Cancer-Related Fatigue

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Cancer-Related Fatigue in Survivors of Breast Cancer: Definition, Prevalence, and Impact

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 more persistent and severe than common physical or mental tiredness and is less likely to be relieved by adequate sleep or rest. CRF is multidimensional; patients with CRF may experience generalized weakness, diminished concentration and attention, decreased motivation, or no interest in engaging in usual activities, and emotional instability. The relationship between CRF and depression is complex. Some of the symptoms of CRF overlap with those of depression. Furthermore, higher levels of depression are associated with higher levels of CRF, and depression has been shown to be one of the strongest predictors of CRF [3–5]. While there is an overlap in characteristics of CRF and depression, data suggests that they have different correlates and different courses over time [6–8].

CRF can occur as a consequence of breast cancer itself [9] and/or its treatments (e.g., chemotherapy, radiation therapy, hormonal and biological therapies) [9–13]. CRF is among the most commonly reported and troublesome symptoms in patients with breast cancer receiving active treatments and survivors after the completion of treatments [14, 15]. Up to 90% of patients with breast cancer experience CRF during chemotherapy and/or radiation therapy. CRF can persist after the completion of treatments and up to 10 years post-diagnosis. Approximately 33% of survivors of breast cancer still report CRF post-treatment [3, 16–23].

CRF has a host of deleterious effects on long-term health outcomes and can have multiple manifestations including physical, mental, and emotional problems. These effects ultimately result in limiting survivors' ability to perform essential daily activities and engage socially, disrupting their quality of life, and reducing survival [3, 13, 24–29]. Survivors of breast cancer report more severe fatigue compared to age-matched healthy controls. This greater level of fatigue is associated with increased depression, pain, and sleep disturbance [3]. Depression and pain are among the strongest predictors of CRF while sleep disturbance serves as a possible mediator

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[3, 30]. Furthermore, it has been shown that CRF intensifies menopausal symptoms [3].

Possible Mechanisms Associated with Cancer-Related Fatigue

Understanding the biological mechanisms of CRF can help identify treatment options. Several biological mechanisms may contribute to CRF in patients and survivors of breast cancer, including inflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and serotonin dysregulation. Additionally, the relative contributions of disease, treatment, and comorbid conditions to CRF in patients with cancer are unclear.

One of the most studied mechanisms of CRF is inflammation [25, 31, 32]. Both cancer and its treatments can lead to the release of pro-inflammatory cytokines from tumors and somatic cells [33–37]. Elevated levels of circulating pro-inflammatory markers, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), C-reactive protein (CRP), and monocyte chemoattractant protein-1 (MCP-1), are associated with CRF in patients with breast cancer [31, 32, 38–40]. Pro-inflammatory marker levels may remain elevated years after the completion of treatment for breast cancer and contribute to long-lasting CRF [40, 41]. Genomic studies suggest that polymorphisms in the promoter regions of pro-inflammatory cytokines may predispose some patients to greater inflammation and CRF in response to cancer and its treatment [42, 43].

The central nervous system has multiple points of contact with the rest of the body to detect systemic inflammation. Cytokines in the blood can be transported directly into the brain. Additionally, circulating pro-inflammatory cytokines stimulate vagal afferent nerve fibers, the circumventricular organs of the brain that lie outside the blood-brain barrier, and receptors on perivascular macrophages and endothelial cells. Together, these mechanisms of detecting systemic inflammation lead to a variety of local central nervous system responses, including responses that result in CRF.

Another proposed mechanism of CRF is dysregulation of the HPA axis, which regulates the basal and stress-induced release of cortisol. Reduced cortisol and adrenocorticotropic hormone (ACTH) release in response to stress, flatter diurnal cortisol slopes, and elevated evening cortisol levels have been shown to be associated with CRF in patients with cancer [44–47]. However, whether altered cortisol regulation is a result or a cause of CRF is yet to be determined [48, 49]. Genetic and social-behavioral factors such as early life stress and coping mechanisms affect the activity of the HPA axis and may play a role in increasing the severity of CRF [48].

Serotonin dysregulation is theorized to play a role in the pathogenesis of CRF based on 1) the co-occurrence of CRF and depression in patients with cancer, 2) the relationship of serotonin to sleep disturbances, and 3) the mutual feedback between the serotonin system, inflammation, and the HPA axis [12]. Although serotonin cannot be measured non-invasively in the human central nervous system, it is hypothesized that CRF may be related to increased or decreased levels of serotonin [49, 50]. However, clinical trials have failed to show that the use of antidepressants, including selective serotonin reuptake inhibitors, reduce CRF in patients with breast cancer, suggesting that serotonin dysregulation may not be a major contributing factor to CRF [51, 52].

Importantly, proposed mechanisms causing CRF have multiple points of overlap and feedback. For example, elevated levels of pro-inflammatory cytokines can alter cortisol release, serotonin regulation, and vagal nerve activation, which in turn can alter inflammatory cytokine regulation. Similarly, serotonin neurotransmission, HPA axis activity, and vagal nerve stimulation can influence each other [12]. These proposed mechanisms of CRF are not fully understood, and further investigation of the role of endocrine mechanisms in the etiology of CRF is needed [49, 53].

Other factors that may contribute to CRF, including anemia, endocrine dysregulation, physical impairment or other cancer-related symptoms, sleep disturbances, stress, and energy/nutritional deficits and imbalance [25, 54, 55],

will be discussed in the later section "Ruling Out Treatable Causes of Fatigue".

Screening and Treatments of Cancer-Related Fatigue

Screening for and treating CRF are priorities of major professional societies and have prompted the development of consensus statements on the topic. In Fig. 10.1, we provide a simplified and practical algorithm based on the ASCO [1, 56], National Comprehensive Cancer Network (NCCN) [57, 58], and Pan-Canadian Clinical Practice Guidelines [59]. We also incorporate information from the Oncology Nursing Society [60] and the best available clinical evidence. This algorithm covers the recommendations on screening, comprehensive and focused assessment, and treatment options for mild, moderate, and severe fatigue.

Screening

Health providers should routinely screen for CRF at the time of initial diagnosis and on subsequent visits, including after the completion of primary treatment. CRF is a subjective sense of tiredness or exhaustion; therefore, patient-reported outcome tools are the most common reliable and validated methods to screen for and assess CRF. CRF can be assessed as one component of a medical outcome survey, quality of life scale, or profile of mood states or by instruments designed specifically to measure multiple dimensions of fatigue. Two systematic reviews identified 40 instruments (3 unidimensional, 37 multidimensional) to assess CRF in patients and survivors with cancer [61, 62]. These instruments vary by the number of items, rating scales, fatigue dimensions/domains, types of cancer population studied, and psychometric properties. They also have different levels of validity and reliability, evalu-

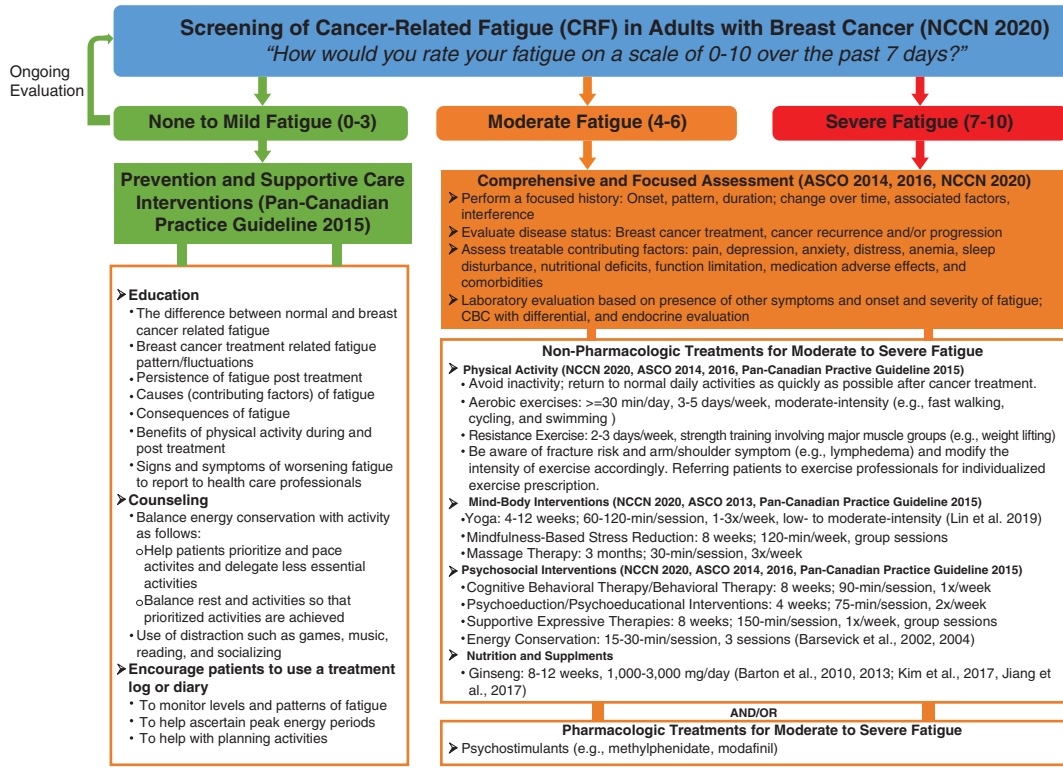

Fig. 10.1 Practical algorithm of screening, assessment, and treatment of cancer-related fatigue

ated by internal consistency, test-retest reliability, and convergent validity, depending on the population studied. According to the systematic reviews, of the 40 instruments available, the following have optimal validity and reliability: the Brief Fatigue Inventory (BFI) [63], the Cancer Fatigue Scale (CFS) [64], the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 Fatigue Scale (EORTC QLQ C30 FA) [65], the Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-F) [66], and the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) [67].

CRF instruments are not universally standardized, and some instruments are more commonly used than others. Table 10.1 lists some commonly used instruments for CRF assessment in patients and survivors with breast cancer [68–70]. A stepwise approach can be used to detect and define CRF. A unidimensional instrument (e.g., EORTC QLQ C30 FA, VAS) is often used as a screening tool for identifying the presence and the severity of CRF. The NCCN guidelines recommend screening for CRF based on the patient's rating of symptoms on an 11-point scale in response to this question: "How would you rate your fatigue on a scale of 0–10 over the past 7 days?" (0 = no fatigue, and 10 = worst fatigue) [58]. The fatigue is then categorized to none to mild (0–3), moderate (4–6), or severe (7–10) based on the scale rating. Some multidimensional instru-

Table 10.1 Commonly used instruments to screen for and assess cancer-related fatigue

Instruments	Number of items	Rating scales	Fatigue dimensions/domains	Evaluation period
Unidimensional				
EORTC QLQ C30 FA [65]	3	4-point (1–4) Likert	Severity of fatigue	Past week
FACIT-F [66]	13	5-point (0–4) Likert	Severity of fatigue	Past week
POMS-F [72]	7	5-point (0–4) Likert	Severity of fatigue	Past week and right now
SF-36 Vitality [73]	4	6-point (1–6) Likert	Severity of fatigue	Past 4 weeks
VAS [74]	1	Analogue	Severity of fatigue	Current
Multidimensional				
BFI [63]	9	11-point (0–10) Likert	Severity and interference of fatigue	Past 24 hours
CFS [64]	15	5-point (1–5) Likert	Physical, affective, and cognitive fatigue	Current
CFQ [75]	14	4-point (0–3) Likert	Physical and mental fatigue	Current
FSI [76]	13	11-point (0–10) Likert	Intensity, duration, and interference of fatigue	Past week, current
MFI-20 [77]	20	5-point (1–5) Likert	Cognitive, physical, and emotional fatigue, reduced activity, reduced motivation	Current
MFSI-SF [67]	30	5-point (0–4) Likert	General, physical, mental, and emotional fatigue, vigor	Past week
PFS [78]	22	11-point (0–10) Likert	Behavioral/severity of fatigue, affective meaning, sensory, cognitive/mood	Now or today
SCFS-6 [79]	6	5-point (1–5) Likert	Physical and perceptual fatigue	Past 2–3 days

EORTC QLQ C30 FA European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 Fatigue Scale, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue subscale, *POMS-F* Profile of Mood Sates-Fatigue subscale, *SF-36* Short Form 36-item Health Survey Vitality Scale, *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, *PFS* Piper Fatigue Scale, *SCFS-6* Schwartz Cancer Fatigue Scale-6

ments can further characterize CRF into different domains: physical, emotional (affective), and cognitive. Once CRF is detected, a multidimensional instrument should be employed to identify the most problematic domain(s) of CRF to prescribe an optimal intervention for patients receiving treatment and survivors' post-treatment. In addition, the time required to complete the CRF instrument should be considered, particularly for patients with advanced cancer. The BFI is a reasonable instrument to choose because it is short, has optimal psychometric properties, and is sensitive to changes of CRF over time [61]. The 3-item fatigue scale of the EORTC QLQ C30 has also been used in patients with advanced cancer [61] and validated with good test-retest reliability [71].

If CRF is detected by screening, the severity should then be defined as "None to Mild," "Moderate," or "Severe" (Fig. 10.1). Recommendations for management are then based on the severity of CRF (Fig. 10.1).

Recommendations for None to Mild Cancer-Related Fatigue

For patients with none to mild fatigue, prevention and supportive care are recommended [59]. Clinicians should educate patients about CRF (e.g., its pattern, causes, consequences), especially those features related to breast cancer, advise patients to self-monitor fatigue levels, and provide general strategies for CRF management [1]. Patients are encouraged to use a treatment log or diary for tracking the progress of CRF. Patients can also learn how to use distractions, such as games, music, and exercise, to demote CRF.

Recommendations for Moderate to Severe Cancer-Related Fatigue

For patients with moderate or severe CRF, clinicians should perform a comprehensive and focused assessment including fatigue history (e.g., onset, pattern, duration), assessment of disease status (breast cancer treatment, cancer recurrence and/or progression), and evaluation for the presence of other treatable contributing factors, such as anemia, sleep disturbance, endocrine dysfunction, anxiety, depression, nutritional deficiency, and medications [1, 56, 58]. Laboratory evaluation (e.g., CBC with differential and endocrine evaluation) may be performed, if indicated.

Ruling Out Treatable Causes of Fatigue

Patients who manifest symptoms of CRF should first be evaluated for treatable conditions that may be contributing to or causing the fatigue. These include anemia, deconditioned status, sleep disturbance, endocrine dysfunction (hypothyroidism), anxiety, depression, nutritional deficiencies, electrolyte disturbance, and medications (Table 10.2). Appropriately managing other contributing conditions may alleviate CRF symptoms.

Many patients with cancer are at risk for anemia, which can contribute to symptoms of fatigue. A thorough history can help to identify reversible causes of anemia, including blood loss, hemolysis, iron or vitamin deficiency, or renal disease. Iron and vitamins (folate, B12) supplements might be suggested for patients with iron and vitamin deficiency to help red blood cells grow. Red blood cell transfusions can also be used in appropriate patients; however, further studies are needed to evaluate efficacy in this patient population [80]. Appropriate management of physical symptoms such as pain, nausea, or shortness of breath can improve fatigue in cancer patients. For patients with advanced cancer, a randomized controlled trial evaluated monitoring and protocolized treatment of physical symptoms and the impact on fatigue symptoms. There were 152 patients randomized to either standard care or an intervention, including meeting with a nurse specialist, treatments to alleviate physical symptoms, and education. Significant improvement in general fatigue as well as in secondary endpoints such as interference of fatigue with daily life and anxiety was observed in the intervention group [81].

Insomnia occurs frequently in cancer patients (also see Chap. 11, Sleep Issues and Insomnia).

Table 10.2 Treatable causes of cancer-related fatigue, risk factors, and screening tests

Treatable causes	Risk factors	Suggested screening tests
Anemia	Nutritional deficiency, prior exposure to chemotherapy, renal disease	CBC with diff, peripheral blood smear, iron studies, B12, folate, FACT-anemia subscale
Anxiety/depression	History of prior mood disorder, family history	Patient health questionnaires 2 (PHQ-2) and 9 (PHQ-9), generalized anxiety disorder 7-item (GAD-7)
Comorbidities	Presence of comorbid conditions including congestive heart failure, chronic obstructive pulmonary disease, human immunodeficiency syndrome, multiple sclerosis, rheumatologic conditions	Focused history
Deconditioning	Poor social support, comorbidities	Focused history of daily activities
Electrolyte disturbance	Poor nutrition, brain tumor, paraneoplastic conditions such as SIADH, nausea, vomiting, diarrhea, or bowel obstruction	A complete metabolic panel including sodium, potassium, calcium, magnesium
Endocrine dysfunction: hypothyroidism	Radiation impacting the hypothalamus, immunotherapy (hypophysitis)	Hypothyroidism: serum free T4 and thyroid-stimulating hormone
Medications	Sedating medications including benzodiazepines, opioids, beta-blockers, first-generation antihistamines	Focused history
Nutritional deficiency	Mild cognitive impairment or dementia, poor social support, esophagitis related to cancer treatment, thrush, older age	Focused nutritional history, weight changes, iron levels, B12 and folate, nutritional assessment, and registered dietitian consultant
Physical symptoms	Uncontrolled pain, dyspnea, nausea	Focused history, quantification can include scales and interference with daily activities
Sleep disturbance	For sleep apnea, elevated BMI, untreated/undertreated pain	Sleep history including symptoms of sleep apnea
Substance use	Use of alcohol, marijuana, opioids, cocaine, or other stimulants	Focused history describing the quantity and frequency of substance use

Fifty-one to 90% of cancer survivors have some type of sleep disturbance, such as difficulty falling asleep and staying asleep, early and frequent awakenings, and excessive daytime sleepiness, which can cause daytime dysfunction [82–84]. For patients with insomnia or other sleep disturbance, treatments to improve sleep may mitigate fatigue symptoms. Cognitive behavioral therapy for insomnia (CBT-I) and behavioral interventions involving sleep management/hygiene education sessions are effective approaches for improving insomnia and sleep disturbance in patients and survivors with breast cancer [85–89]. Berger et al. compared an intervention, using an individualized sleep management plan with components of sleep hygiene, relaxation therapy, stimulus control, and sleep restriction techniques, with a "healthy eating" control in 219 patients with breast cancer. Patients in the intervention arm reported significant improvements in global sleep quality assessed via Pittsford Sleep Quality Index [86]. Another study of a sleep management program including relaxation techniques, sleep hygiene, cognitive techniques, and stimulus control advice also demonstrated improvements in sleep latency, sleep duration, sleep efficiency, sleep quality, and daytime dysfunction [87]. Yoga is another effective approach to improve sleep disturbance in patients and survivors with cancer [89–91]. Mustian et al. demonstrated that cancer survivors who participated in a standardized 4-week yoga program (Yoga for Cancer Survivors, YOCAS©®) had improved sleep quality, reduced daytime dysfunction, and decreased sleep medication use compared to the usual care controls [90]. The authors further

reported that improvements in sleep significantly mediated the positive effect of yoga on CRF in cancer survivors [30]. Physical symptoms, such as pain, anxiety, and depression, are associated with the severity of insomnia in patients with breast cancer [92–94]. Relief of pain, anxiety, and/or depression may help to alleviate sleep disturbance in breast cancer patients suffering from insomnia. If patients do not respond to education or behavioral interventions, medications such as benzodiazepines, antihistamines, melatonin, or non-benzodiazepine hypnotics are suggested. Overall, there are a variety of pharmacologic and non-pharmacologic means to improve sleep in patients with cancer.

Preexisting endocrinopathies or treatment that impairs the function of endocrine organs can lead to fatigue. Radiation, if fields include the thyroid or pituitary, increases the risk of hypothyroidism [95, 96]. Adjuvant endocrine therapy, prescribed for up to 10 years to decrease the risk of cancer recurrence, causes symptoms similar to menopause. Greater than 50% of patients taking aromatase inhibitors report moderate to severe fatigue [97]. For patients on immunotherapy, immune-related adverse events can include hypophysitis, thyroid dysfunction, and insulin-dependent diabetes mellitus [98]. Patients with risk factors for endocrine dysfunction should be screened with appropriate laboratory tests (Table 10.2). If hypothyroidism is present, it should be treated.

Non-Pharmacologic and Pharmacologic Treatments for CRF

If the initial work-up is negative for treatable causes of fatigue, there are proven non-pharmacologic and pharmacologic treatment options for directly managing CRF. Non-pharmacologic options include physical activity interventions (aerobic, anaerobic/strength, or both), mind-body approaches (yoga, mindfulness, acupuncture), psychosocial interventions (cognitive behavioral therapy, psycho-educational interventions.), and nutritional supplements. Pharmacologic options include psychostimulants, antidepressants, and glucocorticoids. Treatment decisions should consider patients' and their caregivers' preferences, physical and mental condition, resource availability, financial burden, and potential harm. A meta-analysis of 113 randomized trials of exercise (aerobic, resistance, or both), psychological interventions, exercise plus psychological interventions, and pharmacologic interventions demonstrated that exercise, psychological interventions, and exercise plus psychological interventions were significantly more effective than pharmacologic interventions [99]. For this reason, non-pharmacologic interventions should be considered first-line treatments.

Non-Pharmacologic Treatments

Physical Activity

Many systematic reviews and meta-analyses have demonstrated a significant and consistent beneficial effect of exercise on CRF among patients and survivors with breast cancer [68–70, 100–102]. Studies have evaluated different types of exercise including walking [103], bicycling [104], resistance training [105, 106], aquatic exercise [107], a combined approach [108], or others in which patients could choose the type of exercise [109]. Exercise interventions have been carried out during [69, 70, 110, 111] and after treatment [100, 110, 112, 113]. The duration of the studied exercise program has varied in studies from 6 weeks to 6 months. Most data support aerobic exercise [114], but resistance exercise also has a significant impact and possibly a larger effect size [115]. ASCO guidelines recommend 150 minutes of moderate or 75 minutes of vigorous aerobic exercise per week with 2–3 sessions of strength training [1, 56].

Breast cancer survivors with known cardiovascular (CVD), metabolic (type 1 and 2 diabetes mellitus), or renal disease or who have any signs or symptoms suggestive of CVD, DM, or renal disease are recommended to obtain medical clearance to start or continue an exercise program. Otherwise, routine cardiac screening is not necessary before starting an exercise program for survivors without known CVD [116]. The type of exercise program undertaken depends not only on preexisting comorbidity, including cardiovas-

cular disease, but also on conditions resulting from previous cancer treatment, such as chemotherapy-induced peripheral neuropathy (CIPN), cardiomyopathy, osteoporosis, arthralgia, and lymphedema. Breast cancer survivors with CIPN may be prone to falls or dropping things, which may impact safety during an exercise program. The presence of balance issues requires greater stability during exercise, such as using a stationary bike rather than walking or running [117]. Past use of chemotherapy or endocrine therapy increases the risk of bone loss, so patients should be monitored using dual-energy x-ray absorptiometry scans to determine fracture risk [117]. Evaluation for arm/shoulder morbidity is recommended before prescribing upper body exercises for breast cancer survivors with lymphedema. Active exercise may be carried out while wearing a compression sleeve on the affected side [118]. Studies have shown that carefully designed exercise programs with progressive upper extremity strength training are safe for women at risk for lymphedema [119, 120]. Exercise prescriptions should be individualized according to the individual's health status, disease trajectory, previous treatment, symptom burden, current fitness level, past and present exercise participation, and individual preferences to ensure safety and effectiveness [121].

Mind-Body Interventions

Mind-body approaches for CRF include mindfulness, meditation, acupuncture, and yoga [30, 122–131]. Rooted in Buddhist and Hindu teaching, mindfulness focuses on attention, awareness, and nonjudgmental acceptance to optimize one's ability to be fully present in the moment. Multiple randomized trials indicate that mindfulness-based approaches are effective in reducing stress in patients with breast cancer [132, 133]. The practice of yoga, which originated in ancient India, involves a group of physical, mental, and spiritual disciplines. Considerable data indicate that yoga reduces CRF [30, 123, 131]. A recent study by Lin et al. suggests that YOCAS©® yoga (gentle Hatha and Restorative yoga-based yoga program) significantly improves CRF and that 22% to 37% of the improvement in CRF from yoga therapy results from improvement in sleep quality and daytime dysfunction [30]. Yoga also leads to decreases in inflammatory mediators, such as IL-6 and IL-1β [131]. Acupuncture originated in traditional Chinese medicine and involves the insertion of very thin needles through the skin at strategic points on the body, thought to stimulate nerves, muscles, and connective tissue in a therapeutic way. The benefits of acupuncture with regard to CRF have been more controversial; some studies have suggested that acupuncture significantly improves CRF [134–136], but other studies did not see additional benefits of acupuncture on CRF when compared to sham acupuncture [137] or to massage only intervention [138].

Psychosocial Interventions

Psychosocial interventions include cognitive behavioral therapy (CBT), psychoeducational therapy, and other supportive therapies. CBT is a type of psychological therapy in which patients work with an experienced CBT therapist; the focus is on modifying dysfunctional thoughts, emotions, and behaviors. Psycho-educational interventions involve providing information, counseling, and strategies for survivors. Many small trials and multiple meta-analyses have shown small to moderate benefits with psychosocial interventions for CRF [99, 139–148]. The design of these interventions has varied by trials, some focusing on energy conservation and activity management interventions [141, 149], while others providing supportive interventions such as emotional and social support and self-care coaching [139]. Studies have shown that CBT may be more effective than other psychosocial approaches in reducing fatigue symptoms [150], with effects maintained at 2 years [151]. For the treatment of CRF, clinicians can refer breast cancer survivors to a provider who can provide CBT-based therapy.

Nutrition and Supplements

Nutritional supplements are commonly used to manage symptoms. Though meta-analyses and overviews regarding nutritional supplements and CRF describe no clear effect [152, 153], several are worthy of mention. A pilot study of

breast cancer survivors by Zick et al. [154], for instance, showed a significant reduction in CRF with a diet rich in fruit, vegetables, whole grains, and omega-3 fatty acid-rich foods. Nutritional supplements, such as omega-3 or omega-6 fatty acids, coenzyme Q10, guaraná, and ginseng, have also been studied for their effects on CRF, due to their antioxidant and/or anti-inflammatory properties. Peppone et al. conducted a 3-arm study comparing omega-3 fatty acids, a combination of omega-3 and omega-6 fatty acids, and omega-6 fatty acid supplements on CRF in 108 breast cancer survivors. Although all participants showed improvement from baseline in their level of CRF, the improvements were significantly greater in those receiving omega-6 fatty acid supplements alone than in the other two arms [155].

Current evidence is insufficient and inconsistent to conclude the effects of coenzyme Q10 and guaraná supplements on CRF. Coenzyme Q10 is a nutrient that occurs naturally in the body. It acts as an antioxidant to protect cells from damage, plays an important role in metabolism, and has a side effect of mild insomnia. Coenzyme Q10 was shown reducing CRF in breast cancer patients receiving chemotherapy when supplementing it with L-carnitine and branched-chain amino acids [156] but did not reduce CRF when supplementing it with vitamin E [157]. Guaraná, derived from the seed of a Brazilian plant native to the Amazon basin, is touted to be helpful for weight loss, enhanced athletic performance, as a stimulant, and to reduce mental and physical fatigue. Stimulant properties of guaraná are likely due to its high caffeine content, which is among the highest of any plant. Compared to coffee which contains 2% caffeine by weight, guaraná contains 3.6–5.8% caffeine by weight. Effects of 2–3 weeks guaraná supplements on CRF in breast cancer patients receiving chemotherapy were also inconsistent [158–160].

Ginseng, used for centuries in Chinese medicine, is derived from the root of a plant and has antioxidant and anti-inflammatory properties. Ginseng appears to have some effects on reducing CRF [161–164]; however, the potential herbal-drug interactions need to be considered, particularly in patients undergoing chemotherapy [165]. A patient developed liver toxicity during chemotherapy when concurrent use of a ginseng supplement [166]. Another case report indicated that the ginseng supplement might lower a patient's response to chemotherapy [167].

Pharmacologic Treatments

Only limited data support the efficacy of pharmacologic treatment for CRF, but a therapeutic trial of medication can be tried if non-pharmacologic interventions are not helpful. Studies to date have evaluated psychostimulants (methylphenidate, dexmethylphenidate, and modafinil), antidepressants (paroxetine, sertraline), and glucocorticoids [51, 168–172]. Of the psychostimulants studied, the most data is available for methylphenidate and modafinil. A 2010 Cochrane review and 2018 meta-analysis both report improvement in CRF with the use of methylphenidate [169, 172]. However, the 2018 meta-analysis did not find that modafinil had any efficacy, and the magnitude of the effect of methylphenidate was of questionable clinical significance [169]. Data for the use of antidepressants for CRF has been disappointing. In the absence of depression, clinical trials have demonstrated no impact of antidepressants on fatigue in cancer survivors [51, 90, 170]. Glucocorticoids can alleviate CRF in cancer patients. In a randomized study of 84 patients with advanced cancer, significant improvements in the level of CRF and physical distress were seen after 15 days of dexamethasone, 4 mg twice daily, versus placebo. No significant increase in adverse events occurred during the short follow-up of this study [168]. Nonetheless, the risk of side effects of glucocorticoid use limits its application for CRF in cancer survivors.

Future Research

Many gaps exist in the area of CRF research. The negative impact of CRF on other outcomes such as healthcare utilization, cost, and survival needs to be studied. Despite studies consistently demonstrating the benefits of physical activity inter-

ventions in CRF, the optimal dose and intensity of exercise remain unclear. Given the multidimensional nature of CRF, a one-size-fits-all approach is likely not sufficient. Combinations of various strategies such as exercise and other nonpharmacologic interventions (e.g., psychological therapies, behavioral modifications) need to be further investigated. With an increasing emphasis on personalized medicine in oncology, an understanding of the biobehavioral mechanisms associated with CRF is necessary to develop individualized care plans and to know which treatment is most effective for whom. Finally, dissemination of the clinical practice guidelines into clinical settings is essential to identify patients with CRF and implement individualized treatment plans.

Conclusion

CRF is a commonly reported, debilitating toxicity experienced by patients surviving after breast cancer diagnosis and treatment and can persist for many years. Screening for CRF should be incorporated into routine cancer care. Nonpharmacologic interventions (e.g., physical activity, mind-body interventions, cognitive-behavioral interventions) can effectively treat CRF and should be prescribed prior to pharmacologic approaches into the care plan for breast cancer survivors with CRF.

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