Cancer-related fatigue—mechanisms, risk factors, and treatments

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Abstract | Fatigue is one of the most common adverse effects of cancer that might persist for years after treatment completion in otherwise healthy survivors. Cancer-related fatigue causes disruption in all aspects of quality of life and might be a risk factor of reduced survival. The prevalence and course of fatigue in patients with cancer have been well characterized and there is growing understanding of the underlying biological mechanisms. Inflammation seems to have a key role in fatigue before, during, and after cancer-treatment. However, there is a considerable variability in the presentation of cancer-related fatigue, much of which is not explained by disease-related or treatment-related characteristics, suggesting that host factors might be important in the development and persistence of this symptom. Indeed, longitudinal studies have identified genetic, biological, psychosocial, and behavioural risk factors associated with cancer-related fatigue. Although no current gold-standard treatment for fatigue is available, a variety of intervention approaches have shown beneficial effects in randomized controlled trials, including physical activity, psychosocial, mind–body, and pharmacological treatments. This Review describes the mechanisms, risk factors, and possible interventions for cancer-related fatigue, focusing on recent longitudinal studies and randomized trials that have targeted fatigued patients.

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Introduction

Fatigue is now recognized as one of the most common and distressing adverse effects of cancer and cancer therapy.[1] Fatigue can be elevated before treatment onset and typically increases during radiotherapy,[2] chemotherapy,[3] and hormonal and/or biological therapies.[4] The estimated prevalence of fatigue during treatment ranges from 25% to 99%, depending on the patient population, type of treatment received, and method of assessment.[1,5] In most studies, 30–60% of patients report moderate to severe fatigue during therapy, which in some cases might lead to treatment discontinuation. Fatigue typically improves in the first year following treatment completion, although 25–30% of patients continue to experience fatigue for years after successful treatment.[6,7] Analyses of cancer survivors suggest that fatigue can persist for up to 5 years after completion of treatment[8] and possibly even longer.[9] Fatigue has a negative impact on work, social relationships, mood, and daily activities, causing significant impairment in overall quality of life during and after treatment.[6,10] Furthermore, elevated fatigue predicted shorter recurrence-free survival and overall survival in a large longitudinal study of patients with breast cancer, over and above clinical and treatment-related factors.[11]

Reports from patients suggest that cancer-related fatigue is more severe, persistent, and debilitating than 'normal' fatigue simply caused by lack of sleep or overexertion, and cancer-related fatigue is not relieved by adequate sleep or rest.[12] Studies have confirmed that the intensity and duration of fatigue experienced by patients with cancer and cancer survivors is greater than healthy controls, although the difference is modest given the prevalence of fatigue in the general population.[13] Cancer-related fatigue might have physical, mental, and emotional manifestations, including generalized weakness, diminished concentration or attention, decreased motivation or interest to engage in usual activities, and emotional liability (Box 1).[7] Although cancer-related fatigue shares some characteristics with depression, including decreased energy, interest, motivation, and concentration, patients experience fatigue as a distinct and central symptom that impairs mood and functional abilities.[12]

Despite the prevalence and negative impact of cancer-related fatigue, this symptom is under-reported by patients, and underestimated and undertreated by clinicians.[14] One of the possible barriers to the proper assessment and management of fatigue is the lack of information about the mechanisms underlying this symptom, risk factors, and effective treatments. This Review summarizes the available evidence on the biological mechanisms that underlie cancer-related fatigue, focusing on inflammation as a key contributing pathway. It will also discuss the risk factors for cancer-related fatigue, as growing evidence suggests that only certain patients are at risk of developing severe and persistent fatigue. Finally, interventions for cancer-related fatigue will be reviewed, including physical activity, psychosocial, mind–body, and pharmacological approaches.

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Key points

- Fatigue is the most common adverse effect of cancer
- Inflammation is a key mechanism of cancer-related fatigue
- Host factors increase risk for fatigue in patients with cancer
- Effective interventions include exercise and targeted psychological and mind–body treatments

Box 1 | Defining and assessing cancer-related fatigue

Cancer-related fatigue has been defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and cancer treatment that is not proportional to recent activity and interferes with usual functioning. Patient self-reporting is the gold-standard method for assessing cancer-related fatigue. A number of measures have been developed to assess fatigue in the cancer context, which vary from single-item assessments of fatigue severity to multidimensional scales assessing different components of fatigue (severity, duration, interference; mental, physical, emotional fatigue).[144] A common approach to assessing fatigue involves asking patients to rate their fatigue on a 0–10 scale, in which mild fatigue is indicated as a score of 1–3, moderate fatigue as 4–6, and severe fatigue as 7–10.[145] In 1998, formal diagnostic criteria were proposed to define a clinical syndrome of cancer-related fatigue.[146] One of the advantages of such criteria is that patients are specifically asked whether the fatigue they are experiencing is a consequence of cancer or cancer therapy. In addition, the criteria attempt to distinguish cancer related fatigue from fatigue that occur secondary to depression. However, these criteria have not been widely used to identify patients or to direct intervention efforts,[147] and might be overly stringent.

Mechanisms of cancer-related fatigue

Fatigue in patients with cancer is multifactorial and can be influenced by a variety of demographic, medical, psychosocial, behavioural, and biological factors.[15] In terms of demographic factors, marital status and level of income have been linked to cancer-related fatigue, with unmarried patients with a lower household income reporting higher levels of fatigue.[6,16] These data suggest that contextual factors, such as the absence of a partner who can provide instrumental and emotional support, can influence the experience of this symptom. Other potential contributing factors include medical comorbidities, medications, nutritional issues, physical deconditioning, mood disturbance, and physical symptoms.[15] However, fatigue often occurs in patients who are otherwise healthy and have few (if any) of these contributing medical factors, suggesting that other processes are important. Of note, treatment-related factors, such as the type of treatment and dose intensity, are not consistently associated with fatigue, particularly in the post-treatment period.[15]

A variety of biological mechanisms of cancer-related fatigue have been investigated over the past two decades.[17,18] These processes include anaemia, cytokine dysregulation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, 5-hydroxytryptophan neurotransmitter dysregulation, and alterations in ATP and muscle metabolism.[15,17,18] To date, the mechanism that has garnered the most empirical attention and supporting evidence is dysregulation of cytokines, with a focus on proinflammatory cytokines.

Inflammation and cancer-related fatigue

The possibility that inflammatory processes are involved in the aetiology of cancer-related fatigue draws from basic research on neural–immune signalling. Peripheral inflammatory cytokines can signal the central nervous system (CNS) and generate symptoms of fatigue or other behavioural changes by altering neural processes (Box 2).[19,20] In the context of cancer, investigators have proposed that tumours and the treatments used to eradicate them can activate the proinflammatory cytokine network, leading to symptoms of fatigue via cytokine signalling in the CNS.[21,22] The inflammatory response can persist long after treatment completion as the host tries to deal with persisting pathogenesis and alterations in homeostasis.[23] Of note, factors other than cancer and its treatment can influence inflammatory activity and might also contribute to fatigue, including psychological, behavioural, and biological risk factors (Figure 1). Studies have now investigated the association between markers of inflammation and fatigue in cancer patients before, during, and particularly after treatment, as reviewed below.

Inflammation and fatigue before treatment

In patients with newly diagnosed acute myelogenous leukaemia (AML) or myelodysplastic syndrome, the levels of several inflammatory markers (IL-6, IL-1 receptor antagonist [IL-1RA], and tumour necrosis factor [TNF]-α) correlated with ratings of fatigue.[24] Similar results were observed in patients with ovarian cancer assessed before surgery, revealing a positive association between plasma concentrations of IL-6 and fatigue.[25,26] Furthermore, studies conducted with patients with breast cancer assessed before treatment with radiotherapy or chemotherapy have shown that fatigue was associated with increased levels of C-reactive protein (CRP);[27,28] of note, most patients in these studies had already undergone surgery, which is known to elicit an inflammatory response. Conversely, another study that analysed patients with breast cancer before surgery did not find elevated levels of CRP in those patients categorized as 'fatigued'.[29] A possible explanation is that small, localized breast tumours might not produce an elevation in the concentration of systemic cytokines that is sufficient to induce symptoms of fatigue.

Inflammation and fatigue during treatment

Radiotherapy and chemotherapy are both associated with increases in the prevalence of fatigue and in the levels of certain inflammatory markers (such as IL-6, IL-10, and soluble TNF receptors).[30–34] Early reports assessing inflammatory markers and fatigue in patients undergoing treatment yielded conflicting results,[28,35–37] which might be due in part to use of nonstandard and/or low-sensitivity assays to detect cytokine levels.[37] In addition, these studies typically did not examine associations between changes in cytokine levels and fatigue, which represent a more-appropriate approach given the dynamic changes in inflammatory processes during treatment. Reports using more-sensitive assays and examining longitudinal changes in inflammatory markers and fatigue have shown more-consistent results.[32–34,38,39] In a study of patients undergoing radiotherapy for early stage breast or

Box 2 | Neural immune signalling and fatigue

Basic research on neuroimmune interactions has documented behavioural effects of peripheral immune activation that are mediated by proinflammatory cytokines.[19] Signals from the peripheral immune system are conveyed to the central nervous system through several routes, including direct neural activation via the afferent vagus nerve, transport of peripheral cytokines across the blood–brain barrier via carrier molecules, and interaction of circulating cytokines with brain cytokine receptors in areas that lack a functional blood–brain barrier and with brain vascular endothelial cells that release second messengers to stimulate cytokine production in the brain.[59] Cytokine signalling leads to changes in neural activity, physiological processes (such as fever), and behaviour.[148] In animal models, injection or induction of proinflammatory cytokines leads to decreased motor activity (presumably a behavioural manifestation of fatigue) as well as reduced food and water intake, social withdrawal, anhedonia, and altered cognition. These behavioural changes have been collectively described as 'sickness behaviour' and are thought to represent a motivational shift designed to facilitate recovery and prevent the spread of infection.[19,59] In humans, pharmacological doses of cytokines given for treatment of cancer or hepatitis C are associated with significant increases in fatigue and other markers of sickness, including depressed mood and sleep disturbance.[149] Experimental studies of cytokine induction in healthy individuals have documented similar effects, with subjects reporting increased fatigue following endotoxin administration that are correlated with elevations in circulating concentrations of proinflammatory cytokines.[150] In observational studies, subclinical levels of inflammatory markers prospectively predict the development of fatigue in otherwise healthy individuals.[151,152] Furthermore, pharmacological agents that block the proinflammatory cytokine TNF-α lead to reduced fatigue among individuals with inflammatory conditions,[135] and this was also observed in pilot studies with cancer patients.[133] Together, this evidence provides a strong biological rationale for inflammation as a potential mechanism underlying cancer-related fatigue.

prostate cancer, we found that increases in serum levels of the inflammatory markers CRP and IL-1RA were associated with increases in fatigue (although increases in IL-1β and IL-6 were not).[34] Among patients with breast cancer undergoing chemotherapy, increases in the level of IL-6 were also associated with increases in fatigue.[38] Moreover, increases in several inflammatory markers were associated with increases in fatigue among patients with locally advanced colorectal, oesophageal, and non-small-cell lung cancer undergoing a combined radiation and chemotherapy treatment.[32,33] Similarly, in a study on patients with AML and myelodysplastic syndrome undergoing allogeneic haematopoietic stem-cell transplantation (which includes high-dose chemotherapy), levels of IL-6 were associated with increased fatigue.[39]

Inflammation and fatigue post-treatment

Fatigue typically abates in the year following cancer treatment; however, persistent fatigue has been reported by approximately 20–30% of cancer survivors, with symptoms lasting for 5 years or more post-treatment.[9] Our group has observed elevated levels of circulating markers of inflammation (including IL-1RA, sTNF-RII, neopterin, and the soluble IL-6 receptor)[40,41] and elevated lipopolysaccharide (LPS)-stimulated cytokine production[41,42] among breast cancer survivors with persistent post-treatment fatigue. Furthermore, elevated levels of sTNF-RII were found to be associated with an increased level of fatigue in breast cancer survivors within 1 month after cessation of treatment; this correlation was particularly strong for women who underwent chemotherapy.[31]

These findings have been confirmed in other studies that analysed larger samples of breast cancer survivors. In a study of 200 breast cancer survivors assessed between 3 months and 48 months post-treatment, those who met criteria for cancer-related fatigue syndrome (Box 1; 30% of the sample) had elevated levels of CRP.[43] Mean levels of CRP were 3.91 mg/dl among the fatigued survivors versus 2.74 mg/dl in the nonfatigued group, suggesting the presence of low-grade inflammation. Similarly, a study of 299 breast cancer survivors assessed 4 years postdiagnosis found a positive association between the level of fatigue and the level of CRP (although no association was found with levels of IL-1RA, IL-6, sTNF-RI, or neopterin).[44] Furthermore, in 633 breast cancer survivors assessed at 30 months and 39 months after diagnosis, higher levels of CRP were associated with an increased probability of these patients being classified as fatigued.[45]

These effects have also been observed in other survivor groups. In a sample of 283 testicular cancer survivors examined between 5 years and 20 years post-treatment, those with persistent fatigue had higher levels of IL-1RA and CRP (though not IL-6, sTNF-RI, or neopterin).[46] In one of the few longitudinal studies that examined the association between changes in inflammation and fatigue following treatment completion, decreases in IL-6 were correlated with declines in fatigue in patients with ovarian cancer in the year after treatment.[47]

Genome-wide expression analyses have been exploited to probe the molecular underpinnings of cancer-related fatigue. Our group found that leukocytes from breast cancer survivors with persistent fatigue showed an increased expression of genes encoding proinflammatory cytokines, such as *IL1B* and *IL6*, and other mediators of immunological activation.[48] Furthermore, a promoter-based bioinformatic analysis indicated an increased activity of the proinflammatory transcription factor nuclear factor (NF)-κB in fatigued survivors, which might explain the elevated expression of inflammation-related genes.[48] Another group, using a different analytical approach, found altered expression of gene sets involved in signalling pathways of B cells and plasma cells in fatigued breast cancer survivors, suggesting that a B-cell-mediated inflammatory process might underlie fatigue in this group.[49] The use of gene-expression profiling has also contributed to the identification of gene transcripts associated with fatigue in patients with prostate cancer, with preliminary evidence showing elevated expression of inflammation-related genes in fatigued patients undergoing treatment with androgen-deprivation therapy[50] or radiotherapy.[51]

Immunity and latent viral reactivation

Pronounced and prolonged alterations in the cellular immune system can occur following cancer treatments.[52,53] Our group has documented alterations in specific immune cell populations in breast cancer survivors with persistent fatigue, including elevations in CD4+ and CD56+ T cells and decreases in activated T cells and myeloid dendritic cells, that correlate with inflammatory processes.[41,54] Other global changes in the cellular

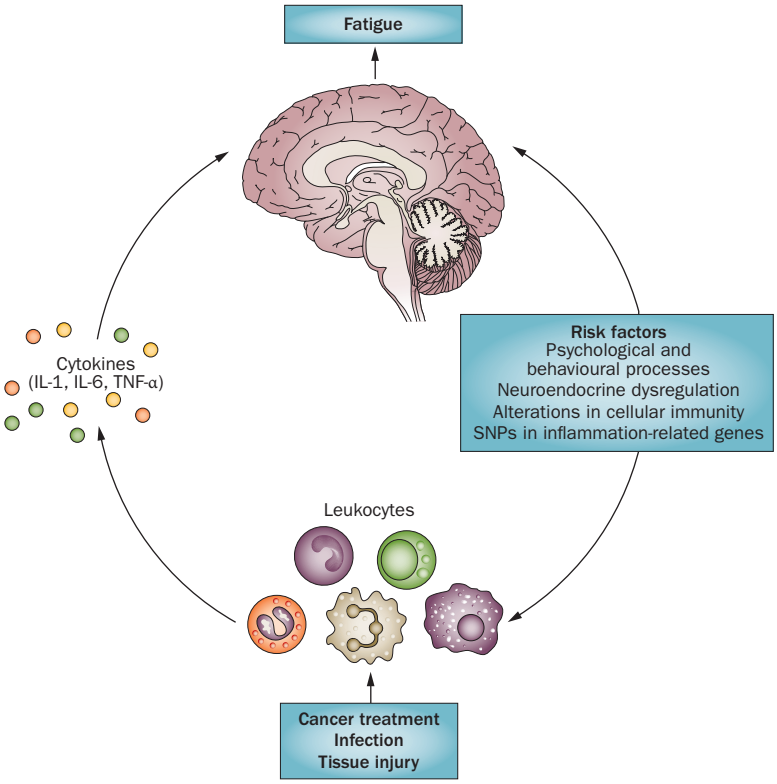

Figure 1 | Mechanisms of cancer-related fatigue. Proinflammatory cytokines, including IL-1β, TNF-α, and IL-6, are released by immune cells following infection or tissue injury. In the context of cancer, proinflammatory cytokines may also be released by the tumour itself or as a result of tissue damage from surgery, radiation, or chemotherapy. These cytokines can signal to the central nervous system, leading to symptoms of fatigue and other behavioural changes. Fatigue and inflammatory processes may also be influenced by psychological and behavioural processes and neuroendocrine dysregulation. Alterations in the cellular immune system, which can arise following cancer treatment, might also contribute to persistent inflammation and associated symptoms of fatigue. Furthermore, the presence of SNPs in genes that regulate proinflammatory cytokine expression has been linked to cancer-related fatigue. Abbreviations: IL, interleukin; SNPs, single nucleotide polymorphisms; TNF, tumour necrosis factor.

immune system in fatigued breast cancer survivors, including elevations in leukocyte numbers, have been reported;[43,49] however, these effects have not been consistently reproduced.[55] One longitudinal study, analysing breast cancer survivors, reported that elevated leukocyte counts in the post-treatment period was predictive of persistent fatigue over a 2–3 year follow-up interval.[56]

Immune dysregulation and reactivation of latent viruses can also contribute to fatigue in the pretreatment period. Elevated titres of cytomegalovirus (CMV) antibody were associated with a greater likelihood of being fatigued—and with higher levels of CRP—in patients with breast cancer before initiation of treatment.[57]

Neuroendocrine alterations

Hypothalamic–pituitary–adrenal axis

Alterations in the HPA axis have been proposed as a mechanism underlying cancer-related fatigue, either directly or through effects on inflammatory processes.[58] The HPA axis is an important regulator of cytokine production and has potent anti-inflammatory effects.[59] These effects can be exerted through alterations in glucocorticoid production (including deregulated circadian profiles) and/or through a decreased sensitivity of the glucocorticoid receptor (GR) for its ligands.[60] Preliminary evidence suggests that alterations in both pathways are detectable among patients with cancer-related fatigue.[42,61,62] In terms of glucocorticoid production, breast cancer survivors with persistent fatigue show alterations in the diurnal cortisol slope, with elevated levels of evening cortisol relative to nonfatigued controls.[62] Fatigued breast cancer survivors also have blunted cortisol responses to psychological stress[61] that are correlated with elevations in stimulated cytokine production and might underlie elevated inflammatory activity.[42] In patients with ovarian cancer, higher levels of evening cortisol and reduced variations in diurnal cortisol are associated with fatigue before treatment onset,[63] whereas normalization of cortisol profiles in the following year are associated with reductions in fatigue.[56]

In terms of GR sensitivity, genome-wide transcriptional profiling of leukocytes from fatigued breast cancer survivors showed a marked downregulation of GR responsive genes, suggesting a state of functional GR resistance.[48] Reduced GR sensitivity might also contribute to the upregulation of NF-κB observed in fatigued survivors, consistent with findings from studies on the healthy population that link GR desensitization to increased activity of the transcription factor NF-κB.[64,65]

Autonomic nervous system dysregulation

The autonomic nervous system, which consists of the sympathetic and parasympathetic branches, regulates physiological processes including immune and inflammatory activity.[59] Preliminary reports suggest that alterations in the autonomic nervous system may also be relevant for cancer-related fatigue.[66,67] In a study of breast cancer survivors, fatigue was associated with elevated levels of noradrenaline (indicating increased sympathetic activity) and lower heart rate variability (indicating reduced parasympathetic activity), both at rest and in response to a psychological challenge.[66] We have recently confirmed the association between cancer-related fatigue and lower resting heart rate variability in a group of premenopausal breast cancer survivors, who are at particular risk for elevated fatigue.[67]

Mechanisms—perspectives

Overall, studies examining links between inflammation and fatigue largely support the hypothesis that inflammatory processes contribute to fatigue during and after cancer treatment, with the strongest evidence from studies of breast cancer survivors. Importantly, most of these studies have controlled for potential biobehavioural confounders, including age and BMI, indicating that links between inflammation and fatigue are not driven by these factors. Findings are not entirely uniform, and associations have not been reported in all patient groups,[68] for all aspects of fatigue (for example, duration versus severity),[34,46,69] or for all inflammatory markers.[31,44] Inconsistency across studies might be due to differences

in the definition and assessment of cancer-related fatigue, disease and treatment-related characteristics, and type (and quality) of immunological assessments. Different components of the proinflammatory cytokine network might be associated with different aspects of fatigue, in different patient groups, at different stages of the cancer trajectory. Thus, it is important to assess key components of the cytokine network, as well as key dimensions of fatigue, using valid and reliable measurement techniques.

Studies have also documented associations between cancer-related fatigue and alterations in the immune and neuroendocrine systems. Because most of these studies have focused on post-treatment survivors, it is unclear whether the alterations associated with fatigue were driven by cancer treatment (such as chemotherapy effects on the cellular immune system) or might have been present before cancer diagnosis and treatment. For example, a recent prospective study conducted with military personnel deployed to a war zone found that predeployment levels of GR sensitivity predicted the development of postdeployment fatigue.[70] Similarly, it is possible that precancer alterations in GR sensitivity and other biological systems might serve as a risk factor for cancer-related fatigue. Prospective, longitudinal studies are required to determine the role of neuroendocrine and immune alterations in the onset and persistence of fatigue and the mechanisms through which this occurs.

Risk factors for cancer-related fatigue

Considerable variability exists in the experience of fatigue before, during, and after treatment,[16,71] suggesting that certain patients are at particular risk for this disabling symptom. Over the past several years, longitudinal studies have begun to examine risk factors for cancer-related fatigue, and particularly fatigue that persists for months or years after cancer treatment. Studies in this field have focused primarily on demographic, medical, behavioural, and psychosocial risk factors, but genetic risk factors is a growing area of interest. Identification of these risk factors is important for advancing our understanding of fatigue and for improving the identification and treatment of patients at risk.

Genetic risk factors

Given the key role that inflammation has in the onset and persistence of cancer-related fatigue, investigators have begun to examine genetic components that influence proinflammatory cytokine activity as potential risk factors for fatigue in the cancer setting. Most of these studies have used a candidate gene approach, focusing on single nucleotide polymorphisms (SNPs) in inflammation-related genes, including *IL1B, IL6*, and *TNFA*. Preliminary evidence suggests that SNPs in these genes are associated with cancer-related fatigue during and after treatment. In longitudinal studies with patients undergoing radiotherapy, polymorphisms in *TNFA* and *IL6* were associated with elevated fatigue before, during, and for 4 months after treatment completion.[72,73] Polymorphisms in *TNFA* and *IL6* were also associated with increase in fatigue in a small longitudinal study of patients with prostate cancer undergoing androgen deprivation therapy.[74]

Furthermore, in two large cross-sectional studies conducted in patients with lung cancer, polymorphisms in *IL8* were associated with increased fatigue before treatment onset,[75] whereas polymorphisms in *IL1B* and *IL1RN* were associated with post-treatment fatigue.[76] SNPs in *TNFA*, *IL6*, and *IL1B* have been associated with elevated fatigue in breast cancer survivors,[77,78] although these findings have not been consistently replicated.[79] Of note, polymorphisms in inflammation-related genes have been linked to fatigue in other patient populations[80,81] and in cancer caregivers,[73] suggesting that inflammation-promoting genes might represent a general risk factor for fatigue symptomatology.

Genome-wide analysis might help to identify other genetic risk factors for fatigue, related to inflammation or other systems.[17]

Psychological and biobehavioural risk factors

Pretreatment fatigue

Across studies, the strongest and most consistent predictor of post-treatment fatigue is pretreatment fatigue.[27,82] Patients who report higher levels of fatigue before radiotherapy and/or chemotherapy also report elevated fatigue immediately after treatment completion,[83] over the following year[27,82,84] and up to 2.5 years later.[85] These findings suggest that the biological, psychological, or behavioural dysregulation contributing to cancer-related fatigue might be present before treatment onset.

Depression

Depression is of particular interest as a risk factor for cancer-related fatigue; in fact, fatigue and depression are strongly correlated in patients with cancer.[86] The association between these two factors is complex; fatigue is a symptom of depression, but might also precipitate depressed mood owing to interference with social, occupational, and leisure activities. Rather than trying to disentangle causality, it might be more informative to examine whether mood disturbance predicts the onset and persistence of fatigue and could, therefore, be used to identify vulnerable patients. Indeed, several longitudinal studies indicate that pretreatment depression and anxiety predict cancer-related fatigue before, during, and after treatment.[56,71,82,83,85,87] Most of these studies did not control for pretreatment fatigue and, therefore, the independent contribution of depression above pre-existing fatigue is not entirely clear. A history of major depressive disorder (and treatment for mental problems before cancer diagnosis) also predicted post-treatment fatigue in several reports,[56,88] with effects observed up to 42 months after treatment completion.[89] Thus, patients with a history of mental illness and those with elevated distress in acute stage of cancer diagnosis and treatment onset seem to be at risk for persistent post-treatment fatigue. A history of stressful experiences in childhood, including experiences of abuse and neglect, has also been associated with higher levels of fatigue in breast cancer survivors.[57,90]

Sleep disturbance

Sleep disturbance is also closely correlated with fatigue in cancer populations, and investigators have hypothesized that sleep problems contribute to daytime symptoms of fatigue.[91] Indeed, studies conducted in patients with breast and prostate cancer undergoing radiotherapy have shown that pretreatment sleep disturbance is associated with higher levels of fatigue before, during, and for up to 6 months after treatment completion.[71,87] In patients with gynaecological cancers who start chemotherapy, higher levels of sleep disturbance (assessed objectively using actigraphy, a method of monitoring human rest/activity cycles by measuring a patient's gross motor activity) predicted subsequent peaks in fatigue.[92] Of note, fatigue predicted subsequent elevations in depressed mood in this study,[92] suggesting a cascade effect among these symptoms in the early stages of cancer treatment. Although sleep disturbance might be a risk factor for cancer-related fatigue, fatigue can persist even when patients report adequate sleep, indicating that other factors contribute to fatigue maintenance over time.

Physical inactivity and body mass index

Physical inactivity is correlated with cancer-related fatigue; patients who are more fatigued typically report lower levels of physical activity.[93,94] The lack of physical activity might lead to physical deconditioning, which makes everyday tasks more challenging and potentially contributes to the development and persistence of fatigue. In fact, cancer survivors diagnosed with cancer-related fatigue syndrome show decreased cardiorespiratory fitness,[95] although the cross-sectional nature of these findings make it difficult to determine causality. Longitudinal studies have shown that low levels of physical activity after treatment completion are predictive of persistent fatigue in breast cancer survivors,[16,96] although elevated fatigue during treatment might have preceded (and precipitated) reduced physical activity in these patients. In either case, low levels of physical activity and associated decreases in cardiorespiratory fitness might have an important role in the development and/or persistence of cancer-related fatigue.

Elevated BMI has also been linked with fatigue, and a longitudinal study of women with early stage breast cancer found that BMI was one of the key predictors of fatigue at 6 months and 42 months post-treatment.[16,89] High BMI was also predictive of persistent fatigue in a longitudinal study of post-treatment breast cancer survivors, above and beyond other risk factors.[56]

Coping and appraisal

Psychological responses to cancer diagnosis and/or to cancer treatment can also influence fatigue symptoms. In particular, the tendency to catastrophize, or engage in negative self-statements and thoughts regarding fatigue, was associated with higher levels of this symptom during[97] and for up to 42 months after treatment[88,89] in patients with breast cancer. In these patients, catastrophizing was one of the strongest predictors of persistent elevations in fatigue. Similarly, patients who expect to experience fatigue are more likely to report higher levels of the symptom after cancer surgery.[98] Thus, patients' negative expectations and coping strategies early on in the cancer trajectory seem to increase the risk for post-treatment fatigue.

Risk factors—perspectives

Although longitudinal studies have now identified a number of potential risk factors for cancer-related fatigue, the mechanisms through which these factors influence fatigue are currently unknown and represent an important goal for future research. Of note, many of these factors are associated with elevated inflammatory activity. It will also be useful to distinguish between factors that increase the risk for fatigue during treatment (precipitating factors) and those that lead to its persistence in the post-treatment period (perpetuating factors).[84] To date, studies have primarily focused either on the period of time during and immediately after treatment, or on the years after treatment completion. Longitudinal studies that follow patients from pretreatment into the survivorship period are needed and will provide better insights on which factors are most important for acute and/or more persistent fatigue. The results of such studies will help to identify appropriate targets for intervention at different stages of the cancer trajectory with potential benefits for the patients.

Treatments for cancer-related fatigue

A diverse range of treatment approaches has been used to address cancer-related fatigue. More than 170 intervention studies in patients with cancer—which included physical activity, psychosocial, mind–body, and pharmacological approaches—had fatigue as a primary or secondary outcome.[15] Currently, no gold-standard for the treatment of cancer-related fatigue is established, possibly owing to the multifactorial aetiology of this symptom and to the lack of knowledge about underlying mechanisms. However, a number of these approaches have been shown to be beneficial in reducing cancer-related fatigue.

Exercise

Meta-analyses indicate that exercise interventions are effective in reducing fatigue during and after cancer treatment, with mean effect sizes in the range of –0.27 to –0.38.[99–101] Effect sizes provide an estimate of the magnitude of a particular effect; in this case, the effect size estimates indicate that exercise interventions have a moderate effect on fatigue. Of note, none of the exercise trials used fatigue as a criteria for study entry. With respect to type of exercise, results from the meta-analyses indicate that aerobic exercise regimens—from home-based programmes[102] to supervised, laboratory-based programmes[103]—are associated with significant reductions in cancer-related fatigue.[99] Mixed effects are reported, instead, for resistance exercise.[99,100,104] Guidelines from the American College of Sports Medicine (ACSM) recommend that patients with cancer and survivors engage in at least 150 min of moderate aerobic activity each week, consistent with the recommendations for

the general population.[105] Exercise trials conducted in patients with cancer often begin with modest levels of physical activity that increase in intensity over time.[102] The ACSM guidelines further recommend that exercise should be tailored to the individual cancer survivor to account for exercise tolerance and specific diagnosis, with patients being closely monitored to safely progress the intensity of exercise and avoid injury.[105]

Of note, fatigue might represent a significant barrier to participation in exercise interventions, particularly among cancer survivors.[106] For these patients, therefore, other strategies might be more appropriate.

Psychosocial interventions

Meta-analyses have reported reductions in cancer-related fatigue following psychosocial interventions, with effect sizes ranging from –0.10 to –0.30, suggesting a small to moderate effect.[107–109] The modest effect sizes observed in these trials relative to exercise interventions might be due to the fact that most were focused on reducing stress and improving general quality of life and did not include fatigue as a primary outcome. We will focus on randomized psychosocial trials that specifically targeted fatigue and/or used fatigue as an entry criteria for trial participation. In one study, patients with breast cancer initiating chemotherapy received three sessions of individualized fatigue education and support delivered in the clinic and at home by phone.[110] This programme reduced the acute increase in fatigue observed in patients undergoing chemotherapy who did not undergo the programme, although this effect did not persist.[110] Another trial conducted with a mixed sample of patients with cancer undergoing chemotherapy found that a three-session individualized intervention focusing on fatigue-related thoughts and behaviour led to greater reductions in fatigue 1 month after treatment completion than usual care.[111] Furthermore, a cognitive-behavioural approach combined with hypnosis has shown beneficial effects on fatigue among patients with breast cancer undergoing radiotherapy; specifically, the intervention buffered the increase in fatigue observed in patients who did not receive the intervention.[112]

Targeted psychoeducational interventions, conducted after cancer treatment, have also demonstrated beneficial effects on fatigue. The Moving Beyond Cancer Trial, a multicentre, randomized controlled trial for patients with breast cancer who had recently completed treatment, found that a brief psychoeducational video that included information on fatigue (as well as examples of physical activity) led to significant improvements in fatigue relative to patients who did not receive the video.[113] Similar results were observed in breast cancer survivors that received a brief group-based psychoeducational intervention for fatigue focusing on active coping strategies and physical activity.[114]

To date, only two psychosocial randomized controlled trials have used fatigue as an entry criteria for study participation, enrolling cancer survivors who reported moderate to severe fatigue (Table 1). In one trial, individual cognitive-behavioural therapy targeting perpetuating factors for persistent fatigue led to a significant decrease in fatigue relative to control patients who received no treatment.[115] This decrease was maintained over a long-term (1–4 years) follow-up period.[116] Positive effects on fatigue were also reported following an internet-based education programme based on National Comprehensive Cancer Network (NCCN) fatigue guidelines relative to the wait-list control group who received no treatment.[117]

Mind–body interventions

A variety of mind–body approaches have been used to treat cancer-related fatigue, including acupuncture, mindfulness-based meditation, yoga, and biofield therapies. We will focus on randomized trials that used fatigue as an entry criteria for participation (Table 1). Three acupuncture trials have targeted cancer survivors with persistent postchemotherapy fatigue. The largest of these trials randomly assigned 302 patients to 6 weeks of acupuncture or usual care, and showed significant improvement in fatigue in the acupuncture group.[118] These findings are consistent with an earlier pilot study conducted by the same authors that saw beneficial effects of acupuncture relative to real or sham acupressure on postchemotherapy fatigue.[119] However, in a trial that compared 6 weeks of acupuncture to sham acupuncture in a mixed group of cancer survivors, fatigue declined in both the control and intervention group with no significant differences between groups.[120] These discrepant findings might be due to differences in the control conditions (usual care, real or sham acupressure, sham acupuncture), although it is worth highlighting that all trials did show reduced fatigue following acupuncture.

Mindfulness-based cognitive therapy focusing on maladaptive automatic thoughts, feelings, and behaviours in cancer-related fatigue led to significant reductions in fatigue in a mixed group of cancer survivors that were maintained over a 6 month follow-up period.[121] Our group found that a specialized Iyengar-based yoga programme for breast cancer survivors with persistent fatigue led to significant improvements in fatigue and energy levels relative to a control group that received health education.[122] Finally, biofield therapy for fatigued breast cancer survivors led to significant reductions in fatigue relative to a no treatment (wait-list) control group; similar reductions in fatigue were also observed in the mock healing group.[123] Of note, several of the mind–body trials that compared 'real' to 'sham' approaches did not find differential effects on fatigue (both were helpful),[120,123] highlighting the importance of including active control conditions in these studies. The same criticism could be applied to psychosocial and physical activity interventions, which typically do not include active control groups. It is also important to note that the mind–body interventions showing positive effects were specifically designed to target fatigue, and nonspecific approaches might be less effective.[124]

Pharmacological interventions

A meta-analysis of 27 randomized controlled trials—including studies of therapy with haematopoietic growth

Table 1 | Nonpharmacological randomized controlled trials using cancer-related fatigue as an entry criteria

Study	Participants (*n*)	Intervention	Duration	Control group(s)	Results
Bower *et al.* (2011)[122]	Breast cancer survivors with moderate to severe fatigue (31)	Iyengar-based yoga focusing on postures that target fatigue, including restorative poses, supported back bends, and inversions	12 weeks, 2 sessions per week	Health education group	Decrease in fatigue in yoga group versus controls at post-intervention; group differences maintained over 3-month follow-up
Deng *et al.* (2013)[120]	Cancer survivors (postchemotherapy) with moderate to severe fatigue (101)	Acupuncture (needled 8 standardized points)	6 weeks, 1 session per week	Sham acupuncture	Both groups showed significant (small) decreases in fatigue at post-intervention
Gielissen *et al.* (2006, 2007)[115,116]	Cancer survivors with severe fatigue (112)	Cognitive behavioral therapy focusing on perpetuating factors for persistent fatigue (such as insufficient coping, fear of recurrence, dysfunctional cognitions, dysregulation of sleep and activity, social support)	Up to 6 months, up to 1 session per week (average = 12.5 sessions)	Wait list (offered intervention at end of treatment period)	Decrease in fatigue in intervention group versus controls at 6 months; intervention group continued to show decreased fatigue at 1–4 years follow-up
Jain *et al.* (2011)[123]	Breast cancer survivors with moderate to severe fatigue (76)	Biofield healing (trained practitioners using standardized hand positions on different body areas)	4 weeks, 2 sessions per week	Mock healing (nonpractitioners using same hand positions) and wait list	Decrease in fatigue in biofield and mock healing groups versus wait-list controls at post-intervention
Molassiotis *et al.* (2012)[118]	Breast cancer survivors (post chemotherapy) with moderate to severe fatigue (302)	Acupuncture (three standardized points)	6 weeks, 1 session per week	Usual care (fatigue information booklet)	Decrease in fatigue in acupuncture group versus controls at post-intervention
Molassiotis *et al.* (2007)[119]	Cancer survivors (post-chemotherapy) with moderate to severe fatigue (47)	Acupuncture (three standardized points)	2 weeks, 3 sessions per week	Acupressure (patients taught to apply pressure to same acupunture points); sham acupressure (patients taught to apply pressure to different points)	Decrease in fatigue in acupuncture group versus acupressure and sham acupressure groups at post-intervention; group differences not maintained at 2-week follow-up
van der Lee *et al.* (2012)[121]	Cancer survivors with severe fatigue (100)	Mindfulness-based cognitive therapy promoting awareness of potentially maladaptive automatic responses related to fatigue	9 weeks, 1 session per week	Wait list	Decrease in fatigue in intervention group versus controls at post-intervention; intervention group continued to show decreased fatigue at 6-month follow-up
Yun *et al.* (2012)[117]	Cancer survivors with moderate to severe fatigue (273)	Internet-based education programme providing tailored information about fatigue, energy conservation, physical activity, nutrition, sleep hygiene, pain control, and distress management	12 weeks	Wait list	Decrease in fatigue in intervention group versus controls at post-intervention

factors, progestational steroids, the psychostimulant methylphenidate, and the antidepressant paroxetine—evaluated the efficacy of pharmacological treatment of cancer-related-fatigue.[125] These trials typically enrolled fatigued patients, often those with advanced-stage disease. In general, treatment with haematopoietic agents led to improvements in fatigue caused by chemotherapy-induced anaemia (effect size for erythropoietin –0.30; effect size for darbepoetin –0.13). The use of methylphenidate also led to greater reductions in fatigue compared with placebo (effect size –0.30), but progestational steroids and paroxetine did not.[125] Another antidepressant, sertraline, had no beneficial effect on fatigue in patients with advanced-stage cancer who were neither fatigued nor depressed.[126] Conversely, treatment with dexamethasone resulted in significant improvements in fatigue and quality of life for patients with advanced-stage cancer who reported moderate to severe symptoms of cancer-related fatigue.[127]

An updated meta-analysis of psychostimulant trials, conducted among patients with advanced-stage disease and mainly using methylphenidate,[128] suggested that psychostimulants were more effective than placebo in improving cancer-related fatigue (effect size –0.28). However, only one of the five studies included reported a statistically significant treatment effect.[129] Two recent studies conducted with larger samples of patients showed no benefit for methylphenidate versus placebo for improving fatigue,[130,131] although in subgroup analyses methylphenidate did seem to be effective for patients with severe fatigue and for those with advanced-stage disease.[131]

Modafinil, a nonamphetamine-based stimulant, represents another potential treatment for cancer-related fatigue. One large multicentre trial of patients undergoing chemotherapy found beneficial effects of modafinil among patients who reported severe fatigue at baseline, but not among those with mild or moderate fatigue.[132]

Based on research suggesting an inflammatory origin for cancer-related fatigue, several small phase II trials have used anticytokine agents to treat fatigue in patients with advanced-stage cancer. In a randomized trial, patients undergoing dose-intensive chemotherapy who received etanercept (a TNF-decoy receptor) reported significantly less fatigue than those receiving chemotherapy alone.[133] A small, nonrandomized study also showed some benefit for treatment with infliximab (an anti-TNF antibody) on fatigue in the palliative care setting.[134] Beneficial effects of anti-TNF agents on fatigue have also been observed among patients with inflammatory conditions, including psoriasis[135] and depression.[136] Although trials of other anti-inflammatories drugs for cancer-related fatigue are ongoing, the effectiveness of other agents (such as minocycline) has not been determined yet.

Despite interest in dietary and herbal supplements to treat fatigue, very few controlled trials have examined the efficacy of these agents in patients with cancer. One large, multisite trial examined the effect of L-cartinine for patients with cancer with moderate to severe fatigue, most of whom had metastatic disease and were undergoing treatment with radiotherapy or chemotherapy.[137] Results showed that 4-week treatment with L-carnitine was not more effective than placebo in reducing fatigue; instead, fatigue decreased in both the treatment and control groups. By contrast, a large multisite trial of American ginseng for patients with cancer-related fatigue did find beneficial effects, particularly among patients undergoing active cancer treatment.[138]

Overall, haematopoietic agents might be effective in improving fatigue that occurs secondary to chemotherapy-induced anaemia. However, because most fatigued patients are not anaemic, these agents are unlikely to benefit most patients with cancer-related fatigue, particularly in the post-treatment period. Despite interest in psychostimulants, such as methylphenidate, the evidence for these agents is quite mixed and recent guidelines do not recommend their use in the management of fatigue in patients who are disease-free following active treatment.[139] Of note, selective serotonin reuptake inhibitors (SSRI), a type of antidepressants, do not seem to have beneficial effects on cancer-related fatigue, supporting the distinction between fatigue and depression in patients with cancer and suggesting that fatigue is not solely an adverse effect of depression.

Mechanisms for intervention effects

Interventions for cancer-related fatigue have different targets and, therefore, might work through different mechanisms. For example, cognitive approaches to treat cancer-related fatigue specifically target thoughts that are associated with more-severe and persistent fatigue, such as catastrophizing.[115] Physical approaches might also work by changing thoughts and beliefs about fatigue; for example, patients felt more confident about their ability to manage fatigue after learning certain yoga postures,[122] which might lead to reductions in fatigue symptoms.

Biological mechanisms for intervention effects are also possible, including changes in inflammatory processes. Individuals who are more physically active show lower inflammatory activity;[140] thus, interventions that increase physical activity (and potentially reduce BMI) can influence fatigue by reducing inflammation and also by improving cardiorespiratory fitness. Mind–body and psychosocial approaches could also be effective in relieving fatigue by reducing inflammatory activity. A targeted yoga programme for fatigued breast cancer survivors was effective in reducing fatigue and also led to reductions in NF-κB activity, a key regulator of inflammation.[141] Similar effects on inflammatory signalling have been observed following mindfulness-based meditation and cognitive-behavioural stress management for patients with breast cancer, although these treatments did not specifically target fatigue.[142,143]

Conclusions

After two decades of research on cancer-related fatigue, we now have a good understanding of the characteristics, prevalence, and course of this symptom and are beginning to elucidate mechanisms, risk factors, and effective treatments. We also have a growing appreciation of the complexity of fatigue, which shows significant interindividual variability in its severity and expression. To advance our understanding of cancer-related fatigue, future research must address some key questions: who is at risk for fatigue, and why? What are the mechanisms that underlie fatigue during and after treatment? To address these questions, longitudinal studies are required that track patients before, during, and after cancer treatment and include comprehensive assessment of biobehavioural risk factors. Together with appropriate statistical techniques (such as multilevel modelling and latent growth mixture modelling), these longitudinal approaches will facilitate the identification of distinct trajectories of fatigue, and associated risk factors. These studies should also include in-depth assessment of underlying mechanisms, which can be used to direct intervention efforts; this aspect is particularly important if the risk factors themselves are not amenable to intervention (as in the case of genetic contributions). Furthermore, identification of factors that influence fatigue onset versus persistence can help in determining which type of interventions can be most useful during or after treatment. Studies should also examine the co-occurrence of fatigue and related symptoms, such as depression and sleep disturbance, to elucidate the complex interactions between them. Finally, the degree to which cancer-related fatigue differs from normal age-related fatigue (and fatigue in other contexts) merits special attention. In fact, cancer and its treatment might accelerate age-related changes in inflammation, aerobic capacity, and other physiological processes, which might contribute to fatigue; thus, the fatigued patient might be 'biologically' older and potentially at greater risk for premature conditions of ageing. Different contributing factors for fatigue in older versus younger patients might also be at play, with implications for treatment.

The identification of underlying mechanisms should guide the development of targeted, individualized interventions for cancer-related fatigue, similar to current personalized approaches to cancer therapy. For example, patients whose fatigue seems to be primarily driven by dysfunctional coping strategies could be more responsive to cognitive-behavioural therapy approaches. By contrast, patients whose fatigue is primarily driven by inflammatory activity could be more responsive to anti-inflammatory therapies (either behavioural or pharmacological). The importance of targeting the treatment to the underlying mechanism was illustrated in a recent trial evaluating the effect of the TNF antagonist infliximab for patients with treatment-resistant depression.[136] In this study, infliximab was only effective for patients with elevated inflammatory markers at baseline.[136] Similarly, anti-inflammatory approaches could be most efficacious for fatigued patients who show evidence of elevated inflammatory activity. Understanding the complexity of cancer-related fatigue can help to identify vulnerable individuals and develop targeted interventions—a critical step for reducing the burden of this symptom and improving the quality of life and well-being in patients with cancer and cancer survivors.

Review criteria

MEDLINE and PubMed were searched for original articles focusing on cancer-related fatigue published through December 2013. The two key search terms were "cancer" and "fatigue"; other search terms included "inflammation", "cytokines", "immune", "biological", "genetic", "longitudinal", and "randomized controlled trial". All papers identified were English-language full text papers. We also searched the reference lists of identified articles for further papers.

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