PERGAMON

European Journal of Cancer 38 (2002) 27–43

European Journal of Cancer

www.ejconline.com

Review

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

P. Servaes[a,*], C. Verhagen[b], G. Bleijenberg[a]

[a]*Department of Medical Psychology, Netherlands Fatigue Research Group, University Medical Centre, Nijmegen, The Netherlands*
[b]*Department of Medical Oncology, Netherlands Fatigue Research Group, University Medical Centre, Nijmegen, The Netherlands*

Received 19 April 2001; received in revised form 14 September 2001; accepted 17 September 2001

Abstract

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

Keywords: Review; Cancer; Fatigue; Interventions

1. Introduction

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

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

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

* Corresponding author at: Medical Psychology (118), University Medical Centre Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31-24-361-9387/361-3608; fax: +31-24-361-3425.
E-mail address: p.servaes@cksmps.azn.nl (P. Servaes).

0959-8049/02/$ - see front matter
PII: S0959-8049(01)00332-X

2. Method

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

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

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

3. Fatigue during treatment for cancer

3.1. Description of the reviewed studies

In Table 1, 26 publications are summarised in which fatigue was investigated in a sample of cancer patients during or immediately after treatment for cancer [1–26]. These 26 publications were based on 22 studies. As indicated in Table 1, some studies were based on the same sample of patients, answering different research questions. In 10 of these 22 studies, a homogenous group of cancer patients was investigated. In six studies, the sample consisted of breast cancer patients. In two studies, patients with prostate cancer were included. In one study, patients with malignant melanoma participated and finally, in one study, patients with advanced lung cancer participated. In the other 12 studies, samples consisted of patients with different cancer diagnoses.

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

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

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

3.2. Prevalence and course of fatigue

Percentages of the presence of fatigue differed in the reviewed studies. Twenty-five percent of a sample of prostate cancer patients reported fatigue during and directly after a course of radiotherapy [19]. Forty-six percent of a mixed sample of cancer patients reported fatigue among the three symptoms that caused them the most distress at the end of a course of radiotherapy [10]. The prevalence of severe fatigue (defined as fatigue greater than that experienced by 95% of the control group) in a combined group of patients with recently diagnosed breast or prostate cancer, patients with inoperable non-small cell lung cancer and patients receiving inpatient palliative care was 48% [23]. In a Japanese study, 51% of a sample of patients with advanced lung

Table 1
Fatigue during treatment for cancer

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire
Blesch, 1991 [1]	In- and out-patients (breast and lung cancer) receiving chemotherapy and/or radiotherapy (50% inpatients)	44 breast cancer patients, age 24–69 years, mean 51 (S.D. 11). 33 lung cancer patients, age 38–74 years, mean 58 (S.D. 9), 75% male	1	VAFS, POMS-fatigue
	Key finding: Fatigue was present to some degree in 99% of the patients. Two-thirds rated their level of fatigue as moderate to severe.			
Cimprich, 1992 [2]	Breast cancer patients during hospitalisation for surgery (mean 3 days after surgery)	32 patients, age 29–84 years, mean 54 (S.D. 14)	1	Attentional fatigue: digit span, alphabet backward, symbol digit modification test, letter cancellation
	Key finding: Patients had a significantly decreased capacity to direct attention in comparison to norm scores.			
Glaus, 1993 [3]	Patients with different cancer diagnoses during treatment with chemotherapy and/or radiotherapy	20 cancer patients age 31–85 years, mean 54 (S.D. 15), 30% male 30 healthy controls age 20–58 years, mean 33 (S.D. 10), 39% male	4 times daily during 7 days	VAFS
	Key finding: The mean fatigue score was significantly higher for cancer patients than for healthy controls (effect size 0.31).			
Irvine, 1994[a] [4]	Patients with lung, breast and gynaecological cancer during chemotherapy or radiotherapy	54 radiotherapy, 47 chemotherapy, age 25–77 years, mean 55 (S.D. 11), 3% male. 53 healthy controls, mean age 63 years, 0% male	2 (start and midpoint of a cycle of chemotherapy or start and end of radiotherapy)	PBFFQ
	Key finding: 61% experienced 'clinical fatigue'. Cancer patients experienced a significant increase in fatigue during therapy. Their fatigue scores were higher than scores of control subjects (effect size 0.65).			
Graydon, 1995[a] [5]	Patients with breast and gynaecological cancer during chemotherapy or radiotherapy	54 radiotherapy, 45 chemotherapy, age 25–77 years, mean 55 (S.D. 11)	2 (start and midpoint of a cycle of chemotherapy or start and end of radiotherapy)	PBFFQ
	Key finding: At second assessment, patients were significantly more fatigued than they had been at first assessment.			
Dean, 1995 [6]	Patients with malignant melanoma during treatment with interferon-alpha	30 patients, age 20–85 years, mean 53 (S.D. 17), 67% male	5 (before treatment and at the end of each 2 weeks)	PFS
	Key finding: Patients were significantly more fatigued mid- or post treatment than they had been at the pre-treatment measurement.			
Richardson, 1996 [7]	Patients with different cancer diagnoses during chemotherapy	129 patients, age 26–82 years, mean 58	Daily during one cycle of chemotherapy	VAFS
	Key finding: 90% reported fatigue at some point during a cycle of chemotherapy.			
Dimeo, 1997 [8]	Patients with different cancer diagnoses in the period between receiving 1–4 chemotherapy cycles and hospital admission for high-dose chemotherapy with stem cell transplantation	78 patients, age 18–60 years, mean 40 (S.D. 11), 40% male	1	POMS-fatigue
	Key finding: A weak correlation was found between fatigue and maximal physical performance (−0.30)			
Irvine, 1998 [9]	Breast cancer patients during radiotherapy *and at 3 and 6 months follow-up*	76 patients, age 33–81 years, mean 60 (S.D. 11)	6 (before radiotherapy, 1 and 2 weeks later, during the last week, and 3 and 6 months later)	PBFFQ
	Key finding: Fatigue increased over the course of treatment, was highest at the last week of treatment and returned to pre-treatment levels by 3 months after treatment.			

(continued on next page)

Table 1 (*continued*)

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire
Smets, 1998[b] [10]	Patients with different cancer diagnoses during radiotherapy	250 patients, mean age 64 years (S.D. 13), 58% male	2 (before the start of treatment and 2 weeks after completion)	MFI-20
	Key finding: Fatigue scores after radiotherapy were significantly higher than pre-treatment scores. After treatment, 46% of the patients reported fatigue as among the three symptoms that caused them most distress.			
Smets, 1998[b] [11]	Patients with different cancer diagnoses during and after radiotherapy	250 patients, mean age 64 years (S.D. 13), 58% male	3 (before the start of treatment, 2 weeks and 9 months after completion)	MFI-20
	Key finding: Fatigue during treatment with radiotherapy is best explained by treatment-related demands (daily travel to hospital and confrontation with other patients) and demands of the social environment (work, children).			
Visser, 1998[b] [12]	Patients with different cancer diagnoses during and after radiotherapy	250 patients, mean age 64 years (S.D. 13), 58% male	3 (before the start of treatment, 2 weeks and 9 months after	MFI-20
	Key finding: Correlations between fatigue and depression were moderate. Depression scores did not change while fatigue scores rose over the course of cancer treatment.			
Richardson, 1998 [13]	Patients with different cancer diagnoses during chemotherapy	109 patients, age 20–89 years, mean 59, 46% male	Daily during one cycle of chemotherapy (21 or 28 days)	VAFS
	Key finding: 89% reported fatigue at some point during a cycle of chemotherapy			
Berger, 1998[c] [14]	Breast cancer patients during chemotherapy	72 patients, age 33–69 years, mean 50 (S.D. 9)	4 days at the start and three days at cycle midpoints during the first 3 cycles of chemotherapy	PFS
	Key finding: Fatigue scores were significantly higher at the day of chemotherapy administration than between treatment courses, but fatigue did not increase over time.			
Miaskowski, 1999 [15]	Patients with different cancer diagnoses with bone metastases during radiotherapy	24 patients, mean age 56 years (S.D. 13), 50% male	During 2 days	LFS
	Key finding: Patients reported moderate amounts of fatigue. Fatigue levels were higher at the end of the day and decreased in the morning following a night's rest.			
Gaston-Johansson, 1999 [16]	Breast cancer patients in the period between receiving chemotherapy and high-dose chemotherapy with stem cell transplantation.	127 patients, age 22–60 years, mean 45 (S.D. 8)	1	PFS, VAFS
	Key finding: 91% reported fatigue at some point.			
Stone, 1999 [17]	Patients with different cancer diagnosis (advanced cancer, but currently not receiving chemotherapy or radiotherapy)	95 patients, age 30–89 years, mean 67, 43% male. 98 healthy controls, age 41–85 years, mean 68, 38% male	2 (baseline and 2 weeks later)	FSS
	Key finding: Prevalence of 'severe subjective fatigue' was found to be 75%.			
Hann, 1999 [18]	Breast cancer patients receiving high-dose chemotherapy with bone marrow transplantation.	31 patients, age 36–74 years, mean 51 (S.D. 15). 49 healthy controls, age 36–55 years, mean 51 (S.D. 8)	3 (prior to treatment, mid-treatment, near treatment completion)	POMS-fatigue, FSI
	Key finding: Cancer patients reported significantly more frequent and severe fatigue than women with no cancer history (effect size POMS 0.75; FSI 0.61).			
Monga, 1999 [19]	Prostate cancer patients during *and after* radiotherapy	36 patients, age 55–79 years, mean 67	4 (pre-, middle- and completion of treatment, and 4–5 weeks follow-up)	PFS
	Key finding: Fatigue scores were significantly higher during and directly after radiotherapy (25%) than at pre-treatment (8%). At 5 week follow-up, fatigue scores were not higher anymore than scores at pre-treatment.			

(continued on next page)

Table 1 (*continued*)

Author	Diagnosis and treatment	Patient characteristics	Number of measurements	Fatigue questionnaire
Jacobsen, 1999 [20]	Breast cancer patients during chemotherapy	54 cancer $n = 54$, age 28–77 years, mean 51 (S.D. 10) 54 control, age 32–77 years, mean 54 (S.D. 11)	3 (before treatment and after completion of the second and third cycle)	POMS-fatigue, FSI
	Key finding: Cancer patients experienced significant worse fatigue than women with no cancer history, before (effect size POMS 0.51) and during chemotherapy (effect size POMS 0.88).			
Berger, 1999[c] [21]	Breast cancer patients during chemotherapy	72 patients, age 33–69 years, mean 50 (S.D. 9)	4 days at the start and 3 days at cycle midpoints during the first three cycles of chemotherapy	PFS
	Key finding: Fatigue has been found to be associated with less daytime activity.			
Stone, 2000 [22]	Patients with prostate cancer during treatment with hormone therapy	58 patients, age 55–80 years, median 69	2 (day they started therapy, 3 months later)	FSS
	Key finding: Prevalence of severe fatigue was found to be 14% at baseline, before treatment started. Median FSS scores increased significantly after 3 months treatment.			
Stone, 2000 [23]	Recently diagnosed patients with breast or prostate cancer awaiting therapy, patients with non-small cell lung cancer referred for palliative chemotherapy and patients with advanced cancer (but currently not receiving chemotherapy or radiotherapy).	227 patients, age 30–89 years, median 66, 56% male 98 control, age 41–85 years, median 68, 38% male	1	FSS
	Key finding: Prevalence of severe fatigue was 48%. Median FSS of the combined patient group was significantly higher than that of the control group.			
Stone, 2000 [24]	Patients with different cancer diagnosis, during different anti-cancer treatment.	576 patients, age 18–89 years, median 59, 37% male	1	FACT-fatigue
	Key finding: 58% reported that fatigue had affected them in the past month. Fatigue affected patients significantly more than any other symptom.			
Okuyama, 2001 [25]	Patients with advanced lung cancer (but currently not receiving anti-cancer treatment).	157 patients, age 27–80 years, mean 63, 71% male	1	CFS, FNS, questions on interference of fatigue with 7 domains of daily activity
	Key finding: 51% was found to experience clinical fatigue.			
Ahsberg, 2001 [26]	Patients with different cancer diagnosis, during *and after* radiotherapy.	81 patients, age 30–70 years, 9% male	4 (before treatment, at the last week of treatment, at 1 and 3 months after completion of treatment)	SOFI
	Key finding: Patients were significantly more fatigued at the end of a course of radiotherapy than they had been before.			

S.D., standard deviation; LFS, Lee Fatigue Scale; SOFI, Swedish Occupational Fatigue Inventory; VAFS, the Visual Analogue Fatigue Scales; FSS, the Fatigue Severity Scale; POMS, the Profile of Mood States; FSI, the Fatigue Symptom Inventory; PBFFQ, Pearson Byars Fatigue Feeling Questionnaire; PFS, the Piper Fatigue Scale; FACT; Functional Assessment of Cancer Therapy; MFI-20, Multidimensional Fatigue Inventory; CFS, Cancer Fatigue Scale; FNS, Fatigue Numerial Scale.

[a] Different studies with *almost* the same sample of patients.

[b] Different studies with the same sample of patients.

[c] Different studies with the same sample of patients.

cancer was found to experience clinical fatigue (which means that they complained of interference of fatigue with at least one domain of daily living activity) [25]. In another study, 58% of a sample of cancer patients undergoing anti-cancer therapy reported that fatigue had affected them in the past month, and that fatigue

affected them significantly more than any other symptom [24]. Furthermore, 61% of a mixed sample of the cancer patients reported clinical fatigue (as defined by a score higher than the midpoint of the fatigue questionnaire) during chemotherapy or radiotherapy [4]. Finally, the prevalence of severe fatigue in patients with advanced cancer was found to be 75% [17]. Studies in which Visual Analogue Fatigue Scales were used, presented even higher percentages of fatigue. In two studies in which a diary was used, 89 and 90% of the investigated patients reported fatigue at some point during a cycle of chemotherapy [7,13]. In two other studies, with only one measurement time, fatigue was present to some degree in 91% [16] and in 99% [1] of the investigated patients. In this last study, two thirds rated their fatigue as moderate to severe.

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

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

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

3.3. Correlates of fatigue

3.3.1. Disease-related variables

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

3.3.2. Treatment-related variables

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

administration. Patients receiving conventional 3- to 4-week cycles of chemotherapy experienced high levels of fatigue for the first 4–5 days after treatment, which gradually declined. In contrast, patients receiving weekly injections of chemotherapy, experienced moderate levels of fatigue that fluctuated cyclically [13].

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

3.3.3. Demographic variables

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

3.3.4. Psychological, physical, social and behavioural variables

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

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

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

3.4. Summary

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

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

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

4. Fatigue after treatment for cancer

4.1. Description of the reviewed studies

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

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

Most studies made use of more than one fatigue questionnaire. Frequently used instruments were the Fatigue Symptom Inventory, the fatigue subscale of the Profile of Mood States, the Piper Fatigue Inventory and the Fatigue Questionnaire. Sample sizes of the disease-free cancer patients in the reviewed articles, ranged from 33 to 1975. The ages of disease-free cancer patients ranged from 18 to 90 years, with means ranging from 32 to 64 years. In seven studies, all of the patients were female, in one study, all the patients were male and, in the other five studies, the distribution of men and women was approximately equal.

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

4.2. Prevalence of 'off treatment-fatigue'

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

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

4.3. Correlates of fatigue

4.3.1. Disease-related variables

The relationship between off-treatment fatigue and disease-related variables has been investigated in seven studies. In these studies, it was found that cancer diag-

Table 2
Fatigue after treatment for cancer

Author	Diagnosis and (time since) treatment	Patients characteristics	Number of measurements	Fatigue questionnaire
Hann, 1997 [27]	Breast cancer patients (3.5–62.5 months, mean 20 months) after treatment with high dose chemotherapy with bone marrow transplantation (BMT)	43 patients age 32–57 years, mean 44 (S.D. 6). 43 controls (noncancer) age 32–56 years, mean 47 (S.D. 6).	1	POMS-fatigue, FSI
	Key finding: Women who had completed BMT reported significantly more frequent and severe fatigue than women with no cancer history (effect size POMS 0.46; FSI 0.40).			
Woo, 1998 [28]	Breast cancer patients (6 months to 28 years after diagnosis, mean 30 months). Treated with chemotherapy, radiotherapy, hormonal therapy or a combination. !! A few patients could have been in active treatment	332 patients, age 31–90 years, mean 52 (S.D. 10)	1	PFS
	Key finding: Women who received combination therapy reported significant higher levels of fatigue compared with those treated with radiotherapy only (effect size 0.97).			
Smets, 1998 [29]	Patients with different cancer diagnoses (9 months) after treatment with radiotherapy	154 patients, age 65 years (S.D. 12), 57% male 139 healthy controls, age 46 years (S.D. 16), 44% male	1	MFI-20
	Key finding: Fatigue in patients did not differ significantly from fatigue in controls.			
Andrykowski, 1998 [30]	Breast cancer patients (3–60 months, mean 25 months) after treatment with chemotherapy, radiotherapy or a combination of these treatments	88 patients, age 35–76, mean 54 (S.D. 9) 88 controls with benign breast problems, age 37–76 years, mean 53 (S.D. 9)	2 (initial and 4 months follow-up)	MOS-vitality, CFS, PFS
	Key finding: Breast cancer patients reported significantly more fatigue, more weakness and less vitality relative to the benign breast cancer patients at two assessment times (initial and 4 months follow-up) (effect size initial assessment MOS 0.30; CFS 0.15; PFS 0.30).			
Broeckel, 1998 [31]	Breast cancer patients (3–36 months, mean 16 months) after treatment with chemotherapy (sometimes in combination with radiotherapy).	61 patients, age 52 years (S.D. 11) 51 healthy controls, age 51 years (S.D. 11)	1	POMS-fatigue, FSI, MFSI
	Key finding: Patients reported more severe fatiguethan healthy controls (effect size POMS 0.47; FSI 0.42; MFSI 0.42).			
Hann, 1998 [32]	Breast cancer patients (5–88 months, mean 22 months) after treatment with radiotherapy	45 patients, age 36–86 years, mean 64 (S.D. 13) 44 healthy controls, age 47–77 years, mean 60 (S.D. 9)	1	POMS-F, FSI
	Key finding: There were no significant differences between the groups on the reported levels of fatigue severity, intensity, frequency and disruptiveness.			
Loge, 1999[a] [33]	Hodgkin's disease survivors (mean observation period 12 years, S.D. 6)	459 patients, mean age 32 years (S.D. 11), 56% male	1	FQ
	Key finding: 26% had substantial fatigue for 6 months or longer. This percentage was significantly higher than the percentage among 2214 controls representative of the general Norwegian population (11%) (effect size 0.51).			
Howell, 2000 [34]	Patients treated for haematological malignancies (1–21 years, mean 8 years) after chemotherapy (sometimes in combination with radiotherapy).	66 patients, age 21–52 years, mean 40, 100% male 44 healthy controls, age 20–59 years, mean 40, 100% male	1	MFI-20
	Key finding: Fatigue scores were higher in men treated for haematological malignancies in comparison with healthy men.			

(continued on next page)

Table 2 (*continued*)

Author	Diagnosis and (time since) treatment	Patients characteristics	Number of measurements	Fatigue questionnaire
Knobel, 2000 [35]	Lymphoma patients (median 6 years) after high dose therapy supported by autologous bone marrow transplantation	33 patients, age 18–59 years, mean 39, 55% male	1	FQ
	Key finding: Lymphoma patients were more fatigued than the Norwegian reference population.			
Bower, 2000 [36]	Breast cancer patients (12 to 60 months, mean 35 months) after treatment with chemotherapy, radiotherapy or a combination of these treatments	1975 patients, mean age 55 years	1	Rand 36-energy/fatigue
	Key finding: 30% reported heightened levels of fatigue relative to women in the general population.			
Okuyama, 2000 [37]	Breast cancer patients (mean 20 months) after treatment with surgery, chemotherapy, radiotherapy or a combination of these treatments	134 patients, age 28–86 years, mean 55 (S.D. 10)	1	CaFS
	Key finding: Fatigue was significantly correlated with dyspnoea, insufficient sleep and depression.			
Curt, 2000[b] [38]	Cancer survivors who completed treatment for chemotherapy (sometimes in combination with radiotherapy) more than 1 year ago	379 patients, mean age 63 years, 21% male	1	Telephone interview, 50 questions on fatigue
	Key finding: 30% experienced fatigue on a daily basis. 91% of those who experienced fatigue reported that it prevented a 'normal life'.			
Loge, 2000[a] [39]	Hodgkin's disease survivors (observation period 3 to 23 years)	421 patients, age 19–74 years, 56% males	1	FQ
	Key finding: Fatigued HDS had higher levels of anxiety and depression than non-fatigued HDS.			
Servaes, 2001 [40]	Patients with different cancer diagnoses (6 months to 12.5 years, mean 36 months) after treatment with chemotherapy and/or radiotherapy	85 patients, age 21–74 years, mean 48 (S.D. 14), 60% male	1	CIS
	Key finding: 19% of a sample of disease-free cancer patients experienced severe fatigue. Their mean fatigue score was significantly higher than a reference score of healthy adults (effect size 0.30).			
Cella, 2001 [41]	Cancer survivors who completed treatment for chemotherapy (sometimes in combination with radiotherapy) more than 1 year ago	379 patients, mean age 63 years, 21% male	1	Telephone interview, 50 questions to establish cancer-related fatigue
	Key finding: 17% met formal diagnostic criteria for cancer-related fatigue.			
Knobel, 2001[a] [42]	Hodgkin's disease survivors (HDS) after radiotherapy (sometimes in combination with chemotherapy), mean observation time 9 years (S.D. 3).	92 patients, age 23-56, mean 37, 59% male	1	FQ
	Key finding: Pulmonary dysfunction is associated with fatigue in HDS. Cardiac sequelae was not associated with fatigue in HDS.			

MOS, Medical Outcome Studies; FQ, the Fatigue Questionnaire; CaFS, Cancer Fatigue Scale; CIS, checklist individual strength; S.D., standard deviation; POMS; the Profile of Mood States; PFS, the Piper Fatigue Scale; MFI-20, Multidimensional Fatigue Inventory; FSI, the Fatigue Symptom Inventory; CFS, Chalder Fatigue Scale; FNS, Fatigue Numerical Scale; MFSI, Multidimensional Fatigue Symptom Inventory.

[a] Different studies with *almost* the same sample of patients.

[b] Different studies with the same sample of patients.

nosis [29,34], disease stage at diagnosis [27,29,31–33,37], size of the original tumour [27,32,37], number of nodes involved [27] and having relapsed [33] were not significantly related to fatigue intensity.

4.3.2. Treatment-related variables

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

The extent of adjuvant therapy patients underwent was unrelated to fatigue severity in eight articles in which this relationship was studied [29–34,37,40]. Current tamoxifen use turned out to be unrelated to fatigue severity as well [27,31,32,36,37]. In contrast, in two studies, severity of post-treatment fatigue was related to the extent of treatment. In these studies, former chemotherapy patients (sometimes in combination with radia-

tion and/or hormonal therapy) reported higher levels of fatigue compared with those treated with radiotherapy [28,36]. It should be noted, however, that in the study by Bower, the association between fatigue and type of treatment was only moderate. Treatment did not emerge as a significant predictor of fatigue in the regression analysis [36]. Furthermore, as noted before, in the study by Woo there is a possibility that some patients were still in active treatment at the time of participation in the study [28].

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

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

4.3.3. Demographic variables

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

4.3.4. Psychological, social, physical and behavioural variables

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

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

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

4.4. Summary

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

5. Interventions to reduce fatigue

5.1. Description of the reviewed studies

In Table 3, 12 controlled intervention studies are summarised. In five of these studies, fatigue was the main dependent variable [48,50–52,54]. In the other seven studies, fatigue was one of the investigated outcome measures [43–47,49,53]. All studies took place while patients were undergoing treatment for cancer or, in one study, just after treatment for cancer had finished (surgery, without adjuvant therapy). To the best of our knowledge, no intervention studies have been conducted to reduce fatigue complaints long after treatment for cancer has finished. With respect to the content of the interventions, three studies investigated the effect of a walking- or exercise programme [50–52]. In these studies, patients walk or perform exercises on 3–7 days a week for approximately 30 min. Five other studies described the effect of individual counselling by professionals [44,45,49,53] or by former cancer patients [46]. Contents of these individual sessions included preparatory information, improving coping skills, psychological support, health education, stress manage-

Table 3
Interventions to reduce fatigue

Author	Diagnosis and treatment	Intervention	Patient characteristics	Number of measurements	Fatigue questionnaire
Spiegel, 1981 [43]	Patients with metastatic breast cancer	Weekly supportive group meetings, during one year	16 intervention, mean age 54 years 14 control, mean age 55 years	4 (initial, and 4, 8, 12 months later)	POMS-fatigue
	Key finding: Those who participated in the weekly group sessions experienced significantly less fatigue at all measurements than controls.				
Worden, 1984 [44]	Patients with different cancer diagnoses, shortly after the time of initial diagnosis.	6 week individual training to lower emotional distress and improve coping	59 intervention 58 control Patients were at risk for emotional distress and poor coping	3 (pre-intervention, 2 and 6 months follow-up)	POMS-fatigue
	Key finding: Two and 6 months after the intervention, the intervention group was significantly less fatigued than the control group.				
Forester, 1985 [45]	Patients with different cancer diagnoses, during radiotherapy	Individual psychotherapy, weekly 10 times	48 intervention, age 23–78 years, mean 62, 54% men 52 control, age 25–81 years, mean 62, 46% men	5 (before psychotherapy, week 3, week 6 (end of radiotherapy), week 10, week 14)	SADS-fatigue
	Key finding: The intervention group reported significantly less fatigue directly after intervention, but the difference disappeared at follow-up (4 and 8 weeks later).				
Houts, 1986 [46]	Gynaecological cancer patients, shortly after the time of initial diagnosis	Individual counselling by former cancer patients (telephone), 10 weeks	14 intervention, mean age 48 years 18 control, mean age 51 years	3 (initial and 6 and 12 weeks after entering the study)	POMS-fatigue
	Key finding: There were no differences in fatigue between the two groups at 6 and 12 weeks after beginning treatment				
Fawzy, 1990 [47]	Patients with malignant melanoma directly after surgery (no adjuvant therapy)	6-week psychiatric group intervention, postsurgical (health education, enhancement of problem solving skills, stress management and psychological support)	38 intervention, mean age 46 years, 47% male 28 control, mean age 38 years, 47% male	3 (pre-, post-intervention and 6 months follow-up)	POMS-fatigue
	Key finding: Directly after the intervention, there were no differences in fatigue scores. At 6 months follow-up, patients in the intervention group reported less fatigue than patients in the control group (effect size 0.61).				
Cimprich, 1993 [48]	Breast cancer patients during treatment (radiotherapy/ chemotherapy/ antihormonal)	Regular participation in activities that engage fascination	16 intervention, age 29–84 years, mean 57 (S.D. 16). 16 control, age 32–77 years, mean 51 (S.D. 13)	4 (3, 18, 60 and 90 days after surgery)	Total Attention Score (sum of standardised objective attentional tests), Attentional Function Index
	Key finding: There was an interaction of experimental intervention and time on attentional capacity. Subjects in the intervention group showed significant improvement in attention capacity over the four time points.				
Fawzy, 1995 [49]	Newly diagnosed patients with malignant melanoma	Nursing intervention, 3 h of individual teaching on two occasions (health education, stress management, coping)	29 intervention, mean age 42 years, 52% male 33 control, mean age 46 years, 58% male	3 (baseline, 6 weeks and 3 months after the intervention)	POMS-fatigue
	Key finding: Patients in the intervention groups reported significantly less fatigue than patients in the control group 3 months after the intervention (effect size 0.40).				

(continued on next page)

Table 3 (*continued*)

Author	Diagnosis and treatment	Intervention	Patient characteristics	Number of measurements	Fatigue questionnaire
Mock, 1997 [50]	Breast cancer patients during treatment with radiotherapy	20–30 min walking four to five times a week	22 exercise, mean age 48 years (S.D. 5) 24 control, mean age 50, (S.D. 8)	3 (pre, mid, and post exercise programme)	PFS
	Key finding: The intervention group reported less fatigue than the control group immediately after intervention.				
Dimeo, 1999 [51]	Patients with different cancer diagnoses during hospitalisation for high dose chemotherapy with stem cell transplantation	Exercise programme, 30 min daily	27 exercise, age 21–59 years, mean 40 years (S.D. 11), 33% male 32 control, age 20–56 years, mean 40 (S.D. 10), 40% male	2 (at hospital admission and hospital discharge)	POMS-fatigue
	Key finding: By the time of hospital discharge, fatigue had increased significantly in the control group but not in the training group.				
Schwartz, 2000 [52]	Patients with breast cancer, during the first 3 cycles of chemotherapy	8-week home-based exercise programme, 3–4 days a week, 15–30 min	16 exercise, age 25–57 years, mean 47 11 control	2 (pre- and post exercise program)	VAFS
	Key finding: Women who adopted exercise experienced fewer days of high fatigue levels than women who did not exercise.				
Gaston-Johansson, 2000 [53]	Breast cancer patients undergoing autologous bone marrow transplantation (ABMT)	Comprehensive coping strategy programme 2 weeks before hospital admission (preparatory information, cognitive restructuring, and relaxation)	52 intervention, age 21% 22–40 years, 50% 41–50 years, 29% $\geqslant 51$ 58 control, age 30% 22–40 years, 56% 41–50 years, 14% $\geqslant 51$	2 (2 days before ABMT and 7 days after ABMT)	VAFS
	Key finding: Patients in the intervention group reported significantly less fatigue than patients in the control group (effect size 0.35).				
Oyama, 2000 [54]	Patients during a cycle of chemotherapy	Bed Wellness System—virtual reality: patients chose a preferred aromatic essential oil and content (lake, forest, country town)	15 intervention, age 29–73 years, mean 54, 20% male 15 control, age 29–73 years, mean 51, 20% male	2 (before chemotherapy and 3–5 days after chemotherapy)	CFS, VAFS
	Key finding: Patients in the intervention group were statistically less fatigued three to five days after chemotherapy than patients in the control group.				

PFS, Piper Fatigue Scale; POMS, Profile of Mood States; SADS, Schedule of Affective Disorders and Schizophrenia; VAFS, Visual Analogue Fatigue scale; S.D., standard deviation; CFS, Cancer Fatigue Scale.

ment, cognitive restructuring and relaxation. Two studies conducted an intervention study in which the effect of supportive group meetings [43] and psychiatric group meetings [47] were investigated. Furthermore, in one study the effect of an intervention to minimise attentional fatigue through regular participation in activities that engage fascination and have other restorative properties was investigated [48]. Finally, in one study, a virtual reality system was used. This system made patients feel that they were somewhere else in a virtual world, while they were given chemotherapy. Patients could chose a content (lake, forest, country town) and an aromatic essential oil [54].

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

5.2. Effect of intervention

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

In addition, in the four studies in which the effect of individual counselling by professionals on fatigue severity was investigated, positive results were found directly after the intervention [44,45,49,53]. Patients in the intervention groups reported significantly less fatigue than patients in the control group. In two studies these results lasted, at 3 [49] and 6 months follow-up [44] but, in the other study, the benefit was no longer present at a 4-week follow-up [45]. A study in which the results of counselling by former cancer patients was investigated failed to find a reduction in fatigue [46].

Furthermore, the studies in which the effects of a group intervention were tested, also reported positive results with regard to a reduction in fatigue [43,47]. In one study, the focus was on the effect of health education, enhancement of problem solving skills, stress management (e.g. relaxation) and psychological support. It was found that the intervention group reported less fatigue than a control group 6 months after the end of the intervention [47]. The other study compared a group of patients who were following weekly supportive group meetings compared with a group of patients who did not follow these meetings. Results indicate that the first group reported less fatigue than the second group [43].

Furthermore, in the study that investigated an intervention to minimise attentional fatigue, the authors found that the intervention group improved significantly more than the control group [48]. Finally, patients who were in the virtual reality intervention group during the administration of chemotherapy, were statistically less fatigued 3–5 days after chemotherapy than patients in the control group [54].

5.3. Summary

All intervention studies were conducted with patients who were undergoing treatment or had just finished treatment at the time of the study. The interventions included, individual counselling (five studies) a walking or exercise programme (three studies) or group meetings (two studies). In 10 of the 12 studies, positive effects on fatigue complaints were reported immediately after the intervention. Follow-up results were presented in only four studies. In three of these studies, the positive effect of the intervention was still apparent at 3 or 6 months follow-up.

6. Discussion

In the last 10 years, the amount of research on the relationship between cancer and fatigue has increased considerably. To give an indication, from the 181 articles we found using Medline, Current Contents and Psychlit, 20 were published between 1980 and 1990, and 161 were published between 1991 and 2001. From these 161 studies, 32 were published between 1991 and 1995 and 129 were published between 1996 and 2001. The conducted research has focused mainly on fatigue complaints during treatment for cancer, while up to now only a few studies have attempted to investigate fatigue in cancer survivors.

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

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

Eight of the 10 reviewed studies in which a control group or norm scores were available reported that fatigue scores were significantly higher for cancer survivors in comparison to control subjects without a cancer history or to norm scores. However, two studies reported contrary findings. In these studies, fatigue does not seem to be an important complaint for cancer patients (long) after they have finished treatment. In addition, in three studies fatigue scores had returned to pre-treatment levels at follow-up. A possible explanation for this contradiction, proposed by the authors of one of these studies, is a problem that has been denoted a ''response

shift''. This means that the experience of fatigue during treatment for cancer, could have changed a patient's standard of measurement concerning fatigue. What has been perceived to be intense fatigue before treatment may be labelled as 'slightly' fatigued after having experienced exhaustion during treatment. The term ''response shift'' thus refers to the change in a person's internal standard for determining his or her level of functioning on a given dimension [55]. However, if this hypothesis is right, it remains unclear why in most studies fatigue scores were significantly higher for cancer survivors in comparison to control subjects.

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

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

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

Apart from the relationships between fatigue and disease- and treatment-related variables, we looked at psychological, social, behaviour and physical correlates of fatigue. The results of many of the studies indicated that both during and after treatment for cancer, fatigue is associated with a negative affect. In addition, intervention studies which focused on psychological well-being reported positive results with regard to fatigue. Still, the data are far from definitive in this regard. Most research has focused on the depression–fatigue association, which is a complex one.

Feelings of depression may result from the fact that one has (or had) a possibly fatal disease, and a depressed state of mind may induce fatigue. However, depression could also be a result of persistent feelings of fatigue [56] and this may especially be the case when treatment for cancer has ended some time ago. Although, the depression–fatigue association cannot be ruled out as an explanation for the experience of fatigue during and after treatment for cancer, it is clearly an incomplete description of the underlying process. We found three indications in the reviewed studies to support this view. First, although correlations between fatigue and depression were moderate, depression scores did not change while fatigue scores rose over the course of cancer treatment [12,19,22]. Second, although breast cancer survivors differed with respect to fatigue scores from women with benign breast problems, the two groups did not differ with regard to depressive symptoms [30]. Thirdly, within a group of severely fatigued disease-free cancer patients, only 19% could be considered as clinically depressed [40].

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

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

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

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

A concept that has not been studied in the reviewed studies is the concept of social support. However, resource-related factors such as the perceived level of social support may be vital. It is important to under-

stand the role social support plays in the perception and management of symptoms such as fatigue.

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

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

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

Acknowledgements

This research was funded by the Dutch Cancer Society.

References

1. Blesch KS, Paice JA, Wickham R, *et al*. Correlates of fatigue in people with breast or lung cancer. *Oncol Nurs Forum* 1991, **18**, 81–87.
2. Cimprich B. Attentional fatigue following breast cancer surgery. *Res Nurs Health* 1992, **15**, 199–207.
3. Glaus A. Assessment of fatigue in cancer and non-cancer patients and in healthy individuals. *Support Care Cancer* 1993, **1**, 305–315.
4. Irvine D, Vincent L, Graydon JE, Bubela N, Thompson L. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with the fatigue experienced by healthy individuals. *Cancer Nurs* 1994, **17**, 367–378.
5. Graydon JE, Bubela N, Irvine D, Vincent L. Fatigue-reducing strategies used by patients receiving treatment for cancer. *Cancer Nurs* 1995, **18**, 23–28.
6. Dean GE, Spears L, Ferrell BR, Quan WD, Groshon S, Mitchell MS. Fatigue in patients with cancer receiving interferon alpha. *Cancer Pract* 1995, **3**, 164–172.
7. Richardson A, Ream E. The experience of fatigue and other symptoms in patients receiving chemotherapy. *Eur J Cancer Care Engl* 1996, **5**(Suppl. 2), 24–30.
8. Dimeo F, Stieglitz RD, Novelli FU, Fetscher S, Mertelsmann R, Keul J. Correlation between physical performance and fatigue in cancer patients. *Ann Oncol* 1997, **8**, 1251–1255.
9. Irvine DM, Vincent L, Graydon JE, Bubela N. Fatigue in women with breast cancer receiving radiation therapy. *Cancer Nurs* 1998, **21**, 127–135.
10. Smets EM, Visser MR, Willems GA, *et al*. Fatigue and radiotherapy: (A) experience in patients undergoing treatment. *Br J Cancer* 1998, **78**, 899–906.
11. Smets EM, Visser MR, Garssen B, Frijda NH, Oosterveld P, de-Haes JC. Understanding the level of fatigue in cancer patients undergoing radiotherapy. *J Psychosom Res* 1998, **45**, 277–293.
12. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? *Support Care Cancer* 1998, **6**, 101–108.
13. Richardson A, Ream E, Wilson BJ. Fatigue in patients receiving chemotherapy: patterns of change. *Cancer Nurs* 1998, **21**, 17–30.
14. Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. *Oncol Nurs Forum* 1998, **25**, 51–62.
15. Miaskowski C, Lee KA. Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: a pilot study. *J Pain Symptom Manage* 1999, **17**, 320–332.
16. Gaston JF, Fall DJ, Bakos AB, Kennedy MJ. Fatigue, pain, and depression in pre-autotransplant breast cancer patients. *Cancer Pract* 1999, **7**, 240–247.
17. Stone P, Hardy J, Broadley K, Tookman AJ, Kurowska A, A'Hern R. Fatigue in advanced cancer: a prospective controlled cross-sectional study. *Br J Cancer* 1999, **79**, 1479–1486.
18. Hann DM, Garovoy N, Finkelstein B, Jacobsen PB, Azzarello LM, Fields KK. Fatigue and quality of life in breast cancer patients undergoing autologous stem cell transplantation: a longitudinal comparative study. *J Pain Symptom Manage* 1999, **17**, 311–319.
19. Monga U, Kerrigan AJ, Thornby J, Monga TN. Prospective study of fatigue in localized prostate cancer patients undergoing radiotherapy. *Radiat Oncol Investig* 1999, **7**, 178–185.
20. Jacobsen PB, Hann DM, Azzarello LM, Horton J, Balducci L, Lyman GH. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. *J Pain Symptom Manage* 1999, **18**, 233–242.
21. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. *Oncol Nurs Forum* 1999, **26**, 1663–1671.
22. Stone P, Hardy J, Huddart R, A'Hern R, Richards M. Fatigue in patients with prostate cancer receiving hormone therapy. *Eur J Cancer* 2000, **36**, 1134–1141.
23. Stone P, Richards M, A' HR, Hardy J. A study to investigate the prevalence, severity and correlates of fatigue among patients with cancer in comparison with a control group of volunteers without cancer. *Ann Oncol* 2000, **11**, 561–567.
24. Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. Cancer-related fatigue: inevitable, unimportant and untrea-

table? Results of a multi-centre patient survey. *Ann Oncol* 2000, **11**, 971–975.
25. Okuyama T, Tanaka K, Akechi T, *et al*. Fatigue in ambulatory patients with advanced lung cancer, prevalence, correlated factors, and screening. *J Pain Symptom Manage* 2001, **22**, 554–564.
26. Ahsberg E, Furst CJ. Dimensions of fatigue during radiotherapy—an application of the Swedish Occupational Fatigue Inventory (SOFI) on cancer patients. *Acta Oncol* 1901, **40**, 37–43.
27. Hann DM, Jacobsen PB, Martin SC, Kronish LE, Azzarello LM, Fields KK. Fatigue in women treated with bone marrow transplantation for breast cancer: a comparison with women with no history of cancer. *Support Care Cancer* 1997, **5**, 44–52.
28. 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.
29. 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.
30. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med* 1998, **21**, 1–18.
31. Broeckel JA, Jacobsen PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1998, **16**, 1689–1696.
32. Hann DM, Jacobsen P, Martin S, Azzarello L, Greenberg H. Fatigue and quality of life following radiotherapy for breast cancer: a comparative study. *J Clin Psychol Med Settings* 1998, **5**, 19–33.
33. Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol* 1999, **17**, 253–261.
34. Howell SJ, Radford JA, Smets EM, Shalet SM. Fatigue, sexual function and mood following treatment for haematological malignancy: the impact of mild Leydig cell dysfunction. *Br J Cancer* 2000, **82**, 789–793.
35. Knobel H, Loge JH, Nordoy T, *et al*. High level of fatigue in lymphoma patients treated with high dose therapy. *J Pain Symptom Manage* 2000, **19**, 446–456.
36. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol* 2000, **18**, 743–753.
37. Okuyama T, Akechi T, Kugaya A, *et al*. Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale. *Support Care Cancer* 2000, **8**, 215–222.
38. Curt GA, Breitbart W, Cella D, *et al*. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist* 2000, **5**, 353–360.
39. Loge JH, Abrahamsen AF, Ekeberg ?, Kaasa S. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. *J Pain Symptom Manage* 2000, **19**, 91–99.
40. 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.
41. Cella D, Davis K, Breitbart W, Curt G. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001, **19**, 3385–3391.
42. Knobel H, Havard-Loge J, Brit-Lund M, Forfang K, Nome O, Kaasa S. Late medical complications and fatigue in Hodgkin's disease survivors. *J Clin Oncol* 2001, **19**, 3226–3233.
43. Spiegel D, Bloom JR, Yalom I. Group support for patients with metastatic cancer. A randomized outcome study. *Arch Gen Psychiatry* 1981, **38**, 527–533.
44. Worden JW, Weisman AD. Preventive psychosocial intervention with newly diagnosed cancer patients. *Gen Hosp Psychiatry* 1984, **6**, 243–249.
45. Forester B, Kornfeld DS, Fleiss JL. Psychotherapy during radiotherapy: effects on emotional and physical distress. *Am J Psychiatry* 1985, **142**, 22–27.
46. Houts PS, Whitney CW, Mortel R, Bartholomew MJ. Former cancer patients as counselors of newly diagnosed cancer patients. *J Natl Cancer Inst* 1986, **76**, 793–796.
47. Fawzy FI, Cousins N, Fawzy NW, Kemeny ME, Elashoff R, Morton D. A structured psychiatric intervention for cancer patients. I. Changes over time in methods of coping and affective disturbance. *Arch Gen Psychiatry* 1990, **47**, 720–725.
48. Cimprich B. Development of an intervention to restore attention in cancer patients. *Cancer Nurs* 1993, **16**, 83–92.
49. Fawzy NW. A psychoeducational nursing intervention to enhance coping and affective state in newly diagnosed malignant melanoma patients. *Cancer Nurs* 1995, **18**, 427–438.
50. Mock V, Dow KH, Meares CJ, *et al*. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncol Nurs Forum* 1997, **24**, 991–1000.
51. Dimeo FC, Stieglitz RD, Novelli FU, Fetscher S, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer* 1999, **85**, 2273–2277.
52. Schwartz AL. Daily fatigue patterns and effect of exercise in women with breast cancer. *Cancer Pract* 2000, **8**, 16–24.
53. Gaston-Johansson F, Fall-Dickson JM, Nanda J, *et al*. The effectiveness of the comprehensive coping strategy program on clinical outcomes in breast cancer autologous bone marrow transplantation. *Cancer Nurs* 2000, **23**, 277–285.
54. Oyama H, Kaneda M, Katsumata N, Akechi T, Ohsuga M. Using the bedside wellness system during chemotherapy decreases fatigue and emesis in cancer patients. *J Med Syst* 2000, **24**, 173–182.
55. Breetvelt IS, van-Dam FS. Underreporting by cancer patients: the case of response-shift. *Soc Sci Med* 1991, **32**, 981–987.
56. Hayes JR. Depression and chronic fatigue in cancer patients. *Prim Care* 1991, **18**, 327–339.