical care. In **chapter 5**, we investigated the screening of fatigue. The Distress Thermometer is implemented in a large number of Dutch hospitals as screening tool for psychological distress. Our findings in a sample of newly diagnosed breast and colorectal cancer patients indicated that the fatigue item of the Problem List of this instrument could be used as quick screening tool for severe fatigue. Given the high number of false

positives, a positive screen of severe fatigue should be followed up with an assessment with a validated fatigue questionnaire.

PART II: ADVANCING COGNITIVE BEHAVIORAL THERAPY

Internet-based cognitive behavioral therapy

In **chapter 6**, the development of an internet-based version of CBT (ICBT) was described. ICBT is therapist-guided and tailored to the individual patient. Patients start with two face-to-face sessions, after which they largely follow their therapy online.

Results of the randomized controlled trial in **chapter 7** showed that ICBT is an effective intervention. After ICBT, patients reported lower fatigue levels compared with a waiting list control group, with a large effect size and the majority demonstrating clinically significant and self-rated improvement. Patients also reported lower levels of functional impairment and psychological distress, and a better quality of life after ICBT.

Comparison of effect sizes of ICBT and face-to-face CBT suggest that both treatment formats were equally effective, but less therapist involvement was required for ICBT: mean therapist time was 13 hours in face-to-face CBT compared with 7 hours in ICBT. However, these comparisons need to be interpreted with caution, as both treatment formats were studied in different patient samples.

Long-term efficacy of CBT

In **chapter 8**, we reported findings of a long-term follow-up study up to 14 years after face-to-face CBT for severe fatigue in cancer survivors. Results of a short-term follow-up had shown that treatment effects were preserved after a mean of two years after CBT. At long term follow-up, beneficial effects of CBT on fatigue severity were maintained in about half of patients: 52% scored within normal ranges at long-term follow-up. However, overall, significant deterioration in fatigue levels occurred and fatigue levels were higher compared with age-matched general population controls. This was still the case after correction for relevant covariates. There was no indication of deterioration of physical functioning after correction for relevant covariates like pain and somatic comorbidities.

GENERAL DISCUSSION

This general discussion will focus on future directions in the research and application of CBT for cancer-related fatigue. The detection of patients who need the intervention, optimization of the intervention and its efficiency, nationwide implementation, and the long-term efficacy of CBT are central topics. As research and clinical implications are closely linked, these will be given in conjunction with each other.

Detection of patients who need CBT

The fatigue item of the distress thermometer in **chapter 4** provides a quick tool to detect severely fatigued patients. However, this tool has its limitations: the rate of false positives was relatively high and fatigue was only measured on a dichotomous scale. Besides, the fact that patients are severely fatigued does not imply that they need a fatigue-oriented intervention like CBT. Suggestions to further improve the screening of cancer-related fatigue are:

The use of a computerized adaptive test

Currently, a fatigue item bank (FIB) is developed as part of the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Roadmap initiative (1,2). This FIB can bring the screening of fatigue to a next level. Items in this bank are calibrated by item response theory models and represent differing levels of a symptom along a standardized continuum. This standardization makes it possible to compare items from different fatigue instruments with each other (2). The FIB already enabled the development of a reliable, computerized adaptive test (CAT), in which items are sequentially selected from the item bank using a computerized algorithm, based on a patient's previous answers (3). This FIB-based CAT needs to be tested in Dutch cancer patients and, if validated, its implementation in Dutch oncology practice is warranted to measure fatigue as precisely and efficient as possible.

Distinguishing unmet care needs

It is hard to recruit patients for intervention studies. In the RCT in **chapter 7**, the uptake of ICBT was lower than the prevalence of severe fatigue suggests. This might partly be explained because not all severely fatigued patients want help. For instance, some patients may feel like fatigue is a normal consequence of cancer and cancer treatment, and are not aware of treatment possibilities. Others could have found ways to cope with fatigue and do not feel limited by it. Future research should not only focus

on the prevalence of severe fatigue, but should also explore if and why it is an unmet care need.

Optimizing CBT

Three RCT's have demonstrated that CBT is effective in reducing fatigue in cancer survivors. However, for which patients CBT works and how changes in fatigue severity are initiated by CBT is still unknown. Both should be clarified in future research to further improve the efficacy of CBT and to personalize interventions.

Mediators of CBT: how does it work?

Mediators are intervening variables that account for the relationship between CBT and the change in fatigue (4). Previous research on face-to-face CBT for cancer survivors with various diagnoses showed that an increase in objective physical activity did not mediate the reduction in fatigue (5). Other mediators have not been explored yet. In CBT, each treatment module addresses a distinct fatigue-perpetuating factor (e.g., a deregulated sleep-wake cycle or dysfunctional cognitions). A first step would be to determine to what extent changes in these fatigue-perpetuating factors account for the effect of CBT on fatigue severity. This would reveal which factors need more or less attention during CBT to target cancer-related fatigue more effectively and efficiently.

Recently, Wolvers et al. examined mechanisms of change of a mobile Health (mHealth) physical activity intervention for fatigue in cancer survivors. Again, analyses showed that an increase in objective physical activity did not explain the effect of the mHealth intervention on fatigue in cancer-related fatigue. Instead, changes in cognitions (i.e., increased self-efficacy and perceived physical activity) were correlated with a reduction of levels of fatigue (6). This is in line with findings on mediators of CBT for patients with chronic fatigue syndrome (7-9) and chronic fatigue in patients which chronic diseases (10,11).

Moderators of CBT: what works for whom?

Moderators influence the direction or magnitude of the relationship between CBT and the change in fatigue (4). Specific moderators of the effect of CBT on cancer-related fatigue have not been explored yet. Although most patients benefit from CBT, recovery is not achieved in about a quarter of patients (12,13). Insight in moderators could reveal characteristics that explain why some patients do and others do not benefit from CBT.

Recently, Mustian e.a. explored moderators of fatigue-oriented interventions in general in meta-regression analyses (14). Fatigue-oriented interventions seemed more beneficial for patients with early stages of disease and patients who had completed

cancer treatment, whereas differences in age, sex, and type of cancer did not influence intervention effects (14).

Building on this, different types of interventions for cancer-related fatigue are probably suitable for different subgroups of patients. For instance, one could hypothesize that exercise interventions are suitable for survivors who have exercised frequently in the past, whereas psychological interventions could be more beneficial for patients with more outspoken dysfunctional cognitions. Exploration of moderators should be continued in further detail to reveal what type of fatigue-oriented interventions work for which subgroups of patients. In this way, patients can be offered the type of intervention from which they are most likely to benefit.

Clustering of symptoms

In case of symptom clusters, treatment should focus on the symptom that is most debilitating and important for a patient. As for CBT, therapy is only started if severe fatigue is the most prominent symptom. However, this does not mean that cancer-related fatigue is an isolated symptom. In the exploration of moderators and mediators, potential clustering of fatigue with other relevant symptoms needs to be taken into account. The systematic review in **chapter 3** showed a high level of evidence for the relation of fatigue with pain and depressive symptoms. This is in accordance with other studies that designated the pain-depression-fatigue cluster as one of the most prevalent symptom clusters in adults with and without a history of cancer (15,16). These symptoms often go hand-in-hand as certain features overlap (e.g., lack of energy and anhedonia), tangling up their assessment and treatment. Given the interrelatedness of the symptoms, effects of CBT on fatigue severity may 'cross-over' and also reduce the burden of depressive symptoms, pain, or both (16). It has not been examined yet if this is also the case in CBT for severe fatigue in cancer survivors. These findings indicate that CBT may influence fatigue, depressive symptoms and pain simultaneously. To optimize personalized CBT, future research needs to determine the role and place of these symptoms in the intervention for individual patients.

Unraveling the process of CBT

Another way to gain understanding in the black box behind the therapeutic effect, is the use of ecological momentary assessments (EMA), consisting of a large number of momentary measures of fatigue and potential perpetuating factors in a patient's natural environment (17). The drawbacks of this method are an increased focus on fatigue and fatigue-perpetuating cognitions, which may decrease the therapeutic effect, and the difficulty of determining appropriate short questions to measure

outcomes. However, the use of EMA during therapy does enable tracking of a patient's individual response and measurement of momentary changes in fatigue and potential perpetuating factors. As a result, more reliable conclusions on causality can be drawn and individualized treatment models can be improved. This may enable us to target cancer-related fatigue more specifically and effectively.

Optimizing treatment efficiency

To improve the limited treatment capacity of CBT, an internet-based version was developed with the intention to reduce the time spend for each patient. **Chapter 7** showed that ICBT seemed more time efficient than face-to-face CBT (reduction in therapist time of 43%), while treatment effects were comparable (13). However, the treatment formats still need to be compared with each other in one study population. Possibilities to further improve time efficiency of ICBT also need to be explored, including:

Use of mobile applications

For an easy and direct registration of sleep and wake times, the graded activity program, and diaries for dysfunctional cognitions, mobile applications could be a useful addition during ICBT. This also provides the possibility to give patients direct, interactive automated feedback on these intervention elements, which could further decrease therapist involvement (18). Evidence already exists for the efficacy of mobile applications in increasing physical activity (19). This evidence includes a physical activity mHealth intervention, developed by Wolvers et al, which was shown to be effective in reducing severe fatigue in cancer survivors (6).

Reduction of treatment duration

The duration of ICBT of six months is long compared with other web-based interventions for fatigue in cancer survivors that took only 9 to 12 weeks to complete (20,21). However, the longer duration may partly account for the more beneficial effect of CBT on fatigue severity. A meta-analysis has identified the duration of psychosocial interventions as the most important moderator of treatment effects on quality of life of cancer patients. Interventions of more than 12 weeks were found to be more effective than shorter interventions (22). It needs to be explored if the duration of ICBT can be shortened without losing efficacy. EMA could be used to determine the optimal dose of therapy by measuring patients' fatigue level frequently during CBT to gain insight in their individual responses to therapy.

Integration of video consults

At some crucial points in therapy, e-mailing might not be effective enough and video consults should be used. Examples are moments when the patient is stuck or considers to discontinue ICBT, and modules that generally require more therapist guidance (e.g., modules addressing dysfunctional cognitions and fear of cancer recurrence). In these kind of situations, more direct communication through video consults may reduce the number of e-mails and therapist time, and could accelerate the treatment process.

Nationwide implementation

The development of evidence-based CBT does not automatically make it available for all patients who need it. Implementation is crucial to enable the uptake of CBT into routine clinical practice, but this is often a bottleneck for care innovations. Approximately two-thirds of organizations' efforts to implement changes fail (23). Consequently, many interventions found to be effective in research settings remain unused and do not end up with the patients who need it (23,24).

In 2016, the Netherlands Comprehensive Cancer Organization has selected face-to-face CBT for fatigue in cancer survivors to enhance its implementation, as part of the project "Implementation of evidence-based psychosocial interventions for people with cancer." ICBT is not within the scope of this project, and would require a different implementation process. For instance, other skills need to be learned to therapists and a web-portal needs to be adopted in the care system of new centers. A separate implementation project for ICBT is required to make it available for all breast cancer survivors who need it. In advance, further insight in the external validity and cost-effectiveness of ICBT must be gained.

External validity

The efficacy of face-to-face CBT has been demonstrated in two previous RCTs on cancer survivors with various tumor types (12, 25). The RCT in **chapter** 7 included a relatively young sample of female breast cancer survivors. Further work is required to prove the effectiveness of ICBT for survivors of other tumor types, with a focus on subgroups that were not represented in the RCTs: males, older patients, and patients who had received other intensive cancer treatments like stem cell transplantation. An RCT in which ICBT is compared with regular care (evidence-based face-to-face CBT) is the gold standard to prove the efficacy of ICBT for survivors of tumor types other than breast cancer (26). However, conducting another RCT might not be attainable due to time and resource constraints.

Alternatively, the next step after our RCT in a well-controlled setting could be a

pragmatic trial without any restrictions regarding patients' tumor type. A pragmatic trial could answer the question if our results are applicable and generalizable to routine clinical practice (27). This would control for the external validity of our RCT results in a broader sense, as efficacy studies are often better resourced. For instance, therapists in a study setting often have a lower clinical load, are more experienced, and receive more training and supervision. As a result, evidence-based interventions are not always (equally) effective in routine clinical practice (27). In case of a pragmatic trial, the control condition should be face-to-face CBT instead of a waiting list condition. This provides the opportunity to compare the efficacy and efficiency of the two intervention formats in one study population.

Another option to determine if ICBT is effective for patients with other tumor types is a single-case experimental study (28). In this design, a participant would receive ICBT after a no-treatment baseline phase. Fatigue would be measured frequently and repeatedly during this baseline phase and assessments continue into the ICBT treatment phase. Experimental control can be established by randomizing a participant to a start point of the ICBT. It has been recommended to perform a series of replicated single-case experiments to demonstrate treatment effectiveness more convincingly, for example with a multiple baseline design across participants (28,29). Single-case experimental studies are particularly appropriate for survivors of rare types of cancer, with separate series of replicated experiments per tumor type.

Cost-effectiveness

An economic evaluation of CBT is also an important issue for future research. Nowadays, reducing the costs of mental health care is increasingly important. As stated in the multiannual plan (2013-2020) of the Dutch Association of Mental Health and Addiction Care (GGZ Nederland), there have been significant cuts in the budget for mental health, and the remaining funds must be spent as efficiently as possible (30). Results in chapter 7 indicated that treatment effects of ICBT were comparable to those of regular face-to-face CBT. At the same time, the intervention seemed more time efficient (13). These findings make it likely that ICBT is more cost-effective, because it is more time-efficient than face-to-face CBT. However, ICBT also comes with additional expenses like costs for web hosting. In line with our recommendation in the previous paragraph, a direct comparison of face-to-face CBT and ICBT in one study population is required to evaluate its cost-effectiveness.

Implementation process

To implement ICBT, a national network of treatment centers that will provide the

intervention needs to be created. In advance, a problem analysis is required to identify potential facilitating and hindering factors of the implementation. Examples of barriers that hamper implementation can occur at various levels: from the involved individual professionals and patients (e.g., lack of knowledge, skills or motivation to change) to a broader social, organizational, economic and political context (e.g., organization of care processes and policies) and the innovation itself (e.g., feasibility and attractiveness) (31).

Strategies to overcome potential barriers for implementation need to be developed. An example is a strategy aimed at a lack of knowledge on the existence of ICBT by potential referrers (e.g., general practitioners and oncologists) and breast cancer survivors who need the intervention. Promotion actions to inform these target populations about the ICBT treatment option is of importance to overcome this barrier. Once started, implementation should be an iterative process that is evaluated continuously (31). A nationwide network of treatment centers that provide ICBT and an implementation manual that enables health care professionals to implement ICBT independently in the future should be end products of the implementation process.

Long-term efficacy

The long-term efficacy of ICBT is open to question for future research. For face-to-face CBT, it has been shown to be effective up to two years after therapy. From that point, fatigue levels tend to deteriorate over time. To get a more complete picture of the efficacy of CBT on the long run, and reasons for relapse, it is necessary to measure patients more frequently during the follow-up period.

General vulnerability for fatigue

Up to 14 years after face-to-face CBT, there had probably been new triggers of fatigue, like distressing life events or somatic comorbidities other than cancer. Patients with a relapse of severe fatigue after successful treatment with CBT could have a general vulnerability for developing fatigue. This vulnerability may partly be explained by underlying personality traits or somatic vulnerability caused by cancer and its treatment in the past.

Knowledge on personality traits of severely fatigued breast cancer survivors is scarce and further research is warranted. Two descriptive studies found that neuroticism predicted patients' level of fatigue after breast cancer treatment after controlling for depression (32,33). Though successfully treated in CBT, this personality trait may increase a patient's risk for relapse of severe fatigue in response to new stressors in life. In addition, a recent review of Saligan et al. revealed several biological

factors that are related with fatigue in cancer patients, including dysregulations in the immune system, metabolic and neuroendocrine functions, and the hypothalamic-pituitary-adrenal axis (34). These biological factors may cause an increased vulnerability for developing fatigue.

Dealing with relapse after CBT

In CBT, patients have learned skills to cope with severe fatigue, which they can reapply after therapy. The use of follow-up booster sessions to help patients with preserving these skills has long been advocated as maintenance strategy of CBT (35). However, findings of the follow-up study in **chapter 8** showed that fatigue levels only start to deteriorate from two years after face-to-face CBT. Starting to provide standard booster sessions after such a long period after therapy is difficult and seems inefficient due to practical constraints.

Initiatives to prevent a relapse would be more feasible. At this point, research on successful strategies in preventing or treating recurrence of severe fatigue in cancer survivors is lacking. Paying more attention to a personalized relapse prevention plan after successful completion of CBT could be of importance. In the current CBT protocol, this plan is discussed in the evaluative session after CBT. However, an extra session can be spent on formulating preventive actions and early signs of a relapse of severe fatigue. This should result in an actual standardized plan for patients to take home after the final face-to-face session and to rely on after completion of therapy. A personalized relapse prevention plan should be added as extra assignment in ICBT as well. Moreover, the option for re-referral in case of recurrence of severe fatigue should be encouraged with referrers and patients.

CLOSING REMARKS

The large body of studies that have already focused on severe fatigue in breast cancer survivors show that this symptom is taken seriously. Hopefully, insights and future directions resulting from this thesis will further improve the effects and availability of CBT for severe fatigue in (breast) cancer survivors. Because after all, it is most important that the burden of this debilitating symptom will be reduced.

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Appendices

NEDERLANDSE SAMENVATTING

Wereldwijd is borstkanker het meest voorkomende tumortype bij vrouwen. Steeds meer patiënten worden succesvol behandeld voor borstkanker en overleven deze ziekte. Een deel van hen heeft echter last van blijvende gevolgen van de ziekte en de behandeling hiervan. Eén van deze gevolgen kan ernstige vermoeidheid zijn. Dit komt veel voor tijdens en na afloop van de behandeling en is belemmerend voor patiënten.

De doelen van dit proefschrift zijn: (1) het vergroten van de kennis over ernstige vermoeidheid na borstkanker (deel I) en (2) het verbeteren van de behandeling van vermoeidheid na borstkanker, met een focus op cognitieve gedragstherapie (deel II). In deze samenvatting worden de belangrijkste resultaten van de onderzoeken uit dit proefschrift besproken.

DEEL I: VERGROTEN VAN KENNIS OVER VERMOEIDHEID NA BORSTKANKER

Het was nog onduidelijk hoeveel procent van de patiënten last heeft van vermoeidheid na borstkanker, wat het beloop is van deze vermoeidheid en welke factoren eraan gerelateerd zijn.

Om hier inzicht in te krijgen, deden we een systematisch literatuuronderzoek, waarin we alle studies over vermoeidheid na borstkanker bij elkaar zochten (systematische review). We hadden de beschikking over de gegevens van 27 verschillende studies met in totaal 12,327 patiënten. Deze gegevens hebben we geanalyseerd in een zogenaamde meta-analyse.

In **hoofdstuk 2** rapporteren we de resultaten van meta-analyses naar de prevalentie en risicofactoren van vermoeidheid na borstkanker. In **hoofdstuk 3** geven we een overzicht van de factoren die gerelateerd zijn aan vermoeidheid na borstkanker, op basis van 57 studies. We beschrijven de samenhang van vermoeidheid met aspecten van kwaliteit van leven en psychologische factoren. Tevens bepalen we hoeveel bewijs er is voor de samenhang met vermoeidheid.

Prevalentie en beloop

De prevalentie van ernstige vermoeidheid varieert sterk tussen studies: het percentage vermoeide patiënten loopt uiteen van 7 tot 52%. Als we alle percentages samennemen in een meta-analyse, komen we tot een gepoolde prevalentie van 27%. Dit betekent dat ongeveer één op de vier patiënten ernstig vermoeid is na behandeling van borstkanker. Deze schatting moet voorzichtig geïnterpreteerd worden vanwege grote verschillen tussen de studies.

De prevalentie van vermoeidheid neemt af in de eerste zes maanden na de behandeling van borstkanker. Nadien wisselt het beloop sterk, zonder duidelijke afname.

Relatie van vermoeidheid met andere factoren

(1) Demografische factoren

Het hebben van een partner geeft een kleine vermindering van het risico op ernstige vermoeidheid na borstkanker.

(2) Ziekte-gerelateerde factoren

Patiënten met een hoger ziektestadium (stadium II of III) hebben een hoger risico op ernstige vermoeidheid dan patiënten met een lager ziektestadium (stadium 0 of I). Ziektestadia geven aan hoeverre de ziekte zich in het lichaam heeft uitgebreid. Dit wordt bepaald door de grootte van de tumor, het aantal uitzaaiingen in de lymfeklieren en het aantal uitzaaiingen op afstand.

(3) Behandelingsgerelateerde factoren

Het risico op ernstige vermoeidheid is hoger bij patiënten die behandeld zijn met chemotherapie. We keken ook naar verschillende combinaties van behandelingen voor kanker. Het risico op ernstige vermoeidheid is hoger bij patiënten behandeld met een combinatie van een operatie, chemotherapie en radiotherapie, met of zonder hormoontherapie. Het risico is lager bij patiënten die alleen zijn behandeld met een operatie, met of zonder radiotherapie.

(4) Kwaliteit van leven

We vonden sterk bewijs voor een negatieve relatie tussen de ernst van de vermoeidheid en de kwaliteit van leven van patiënten: hoe vermoeider patiënten zijn, des te lager is hun kwaliteit van leven. Ook vonden we matig tot sterk bewijs voor de samenhang van meer vermoeidheid met meer pijn, een lager werkvermogen, een slechtere mentale gesteldheid, en een verminderd functioneren (lichamelijk, rol, cognitief, emotioneel, sociaal, en seksueel functioneren). Hieruit kunnen we concluderen dat vermoeidheid samenhangt met een scala aan beperkingen in het dagelijks leven van patiënten.

(5) Psychologische factoren

We vonden sterk bewijs voor een relatie van vermoeidheid na borstkanker met meer depressieve symptomen, meer angst, meer slaapstoornissen, een hogere neiging

tot catastroferen (doemdenken) over symptomen. Tot slot vonden we matig bewijs voor de relatie van meer vermoeidheid met meer distress (de algemene psychische last die mensen ervaren), een lager lichamelijk activiteitenniveau, een lagere slaapkwaliteit en meer moeite met verwerking van de ziekte (lichaamsbeeld en zorgen over toekomstige gezondheid). Het is van belang om in behandelingen voor vermoeidheid na borstkanker aandacht te besteden aan deze factoren.

Vermoeidheid na behandeling van DCIS

Hoofdstuk 4 is specifiek gericht op patiënten met een ductaal carcinoom in situ (DCIS). Dit is een voorstadium van borstkanker, dat behandeld wordt met een operatie en/of radiotherapie. Patiënten met DCIS hebben geen kanker, maar krijgen wel dezelfde behandelingen als patiënten met kanker. Dit kan DCIS een verwarrende diagnose maken voor patiënten.

We brachten vermoeidheid in kaart bij 89 vrouwen die zijn behandeld voor DCIS. In totaal is 23% van hen ernstig moe. Deze prevalentie is vergelijkbaar met vrouwelijke leeftijdsgenoten die zijn behandeld voor borstkanker (25%). Ernstige vermoeidheid komt aanzienlijk minder vaak voor bij gezonde vrouwelijke leeftijdsgenoten (6%).

Vermoeidheid hangt samen met meer slaapproblemen, vermijding van activiteiten, 'alles-of-niets' gedrag, gebrek aan sociale steun, niet-helpende gedachten over vermoeidheid, moeite met verwerking van de diagnose DCIS, en angst om in de toekomst kanker te krijgen. Van deze factoren is bekend dat ze vermoeidheid na kanker in stand kunnen houden. Deze factoren worden daarom aangepakt in cognitieve gedragstherapie voor vermoeidheid na kanker. Dit is een bewezen effectieve psychologische behandeling voor vermoeidheid.

Aangezien vermoeidheid veel voorkomt na behandeling van DCIS, is het waardevol om hier ook een specifieke behandeling voor te ontwikkelen. Factoren die gerelateerd zijn aan vermoeidheid na kanker en vermoeidheid na DCIS komen overeen. De behandeling voor vermoeidheid na DCIS kan daarom gebaseerd worden op bestaande cognitieve gedragstherapie voor vermoeidheid na kanker. Hierbij moet wel rekening worden gehouden met DCIS-specifieke factoren, zoals verwerking van de soms verwarrende diagnose.

Opmerken van ernstige vermoeidheid in de dagelijkse praktijk

Een juiste aanpak van ernstige vermoeidheid na kanker begint met het signaleren van dit symptoom in de klinische praktijk. De Lastmeter wordt in veel Nederlandse ziekenhuizen gebruikt als screeningsinstrument voor de last die mensen ervaren op lichamelijk, emotioneel, sociaal en praktisch gebied tijdens en na behandeling van

kanker. De Lastmeter bevat een 'Probleemlijst', waarin patiënten aankruisen of ze last hebben van bepaalde problemen, waaronder vermoeidheid. We onderzochten of we deze vermoeidheidsvraag kunnen gebruiken om ernstige vermoeidheid te signaleren in een groep patiënten met borst- en darmkanker.

Door de vermoeidheidsvraag te gebruiken, spoorden we vrijwel alle patiënten met ernstige vermoeidheid op. De Lastmeter lijkt daarmee een zinvol screeningsinstrument om vermoeidheid in de dagelijkse praktijk op te sporen.

Wel was er bij gebruik van de vermoeidheidsvraag sprake van een overschatting, doordat een deel van de patiënten onterecht als ernstig moe werd gezien. Na een positieve screening moet daarom een uitgebreidere vermoeidheidsvragenlijst worden afgenomen om de ernst van de vermoeidheid te bepalen.

DEEL II: VERBETERING VAN COGNITIEVE GEDRAGSTHERAPIE

Er zijn verschillende behandelingen ontwikkeld voor vermoeidheid na kanker. Er is bewijs voor de werkzaamheid van cognitieve gedragstherapie, waaronder de behandeling die is ontwikkeld door het Nederlands Kenniscentrum voor Chronische Vermoeidheid (NKCV).

Bij cognitieve gedragstherapie gaat men ervan uit dat de vermoeidheid is ontstaan in de periode van de diagnose en behandeling van kanker. Na afloop van behandeling vormen de ziekte en behandeling geen verklaringen meer voor het aanhouden van de vermoeidheid. Andere factoren komen dan in het spel en houden vermoeidheidsklachten in stand. Voorbeelden hiervan zijn ontregelingen in het slaap-waakritme en een sterk wisselend activiteitenniveau. Via cognitieve gedragstherapie leren patiënten hoe ze deze instandhoudende factoren zelf kunnen aanpakken, door doen en denken in reactie op de vermoeidheid te veranderen.

Eerder onderzoek had reeds laten zien dat cognitieve gedragstherapie met gesprekken tussen patiënt en therapeut leidt tot een vermindering van vermoeidheid na kanker. Maar de behandelcapaciteit is beperkt; er is vaak een wachttijd voor patiënten voordat zij kunnen starten met behandeling. De gesprekstherapie bestaat uit gemiddeld 12 tot 14 sessies in een periode van 6 maanden. Er zijn maar een paar behandelcentra in Nederland waar de therapie als behandeloptie beschikbaar is.

De internettherapie Op weg naar herstel

Wij ontwikkelden een internetvariant van de cognitieve gedragstherapie om behandelcapaciteit te vergroten en de behandeling minder belastend te maken voor patiënten. In hoofdstuk 6 beschrijven we de ontwikkeling van deze internettherapie 'Op weg naar herstel'. De internettherapie betreft een online versie van de bewezen

effectieve gesprekstherapie en is ontwikkeld voor vermoeidheid na borstkanker. De internettherapie wordt begeleid door een ervaren en getrainde therapeut via e-mail, telefonische consulten en video-consulten. Patiënten starten met twee gesprekken, waarna ze de therapie via het internet volgen. In de therapie leren patiënten hoe ze de factoren kunnen aanpakken die de vermoeidheid in stand houden. De therapie bestaat uit acht behandelonderdelen en wordt op maat gemaakt voor de patiënt. Dit betekent dat patiënten alleen de onderdelen volgen die voor hen relevant zijn. Welke onderdelen van toepassing zijn, wordt bepaald met vragenlijsten en een actometer (bewegingsmeter).

Studie naar het effect

De resultaten van de studie in **hoofdstuk 7** laten zien dat de internettherapie Op weg naar herstel effectief is. In totaal deden er 132 vrouwen met ernstige vermoeidheid na borstkanker mee aan de gerandomiseerde en gecontroleerde studie. Patiënten werden via loting willekeurig ingedeeld in (1) een groep die de internettherapie volgde of (2) een groep die op de wachtlijst werd geplaatst voor de reguliere gesprekstherapie (controlegroep). Wij volgden alle deelnemers gedurende een periode van zes maanden. Vermoeidheid en bijkomende klachten werden op twee momenten gemeten: bij start van het onderzoek en na zes maanden.

Na zes maanden rapporteren patiënten die internettherapie hebben gevolgd minder vermoeidheid vergeleken met de controlegroep. In totaal herstelt 73% van de patiënten en is niet langer ernstig moe, vergeleken met 27% van de patiënten uit de controlegroep. Ook rapporteren patiënten na internettherapie minder beperkingen in hun dagelijks leven, minder psychologische last, en een betere kwaliteit van leven dan de controlegroep.

De effecten van internet- en gesprekstherapie op vermoeidheid na kanker zijn vergelijkbaar. Maar internettherapie kost therapeuten minder tijd (gemiddeld 7 uur) dan gesprekstherapie (gemiddeld 13 uur). De behandelvormen zijn echter niet in één studie onderzocht, maar in twee verschillende groepen patiënten. De verschillen tussen de twee therapievormen moeten daarom voorzichtig worden geïnterpreteerd.

Lange termijn effect van cognitieve gedragstherapie

Het is belangrijk om te weten of effecten van de reguliere cognitieve gedragstherapie voor vermoeidheid met gesprekken ook op de langere termijn behouden blijven. Resultaten van een eerdere follow-up studie lieten al zien dat de positieve effecten op vermoeidheid en beperkingen tot ongeveer twee jaar na behandeling blijven bestaan. Het was echter onbekend hoe het patiënten daarna vergaat.

In de studie in **hoofdstuk 8** onderzoeken we vermoeidheid tot 14 jaar na reguliere cognitieve gedragstherapie. We bekijken of patiënten die na cognitieve gedragstherapie hersteld waren van ernstige vermoeidheid, nog steeds hersteld zijn op de lange termijn. In totaal scoort 52% van hen binnen normaalwaarden op vermoeidheid tot 14 jaar na de therapie.

Ook hebben we gemiddelde vermoeidheidsscores in de totale groep patiënten geanalyseerd (wel en niet hersteld van ernstige vermoeidheid na cognitieve gedragstherapie). Hierbij zagen we dat gemiddelde vermoeidheidsscores verslechteren op de lange termijn. De vermoeidheidsscores zijn hoger dan de scores van leeftijdsgenoten uit de algemene bevolking. Dit verandert niet na correctie voor mogelijke verstorende variabelen (zoals de aanwezigheid van lichamelijke ziekten en pijnklachten).

Daarnaast hebben we het gemiddelde scores op het lichamelijk functioneren bekeken in de totale groep patiënten. We zagen geen verslechtering in scores op het lichamelijk functioneren; ook niet na correctie voor mogelijke verstorende variabelen. Dit laat zien dat effecten op het lichamelijk functioneren van cognitieve gedragstherapie behouden blijven op de lange termijn.

Toekomstig onderzoek en verdere ontwikkeling van cognitieve gedragstherapie

In **hoofdstuk 9** bespreken we aandachtspunten voor vervolgonderzoek naar cognitieve gedragstherapie voor vermoeidheid na kanker en de toepassing hiervan in de klinische praktijk. We geven aanbevelingen voor het opsporen van patiënten die baat kunnen hebben bij de behandeling. Ook gaan we in op verdere optimalisatie van de internettherapie, waarbij we mogelijkheden benoemen om de effectiviteit en efficiëntie van de therapie verder te verbeteren. Tevens geven we suggesties voor landelijke verspreiding van de internettherapie. Tot slot bespreken we mogelijkheden om meer inzicht te krijgen in het lange-termijn effect van de behandeling en positieve behandeleffecten te behouden.

Slotwoord

Veel studies hebben zich al gericht op ernstige vermoeidheid na borstkanker. Dit laat zien dat dit onderwerp serieus wordt genomen. Uiteindelijk gaat het er om dat de last en belemmeringen die patiënten ondervinden door vermoeidheid na kanker worden verminderd. Hopelijk zullen de bevindingen van dit proefschrift de effectiviteit en beschikbaarheid van behandelingen voor ernstige vermoeidheid na (borst)kanker verbeteren.

LIST OF PUBLICATIONS

Published articles

Abrahams HJG, Gielissen MFM, Schmits I, Verhagen CAHHVM, Rovers M, Knoop H. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. Ann Oncol 2016;27:965-74.

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Abrahams HJG, Gielissen MFM, de Lugt de M, Kleijer EFW, Roos de WK, Balk E, Verhagen CAHHVM, Knoop H. The Distress Thermometer for screening for severe fatigue in newly diagnosed breast and colorectal cancer patients. Psychooncology 2017;26:693–7.

Abrahams HJG, Gielissen M, Goedendorp M, Berends T, Peters MEWJ, Poort H, Verhagen CAHHVM, Knoop H. A randomized controlled trial of web-based cognitive behavioral therapy for severely fatigued breast cancer survivors (CHANGE-study): study protocol. BMC cancer. 2015;15:765.

Abrahams HJG, Gielissen MFM, Donders RRT, Goedendorp MM, Wouw AJ van der, Verhagen CAHHVM, Knoop H. The efficacy of Internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: A randomized controlled trial. Cancer 2017;123(19):3825-34.

Submitted articles

Gessel LD, **Abrahams HJG**, Prinsen H, Bleijenberg G, Heins M, Twisk J, Van Laarhoven HWM, Verhagen CAHHVM, Gielissen MFM, Knoop H. Are the effects of cognitive behaviour therapy for severe fatigue in cancer survivors sustained up to 14 years after therapy? *Revised manuscript submitted for publication.*

Abrahams HJG, Gielissen MFM, Verhagen CAHHVM, Knoop H. The relationship of fatigue with quality of life and psychological factors in breast cancer survivors: a systematic review. *Manuscript submitted for publication.*

Thewes B, Rietjens JAC, van den Berg SW, Compen FR, **Abrahams HJG**, Poort H, Wal M van de, Schellekens MPJ. Peters MEWJ, Speckens AEM, Knoop H, Prins JB. One way or another: The opportunities and pitfalls of self-referral and consecutive sampling as recruitment strategies for psycho-oncology intervention trials. *Manuscript submitted for publication.*

Poort H, Onghena, P, **Abrahams HJG**, Jim HSL, Jacobsen PB, Blijlevens NMA, Hans Knoop H. Cognitive Behavioral Therapy for Treatment-Related Fatigue in Chronic Myeloid Leukemia Patients on Tyrosine Kinase Inhibitors: A Mixed-Method Study. *Manuscript submitted for publication.*

PHD PORTFOLIO

Name PhD candidate: Harriët Abrahams
Department: Department of Medical Psychology
Graduate School: Radboud Institute for Health Sciences

PhD period: 01/04/2013 - 01/08/2017
Promotors: Prof. Dr. Maroeska Rovers, Prof. Dr. Hans Knoop
Co-promotors: Dr. Marieke Gielissen, Dr. Stans Verhagen

Training activities

Courses & Workshops	Year(s)	ECTS
NCEBP (RIHS) introductie cursus	2013	2.0
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2013	2.0
Endnote workshop Radboudumc	2013	0.1
Advanced conversation	2013	2.0
NCEBP (RIHS) PhD retreat	2013	1.0
Academic Writing	2014	3.0
The art of presenting science	2014	1.5
Management voor promovendi	2015	2.0
Wetenschapsjournalistiek	2015	3.0
Onderzoeksdag Medische Psychologie	2016	1.0
Education in a nutshell	2016	1.0
ICBM conference workshop e-health	2017	0.5
Seminars & lectures	N/A	N/A
Symposia & congresses		
IPOS congress, Rotterdam (oral)	2013	0.5
ICBM congress, Groningen (visitor)	2014	0.5
VNO-ChroVer, Nijmegen (oral)	2014	0.5

	Year(s)	ECTS
Nationaal mammacongres, Ermelo (oral)	2015	0.5
IPOS congress, Dublin, United Kingdom (3 orals)	2016	1.5
Theme meeting 'Women's health' (laptop demonstration)	2016	0.5
A-CaRe symposium, Amsterdam (visitor)	2016	0.5
Annual health meeting, Amsterdam (poster)	2016	0.5
VGCT congress, Veldhoven (laptop demonstration)	2017	1.5
ICBM congress, Melbourne, Australia (3 orals)	2017	1.0
ARPH congress, Leiden (oral)	2017	0.5
IPOS congress, Berlin (1 oral; 1 poster)	2017	1.5
Other		
VNO-ChroVer, secretary	2013, 2014	0.5
Journal Club Psychosocial Oncology	2013-2017	5.0
Reviewer: 2 scientific papers for peer-reviewed journals	2017	0.2
Teaching activities		
Lecturing		
Tutor Cancer Research, Bachelor Biomedische Wetenschappen, Radboudumc	2013	2.0
Supervision of internships / other		
Thesis supervisor, Bachelor Medical Sciences, Radboudumc	2013, 2014,	3.0
Thesis supervisor, Master Medical Sciences, Radboudumc	2015	1.5
TOTAL		**40.8**

DANKWOORD

Alone we can do so little; together we can do so much.

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CURRICULUM VITAE

Harriët Abrahams werd op 19 januari 1989 geboren in Tilburg en groeide op in Hilvarenbeek. In 2007 behaalde zij haar gymnasiumdiploma aan het Mill-Hill college te Goirle. Daarna begon ze aan de bachelor Psychologie & Gezondheid aan de Universiteit van Tilburg. Na het afronden van haar bacheloropleiding in 2010 koos ze voor de tweejarige masteropleiding Medische Psychologie. In het tweede jaar heeft ze haar klinische stage voltooid op de afdeling Psychiatrie van het St. Elisabeth ziekenhuis te Tilburg. Haar onderzoeksstage voerde zij uit op de afdeling Medische Psychologie en Klinische Neuropsychologie van de Universiteit van Tilburg. Deze stage richtte zich op het cognitief functioneren van vrouwen met borstkanker. Naast haar opleiding was ze werkzaam als onderzoeksassistent bij een e-health project, gericht op een online interventie voor angst en depressie bij patiënten met een implanteerbare cardioverter defibrillator. In 2012 is Harriët cum laude afgestudeerd, waarop ze in 2013 werd aangesteld als promovenda bij het Nederlands Kenniscentrum Chronische Vermoeidheid (NKCV) bij het Radboudumc. Centraal in dit promotieonderzoek stond de ontwikkeling van 'Op weg naar herstel', een online cognitieve gedragstherapie voor vrouwen met ernstige vermoeidheid na borstkanker. De resultaten van dit onderzoek zijn te lezen in dit proefschrift.

Inmiddels is het NKCV over gegaan naar Amsterdam en momenteel werkt Harriët als therapeut bij dit centrum. Ze behandelt patiënten met vermoeidheid na kanker, het chronisch vermoeidheidssyndroom en vermoeidheid bij chronische ziekten. Ze combineert deze baan in de klinische praktijk met een functie als postdoctoraal onderzoeker. Zij werkt aan een alliantieproject van afdeling Medische Psychologie van het Academisch Medisch Centrum (AMC) en de afdeling Epidemiologie en Biostatistiek van het VU Medisch Centrum te Amsterdam. Met behulp van reeds verzamelde data vanuit een internationaal consortium (Polaris-studie) onderzoekt ze de werkingsmechanismen van psychosociale interventies voor kankergerelateerde vermoeidheid.