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Cancer-Related Fatigue: Predictors and Effects of Rehabilitation

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Key Words. Cancer patients • Fatigue • Rehabilitation • Predictors • Clinical relevance

Abstract

Background. **The aims of the study were to examine the effects of a multidimensional rehabilitation program on cancer-related fatigue, to examine concurrent predictors of fatigue, and to investigate whether change in fatigue over time was associated with change in predictors.**

Methods. **Sample: 72 cancer survivors with different diagnoses. Setting: rehabilitation center. Intervention: 15-week rehabilitation program. Measures: Fatigue (Multidimensional Fatigue Inventory), demographic and disease/treatment-related variables, body composition (bioelectrical impedance), exercise capacity (symptom-limited bicycle ergometry), muscle force (handheld dynamometry), physical and psychological symptom distress (Rotterdam Symptom Check List), experienced physical and psychological functioning (RAND- 36), and self-efficacy (General-Self-Efficacy Scale, Dutch version). Measurements were performed before (T0) and after rehabilitation (T1).**

Results. **At T1 (*n* = 56), significant improvements in fatigue were found, with effect sizes varying from −0.35 to −0.78. At T0, the different dimensions of fatigue were predicted by different physical and psychological variables. Explained variance of change in fatigue varied from 42%–58% and was associated with pre-existing fatigue and with change in physical functioning, role functioning due to physical problems, psychological functioning, and physical symptoms distress.**

Conclusions. **Within this selected group of patients we found that (a) rehabilitation is effective in reducing fatigue, (b) both physical and psychological parameters predicted different dimensions of fatigue at baseline, and (c) change in fatigue was mainly associated with change in physical parameters. *The Oncologist*** 2006;11:184–196

Introduction

Fatigue is one of the most frequently reported complaints in cancer patients and survivors. Fatigue is a subjective condition, commonly defined as a patient's feeling of lack of energy, weariness, or as "a persistent, subjective sense of tiredness related to cancer that interferes with usual functioning" [1]. In contrast to the tiredness sometimes felt by a healthy individual, cancer-related fatigue is perceived as being of greater magnitude, disproportionate to activity or exertion, and not relieved by rest [2]. Some cancer patients perceive fatigue as a psychological alteration, whereas others perceive fatigue as the most distressing symptom

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because of its impairing consequences on their physical activity level [3]. Whether fatigue has more psychological, physical, or combined consequences, patients generally associate fatigue with a high level of impairment in daily living and, therefore, a low quality of life [4].

The extent of the problem of cancer-related fatigue in the short and longer term is unclear. About 70% of people with cancer report feelings of fatigue during radiotherapy [5], chemotherapy [6], bone marrow transplantation [7, 8], or after surgery [9]. However, a minimal increase in fatigue after radiotherapy was also reported [10]. That fatigue may be a serious problem in the longer term is shown by the reported percentage of up to 30% of cancer survivors who experience fatigue for years after the end of their treatment [4, 11]. Whatever the percentages are, the problem of fatigue is still underestimated by oncologists [12].

The determinants of the onset and persistence of fatigue are still poorly understood [13]. Cancer-related fatigue is attributed to a variety of disease-related and treatment-related factors such as the cancer itself, anemia [12, 14, 15], cytokines, nutritional and fluid imbalances, etc. [3, 5]. Cancer-related fatigue is associated with treatment-related physiological and psychological mechanisms. Physiological mechanisms include the occurrence of reduced aerobic capacity, physical performance, and muscle wasting as a side effect of anticancer treatment [3, 4, 16]. These physiological mechanisms may be aggravated by the inactivity resulting from the advice of bed rest and to downscale activities. A low activity pattern may lead to more muscle deconditioning and disuse atrophy [17], which in turn may aggravate the feelings of fatigue [18]. In fact, a vicious circle may occur and account for the persistence of fatigue in the longer term [3, 16].

Psychological factors are related to the onset and the persistence of fatigue in cancer patients. Over time, the different stages and phases of cancer, varying from diagnosis to treatment and post-treatment, have been associated with psychological symptoms such as anxiety and depression [14, 19], reduced self-efficacy [20], sleep disorders, distress [21], and difficulty coping [3]. However, whether fatigue is a cause or an effect of these factors is still unknown [22]. There are even studies that suggest that there is no strong cause-and-effect relationship between fatigue and, for example, depression [23].

Although the exact determinants of cancer-related fatigue need more scientific research, its multifactorial nature seems to be generally acknowledged [22]. Therefore, a diversity of psychological and physical interventions that have the potential to reduce cancer-related fatigue have been described. The described psychological interventions were aimed at reducing fatigue in cancer patients through facilitating coping with the disease and improving quality of life [21, 24, 25]. Since fatigue seems to be associated with a physical and a functional component, a growing number of studies reported on the effectiveness of physical training, that is, exercise training [26–29]. Exercise training is reported to be beneficial for cancer patients because it is aimed at improving functional capacity and muscle strength and at decreasing cancer-related fatigue, which may in turn contribute to a better overall quality of life [7, 29–32].

For the present study, because of the associations found between cancer-related fatigue and physical and psychological factors, we acknowledged fatigue as a problem with different dimensions, as previously proposed by others [33]. Accordingly, we theorized that such a multidimensional problem might require a multidimensional intervention that included physical and psychological components. Therefore, we developed a multidimensional rehabilitation program that includes exercise, sports and games, information, and psychoeducation. We first hypothesized that the multidimensional rehabilitation program would have beneficial effects on fatigue. Secondly, we hypothesized that different physical and psychological variables would be associated with different domains of fatigue and that decreased fatigue after the program would be associated with changes in both physical and psychological variables.

Patients and Methods

Sample

Patients were eligible for the study if they met the following criteria: age ≥18 years; referred by hospital specialists or general practitioners; last cancer-related treatment >3 months ago; estimated life expectancy ≥1 year, and an indication for rehabilitation. The latter meant a minimum of three positive findings on the following questions, as judged by a physician:

(a) Physical complaints like aching muscles, problems with coordination, headache, nausea, heart palpitations, shortness of breath;

(b) Reduced physical capacity compared with before the illness (for example, less able to walk or cycle);

(c) Psychological problems like increased anxiety level, depression, uncertainty, lack of energy, or nervousness;

(d) Increased levels of fatigue;

(e) Sleep disturbances;

(f) Problems in coping with reduced physical and psychosocial functioning due to cancer.

Patients were not included if they met one of the following criteria: (a) a very low level of activity according to the classification of Winningham [31], for example, <50% of their daytime ambulant, rapid fatigue appearance on performance of low physical activity and activity of daily living dependency; (b) inability to travel independently to the rehabilitation center; (c) cognitive disturbances that may interfere with participation in the rehabilitation program; and (d) serious psychopathology or emotional instability that may impede participation in the rehabilitation program.

Design

A pre–post test design was used to examine the effects of a multidimensional rehabilitation program on fatigue. The design allowed us to examine concurrent predictors of fatigue and, more importantly, to investigate whether change in fatigue over time was associated with change in predictors.

Procedures

All patients gave written informed consent to participate in the study and for the acquisition of medical information from their hospital charts. Medical data were verified by record linkage with the population-based cancer registry of the Comprehensive Cancer Center North-Netherlands (CCCNN). The Medical Ethics Committee of the University Medical Center Groningen approved the study.

After being referred to the study, patients were consecutively enrolled in groups of 8–12 patients. Then, an information session, including a video session, was organized to inform patients about the content of the four components of the multidimensional rehabilitation program.

Setting/Intervention

The 15-week program was offered at the Center for Rehabilitation of the University Medical Center Groningen in an outpatient setting. The choice for a multidimensional program was based on the acknowledgment of fatigue as a multidimensional construct [33]. The entire rehabilitation program consisted of (a) individual exercise, (b) sports, (c) psychoeducation, and (d) information (Fig. 1). Participants were urged to be present at all sessions. According to the session leaders, absence was negligible.

Individual Exercise

The exercise program consisted of 15 sessions of 1.5 hours each and was supervised by a physical therapist. The exercise program was divided into an aerobic bicycle training and a muscle force training program. The bicycle training was performed at a trainings heart rate (THR) of HRrest + 50%–60% (HRmax – HRrest) during weeks 1–3 and at a THR of HRrest + 70%–80% (HRmax – HRrest) during weeks 4–9 [34]. General muscle force training of trunk and lower and upper extremities was performed and based on the individual 1-repetition maximum (1-RM) [35]. Individual intensity of muscle force training started at 50% of the 1-RM during the first week and was increased by 5%–10% during the following weeks with a frequency of 12 repetitions over three series. The rationale to include aerobic exercise training and muscle force training in the program is that it may mitigate fatigue because of physiological improvements [36].

Sports

The sports program consisted of 17 sessions of 1 hour each. The sessions were supervised by a physical therapist and were directed toward "enjoying sports," "self-confidence," and "body knowledge." During the performance of a diversity of sports activities, patients were instructed to become aware of physical sensations or limitations so they would recognize and respect limitations when performing sports or recreational activities at home. Sports were included in the program to stimulate patients to perform and enjoy sports and, consequently, to increase their level of activity in leisure times so that they may break through the vicious circle of a low activity pattern, muscle deconditioning, and fatigue [16, 17].

Week:	1		2		3		4		5		6		7		8		9		11		15	
Day:	2	5	2	5	2	5	2	5	2	5	2	5	2	5	2	5	2	5	2	5	2	5
I.E (1.5 hours)	+	+	+	+	+	+	+	+	+	+	+	+		+		+		+				
Sp (1 hour)	+	+	+	+	+	+	+	+	+	+	+	+		+		+		+		+		+
PE (2 hours)		+		+		+		+		+		+		+		+		+				
Inf (1 hour)	+		+		+		+		+		+			+		+		+		+		+

Figure 1. The content and frequency of the program components. Abbreviation: I.E, Individual Exercise; Sp, Sports; PE, Psycho-education; Inf, Information.

Psychoeducation

The psychoeducational program consisted of nine sessions of 2 hours each. The aims of the psychoeducational program were to reduce negative emotions, improve coping with the disease, and learn effective stress management techniques that may reduce fatigue [22]. A psychosocial specialist with several years of experience in conducting group sessions with cancer survivors led the psychoeducational program. Over several sessions, expressive–supportive techniques, breathing exercises, relaxation exercises, and exercises from Rational-Emotive Therapy were used to provide patients with stress-management techniques.

Information

The information program consisted of 10 sessions of 1 hour each. The aim of this program was to reduce the uncertainty resulting from a lack of knowledge of the disease by providing information with respect to cancer-related subjects. Better knowledge about cancer and cancer-related fatigue may lead to a better understanding of fatigue as a cancer treatment–related symptom, to change of irrational illness perceptions [37], and to the adoption of management strategies [22].

Measures

Demographic Variables

Age and gender were assessed.

Disease- and Treatment-Related Variables

Diagnosis, stage of disease, time since diagnosis, type of treatment received, and time since end of treatment were recorded from the patient's medical record.

Fatigue

Fatigue was measured with the Multidimensional Fatigue Inventory (MFI), which measures the following five dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue [10]. Every dimension contains four items and answers are given on a 5-point Likert-type scale. Scores have a range of 4–20, and a higher score reflects a greater sense of fatigue. Chronbach's α of the present study ranged from 0.71–0.83.

Body Composition

Besides body weight and height, lean body mass (LBM) and body fat (BF) were assessed by bioelectrical impedance analyses (Bodystat®1500, Douglas, Isle of Man, British Islands). Bioelectrical impedance measures resistance, LBM, and BF with a frequency of 50 kHz, using empirically-derived formulas. Measurements were taken with the patient in the supine position at the right side with electrodes on the third metacarpal bone, wrist, the second metatarsal bone, and the dorsum of the ankle. Patients were asked to refrain from ingesting food or beverages prior to the measurement. Body Mass Index (BMI) is calculated as weight (kg)/height (m^2). BMI has been used in evaluating cachexia and obesity. The normal range proposed by the World Health Organization (WHO) is 18.5–24.9 kg/m^2.

Physiological Functioning

Exercise capacity. A symptom-limited bicycle ergometry test was performed using a ramp 10, 15, or 20 protocol, depending on the patient's fitness. The load was increased every minute by 10, 15, or 20 Watts, respectively, in such a way that patients could reach their maximal workload within 10 minutes. The test was terminated on the basis of the patient's symptoms or at the physician's discretion [38]. Maximal workload in Watts at maximal performance was taken for analysis.

Muscle force. Maximal voluntary isometric muscle force of the right and left extremity of the following muscle groups was measured: extension of the knee, flexion of the elbow, and extension of the elbow, using a handheld dynamometer (Force Evaluating & Testing (microFET), Hoggan Health Industries Inc, West Jordan, UT). The "break method" was used for all measurements. To use this technique, the examiner gradually overcomes the force produced by the patient until the extremity gives way [39]. All measurements were performed at least three times with recovery intervals of at least 10 seconds. Peak forces (in Newtons) were recorded and mean values of three technically correct measurements were taken for analysis.

Physical Symptoms and Psychological Distress

The Rotterdam Symptom Check List, a self-report questionnaire, was used to assess disease-related quality of life. The checklist contains 23 items for physical symptom distress and seven items for psychological distress. Responses are presented on a 4-point Likert-type scale. A higher score reflects a higher level of burden of impairment. Normal scores for the general population are available [40]. Chronbach's α for the present study ranged from 0.67–0.87.

Perceived Physical Functioning, Mental Functioning, and Role Limitations

Three subscales, Physical Functioning (10 items), Role Limitations due to physical problems (four items), and Mental Health (five items), of the RAND-36, which is a multidimensional self-report questionnaire, were used to assess global health-related quality of life. After recoding and transformation, scores range from 0–100, and a higher score represents better health. Normal scores for the general population are available [41]. Chronbach's α for the present study ranged from 0.84–0.85.

Self-Efficacy

The feeling of competence or having control over one's life was measured with the ALCOS (16 items), which is the Dutch version of the General-Self-Efficacy Scale [42]. Responses are presented on a 5-point Likert-type scale. A higher score reflects a higher level of self-efficacy. Crohnbach's α for the present study was 0.82.

Data Analyses

Descriptive statistics were used to describe the study population. Paired *t*-tests were used to assess differences between the two measurement times, T0 and T1. The effect size (ES) and threshold at the 5% level were calculated as indices measuring the magnitude of a treatment effect [43]. Middel et al. [44] showed that ES reflects clinical relevance. An ES <0.20 indicates "no change," an ES ≥0.20 but <0.50 indicates "a small change," an ES ≥0.50 but <0.80 indicates "a moderate change," and an ES ≥0.80 indicates "a considerable change."

To examine the effects of the different predictor variables on fatigue at baseline, the following analyses were performed. First, univariate relationships between MFI dimensions on the one hand and demographic variables, disease- and treatment-related variables, body composition, physiological variables, physical and psychological symptoms, and perceived functioning on the other hand were examined using Pearson's correlation analyses. In cases of dichotomous variables, differences were assessed by independent *t*-tests. Analysis of variance (ANOVA) was used to assess differences between treatment groups. Second, to investigate the main determinants of fatigue at baseline, variables significantly related to a subscale of the MFI were entered into a multiple regression model and analyzed stepwise. Five separate multiple regression analyses were performed, a separate one for each fatigue subscale. For nominal variables (treatment, diagnosis), we created dummy variables.

To examine whether change in fatigue was associated with change in baseline predictors, we performed five separate hierarchical multiple regression analyses. The subscales of fatigue postintervention were the dependent variables in the five regression models. The effect of fatigue at baseline (T0) on subsequent fatigue (T1) was first entered to control for earlier levels of fatigue. In the second step, the difference (Δ) between a predictor variable score at baseline (T0) and a subsequent predictor variable score (T1) was entered into the regression model. These analyses allow the examination of associations between change in fatigue and change in physical or psychological variables. Only those predictor variables that had a significant unique effect on preintervention fatigue were entered into the models.

Correlational analyses between the independent variables and variance inflation factors ($VIF = 1/1 - R^2$) were calculated to assess multicollinearity. Multicollinearity is present if the mean VIF is considerably larger than one and the largest VIF is greater than 10 [45].

Results

Patient Characteristics

Seventy-two patients entered the program. Fifteen percent of the participants were male. The mean (standard deviation [SD]) age of the participants was 51.4 (9.6) years. Sixty-one percent of the patients were women with breast cancer, and 39% had other cancer diagnoses. Two thirds of the patients had stage I or stage II disease. Two thirds of the participants had completed treatment during the preceding year (Table 1). The most often reported indication for referral to the rehabilitation program was fatigue. Fifty-six patients (77.8%) completed the program and the questionnaires: 10 patients developed cancer recurrence and dropped out of the program of their own volition. A further six patients left the program: for personal reasons (two patients), because of malaise (two patients), and for unknown reasons (two patients). Dropout was therefore 22.3%. χ^2 tests and *t*-tests revealed no significant differences between dropouts and those that stayed in with respect to gender, age, cancer diagnosis, time since diagnosis, time since completion of treatment, and fatigue at T0. χ^2 tests revealed significantly more cancer recurrences in the dropout group than in the stay-in group ($p < .001$).

Effects of the Multidimensional Rehabilitation Program on the Different Dimensions of Cancer-Related Fatigue

Paired *t*-tests of mean scores at T0 and T1 showed that patients reported significant improvements in every domain of the MFI after the cancer rehabilitation program (Table 2). The ES of T0 and T1 with respect to fatigue after the intervention varied from –0.35 (small change) to –0.78 (moderate change).

Mann-Whitney tests were performed to examine the effect of time since completion of treatment. The choice for this test was made because the distribution of time since completion was skewed; categorization was based on the median of 6.7 months. No significant differences were found between patients with a time since completion of treatment shorter than 6.7 months and patients with a longer time in any domain of fatigue before and after the program.

Table 1. Patient characteristics at time of inclusion (T0), $n = 72$

	n	**%**
Physician-reported indication criteria for rehabilitation (yes)		
Physical complaints	44	61.1
Reduced physical capacity	55	76.4
Psychological problems	48	66.7
Fatigue	59	81.9
Sleep disturbances	45	62.5
Coping/acceptance problems	29	40.3
Diagnosis		
Breast cancer	44	61.1
Non-Hodgkin's lymphoma/Hodgkin's disease	6	8.4
Gynecological cancer	5	7.0
Head and neck cancer	4	5.6
Other (<5%)	13	17.9
Stage of disease		
In situ	1	1.4
Stage I	12	16.7
Stage II	37	51.4
Stage III	14	19.4
Stage IV	3	4.2
Missing	5	6.9
Cancer treatment before rehabilitation		
Chemotherapy with/without surgery	14/2	19.4/2.8
Radiotherapy with/without surgery	17/4	23.6/5.6
Combination (chemotherapy and radiotherapy) with/without surgery	29/1	40.3/1.4
Surgery	4	5.6
Bone marrow transplant	1	1.4
Time between completion of treatment and rehabilitation program		
≤6 months	28	38.3
>6–12 months	21	29.2
>12–18 months	13	18.1
>18 months	8	11.1
Missing	2	2.8
Mean (SD) in months 10.8 (13.4)		
Anthropometry	Male	Female
Weight, mean (SD) in kg	84.8 (17.4)	72.1 (15.0)
Height, mean (SD) in cm	184.5 (6.8)	168.5 (7.8)
BMI, mean (SD) in kg/m^2	24.8 (3.9)	25.6 (5.8)
Lean body mass, mean (SD) in kg	64.1 (9.6)	45.9 (5.3)
Body fat, mean (SD) in %	23.7 (4.8)	36.5 (7.0)
Age, mean (SD) years	**51.4 (9.6)**	
Gender, male: female, *n* (%)	**11 (15.3): 61 (84.7)**	

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2. Descriptives and comparison of Multidimensional Fatigue Inventory scores between patients before (T0) and after (T1) the rehabilitation program, based on paired *t*-tests and effect size (ES) with a 95% confidence interval (CI). A higher score represents more fatigue

	Patients at T0 *n* = 56 Mean (SD)	**Patients at T1 *n* = 56 Mean (SD)**	***t***	**Effect size**	**95% CI for ES**
General fatigue	15.0 (3.9)	12.9 (4.7)[a]	4.51	−0.48	−0.86 to −0.11
Physical fatigue	14.9 (4.2)	11.6 (4.2)[a]	7.17	−0.78	−1.16 to −0.40
Reduced activity	12.9 (4.0)	10.7 (4.1)[a]	4.22	−0.54	−0.92 to −0.16
Reduced motivation	10.4 (3.7)	09.1 (3.6)[b]	3.26	−0.35	−0.73 to −0.02
Mental fatigue	13.2 (4.1)	11.7 (4.2)[b]	2.98	−0.36	−0.73 to −0.01

[a]$p < .001$; [b]$p < .01$.
Abbreviations: SD, standard deviation.

Main Predictors of Cancer-Related Fatigue in Patients Referred to a Cancer Rehabilitation Program

Correlational analyses between the predictor variables showed low to moderate coefficients ranging from 0.27 (physical functioning and mental functioning) to 0.74 (mental functioning and psychological distress).

MFI– General Fatigue

ANOVA showed that patients who had received radiotherapy combined with surgery had higher scores on general fatigue at baseline than those who had received chemotherapy or combined therapy with surgery. Correlational analyses showed that general fatigue at baseline was negatively associated with maximal workload, muscle force of lower extremity, physical functioning, role limitations, and psychological functioning. General fatigue appeared positively related to physical symptom distress and psychological distress (Table 3). Multiple stepwise regression analysis showed that physical functioning was the strongest predictor, followed by radiotherapy (with surgery) and physical symptom distress. Total variance explained was 48.8% (Table 4). VIFs ranged from 1.0–1.69.

MFI–Physical Fatigue

Physical fatigue at baseline appeared to be negatively associated with maximal workload, muscle force of upper extremity and lower extremity, physical functioning, role

Table 3. Fatigue at baseline: independent t-tests and analysis of variance of demographic characteristics and disease and treatment-related variables, and Pearson correlational analyses of physiological variables , symptom distress, and perceived functioning and the different sub-scales of fatigue pre intervention, *n*=72.

	General Fatigue		**Physical Fatigue**		**Reduced Activity**		**Reduced Motivation**		**Mental Fatigue**	
	F	***r***	***t***	***r***	***t***	***r***	***t***	***r***	***t***	***r***
Demographic variables										
Age						.28[a]		.26[a]		
Gender (female = 1, male = 0)										
Disease and treatment-related variables										
Diagnosis (breast cancer = 1, other = 0)										
Type of treatment										
- Chemotherapy with surgery										
- Radiotherapy with surgery	4.42[a]									
- Combined therapy with surgery										
Time since diagnosis										
Time since end of treatment										
Recurrence										
Anthropometry										
Lean body mass										
Physiological variables										
Maximal workload		-.33[b]		-.50[c]		-.24[a]		-.26[a]		
Muscle force upper extremity				-.34[b]						
Muscle force lower extremity		-.39[b]		-.42[b]				-.30[a]		
Symptom distress variables										
Physical symptoms (RSCL)		.53[c]		.49[c]				.31[b]		.49[c]
Psychological symptoms (RSCL)		.34[b]						.31[b]		.30[a]
Perceived functioning variables										
Physical functioning (Rand-36)		-.53[c]		-.57[c]				-.35[b]		-.29[a]
Mental health (Rand-36)		-.37[b]		-.31[b]		-.32[b]		-.50[b]		-.29[a]
Role limitations physical problems (Rand-36)		-.53[c]		-.62[c]		-.44[c]		-.34[b]		-.34[b]
Self-efficacy (ALCOS)				-.25[a]		-.28[a]		-.52[c]		-.26[a]

Only significant relationships are depicted.
[a] p<.05, [b] p<.01, [c] p<.001.
Abbreviations: RSCL, Rotterdam Symptom Check List.

Table 4. Multiple regression (stepwise) analyses of fatigue at baseline, beta and total R^2

	General fatigue β	Physical fatigue β	Reduced activity β	Reduced motivation β	Mental fatigue β
Demographic characteristics					
Age			0.19	−0.23[a]	
Disease- and treatment-related variables					
Type of treatment (radiotherapy with surgery, 1; other, 0)	0.36[b]				
Physiological variables					
Maximal workload	−0.001	−0.40[b]	−0.07	0.07	
Muscle force upper extremity		0.03			
Muscle force lower extremity	−0.03	0.02		0.04	
Symptom distress variables					
Physical symptoms (RSCL)	0.27[a]	0.13		0.01	0.50[c]
Psychological symptoms (RSCL)	0.16			0.06	0.14
Perceived functioning					
Physical functioning (RAND-36)	−0.40[b]	−0.20		−0.27[a]	−0.13
Psychological functioning (RAND-36)	−0.11	−0.14	−0.23[a]	−0.15	−0.09
Role limitations physical problems (RAND-36)	−0.12	−0.44[c]	−0.40[b]	−0.10	−0.13
Self-efficacy (ALCOS)		−0.06	−0.10	−0.40[b]	−0.11
Total R^2	48.8%	54.6%	26.2%	38.7%	25.4%

Only variables entered into the model are depicted.
[a]$p < .05$; [b]$p < .01$; [c]$p < .001$.
Abbreviations: RSCL, Rotterdam Symptom Check List.

limitations, psychological functioning, and self-efficacy. Physical fatigue appeared to be positively related to physical symptom distress (Table 3). Multiple stepwise regression analysis showed that role limitation due to physical problems was the strongest predictor, followed by maximal workload. Total variance explained was 54.6% (Table 4). VIFs ranged from 1.02–2.03.

MFI–Reduced Activity

Reduced activity at baseline was negatively associated with maximal workload, role limitations, psychological functioning, and self-efficacy. Reduced activity appeared positively related to age (Table 3). Multiple stepwise regression analysis showed that role limitation due to physical problems was the strongest predictor of reduced activity at baseline, followed by psychological functioning. Total variance explained was 26.2% (Table 4). VIFs ranged from 1.0–1.84.

MFI–Reduced Motivation

Reduced motivation at baseline was negatively associated with maximal workload, muscle force of lower extremity, physical functioning, role functioning, psychological functioning, and self-efficacy. Reduced motivation appeared positively associated with age, physical symptom distress, and psychological distress (Table 3). Multiple stepwise regression analysis showed that self-efficacy was the strongest predictor, followed by physical functioning and age. Total variance explained was 38.7% (Table 4). VIFs ranged from 1.0–1.99.

MFI–Mental Fatigue

Mental fatigue at baseline was negatively associated with physical functioning, role limitations, psychological functioning, and self-efficacy. Mental fatigue appeared positively related to physical symptom distress and psychological distress (Table 3). Multiple stepwise regression analysis showed that physical symptom distress was the only significant predictor of mental fatigue at baseline. Total variance explained was 25.4% (Table 4). VIFs ranged from 1.0–1.29. Posthoc analyses revealed that female patients had a lower LBM and a higher percentage BF than male patients (p = <.001). LBM was significantly correlated with muscle force ($r = 0.46$; $p < .001$), but not associated with any of the domains of fatigue.

Table 5. Hierarchical multiple regression analyses of change in fatigue

Predictors	General fatigue T1				Physical fatigue T1				Reduced activity T1				Reduced motivation T1				Mental fatigue T1			
	β	R^2ch	Fch	p	β	R^2ch	Fch	p	β	R^2ch	Fch	p	β	R^2ch	Fch	p	β	R^2ch	Fch	p
Step 1		.46	46.3	<.001		.41	26.9	<.001		.38	31.2	<.001		.44	42.3	<.001		.36	30.0	<.001
Fatigue preintervention (T0)	.68[c]				0.64[c]				.62[c]				.67[c]				.60[c]			
Step 2		.07	3.8	<.05		17	7.1	<.001		.11	5.1	<.01		.08	4.2	<.01		.06	5.6	<.01
Physiological variables																				
ΔMaximal workload					–.02															
ΔMuscle force upper extremity																				
ΔMuscle force lower extremity																				
Symptom distress variables																				
ΔPhysical symptoms	.08																.25[a]			
ΔPsychological symptoms																				
Perceived functioning																				
ΔPhysical functioning	–.23[a]												–.27[b]							
ΔPsychological functioning									–.25[a]											
ΔRole limitations physical problems					–.42[c]				–.21[a]											
ΔSelf-efficacy													–.06							
Total R^2 (%)	53%				58%				49%				52%				42%			

[a]$p < .05$; [b]$p < .01$; [c]$p < .001$.
Δ, difference between T0 and T1.

Associations Between Change in Fatigue Following the Rehabilitation Program and Change in Predictors Identified as Having an Independent Effect on Fatigue at Baseline (Table 5)

MFI–Change in General Fatigue

General fatigue at baseline accounted for 46% of the variance in fatigue postintervention (step 1). The variables entered into the second step accounted for a significant increment of 7%. Change in physical functioning had significant unique effects, but change in physical symptom distress did not. Thus, decreased general fatigue was associated with better physical functioning. Total variance explained was 53%. VIFs ranged from 1.0–1.08.

MFI–Change in Physical Fatigue

Physical fatigue at baseline accounted for 41% of the variance in fatigue postintervention. The variables entered into the second step accounted for a significant increment of 17%. Change in role limitations due to physical problems had a significant unique effect, but change in maximal workload did not. (Assessment of maximal workload was not possible in 12 patients due to mechanical breakdown of the apparatus [3], nausea [2], claustrophobia [1], or perceived irrelevance, painfulness, discomfort, or strenuousness of the test [6]. Consequently, the analysis examining change in physical fatigue was performed on 44 patients.) Thus, decreased physical fatigue was associated with fewer role limitations. Total variance explained was 58%. VIFs ranged from 1.0–1.3.

MFI–Change in Reduced Activity

Reduced activity at baseline accounted for 38% of the variance in fatigue postintervention. The variables entered into the second step accounted for a significant increment of 11%. Change in role limitations due to physical problems and change in psychological functioning appeared to have a significant unique effect. Thus, a decrease in reduced activity was associated with fewer role limitations and better psychological functioning. Total variance explained was 49%. VIFs ranged from 1.0–1.01.

MFI–Change in Reduced Motivation

Reduced motivation at baseline accounted for 44% of the variance in fatigue postintervention. The variables entered in the second step accounted for a significant increment of 8%. Change in physical functioning had a significant unique effect, but change in self-efficacy did not. Thus, a decrease in reduced motivation was associated with better physical functioning. Total variance explained was 52%. VIFs ranged from 1.0–1.02.

MFI–Change in Mental Fatigue

Mental fatigue at baseline accounted for 36% of the variance in fatigue postintervention. Change in physical symptom distress entered in the second step accounted for a significant increment of 6%. Thus, decreased fatigue was associated with reduced physical symptom distress. Total variance explained was 42%. VIFs were all 1.0.

Discussion

The present study assessed fatigue multidimensionally in a selected group of cancer patients referred to a rehabilitation program. Within this group of patients, we found that (a) rehabilitation is effective in reducing fatigue, (c) both physical and psychological parameters predicted different dimensions of fatigue, and (c) change in fatigue is mainly associated with change in physical parameters.

The first aim of the study was to assess the effects of a multidimensional rehabilitation program on cancer-related fatigue, a program of which the beneficial effects on quality of life have recently been reported [46]. The results of the present study showed that patients reported statistically significant and, more importantly, clinically relevant reductions in cancer-related fatigue after completion of the multidimensional program. Most reductions in fatigue were found in the domain of physical fatigue. One could argue that the effect found was due to maturation [47] rather than to the intervention. However, patients were eligible for the rehabilitation program only when (a) treatment had been completed at least 3 months prior to rehabilitation so that patients had time to naturally recover from cancer-related treatment effects and (b) the physician had judged that the presence of physical and psychological problems were persisting. In addition, the finding that there were no associations between time since completion of treatment and fatigue before and after the program argues against a maturation effect. This suggests that the beneficial effects on fatigue could be attributed to the intervention.

The second aim of the study was to examine the contribution of different variables to the determination of cancer-related fatigue reported by patients referred to a cancer rehabilitation program. Our study showed that gender was not a significant determinant of fatigue at baseline. Other studies reported that women suffer more from fatigue than men do [48]. We did not observe such a relationship perhaps because of the low number of men in our study. With respect to age, we found that age was not associated with any domain of fatigue except a greater reduction in motivation. This finding is in accordance with several other studies reporting no relationship between age and fatigue in cancer patients. However, it is in contrast to studies in the normal population reporting more fatigue in older people [48, 49]. With respect to disease- and treatment-related factors, we found no associations between type of cancer, time since diagnosis or completion of treatment, or type of treatment received and the different domains of fatigue, except that those who had undergone radiotherapy with surgery reported more fatigue than those who had received chemotherapy with surgery or a combination of chemotherapy, radiotherapy, and surgery. LBM and BF percentage appeared not to be related to any of the domains of fatigue.

Correlational analyses of the baseline data showed that the different dimensions of fatigue at baseline were associated with different physical and psychological parameters, supporting the notion that cancer-related fatigue is a multidimensional construct in nature. Regression analyses showed that maximal workload, physical symptoms, perceived physical functioning, psychological functioning, role limitations due to physical problems, and self-efficacy were the main determinants of fatigue at baseline.

The findings that physical and psychological parameters are predictive of fatigue are in agreement with our second hypotheses and are in accordance with earlier studies of cancer patients [50–52]. In addition, our results support the notion [51] that it is important to systematically assess and manage both physical and psychological symptoms of cancer-related fatigue.

An interesting finding was that physical fatigue was determined by maximal workload. Other authors used the 6- or 12-minute walk test [53] to assess exercise capacity. However, those authors did not statistically examine the relationship between fatigue and the 6- or 12-minute walk test. Furthermore, the 6- and 12-minute walk test has the disadvantage that it is a self-paced and submaximal test [54] that reflects more general functional ability [53] rather than genuine exercise capacity. The extra value of our study is that we included bicycle ergometry with a protocol that forced patients to maximal performance, which has been reported to be a more adequate measure of maximal exercise capacity [38, 55].

Furthermore, we found that self-efficacy was a significant predictor of reduced motivation only. Apparently, self-efficacy seems to be a less important variable in cancer patients than has been suggested in studies of chronic fatigue syndrome [50] and rheumatoid arthritis [56], which indicate that patients with a lower self-efficacy perceive more fatigue in general. In addition, baseline results revealed that mental fatigue was not determined by psychological variables but by physical symptom distress only, indicating that patients with a high level of physical symptom distress experienced more mental fatigue.

The proportion of the variance of fatigue at baseline explained by the variables included in the regression models varied from 25.4%–54.6%. The proportion of variance explained in the domains general fatigue and physical fatigue was higher than that in the domains of reduced motivation, reduced activity, and mental fatigue. Apparently, the variables included in our study were more relevant in predicting the more physical areas of fatigue than the more 'psychologically' oriented areas of fatigue.

The results regarding the associations between change in fatigue and change in physical and psychological variables revealed that fatigue at baseline was the most powerful predictor. This finding is in line with an earlier study showing that fatigue after radiation was mainly determined by fatigue prior to radiation [10].

A further finding of the study was that a decrease in the different dimensions of fatigue was mainly associated with improvements in physical parameters, including a decrease in physical symptoms and an improvement in perceived physical functioning and perceived role limitations due to physical problems. These findings are partly in agreement with our second hypothesis.

Change in physical and, to a lesser degree, psychological variables accounted for a significant but small increment (6%–17%) in the prediction, suggesting that other variables not included in the present study may be more relevant and should be taken into account in future studies. Possible suggestions are personality characteristics, social support, pain, and quality of sleep.

Although the predictive power of change in physical and psychological variables is relatively small, such change may be clinically important. Any alleviation of fatigue induced by cancer rehabilitation may be relevant for patients, considering the 20%–40% of patients who continue to suffer from fatigue long after cancer treatment. Furthermore, there may be an additional indirect effect of the program, that is, that patients with less fatigue may have more potential to break through the vicious circle of inactivity, muscle deconditioning, and fatigue.

The question of which component of the presented rehabilitation intervention may have accounted for the results is difficult to answer on the basis of the present study design. It is not possible to compare the effects of the physical or psychological components separately. However, the finding that change in fatigue was predominantly associated with change in physical parameters may suggest that a program consisting only of physical components might be effective enough.

The results may further suggest that future research should examine whether early screening of cancer-related fatigue, suggested to take place at the patient's initial contact with an oncologist [22], is feasible and effective in fatigue management and health-related quality of life.

Study Limitations and Clinical and Research Implications

With respect to the longitudinal design of the present study, the following remarks can be made. The interpretation of the results with respect to the effectiveness of the program should be made with caution because we did not include a control group. However, changes found in our study were not only statistically significant, but also appeared to be clinically relevant. In addition, the achieved beneficial effects on fatigue may be attributed to genuine effects of the intervention, regarding the long natural recovery time in most of the referred patients. In further research, a prospective randomized controlled study including a physical intervention, a psychological intervention, and/or a combined intervention seems to be necessary to examine the effects more thoroughly.

The strength of the longitudinal study design is that we were not only able to determine predictors of fatigue at baseline, but were also able to determine that change in fatigue was predominantly associated with change in physical parameters.

Multicollinearity between the independent variables may be a point of concern with respect to the regression models of fatigue. However, correlation analyses ranging from low to moderate and the low VIFs show that multicollinearity does not seem to be a point of concern in this study.

Conclusion

Different dimensions of fatigue at baseline are associated with different physical and psychological symptom parameters, suggesting that cancer-related fatigue is a multidimensional construct in nature. The multidimensional rehabilitation program presented in the current study had statistically and clinically relevant and positive effects on cancer-related fatigue. Decreases in fatigue were found to be predominantly associated with beneficial changes in physical parameters such as a decrease in physical symptoms and an improvement in perceived physical (role) functioning. The results suggest that future interventions should at least include a physical training/sport component to reduce fatigue in cancer patients.

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Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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