Psycho-Oncology
Psycho-Oncology **16**: 787–795 (2007)
Published online 6 November 2006 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pon.1120

The course of severe fatigue in disease-free breast cancer patients: A longitudinal study

P. Servaes[1], M. F. M. Gielissen[2], S. Verhagen[3] and G. Bleijenberg[2]*

[1] *Department of Medical Psychology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands*

[2] *Department of Expert Centre Chronic Fatigue, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands*

[3] *Department of Medical Oncology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands*

** Correspondence to: Radboud University Nijmegen Medical Centre, Expert Centre Chronic Fatigue, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands*
E-mail: G.Bleijenberg@nkcv.umcn.nl

Received: 6 February 2006
Revised: 13 July 2006
Accepted: 29 September 2006

Abstract

Background: **We investigated whether fatigue is a persistent problem, and whether persistent fatigue is related to former treatment modalities. In addition, we studied the predictors of persistent fatigue.**

Methods: **At baseline ($n = 150$, mean time since cancer treatment = 29 months) patients were asked to fill out several questionnaires on psychological, physical, social, cognitive and behavioral aspects (*Ann. Oncol.* 2002;13:589–598). During the 2 years after baseline patients were asked to fill out monthly a fatigue questionnaire (CIS-fatigue). Hundred-twenty-one patients completed the study, 10 dropped out and 19 had a disease recurrence.**

Results: **Twenty-four percent of the patients experienced persistent severe fatigue complaints during the 2-year observation period. Persistent fatigue seemed to be related to the duration of former treatment but unrelated to type of surgery, type of adjuvant therapy and time since treatment finished. High anxiety, high impairment in role functioning and low sense of control over fatigue symptoms at baseline were predictors of persistent fatigue.**

Conclusion: **Fatigue appears to be a persistent problem for a quarter of a sample of disease-free breast cancer patients during a 2-year period. The predictors of persistent fatigue found in this study can be helpful for the development of interventions to reduce post-treatment fatigue.**

Keywords: persistent fatigue; cancer; oncology; survivors; longitudinal design

Introduction

Fatigue is a well-known problem of cancer patients during active treatment. The malignancy itself, the treatment and its side effects like anemia all have impact on fatigue. Many quality of life instruments use the complaint fatigue as an important independent factor to differentiate between more or less harmful interventions or to measure the clinical importance of expensive supportive treatments like additional use of erythropoietin. When the patient has been cured, cancer treatment is stopped and the hemoglobin level has been normalized, it is expected that all complaints subside within a reasonable period of time.

However, based on cross-sectional studies, we may conclude that fatigue is a frequent complaint in former cancer patients even up to 10 years after successful treatment for cancer [1–5]. So far, most longitudinal studies that have been published focused on fatigue complaints in cancer patients while they were undergoing active treatment for cancer [6–9] and in the year after completion of treatment [10–13]. Few longitudinal studies have been performed in which fatigue is examined over a longer period of time in cancer survivors [14–17]. In none of these studies the course of fatigue has been investigated.

In a previous cross-sectional study we investigated and discussed the prevalence and correlates of severe fatigue in a group of disease-free breast cancer patients [18]. Results indicated that severe fatigue was a problem for nearly 40% of a sample of 150 breast cancer survivors who completed cancer treatment a mean of 29 months earlier, compared to 11% in a matched sample of women without a cancer history. Fatigue was measured with a multidimensional assessment method. Based on previous research in fatigued patients with several chronic diseases, this method has identified nine dimensions, namely fatigue severity, psychological well-being, functional impairment in daily life, sleep disturbance, physical activity, neuropsychological impairment, social functioning/social support, self-efficacy and causal attributions [19]. These dimensions appeared to be relatively independent, meaning that each dimension uniquely contributed to the description of a patient. A regression analyses on the cross-sectional data indicated that depression, physical inactivity, the

need to sleep and rest during the day and the tendency to attribute fatigue symptoms to the breast cancer experience, contributed significantly to the severity of fatigue [18].

The present longitudinal study focuses on the follow-up of this same cohort of women during a 2-year period. During these 2 years, patients filled out every month a fatigue questionnaire. We will try to answer three questions in a prospective way:

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

Furthermore, we will exploratory describe the course of fatigue for those patients that had a disease recurrence during the 2 years of our study.

Methods

Sample

In order to select a relatively homogeneous group of patients for this study, patients had to be premenopausal and younger than 50 years by time of primary diagnosis. All these patients have been treated according to the same protocol, the Comprehensive Cancer Center East for premenopausal breast cancer patients. At the baseline assessment [18], patients had completed treatment for breast cancer a minimum of 6 months earlier and had no evidence of disease recurrence. During the 2 years of this study patients went to their own oncologist for medical follow-up. Patients with a disease recurrence during this 2 year period were not included in the analyses to answer the three research questions, but were described separately.

Recruitment procedure

Patients were recruited from one university hospital and 6 regional hospitals. All patients who met the eligibility criteria at the university hospital and at three regional hospitals, were initially informed about the study by mail with an introductory letter from their oncologist. At the other three regional hospitals, patients were informed by their oncologist during control-visits. In the following week, patients were contacted by telephone by the psychologist-researcher (PS). Those patients who agreed to take part in the study were invited to our department of the Radboud University Nijmegen Medical Center for a baseline measurement [18]. After this baseline assessment, patients filled out a fatigue questionnaire at the end of every month for a 2-year period. The ethics committee of all participating hospitals agreed with this study.

Measurement

At the baseline measurement we investigated all nine dimensions by validated questionnaires. Furthermore, patients performed two standardized tests to assess neuropsychological functioning. In addition, they were asked to fill out a daily Self Observation List and to wear an actometer during a period of 12 days at home and to fill out a fatigue questionnaire (Checklist Individual Strength) at the end of every month, during a 2-year period.

All measures are mentioned below. For a more extensive description of the measures we refer to the articles in which the baseline data of the present study are described [18,20].

Fatigue severity has been measured by the fatigue severity subscale (CIS-fatigue) of the Checklist Individual Strength (CIS) [19,21]. The CIS-fatigue consists of 8 items and each item is scored on a 7-point Likert scale. A score of 35 or higher on the subscale fatigue severity indicates severe feelings of fatigue [19]. A score between 27 and 35 indicates heightened experience of fatigue [22]. Because patients filled out the CIS at the end of every month during the 2 years of our study we calculated a mean CIS-fatigue score over 24 months, which we refer to as the 'persistent fatigue score'. Patients with a persistent fatigue score of 35 or higher are referred to as persistently severely fatigued.

Psychological well-being has been measured with the Beck Depression Inventory for primary care (BDI-pc) [23], the Spielberger Trait Anxiety Inventory (STAI) [24] the Rosenberg Self Esteem Scale (RSE) [25], the Symptom Checklist (SCL-90) [26] and the emotional functioning subscale of the Quality of Life Questionnaire- C30 of the European Organisation for Research and Treatment of Cancer (QLQ- C30) [27].

Functional impairment has been measured with the subscales home management, work, and recreation and pastimes from the Sickness Impact Profile (SIP) [28] and the role functioning subscale of the QLQ-C30. In addition, hours of work (outside the home and household activities) are registered in the Self Observation List.

Sleep disturbances have been measured with the Groninger Sleep Quality Scale (GSQS) [29]. In the present study we decided to delete two items because these items strongly overlap with fatigue complaints (GSQS-2; Cronbach's alpha = 0.87). Furthermore, the sleep/rest subscale of the SIP and the sleep subscale of the SCL were used. Finally, quality of sleep is registered daily in the Self Observation List.

DOI: 10.1002/pon

Physical activity has been measured with the physical functioning subscale of the QLQ-C30, the mobility and ambulation subscales of the SIP. In addition, physical activity is registered once a day in the Self Observation List. Finally, actual physical activity has been measured with the actometer [30,31].

Neuropsychological functioning has been measured with the cognitive functioning subscale of the QLQ-C30 and the alertness behavior subscale of the SIP. Furthermore, actual neuropsychological functioning is measured by the Complex Reaction Time task (CRT) [32] and the Symbol Digit subtest of the WAIS [33].

Social functioning and social support have been measured with the social functioning subscale of the QLQ-C30, the social interaction subscale of the SIP and the van Sonderen Social Support Inventory (SSL) [34].

Self-efficacy has been measured with the Self Efficacy Scale (SES). The SES consisted of five questions that measured sense of control with respect to fatigue [35,36].

Causal attributions with regard to fatigue complaints have been measured with the Causal Attribution List (CAL). This questionnaire consists of nine items divided over two subscales, psychological (e.g. ruminate, sleep problems) and breast cancer related attributions (e.g. surgery for breast cancer, adjuvant therapy for breast cancer).

Statistical analysis

Data analysis was performed using SPSS (version 8.0). Paired sample *t*-tests were performed to analyze differences between baseline and follow-up percentages of severe fatigue. *t*-tests, and general linear model (GLM)-general factorial have been performed to test differences between groups. Pearson correlations between the persistent fatigue score and the baseline measures were used as preparatory analyses in order to examine the contribution of the baseline measures to persistent fatigue. Those measures that correlated highest with the persistent fatigue score were used as independent variables in a linear regression analyses (enter-method).

Results

Description of the sample

At baseline, 150 disease-free breast cancer patients participated in this study. Numbers and reasons for non-participation have been described in our previous publication [18]. From these 150 participating patients, 10 patients dropped out for several reasons during the 2-year period of this study (e.g. taking part in research takes too much time, family circumstances). Furthermore, 19 women had a disease recurrence during the 2-year period. Hundred-twenty-one patients thus completed the study. Compliance with respect to the completion of the monthly fatigue questionnaires was high. Fifty-six percent of the patients ($n = 68$) returned all 24 monthly questionnaires. Twenty-seven percent of the patients ($n = 33$) returned 20–23 questionnaires, and 17% returned 16–19 questionnaires ($n = 20$). There was no difference in the number of monthly questionnaires returned by patients with or without persistent fatigue complaints (respectively, an average of 22.0 (S.D. 3.0) vs 22.3 (S.D. 3.0), *t*-test; $p = 0.680$).

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

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

For the total group of disease-free breast cancer patients the mean CIS-fatigue score at baseline was 28.9 (S.D. 13.5), and at follow-up 25.0 (S.D. 13.2) (paired sample *t*-test; $p < 0.001$). The correlation between baseline and follow-up CIS-fatigue scores is 0.65 ($p < 0.01$). Both the mean baseline and follow-up CIS-fatigue scores are significantly higher than the mean scores of a matched group of healthy women without a cancer history (CIS-fatigue 19.4 (S.D. 11.0)) [18].

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

In Table 2 we indicated the number (and percentages) of patients that were classified as severely, heightened or not fatigued at follow-up, on basis of their classification as severely, heightened or not fatigued at baseline. Almost half of the patients (49%) that were identified as severely fatigued at baseline were also identified as severely fatigued at follow-up. In addition, 28% of these patients were identified as heightened fatigued at follow-up. Furthermore, most patients (85%) that were identified as not fatigued at baseline were also identified as not fatigued at follow-up.

The monthly CIS-fatigue scores of the total sample are depicted in Figure 1. In addition, the monthly CIS-fatigue scores are displayed for those women who were severely fatigued at baseline, and

DOI: 10.1002/pon

Table 1. Baseline demographic characteristics and medical characteristics

	Disease-free breast cancer patients $N=121$	Patients with a tumor relapse $N=19$	Drop-outs for other reasons $N=10$
Mean age	46.7 (S.D. 5.9)	43.3 (S.D. 6.2)	41.8 (S.D. 8.3)
Marital status			
Married	106 88%	16 84%	8 80%
Unmarried	4 3%	2 11%	1 10%
Divorced	8 7%	1 5%	1 10%
Widowed	3 2%	—	—
Higher education (⩾12 years)	45 37%	8 42%	4 40%
Employment			
Paid work outside home	75 62%	10 53%	7 70%
Home management	106 88%	15 79%	7 70%
Disablement insurance act	15 12%	1 5%	2 20%
Surgery			
Mastectomy	78 65%	12 63%	5 50%
Lumpectomy	43 35%	7 37%	5 50%
Adjuvant therapy			
No adjuvant therapy	18 15%	1 6%	—
Only radiotherapy	24 20%	5 26%	2 20%
Only chemotherapy	28 23%	4 21%	1 10%
Radiotherapy and chemotherapy	51 42%	9 47%	7 70%
Duration of treatment (months)[a]	Mean 6 (S.D. 3)	Mean 6 (S.D. 3)	Mean 6 (S.D. 2)
<1 month	16 13%	—	2 20%
>1 month, <6 months	38 32%	12 63%	5 50%
> 6 months	67 55%	7 37%	3 30%
Time since treatment (months)[b]	Mean 30 (S.D. 18)	Mean 25 (S.D. 13)	Mean 26 (S.D. 18)
Between 6 and 12 months ago	12 10%	2 11%	1 10%
Between 13 and 24 months ago	44 36%	10 52%	4 40%
Between 25 and 36 months ago	26 22%	3 16%	1 10%
Between 37 and 48 months ago	17 14%	3 16%	3 30%
Between 49 and 60 months ago	11 9%	—	1 10%
More than 60 months ago	11 9%	1 5%	—

[a] Defined as the period from the time of surgery until the end of adjuvant therapy.
[b] Defined as the period from the end of adjuvant therapy until the day of the baseline measurement [18].

Table 2. Numbers (and percentages) of patients that were classified as severely, heightened or not fatigued at follow up, on basis of their classification as severely, heightened or not fatigued at baseline

	n
Severe fatigue at baseline	47
Severely fatigue at follow-up	23 49%
Heightened fatigue at follow-up	13 28%
No fatigue at follow-up	11 23%
Heightened fatigue at baseline	21
Heightened fatigue at follow-up	8 38%
No fatigue at follow-up	11 52%
Severe fatigue at follow-up	2 10%
No fatigue at baseline	53
No fatigue at follow-up	45 85%
Heightened fatigue at follow-up	5 9%
Severe fatigue at follow-up	3 6%

for those who were not severely fatigued at baseline. Results indicate that the monthly fatigue score dropped a little within a 2-year period. For the total group of 121 disease-free breast cancer patients, the monthly fatigue score dropped from 27 at first measurement to 25 at last measurement. This descent is due to the descent of fatigue scores in patients who were severely fatigued at baseline. Their monthly fatigue score dropped from 38 to 34. Monthly fatigue scores of patients who were not severely fatigued at baseline remained equal.

The persistent fatigue score, which is the mean of all monthly fatigue scores, was 25.9 (S.D. 11.1) for the total sample. Further, the number of patients with a persistent fatigue score of 35 or higher was 29 (24%). In addition, 25 patients (21%) had a persistent fatigue score between 27 and 35.

Is persistent fatigue related to former treatment modalities?

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

Also for patients with different types of adjuvant therapy the mean persistent fatigue score was not statistically different, although patients who did not receive any kind of adjuvant therapy at all had a relatively low persistent fatigue score. The mean persistent fatigue score was 28.2 (S.D. 11.4) for patients who received radiotherapy, 24.9

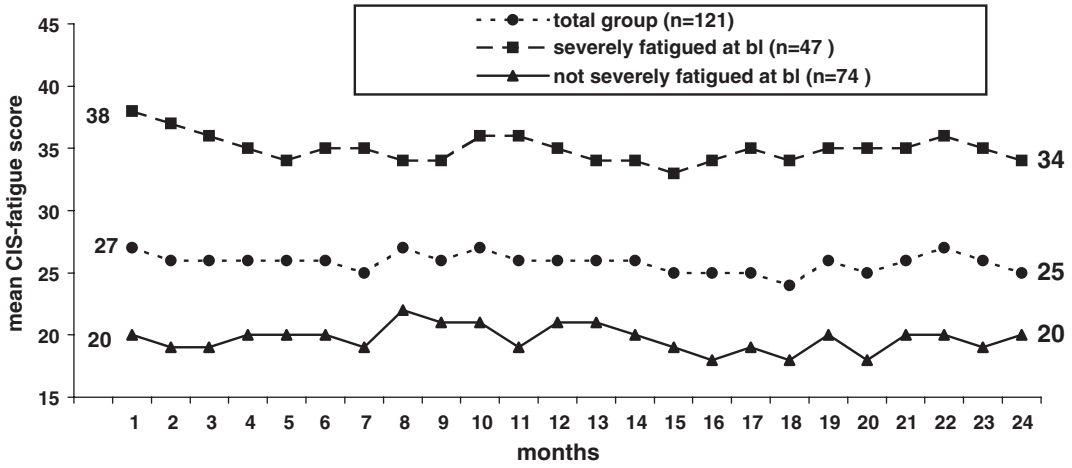

Figure 1. Mean CIS-fatigue scores over 24 months

(S.D. 11.4) for patients who received chemotherapy, 27.1 (S.D. 11.1) for patients who received both radiotherapy and chemotherapy, and 21.7 (10.5) for patients who did not receive adjuvant therapy (GLM-general factorial; $p = 0.244$). Patients that used tamoxifen during a two year period ($n = 11$) had equal fatigue scores to patients that did not use tamoxifen. Their fatigue score were, respectively, 23.5 (S.D. 11.8) and 26.2 (S.D. 11.2) (*t*-test; $p = 0.436$).

Furthermore, there appeared to be a relation between persistent fatigue and the duration of cancer treatment. The mean persistent fatigue score was 19.5 (S.D. 8.7) for patients who finished treatment within 1 month, 27.0 (11.3) for patients who finished treatment within 6 months and 27.0 (11.3) for patients who were treated for cancer for more than 6 months (GLM-general factorial; $p = 0.045$).

Finally, we found no relation between persistent fatigue and time since treatment finished (GLM-general factorial; $p = 0.997$).

Table 3. Linear regression analyses to predict the persistent fatigue score (range 8–56); with baseline CIS-fatigue score (A) and without baseline CIS-fatigue score (B)

	A		B	
	Beta	adj R^2	Beta	adj R^2
Fatigue (CIS)	0.377***			
		0.510		
Trait anxiety (STAI)	0.136		0.324**	
Role functioning (QLQ-C30)	−0.153		−0.271**	
Sleep (SCL)	0.053		0.058	
Physical functioning (QLQ-C30)	−0.085		−0.140	
Cognitive functioning (QLQ-C30)	−0.084		−0.063	
Social functioning (QLQ-C30)	0.103		0.182	
Amount of negative interactions (SSL-N)	0.022		−0.005	
Self-efficacy (SES)	−0.214**		−0.303***	
Psychological attributions (CAL)	−0.148		−0.156	
		0.090		0.525
	total adj R^2	0.600	total adj R^2	0.525

** $p < 0.01$.
*** $p < 0.001$.

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

Results of the preparatory analyses indicated that within the different dimensions one or more baseline measures correlated significantly with the persistent fatigue score. In summary (highest correlations are described), women with higher persistent fatigue scores report more psychological distress (trait anxiety (STAI) $r = 0.612$, $p < 0.001$), functional impairment (role functioning (QLQ-C30), $r = -0.537$, $p < 0.001$), sleep disturbances (sleep (SCL) $r = 0.438$, $p < 0.001$), physical impairment (physical functioning (QLQ-C30) $r = -0.477$, $p < 0.001$), neuropsychological impairment (cognitive functioning (QLQ-C30) $r = -0.514$, $p < 0.001$) and more problems with regard to social functioning and social support (social functioning (QLQ-C30) $r = -0.444$, $p < 0.001$). Furthermore, these women had a lower sense of control (self-efficacy (SES) $r = -0.489$, $p < 0.001$) and stronger psychological attributions with respect to their fatigue complaints (psychological attributions (CAL) $r = -0.479$, $p < 0.001$).

The regression analyses (Table 3) showed that 51% of the persistent fatigue score was predicted by the baseline CIS-fatigue score. The other selected measures predicted an additional 9%. Apart from a high baseline CIS-fatigue score, high

DOI: 10.1002/pon

persistent fatigue was also predicted by low self-efficacy. Thus, less perceived control over symptoms predicted higher persistent fatigue.

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

Description of the course of fatigue in those women who had a disease recurrence

The mean CIS-fatigue score at baseline for those women who had a disease recurrence within the 2-year period of our study was 23.9 (S.D. 14.5) at baseline. Further, the number of severely fatigued patients at baseline was five (26%) and one patient (5%) experienced heightened fatigue.

In Figure 2 mean monthly fatigue scores are depicted for the 19 women who had a disease-recurrence during the study period. The CIS-fatigue scores rose from 23 (12 months before the diagnosis of a disease recurrence) to 31 in the month that the disease recurrence was diagnosed. Within the group of disease-free breast cancer patients who did not have a disease recurrence a matched 'control group' was constituted ($n = 19$). The group with and without disease recurrence were matched on the baseline CIS-fatigue score. In addition, the two groups were comparable with respect to type of surgery, age, adjuvant therapy, duration of treatment and time since treatment. In Figure 2 the mean monthly fatigue scores are depicted for this matched group. There was no clear rise of the monthly CIS-fatigue scores in this control group of persistent disease-free women. Their monthly CIS-fatigue score varied from 19 to 26.

Discussion

The unique quality of this study lies in the fact that we studied fatigue in disease-free breast cancer patients during a longer period of time. Because of that we were able to take a closer look at the course of fatigue complaints and we were able to identify those patients that experienced persistent fatigue complaints.

Based on the monthly fatigue scores we concluded that severe fatigue is a persistent problem for 24% of a group of disease-free breast cancer patients. This is a decrease with respect to the baseline assessment, at which 38% of the disease-free breast cancer patients experienced severe fatigue 2.5 years after curative treatment ended [18]. Bower *et al.* [17] also found a decrease of patients with severe fatigue in a longitudinal study, namely from 35 (3.5 years after treatment) to 21% (6.3 years after treatment). In one of our previous publications a sample of patients with bone or soft tissue tumor were also assessed two times in a period of 2 years. In this sample of patients who finished cancer treatment with an average of 6 years ago (range 1–15 years), the percentage of severe fatigue remained about equal, namely 28% to 26% [16]. Hjermstad *et al.* [14] investigated disease-free cancer patients 16 years and 24 years after treatment for cancer. In this longitudinal study the percentage of fatigued cancer survivors also remained about equal, that is 25–28%. These results seem to suggest that fatigue complaints continue to decrease during the first 3–4 years after curative treatment. For about a quarter of the cancer survivors fatigue remains a continuous problem with profound effects on functional status, like role functioning, work, home management and recreation and pastimes.

The duration of severe fatigue was determined prospectively by calculating the mean CIS-fatigue score over the 24 months that patients filled out the fatigue questionnaire. Patients with a fatigue score

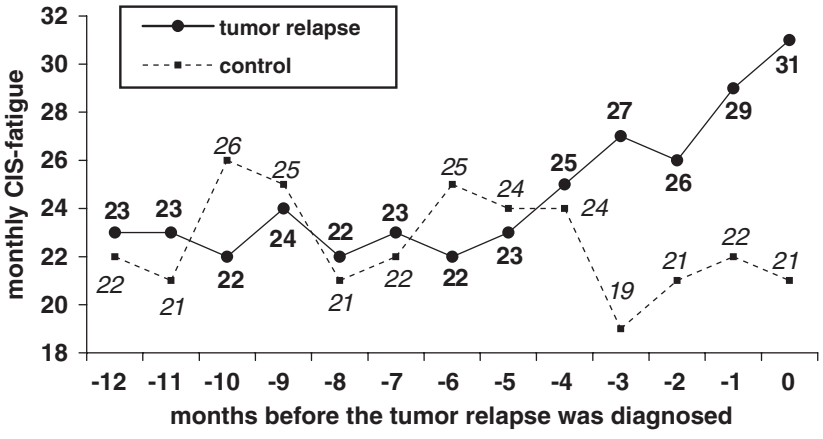

Figure 2. Mean monthly fatigue scores for women who developed a tumor relapse ($n = 19$) in the 12 months before the tumor relapse was diagnosed compared to a matched control group ($n = 19$)

DOI: 10.1002/pon

of 35 or higher were referred to as 'persistently severely fatigued'. We realize that this technique has some shortcomings, for example, a few months of very high fatigue might place a person in the 'persistently severely fatigued' category even if most of her monthly scores fell below the cut-point of 35. Because of this shortcoming we additionally calculated the persistent fatigue score according to another approach. We calculated the percentage of times that scores fell above the cut-point of 35. However, this technique has some shortcomings as well. For example, a person that has many fatigue scores just under 35, will not be labeled as persistently fatigued, while this is probably untrue. In spite of the shortcomings of both techniques it is reassuring to know that the Pearson correlation between these differently obtained persistent fatigue scores turned out to be very high; 0.90 ($p < 0.000$).

Most studies find no strong association between cancer treatments and fatigue in long-term cancer survivors [5,37]. However, in the current study we found that patients who did not receive any kind of adjuvant therapy and who did not experience any kind of complications during treatment, i.e. those patients that completed treatment for cancer within 1 month, were at lower risk for persistent fatigue. A possible explanation for the low persistent fatigue scores in patients whose treatment duration was short may be due to the fact that they had not been subjected to the harmful effects of adjuvant therapy and/or multiple operations (and anesthetics) because of complications. In addition, for this group of patients the period of great uncertainty had been limited and they had been spared many hours of traveling to and from the hospital, which can cause exhaustion as well. Some other studies also found evidence for the assumption that patients with more aggressive treatments are more at risk for persistent fatigue [16,17,38].

Breast cancer patients often become menopausal as a result of chemotherapy. Menopausal symptoms seem to be both more prevalent and more severe in cancer survivors than in healthy women [39,40], and can therefore be of influence on the persistent of fatigue. In a subgroup of 80 patients we measured with the self-observation list the intensity of hot flashes four times a day during a 12-day period. Patients with severe fatigue had a higher score than non-fatigued patients. This difference approached significance (t-test $p < 0.071$).

Some studies suggest an association between fatigue and adjuvant hormonal therapy [39,40]. Patients in our study were treated for cancer according to the guidelines of that time and therefore only a minority of the breast cancer patients ($n = 11$) was treated with tamoxifen. In this small group no differences in fatigue were found between patients with or without tamoxifen.

Due to the recruitment procedure it is possible that a selection bias exists in this study. In our previous publication about this cohort of breast cancer survivors, we looked at differences between responders and non-responders with respect to background variables [18]. Reasons for non-participations were, e.g., takes too much time, too emotional, problems with transport, too tired, etc. Non-responders (41%) did not differ from the responders with regard to age, type of surgery, radiotherapy and time since treatment completion. Non-responders received chemotherapy less often: 41% compared with 66% (chi-square; $p < 0.001$). Therefore, duration of treatment was significantly lower for non-responders (4 compared with 6 months for responders; t-test; $p < 0.001$). Because of these differences it is possible that the responders experience more fatigue and the percentage of fatigue in breast cancer survivors might be worse than in reality. However, the percentages found in our studies were similar to percentages in other longitudinal and cross-sectional studies on fatigue in disease-free cancer patients [14,16,17,41,42].

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

In understanding off-treatment fatigue in disease-free cancer patients it is important to make a distinction between initiating factors and perpetuating factors of fatigue. This model appeared to be useful in patients with chronic fatigue syndrome (CFS) [35,36], but can be applied in fatigued cancer survivors too. We know that fatigue arises during the active treatment of cancer in nearly all patients. For about a quarter of the cancer survivors persistent fatigue becomes an invalidating long lasting side effect of the cancer treatment [5,37,14,17,42]. Because almost no relations were found between initial disease- and treatment variables and off-treatment fatigue [5,37], other factors seem to be responsible for the persistence of fatigue complaints.

In this study persistent fatigue was very well predicted by the questionnaires that we used to measure psychological well-being, functional impairment, sleep disturbances, physical activity,

DOI: 10.1002/pon

neuropsychological functioning, social functioning, social support, self-efficacy and causal attributions. With use of several selected baseline measures, the percentage of explained variance was 60%. Based on the results of the current study we might expect that low sense of control, anxiety and impairment might be important perpetuating factors.

In managing fatigue in cancer survivors exercise has been proposed in the literature as a useful strategy [43–45]. However, to our knowledge there have been no published randomized controlled intervention studies in which the main object was to reduce fatigue complaints in cancer survivors. For CFS patients, cognitive behavior therapy (CBT) has proven to be successful in reducing fatigue complaints [36,46,47]. CBT may also be a useful intervention in reducing post-cancer fatigue. Servaes *et al*. [1,48] made clear that the perpetuating factors in former cancer patients differ from factors in the CFS model and interindividual differences are larger in fatigued cancer survivors than in CFS patients. Therefore, CBT for post-cancer fatigue should be adapted to each individual cancer survivor and directed, among others, at the predictors of persistent fatigue found in this follow-up study.

Acknowledgements

This research was funded by the Dutch Cancer Society: KUN 97-1390

References

1. Servaes P, van der Werf S, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with Chronic Fatigue Syndrome. *Support Care Cancer* 2001;**9**:11–17.
2. Ruffer JU, Flechtner H, Tralls P *et al*. Fatigue in long-term survivors of Hodgkin's Lymphomal; a report from the German Hodgkin Lymphoma Study Group (GHSG). *EurJ Cancer* 2003;**39**:2179–2186.
3. Bennet B, Goldstein D, Lloyd A, Davenport T, Hickie I. Fatigue and psychological distress—exploring the relationship in women treated for breast cancer. *Eur J Cancer* 2004;**40**:1689–1695.
4. Sugawara Y, Akechi T, Okuyama T *et al*. Occurence of fatigue and associated factors in disease-free breast cancer patients without depression. *Support Care Cancer* 2005;**13**:628–636.
5. Prue G, Rankin J, Allen J *et al*. Cancer related fatigue: a critical appraisal. *Eur J Cancer* 2006;**42**:846–863.
6. Irvine DM, Vincent L, Graydon JE, Bubela N. Fatigue in women with breast cancer receiving radiation therapy. *Cancer Nurs* 1998;**21**:127–135.
7. Monga U, Kerrigan AJ, Thornby J, Monga TN. Prospective study of fatigue in localized prostate cancer patients undergoing radiotherapy. *Radiat Oncol Invest* 1999;**7**:178–185.
8. Ahsberg E, Furst CJ. Dimensions of fatigue during radiotherapy—an application of the Swedish Occupational Fatigue Inventory (SOFI) on cancer patients. *Acta Oncol* 2001;**40**:37–43.
9. Donovan KA, Jacobsen PB, Andrykowski MA *et al*. Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. *J Pain Symptom Manage* 2004;**28**(4):373–380.
10. Smets EM, Visser MR, Willems GA, Garssen B, Schuster UA, de Haes JC. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. *Br J Cancer* 1998;**78**:907–912.
11. Shimozuma K, Ganz PA, Petersen L, Hirji K. Quality of life in the first year after breast cancer surgery: rehabilitation needs and patterns of recovery. *Breast Cancer Res Treat* 1999;**56**(1):45–57.
12. Given CW, Given B, Azzouz F, Kozachik RN, Stommel M. Predictors of pain and fatigue in the year following diagnosis among elderly cancer patients. *J Pain Symptom Manage* 2001;**21**:456–466.
13. de Graeff A, de Leeuw JRJ, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM. Voorspelling van kwaliteit van leven na behandeling voor kanker in het hoofd/halsgebied. *Gedrag Gezond* 2002;**30**:178–191.
14. Hjermstad MJ, Fossa SD, Oldervoll L, Jacobsen AB, Loge JH. Fatigue in long-term hodgkin's disease survivors: a follow-up study. *J Clin Oncol* 2005;**23**:6587–6595.
15. Mar Fan HG, Houede-Tcen N, Yi QL *et al*. Fatigue, menopausal symptoms, and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study. *J Clin Oncol* 2005;**23**(31):8025–8032.
16. Servaes P, Verhagen C, Schreuder BHW, Veth RPH, Bleijenberg G. Fatigue after treatment for malignant and benign bone and soft tissue tumors. *J Pain Symptom Manage* 2003;**26**:1113–1122.
17. Bower JE, Ganz PA, Desmond KA, Bernaards C *et al*. Fatigue in long-term breast carcinoma survivors. A longitudinal investigation. *Cancer* 2006;**106**(4):751–758.
18. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Ann Oncol* 2002;**13**: 589–598.
19. Vercoulen JH, Swanink CM, Fennis JFM, Galama JMD, van der Meer JWM, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;**38**:383–392.
20. Servaes P, Verhagen C, Bleijenberg G. The relations between fatigue, neuropsychological functioning and physical activity after treatment for breast cancer; daily self-report and actual behavior. *Cancer* 2002;**95**:2017–2026.
21. Dittner AJ, Wessley SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004;**56**:157–170.
22. Vercoulen JH, Alberts M, Bleijenberg G. De Checklist individual strength (CIS). *Gedragstherapie* 1999;**32**:131–136.
23. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behav Res Ther* 1997;**35**:785–791.
24. van der Ploeg HM. Validity of the Zelf-Beoordelings-Vragenlijst (A Dutch version of the Spielberger State-Trait Anxiety Inventory). *Ned Tijdschr Psychol haar Grensgebieden* 1980;**35**:243–249.
25. Rosenberg M. *Society and the Adolescent Self-Image*. Princeton University Press: Princeton NY, 1965.
26. Arindell WA, Ettema JHM. *SCL-90, Handleiding bij een Multidimensionele Psychopathologie-Indicator*. Swets & Zeitlinger B.V.: Amsterdam, 1986.
27. Aaronson NK, Ahmedzai S, Bergman B *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Nat Cancer Inst* 1993;**85**:365–376.

28. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 1981;**19**:787–805.
29. Meijman TF. *Handleiding VBBA, SKB*, Amsterdam, 1997.
30. Vercoulen JH, Bazelmans E, Swanink CM *et al*. Physical activity in chronic fatigue syndrome: assessment and its role in fatigue. *J Psychiatr Res* 1997;**31**: 661–673.
31. van der Werf SP, Prins JB, Vercoulen JH, van der Meer, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. *J Psychosom Res* 2000;**49**:373–379.
32. Houx PJ, Jolles J. Age-related decline of psychomotor speed: effects of age, brain health, sex, and education. *Perceptual Motor Skills* 1993;**76**:195–211.
33. Stinissen J, Willems PJ, Coetsier L. *Handleiding bij de Nederlandse bewerking van de WAIS [Manual of the Dutch edition of the WAIS]*. Swets and Zeitlinger: Amsterdam, 1970.
34. van Sonderen E. *Sociale Steun Lijst- Interacties (SSL-I) en Sociale Steun Lijst- Disrepanties (SSL-D)*. Noorderlijk Centrum voor Gezondheidsvraagstukken, Groningen, 1993.
35. Vercoulen JH, Swanink CM, Galama JM *et al*. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. *J Psychosom Res* 1998;**45**:507–517.
36. Prins JB, Bleijenberg G, Bazelmans E *et al*. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet* 2001; **357**:841–847.
37. Servaes P, Verhagen S, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer* 2002;**38**:27–43.
38. Woo B, Dibble Sl, Piper BF, Keating SB, Weiss MC. Differences in fatigue by treatment methods in women with breast cancer. *Oncol Nurs Forum* 1998;**25**:915–920.
39. Stein KD, Jacobsen PB, Hann DM, Greenberg H, Lyman G. Impact of hot flashes on quality of life among postmenopausal women being treated for breast cancer. *J Pain Symptom Manage* 2000;**19**:436–445.
40. Harris PF, Remington PL, Trentham-Dietz A, Allen CI, Newcomb PA. Prevalence and treatment of menopausal symptoms among breast cancer survivors. *J Pain Symptom Manage* 2002;**23**:501–509.
41. Loge HJ, Abrahamsen AF, Ekeberg Ø, Kaasa S. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. *J Pain Symptom Manage* 2000;**19**: 91–99.
42. Fossa SDD, Dahl AA, Loge JH. Fatigue, anxiety, and depression in long-term survivors of testicular cancer. *J Clin Oncol* 2003;**21**(7):1249–1254.
43. Oldervoll LM, Kaasa S, Knobel H, Loge JH. Exercise reduces fatigue in chronic fatigued Hodgkins disease survivors—results from a pilot study. *Eur J Cancer* 2003;**39**:57–63.
44. Wilson RW, Jacobsen PB, Fields KK. Pilot study of a home-based aerobic exerice program for sedentary cancer survivors treated with hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2005;**35**: 721–727.
45. Carlson LE, Smith D, Russell J, Fibich C, Whittaker T. Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study. *Bone Marrow Transplant* 2006;**37**:945–954.
46. Deale A, Chalder T, Marks I, Wessely S. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry* 1997;**154**:408–414.
47. Stulemeijer M, de Jong LWAM, Fiselier TJW, Hoogveld SWB, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *Br Med J* 2005;**330**: 7481–7486.
48. Servaes P, Prins J, Verhagen S, Bleijenberg G. Fatigue after breast cancer and in Chronic Fatigue Syndrome. Similarities and differences. *J Psychosom Res* 2002;**52**: 453–459.

DOI: 10.1002/pon