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Breast Cancer and Fatigue

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Synopsis

Fatigue is a common and disabling symptom in breast cancer patients and survivors. A rather nebulous concept, fatigue overlaps with sleepiness and depressed mood. In this chapter, we cover methods for assessing fatigue; describe the occurrence of fatigue before, during and after initial treatment; present possible underlying mechanisms of fatigue; and, enumerate approaches to its treatment.

Keywords

Fatigue; breast cancer; sleep; mood; fatigue assessment

Fatigue is a common and frequently disabling symptom in cancer patients and cancer survivors.[1,2] Fatigue is also often a presenting symptom at cancer diagnosis.[3-5] Cancer fatigue differs from other manifestations of fatigue in that it is generally not alleviated by sleep or rest, is typically of greater duration and severity, is often associated with high levels of distress, and is disproportionate to the level of exertion.[6-11] Cancer-related fatigue often co-occurs with other troublesome symptoms such as pain, sleep disturbance, and depression.[12-14] Thus, the impact of cancer fatigue on health-related quality of life can be substantial, reducing the patient's engagement in work, personal and social activity.[2,15-17] Some studies have reported that fatigue in cancer patients has a greater negative impact on quality of life than all other symptoms, including nausea, pain and depression.[2,18] Treatment of cancer-related fatigue has been recently identified as a priority by the National Institutes of Health.[19]

Specific to breast cancer, fatigue is reported by a substantial majority of patients during their initial treatment (surgery, radiation, and/or chemotherapy). In addition, although estimates vary widely, approximately 33% of individuals with breast cancer report persistent fatigue up to ten years into survivorship.[6,20,21]

Fatigue is a rather nebulous symptom; hence, numerous definitions of this construct are found in the literature.[6,22] Complicating this situation is the fact that breast cancer patients and survivors commonly complain of both sleepiness and fatigue.[23] These terms are often used interchangeably, and both have been linked to decrements in various aspects of health-related

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quality of life and with the restriction of daytime activities. Nonetheless, there are important differences in these concepts.

Sleepiness involves a propensity to fall asleep, whether at bedtime or during the day at times when wakefulness is desired (e.g., daytime sleepiness). Sleepiness is thought to be the overt manifestation of an underlying physiological need for sleep and can be subjectively measured (e.g. with the Epworth Sleepiness Scale) or objectively quantified using daytime tests (e.g., the Maintenance of Wakefulness Test or the Multiple Sleep Latency Test). By comparison, fatigue is a poorly understood but highly prevalent complaint in patients with breast and other cancers. Fatigue includes physical and psychological features, as well as cultural and social factors. Thus, the conceptual borders of fatigue are imprecisely defined, overlapping with related concepts such as lack of energy or vigor, lethargy, feeling tired, decreased strength, and trouble concentrating.[24] One definition of cancer-related fatigue is: '...a subjective state of overwhelming and sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest.'[25] Another accepted definition is 'a persistent and subjective sense of tiredness that interferes with usual functioning'.[3,22,26] Both include the subjective phenomenological experience of fatigue as well as its observable impact on usual levels of functioning. As is the case with pain, fatigue is a complaint that is almost always evaluated using self-report scales.[6,24] Therefore, by default, fatigue is ultimately defined by the instruments employed for its measurement. In the next section we provide an overview of several types of scales for assessing fatigue.

Assessment of Fatigue

There are numerous self-report instruments used to assess fatigue in general as well as cancer-related fatigue (Table 1). In the past, fatigue was commonly assessed as one component of a symptom checklist, or a quality of life or mood scale (i.e., as an item or subscale of items on an instrument having the primary purpose of measuring symptoms, mood or quality life).[6,27] Thus, the approach to measurement of this construct has historically been unidimensional. Examples of scales that use this unidimensional approach to the measurement of fatigue are the Symptom Distress Scale,[28] Rotterdam Symptom Checklist,[29] Profile of Mood States (POMS) Fatigue subscale[30] and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Vitality (Energy/Fatigue) subscale.[31]

More recently, research into the multidimensional nature of general (not cancer-specific) fatigue has resulted in the development of instruments which often yield an overall total fatigue score as well as subscale scores for various dimensions of fatigue (e.g., physical, mental, emotional). Vigor, a construct thought to be related to, but not necessarily the opposite of fatigue, has also been assessed on both mood measures (e.g., Profile of Mood States Vigor subscale)[30] and multidimensional fatigue scales (e.g., Multidimensional Fatigue Symptom Inventory Vigor subscale).[32]

Fatigue assessment has also been expanded through the development of instruments either designed for, or specifically normed, on particular patient groups. For example, the Fatigue Symptom Inventory (FSI)[33] and the Multidimensional Fatigue Symptom Inventory (MFSI),[32] while appropriate for assessing fatigue in non-patient populations, were also originally normed on breast cancer patients.[32] The 83-item MFSI yields a total fatigue score as well as subscale scores for general, mental, emotional, and physical fatigue, and vigor. A 30-item short form of this instrument (MFSI-SF) has also shown excellent psychometric properties and includes the same subscales as the full-version of the MFSI.[34] The Functional Assessment of Cancer Therapy—Fatigue scale was designed to assess fatigue specifically in cancer patients.[17]

One drawback to all these questionnaires is that they only capture information from one time point. Ecological momentary assessment—data collected several times a day, over several days —confirms that the level of fatigue reported varies throughout the day.[35] Newer approaches to the measurement of fatigue may be needed.

A recent focus of research into fatigue has been on the development of a clinical syndrome (symptom cluster) approach to defining and assessing cancer-related fatigue.[25,26] For this purpose, a structured clinical interview has been devised (the Diagnostic Interview Guide for Cancer-Related Fatigue[25]), using the proposed ICD-10 Criteria for Cancer-Related Fatigue (see Table 2)[27]. This approach holds promise for improving the sensitivity and specificity of the assessment of cancer-related fatigue. For example, Andrykowski *et al.* (2005) evaluated a group of 288 women who were receiving adjuvant treatment for early-stage (Stage 0 to Stage II) breast cancer.[26] The authors observed that 10% of these patients met all criteria for cancer-related fatigue immediately after surgery, increasing to 26% after completion of the initial course of adjuvant treatment.[26] They reported that the etiology of cancer-related fatigue is multifactorial and their results supported the use of this case definition approach to define cancer-related fatigue.[26] However, to date this approach has only been used in limited settings.[6]

Fatigue Prior to Treatment

Several studies have now shown that women with breast cancer complain of fatigue even before the start of treatment.[5,36] Ancoli-Israel *et al.*[5] found that women diagnosed with breast cancer had increased fatigue, disturbed sleep, and increased daily dysfunction before the start of chemotherapy, and that those patients with fatigue, poor sleep, and depression pre-chemotherapy experienced more fatigue and poor quality of life (QOL) during chemotherapy than women with fewer pre-treatment symptoms.[37] These data suggest that fatigue is not just a result of radiation or chemotherapy, but rather is multifactorial.

Fatigue During Treatment

The most widespread and distressing symptom of cancer and its initial adjuvant treatment (chemotherapy, radiotherapy, and/or biological response modifier therapy) is fatigue.[1,16,38] Estimates of cancer-related fatigue during initial treatment range from approximately 60% to 90%,[2,39-42] with the highest reported frequency in patients undergoing chemotherapy (80% to 96%)[40,43] compared with those treated with radiation (60% to 93%).[16,39,44] For example, in the study by Andrykowski *et al.*, patients undergoing adjuvant chemotherapy were more than two-times as likely to report cancer-related fatigue during treatment compared with patients who were receiving adjuvant radiation therapy.[26]

Bower has suggested that a key mechanism in the fatigue experienced during adjuvant radiation treatment may be the activation of proinflammatory cytokines.[6] In her longitudinal study of 49 early-stage breast or prostate cancer patients receiving adjuvant radiotherapy, a positive relationship was found between cumulative cytokine exposure and fatigue.[45] While prior studies have been inconsistent on the role of inflammation in radiation treatment-related fatigue, the Bower study, which involved five assessment points prior to and during radiation treatment, provides some of the strongest evidence to date of the possible mechanistic role of inflammation vis-à-vis fatigue in cancer patients.

Fatigue During Survivorship

While most common during the treatment phase, fatigue also affects a substantial subpopulation of individuals with breast cancer for months and even years into survivorship.[3,20] Approximately 30% of breast cancer survivors experience moderate to severe fatigue after

completion of initial treatment,[3,20,46] and fatigue in these survivors has been shown to endure for up to ten years post-diagnosis.[3]

The functioning/quality of life impact of this enduring fatigue is significant and has been associated with decrements in physical activity.[3,47,48] Thus, while increased physical activity has been shown to alleviate symptoms of fatigue, greater fatigue is nonetheless associated with lower levels of physical activity. This suggests a possible self-perpetuating cycle of increasing fatigue leading to decreasing physical activity leading to even greater fatigue, and so on.

Underlying Mechanisms of Fatigue

The etiology of fatigue, whether experienced during initial treatment or during survivorship, is far from being definitively characterized. The underlying mechanisms likely vary from patient to patient and the candidate causes surely co-vary considerably. This variability adds to the complexity of understanding this rather vague, but common and potentially disabling complaint. In addition to the usual suspects, such as dysphoric mood, disrupted sleep, anemia, recent studies have suggested some possible novel mechanisms (e.g., inflammation, immune system dysregulation). Thus, fatigue is multiply determined, with a likely mixture of both biological and psychological underpinnings.[3] For example, evidence implicates anemia, ATP, links between the HPA axis, cytokines and circadian rhythms, and vagal afferents.[8,9,11,49-52]

Because most previous studies of cancer fatigue involved cross-sectional research designs, the direction of causality between these candidate risk factors and the experience of cancer-related fatigue cannot be determined with certainty. Nonetheless, the literature suggests important possible links between fatigue and a wide range of potential underlying mechanisms.

Depression

Fatigue is a common component of, and one of several key diagnostic criteria for, major depressive disorder, dysthymia, and other clinical mood disorders.[53] There is a substantial body of research that examines the interplay of fatigue and mood in patients with chronic medical illnesses. One might assume that fatigue and mood would worsen in tandem as disease severity progresses. However, findings are conflicting, even when disease severity is taken into account.[24,54]

It is difficult to determine the direction of causation between mood and fatigue, particularly in patients dealing with chronic medical conditions, such as breast cancer. Nonetheless, depression or general psychological distress has been associated with cancer-related fatigue in many studies.[20,26,55-58] For example, in a pre-/post-treatment study of 288 women undergoing treatment for early-stage breast cancer, a significant association was observed between cancer-related fatigue and major depressive disorder. [26] Nearly one in five of the patients reporting cancer-related fatigue post-treatment also reported symptoms consistent with a major depressive disorder diagnosis. By comparison, only approximately one in twenty patients who did not report cancer-related fatigue experienced major depression.[26] In addition, a history of major depressive disorder was linked in this study with cancer-related fatigue after initial treatment. [26]

In a recent cross-sectional analysis of 2613 women with a history of early-stage (Stages I (≥ 1 cm.), II, or IIIA) breast cancer, we reported that cancer-specific factors (i.e., cancer stage at diagnosis, type of initial treatment received, ongoing use of Tamoxifen, and number of months since breast cancer diagnosis) were unimportant in understanding risk for fatigue. [59] Rather, worse physical health, less exercise, and more depressive symptoms were the risk factors most

strongly linked with fatigue in these women who had completed initial treatment within the previous four years.[59]

Thus, the evidence linking mood disturbance and cancer-related fatigue is variable. It is difficult to tease out the effects of the medical illness versus those of mood symptoms on fatigue in the chronically medically ill.[24,54] Nonetheless, the fact that four out of five breast cancer patients with cancer-related fatigue do not experience a concurrent major depressive disorder suggests that mood and fatigue in cancer are overlapping but far from fully redundant concepts.[26]

Personality Characteristics

In their study, Andrykowski *et al.* observed that a tendency to catastrophize over fatigue, predicted greater cancer-related fatigue post-treatment.[26] They also observed weaker evidence for a link between symptom-focused coping (compared with a tendency to accommodate to the cancer) accompanied by a sense of helplessness and an elevated risk for developing cancer-related fatigue.[26] Links between lower levels of optimism and greater levels of fatigue have also been previously reported.[59] Thus, various aspects of personality have been associated with fatigue in cancer patients/survivors.

Sleep

Sleep disturbances, particularly difficulty falling or staying asleep, are common in cancer patients, [23,60] with prevalence rates of sleep difficulty in newly diagnosed breast cancer patients of between 30−50%. [61] Insomnia complaints have been reported to be chronic (> 6 months) for a majority of cancer patients, [62] yet these sleep problems are often neglected.[63] Specific sleep disorders such as sleep disordered breathing and restless legs syndrome are also common in cancer patients (for full recent reviews see [64,65]). Although there are not an abundance of studies addressing relationships between sleep disruption and fatigue in breast cancer, results suggest that relationships between these two constructs are stronger before and during treatment than after treatment. Part of the difficulty in determining the relationship between sleep and fatigue is the fact that both can be a result of multiple factors such as mood, pain, inflammation, hot flashes, other medical illnesses, medications, etc. This makes casual relationships difficult to distinguish.

The rates of sleep disturbances (in 30% to 75%) of newly diagnosed or recently treated cancer patients,[60,64] are about twice as high as those in the general population.[66] Objective sleep estimates suggest that patients with breast cancer already complain of sleep problems and of fatigue before the start of chemotherapy,[67] sleeping for only 77% of the night. Disturbed sleep pre-treatment correlates with fatigue, depressive symptoms and functional outcome.[67] Although the causal relationship between sleep and these factors cannot be determined from these data, pre-treatment sleep disturbance predicted more fatigue, more depressive symptoms, and worse QOL throughout the chemotherapy.[68,69]

As shown in Table 3, some inflammatory markers are abnormally elevated or reduced during chemotherapy and the elevated levels are at times associated with fatigue. Elevated inflammatory markers are also associated with more disrupted sleep during chemotherapy.[70] Savard *et al.*,[71] when examining the relationship between insomnia and the immune system in breast cancer survivors, found that after successful treatment of the insomnia with behavioral therapies, participants also had improved levels of some inflammatory markers.

Hot flashes, reported by 40−70% of breast cancer survivors, have been associated with more disturbed sleep - increased wake and decreased stage 2 sleep, with more stage shifts to lighter sleep around the time of hot flashes. [72] In other studies of breast cancer survivors, self-report

of insomnia was not a significant predictor of fatigue in those up to four years post-diagnosis.[59] Similarly, in a separate analysis, using insomnia as the outcome variable, fatigue was not significantly associated with insomnia.[73]

We recently reported a four-year repeated measures analysis of risk factors for self-reported insomnia [59,73] in this same group of breast cancer survivors. Using three different methods of statistical analysis (multinomial logistic regression, mixed modeling, and a generalized estimating equation), we were still unable to observe a significant association between insomnia and fatigue in survivors.[74]

Treatment studies however, as described below, have shown that treating insomnia in breast cancer patients often results in improvement in fatigue as well. Additional studies are needed to help understand the relationship between poor sleep and fatigue.

Anemia

Low white blood cell count and low levels of hemoglobin are commonly thought to be causative factors in fatigue. While likely playing a role, they do not account for all of the variance in cancer-related fatigue,[40,75] and results regarding low concentration of hemoglobin have been mixed. [76-78]

Inflammation

A relatively new area of investigation involves the role of inflammation as a causative factor in breast cancer fatigue. A recent quantitative review of the literature on inflammation and fatigue in cancer patients by Schubert and colleagues[76] examined eighteen studies of moderately high methodological quality which involved 1037 patients (averaging 58 participants per study). A significant positive association was observed between cancer-related fatigue and circulating levels of various markers of inflammation. When examining individual inflammatory markers, fatigue was observed to be positively associated with IL-6, IL-1ra, and neopterin, but not with IL-1β or TNF-α.[76]

As shown in Table 3, of the eighteen studies mentioned above, eight were conducted on breast cancer patients or survivors. Of these, three found no significant association between inflammatory markers and fatigue.[77-79] The other five studies did observe significant inflammation—fatigue links, but findings regarding the specific inflammatory markers varied. Thus, while findings remain inconsistent, several studies suggest a role for underlying inflammation in breast cancer-related fatigue.

Treatment of Fatigue in Breast Cancer Patients and Survivors

Clinical trials of treatment regimens for the alleviation and management of cancer-related fatigue have been limited compared with those focused on the alleviation of pain and suffering.[3] Treatment of cancer-related fatigue can be complex because of the links observed between fatigue and various physical and psychological variables. Thus, a multidisciplinary approach to treatment and management of cancer-related fatigue is likely to be necessary for many cancer patients and survivors[80] and treatments must be individualized based on underlying pathology.[81]

To recap, in two large studies four and five years post-diagnosis or treatment of breast cancer, survivors fatigue was most strongly linked with depressive symptoms, pain and sleep disturbance[20] and with worse physical health, less physical activity, and depressive symptoms.[59] Depressed mood, cardiovascular problems, and cancer treatment modality were also linked with ongoing fatigue.[20] Thus, several possible underlying factors have been implicated in cancer fatigue, many of which respond well to conventional treatments.

Pharmacotherapy

Clinical trials of pharmacotherapeutic agents for cancer-related fatigue have only emerged over the past 20 to 25 years, likely because fatigue has commonly been seen as a rather ubiquitous or inevitable sequela of cancers and their treatment.[11] Since then, various pharmacotherapeutic agents have been used in the treatment of cancer-related fatigue. These include psychostimulants, antidepressants, erythropoiesis-stimulating agents, and cytokine antagonists, among others.

Psychostimulants such as methylphenidate (Ritalin) have been used in various settings with the goal of improving energy levels in patients having illness-related fatigue. While methylphenidate improved cancer-related fatigue in open-label studies,[82,83] there was not a significant therapeutic effect in a placebo-controlled trial.[11,84] However, dexmethylphenidate (Focalin) did show significant effects on fatigue in a placebo-controlled trial in non-anemic cancer patients.[11,85]

Modafinil (Provigil; Attenance), an agent which promotes wakefulness, has only recently been studied for its effects on cancer-related fatigue but has shown promising results in a couple of studies, including one with breast cancer survivors.[11,86,87]

Antidepressants have been shown to reduce fatigue as well as other symptoms of depression in various patient groups. The atypical antidepressant Buproprion (Wellbutrin-SR) has been shown to improve cancer-related fatigue in two open-label case series studies, but placebo-controlled trials are needed.[11,88,89] At least two recent studies in breast cancer and other patients undergoing initial treatment for their cancer have not been as promising. While the authors were able to demonstrate an effect of the selective serotonin reuptake inhibitor (SSRI) Paroxetine (Paxil) on other depressive symptoms, no significant effect was observed in reported levels of fatigue.[90,91]

Erythropoiesis-stimulating agents (ESAs; e.g., Epoetin alfa—Epogen, Procrit) have been used to increase hemoglobin concentration in cancer patients with a positive effect on fatigue in diverse populations of cancer patients, including breast cancer.[11,92] However, not all breast cancer patients experience anemia during initial treatment, and there is some evidence that use of erythropoietin-α may be linked with worse outcomes (disease progression, thromboembolic complications).[93]

Because of the growing evidence for links between inflammation and fatigue (see Table 3), a potentially promising area of clinical research is on the use of cytokine antagonists for the reduction of fatigue.[6] Monk *et al.* observed in advanced cancer patients that the use of Etanercept (Enbrel), which works by reducing the effects of TNF, safely and effectively reduced their reported levels of fatigue.[94]

Physical Activity

Exercise is likely the most evaluated treatment for cancer-related fatigue and there is strong evidence for its use, primarily from studies of cancer patients during initial treatment.[95] While somewhat counterintuitive, increasing physical activity has been associated with significant improvements in fatigue in many studies. For example, Schneider *et al.* recently observed that individualized, prescribed physical activity of moderate intensity resulted in significant reductions in cancer-related fatigue during initial treatment and even into survivorship.[96]

Cognitive-Behavioral Therapies

As reviewed by Fiorentino and Ancoli-Israel,[97] Cognitive Behavioral Therapy for Insomnia (CBT-I) has been shown to be both efficacious and suitable in the breast cancer population.

CBT-I uses a tailored approach to treating insomnia, addressing the specific needs of breast cancer patients by targeting fatigue. In addition, as reviewed by Theobald, treating insomnia in cancer patients with a combination of pharmacologic and nonpharmacologic therapy may have a positive impact not only on the insomnia itself, but also on related symptoms, including pain, fatigue, and psychological distress.[98]

Summary and Future Directions

While research into the etiology, course, and treatment of cancer-related fatigue is relatively new, much progress has been made in recent years; however, considerable opportunities remain. While some well-powered studies have examined risk factors for fatigue in breast cancer patients and survivors, most studies examining underlying mechanisms have involved small to very small sample sizes. While a few studies employing repeated-assessments have been conducted, most have been cross-sectional in design. Thus, more longitudinal studies that involve assessment of cancer patients pre-/post-completion of initial treatment and into survivorship are needed. While multiple factors have been observed to be linked with cancer-related fatigue, it has yet to be determined which factors predispose, precipitate or exacerbate/maintain the patients' experience of fatigue. For example, longitudinal studies examining and comparing the effects of chemotherapy- and radiation-induced inflammation on functioning during survivorship are warranted. Also, additional studies employing statistical analytic techniques that can evaluate hypotheses about causal pathways are needed. These will require multiple assessments of established or promising biomarkers of fatigue. Such studies should also assess fatigue using multidimensional scales normed on and/or tailored to breast cancer patients.

The use of a case-definition approach, using a structured clinical interview, has much promise for improving the assessment of cancer-related fatigue. This improvement should be very much in line with the greater sensitivity and specificity of diagnosis of mood disorders via structured clinical interview compared with the use of pencil-and-paper scales. In addition, further evaluation is needed of the scientific value of the cancer-related fatigue criteria, including the comparison of functioning in patients who meet versus do not meet the case definition criteria.

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Table 1

Frequently-used Self-Report Instruments for Assessing Cancer Fatigue.

Self-report instrument	Items	Measurement focus/Scoring	Time frame
Fatigue Severity Scale (FSS) [99]	9	Series of statements about life domains that affect, or bring on, fatigue. Rated using a 7-point response format (1='Strongly Disagree; 7='Strongly Agree'). Yields a total fatigue severity score.	During the past two weeks
Functional Assessment of Cancer Therapy—Fatigue Scale (FACT-F) [17]	41 (13 of which assess fatigue)	Addresses concerns or problems associated with cancer-related fatigue. Rated on a 5-point scale indicating how true each statement was for the respondent during the last week (0=not at all; 4=very much so). Yields a total fatigue score.	During the past week
Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36) [31,100]	4	The SF-36 is designed to assess physical and mental health-related disability. Includes four items comprising the Vitality (energy/ fatigue) subscale. Scored 0 (more fatigue)-100 (more energy). Yields a total fatigue score.	During the past four weeks
Multidimensional Fatigue Symptom Inventory (MFSI) [32]	83	A series of statements designed to assess the principal manifestations of fatigue. Used in various patient and non-patient groups; norms for women with breast cancer. Rated on a 5-point scale indicating how true each statement was for the respondent (0 = not at all; 4 = extremely). Yields general, physical, emotional, and mental fatigue and vigor subscales and a total fatigue score.	During the past week
Multidimensional Fatigue Symptom Inventory Short Form (MFSI-sf) [34]	30		
Piper Fatigue Scale [101]	27	22 fatigue-related items scored using 11-point Likert scales, plus 5 open-ended questions. Yields behavioral-severity, affective meaning, sensory, and cognitive-mood subscales and a total fatigue score.	Current
Profile of Mood States (POMS) Fatigue-Inertia Subscale; [30]	65 (7 fatigue items)	Adjective checklist assessing various psychological parameters including fatigue-inertia. Rated on a 5-point scale indicating how true each statement was for the respondent (0 = not at all; 4 = extremely). Yields a total fatigue score.	During the past week
POMS Short Form (POMS-sf) Fatigue-Inertia Subscale [30]	30 items (5 fatigue items)		

Table 2

Diagnostic Interview Guide for Cancer-Related Fatigue using the proposed ICD-10 Criteria for Cancer-Related Fatigue[25,27]

1. Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, and at least one of the symptoms is significant fatigue (item 1).
   a. Significant fatigue, diminished energy, or increased need to rest disproportionate to any recent change in activity level;
   b. Complaints of generalized weakness or limb heaviness;
   c. Diminished concentration or attention;
   d. Decreased motivation or interest to engage in usual activities;
   e. Insomnia or hypersomnia;
   f. Experience of sleep as unrefreshing or nonrestorative;
   g. Perceived need to struggle to overcome inactivity;
   h. Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued;
   i. Difficulty completing daily tasks attributed to feeling fatigued;
   j. Perceived problems with short-term memory;
   k. Post-exertional malaise lasting several hours.
2. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
3. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.
4. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

Table 3

Inflammatory Markers and Fatigue

Inflammatory Marker	Study Reference	Relationship with fatigue
IL-1ra	Bower et al. [47]	+
	Collado-Hidalgo et al. [102]	+
IL1β	Savard et al. [71]	+
	Bower et al. [47]	Not significant
IL-6	Wratten et al. [103]	+
	Mills et al. [75]	Not significant
	Collado-Hidalgo et al. [102]	Not significant
sIL-6r	Collado-Hidalgo et al. [102]	+
sTNF-RII	Bower et al. [47]	+
	Collado-Hidalgo et al. [102]	Not significant
neopterin	Bower et al. [47]	+
ICAM-1	Wratten et al. [103]	+
	Mills et al. [75]	Not significant
VEGF	Mills et al. [75]	+
INF-gamma	Savard et al. [71]	+