Curr. Treat. Options in Oncol. (2020) 21: 17
DOI 10.1007/s11864-020-0707-5

Palliative and Supportive Care (MP Davis, Section Editor)

Cancer-Related Fatigue: Causes and Current Treatment Options

Melissa S.Y. Thong[1,*]
Cornelis J. F. van Noorden[2,3]
Karen Steindorf[4]
Volker Arndt[1]

Address
[*,1]Unit of Cancer Survivorship, Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), P.O. Box 101949, 69009, Heidelberg, Germany
Email: m.thong@dkfz.de
[2]Department of Medical Biology, Amsterdam University Medical Centers, AMC, Amsterdam, Netherlands
[3]Department of Genetic Toxicology and Tumor Biology, National Institute of Biology, Ljubljana, Slovenia
[4]Division of Physical Activity, Prevention and Cancer, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany

Published online: 5 February 2020

This article is part of Topical Collection on *Palliative and Supportive Care*

Keywords Cancer-related fatigue · Cytokines · Physical activity · Pharmacologic · Complementary and alternative medicine

Opinion statement

Cancer-related fatigue (CRF) is a problem for a significant proportion of cancer survivors during and after active cancer treatment. However, CRF is underdiagnosed and undertreated. Interventions are available for CRF although there is no gold standard. Based on current level of evidence, exercise seems to be most effective in preventing or ameliorating CRF during the active- and posttreatment phases.

Introduction

Fatigue is a symptom commonly experienced by survivors of cancer through all stages of the disease trajectory. Survivors identify fatigue as a significant problem which is not adequately addressed by healthcare providers [1•]. Being fatigued has a greater negative impact on functioning and health-related quality of life (HRQoL) than other symptoms such as pain or depression [2, 3]. Fatigued survivors are more likely to have reduced

employment participation [4, 5], greater financial stress [6], and higher healthcare utilization [6, 7]. Moreover, fatigue may reduce survival; feeling fatigued at diagnosis [6, 8] and during survivorship [9] is associated with higher mortality.

This review aims to provide a summary on the current state of research on cancer-related fatigue (CRF) of survivors with local disease treated with curative intent. We briefly summarize the prevalence, definition, evaluation, and etiology of CRF. Due to the volume of research on CRF treatments, we provide a non-exhaustive overview of treatments for CRF published within the last 5 years (guidelines, meta-analyses, reviews, randomized trials).

Prevalence of CRF

Cancer and its treatments are often the main triggers of fatigue, either induced directly or indirectly by associated toxicities [10]. The prevalence of CRF varies, depending on whether it is assessed during active treatment or after treatment is completed. Most survivors of cancer, defined as all individuals with a cancer experience from the time of diagnosis through to the balance of his or her life by the US National Coalition for Cancer Survivorship [11], experience CRF during active treatment, which often peaks toward end of active treatment and diminishing thereafter [6, 12-15]. Nevertheless, a significant proportion of survivors who are disease-free still feel fatigued years after active treatment had ended [16, 17].

Active or maintenance treatment phase

Among survivors undergoing active treatment, CRF rates vary between 62% and 85%, of which 9% to 45% reported moderate-to-severe CRF [18, 19]. Survivors on maintenance therapy such as adjuvant endocrine therapy or androgen deprivation therapy (ADT) are more likely to experience CRF [20, 21]. Fifty-six percent of survivors of breast cancer receiving aromatase inhibitors report moderate-to-severe CRF [22]. Survivors of prostate cancer who currently use ADT or had used ADT in the past were more likely to report CRF than survivors who never used ADT (38% current vs 23% past vs 16% never, $p < 0.0001$) [23].

Survivorship phase

Prevalence rates of CRF also vary during the survivorship phase, depending on the time since diagnosis, short-term (< 5 years post-diagnosis) or long-term (≥ 5 years post-diagnosis).

Short-term CRF

Sixty percent of survivors of breast cancer reported moderate-to-severe tiredness 12 months after diagnosis [24]. Between 21% and 52% of survivors still experience severe CRF up to 3 years post-diagnosis [18, 25, 26].

Long-term CRF

During long-term survivorship, a significant proportion of survivors report being fatigued. One in four survivors of adolescent and young adult (AYA) cancers is still chronically fatigued 5-30 years after diagnosis [27]. Rates of

chronic CRF ranging between 23% and 49% have been reported by long-term adult survivors of cervical [28], lower gastrointestinal [17], breast [29], lymphoma [30], and mixed cancers [31]. Constant levels of fatigue have also been observed from 5 to 15 years post-diagnosis in survivors of breast, colorectal, and prostate cancer [32].

Age-related CRF

The perceived severity of CRF differs significantly by age. Intuitively, we expect fatigue to be more prominent among the elderly, with or without cancer [33]. However, the burden of fatigue seems to be greater among younger survivors of cancer when compared with non-cancer controls of comparable age [34]. The prevalence of fatigued survivors of AYA cancers is more than double that of age- and sex-matched peers [35], with 85% survivors of AYA cancers reported experiencing fatigue in the past month [36]. AYA survivors of sarcoma were more likely to report daytime CRF compared to middle-aged or elderly survivors [37]. AYA and adult, but not elderly, survivors of thyroid cancer reported clinically relevant higher levels of fatigue than non-cancer controls [38].

Definition

The most comprehensive and commonly used definition, from the National Comprehensive Cancer Network (NCCN), describes CRF as "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 functioning" [39••]. Of note, this definition acknowledges the multiple dimensions of CRF, and that CRF is often not relieved by rest unlike fatigue experienced by healthy individuals.

There is debate whether CRF is the expression of different dimensions of one symptom (multidimensional concept) or that it comprises separate symptoms collectively called fatigue (multiple symptom concept) [40, 41]. The heterogeneous relationship between mental and physical fatigue, each having different correlates, suggests that these symptoms are separate phenomena, giving credence to the multiple symptom concept of CRF [42, 43]. The challenge of adopting a standard definition of CRF needs to be resolved as it can have implications for the development of treatment guidelines and research into CRF [44•].

Evaluation

Despite its prevalence and debilitating nature, CRF is underdiagnosed and undertreated [18, 45]. Up to 50% of survivors reported not discussing, getting advice, nor receiving desired help for CRF [18, 36, 46], even though clinical guidelines recommend systematic screening and management of CRF from diagnosis through to follow-up [47]. For example, the NCCN guidelines outline four general steps involving screening, evaluation, intervention, and reevaluation of CRF [39••]. Screening for CRF should be implemented for all survivors of cancer, and it can be conducted at any phase of the cancer trajectory. Survivors positively screened for CRF should then undergo a more comprehensive history and physical examination, encompassing clinical information (e.g., disease

status, treatment received) and details on CRF such as the onset, pattern, duration, alleviating factors, and interference with function. Detailed evaluation of CRF is necessary not only for planning of treatment but also to rule out depression. Fatigue is a feature characteristically associated with depression [48, 49]. Interventions for CRF include pharmacologic and non-pharmacologic options. Reevaluation for CRF is recommended to assess the efficacy of the management strategy. This 4-step process is best conducted periodically, at first visit, during active treatment, after completion of treatment, and during follow-up.

Self-reported questionnaires

As CRF is considered to be a subjective phenomenon, it is appropriate to use self-report questionnaires for assessment [39••]. Significant discrepancies in ratings of CRF severity have been observed between physician and survivor reports, with physician ratings much lower than that of the survivor [50]. For screening purposes, a valid and reliable instrument such as a numeric score with determined cutoffs is an option [39••]. Commonly used uni- or multidimensional questionnaires include the Brief Fatigue Inventory, European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 fatigue subscale, Functional Assessment of Cancer Therapy - Fatigue, Piper Fatigue Scale [51, 52]. The EORTC has recently developed a questionnaire module that specifically assesses multiple dimensions of CRF (physical, cognitive, emotional) [53].

Barriers to implementation of clinical management of CRF

Barriers at survivor and clinical levels contribute to the underdiagnosis and undertreatment of CRF [39••]. Survivors of cancer may perceive that CRF is inexorable, something they "have to live with" and only 19% believe that "something could be done" about CRF [36]. Often, survivors do not discuss CRF with their physician for a variety of reasons; they think CRF is unimportant; they fear either dose reduction or treatment discontinuation if they mention that they feel fatigued [47]. Although 41% of survivors have not been recommended CRF treatments [36], of those who have received either pharmacological or non-pharmacological treatments, 52% perceived that treatment was effective [18]. Likewise, clinicians may not initiate a discussion on CRF, either having perceptions similar to that of the survivors [39••] or due to lack of resources [54•].

Mechanisms underlying CRF

Despite its prevalence and debilitating effects, the etiology underlying CRF is still not well-understood. Evidence suggests the involvement of complex multifactorial processes linked to a range of molecular/physiological, clinical, and psychological factors.

Molecular/physiological factors

Potential disruptions originating in the central (inflammation, hypothalamic-pituitary-adrenal axis) and/or peripheral (e.g., reduced energy metabolism)

nervous systems may induce CRF [44•]. Central fatigue can be characterized as a perceived reduced ability to complete physical or mental tasks without demonstrable cognitive or motor deficiencies [55, 56]. Peripheral fatigue is ascribed as the inability of muscles to perform a task in response to stimulation ("muscle fatigue") or reduced endurance [44•, 57•].

Inflammation and immune system

CRF often co-occurs with symptoms such as pain, insomnia, lethargy, altered mood, and cognitive impairment, which are similar to symptoms collectively known as "sickness behavior" [58•, 59]. Sickness behavior is an adaptive response to inflammation, and there is sufficient evidence of the role of inflammation in CRF [44•, 60]. Cancer and its treatments can activate the peripheral pro-inflammatory cytokine network, producing symptoms of CRF via the cytokine signaling in the central nervous system [61•, 62]. Neuroinflammation has been postulated as a possible mechanism for persistent CRF [58•], after cessation of chemotherapy [63].

Hypothalamic-pituitary-adrenal (HPA) axis

Related to the activation of the inflammatory response and the immune system is the dysregulation of the HPA axis in the direct or indirect development of CRF [44•]. Cytokines released as a result of the cancer and/or its treatments into the central nervous system can stimulate the HPA axis [58•]. One function of the HPA axis is to regulate the release of cortisol during times of stress. Cortisol can inhibit cytokine production to protect the body from overactivation of the immune system and can minimize tissue damage due to inflammation [44•]. Dysregulation of cortisol levels in the blood has been associated with physical fatigue in survivors of breast cancer [64]. Altered cortisol levels have also been associated with disruption of the circadian rhythm and sleep deficiency [65•]. Flattened circadian rhythms [66] and disturbed sleep [67] during chemotherapy have been associated with CRF in survivors of breast cancer.

Reduced energy metabolism

A disrupted energy metabolism (adenosine triphosphate (ATP) production), as a consequence of cachexia or damage of the sarcoplasmic reticulum and/or mitochondria after chemotherapy or radiotherapy, can cause possible long-term side effects to all tissues and in particular to skeletal muscle [44•, 58•]. This effect on skeletal muscle could, in turn, increase the risk of peripheral fatigue.

Clinical factors

Comorbidity

A significant proportion of survivors have problems with fatigue even before the start of treatment [68, 69], and this problem can persist [50] or even exacerbate during follow-up [14]. Pre-existing comorbid conditions such as anemia, cardiac conditions, diabetes mellitus, or psychiatric conditions could contribute to fatigue severity at the start of cancer treatment [69, 70]. Medications to treat

these conditions (e.g., beta-blockers, antidepressants) could also increase fatigue [39••]. Comorbid conditions are also associated with CRF in long-term survivorship [9, 71].

Cancer treatment

Treatment for cancer such as surgery [72], chemotherapy [73, 74], hormone therapy [75], endocrine therapy [76], and radiotherapy [77] can result in CRF, either as a direct consequence or as a secondary effect. Of interest, although radiotherapy increased CRF in some cancers [78-80], it does not seem to be an associated risk factor in breast cancer [15, 73]. Cumulative effects of treatment and CRF are possible because survivors who received trimodal (surgery, chemotherapy, and radiotherapy, with or without hormone therapy) treatment reported higher levels of CRF than survivors receiving other treatment combinations [17, 73]. Conditions consequent to cancer treatment such as anemia [75], hypothyroidism [81], insomnia [2], pain [2], and hypopituitarism [80] could also contribute to CRF. Clinicians should be aware of and manage potentially preventable treatment-related toxicities so as to reduce the burden of CRF.

Psychological factors

Psychological factors such as a history of depression or psychosocial distress at baseline have been associated with CRF [68, 82]. Survivors who have a tendency toward negative exaggeration and attention to symptoms ("catastrophizing") were more likely to be more fatigued [83]. Fear of recurrence of cancer is also associated with CRF [34].

Treatment options for CRF

Pharmacological and non-pharmacological treatments are currently used to manage CRF. However, these interventions yield, at most, moderate benefits in meta-analyses.

Pharmacologic

Although pharmacologic treatments have been used to treat CRF, results from a meta-analysis by Mustian et al. suggest that such treatments, in comparison with non-pharmacologic (exercise and psychological) interventions, are the least effective for CRF [84••].

Stimulants

The rationale for using stimulants for the management of CRF is its potential rapid effect to counteract the feelings of low energy, lowered mental capabilities, or lethargy associated with fatigue [85•].

Methylphenidate, originally indicated for attentional deficit disorder, has been extensively studied for its efficacy to reduce CRF. Although clinical studies suggest that methylphenidate is superior to placebo, results from meta-analyses indicate modest effects backed by weak evidence [86, 87, 88••, 89]. Methylphenidate is generally well-tolerated. Nevertheless, it has been associated with

nonserious adverse side effects such as sleep problems or decreased appetite, which could exacerbate CRF [90]. It is also contraindicated in cases of uncontrolled hypertension or cardiac problems [85•]. As such, methylphenidate should not be routinely prescribed for CRF management but selectively used for survivors whose benefits from its use outweigh the disadvantages [88••].

Modafinil is a wakefulness-inducing compound [91]. However, meta-analyses suggest that modafinil was no better than placebo in ameliorating CRF [86, 88••, 92].

Corticosteroids are not associated with reduction in CRF [88••].

Antidepressants

Research on the use of antidepressants in managing CRF is limited [88••]. Bupropion could be helpful for CRF when it co-occurs with depression, although it should be administered with care to survivors with anxiety problems [85•, 93•].

Erythropoietin

Erythropoietin can be effective in ameliorating CRF if it is associated with anemia (either at the start of or during active cancer treatment) by increasing levels of hemoglobin [88••]. However, current clinical guidelines recommend erythropoiesis-stimulating agents as treatment for anemia for only selected patients due to safety concerns regarding tumor growth and increased risk of cardiovascular events [94•, 95•].

Non-pharmacologic

Non-pharmacologic treatments for the management of CRF during active treatment phase are more widely accepted, with a choice of options. There is ample evidence from clinical trials, systematic reviews, and meta-analyses attesting to their efficacy, to varying degrees.

Exercise/physical activity

Although some uncertainty still remains about the benefits of exercise in reducing CRF in general, there is compelling evidence that it does not increase CRF [96•]. A meta-analysis reported that exercise during adjuvant radiotherapy for breast cancer was more effective in reducing fatigue than a control intervention [97•]. Similarly, Hilfiker et al. showed that exercise during active cancer treatment was associated with reduced CRF [98•]. In their meta-analysis, Mustian et al. compared the effectiveness of pharmacologic, psychological, and exercise treatments for CRF. They reported that exercise interventions showed the greatest effect in reducing CRF, albeit of moderate efficacy [84••]. A Cochrane review concluded that aerobic exercise showed moderate level of evidence in reducing CRF in adult survivors of hematological cancers [99••]. In another meta-analysis, Kessels et al. reported a large pooled effect of exercise on CRF [100•].

There is increasing clinical and empirical support to provide interventions in the preoperative phase ("prehabilitation") to optimize functional status and reduce the incidence or severity of postoperative complications [101, 102]. These interventions are often multimodal, incorporating exercise/physical

activity, psychological, and nutritional aspects to enhance postoperative functioning [103]. However, these interventions are developed not specifically to reduce CRF. A study from 2011 reported on an education intervention provided prior to radiotherapy to enhance self-management of CRF [104]. Although the intervention showed no effect in reducing CRF, it did increase physical activity participation. Despite its promise in reducing postoperative morbidity and improving physical functioning, efficacy of prehabilitation programs still lacks strong evidence and may not be suitable for all survivors [105, 106].

Regarding the mode of exercise intervention (e.g., aerobic, strength/resistance, or combination of both), results on efficacy against CRF are mixed [107]. In Mustian et al.'s meta-analysis, mode of intervention was not associated with intervention effectiveness [84••]. However, in other meta-analyses, aerobic exercise (alone or in combination) was associated with large effects in reducing CRF [97•, 100•], during and after cancer treatment [98•]. A meta-analysis of randomized controlled trials of aerobic exercise and CRF suggest that exercise of longer duration can have a significant effect on CRF, especially if provided after completion of adjuvant therapy [108•].

Group-based or in-person/supervised exercise programs [84••, 100•, 107, 108•] may have an added benefit of facilitating engagement and improving adherence to the intervention [107]. In studies with high adherence, a large effect size of exercise on CRF was noted [100•].

Assessment of the long-term efficacy of exercise, post-intervention, is hampered by the generally short period of follow-up. However, evidence suggests that the positive effects of exercise could be maintained in the long term. A randomized controlled trial, involving an 18-week supervised intervention among survivors of breast and colon cancer, reported that at 4-year follow-up since start of intervention, survivors in the intervention arm reported higher levels of moderate-to-vigorous physical activity levels [109]. Although levels of physical fatigue were lower in the intervention arm, this difference was not significant.

Psychological/psycho-education

Psychological interventions have been shown to be modestly effective in reducing CRF, second to exercise interventions [84••].

Of the psychological interventions available, cognitive behavioral therapy (CBT) was the most effective in reducing CRF, especially if provided after end of active treatment [84••, 98•]. Furthermore, CBT has been shown to be effective in addressing insomnia, a symptom commonly coexisting with CRF, thus reducing CRF [92].

Mindfulness-based interventions are designed to enhance the emotion-focused coping of uncertainties and anxieties resulting from cancer and treatment [110]. Results from two meta-analyses and a Cochrane review indicated its effectiveness in reducing CRF in the short term, in comparison with usual care [111•, 112•, 113••]. Medium-term effects of such interventions on CRF were not significant. Most studies have focused on survivors of breast cancer [112•].

As a significant proportion of survivors of cancer may have erroneous perceptions about CRF that prevents them from seeking help [36, 39••], educational interventions could be an effective option to address these possible

misconceptions. However, a Cochrane review concluded that educational interventions may have a small effect in ameliorating CRF intensity and interference on daily life and a moderate effect on reducing CRF distress [114•]. The review also recommended that efficacy of educational interventions may improve, if provided in combination with other interventions.

Mixed modal interventions (e.g., exercise and psychological or psycho-education), delivered after completion of active treatment, have been shown to be effective in reducing posttreatment CRF [84••, 98•].

Mind/body wellness training

A plethora of interventions aimed at improving mind/body wellness and reducing CRF is currently available, although they may not be efficacious.

Yoga is a mind/body practice of South Asian origin and is increasingly popular for the management of cancer-related symptoms. Nevertheless, clinical evidence of its effectiveness in managing CRF is equivocal. A Cochrane review indicated that there is a moderate level of evidence supporting the short-term benefits of yoga in reducing CRF when compared with either no treatment or psychosocial/educational interventions [115••]. A review of results from randomized controlled trials suggests that yoga can be effective in reducing CRF during treatment and posttreatment [116]. Clinical guidelines have upgraded the level of evidence for yoga to a "C" as a management option for posttreatment CRF [117••]. However most studies have been conducted on survivors of breast cancer and have methodological issues which need to be addressed in future studies [116].

Qigong and tai chi have also been advocated for the reduction of CRF. Both forms of intervention are rooted in Eastern traditional medical practice. Therapeutic qigong has a theoretical foundation in supporting/strengthening the psychoneuroimmunologic system [118]. The practice focuses on the restoration, rejuvenation, and healing of the body through a series of rhythmic and flowing movements including breath regulation and mindful meditation. Although tai chi has its foundation in the martial arts, when performed for therapeutic purposes, it can be considered as a form of qigong [118]. Using Bayesian network analysis, two meta-analyses found no association between qigong/tai chi and reduction in CRF [98•, 119]. Two recent meta-analyses concluded that qigong/tai chi shows promise in reducing CRF and improving HRQOL, but evidence of its efficacy needs to be strengthened [120•, 121•]. A meta-analysis of randomized controlled trials on tai chi reported that the intervention was effective in reducing CRF during the period of intervention [122]. However, long-term post-intervention effect on CRF is unclear. Future studies involving larger and heterogeneous samples, better designed with sound methodology, and longer follow-up are needed.

Acupuncture for the management of CRF has shown mixed results. Duong et al. reported in their meta-analysis that acupuncture was not effective in reducing the severity of CRF in survivors of cancer and recipients of hematopoietic stem cell transplantation [111•]. Likewise, a meta-analysis using Bayesian network analysis ranked acupuncture as the lowest in its efficacy in reducing CRF [119]. On the other hand, in their meta-analysis of 10 studies conducted mainly among survivors of breast and gynecological cancers, Zhang et al. concluded that acupuncture could be an effective option in the arsenal of CRF

interventions [123]. In the clinical guidelines on integrative therapies, acupuncture for treatment of CRF had a classification of low strength of evidence and may be considered as an option for improving posttreatment CRF [117••].

Although massage has been promoted to relieve CRF, there is a paucity of evidence regarding its efficacy against CRF [111•]. Massage was not mentioned as a potential therapy for CRF in the guidelines on integrative therapies [117••]. A 2016 Cochrane review on the efficacy of massage on cancer-related symptoms including CRF concluded that there was no evidence of clinical effectiveness of massage to ameliorate CRF [124•]. In contrast, a meta-analysis in 2018 suggests that massage, given during active treatment, was effective against CRF [98•]. A recent randomized single-blind study with 66 posttreatment survivors of breast cancer reported that a 6-week Swedish massage intervention was significantly superior to light touch or waitlist control in reducing CRF [125].

Relaxation techniques which can include progressive muscle relaxation, self-hypnosis, or deep breathing have been shown to be effective in reducing CRF, [111•, 117••] especially during cancer treatment [98•]. Nevertheless, the level of evidence for relaxation techniques is low, and clinical guidelines recommend that hypnosis (self-induced or facilitated by a specialist) may be considered for reducing CRF during cancer treatment [117••]. A 12-week supervised group intervention compared the effect of resistance exercise and relaxation on CRF [126]. Results showed that resistance exercise was superior to relaxation in reducing CRF of survivors of breast cancer undergoing chemotherapy.

Reduced exposure to bright light during cancer treatment has been associated with CRF, possibly due to disruption of the circadian activity rhythm [66, 127]. Bright light therapy (BLT) is a relatively new therapy for management of CRF which requires survivors to expose themselves to bright white light in the morning for a period of time [128]. Compared with other CRF treatments such as exercise or psychological interventions, BLT is considered a safe and accessible option that requires relatively low input from survivors [129]. Results from a recent blinded randomized controlled trial were promising; the BLT group showed a 17% reduction in CRF at the end of the 4-week intervention [130]. However, research on the efficacy of BLT on CRF is limited, but another multicenter randomized trial with a longer follow-up is currently in progress [131].

Nutritional and dietary supplements

Healthcare providers often are not aware of the common use of nutritional and dietary supplements among survivors of cancer to manage cancer-related symptoms [132]. Clinical trials on the use of nutritional and dietary supplements to improve CRF are still limited [133•, 134]. Most studies have small sample sizes and are conducted mainly with survivors of breast cancer [135].

The most studied natural medicine to combat CRF is ginseng, comprising either the Asian (*Panax ginseng*) or American (*Panax quinquefolius*) ginseng. A systematic review on fatigue in general concluded that ginseng, regardless of type, seems to have modest efficacy in reducing fatigue although there are issues with small sample sizes and generalizability of results [136]. Another systematic review focused on survivors of breast cancer, reported mixed results from 2 studies on the efficacy of ginseng [132]. Clinical guidelines on integrative therapies rated ginseng a "C" based on the level of evidence of its efficacy in reducing CRF during active cancer treatment [117••].

Guarana is a stimulant derived from a plant native to the Amazon basin. The few studies on its efficacy to reduce CRF have small sample sizes, and results are inconsistent [132]. A double-blind crossover randomized clinical trial found no effect of guarana on fatigued survivors of breast cancer undergoing chemotherapy [137]. Based on current levels of evidence, clinical practice guidelines on integrative therapies do not recommend the use of guarana for reducing CRF during cancer treatment [117••].

Although some studies have recommended the use of L-carnitine or appetite stimulants for the management of CRF, the number of studies on these treatments are limited to allow for data synthesis in a meta-analysis [88••]. A systematic review on dietary supplements reported that L-carnitine, on its own, did not improve CRF and had associated side effects such a neuropathy and decreased functioning [135]. Based on current levels of evidence, clinical practice guidelines on integrative therapies do not recommend the use of L-carnitine for CRF reduction during cancer treatment [117••].

Discussion

CRF is a prevalent and distressing problem for a significant proportion of survivors of cancer during active treatment and in the survivorship phase. Although there is a range of interventions available, the gold standard for the treatment of CRF remains elusive. Current levels of evidence for the treatment of CRF show, at most, moderate effects. Of the interventions available for CRF, exercise-based interventions are the most promising and are recommended as first-line treatment for CRF [84••].

It is possible that the modest treatment efficacy could be attributed to suboptimal delineation of CRF; i.e., the multidimensional nature of CRF is not considered when planning treatments [43]. As such, treatments may not be personalized to survivors' CRF experience. It is clinically intuitive that a better classification of CRF and a more accurate identification of survivors at-risk for long-term CRF have implications for treatment response and prognosis, for example, targeting physical activity interventions to those in need, e.g., survivors with complaints of physical but not mental fatigue [138]. In contrast, survivors more burdened by mental fatigue may find relief with psychosocial interventions [12].

Although the body of research on CRF is substantial and growing, studies on interventions are still hampered by a myriad of issues such as limited heterogeneity of samples (e.g., focus mainly on survivors of breast cancer), small sample sizes, or poor methodological design with short follow-ups.

Funding

Open Access funding enabled and organized by Projekt DEAL.

Compliance with Ethical Standards

Conflict of Interest

Melissa S.Y. Thong declares that she has no conflict of interest.

Cornelis J. F. van Noorden declares that he has no conflict of interest.

Karen Steindorf has received speaker's honoraria from adViva Heidelberg, BIG Health Insurance (Dortmund), Preventon (Frankfurt); has received reimbursement for travel expenses from Asklepios Clinics (Hamburg), BIG

Health Insurance (Dortmund), and Preventon (Frankfurt); and has received compensation from Pfizer for consulting on/writing a brochure on physical activity and cancer for breast cancer patients.
Volker Arndt declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Open Access

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• National Coalition for Cancer Survivorship. Cancer survivorship survey: findings from an online survey of adult cancer patients. 2019. https://www.canceradvocacy.org/wp-content/uploads/2019/09/NCCS-Survivorship-Survey-Final-Report.pdf. Accessed 16 October 2019
Fatigue was identified as one of the most severe side effects experienced by survivors but is not adequately addressed by health care providers.

2. Cheng KK, Lee DT. Effects of pain, fatigue, insomnia, and mood disturbance on functional status and quality of life of elderly patients with cancer. Crit Rev Oncol Hematol. 2011;78:127-37. https://doi.org/10.1016/j.critrevonc.2010.03.002.

3. Arndt V, Stegmaier C, Ziegler H, Brenner H. A population-based study of the impact of specific symptoms on quality of life in women with breast cancer 1 year after diagnosis. Cancer. 2006;107:2496-503. https://doi.org/10.1002/cncr.22274.

4. Duijts SF, van Egmond MP, Spelten E, van Muijen P, Anema JR, van der Beek AJ. Physical and psychosocial problems in cancer survivors beyond return to work: a systematic review. Psychooncology. 2014;23:481-92. https://doi.org/10.1002/pon.3467.

5. Ekenga CC, Pérez M, Margenthaler JA, Jeffe DB. Early-stage breast cancer and employment participation after 2 years of follow-up: a comparison with age-matched controls. Cancer. 2018;124:2026-35. https://doi.org/10.1002/cncr.31270.

6. Behringer K, Goergen H, Müller 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;34:4329-37. https://doi.org/10.1200/jco.2016.67.7450.

7. Heins MJ, Korevaar JC, Rijken PM, Schellevis FG. For which health problems do cancer survivors visit their general practitioner? Eur J Cancer. 2013;49:211-8. https://doi.org/10.1016/j.ejca.2012.07.011.

8. Groenvold M, Petersen MA, Idler E, Bjorner JB, Fayers PM, Mouridsen HT. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. Breast Cancer Res Treat. 2007;105:209-19. https://doi.org/10.1007/s10549-006-9447-x.

9. Adam S, van de Poll-Franse LV, Mols F, Ezendam NPM, de Hingh I, Arndt V, et al. The association of cancer-related fatigue with all-cause mortality of colorectal and endometrial cancer survivors: results from the population-based PROFILES registry. Cancer Med. 2019;8:3227-36. https://doi.org/10.1002/cam4.2166.

10. Santos JC, Pyter LM. Neuroimmunology of behavioral comorbidities associated with cancer and cancer treatments. Front Immunol. 2018;9. https://doi.org/10.3389/fimmu.2018.01195.

11. National Coalition for Cancer Survivorship. http://www.canceradvocacy.org/. Accessed 26 September 2017.

12. Schmidt ME, Wiskemann J, Schneeweiss A, Potthoff K, Ulrich CM, Steindorf K. Determinants of physical, affective, and cognitive fatigue during breast cancer therapy and 12 months follow-up. Int J Cancer. 2018;142:1148-57. https://doi.org/10.1002/ijc.31138.

13. Zhao F, Cella D, Manola J, DiPaola RS, Wagner LI, Haas NSB. Fatigue among patients with renal cell carcinoma receiving adjuvant sunitinib or sorafenib: patient-reported outcomes of ECOG-ACRIN E2805 trial. Support Care Cancer. 2018;26:1889-95. https://doi.org/10.1007/s00520-017-4027-7.

14. Reinertsen KV, Engebraaten O, Loge JH, Cvancarova M, Naume B, Wist E, et al. Fatigue during and after breast cancer therapy—a prospective study. J Pain Symptom Manag. 2017;53:551-60. https://doi.org/10.1016/j.jpainsymman.2016.09.011.

15. Velikova G, Williams LJ, Willis S, Dixon JM, Loncaster J, Hatton M, et al. Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. Lancet Oncol. 2018;19:1516-29. https://doi.org/10.1016/S1470-2045(18)30515-1.
16. Crossnohere NL, Richardson DR, Reinhart C, O'Donoghue B, Love SM, Smith BD, et al. Side effects from acute myeloid leukemia treatment: results from a national survey. Curr Med Res Opin. 2019:1-6. https://doi.org/10.1080/03007995.2019.1631149.
17. Frick MA, Vachani CC, Hampshire MK, Bach C, Arnold-Korzeniowski K, Metz JM, et al. Survivorship after lower gastrointestinal cancer: patient-reported outcomes and planning for care. Cancer. 2017;123:1860-8. https://doi.org/10.1002/cncr.30527.
18. Roila F, Fumi G, Ruggeri B, Antonuzzo A, Ripamonti C, Fatigoni S, et al. Prevalence, characteristics, and treatment of fatigue in oncological cancer patients in Italy: a cross-sectional study of the Italian network for supportive care in cancer (NICSO). Support Care Cancer. 2019;27:1041-7. https://doi.org/10.1007/s00520-018-4393-9.
19. Wang XS, Zhao F, Fisch MJ, O'Mara AM, Cella D, Mendoza TR, et al. Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. Cancer. 2014;120:425-32. https://doi.org/10.1002/cncr.28434.
20. Bower JE, Wiley J, Petersen L, Irwin MR, Cole SW, Ganz PA. Fatigue after breast cancer treatment: biobehavioral predictors of fatigue trajectories. Health Psychol. 2018;37:1025-34. https://doi.org/10.1037/hea0000652.
21. Langston B, Armes J, Levy A, Tidey E, Ream E. The prevalence and severity of fatigue in men with prostate cancer: a systematic review of the literature. Support Care Cancer. 2013;21:1761-71. https://doi.org/10.1007/s00520-013-1751-5.
22. Mao H, Bao T, Shen X, Li Q, Seluzicki C, Im E-O, et al. Prevalence and risk factors for fatigue among breast cancer survivors on aromatase inhibitors. Eur J Cancer. 2018;101:47-54. https://doi.org/10.1016/j.ejca.2018.06.009.
23. Gavin AT, Drummond FJ, Donnelly C, O'Leary E, Sharp L, Kinnear HR. Patient-reported 'ever had' and 'current' long-term physical symptoms after prostate cancer treatments. BJU Int. 2015;116:397-406. https://doi.org/10.1111/bju.13036.
24. Davis LE, Bubis LD, Mahar AL, Li Q, Sussman J, Moody L, et al. Patient-reported symptoms after breast cancer diagnosis and treatment: a retrospective cohort study. Eur J Cancer. 2018;101:1-11. https://doi.org/10.1016/j.ejca.2018.06.006.
25. Koole JL, Bours MJL, Breedveld-Peters JJL, van Roekel EH, Breukink SO, Janssen-Heijnen MLG, et al. Is dietary supplement use longitudinally associated with fatigue in stage I-III colorectal cancer survivors? Clin Nutr. 2019. https://doi.org/10.1016/j.clnu.2018.12.037.
26. Matias M, Baciarello G, Neji M, Di Meglio A, Michiels S, Partridge AH, et al. Fatigue and physical activity in cancer survivors: a cross-sectional population-based study. Cancer Med. 2019;8:2535-44. https://doi.org/10.1002/cam4.2060.
27. Bøhn S-KH, Thorsen L, Kiserud CE, Fosså SD, Lie HC, Loge JH, et al. Chronic fatigue and associated factors among long-term survivors of cancers in young adulthood. Acta Oncol. 2019;58:753-62. https://doi.org/10.1080/0284186X.2018.1557344.
28. Steen R, Dahl AA, Hess SL, Kiserud CE. A study of chronic fatigue in Norwegian cervical cancer survivors. Gynecol Oncol. 2017;146:630-5. https://doi.org/10.1016/j.ygyno.2017.05.028.
29. Reinertsen KV, Cvancarova M, Loge JH, Edvardsen H, Wist E, Fosså SD. Predictors and course of chronic fatigue in long-term breast cancer survivors. J Cancer Surviv. 2010;4:405-14. https://doi.org/10.1007/s11764-010-0145-7.
30. Smeland KB, Loge JH, Aass HCD, Aspelin T, Bersvendsen H, Bolstad N, et al. Chronic fatigue is highly prevalent in survivors of autologous stem cell transplantation and associated with IL-6, neuroticism, cardiorespiratory fitness, and obesity. Bone Marrow Transplant. 2019;54:607-10. https://doi.org/10.1038/s41409-018-0342-y.
31. Husson O, Mols F, van de Poll-Franse L, de Vries J, Schep G, Thong MSY. Variation in fatigue among 6011 (long-term) cancer survivors and a normative population: a study from the population-based PROFILES registry. Support Care Cancer. 2015;23:2165-74. https://doi.org/10.1007/s00520-014-2577-5.
32. Arndt V, Koch-Gallenkamp L, Jansen L, Bertram H, Eberle A, Holleczek B, et al. Quality of life in long-term and very long-term cancer survivors versus population controls in Germany. Acta Oncol. 2017;56:190-7. https://doi.org/10.1080/0284186x.2016.1266089.
33. Gresham G, Dy SM, Zipunnikov V, Browner IS, Studenski SA, Simonsick EM, et al. Fatigability and endurance performance in cancer survivors: analyses from the Baltimore longitudinal study of aging. Cancer. 2018;124:1279-87. https://doi.org/10.1002/cncr.31238.
34. Tibubos AN, Ernst M, Brähler E, Fischbeck S, Hinz A, Blettner M, et al. Fatigue in survivors of malignant melanoma and its determinants: a register-based cohort study. Support Care Cancer. 2019;27:2809-18. https://doi.org/10.1007/s00520-018-4587-1.
35. Poort H, Kaal SEJ, Knoop H, Jansen R, Prins JB, Manten-Horst E, et al. Prevalence and impact of severe fatigue in adolescent and young adult cancer patients in comparison with population-based controls. Support Care Cancer. 2017;25:2911-8. https://doi.org/10.1007/s00520-017-3746-0.
36. Spathis A, Hatcher H, Booth S, Gibson F, Stone P, Abbas L, et al. Cancer-related fatigue in adolescents and young adults after cancer treatment: persistent and poorly managed. J Adolesc Young Adult Oncol. 2017;6:489-93. https://doi.org/10.1089/jayao.2017.0037.
37. Younger E, Husson O, Bennister L, Whelan J, Wilson R, Roast A, et al. Age-related sarcoma patient experience: results from a national survey in England. BMC Cancer. 2018;18:991. https://doi.org/10.1186/s12885-018-4866-8.
38. Mols F, Schoormans D, Smit JWA, Netea-Maier RT, Links TP, van der Graaf WTA, et al. Age-related differences in health-related quality of life among thyroid cancer survivors compared with a normative sample:

results from the PROFILES registry. Head Neck. 2018;40:2235-45. https://doi.org/10.1002/hed.25325.

39.•• NCCN Clinical Practice Guidelines in Oncology. Cancer-related fatigue version 1.2019. 2019. www.nccn.org. Accessed 11 July 2019.

Most current guidelines on CRF

40. de Raaf PJ. Cancer-related fatigue: a multidimensional approach. Rotterdam, P.J. de Raaf, 2013.

41. de Raaf PJ, de Klerk C, van der Rijt CC. Elucidating the behavior of physical fatigue and mental fatigue in cancer patients: a review of the literature. Psychooncology. 2013;22:1919-29. https://doi.org/10.1002/pon.3225.

42. de Raaf PJ, de Klerk C, Timman R, Hinz A, van der Rijt CC. Differences in fatigue experiences among patients with advanced cancer, cancer survivors, and the general population. J Pain Symptom Manag. 2012;44:823-30. https://doi.org/10.1016/j.jpainsymman.2011.12.279.

43. Thong MSY, Mols F, van de Poll-Franse LV, Sprangers MAG, van der Rijt CCD, Barsevick AM, et al. Identifying the subtypes of cancer-related fatigue: results from the population-based PROFILES registry. J Cancer Surviv. 2018;12:38-46. https://doi.org/10.1007/s11764-017-0641-0.

44.• O'Higgins CM, Brady B, O'Connor B, Walsh D, Reilly RB. The pathophysiology of cancer-related fatigue: current controversies. Support Care Cancer. 2018;26:3353-64. https://doi.org/10.1007/s00520-018-4318-7.

Provides a narrative overview of central and peripheral pathophysiologic hypotheses underlying CRF.

45. James S, Wright P, Scarlett C, Young T, Jamal H, Verma R. Cancer-related fatigue: results from patient experience surveys undertaken in a UK regional cancer centre. Support Care Cancer. 2015;23:2089-95. https://doi.org/10.1007/s00520-014-2565-9.

46. Smith TG, Troeschel AN, Castro KM, Arora NK, Stein K, Lipscomb J, et al. Perceptions of patients with breast and colon cancer of the management of cancer-related pain, fatigue, and emotional distress in community oncology. J Clin Oncol. 2019;37:1666-76. https://doi.org/10.1200/jco.18.01579.

47. Ripamonti CI, Antonuzzo A, Bossi P, Cavalieri S, Roila F, Fatigoni S. Fatigue, a major still underestimated issue. Curr Opin Oncol. 2018;30:219-25. https://doi.org/10.1097/cco.0000000000000451.

48. Thompson LMA, Bobonis BM. Distinguishing depressive symptoms from similar cancer-related somatic symptoms: implications for assessment and management of major depression after breast cancer. South Med J. 2017;110:667-72. https://doi.org/10.14423/SMJ.0000000000000705.

49. Schellekens MPJ, Wolvers MDJ, Schroevers MJ, Bootsma TI, Cramer AOJ, van der Lee ML. Exploring the interconnectedness of fatigue, depression, anxiety and potential risk and protective factors in cancer patients: a network approach. J Behav Med. 2019:1-11. https://doi.org/10.1007/s10865-019-00084-7.

50. Smet S, Pötter R, Haie-Meder C, Lindegaard JC, Schulz-Juergenliemk I, Mahantshetty U, et al. Fatigue, insomnia and hot flashes after definitive radiochemotherapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. Radiother Oncol. 2018;127:440-8. https://doi.org/10.1016/j.radonc.2018.03.009.

51. Agasi-Idenburg C, Velthuis M, Wittink H. Quality criteria and user-friendliness in self-reported questionnaires on cancer-related fatigue: a review. J Clin Epidemiol. 2010;63:705-11. https://doi.org/10.1016/j.jclinepi.2009.08.027.

52. Minton O, Stone P. A systematic review of the scales used for the measurement of cancer-related fatigue (CRF). Ann Oncol. 2009;20. https://doi.org/10.1093/annonc/mdn537.

53. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International psychometric validation of an EORTC quality of life module measuring cancer related fatigue (EORTC QLQ-FA12). JNCI. 2017;109. https://doi.org/10.1093/jnci/djw273.

54.• Pearson EJM, Morris ME, McKinstry CE. Cancer related fatigue: implementing guidelines for optimal management. BMC Health Serv Res. 2017;17:496. https://doi.org/10.1186/s12913-017-2415-9.

Barriers to the implementation of CRF guidelines are identified and recommendations to overcome barriers are discussed.

55. Fernandez C, Firdous S, Jehangir W, Behm B, Mehta Z, Berger A, et al. Cancer-related fatigue: perception of effort or task failure? Am J Hosp Palliat Care. 2019;1049909119849420. https://doi.org/10.1177/1049909119849420.

56. Kisiel-Sajewicz K, Davis MP, Siemionow V, Seyidova-Khoshknabi D, Wyant A, Walsh D, et al. Lack of muscle contractile property changes at the time of perceived physical exhaustion suggests central mechanisms contributing to early motor task failure in patients with cancer-related fatigue. J Pain Symptom Manag. 2012;44:351-61. https://doi.org/10.1016/j.jpainsymman.2011.08.007.

57.• Davis MP, Walsh D. Mechanisms of fatigue. J Support Oncol. 2010;8:164-74.

Overview of central and peripheral mechanisms of CRF.

58.• Yang S, Chu S, Gao Y, Ai Q, Liu Y, Li X, et al. A narrative review of cancer-related fatigue (CRF) and its possible pathogenesis. Cells. 2019;8. https://doi.org/10.3390/cells8070738.

Provides a narrative overview of possible pathogenesis of CRF involving mitochondrial dysfunction, the HPA axis and immune/inflammation activation.

59. Cleeland CS, Bennet GJ, Dantzer R, Dougherty PM, Dunn AJ, Meyers CA. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer. 2003;97. https://doi.org/10.1002/cncr.11382.

60. Saligan LN, Olson K, Filler K, Larkin D, Cramp F, Yennurajalingam S, et al. The biology of cancer-related fatigue: a review of the literature. Support Care Cancer.

2015;23:2461-78. https://doi.org/10.1007/s00520-015-2763-0.

61.• Bower JE. Cancer-related fatigue: mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014;11:597-609. https://doi.org/10.1038/nrclinonc.2014.127

This review touches on the mechanisms (focus on inflammation), risk factors, and interventions for CRF.

62. Kim S, Miller BJ, Stefanek ME, Miller AH. Inflammation-induced activation of the indoleamine 2,3-dioxygenase pathway: relevance to cancer-related fatigue. Cancer. 2015;121:2129-36. https://doi.org/10.1002/cncr.29302.

63. Vichaya EG, Chiu GS, Krukowski K, Lacourt TE, Kavelaars A, Dantzer R, et al. Mechanisms of chemotherapy-induced behavioral toxicities. Front Neurosci. 2015;9. https://doi.org/10.3389/fnins.2015.00131.

64. 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. https://doi.org/10.1016/j.bbi.2015.10.005.

65.• Charalambous A, Berger AM, Matthews E, Balachandran DD, Papastavrou E, Palesh O. Cancer-related fatigue and sleep deficiency in cancer care continuum: concepts, assessment, clusters, and management. Support Care Cancer. 2019;27:2747-53. https://doi.org/10.1007/s00520-019-04746-9.

Provides an overview of the relationships of CRF with sleep problems and depression.

66. 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;1:12-26. https://doi.org/10.1080/21641846.2012.741782.

67. Ratcliff CG, Lam CY, Arun B, Valero V, Cohen L. Ecological momentary assessment of sleep, symptoms, and mood during chemotherapy for breast cancer. Psychooncology. 2014;23:1220-8. https://doi.org/10.1002/pon.3525.

68. Bower JE, Asher A, Garet D, Petersen L, Ganz PA, Irwin MR, et al. Testing a biobehavioral model of fatigue before adjuvant therapy in women with breast cancer. Cancer. 2019;125:633-41. https://doi.org/10.1002/cncr.31827.

69. Kreissl S, Mueller H, Goergen H, Mayer A, Brillant C, Behringer K, et al. Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin study group. Lancet Oncol. 2016;17:1453-62. https://doi.org/10.1016/S1470-2045(16)30093-6.

70. Nelson AM, Gonzalez BD, Jim HSL, Cessna JM, Sutton SK, Small BJ, et al. Characteristics and predictors of fatigue among men receiving androgen deprivation therapy for prostate cancer: a controlled comparison. Support Care Cancer. 2016;24:4159-66. https://doi.org/10.1007/s00520-016-3241-z.

71. Oerlemans S, Mols F, Issa DE, Pruijt JHFM, Peters WG, Lybeert M, et al. A high level of fatigue among long-term survivors of non-Hodgkin's lymphoma: results from the longitudinal population-based PROFILES registry in the south of the Netherlands. Haematologica. 2013;98:479-86. https://doi.org/10.3324/haematol.2012.064907.

72. Guinan EM, Bennett AE, Doyle SL, O'Neill L, Gannon J, Foley G, et al. Measuring the impact of oesophagectomy on physical functioning and physical activity participation: a prospective study. BMC Cancer. 2019;19:682. https://doi.org/10.1186/s12885-019-5888-6.

73. Abrahams HJG, Gielissen MFM, Schmits IC, Verhagen CAHHVM, Rovers MM, Knoop H. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. Ann Oncol. 2016;27:965-74. https://doi.org/10.1093/annonc/mdw099.

74. Vardy JL, Dhillon HM, Pond GR, Renton C, Dodd A, Zhang H, et al. Fatigue in people with localized colorectal cancer who do and do not receive chemotherapy: a longitudinal prospective study. Ann Oncol. 2016;27:1761-7. https://doi.org/10.1093/annonc/mdw252.

75. Gagliano-Jucá T, Pencina KM, Ganz T, Travison TG, Kantoff PW, Nguyen PL, et al. Mechanisms responsible for reduced erythropoiesis during androgen deprivation therapy in men with prostate cancer. Am J Physiol Endocrinol Metab. 2018;315:E1185-93. https://doi.org/10.1152/ajpendo.00272.2018.

76. Marschner N, Trarbach T, Rauh J, Meyer D, Müller-Hagen S, Harde J, et al. Quality of life in pre- and postmenopausal patients with early breast cancer: a comprehensive analysis from the prospective MaLife project. Breast Cancer Res Treat. 2019;175:701-12. https://doi.org/10.1007/s10549-019-05197-w.

77. Tanguturi SK, Alexander BM. Neurologic complications of radiation therapy. Neurol Clin. 2018;36:599-625. https://doi.org/10.1016/j.ncl.2018.04.012.

78. Couwenberg AM, Burbach JPM, van Grevenstein WMU, Smits AB, Consten ECJ, Schiphorst AHW, et al. Effect of neoadjuvant therapy and rectal surgery on health-related quality of life in patients with rectal cancer during the first 2 years after diagnosis. Clin Colorectal Cancer. 2018;17:e499-512. https://doi.org/10.1016/j.clcc.2018.03.009.

79. Fosså SD, Bengtsson T, Borre M, Ahlgren G, Rannikko A, Dahl AA. Reduction of quality of life in prostate cancer patients: experience among 6200 men in the Nordic countries. Scand J Urol. 2016;50:330-7. https://doi.org/10.1080/21681805.2016.1201859.

80. Kamal M, Rosenthal DI, Batra A, Volpe S, Elgohari B, Goepfert RP, et al. Fatigue following radiation therapy in nasopharyngeal cancer survivors: a dosimetric analysis incorporating patient report and observer rating. Radiother Oncol. 2019;133:35-42. https://doi.org/10.1016/j.radonc.2018.12.023.

81. Arnaud J, Penel N, Ladsous M, Christine Vantyghem M, Christine DC. Tyrosine kinase inhibitors and immune checkpoint inhibitors-induced thyroid disorders. Crit Rev Oncol Hematol. 2019. https://doi.org/10.1016/j.critrevonc.2019.05.015.
82. Kishan AU, Wang P-C, Sharif J, Kupelian PA, Steinberg ML, McCloskey SA. Clinical indicators of psychosocial distress predict for acute radiation-induced fatigue in patients receiving adjuvant radiation therapy for breast cancer: an analysis of patient-reported outcomes. Int J Radia Oncol Biol Physics. 2016;95:946-55. https://doi.org/10.1016/j.ijrobp.2016.01.062.
83. Lukkahatai N, Saligan LN. Association of catastrophizing and fatigue: a systematic review. J Psychosom Res. 2013;74:100-9. https://doi.org/10.1016/j.jpsychores.2012.11.006.
84.•• 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;3:961-8. https://doi.org/10.1001/jamaoncol.2016.6914.

Results from meta-analysis showed that exercise had the greatest effect in reducing CRF, followed by psychological interventions. Pharmacologic interventions were least effective.

85.• Thekdi SM, Trinidad A, Roth A. Psychopharmacology in cancer. Curr Psychiatry Rep. 2015;17:529. https://doi.org/10.1007/s11920-014-0529-x.

Brief overview of the use and contra-indication of antidepressants and psychostimulants for cancer-related fatigue.

86. Qu D, Zhang Z, Yu X, Zhao J, Qiu F, Huang J. Psychotropic drugs for the management of cancer-related fatigue: a systematic review and meta-analysis. Eur J Cancer Care. 2016;25:970-9. https://doi.org/10.1111/ecc.12397.
87. Rojí R, Centeno C. The use of methylphenidate to relieve fatigue. Curr Opin Support Palliat Care. 2017;11:299-305. https://doi.org/10.1097/spc.0000000000000296.
88.•• Tomlinson D, Robinson PD, Oberoi S, Cataudella D, Culos-Reed N, Davis H, et al. Pharmacologic interventions for fatigue in cancer and transplantation: a meta-analysis. Curr Oncol. 2018;25:e152-67. https://doi.org/10.3747/co.25.3883.

Methylphenidate and erythropoietin are associated with reduced CRF but safety concerns could limit their use.

89. Andrew BN, Guan NC, Jaafar NRN. The use of methylphenidate for physical and psychological symptoms in cancer patients: a review. Curr Drug Targets. 2018;19:877-87. https://doi.org/10.2174/1389450118666170317162603.
90. Storebo OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). Cochrane Database Syst Rev. 2015:CD009885. https://doi.org/10.1002/14651858.CD009885.pub2.
91. Murillo-Rodríguez E, Barciela Veras A, Barbosa Rocha N, Budde H, Machado S. An overview of the clinical uses, pharmacology, and safety of modafinil. ACS Chem Neurosci. 2018;9:151-8. https://doi.org/10.1021/acschemneuro.7b00374.
92. Heckler CE, Garland SN, Peoples AR, Perlis ML, Shayne M, Morrow GR, et al. Cognitive behavioral therapy for insomnia, but not armodafinil, improves fatigue in cancer survivors with insomnia: a randomized placebo-controlled trial. Support Care Cancer. 2016;24:2059-66. https://doi.org/10.1007/s00520-015-2996-y.
93.• Grassi L, Nanni MG, Rodin G, Li M, Caruso R. The use of antidepressants in oncology: a review and practical tips for oncologists. Ann Oncol. 2017;29:101-11. https://doi.org/10.1093/annonc/mdx526.

Outlines the characteristics and safety issues of antidepressants suitable for use on CRF.

94.• Bohlius J, Bohlke K, Castelli R, Djulbegovic B, Lustberg MB, Martino M, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clin Oncol. 2019;37:1336-51. https://doi.org/10.1200/jco.18.02142.

Updated ASCO/ASH recommendations on the use of erythropoiesis-stimulating agents.

95.• Aapro M, Beguin Y, Bokemeyer C, Dicato M, Gascón P, Glaspy J, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines†. Ann Oncol. 2018;29:iv96-iv110. https://doi.org/10.1093/annonc/mdx758.

Updated ESMO guidelines for the management of anemia and iron deficiency.

96.• Kelley GA, Kelley KS. Exercise and cancer-related fatigue in adults: a systematic review of previous systematic reviews with meta-analyses. BMC Cancer. 2017;17:693-17. https://doi.org/10.1186/s12885-017-3687-5.

Meta-analysis of previous systematic reviews assessing efficacy of aerobic and/or resistance training for CRF. Results are inconclusive although evidence supports that exercise does not increase CRF.

97.• 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. https://doi.org/10.1016/j.breast.2017.02.002.

This meta-analysis showed that exercise during adjuvant radiotherapy can be beneficial in reducing CRF in breast cancer survivors.

98.• Hilfiker R, Meichtry A, Eicher M, Nilsson Balfe L, Knols RH, Verra ML, et al. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. Br J Sports Med. 2018;52:651-8. https://doi.org/10.1136/bjsports-2016-096422.

The efficacy of various non-pharmacologic interventions are assessed and ranked using Bayesian approach. Survivors who are fatigued can have option of deciding on an intervention that best suits them.

99.•• Knips L, Bergenthal N, Streckmann F, Monsef I, Elter T, Skoetz N. Aerobic physical exercise for adult patients with haematological malignancies. Cochrane Database Syst Rev. 2019. https://doi.org/10.1002/14651858.CD009075.pub3.

Moderate- to very low-quality evidence is available for the efficacy of aerobic exercise on CRF in adult survivors of hematological cancers.

100.• Kessels E, Husson O, van der Feltz-Cornelis CM. The effect of exercise on cancer-related fatigue in cancer survivors: a systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2018;14:479-94. https://doi.org/10.2147/NDT.S150464.

Aerobic interventions with high adherence levels showed the most effect in reducing CRF.

101. Carli F, Gillis C, Scheede-Bergdahl C. Promoting a culture of prehabilitation for the surgical cancer patient. Acta Oncol. 2017;56:128-33. https://doi.org/10.1080/0284186X.2016.1266081.

102. Macmillan Cancer Support. Prehabilitation for people with cancer: Principles and guidance for prehabilitation within the management and support of people with cancer. 2019. https://www.macmillan.org.uk/assets/prehabilitation-guidance-for-people-with-cancer.pdf. Accessed 9 October 2019.

103. Treanor C, Kyaw T, Donnelly M. An international review and meta-analysis of prehabilitation compared to usual care for cancer patients. J Cancer Surviv. 2018;12:64-73. https://doi.org/10.1007/s11764-017-0645-9.

104. Purcell A, Fleming J, Burmeister B, Bennett S, Haines T. Is education an effective management strategy for reducing cancer-related fatigue? Support Care Cancer. 2011;19:1429-39. https://doi.org/10.1007/s00520-010-0970-2.

105. Agasi-Idenburg CS, Zuilen MK-V, Westerman MJ, CJA P, Aaronson NK, Stuiver MM. "I am busy surviving" - Views about physical exercise in older adults scheduled for colorectal cancer surgery. J Geriatr Oncol. 2019. https://doi.org/10.1016/j.jgo.2019.05.001.

106. Giles C, Cummins S. Prehabilitation before cancer treatment. BMJ. 2019;366:l5120. https://doi.org/10.1136/bmj.l5120.

107. Abdin S, Lavallee JF, Faulkner J, Husted M. A systematic review of the effectiveness of physical activity interventions in adults with breast cancer by physical activity type and mode of participation. Psychooncology. 2019;28:1381-93. https://doi.org/10.1002/pon.5101.

108.• 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;24:969-83. https://doi.org/10.1007/s00520-015-2953-9.

This systematic review concluded that aerobic exercise in the post-adjuvant treatment phase, is effective for CRF.

109. Witlox L, Hiensch AE, Velthuis MJ, Steins Bisschop CN, Los M, Erdkamp FLG, et al. Four-year effects of exercise on fatigue and physical activity in patients with cancer. BMC Med. 2018;16:86. https://doi.org/10.1186/s12916-018-1075-x.

110. Carlson LE. Mindfulness-based interventions for coping with cancer. Ann N Y Acad Sci. 2016;1373:5-12. https://doi.org/10.1111/nyas.13029.

111.• Duong N, Davis H, Robinson PD, Oberoi S, Cataudella D, Culos-Reed SN, et al. Mind and body practices for fatigue reduction in patients with cancer and hematopoietic stem cell transplant recipients: a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017;120:210-6. https://doi.org/10.1016/j.critrevonc.2017.11.011.

Mindfulness-based and relaxation interventions were most effective in reducing CRF.

112.• Haller H, Winkler MM, Klose P, Dobos G, Kümmel S, Cramer H. Mindfulness-based interventions for women with breast cancer: an updated systematic review and meta-analysis. Acta Oncol. 2017;56:1665-76. https://doi.org/10.1080/0284186X.2017.1342862.

This meta-analysis concluded that mindfulness-based interventions may provide short-term relief for CRF in breast cancer survivors.

113.•• Schell LK, Monsef I, Wöckel A, Skoetz N. Mindfulness-based stress reduction for women diagnosed with breast cancer. Cochrane Database Syst Rev. 2019. https://doi.org/10.1002/14651858.CD011518.pub2.

The benefits of mindfulness-based interventions on CRF are short-term and do not extend beyond end of intervention.

114.• Bennett S, Pigott A, Beller EM, Haines T, Meredith P, Delaney C. Educational interventions for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2016. https://doi.org/10.1002/14651858.CD008144.pub2.

Educational interventions may have small effects in reducing CRF and could be better provided in combination with other interventions.

115.•• Cramer H, Lauche R, Klose P, Lange S, Langhorst J, Dobos GJ. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. Cochrane Database Syst Rev. 2017;1:CD010802. https://doi.org/10.1002/14651858.CD010802.pub2.

Moderate quality evidence suggests that yoga could reduce CRF.

116. Danhauer SC, Addington EL, Cohen L, Sohl SJ, Van Puymbroeck M, Albinati NK, et al. Yoga for symptom management in oncology: a review of the evidence base and future directions for research. Cancer. 2019;125:1979-89. https://doi.org/10.1002/cncr.31979.

117.•• Greenlee H, DuPont-Reyes MJ, Balneaves LG, Carlson LE, Cohen MR, Deng G, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. CA Cancer J Clin. 2017;67:194-232. https://doi.org/10.

3322/caac.21397.

Integrative therapies recommended for management of CRF received no higher than a 'C' grade on strength of evidence.

118. Klein PJ, Schneider R, Rhoads CJ. Qigong in cancer care: a systematic review and construct analysis of effective qigong therapy. Support Care Cancer. 2016;24:3209-22. https://doi.org/10.1007/s00520-016-3201-7.

119. Lin W-F, Zhong M-F, Zhou Q-H, Zhang Y-R, Wang H, Zhao Z-H, et al. Efficacy of complementary and integrative medicine on health-related quality of life in cancer patients: a systematic review and meta-analysis. Cancer Manag Res. 2019;11:6663-80. https://doi.org/10.2147/CMAR.S195935.

120.• Wayne PM, Lee MS, Novakowski J, Osypiuk K, Ligibel J, Carlson LE, et al. Tai chi and qigong for cancer-related symptoms and quality of life: a systematic review and meta-analysis. J Cancer Surviv. 2018;12:256-67. https://doi.org/10.1007/s11764-017-0665-5.

Although tai-chi seems effective in reducing CRF, no definite conclusion can be drawn as current studies have issues with sample size and methodology.

121.• Zeng Y, Xie X, Cheng ASK. Qigong or tai chi in cancer care: an updated systematic review and meta-analysis. Curr Oncol Rep. 2019;21:48-6. https://doi.org/10.1007/s11912-019-0786-2.

Qigong/tai-chi shows promise in reducing CRF but conclusions of its effectiveness is not definitive.

122. Song S, Yu J, Ruan Y, Liu X, Xiu L, Yue X. Ameliorative effects of tai chi on cancer-related fatigue: a meta-analysis of randomized controlled trials. Support Care Cancer. 2018;26:2091-102. https://doi.org/10.1007/s00520-018-4136-y.

123. Zhang Y, Lin L, Li H, Hu Y, Tian L. Effects of acupuncture on cancer-related fatigue: a meta-analysis. Support Care Cancer. 2018;26:415-25. https://doi.org/10.1007/s00520-017-3955-6.

124.• Shin ES, Seo KH, Lee SH, Jang JE, Jung YM, Kim MJ, et al. Massage with or without aromatherapy for symptom relief in people with cancer. Cochrane Database Syst Rev. 2016;6:CD009873. https://doi.org/10.1002/14651858.CD009873.pub3.

Massage was not associated with reduced CRF.

125. Kinkead B, Schettler PJ, Larson ER, Carroll D, Sharenko M, Nettles J, et al. Massage therapy decreases cancer-related fatigue: results from a randomized early phase trial. Cancer. 2018;124:546-54. https://doi.org/10.1002/cncr.31064.

126. Schmidt ME, Wiskemann J, Armbrust P, Schneeweiss A, Ulrich CM, Steindorf K. Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: a randomized controlled trial. Int J Cancer. 2015;137:471-80. https://doi.org/10.1002/ijc.29383.

127. Liu L, Marler MR, Parker BA, Jones V, Johnson S, Cohen-Zion M, et al. The relationship between fatigue and light exposure during chemotherapy. Support Care Cancer. 2005;13:1010-7. https://doi.org/10.1007/s00520-005-0824-5.

128. Johnson JA, Garland SN, Carlson LE, Savard J, Simpson JSA, Ancoli-Israel S, et al. The LITE study: rationale and protocol for a randomized controlled trial of light therapy for cancer-related fatigue in cancer survivors. Contemp Clin Trials. 2016;49:166-73. https://doi.org/10.1016/j.cct.2016.07.004.

129. Ormel HL, van der Schoot GGF, Sluiter WJ, Jalving M, Gietema JA, Walenkamp AME. Predictors of adherence to exercise interventions during and after cancer treatment: a systematic review. Psychooncology. 2018;27:713-24. https://doi.org/10.1002/pon.4612.

130. Johnson JA, Garland SN, Carlson LE, Savard J, Simpson JSA, Ancoli-Israel S, et al. Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. J Cancer Surviv. 2018;12:206-15. https://doi.org/10.1007/s11764-017-0659-3.

131. Starreveld DEJ, Daniels LA, Valdimarsdottir HB, Redd WH, de Geus JL, Ancoli-Israel S, et al. Light therapy as a treatment of cancer-related fatigue in (non-)Hodgkin lymphoma survivors (SPARKLE trial): study protocol of a multicenter randomized controlled trial. BMC Cancer. 2018;18:880. https://doi.org/10.1186/s12885-018-4746-2.

132. Leggett S, Koczwara B, Miller M. The impact of complementary and alternative medicines on cancer symptoms, treatment side effects, quality of life, and survival in women with breast cancer–a systematic review. Nutr Cancer. 2015;67:373-91. https://doi.org/10.1080/01635581.2015.1004731.

133.• Luo C, Xu X, Wei X, Feng W, Huang H, Liu H, et al. Natural medicines for the treatment of fatigue: bioactive components, pharmacology, and mechanisms. Pharmacol Res. 2019;148:104409. https://doi.org/10.1016/j.phrs.2019.104409.

Of the natural medicines, ginseng is the most researched for its efficacy in reducing CRF. However, evidence of its effect is weak.

134. Inglis JE, Lin P-J, Kerns SL, Kleckner IR, Kleckner AS, Castillo DA, et al. Nutritional interventions for treating cancer-related fatigue: a qualitative review. Nutr Cancer. 2019;71:21-40. https://doi.org/10.1080/01635581.2018.1513046.

135. Pereira PTVT, Reis AD, Diniz RR, Lima FA, Leite RD, da Silva MCP, et al. Dietary supplements and fatigue in patients with breast cancer: a systematic review. Breast Cancer Res Treat. 2018;171:515-26. https://doi.org/10.1007/s10549-018-4857-0.

136. Arring NM, Millstine D, Marks LA, Nail LM. Ginseng as a treatment for fatigue: a systematic review. J Altern Complement Med. 2018;24:624-33. https://doi.org/10.1089/acm.2017.0361.

137. Sette CVM, Ribas de Alcântara BB, JHM S, Cruz FM, Cubero DIG, Pianowski LF, et al. Purified dry *Paullinia cupana* (PC-18) extract for chemotherapy-induced fatigue: results of two double-blind randomized clinical

trials. J Diet Suppl. 2018;15:673-83. https://doi.org/10.1080/19390211.2017.1384781.

138. Buffart LM, Sweegers MG, May AM, Chinapaw MJ, van Vulpen JK, Newton RU, et al. Targeting exercise interventions to patients with cancer in need: an individual patient data meta-analysis. J Natl Cancer Inst. 2018;110:1190-200. https://doi.org/10.1093/jnci/djy161.

Publisher's note