Fatigue

8

Karen M. Mustian, Po-Ju Lin, Kah Poh Loh, and Ian R. Kleckner

8.1 Definition of Cancer-Related Fatigue

Cancer-related fatigue (CRF) is a distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [1, 2]. CRF is different from common physical or mental tiredness in that CRF is not relieved by sleep or rest, whereas general fatigue (i.e., physical or mental tiredness) is a transient inability to maintain optimal performance that is relieved by rest [3]. CRF negatively interferes with patients' ability to complete their cancer treatments and their ability to complete activities of daily living, and it reduces quality of life [3].

K. M. Mustian (✉)
University of Rochester Medical Center, School of Medicine and Dentistry, Rochester, NY, USA
e-mail: Karen_Mustian@URMC.Rochester.edu

P.-J. Lin
University of Rochester, Surgery-Cancer Control, University of Rochester Medical Center, Rochester, NY, USA

K. P. Loh
James Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, USA

I. R. Kleckner
Department of Surgery, Cancer Control (SMD), University of Rochester Medical Center, Rochester, NY, USA

8.2 Prevalence of Cancer-Related Fatigue

CRF can occur as a consequence of the cancer itself [4] or cancer treatment. It is the most commonly reported [5] and also the most distressing [6] side effect of cancer treatments including chemotherapy [7–9], radiation therapy [4, 10], or selected biologic modifiers [11]. As many as 40% of patients with cancer report CRF at the initial time of diagnosis [4], and the majority of patients experience CRF during the course of their treatment. Up to 90% [4, 10] of patients with a variety of cancer subtypes undergoing radiation therapy and up to 80% [7, 8] of those receiving chemotherapy experience CRF. While CRF will resolve for some survivors after completion of treatments, there are still approximately 30–40% of cancer survivors reported to have persistent CRF up to 10 years posttreatment [1, 3, 12–22]. In survivors of Hodgkin lymphoma, CRF has been shown to have a major impact on treatment outcomes and social reintegration [23].

8.3 Measurement of Cancer-Related Fatigue

Self-report assessment tools, also referred to as patient-reported outcome tools, are the most commonly used, reliable, and valid methods for

M. Feuerstein, L. Nekhlyudov (eds.), *Handbook of Cancer Survivorship*,
https://doi.org/10.1007/978-3-319-77432-9_8

both clinical and research measurement of CRF. There are many patient-reported instruments that can quantify CRF. A systematic review of 1453 published studies evaluating CRF instruments in patients with cancer and survivors [24] identified 37 studies and 40 instruments. The instruments were classified as three unidimensional and 37 multidimensional. These instruments vary by CRF dimensions, number of items, rating scales, types of cancer population studied, and psychometric properties. The validity and reliability were evaluated by internal consistency, test-retest reliability, and convergent validity. Of these 40 instruments, five instruments including:

1. Brief Fatigue Inventory (BFI) [25]
2. Cancer Fatigue Scale (CFS) [26]
3. Chinese CFS (C-CFS)
4. Functional Assessment of Cancer Therapy-Fatigue (FACT-F) [27], and
5. Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) [28]

have been optimally tested for validity and reliability with an internal consistency of 0.9 by Cronbach α coefficient and a concurrent validity ≥0.45 by Pearson correlation [24]. The type and the stage of cancer may affect CRF. Most of the CRF instruments were used in mixed cancer populations, and only a number of them used a homogenous cancer patient population, including the BFI [25], FACT-F [27], Fatigue Functional Impact Scale [29], MFSI-SF [28], Piper Fatigue Scale [30], Visual Analogue Scale (VAS) [31], and Wu Cancer Fatigue Scale [32].

Although the measurement of CRF is not universally standardized, some instruments are more commonly used than others, as listed in Table 8.1. The authors of a systematic review review suggest use of a simple unidimensional measure that includes a rating of severity (such as the FACT-F and VAS) as an initial step for identifying the presence of CRF among survivors. If CRF is present, a multidimensional instrument can be considered to further identify the most problematic domain(s) of CRF. Oncologists and clinicians then can prescribe the optimal treatment specifically targeting the problematic domains for patients at early stages of cancer and survivors who have completed primary treatments but are still receiving hormone therapies or biologics. The authors of the systematic review recommended using BFI to evaluate CRF in patients with advanced cancer undergoing palliative treatment given the short length of the questionnaire (fewer than 10 items) and its optimal psychometric properties [24]. In addition, BFI is sensitive when measuring change of CRF over time. The three items related to fatigue included in the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 [33] have also been used among patients with advanced cancer [24] and validated with good test-retest reliability [34].

8.4 Possible Mechanisms Associated with Cancer-Related Fatigue

A number of mechanisms associated with the development of CRF have been proposed in recent decades. Some of these include (1) anemia, (2) circadian rhythm disruption, (3) stress and cytokine dysregulation, (4) psychological distress, (5) pain and neuroimmunologic changes, (6) cardiovascular and physical dysfunction, and (7) energy, nutritional deficits, and imbalance [42–44]. Of these potential mechanisms, cytokine dysregulation has been the most studied to date. Research has shown that cancer may activate pro-inflammatory cytokines, such as interleukin-6 (IL-6), and markers of inflammation, such as C-reactive protein (CRP), resulting in the development of CRF prior to cancer treatment initiation [45–50]. In addition, cancer treatments continue to prolong activation of pro-inflammatory cytokines during treatment [45, 51] and after treatment completion [43].

The use of radiation therapy and chemotherapy is also associated with increased inflammation (e.g., CRP, IL-1 receptor antagonist, IL-6). Patients with breast and prostate cancer have been shown to have elevated levels of CRP and IL-1 receptor antagonist [52]. In another sample of 53 patients with breast cancer receiving chemotherapy, serum IL-6 was found to be

Table 8.1 Commonly used instruments for measurement of cancer-related fatigue

Instruments	Dimensions	Number of items	Scales	Evaluation period	Description
Unidimensional					
EORTC QLQ C30 [33]	Severity of fatigue	3	4-point (1–4) Likert	Past week	Three items are: "Did you need to rest?" "Have you felt weak?" and "Were you tired?"
FACT-F [27]	Severity of fatigue	13	5-point (0–4) Likert	Past week	A 13-item stand-alone statement as a part of FACT is used to assess the severity of fatigue
POMS-F [35]	Severity of fatigue	7	5-point (0–4) Likert	Past week and right now	A seven-item fatigue subscale of POMS assesses the severity of recent fatigue
VAS [36]	Severity of fatigue	1	Analogue	Current	Patients mark fatigue severity between a linear scale with end points between "I am not tired at all" and "I am totally exhausted"
Multidimensional					
BFI [25]	Severity and interference of fatigue	9	11-point (0–10) Likert	Past 24 h	Three items assess the severity of fatigue "now," "usually," and at its "worst." Six items assess the interference of fatigue on daily function, including general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life
CFS [26]	Physical, affective, and cognitive fatigue	15	5-point (1–5) Likert	Current	Seven items assess physical fatigue, and four items assess affective and cognitive fatigue. Total score is the sum of the three subscales. CFS is easy and short and can be completed by patients with advanced cancer
CFQ [37]	Physical and mental fatigue	14	4-point (0–3) Likert	Current	Eight items assess physical symptoms, and the remaining six items assess mental fatigue symptoms. CFQ is a brief, easy to administer instrument
FSI [38]	Intensity, duration, and interference of fatigue	13	11-point (0–10) Likert	Past week, current	Four items assess the severity of fatigue at its "most," "least," and "average" during the past week and "right now." Seven items assess the interference of fatigue on daily function, including general activity, ability to perform daily-living activities, normal work, ability to concentrate, relations with other people, enjoyment of life, and mood. Two items assess the duration and intensity of fatigue
MFI-20 [39]	Cognitive, physical, and emotional fatigue, reduced activity, reduced motivation	20	5-point (1–5) Likert	Current	Four items are presented for each dimension, two of which indicate fatigue, and the remaining two are contradictory of fatigue
MFSI-SF [40]	General, physical, mental, and emotional fatigue, vigor	30	5-point (0–4) Likert	Past week	Six items are included in each dimension. Total MFSI score is calculated as (general + physical + mental + emotional) – vigor
Piper Fatigue Scale [30]	Behavioral/severity of fatigue, affective meaning, sensory, cognitive/mood	22	11-point (0–10) Likert	Now or today	Six items assess behavioral/severity, five items each assess affective meaning and sensory, and six items assess cognitive/mood
SCFS-6 [41]	Physical and perceptual fatigue	6	5-point (1–5) Likert	Past 2–3 days	SCFS-6 was developed from the original SCFS with 28 items. Patients rate six items that describe feelings associated with fatigue from 1 = "not at all" to 5 = "extremely"

EORTC QLQ C30 European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, *FACT-F* Functional Assessment of Cancer Therapy-Fatigue subscale, *POMS-F* Profile of Mood Sates-Fatigue subscale, *VAS* Visual Analogue Scale, *BFI* Brief Fatigue Inventory, *CFS* Cancer Fatigue Scale, *CFQ* Chalder Fatigue Scale, *FSI* Fatigue Symptom Inventory, *MFI-20* Multidimensional Fatigue Inventory-20 items, *MFSI-SF* Multidimensional Fatigue Symptom Inventory-Short Form, *SCFS-6* Schwartz Cancer Fatigue Scale-6

increased after treatment [53]. These inflammatory markers are positively associated with increased self-reported CRF [47, 50, 53–62]. Clevenger et al. [47] showed that in 136 women with ovarian cancer, higher levels of plasma IL-6 was associated with greater CRF prior to surgery. Pertl et al. [50] also reported a positive association of plasma CRP levels and self-reported CRF in 61 patients with breast cancer prior to initiation of chemotherapy. In 103 breast cancer survivors, elevated plasma soluble tumor necrosis factor receptor type II (sTNFRII), which is a downstream marker of TNF activity, was associated with persistence of CRF one month after treatment [58]. Breast cancer survivors who received chemotherapy had higher levels of CRF and sTNFRII level compared to those who did not receive chemotherapy. Other studies also reported the positive associations of CRF with CRP [56, 60, 61], IL-6 [62], and IL-1 receptor antagonist [60] in long-term cancer survivors who received any modality of treatment. In addition, cancer survivors with persistent CRF showed increased expression of genes encoding pro-inflammatory cytokines [57, 59]. However, the association of CRF and inflammation markers is not consistent. CRP and IL-1 receptor antagonist were not found in association with CRF in women newly diagnosed with breast cancer [48] or shortly after primary treatment [58]. Also, IL-6 was not correlated with CRF in breast cancer patients prior to chemotherapy [50].

The dysregulation of pro-inflammatory cytokines may influence CRF directly or indirectly. Disruption can occur via the hypothalamic-pituitary-adrenal axis (HPA axis), autonomic nervous system, and circadian rhythm modulation. The HPA axis controls the secretion of cortisol during stress. Bower et al. [63] reported that breast cancer survivors without CRF responded to stress with an increased cortisol level, while those with CRF demonstrated a blunted cortisol response to stress.

Circulating cortisol concentration also changes throughout the day based on the circadian rhythm [64]. In a healthy adult, the blood level of cortisol quickly increases after awakening and reaches a peak level 30 min after waking up. This is followed by a decline throughout the day, and the level reaches its minimum at night during sleep [64–66].

However, a disrupted circadian rhythm was observed in patients with cancer irrespective of stage or treatment. The disrupted circadian rhythm may be associated with the occurrence of CRF [64, 67, 68]. Studies have shown that patients with cancer and persistent CRF had an altered diurnal cortisol slope and elevated evening cortisol levels during adjuvant therapy [69] and after cancer treatment [70].

CRF is also associated with elevated norepinephrine and lower heart rate variability in breast cancer survivors at least two to three months post-treatment [71, 72]. However, these findings are not conclusive, and more studies are warranted to fully understand the relationship between the autonomic nervous system and CRF.

8.5 Treatment of Cancer-Related Fatigue

Many randomized clinical trials have attempted to treat CRF using interventions such as exercise, psychological therapies, mind-body approaches, pharmacological interventions, and others [43]. In a recent meta-analysis of 113 randomized clinical trials using exercise, psychological, the combination of exercise and psychological, or pharmacological interventions to treat CRF in adult cancer patients and survivors, Mustian et al. [73] demonstrated that exercise, psychological, and the combination of exercise and psychological interventions reduced CRF during and after treatment, whereas pharmacological interventions alone did not reduce CRF. We elaborate on different interventions in the following sections.

8.5.1 Exercise

Over a dozen systematic reviews and meta-analyses have been conducted to assess the effect of exercise on CRF in adult patients [74–86], children, and adolescents with cancer [87–89] during

and after cancer treatment. Overall, supervised aerobic and/or the combination of aerobic and resistance exercise with or without stretching have been found to be effective in reducing CRF, particularly in the domains of general and physical fatigue [76]. The positive impact of exercise on CRF was shown in adult patients with cancer during [75, 76, 82, 85] and after treatment [77, 78, 82, 84]. Given that multiple studies demonstrated the benefits of exercise, the American College of Sports Medicine (ACSM) recommends that patients with cancer and cancer survivors start low and increase to 150 min weekly of moderate intensity or 75 min of vigorous intensity aerobic exercise accompanied by 20–30 min of strength training across all the major muscle groups two to three times with daily stretching [90]. Despite this recommendation, an estimated 70% of cancer survivors do not meet the standard established by the ACSM physical activity guideline [91].

The appropriate exercise mode, intensity, frequency, and duration need to be carefully considered, and an individualized exercise prescription is strongly recommended when discussing exercise with cancer populations. Mustian et al. [92] suggested that exercise prescriptions for cancer patients and survivors should be individualized and tailored based on the individual's health status, disease trajectory, previous and/or current treatment, symptom burden, current fitness level, past and present exercise participation, and individual preferences to ensure that the exercise is safe and effective. This is illustrated by Tian et al. [77] who reported that supervised aerobic exercise for 50 min/session, two sessions/week for eight weeks, had a moderate effect on CRF, while the same exercise only had a small effect on CRF when it was performed using shorter sessions occurring more frequently: 20–30 min/session, three sessions/week. Clinicians should also consider barriers that cancer patients face in completing exercise and should consider the use of new technologies in improving and tracking exercise adherence [93]. In children and adolescents with cancer, the effects of exercise on CRF are not consistent and are likely due to the lack of rigorous studies [87, 88].

8.5.2 Psychosocial Therapy

Some meta-analyses have demonstrated that psychosocial therapy has small to moderate effect sizes on CRF reduction relative to a control [73, 94–96]. For example, three randomized controlled trials of psychosocial interventions in patients with breast cancer undergoing chemotherapy or radiation therapy who received a three-session individualized CRF education and support program showed improvement in CRF compared to controls [97–99]. These benefits were also seen in the posttreatment period. One of the largest trials, The Moving Beyond Cancer Trial, with 418 breast cancer patients who recently ($\leq$ 6 weeks) completed surgery, showed that a 23-min psychoeducational video, which addresses reentry challenges in physical health, emotional well-being, interpersonal relations, and life perspectives, significantly improved CRF six months after the intervention compared to the control group [100].

8.5.3 Mind-Body Approaches

In recent years, mind-body approaches such as yoga, acupuncture, and meditation have been commonly studied in adult cancer populations for management of CRF [101–116]. Some studies evaluated the effects of yoga on CRF in patients with cancer receiving chemotherapy or radiotherapy [105, 108, 109, 111, 113, 114]; others investigated the efficacy of yoga on CRF in cancer survivors after the completion of cancer treatment [101–104, 106, 107, 109–112, 115, 116]. Eight studies showed that yoga significantly reduced CRF at the end or months after the intervention has been completed compared to the control group, which was usual cancer care [101, 104, 106, 115, 116] or a health education intervention [102, 103, 114]. However, six studies did not find a group difference for the effects of the mind-body intervention on CRF [108–113]. These studies are heterogeneous in terms of the type, duration, intensity, frequency, and length of the yoga intervention. Taken together, studies that

showed benefits of yoga on CRF reduction suggest that gentle yoga performed in 60- to 120-min sessions, at low to moderate intensity, one to three times per week over a period of four to 12 weeks, may improve CRF in patients with cancer and survivors [117].

In another two studies that evaluated the effect of acupuncture on CRF in 429 patients with a variety of cancer subtypes, authors found patients who received acupuncture had significantly improved CRF compared to patients in the usual care group [118, 119]. However, when acupuncture was compared to sham acupuncture, no difference in CRF was noted [120]. While a number of systematic reviews of acupuncture and its effect on CRF have been conducted [121–125], results are inconsistent. More rigorous randomized control trials are needed.

8.5.4 Pharmacological Interventions

There have been over 14 randomized trials examining pharmacological interventions, but the evidence supporting their ability to treat CRF among cancer survivors is limited [73]. Existing studies showed mixed findings, often did not use rigorous trial designs, and included only small sample sizes [126]. Modafinil and methylphenidate were most commonly studied. In a randomized controlled trial of 631 patients with mixed cancer types undergoing chemotherapy, only those with severe CRF (score ≥ 7 on the scale of 0–10 in the BFI item 3 "What is your worst level of CRF during the past week?") benefited from modafinil [127]. In contrast, another randomized controlled trial of 208 patients with non-small cell lung cancer showed that patients who received modafinil demonstrated no improvement in CRF [128]. For methylphenidate, a meta-analysis of five studies [129] suggested possible benefits in three studies [130–132] where CRF was evaluated by Functional Assessment for Chronic Illness Therapy-Fatigue (FACIT-F) but not in the other two studies [133, 134] where CRF was measured by BFI. In addition, methylphenidate may be associated with vertigo, anxiety, anorexia, and nausea [129]. Given the limited evidence, most guidelines from professional societies recommend using pharmacologic interventions after ruling out other causes of fatigue or if behavioral interventions have failed.

8.6 Clinical Practice Guidelines for Cancer-Related Fatigue

The American Society of Clinical Oncology, National Comprehensive Cancer Network, and Pan-Canadian Clinical Practice Guidelines for clinicians and health professionals are summarized in Table 8.2. Each of these guidelines includes recommendations on screening, comprehensive and focused assessment, and treatment options.

8.6.1 Screening

All healthcare providers should routinely screen for the presence of CRF at the time of initial diagnosis and on subsequent visits, including after the completion of primary treatment. Screening should be performed and documented using a quantitative or semiquantitative, valid, and reliable tool (see Table 8.1) to assess CRF (e.g., asking patients "How would you rate your fatigue on a sale of 0–10 over the past seven days?" from 0 to 10 as 0 = no fatigue and 10 = worse fatigue or using a rating of mild, moderate, or severe).

8.6.2 Comprehensive and Focused Assessment

History and physical examination, including fatigue history (onset, pattern, duration, changes over time), disease status (progression, recurrence), medication/supplement usage and side effects, social support, and economic status should be incorporated during these visits. Laboratory evaluation, such as complete blood count with differential and comprehensive metabolic panel, should be considered depending on the presence, onset, and severity of CRF as well

Table 8.2 Current screening, assessment, and treatment clinical practice guidelines for cancer-related fatigue

	American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Adaptation [3]	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology- Cancer-Related Fatigue (version 2.2017, NCCN.org) [1]	NCCN Clinical Practice Guidelines® in Oncology-Survivorship (version 2.2017) [135]	Pan-Canadian Guideline (version 2.2015) [2]
Clinical question	What are the optimal screening, assessment, and treatment approaches in the management of adult cancer survivors who are experiencing symptoms of CRF after completion of primary treatment?	N/A	N/A	What are the optimum assessment parameters following screening and effective interventions for management of CRF in adults with cancer who are identified as experiencing symptoms of CRF or tiredness on the Edmonton Symptom Assessment System (ESAS)?
Definition of cancer-related fatigue (CRF)	Adopted NCCN definition of CRF	CRF is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.	Same as NCCN definition of CRF; however, these guidelines are focused on CRF after the completion of cancer treatment and/or inpatients who are in clinical remission.	Adopted NCCN definition of CRF
Screening	All healthcare providers should routinely screen for the presence of CRF from the point of diagnosis onward, including after completion of primary treatment. All patients should be screened for CRF as clinically indicated and at least annually. Screening should be performed and documented using a quantitative or semiquantitative assessment.	Screen every patient for the presence or absence of CRF If CRF is present, a quantitative or semiquantitative assessment should be performed and documented. For example, fatigue rating scale: 0 = no fatigue and 10 = worst fatigue; 1–3 = mild, 4–6 = moderate, 7–10 severe fatigue. If the screening process determines that CRF is absent or at a mild level, the patient and family should receive education and common management strategies for CRF. Periodic rescreening and reevaluation are recommended. Inpatients should be screened daily, and outpatients should be screened at a subsequent routine and follow-up visits. It should be emphasized that survivors or patients who have completed treatment must still be monitored for CRF because CRF may exist beyond the period of active treatment.	Sample survivorship care survey: Do you feel persistent CRF despite a good night's rest? Yes/no Does CRF interfere with your usual activities? Yes/no How would you rate your CRF on a scale of 0 (none) to 10 (extreme) over the past month? 0–10	All healthcare providers should routinely screen for the presence of CRF from the point of diagnosis onward. All patients should be screened for CRF at their initial cancer clinic visit, at appropriate intervals (e.g., daily for inpatients, routine and follow-up visits for outpatients, and self-monitoring for those posttreatment) and as clinically indicated, especially with changes in disease status. Screen with a valid and reliable tool that includes reportable scores (dimensions) that are clinically meaningful and have established cut-offs (e.g., asking patients "How would you rate your fatigue on a sale of 0–10 over the past 7 days" with ESAS scale from 0–10 as 0 = no fatigue, 10 = worse fatigue. The cut-off scores are 0–3 none to mild, 4–6 moderate, and 7–10 severe CRF. For patients who are unable to assign a numeric value to rate their CRF, a rating of mild, moderate, or severe may be used.) ESAS is a valid and reliable assessment tool to assess severity for nine common cancer symptoms, including pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath.

(continued)

Table 8.2 (continued)

	American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Adaptation [3]	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology- Cancer-Related Fatigue (version 2.2017, NCCN.org) [1]	NCCN Clinical Practice Guidelines® in Oncology-Survivorship (version 2.2017) [134]	Pan-Canadian Guideline (version 2.2015) [2]
Comprehensive and focused assessment	**History and physical** Perform a focused CRF history Evaluate disease status Assess treatable contributing factors As a shared responsibility, the clinical team must decide when referral to an appropriately trained professional (e.g., cardiologist, endocrinologist, mental health professional, internist) is needed. **Laboratory evaluation** Consider performing laboratory evaluation based on the presence of other symptoms and onset and severity of CRF	When CRF is rated as moderate to severe with a score 4–10, a more focused history and physical examination should be conducted. **Focused history** Disease status and treatment Consider recurrence and/or progression Prescription medications, over-the-counter drugs, and supplements Review of systems In-depth CRF history Onset, pattern, duration Change over time Associated or alleviating factors Interference with function Social support status/availability of caregivers Economic status and resources for obtaining tangible support **Assessment of treatable contributing factors** Pain Emotional distress Depression Anxiety Anemia Sleep disturbance/poor sleep hygiene (e.g., insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome) Nutritional deficits/imbalance Weight/caloric intake changes Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium Decreased functional status Physical activity level Deconditioning Medications/side effects (e.g., sedation) Comorbidities Alcohol/substance abuse Cardiac dysfunction Endocrine dysfunction (e.g., hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency)	Primary evaluation fatigue score: moderate or severe (4–10) **History and physical** Focused CRF history Onset, pattern, duration Change over time Associated or alleviating factors Interference with function Evaluation disease status Evaluate risk of recurrence based on stage, pathologic factors, and treatment history Perform review of systems to determine if other symptoms substantiate suspicion for recurrence Assessment of treatable contributing factors Comorbidities Alcohol/substance abuse Cardiac dysfunction Endocrine dysfunction (e.g., hypothyroidism, hypogonadism, adrenal insufficiency) Pulmonary dysfunction Renal dysfunction Anemia Arthritis Prescribed or OTC medications (e.g., sleep aids, pain medications, antiemetics) Emotional distress (screen for anxiety and depression) Sleep disturbances (e.g., insomnia, sleep apnea, vasomotor symptoms, restless leg syndrome) Pain Nutritional issues Weight/caloric intake changes Deconditioning/loss of muscle mass **Laboratory evaluation** Consider performing laboratory evaluation based on presence of other symptoms, onset, and severity of CRF CBC with differential Compare end-of-treatment hemoglobin/hematocrit with current values Assess other cell lines (WBC and platelets) Comprehensive metabolic panel Assess electrolytes	Screen for CRF and if moderate or severe CRF is detected through screening (ESAS tiredness greater than 4); individuals should have a comprehensive and focused assessment to identify the nature and extent of the CRF symptoms. Medical and substance-induced causes of CRF should be ruled out (e.g., anemia, infection, nutrition, deficiencies, medication or treatment side effects). Assessments should be a shared responsibility of the clinical team, with designation of those who are expected to conduct assessments based on scope of practice. Assessment should include a history of CRF (e.g., disease status, pretreatment activity levels, CRF onset, pattern, duration, changes over time, interference with function and daily living), contributing risk factors (e.g., depression, anemia, pain, nausea, sleep disturbance, comorbidities), a physical exam, a review of symptoms, and a self-assessment of causes contributing to CRF. Promote open communication among the patient, family, and the clinical team to facilitate discussions about the experience of CRF and its effects on daily functioning. As a shared responsibility, the clinical team must decide when referral to an appropriately trained professional is needed (e.g., all patients with an ESAS score in the severe range, with certain accompanying factors or symptoms, or a cut-off score identified using valid and reliable tools for assessment of symptoms of CRF.

		Gastrointestinal dysfunction Hepatic dysfunction Infection Neurologic dysfunction Pulmonary dysfunction Renal dysfunction	Assess hepatic and renal function Endocrine evaluation TSH, especially in patients who have received prior head/neck, torso, or breast radiation Consider more comprehensive evaluation or referral to specialist if other symptoms present Cortisol stimulation test, if history of prolonged steroid use **Other diagnostic testing** Consider radiologic assessment only if there is a high risk of disease recurrence or if accompanying signs and symptoms suggest presence of metastatic disease Consider cardiac testing (e.g., echocardiogram) for patients treated with an anthracycline, trastuzumab, bevacizumab, other VEGF- or HER2-targeted therapy, or other therapy known to cause cardiac dysfunction Chest x-ray and oxygen saturation testing for pulmonary complaints (refer to a pulmonologist for pulmonary complaints)	
Treatment and care options	**Education and counseling** All patients should be offered specific education about CRF after treatment (e.g., information about the difference between normal and CRF, persistence of CRF after treatment, and causes and contributing factors). Patients should be offered advice on general strategies that help manage CRF. If treated for CRF, patients should be observed and reevaluated on a regular basis to determine whether treatment is effective or needs to be reassessed. **Contributing factors** Address all medical and treatable contributing factors first (e.g., pain, depression, anxiety, emotional distress, sleep disturbance, nutritional deficit, activity level, anemia, medication adverse effects, and comorbidities). **Physical activity** Initiating/maintaining adequate levels of physical activity can reduce CRF in posttreatment survivors. Actively encourage all patients to engage in a moderate level of physical activity after cancer treatment (e.g., 150 min/week of moderate aerobic exercise, such as fast walking, cycling, or swimming, with an additional 2–3 strength training sessions/week, such as weight lifting, unless contraindicated). Walking programs are generally safe for most cancer survivors; the ACSM recommends that cancer survivors can begin this type of program after consulting with their physicians but without any formal exercise testing, such as stress test.	**Patient/family education and counseling** Information about known pattern of CRF during and following treatment **General strategies for management of CRF** Monitor CRF levels Energy conservation Set priorities and realistic expectations Pace Schedule activities at times of peak energy Limit naps to <1 hour to not interfere with night-time sleep quality Structured daily routine Attend to one activity at a time Use distraction (e.g., games, music, reading, socializing) Find meaning in current situation Emphasis on meaningful interactions Promote dignity of patient **Non-pharmacologic interventions** Physical activity Maintain optimal level of activity Consider initiation of exercise program of both endurance and resistance exercise Consider referral to rehabilitation physical therapy, occupational therapy, physical medicine Caution: late effects of treatment (e.g., cardiomyopathy)	**Treat contributing factors** Medication/side effects Pain Emotional distress Anemia Treat iron, B12, and folate deficiency, if present Consider referral/further evaluation for anemia or cytopenias Sleep disturbance Nutritional deficit/imbalance Comorbidities **Patient/family education and counseling** Provide information about patterns of CRF during and after treatment Self-monitoring of CRF levels Energy conservation Set priorities Pace Schedule activities at times of peak energy **Physical activity** Maintain adequate levels of physical activity Survivors at higher risk of injury (e.g., those living with neuropathy, cardiomyopathy, lymphedema, or other long-term effects of therapy or other comorbidities) should be referred to a physical therapist or exercise specialist Mark use of local resources to help patients increase exercise	Address all medical and treatable contributing factors first (e.g., pain, depression, anxiety, emotional distress, sleep disturbance, nutritional deficit, activity level, anemia, medication adverse effects, and comorbidities). Actively encourage all patients to engage in a moderate level of physical activity during and after cancer treatment (e.g., 30 min/week of moderate intensity activity most days) unless contraindicated. Moderate activity includes aerobic (e.g., fast walking, cycling, or swimming) and resistance training (e.g., weights). Additional non-pharmacologic interventions include nutrition consultation, optimizing sleep quality, psychosocial interventions to improve coping with CRF (e.g., cognitive behavioral therapy, stress management, or support groups), relaxation, massage, and attention restoring therapy (e.g., exposure to natural environments). For patients on active treatment or on long-term follow-up posttreatment who have moderate to severe CRF, consider referral to rehabilitation (e.g., physical or occupational therapy and physical medicine).

(continued)

Table 8.2 (continued)

	American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Adaptation [3]	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology- Cancer-Related Fatigue (version 2.2017, NCCN.org) [1]	NCCN Clinical Practice Guidelines® in Oncology-Survivorship (version 2.2017) [134]	Pan-Canadian Guideline (version 2.2015) [2]
	Survivors at higher risk of injury (e.g., those living with neuropathy, cardiomyopathy, or other long-term effects of therapy) and patients with severe CRF interfering with function should be referred to a physical therapist or exercise specialist. Breast cancer survivors with lymphedema should also consider meeting with an exercise specialist before initiating upper-body strength training. **Psychosocial interventions** Cognitive behavioral therapy/behavioral therapy can reduce CRF in posttreatment survivors. Psychoeducational therapies/educational therapies can reduce CRF in posttreatment survivors. Survivors should be referred to psychosocial service providers who specialize in cancer and are trained to deliver empirically based interventions. Psychosocial resources that address CRF may also be available through the NCI and other organizations **Mind-body interventions** Some evidence showed that mindfulness-based approaches such as yoga and acupuncture can reduce CRF in cancer survivors. Additional research, particularly in the posttreatment population, is needed for biofield therapies (touch therapy), massage, music therapy, relaxation, reiki, and qigong. Survivors should be referred to practitioners who specialize in cancer and who use protocols that have been empirically validated in cancer survivors. **Pharmacologic interventions** Evidence suggests that psychostimulants (e.g., methylphenidate) and other wakefulness agents (e.g., modafinil) can effectively manage CRF in patients with advanced disease or those receiving active treatment. However, there is limited evidence of their effectiveness in reducing CRF in patients who have completed primary treatment and are currently disease-free. Small pilot studies have evaluated the impact of supplements, such as ginseng, vitamin D, and others, on CRF. However, there is no consistent evidence of their effectiveness.	Psychosocial interventions CBT/BT Mindfulness-based stress reduction Psychoeducational therapies/educational therapies Supportive expressive therapies Nutrition consultation CBT for sleep Stimulus control Sleep restriction Sleep hygiene **Pharmacologic interventions** Consider psychostimulants (methylphenidate) after ruling out other causes of CRF. Treat for pain, emotional distress, and anemia as indicated per NCCN guidelines Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities Repeat screening and evaluation	Exercise classes at cancer centers Community programs focused on cancer survivors Exercise professional certified by the American College of Sports Medicine For patients with CRF interfering with function, consider referral to a physical therapist or physiatrist **Other interventions** Psychosocial interventions Cognitive behavioral therapy/behavioral therapy Psychoeducational therapies/educational therapies Supportive expressive therapies Nutrition consultation Cognitive behavioral therapy for sleep Stimulus control Sleep restriction Sleep hygiene Acupuncture **Pharmacologic** Consider psychostimulants (methylphenidate) after ruling out other causes of CRF and failure of other interventions	All patients should be offered specific education about CRF prior to the start of treatment when CRF is identified and provided with strategies (e.g., physical activity, energy conservation, stress reduction and distraction) to manage CRF. To date, the use of pharmacologic agents to treat CRF is considered experimental (e.g., psychostimulants, sleep medications, low-dose corticosteroids such as prednisone or dexamethasone); therefore, it is not recommended except for selected patients at the end of life with severe CRF. Promote ongoing self-monitoring of CRF levels because CRF is still a common cancer-related side effect occurring in posttreatment survivors. For patients with advanced and progressive disease or are receiving active treatment, repeat ESAS screening and assessment as needed to determine any change in both subjective and objective aspects of CRF.

as the presence of concurrent symptoms such as anemia. Other potential treatable contributing factors including pain, emotional distress, sleep disruption, impaired functional status, medications, nutritional deficits, and comorbidities should also be assessed.

8.7 Treatment Options

All patients and/or their caregivers should be educated and counseled on the occurrence of CRF. Contributing factors that are identified should be treated accordingly. Non-pharmacological interventions such as exercise, psychosocial therapy, and mind-body approaches could be considered. The evidence for pharmacological interventions is limited and should be used judiciously.

8.8 Future Directions

As described above, much progress has been made in our understanding of CRF in the past decade. There is now a greater awareness and recognition that CRF is a major concern among cancer patients and survivors and that it is a multidimentional problem. The development of reliable and valid methods to measure CRF have facilitated better communication between healthcare teams and also allowed longitudinal monitoring of CRF. Knowledge in this area has also facilitated the selection of endpoints for clinical trials evaluating interventions targeting CRF. Published clinical trials in CRF have provided us a better understanding of the available options for managing CRF, specifically exercise, psychosocial therapy, and mind-body approaches. With increasing availability of well-conducted studies, multiple clinical practice guidelines have been created for the management of CRF. Lastly, we have an improved understanding of the biobehavioral mechanisms associated with the development of CRF.

Despite the progress, many research gaps exist in the area of CRF. The negative impact of CRF on other outcomes such as healthcare utilization, cost, and survivorship needs to be studied. Although studies have consistently demonstrated the benefits of exercise in CRF, the dose and intensity of exercise remain unclear. Given the multidimentional nature of CRF, a one-size-fits-all approach is likely not sufficient. Combinations of various strategies such as exercise and various psychological or biobehavioral interventions need to be further investigated. With an increasing emphasis of personalized medicine in oncology, it is crucial for us to understand the biobehavioral mechanisms associated with CRF in order to develop individualized interventions for patients and to know for whom and when specific treatments for CRF can be best prescribed. Finally, we need to disseminate the clinical practice guidelines into clinical settings in order to identify patients with CRF and implement these interventions for patients with cancer.

In conclusion, CRF is a common and debilitating toxicity for cancer patients and survivors and can persist for many years after treatment. Many instruments exist for measuring CRF and may be incorporated in the routine assessment of CRF. Exercise and psychological interventions have consistently demonstrated benefits in treating CRF and should be incorporated in the care of cancer patients and survivors.

References

1. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, et al. Cancer-related fatigue, version 2.2015. J Natl Compr Cancer Netw. 2015;13(8):1012–39.
2. Howell D, Keller-Olaman S, Oliver TK, Hack TF, Broadfield L, Biggs K, et al. A pan-Canadian practice guideline and algorithm: screening, assessment, and supportive care of adults with cancer-related fatigue. Curr Oncol. 2013;20(3):e233–46.
3. Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. J Clin Oncol. 2014;32(17):1840–50.
4. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. Oncologist. 2007;12(Suppl 1):4–10.

5. Prue G, Rankin J, Allen J, Gracey J, Cramp F. Cancer-related fatigue: a critical appraisal. Eur J Cancer. 2006;42(7):846–63.
6. Rotonda C, Guillemin F, Bonnetain F, Conroy T. Factors correlated with fatigue in breast cancer patients before, during and after adjuvant chemotherapy: the FATSEIN study. Contemp Clin Trials. 2011;32(2):244–9.
7. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. Support Care Cancer. 2008;16(7):791–801.
8. Morrow GR, Andrews PL, Hickok JT, Roscoe JA, Matteson S. Fatigue associated with cancer and its treatment. Support Care Cancer. 2002;10(5):389–98.
9. 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 Manag. 1999;18(4):233–42.
10. Hickok JT, Roscoe JA, Morrow GR, Mustian K, Okunieff P, Bole CW. Frequency, severity, clinical course, and correlates of fatigue in 372 patients during 5 weeks of radiotherapy for cancer. Cancer. 2005;104(8):1772–8.
11. Phillips KM, Pinilla-Ibarz J, Sotomayor E, Lee MR, Jim HS, Small BJ, et al. Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a controlled comparison. Support Care Cancer. 2013;21(4):1097–103.
12. 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(4):743–53.
13. Bower JE, Ganz PA, Aziz N, Fahey JL, Cole SW. T-cell homeostasis in breast cancer survivors with persistent fatigue. J Natl Cancer Inst. 2003;95(15):1165–8.
14. Crom DB, Hinds PS, Gattuso JS, Tyc V, Hudson MM. Creating the basis for a breast health program for female survivors of Hodgkin disease using a participatory research approach. Oncol Nurs Forum. 2005;32(6):1131–41.
15. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. Ann Oncol. 2002;13(4):589–98.
16. Fossa SD, Dahl AA, Loge JH. Fatigue anxiety, and depression in long-term survivors of testicular cancer. J Clin Oncol. 2003;21(7):1249–54.
17. Ruffer JU, Flechtner H, Tralls P, Josting A, Sieber M, Lathan B, et al. Fatigue in long-term survivors of Hodgkin's lymphoma; a report from the German Hodgkin Lymphoma Study Group (GHSG). Eur J Cancer. 2003;39(15):2179–86.
18. Servaes P, Verhagen S, Schreuder HW, Veth RP, Bleijenberg G. Fatigue after treatment for malignant and benign bone and soft tissue tumors. J Pain Symptom Manag. 2003;26(6):1113–22.
19. Olson K, Krawchuk A, Quddusi T. Fatigue in individuals with advanced cancer in active treatment and palliative settings. Cancer Nurs. 2007;30(4):E1–10.
20. Olson K. A new way of thinking about fatigue: a reconceptualization. Oncol Nurs Forum. 2007;34(1):93–9.
21. Bower JE, Ganz PA, Desmond KA, Bernaards C, Rowland JH, Meyerowitz BE, et al. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer. 2006;106(4):751–8.
22. Servaes P, Gielissen MF, Verhagen S, Bleijenberg G. The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. Psycho-Oncology. 2007;16(9):787–95.
23. Behringer K, Goergen H, Muller H, Thielen I, Brillant C, Kreissl S, et al. Cancer-related fatigue in patients with and survivors of Hodgkin lymphoma: the impact on treatment outcome and social reintegration. J Clin Oncol. 2016;34(36):4329–37.
24. Seyidova-Khoshknabi D, Davis MP, Walsh D. Review article: a systematic review of cancer-related fatigue measurement questionnaires. Am J Hosp Palliat Care. 2011;28(2):119–29.
25. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. Cancer. 1999;85(5):1186–96.
26. Okuyama T, Akechi T, Kugaya A, Okamura H, Shima Y, Maruguchi M, et al. Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. J Pain Symptom Manag. 2000;19(1):5–14.
27. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manag. 1997;13(2):63–74.
28. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. J Pain Symptom Manag. 2004;27(1):14–23.
29. Cella D, Viswanathan HN, Hays RD, Mendoza TR, Stein KD, Pasta DJ, et al. Development of a fatigue and functional impact scale in anemic cancer patients receiving chemotherapy. Cancer. 2008;113(6):1480–8.
30. Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. Oncol Nurs Forum. 1998;25(4):677–84.
31. Banthia R, Malcarne VL, Roesch SC, Ko CM, Greenbergs HL, Varni JW, et al. Correspondence between daily and weekly fatigue reports in breast cancer survivors. J Behav Med. 2006;29(3):269–79.
32. Wu HS, Wyrwich KW, McSweeney M. Assessing fatigue in persons with cancer: further validation of the Wu Cancer Fatigue Scale. J Pain Symptom Manag. 2006;32(3):255–65.

33. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.
34. Pater JL, Zee B, Palmer M, Johnston D, Osoba D. Fatigue in patients with cancer: results with National Cancer Institute of Canada Clinical Trials Group studies employing the EORTC QLQ-C30. Support Care Cancer. 1997;5(5):410–3.
35. Moore K, Stanley R, Burrows G. Profile of mood states: Australian normative data. Psychol Rep. 1990;66(2):509–10.
36. Glaus A. Assessment of fatigue in cancer and non-cancer patients and in healthy individuals. Support Care Cancer. 1993;1(6):305–15.
37. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res. 1993;37(2):147–53.
38. Hann DM, Denniston MM, Baker F. Measurement of fatigue in cancer patients: further validation of the Fatigue Symptom Inventory. Qual Life Res. 2000;9(7):847–54.
39. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39(3):315–25.
40. Stein KD, Martin SC, Hann DM, Jacobsen PB. A multidimensional measure of fatigue for use with cancer patients. Cancer Pract. 1998;6(3):143–52.
41. Schwartz A, Meek P. Additional construct validity of the Schwartz Cancer Fatigue Scale. J Nurs Meas. 1999;7(1):35–45.
42. Aistars J. Fatigue in the cancer patient: a conceptual approach to a clinical problem. Oncol Nurs Forum. 1987;14(6):25–30.
43. Bower JE. Cancer-related fatigue – mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014;11(10):597–609.
44. Barsevick A, Frost M, Zwinderman A, Hall P, Halyard M. I'm so tired: biological and genetic mechanisms of cancer-related fatigue. Qual Life Res. 2010;19(10):1419–27.
45. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res. 2009;15(2):425–30.
46. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860–7.
47. Clevenger L, Schrepf A, Christensen D, DeGeest K, Bender D, Ahmed A, et al. Sleep disturbance, cytokines, and fatigue in women with ovarian cancer. Brain Behav Immun. 2012;26(7):1037–44.
48. Fagundes CP, Glaser R, Alfano CM, Bennett JM, Povoski SP, Lipari AM, et al. Fatigue and herpesvirus latency in women newly diagnosed with breast cancer. Brain Behav Immun. 2012;26(3):394–400.
49. Lutgendorf SK, Weinrib AZ, Penedo F, Russell D, DeGeest K, Costanzo ES, et al. Interleukin-6, cortisol, and depressive symptoms in ovarian cancer patients. J Clin Oncol. 2008;26(29):4820–7.
50. Pertl MM, Hevey D, Boyle NT, Hughes MM, Collier S, O'Dwyer AM, et al. C-reactive protein predicts fatigue independently of depression in breast cancer patients prior to chemotherapy. Brain Behav Immun. 2013;34:108–19.
51. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. Lancet Oncol. 2003;4(9):529–36.
52. Bower JE, Ganz PA, Tao ML, Hu W, Belin TR, Sepah S, et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin Cancer Res. 2009;15(17):5534–40.
53. Liu L, Mills PJ, Rissling M, Fiorentino L, Natarajan L, Dimsdale JE, et al. Fatigue and sleep quality are associated with changes in inflammatory markers in breast cancer patients undergoing chemotherapy. Brain Behav Immun. 2012;26(5):706–13.
54. Wang XS, Shi Q, Williams LA, Mao L, Cleeland CS, Komaki RR, et al. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. Brain Behav Immun. 2010;24(6):968–74.
55. Wang XS, Williams LA, Krishnan S, Liao Z, Liu P, Mao L, et al. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. Brain Behav Immun. 2012;26(5):699–705.
56. Alfano CM, Imayama I, Neuhouser ML, Kiecolt-Glaser JK, Smith AW, Meeske K, et al. Fatigue, inflammation, and omega-3 and omega-6 fatty acid intake among breast cancer survivors. J Clin Oncol. 2012;30(12):1280–7.
57. Bower JE, Ganz PA, Irwin MR, Arevalo JM, Cole SW. Fatigue and gene expression in human leukocytes: increased NF-kappaB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue. Brain Behav Immun. 2011;25(1):147–50.
58. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? J Clin Oncol. 2011;29(26):3517–22.
59. Light KC, Agarwal N, Iacob E, White AT, Kinney AY, VanHaitsma TA, et al. Differing leukocyte gene expression profiles associated with fatigue in patients with prostate cancer versus chronic fatigue syndrome. Psychoneuroendocrinology. 2013;38(12):2983–95.
60. Orre IJ, Murison R, Dahl AA, Ueland T, Aukrust P, Fossa SD. Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue. Brain Behav Immun. 2009;23(6):868–74.
61. Orre IJ, Reinertsen KV, Aukrust P, Dahl AA, Fossa SD, Ueland T, et al. Higher levels of fatigue are associated with higher CRP levels in disease-

free breast cancer survivors. J Psychosom Res. 2011;71(3):136–41.
62. Schrepf A, Clevenger L, Christensen D, DeGeest K, Bender D, Ahmed A, et al. Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. Brain Behav Immun. 2013;30(Suppl):S126–34.
63. Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom Med. 2005;67(2):277–80.
64. Innominato PF, Roche VP, Palesh OG, Ulusakarya A, Spiegel D, Levi FA. The circadian timing system in clinical oncology. Ann Med. 2014;46(4):191–207.
65. Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): facts and future directions. Int J Psychophysiol. 2009;72(1):67–73.
66. Kudielka BM, Federenko IS, Hellhammer DH, Wust S. Morningness and eveningness: the free cortisol rise after awakening in "early birds" and "night owls". Biol Psychol. 2006;72(2):141–6.
67. Liu L, Rissling M, Neikrug A, Fiorentino L, Natarajan L, Faierman M, et al. Fatigue and circadian activity rhythms in breast cancer patients before and after chemotherapy: a controlled study. Fatigue. 2013;1(1–2):12–26.
68. Miaskowski C, Lee KA. Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: a pilot study. J Pain Symptom Manag. 1999;17(5):320–32.
69. Schmidt ME, Semik J, Habermann N, Wiskemann J, Ulrich CM, Steindorf K. Cancer-related fatigue shows a stable association with diurnal cortisol dysregulation in breast cancer patients. Brain Behav Immun. 2016;52:98–105.
70. Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology. 2005;30(1):92–100.
71. Fagundes CP, Murray DM, Hwang BS, Gouin JP, Thayer JF, Sollers JJ 3rd, et al. Sympathetic and parasympathetic activity in cancer-related fatigue: more evidence for a physiological substrate in cancer survivors. Psychoneuroendocrinology. 2011; 36(8):1137–47.
72. Crosswell AD, Lockwood KG, Ganz PA, Bower JE. Low heart rate variability and cancer-related fatigue in breast cancer survivors. Psychoneuroendocrinology. 2014;45:58–66.
73. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. JAMA Oncol. 2017;3:961.
74. Scott K, Posmontier B. Exercise interventions to reduce cancer-related fatigue and improve health-related quality of life in cancer patients. Holist Nurs Pract. 2017;31(2):66–79.
75. Lipsett A, Barrett S, Haruna F, Mustian K, O'Donovan A. The impact of exercise during adjuvant radiotherapy for breast cancer on fatigue and quality of life: a systematic review and meta-analysis. Breast. 2017;32:144–55.
76. van Vulpen JK, Peeters PH, Velthuis MJ, van der Wall E, May AM. Effects of physical exercise during adjuvant breast cancer treatment on physical and psychosocial dimensions of cancer-related fatigue: a meta-analysis. Maturitas. 2016;85:104–11.
77. Tian L, Lu HJ, Lin L, Hu Y. Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials. Support Care Cancer. 2016;24(2):969–83.
78. Dennett AM, Peiris CL, Shields N, Prendergast LA, Taylor NF. Moderate-intensity exercise reduces fatigue and improves mobility in cancer survivors: a systematic review and meta-regression. J Physiother. 2016;62(2):68–82.
79. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al. Exercise for men with prostate cancer: a systematic review and meta-analysis. Eur Urol. 2016;69(4):693–703.
80. Smith-Turchyn J, Richardson J. A systematic review on the use of exercise interventions for individuals with myeloid leukemia. Support Care Cancer. 2015;23(8):2435–46.
81. Paramanandam VS, Dunn V. Exercise for the management of cancer-related fatigue in lung cancer: a systematic review. Eur J Cancer Care. 2015;24(1):4–14.
82. Minton O, Jo F, Jane M. The role of behavioural modification and exercise in the management of cancer-related fatigue to reduce its impact during and after cancer treatment. Acta Oncol. 2015;54(5):581–6.
83. Meneses-Echavez JF, Gonzalez-Jimenez E, Ramirez-Velez R. Supervised exercise reduces cancer-related fatigue: a systematic review. J Physiother. 2015;61(1):3–9.
84. Meneses-Echavez JF, Gonzalez-Jimenez E, Ramirez-Velez R. Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: a systematic review and meta-analysis. BMC Cancer. 2015;15:77.
85. Meneses-Echavez JF, Gonzalez-Jimenez E, Ramirez-Velez R. Effects of supervised multimodal exercise interventions on cancer-related fatigue: systematic review and meta-analysis of randomized controlled trials. Biomed Res Int. 2015;2015:328636.
86. Mustian KM, Sprod LK, Janelsins M, Peppone LJ, Mohile S. Exercise recommendations for cancer-related fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction: a review. Oncol Hematol Rev. 2012;8(2):81–8.
87. Braam KI, van der Torre P, Takken T, Veening MA, van Dulmen-den Broeder E, Kaspers GJ. Physical exercise training interventions for children and young adults during and after treatment for

childhood cancer. Cochrane Database Syst Rev. 2016;(3):Cd008796.
88. Lopes-Junior LC, Bomfim EO, Nascimento LC, Nunes MD, Pereira-da-Silva G, Lima RA. Non-pharmacological interventions to manage fatigue and psychological stress in children and adolescents with cancer: an integrative review. Eur J Cancer Care. 2016;25(6):921–35.
89. Spathis A, Booth S, Grove S, Hatcher H, Kuhn I, Barclay S. Teenage and young adult cancer-related fatigue is prevalent, distressing, and neglected: it is time to intervene. A systematic literature review and narrative synthesis. J Adolesc Young Adult Oncol. 2015;4(1):3–17.
90. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409–26.
91. Irwin ML. Physical activity interventions for cancer survivors. Br J Sports Med. 2009;43(1):32–8.
92. Mustian KM, Cole CL, Lin PJ, Asare M, Fung C, Janelsins MC, et al. Exercise recommendations for the management of symptoms clusters resulting from cancer and cancer treatments. Semin Oncol Nurs. 2016;32(4):383–93.
93. Kleckner IR, Dunne RF, Asare M, Cole CL, Fleming F, Fung C, et al. Exercise for toxicity management in cancer: a narrative review. Oncol Hematol Rev. 2018;14(1):28–37.
94. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. Cochrane Database Syst Rev. 2009;(1):Cd006953.
95. Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. Health Psychol. 2007;26(6):660–7.
96. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. Psychol Bull. 2008;134(5):700–41.
97. Yates P, Aranda S, Hargraves M, Mirolo B, Clavarino A, McLachlan S, et al. Randomized controlled trial of an educational intervention for managing fatigue in women receiving adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol. 2005;23(25):6027–36.
98. Armes J, Chalder T, Addington-Hall J, Richardson A, Hotopf M. A randomized controlled trial to evaluate the effectiveness of a brief, behaviorally oriented intervention for cancer-related fatigue. Cancer. 2007;110(6):1385–95.
99. Montgomery GH, Kangas M, David D, Hallquist MN, Green S, Bovbjerg DH, et al. Fatigue during breast cancer radiotherapy: an initial randomized study of cognitive-behavioral therapy plus hypnosis. Health Psychol. 2009;28(3):317–22.
100. Stanton AL, Ganz PA, Kwan L, Meyerowitz BE, Bower JE, Krupnick JL, et al. Outcomes from the Moving Beyond Cancer psychoeducational, randomized, controlled trial with breast cancer patients. J Clin Oncol. 2005;23(25):6009–18.
101. Banasik J, Williams H, Haberman M, Blank SE, Bendel R. Effect of Iyengar yoga practice on fatigue and diurnal salivary cortisol concentration in breast cancer survivors. J Am Acad Nurse Pract. 2011;23(3):135–42.
102. Bower JE, Garet D, Sternlieb B, Ganz PA, Irwin MR, Olmstead R, et al. Yoga for persistent fatigue in breast cancer survivors: a randomized controlled trial. Cancer. 2012;118(15):3766–75.
103. Bower JE, Greendale G, Crosswell AD, Garet D, Sternlieb B, Ganz PA, et al. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial. Psychoneuroendocrinology. 2014;43:20–9.
104. Johns SA, Brown LF, Beck-Coon K, Monahan PO, Tong Y, Kroenke K. Randomized controlled pilot study of mindfulness-based stress reduction for persistently fatigued cancer survivors. Psycho-Oncology. 2015;24(8):885–93.
105. Lotzke D, Wiedemann F, Rodrigues Recchia D, Ostermann T, Sattler D, Ettl J, et al. Iyengar-yoga compared to exercise as a therapeutic intervention during (neo)adjuvant therapy in women with stage I-III breast cancer: health-related quality of life, mindfulness, spirituality, life satisfaction, and cancer-related fatigue. Evid Based Complement Alternat Med. 2016;2016:5931816.
106. Sprod LK, Fernandez ID, Janelsins MC, Peppone LJ, Atkins JN, Giguere J, et al. Effects of yoga on cancer-related fatigue and global side-effect burden in older cancer survivors. J Geriatr Oncol. 2015;6(1):8–14.
107. Stan DL, Croghan KA, Croghan IT, Jenkins SM, Sutherland SJ, Cheville AL, et al. Randomized pilot trial of yoga versus strengthening exercises in breast cancer survivors with cancer-related fatigue. Support Care Cancer. 2016;24(9):4005–15.
108. Chandwani KD, Thornton B, Perkins GH, Arun B, Raghuram NV, Nagendra HR, et al. Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer. J Soc Integr Oncol. 2010;8(2):43–55.
109. Cohen L, Warneke C, Fouladi RT, Rodriguez MA, Chaoul-Reich A. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. Cancer. 2004;100(10):2253–60.
110. Culos-Reed SN, Carlson LE, Daroux LM, Hately-Aldous S. A pilot study of yoga for breast cancer survivors: physical and psychological benefits. Psycho-Oncology. 2006;15(10):891–7.
111. Danhauer SC, Mihalko SL, Russell GB, Campbell CR, Felder L, Daley K, et al. Restorative yoga for women with breast cancer: findings from a randomized pilot study. Psycho-Oncology. 2009;18(4):360–8.
112. Littman AJ, Bertram LC, Ceballos R, Ulrich CM, Ramaprasad J, McGregor B, et al. Randomized

controlled pilot trial of yoga in overweight and obese breast cancer survivors: effects on quality of life and anthropometric measures. Support Care Cancer. 2012;20(2):267–77.
113. Moadel AB, Shah C, Wylie-Rosett J, Harris MS, Patel SR, Hall CB, et al. Randomized controlled trial of yoga among a multiethnic sample of breast cancer patients: effects on quality of life. J Clin Oncol. 2007;25(28):4387–95.
114. Vadiraja SH, Rao MR, Nagendra RH, Nagarathna R, Rekha M, Vanitha N, et al. Effects of yoga on symptom management in breast cancer patients: a randomized controlled trial. Int J Yoga. 2009;2(2):73–9.
115. Carson JW, Carson KM, Porter LS, Keefe FJ, Seewaldt VL. Yoga of awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial. Support Care Cancer. 2009;17(10):1301–9.
116. Kiecolt-Glaser JK, Bennett JM, Andridge R, Peng J, Shapiro CL, Malarkey WB, et al. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. J Clin Oncol. 2014;32(10):1040–9.
117. Lin P, Peppone LJ, Janelsins MC, Mohile SG, Kamen C, Kleckner IR, et al. Yoga for the management of cancer treatment-related toxicities. Curr Oncol Rep. 2018;20(1):5.
118. Molassiotis A, Bardy J, Finnegan-John J, Mackereth P, Ryder DW, Filshie J, et al. Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial. J Clin Oncol. 2012;30(36):4470–6.
119. Molassiotis A, Sylt P, Diggins H. The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure: a randomised controlled trial. Complement Ther Med. 2007;15(4):228–37.
120. Deng G, Chan Y, Sjoberg D, Vickers A, Yeung KS, Kris M, et al. Acupuncture for the treatment of post-chemotherapy chronic fatigue: a randomized, blinded, sham-controlled trial. Support Care Cancer. 2013;21(6):1735–41.
121. Finnegan-John J, Molassiotis A, Richardson A, Ream E. A systematic review of complementary and alternative medicine interventions for the management of cancer-related fatigue. Integr Cancer Ther. 2013;12(4):276–90.
122. Grant SJ, Smith CA, de Silva N, Su C. Defining the quality of acupuncture: the case of acupuncture for cancer-related fatigue. Integr Cancer Ther. 2015;14(3):258–70.
123. He XR, Wang Q, Li PP. Acupuncture and moxibustion for cancer-related fatigue: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2013;14(5):3067–74.
124. Ling WM, Lui LY, So WK, Chan K. Effects of acupuncture and acupressure on cancer-related fatigue: a systematic review. Oncol Nurs Forum. 2014;41(6):581–92.
125. Posadzki P, Moon TW, Choi TY, Park TY, Lee MS, Ernst E. Acupuncture for cancer-related fatigue: a systematic review of randomized clinical trials. Support Care Cancer. 2013;21(7):2067–73.
126. Wirz S, Nadstawek J, Kuhn KU, Vater S, Junker U, Wartenberg HC. Modafinil for the treatment of cancer-related fatigue : an intervention study. Schmerz. 2010;24(6):587–95.
127. Jean-Pierre P, Morrow GR, Roscoe JA, Heckler C, Mohile S, Janelsins M, et al. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. Cancer. 2010;116(14):3513–20.
128. Spathis A, Fife K, Blackhall F, Dutton S, Bahadori R, Wharton R, et al. Modafinil for the treatment of fatigue in lung cancer: results of a placebo-controlled, double-blind, randomized trial. J Clin Oncol. 2014;32(18):1882–8.
129. Gong S, Sheng P, Jin H, He H, Qi E, Chen W, et al. Effect of methylphenidate in patients with cancer-related fatigue: a systematic review and meta-analysis. PLoS One. 2014;9(1):e84391.
130. Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol. 2006;24(13):2073–8.
131. Butler JM, Jr., Case LD, Atkins J, Frizzell B, Sanders G, Griffin P, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. Int J Radiat Oncol Biol Phys 2007;69(5):1496–1501.
132. Lower EE, Fleishman S, Cooper A, Zeldis J, Faleck H, Yu Z, et al. Efficacy of dexmethylphenidate for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. J Pain Symptom Manag. 2009;38(5):650–62.
133. Moraska AR, Sood A, Dakhil SR, Sloan JA, Barton D, Atherton PJ, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. J Clin Oncol. 2010;28(23):3673–9.
134. Roth AJ, Nelson C, Rosenfeld B, Scher H, Slovin S, Morris M, et al. Methylphenidate for fatigue in ambulatory men with prostate cancer. Cancer. 2010;116(21):5102–10.
135. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology-Survivorship Version 2.2017-July 28. 2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf.