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Cancer-Related Fatigue and Sleep Disorders

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ABSTRACT

Sleep disorders, such as difficulty falling asleep, problems maintaining sleep, poor sleep efficiency, early awakening, and excessive daytime sleepiness, are prevalent in patients with cancer. Such problems can become chronic in some patients, persisting for many months or years after completion of cancer therapy. For patients with cancer, sleep is potentially affected by a variety of factors, including the biochemical changes associated with the process of neoplastic growth and anticancer treatments, and symptoms that frequently accompany cancer, such as pain, fatigue, and depression.

Fatigue is highly prevalent and persistent in patients with cancer and cancer survivors. Although cancer-related fatigue and cancer-related sleep disorders are distinct, a strong interrelationship exists between these symptoms, and a strong possibility exists that they may be reciprocally related. The majority of studies that have assessed both sleep and fatigue in patients with cancer provide evidence supporting a strong correlation between cancer-related fatigue and various sleep parameters, including poor sleep quality, disrupted initiation and maintenance of sleep, nighttime awakening, restless sleep, and excessive daytime sleepiness.

This paper reviews the data from these studies with a view toward suggesting further research that could advance our scientific understanding both of potential interrelationships between sleep disturbance and cancer-related fatigue and of clinical interventions to help with both fatigue and sleep disturbance. ***The Oncologist*** 2007;12(suppl 1):35–42

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INTRODUCTION

Fatigue and sleep disturbance are two of the most frequent side effects experienced by patients with cancer. Although sleep disruption is common in these patients, it has been a neglected problem. This is partly because it has been seen as a normal and transient reaction to cancer and cancer treatment, and partly because of the underreporting of sleep disturbances by patients [1–4].

Patients with cancer report insomnia, poor sleep quality, and short sleep duration. On testing, they are frequently found to have low sleep efficiency (the ratio of time asleep to total time in bed) [5]. Precipitating factors for insomnia in patients with cancer include the diagnosis of cancer, the type and stage of cancer, pain, side effects of treatment (e.g., nausea, vomiting, etc.), and/or the direct iatrogenic effects of treatment on sleep. Once

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it begins, insomnia is often self-perpetuating because of the natural tendency of patients to compensate for sleep loss by extending their sleep opportunity, for example, by napping, going to bed earlier, and getting out of bed later. Such behavioral changes are enacted by patients in order to try to "recover what has been lost," but they lead to a mismatch between sleep opportunity and sleep ability and result in more frequent and longer awakenings. It may also be that the fatigue that occurs with cancer and/or anticancer therapy may, in and of itself, prompt patients to extend their sleep opportunity and thus it too becomes a contributing factor for ongoing insomnia [6].

The occurrence of insomnia in patients with cancer is frequent and is often severe enough to warrant medical intervention. Approximately 25%–50% of all prescriptions written for patients with cancer are for hypnotics [7,8]. Additionally, sleep disruptions can persist in cancer survivors for many years after diagnosis and completion of treatment, making it one of the most pervasive problems faced by patients with cancer [9,10].

Reports over the past 20–25 years have begun to shed light on the putative relationship between cancer-related sleep disorders and cancer-related fatigue (CRF). Cancer survivors often experience cancer-related sleep disorders and CRF simultaneously, although to date the interrelationships between these symptoms have not been completely defined [11–17]. While most of the studies in this area are correlative in nature, it is generally the case that sleep disturbance is: (a) positively correlated with fatigue, (b) more severe in fatigued than in nonfatigued patients, and (c) a significant predictor of fatigue (e.g., the studies reported in [11,18–20]). These findings are consistent with the concept that fatigue and insomnia are reciprocally related and suggest the possibility that treatment for one may impact the other.

This review of the current literature on sleep disruption and fatigue in patients with cancer outlines both correlative analyses and longitudinal studies that have used self-report and actigraphy measures to evaluate sleep disturbance.

Evaluating the Association Between Cancer-Related Fatigue and Sleep

Symptom Clusters

CRF and cancer-related sleep disorders are increasingly reported as part of a cluster of three or more interrelated symptoms, including pain, depression, and loss of concentration and other cognitive functions [21–23], suggesting that CRF and cancer-related sleep disorders may share a common underlying etiology. A longitudinal study of 93 patients undergoing chemotherapy revealed that a symptom cluster consisting of pain, fatigue, and sleep disturbance adversely and synergistically affected patient functional status (Karnofsky Performance Scale) [24]. In addition, the three symptoms were correlated with one another, albeit only to a small degree (fatigue to sleep insufficiency, $r = -0.13$; pain to sleep insufficiency, $r = -0.06$; pain to fatigue, $r = 0.22$). In another study of the same symptom cluster, Given and colleagues [25] showed that pain, fatigue, and insomnia were significant and independent predictors of reductions in patient functioning 8 weeks after diagnosis compared with 3 months prior to diagnosis. Most recently, an analysis of the results of questionnaire assessments of fatigue, pain, and sleep disturbances in 84 patients with multiple primary cancer diagnoses revealed that pain influenced fatigue, both directly and indirectly, via its effect on sleep [26]. Of the 20% variation in fatigue that was explained by pain in this population, 35% was mediated by sleep disturbances.

Evidence from Prospective Studies

The majority of studies that have prospectively assessed the relationship between fatigue and sleep in patients with cancer or cancer survivors reveal strong correlations between fatigue and various sleep parameters, including poor sleep quality, disturbed initiation and maintenance of sleep, lower perceived adequacy of sleep, insufficient sleep, sleep disturbance, nighttime awakening, and restless sleep (Table 1) [11,18–20,27–47]. While most studies have been conducted in patients with breast cancer undergoing chemotherapy, correlations between fatigue and sleep disorders have also been noted in patients undergoing radiotherapy and surgery, as well as in a variety of other cancer types (Table 1).

Evidence Using Patient-Reported Assessment of Fatigue and Sleep Disturbance

Most studies of insomnia have evaluated the condition using single-item assessments and have not taken into consideration the related symptoms of fatigue and excessive sleepiness. There is, however, one large-scale study that provides data on the various insomnia phenotypes (i.e., the type of insomnia complaint—whether early, middle, or late) [34]. In that study of 982 patients (mean age, 65 years) with six different types of cancer (breast, gastrointestinal, gynecologic, genitourinary, lung, and nonmelanoma skin cancer), a "sleep survey" questionnaire was used to evaluate the presence of various sleep problems (e.g., insomnia due to difficulty falling asleep, waking up several times a night, waking up for a long time, or waking up too early). The most prevalent problems reported by this patient sample were: fatigue (44%), insomnia (31%), and excessive sleepiness

Table 1. Studies investigating correlations between cancer-related fatigue (CRF) and cancer-related sleep disorders (CRSDs)

Study reference	Population	Cancer type	Study timing	Variable(s) related to key findings	Methods and instruments	Key findings related to a correlation between CRF and CRSDs
Åhsberg and Fürst [27]	$n = 81$, male and female, aged >18 yrs	Cancer located within the trunk (i.e., thorax, abdomen, pelvis, or back)	During and up to 3 months after radiotherapy	Perceived fatigue	Swedish Occupational Fatigue Inventory scale, Category Ratio 10 Scale, and Karolinska Sleepiness Scale	Sleepiness was a significant predictor of perceived level of fatigue
Ancoli-Israel et al. [28]	$n = 85$, female, aged 34–79 yrs	Stage I–III breast cancer	Prior to chemotherapy	(a) Fatigue, (b) objective sleep quality, (c) subjective sleep quality, (d) circadian rhythm	(a) Multidimensional Fatigue Symptom Inventory – short form, (b) actigraphy, (c) Pittsburgh Sleep Quality Index, (d) actigraphy	Significant ($p < .0001$) correlations between subjective measures of sleep and fatigue; no significant correlations between reports of fatigue and objective sleep parameters or circadian rhythm variables
Anderson et al. [18]	$n = 354$, male and female, aged 18–88 yrs	Various	Not related to treatment	(a) Fatigue, (b) sleep disturbance	(a) Brief Fatigue Inventory, (b) Sleep Disturbance Scale	Sleep disturbance was a statistically significant ($p < .001$) predictor of fatigue
Andrykowski et al. [29]	$n = 88$, female, aged 35–76 yrs	Stage I–IIIA breast cancer	3–60 months after primary cancer treatment (including surgery, radiotherapy, and chemotherapy)	(a) Fatigue, (b) sleep quality	(a) Chalder Fatigue Scale and Piper Fatigue Scale, (b) Pittsburgh Sleep Quality Index	There was a significant correlation between fatigue and sleep quality
Berger [30]	$n = 72$, female, aged 33–69 yrs	Stage I/II breast cancer	Four-day period following chemotherapy and at midcycle	(a) Fatigue, (b) activity and rest cycles	(a) Piper Fatigue Scale, (b) wrist actigraph	Fatigue and disrupted activity/sleep inversely related ($p < .05$)
Berger and Farr [31]	$n = 72$, female, aged 33–69 yrs	Stage I/II breast cancer	Four-day period following chemotherapy and at midcycle	(a) Fatigue, (b) circadian activity/rest indicators	(a) Piper Fatigue Scale, (b) wrist actigraph	Reduced daytime activity, increased daytime sleep, and increased nighttime awakenings were associated with increased fatigue
Berger and Higginbotham [32]	$n = 14$, female, aged 32–69 yrs	Stage I/II breast cancer	During chemotherapy and 2 months following final treatment	(a) Activity, (b) sleep, (c) symptom distress, (d) fatigue	(a) Wrist actigraph, (b) Morin Sleep Diary, (c) Symptom Experience Scale, (d) Piper Fatigue Scale	Low activity, disrupted sleep patterns, and increased symptom distress were all correlated with fatigue
Bower et al. [11]	$n = 1{,}957$, female, mean age 55 yrs	Stage 0–III breast cancer	Following treatment	(a) Fatigue, (b) sleep disturbance	(a) Energy fatigue subscale of the Medical Outcomes Study Short-Form (36-Item) Health Survey 1.0, (b) Medical Outcomes Study Sleep Scale	When present, fatigue was found to be strongly associated with sleep disturbance
Broeckel et al. [19]	$n = 61$, female, aged 29–75 yrs	Breast cancer	Mean of 471 days following chemotherapy	(a) Fatigue severity, (b) sleep quality	(a) The Fatigue Scale from the Profile of Mood States, (b) Pittsburgh Sleep Quality Index	Severe fatigue was significantly correlated with poorer sleep quality ($p < .05$) and sleeping during the day ($p < .001$)
Curran et al. [33]	$n = 25$, female, aged 28–63 yrs	Stage 0–III breast cancer	6–30 months following chemotherapy and/or radiotherapy	(a) Diurnal pattern of fatigue, (b) sleep duration	(a) 10-point Likert scale within Ecological Momentary Assessment, (b) diary recording of sleep duration	While fatigue was experienced following treatment, it was not correlated with sleep duration
Davidson et al. [34]	$n = 982$, male and female, mean age 65 yrs	Various	33% received therapy in previous 6 months	Various "sleep phenomena," including excessive fatigue	Sleep survey questionnaire	Patients who reported being overly fatigued were 2.5 times more likely to have insomnia than others
Faithfull and Brada [35]	$n = 19$, male and female, aged 20–71 yrs	Brain tumor	Following treatment	(a) Fatigue, (b) drowsiness	(a) Daily diary of visual analog scale score, (b) daily diary of visual analog scale score	Fatigue was correlated with drowsiness ($p < .01$)

(*Continued*)

Table 1 (*Continued*)

Study reference	Population	Cancer type	Study timing	Variable(s) related to key findings	Methods and instruments	Key findings related to a correlation between CRF and CRSDs
Hwang et al. [36]	$n = 180$, male, aged 30–89 yrs	Various	During treatment	(a) Fatigue, (b) feeling drowsy	(a) Brief Fatigue Inventory, Functional Assessment of Cancer Therapy-Fatigue; (b) Memorial Symptom Assessment Scale (Short Form)	In patients with clinically significant fatigue, 71% reported feeling drowsy and 51% reported difficulty sleeping; feeling drowsy was found to be a significant ($p < .001$) independent predictor of clinically significant fatigue
Jacobsen et al. [37]	$n = 54$, female, aged 28–77 yrs	Stage I–III breast cancer	During chemotherapy	(a) Fatigue, (b) sleep problems	Memorial Symptom Assessment Scale	The more frequent occurrence of sleep problems was associated with significant increases in fatigue severity
Miaskowski and Lee [38]	$n = 24$, male and female, mean age 57 yrs	Bone metastasis	During radiotherapy	(a) Fatigue, (b) sleep disturbances	(a) Lee Fatigue Scale, (b) wrist actigraph	Improvement in morning fatigue compared with evening fatigue was significantly correlated with better sleep efficiency
Mormont et al. [39]	$n = 200$, male and female, aged 20–75 yrs	Metastatic colorectal cancer	During chronomodulated chemotherapy	(a) Quality of life, including fatigue; (b) rest–activity rhythm	(a) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, (b) actigraphy	Fatigue was correlated with circadian rhythm disruptions ($p = .05$)
Okuyama et al. [40]	$n = 134$, female, aged 28–86 yrs	Stage 0–III breast cancer	18–1,894 days following treatment (surgery, radiotherapy, or chemotherapy)	(a) Fatigue, (b) sleep	(a) Cancer Fatigue Scale, (b) ad hoc self-administered questionnaire with 5-point Likert scale	Insufficient sleep was found to be one of the main determinants of fatigue
Redeker et al. [20]	$n = 263$, male and female, aged 19–82 yrs	Various	During chemotherapy	(a) Fatigue, (b) insomnia	Symptom Distress Scale	A significant correlation was observed between insomnia and fatigue
Richardson and Ream [41]	$n = 129$, male and female, aged 26–82 yrs	Various	During chemotherapy	(a) Fatigue, (b) perceived cause of fatigue	(a) Visual analog scale, (b) interview	Sleep–wake patterns were reported as one of the perceived causes of fatigue
Roscoe et al. [42]	$n = 78$, female, aged 34–79 yrs	Breast cancer	During chemotherapy	(a) Fatigue, (b) circadian sleep rhythm	(a) Fatigue Symptom Checklist, Multidimensional Assessment of Fatigue, (b) actigraphy	Increased symptoms of fatigue correlated with disruption of the circadian rhythm
Sarna [43]	$n = 69$, female, mean age 61 yrs	Lung cancer	43% receiving therapy	(a) Fatigue, (b) insomnia	Symptom Distress Scale	31% of patients with serious fatigue also experienced insomnia
Savard et al. [44]	$n = 327$, male, aged 47–80 yrs	Prostate cancer	Within 10 years following surgery	(a) Fatigue, (b) sleep	(a) Multidimensional Fatigue Index, (b) Insomnia Severity Index	No association between fatigue and insomnia
Sela et al. [45]	$n = 100$, male and female, aged 21–86 yrs	Various	During pain and symptom control treatment	(a) Fatigue, (b) sleep	(a) Edmonton Symptom Assessment Scale, (b) self-reported sleep questionnaire	Difficulty falling asleep, difficulty staying asleep, sleeping fewer hours, and early awakening were all significantly correlated with fatigue
Servaes et al. [46]	$n = 150$, female, mean age 46 yrs	Breast cancer	6–70 months following treatment (combination of surgery, radiotherapy, or chemotherapy)	(a) Complaints of fatigue, (b) sleep disturbance	(a) Daily Observed Fatigue Score of the Self-Observation List and Fatigue severity subscale of the Checklist Individual Strength questionnaire, (b) Groningen Sleep Quality Scale, Sleep/rest subscale of the Sickness Impact Profile, and Sleep subscale of the Symptom Checklist	Sleep disturbance was significantly greater in severely fatigued versus nonfatigued disease-free patients
Smets et al. [47]	$n = 250$, male and female, mean age 64 yrs	Various	During radiotherapy	(a) Fatigue, (b) sleep	(a) Multidimensional Fatigue Inventory, (b) Groningen Sleep Quality Scale	Both quality of sleep and hours of sleep were significantly associated with fatigue

(28%). The authors noted that patients who reported being overly fatigued were 2.5 times more likely to have insomnia than others. Of the 300 patients reporting insomnia, 76% noted waking several times a night, 44% had difficulty falling asleep, 35% reported waking for a long time, and 33% woke up too early. The duration of insomnia was 6 months or longer in 75% of cases.

Many studies have indicated strong positive correlations between self-reported changes in sleep and the fatigue experienced by patients with cancer [5,19,37,40,41,48]. Correlations between fatigue and sleep problems are still evident in some patients with cancer more than a year after completion of their treatment [11,19]. Servaes and colleagues [46] examined the differences in a range of quality-of-life measures in disease-free breast cancer survivors at a mean of 29 months after completion of treatment. Women who were severely fatigued experienced significantly greater sleep disturbance than women with less fatigue.

Not all published data support a correlation between sleep disorders and CRF. In a study of the diurnal pattern of off-treatment fatigue in breast cancer survivors, survivors had significantly greater levels of fatigue than either age-matched women with benign breast problems or healthy controls [33]. Surprisingly, however, there were no significant group or time effects and no significant group–time interaction for fatigue and sleep duration. In addition, no difference in the diurnal pattern of fatigue among the three groups was found. Similarly, Savard and colleagues [44] found no relationship between insomnia and fatigue in men treated with radical prostatectomy for prostate cancer. The authors noted the uniqueness of this negative finding, and suggested that this lack of association between fatigue and insomnia may be a result of the high correlation between fatigue and other risk factors determined in this study (i.e., depression, anxiety, and pain).

Objective Measurement of Sleep Continuity

A number of studies have also found correlations between an objective measure of sleep continuity—i.e., actigraphy—and self-reported fatigue [30–32,39,42]. Actigraphy is a simple, noninvasive method of measuring levels of daytime and nighttime activity that can be used to accurately estimate the duration of both daytime and nighttime sleep. In addition, activity patterns over several consecutive days can be analyzed using autocorrelational techniques to examine sleep consistency and continuity over time [49,50]. The actigraph is a device approximately the size of a watch that is worn on the wrist and contains an accelerometer, a microprocessor, and retrievable memory. Activity counts are stored to memory, typically in 30–60-second epochs for 24-hour intervals. These data provide diurnal activity counts, nocturnal activity counts, and the means by which to infer sleep continuity parameters, for example, time in bed (sleep period), time awake after sleep onset, total sleep time, and potentially, sleep latency.

Figure 1 shows representative actigraphy data from a patient undergoing treatment for cancer. The top graph shows activity measured over a 24-hour period following the second treatment cycle. The bottom graph is a 24-hour period after the fourth treatment cycle, 8 weeks later, when the patient reported increased fatigue. Each graph is an activity histogram with the *y*-axis representing frequency of activity and the *x*-axis representing 24 hours of measurement. As can be seen, the patient was in bed for much longer following the later treatment compared with the earlier one (>9 hours versus <6 hours). While it is unknown why patients tend to increase their sleep opportunity (time in bed) in this manner, this behavioral change can be expected to be insomniogenic [51]. In addition, the substantial increase in time in bed is likely to correspond to "shallower" sleep (more stage I sleep and/or less slow-wave sleep), as

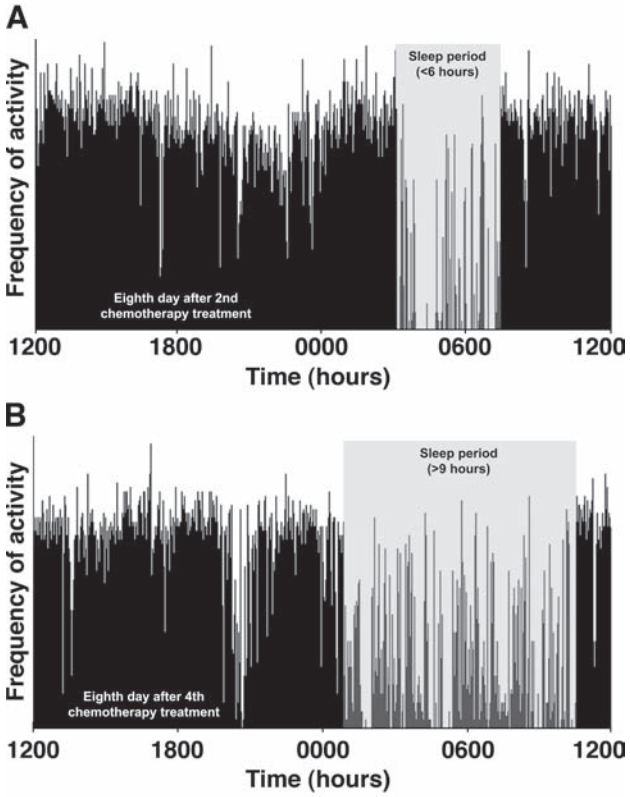

Figure 1. Activity patterns during fatigue. Twenty-four-hour activity patterns measured by actigraphy in a patient with cancer undergoing treatment, showing activity following the second treatment (top), and the activity pattern 8 weeks later after the fourth treatment, when the patient reported increased fatigue (bottom).

measured by polysomnography. This phenomenon is evident in the actigraphic data in this example, which show a 50% increase in nocturnal activity in this patient.

Several studies have used actigraphy to demonstrate the relationship between sleep continuity and fatigue. For example, Mormont and colleagues [39] found a significant inverse relationship between rest–activity patterns and fatigue in patients with metastatic colorectal cancer prior to chemotherapy. Berger and colleagues conducted studies using wrist actigraphy to monitor rest–activity patterns in patients with breast cancer who were receiving chemotherapy [30–32]. Those studies showed that patients who were less active in the day and had more restless sleep experienced significantly more intense fatigue ($p < .05$), and that the strongest association was between the number of nighttime awakenings and the degree of fatigue. The relationship between fatigue and sleep disruption was maintained up to 2 months after completion of therapy [32]. Fatigue following radiotherapy also correlates with sleep disorders. For example, a study using wrist actigraphy and the Lee Fatigue Scale explored the relationship between sleep disturbances and fatigue in 24 patients receiving radiation therapy for bone metastasis [38]. The study found that the improvement noted in morning fatigue scores compared with evening fatigue scores was significantly correlated with better sleep efficiency ($r = 0.37$) and decreased number of awakenings ($r = 0.30$).

Our group has used actigraphy to assess the association between sleep and sleep–wake patterns and fatigue in 78 patients with breast cancer at their second and fourth on-study chemotherapy cycles [42]. Severity of fatigue was assessed using two standard subjective measures on the seventh day after each treatment. Patients also wore an actigraph for 72 hours starting 6 days after each treatment. Daily patterns of sleep and activity were compared across the 3-day period by autocorrelation analyses to calculate a "consistency of sleep–wake pattern" score for each patient. Comparisons after the second cycle indicated that the two paper-and-pencil measures of fatigue correlated well with the actigraphic measure of sleep–wake pattern stability (both $p < .05$). The two subjective measures of fatigue were not significantly related to total daily sleep. They were, however, associated with increased daytime napping (both $p < .05$). Changes in fatigue from the second to the fourth on-study treatment were also significantly correlated with concurrent changes in the consistency of the sleep–wake pattern (both $p < .05$). Thus, overall, more fatigue was reported by patients with less stable sleep–wake patterns who frequently napped.

Most recently, Ancoli-Israel and colleagues [28] reported that sleep disorders and fatigue were prevalent in patients with breast cancer prior to the start of chemotherapy. However, while subjective measures of the two symptoms were significantly correlated, no significant correlation was found between subjective measures of fatigue and objective evaluation of sleep (by actigraphy).

Correlations with Daytime Symptoms of Sleep Disturbance

Correlations have also been noted between fatigue and daytime symptoms of sleep problems such as feeling drowsy, daytime sleepiness, and napping [11,27,31,36]. Åhsberg and Fürst [27] examined different aspects of perceived fatigue in patients undergoing radiotherapy and found correlations for lack of energy and sleepiness with fatigue (Fig. 2). Using a multidimensional model, Hwang and coworkers [36] showed a significant correlation between a parameter of sleep rarely reported—feeling drowsy—and CRF.

Cancer-Related Fatigue and Sleep Disorders

In general, the evidence supports a close association between CRF and sleep disorders. Several recent reviews [3,6,52–56] indicate that CRF and cancer-related sleep disorders are associated, and their prevalence and association depends on the timing of assessment (before diagnosis, before treatment, during treatment, and at various times after treatment). Following a review of the epidemiology of insomnia in patients with cancer, Savard and Morin [2] concluded that insomnia disorder added "an additional risk for experiencing intense and persistent fatigue after cancer treatment." Other investigators have suggested that CRF and sleep disturbances should be considered as a clinical

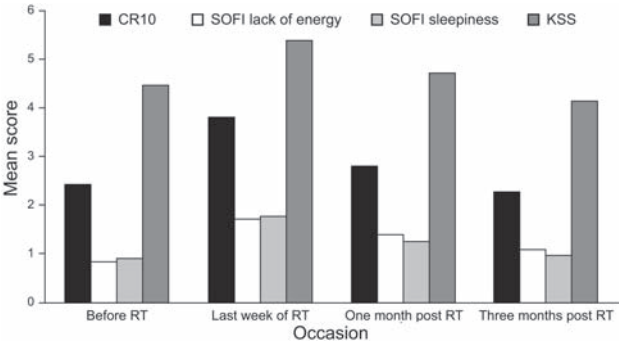

Figure 2. Perceived fatigue in patients with cancer receiving radiotherapy. Intensity of fatigue was measured using a category ratio scale (CR10); "lack of energy" was evaluated using the Swedish Occupational Fatigue Inventory (SOFI); sleepiness was assessed using the SOFI and the Karolinska Sleepiness Scale (KSS).
Abbreviation: RT, radiotherapy.
Based on data from Åhsberg E, Fürst CJ. Dimensions of fatigue during radiotherapy—an application of the Swedish Occupational Fatigue Inventory (SOFI) on cancer patients. Acta Oncol 2001;40:37–43.

syndrome [57]. Most of the work done in this area does indicate that poor sleep is a major factor in CRF. Indeed, in a recent review, O'Donnell [56] purported that although the two conditions of CRF and insomnia are distinct, evidence in the literature suggests a strong interrelationship.

Conclusions

Sleep disorders are a common and often chronic problem for both patients with cancer and cancer survivors. Until recently, such symptoms have attracted little attention. Although CRF and sleep disturbances are distinct conditions, they are closely linked in terms of prevalence, often occurring as part of a multisymptom cluster. Further investigation is warranted in order to better understand the nature of sleep disturbances, the complex relationship they have with CRF, and their association with other symptoms commonly reported by patients with cancer, such as depression, pain, and anxiety. Current understanding of the possible link between CRF and sleep disturbances suggests that interventions targeting disordered sleep and daytime sleepiness could provide promising potential treatments for CRF. Given the emerging data that suggest sleep disturbance is common in patients with cancer and that it may be both a cause of and caused by fatigue, it follows that targeted treatment of either symptom may positively affect the other.

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Disclosure of Potential Conflicts of Interest

G.R.M. has acted as a consultant for MGI Pharma and Cephalon.

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Cancer-Related Fatigue and Sleep Disorders

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