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The Role of Physical Activity in Managing Fatigue in Cancer Survivors

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Abstract

Purpose of Review This review provides an up-to-date overview of the evidence relating to how physical inactivity ameliorates cancer-related fatigue. A summary of the postulated biological mechanisms underpinning the relationship is presented.

Recent Findings Systematic reviews and meta-analyses synthesising the results of randomised controlled trials of physical activity interventions to reduce fatigue broadly conclude that aerobic and combination exercise may be the most helpful, while resistance training alone is less efficacious. Further, light- and moderate-intensity physical activity interventions appeared to reduce fatigue, whereas vigorous-intensity activity may exacerbate the condition. Physical activity interventions result in greater reductions in cancer-related fatigue when delivered post-treatment. Biological mechanisms that may explain how physical activity can improve different elements of cancer-related fatigue include inflammation; the hypothalamic–pituitary–adrenal (HPA) axis and circadian rhythm dysregulation; serotonin dysregulation; and alterations in ATP and muscle metabolism.

Summary Physical activity is well tolerated by cancer survivors and results in modest improvements in cancer-related fatigue. Much of the research in this field has been from small-scale feasibility trials. In order to help clinicians and allied health professionals tailor exercise prescriptions to individual needs, further research is required. New trials in this field should implement rigorous inclusion criteria, be fully powered to detect effects in sub-group analyses, incorporate multiple sites, and have well-defined control conditions. There is also a need to better understand how physical activity affects different subtypes of cancer-related fatigue.

Keywords Physical activity · Exercise · Interventions · Cancer-related fatigue · Cancer survivorship · Biological mechanisms

Introduction

Fatigue is one of the most commonly reported side effects of cancer diagnosis and treatment [1••, 2]. Cancer-related fatigue is described as a subjective, pervasive sense of tiredness, and an objective decrement of performance persisting over time. It interferes with activities of daily living and is not relieved by rest or sleep [3]. This side effect of cancer and its treatments is frequently reported as being more distressing than pain and nausea [1••]. Cancer-related fatigue is a multidimensional concept and can be experienced within physical and psychosocial domains [4••].

The prevalence of cancer-related fatigue depends on the cancer type, treatment received, and the method of assessment. Estimates suggest that between 30 and 60% of patients report cancer-related fatigue while undergoing treatment [1••]. Cancer-related fatigue has been reported to persist for decades in a proportion of cancer survivors, but for most fatigue tends to improve following completion of treatment [1••].

Physical activity and exercise (referred to collectively as 'physical activity' from here on) have been studied in relation to cancer-related fatigue for decades, and there is a prevailing acceptance that physical activity reduces fatigue experienced by cancer survivors. However, questions remain in relation to optimal timing and dose of physical activity to prevent or attenuate cancer-related fatigue. The aims of this manuscript

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are twofold: (i) to summarise findings from key systematic reviews conducted in the past 5 years of intervention trials examining the effect of physical activity on fatigue in cancer survivors and (ii) to describe the main biological mechanisms hypothesised to be involved in the development of cancer-related fatigue, and how physical activity may act upon these pathways.

Synthesis of Systematic Reviews

A literature search for systematic reviews and meta-analyses was performed using PubMed and PsycINFO from January 2013 to June 2018. The search strategy for each database is provided in the Appendix. We identified 18 systematic reviews that examined the effects of physical activity on cancer-related fatigue [4•, 5–12, 13–21]. Of these, 2 were umbrella reviews [11•, 16•] and 15 incorporated meta-analysis [4•, 5–10, 12, 13–15, 17, 18, 20, 21]. Eight of the 18 systematic reviews included a mix of cancer sites [5, 6, 11•, 12, 14, 16•, 18, 20], five included only trials in breast cancer survivors [4•, 8, 9, 13, 21], two were focussed on colorectal cancer [7, 17], one was focussed on prostate cancer [15], one was focussed on gynaecological cancer [19], and one was focussed on haematological cancers [10]. The key elements of these reviews are described in Table 1.

Quality of Systematic Reviews

Nine [4•, 5, 10, 11•, 13, 14, 16•, 18, 19] of the systematic reviews registered their study protocol in advance, as per the recommendations and guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions [22] or the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [23]. All reviews incorporated some form of quality assessment, the most commonly applied were Physiotherapy Evidence Database (PEDro) scale [24] and the Cochrane risk of bias (ROB) scale [25].

Meta-analysis Methods

Authors generally pooled fatigue data using weighted mean differences if studies measured fatigue on the same scale, or standardised mean differences when studies used a different scale [7–10, 12, 13, 15, 17, 18, 21, 26], with one study using weighted mean differences [20]. Heterogeneity was primarily assessed by the I^2 statistic [5, 7–10, 12, 13, 15, 17, 18, 20, 21, 26]. Most studies applied random effects models in their meta-analysis [5, 7–10, 17, 18, 20, 26], but a few used both random and fixed effects models (depending on whether heterogeneity was observed) [12, 13, 15, 21]. Mustian et al. used fixed effects models to combine effect sizes (Cohen's *d*) of the studies reporting exercise interventions [6]. van Vulpen et al. used random effects models to pool effect sizes within each dimension of fatigue considered [4•].

Results

The two umbrella reviews concluded that physical activity reduces fatigue in cancer survivors, but that the effect is small. The umbrella reviews noted that the evidence accrued to date was limited by the low quality of, and high heterogeneity between, trials [11•, 16•]. The majority of the systematic reviews and meta-analyses reviewed (Table 1) reported modest but statistically significant improvements in fatigue following the delivery of a physical activity intervention [4•, 5, 6, 8–10, 12, 13, 17, 18, 26]. Most reviews included a mix of cancer sites, but these studies were mostly populated by breast cancer trials. Accordingly, positive effects on fatigue were noted in nearly all systematic reviews and meta-analyses examining mixed sites [5, 6, 10, 12, 16•, 18, 26] and breast cancer [4•, 8, 9, 13]. Neither review examining effects of physical activity on fatigue in colorectal cancer survivors reported significant reductions [7, 17]. For prostate cancer, Yunfeng et al. reported no overall effect, but stratified analyses showed fatigue reductions occurred for physical activity interventions of 6-month duration or longer [15]. The systematic review of interventions delivered to gynaecological cancer survivors did not find enough trials reporting fatigue as an outcome to undertake a meta-analysis. Lin et al. reported mixed results across the three trials included in their review [19].

The systematic reviews included in Table 1 also highlight how differences in the type, dose, delivery, and timing of physical activity intervention are likely to exert different effects on cancer-related fatigue.

Type of Physical Activity Intervention The main types of interventions delivered to cancer survivors include aerobic, resistance, neuromuscular (yoga, tai chi, qigong etc.), or a combination (most typically a combination of aerobic and resistance training). Broadly, aerobic activity [5, 12, 21] or combination interventions [9, 14] appeared to have the greatest effect on fatigue in cancer survivors. Further, the type of aerobic exercise (e.g. walking, cycling, swimming) did not seem to influence the effect [12]. Resistance training alone did not appear efficacious [16•, 18]. One systematic review of physical activity interventions delivered to breast cancer patients undergoing adjuvant therapy concluded that neuromuscular interventions achieved the greatest reductions in fatigue [13].

Dose of Physical Activity Limited data exist comparing the effects of different doses of physical activity (different frequency, intensity, duration). A meta-regression analysis performed by Kessels et al. suggested greater reductions in cancer-related fatigue for lower intensity physical activity

Table 1 Summary of systematic reviews examining physical activity and cancer-related fatigue, 2013–2018

Authors, year	Cancer population, total sample	Method	Search dates, studies retrieved/ included	Physical activity intervention	Fatigue assessment	Key findings
Brandenbarg et al., 2018 [7].	Colorectal, on-treatment through to long-term survivors, $n = 630$	Systematic review and meta--analysis	Through to Dec 2015, 1196/5	Aerobic, resistance, neuromotor, combination. Supervised, unsupervised. Median duration = 13 weeks	FACT-F	- Non-significant reduction in fatigue in intervention arm - Trial participants has similar fatigue levels to general population; possible ceiling effect - Based on data, cannot draw definite conclusion about the effects of activity on fatigue
Fuller et al., 2018 [16•]	Mixed sites, on-treatment and post-treatment, $n = 1365$	Umbrella review	Through to Oct 2017, 4258/42	Aerobic, resistance, combination. Supervised, unsupervised. Median duration = NR	BFI, EORTC QoL-C30, FACT-F, MFI, PFS, PMS SCFS	- Most evidence derived from breast cancer survivor studies - High-quality meta-analyses suggest physical activity has small, beneficial effect on fatigue - Physical activity post-treatment achieved greater reductions on fatigue than activity on-treatment - Resistance training alone had less effect on fatigue
Kessels et al., 2018 [5]	Mixed sites, on-treatment and post-treatment, $n = 188$	Systematic review and meta--analysis	Jan 2000–Aug 2016, 276/6	Aerobic, resistance, combination. Supervised, unsupervised. Median duration = NR	EORTC QoL-C30, FACT-F, MFSI-SF, PFS, PROMIS	- Physical activity had large effect on fatigue - Greater effect shown in aerobic only interventions, versus combined aerobic/resistance - Higher adherence to intervention associated with greater reductions in fatigue
Oberoi et al., 2018 [10]	Mixed sites plus HSCT recipients, on-treatment and post-treatment, n = NR		1980–May 2017, 11,793/17-0.	Aerobic, resistance, neuromotor, combination. Supervised, unsupervised. Duration < 12 weeks = 33%, ≥ 12 weeks = 54%, not reported = 13%.	23 scales used (FACT-F, EORTC QoL-C30, BFI most frequently used)	- Physical activity reduced fatigue - Effects smaller for resistance training - Effects did not differ by cancer site or stage, timing or duration of intervention, supervised vs unsupervised, group vs non-group setting
Juvet et al., 2017 [9]	Breast, on-treatment and post-treatment, $n = 3418$	Systematic review and meta--analysis	Through to Oct 2014, 11,022/16.	Aerobic, resistance, combination. Supervised, unsupervised. Median duration = NR	EORTC QoL-C30, FACIT, FACT-F, FI, MFI, PFS, PMS, SCFS	- Meta-analysis showed small, beneficial effect of physical activity on fatigue - Reductions in fatigue evident for interventions delivered on-treatment and post-treatment (post-treatment effects greater) - Combination of exercise types achieved greatest benefit
Kelley and Kelley, 2017 [11•]	All sites, on-treatment and post-treatment, n = NR	Umbrella review	2007–2016, 278/16	Aerobic, resistance, combination. Supervised, unsupervised. Median duration = 14 weeks	24 scales used (FACT scales, PFS most frequently used)	- Results generally indicate small beneficial effect of physical activity on fatigue - Large proportion of meta-analyses with overlapping 95% confidence intervals (43%) and 95% prediction intervals (88%) suggest caution in attributing effect to intervention
Lipsett et al., 2017 [8]	Breast, on-treatment (radiotherapy), $n = 802$	Systematic review and meta--analysis	1966–2015, 62/9.	Aerobic, resistance, combination. Supervised, unsupervised. Duration range 5–12 weeks	BFI, FACT-C, FAS, PFS	- Physical activity interventions achieved a medium-sized effect on fatigue reduction, however large heterogeneity noted - Effects on fatigue (standardised mean difference) same for supervised and unsupervised, however unsupervised effects non-significant - No differences in fatigue between intervention and control groups at long-term follow-up.

Table 1 (continued)

Authors, year	Cancer population, total sample	Method	Search dates, studies retrieved/ included	Physical activity intervention	Fatigue assessment	Key findings
Mustian et al., 2017 [6]	All sites, on-treatment and post-treatment, *n* = 11,525	Systematic review and meta--analysis	Jan 1999–May 2016, 17,033/11-3.	Aerobic, resistance, combination. Supervised, unsupervised. Duration range 5–12 weeks	30 scales used	- Significant, moderate improvements in fatigue for exercise interventions - Exercise interventions achieved greatest reductions in fatigue (over psychological, exercise and psychological, and pharmaceutical interventions)
Yunfeng et al., 2017 [15]	Prostate, on-treatment (ADT), *n* = 641	Systematic review and meta--analysis	Through to Mar 2017, 1245/7	Aerobic, resistance, combination. Supervised, unsupervised. Duration range 12 weeks–24 months	NR	- Overall, physical activity interventions had no effect on fatigue - Stratified analyses show that physical activity interventions of 6-month duration or longer reduced fatigue significantly
Dennett et al., 2016 [18]	All sites, on-treatment and post-treatment, *n* = 2969	Systematic review and meta--analysis	Through to Apr 2015, 677/31	Aerobic, resistance, combination. Supervised, unsupervised. Duration range 4–52 weeks	14 scales used (EORTC QoL-C30, FACT scales most frequently used)	- Exercise interventions had positive effect on fatigue - Effects significant for solid tumours, but no effect seen for haematological cancers - Resistance training alone did not reduce fatigue
Lin et al., 2016 [19]	Gynaecological, on-treatment and post-treatment, *n* = 80	Systematic review	Through to Sep 2014, 882/3	Aerobic, resistance, combination. Unsupervised. Duration range 12 weeks–6 months	FACIT-F, FACT-F, MFSI-SF	- Mixed findings from three trials - Meta-analysis was performed for other outcomes, but not fatigue
Tian et al., 2016 [12]	All sites, on-treatment and post-treatment, *n* = 2830	Systematic review and meta--analysis	Through to Dec 2014, 1428/26	Aerobic	BFI, FACT-F, LASA, PFS, R-PFS, PMS	- Aerobic exercise found to have a small but significant effect on fatigue - Significant effects found in studies employing the BFI and revised PFS, whereas the FACT-F did not detect effects - Effects not significant in breast cancer survivor samples
van Vulpen et al., 2016 [4•]	Breast, on-treatment, *n* = 784	Systematic review and meta--analysis	Through to Jun 2015, 2023/5	Aerobic, resistance. Supervised, unsupervised. Duration range up to 18 weeks	FAQ, MFI	- Physical activity interventions reduced general fatigue and physical fatigue - No effect was noted on affective fatigue or cognitive fatigue - Physical activity also improves symptoms of reduced activity and reduced motivation
Carayol et al., 2015 [13]	Breast, on-treatment, *n* = 2723	Systematic review and meta--analysis	Through to Jun 2014, 629/33.	Aerobic, resistance, neuromotor, combination. Supervised, unsupervised. Mean duration = 16 weeks	NR	- Physical activity interventions had significant positive impact on fatigue - Effects diminished in trials where all participants undergoing chemotherapy - Neuromuscular interventions found to have greatest effect on fatigue
Meneses-Echávez et al., 2015 [14]	All sites, on-treatment and post-treatment, *n* = 1530	Systematic review and meta--analysis	Through to Sep 2013, 18,471/11	Aerobic, resistance, combination. Supervised. Duration 3–48 weeks	EORTC QoL-C30, FACT-F, MFI, PFS, SCFS	- A moderate reduction in fatigue was found for supervised exercise - Combined modalities achieved greatest reductions in fatigue
Cramer et al., 2014 [17]	Colorectal, post-treatment, *n* = 238	Systematic review and	Through to Dec 2012, 414/3	Aerobic, resistance, combination. Supervised, unsupervised. Duration 12–16 weeks	FACT-F.	- No effect found on fatigue

Table 1 (continued)

Authors, year	Cancer population, total sample	Method	Search dates, studies retrieved/ included	Physical activity intervention	Fatigue assessment	Key findings
		meta-analysis				
Zou et al., 2014 [21]	Breast, on-treatment, $n = 1014$	Systematic review and meta-analysis	Through to Jul 2013, 126/12	Aerobic. Supervised, unsupervised. Duration 4–12 weeks	FACIT-F, revised PFS	- Aerobic exercise interventions achieved significant reductions in fatigue measured by revised PFS - No effect for studies using the FACIT-F
Strasser et al., 2013 [20]	All sites, on-treatment and post-treatment, $n = 437$	Systematic review and meta-analysis	Through to Dec 2012, 259/4	Resistance. Supervised. Duration 12–52 weeks	FACT-F	- Small, positive but non-significant effect on fatigue

Abbreviations: *ADT*, androgen deprivation therapy; *BFI*, Brief Fatigue Inventory; *EORTC QoL-C30*, European Organization for Research and Treatment of Cancer Quality of Life-Core 30; *FACIT*, Functional Assessment of Chronic Illness Therapy; *FACT-F*, Functional Assessment of Cancer Therapy-Fatigue; *FAQ*, Fatigue Assessment Questionnaire; *FI*, Fatigue Instrument; *HSCT*, haematopietic stem cell transplant; *LASA*, Linear Analog Self-Assessment; *MFI*, Multidimensional Fatigue Inventory; *MFSI-SF*, Multidimensional Fatigue Symptom Inventory-Short Form; *NR* not reported; *PFS*, Piper Fatigue Scale; *PMS*, Profile of Mood States; *PROMIS*, Patient-Reported Outcomes Measurement Information System; *SCFS*, Schwartz Cancer Fatigue Scale

[5], and Dennett et al. reported an inverse association between aerobic exercise intensity and fatigue [18]. Conversely, Tian et al. reported that moderate-intensity physical activity was superior to light- and vigorous-intensity activities for reducing fatigue, and that the optimal duration for each intervention session was 50 min [12]. Yunfeng et al. reported that only interventions delivered for 6 months or more achieved significant reductions in the fatigue reported by men receiving androgen deprivation therapy for prostate cancer [15].

Delivery of Physical Activity Intervention The meta-analyses that compared the efficacy of supervised versus unsupervised physical activity interventions found that superior results were obtained by the supervised interventions [6, 10, 12]. Supervised interventions achieve higher adherence, which in itself is strongly predictive of a reduction in cancer-related fatigue [5].

Timing of Physical Activity Intervention A number of published meta-analyses concluded that physical activity interventions delivered after the conclusion of cancer therapy achieved greater reductions in fatigue than interventions delivered concurrently with therapy [6, 9, 12, 16•]. However, it is clear that physical activity performed across the cancer continuum may reduce fatigue: activity prior to commencing treatment may have a prophylactic effect (prevent treatment-related side effects including fatigue) whereas activity during and following treatment may act therapeutically [10].

Discussion

The consensus from the evidence to date is that physical activity has a beneficial effect on cancer-related fatigue; however, the effect is generally small. Some authors have urged caution in attributing a meaningful effect on physical activity interventions, because of the low quality of many trials, non-significant pooled effects, and overlapping prediction intervals identified in some systematic reviews. However, it must be noted that none of the reviews included, above, reported increases in fatigue attributable to physical activity. This is an important consideration that refutes the pervasive perception that physical activity increases fatigue experienced by cancer survivors, and supports the current expert view that physical activity for cancer survivors is safe and well tolerated [27, 28].

A key finding our evidence synthesis is that light- and moderate-intensity physical activities appear to achieve the greatest reductions in cancer-related fatigue, and that vigorous-intensity activity may exacerbate the condition. Recent research demonstrates that the mind-body techniques, such as mindfulness and relaxation, that accompany the physical activity elements of neuromuscular interventions are effective in reducing cancer-related fatigue [29].

Research has tended to conceptualise cancer-related fatigue as a singular concept; only one systematic review considered the multidimensional nature of the condition [4•]. Little research has been conducted into the subtypes or domains of cancer-related fatigue, but a recent study of colorectal cancer survivors identified three distinct classes of fatigue, using latent class analysis. Thong et al. found that the three fatigue classes could be differentiated by sleep quality, anxiety, anhedonia, and lifestyle factors [30]. This study highlights the need for more nuanced approaches to understanding determinants of, and treatment for, cancer-related fatigue in the future. Similarly, there is little benefit to trying to discern a singular, 'ideal' physical activity prescription for preventing or treating cancer-related fatigue. Optimal responses will likely be achieved by identifying physical activity interventions that best suit different cancer sites, treatments, points on the cancer continuum, and personal characteristics of the patient population (e.g. physical fitness, psychological well-being) [1••, 31].

Many of the primary studies conducted to date have been small, pilot studies that are insufficiently powered to detect clinically meaningful effects. It is not uncommon for trials to report less than 20 participants in each arm. A number of other methodological limitations were noted in the primary studies included in the meta-analyses reviewed. Few studies included patients with advanced disease, despite these patients experiencing elevated levels of cancer-related fatigue [31]. Similarly, there has been a dearth of studies including (or focussing on) octogenarian cancer survivors. This growing population experiences a heavy burden of comorbid disease and is particularly vulnerable to cancer-related fatigue. It has been suggested that older cancer survivors benefit less from physical activity interventions, although this may a function of poorer adherence [7]. There has also been limited research relating to how physical activity may alleviate fatigue in patients/survivors of less common cancers; the literature in this field is dominated by studies of breast cancer survivors.

Biological Mechanisms Underpinning Associations of Physical Activity with Fatigue in Cancer Survivors

Although there is a substantial body of evidence showing the physical activity interventions may reduce fatigue complaints in cancer survivors, the underlying biological mechanisms are still not well understood [6]. A better understanding of the biological mechanisms underlying associations of physical activity and sedentary behaviour with fatigue can give more information about the potential causal pathway of these associations [32]. Furthermore, it will help to develop more effective interventions for reducing fatigue after cancer by tailoring these towards the main causal factors and biological mechanisms involved. In addition, it can inform screening strategies for identifying at-risk individuals and target them with preventive measures. Here, we describe the main biological mechanisms that are currently hypothesised to be involved in the development of cancer-related fatigue as well as how these mechanisms may be associated with physical activity and sedentary behaviour (Fig. 1).

Inflammation

To date, the most studied and hypothesised mechanism to be implied in cancer-related fatigue is inflammation, in particular a dysregulation of cytokines with a specific focus on pro-inflammatory cytokines [1••]. It is thought that the tumour and/or its treatment cause an increased release of pro-inflammatory cytokines which influence central nervous system signalling leading to symptoms of fatigue [33, 34]. Indeed, a number of studies have identified associations of circulating levels of inflammatory markers with levels of fatigue during and after treatment, with the majority of research being done in breast cancer survivors. For example, increases over time in fatigue complaints have been associated with increases in the inflammatory markers C-reactive protein (CRP) and interleukin-1 receptor antagonist (IL-1RA) in breast and prostate cancer patients receiving radiotherapy [35] and interleukin-6 (IL-6) in breast cancer patients undergoing chemotherapy [36] and with a range of inflammatory markers in patients with locally advanced colorectal, oesophageal, and non-small-cell lung cancer receiving combined radiation and chemotherapy treatment [37, 38]. In the post-treatment trajectory, multiple studies have found that breast cancer survivors with persistent fatigue have higher levels of CRP [39–41] as well as of several other pro-inflammatory markers [42–44], compared to non-fatigued survivors. Similarly, persistently fatigued testicular cancer survivors were found to have higher levels of IL-1RA and CRP [45], and declines in fatigue in the 1-year post-treatment period have been correlated with a decline in IL-6 in ovarian cancer survivors [46]. Furthermore, genome-wide expression analyses have shown increased expression in leukocytes of genes encoding pro-inflammatory markers such as IL-1B and IL-6, and the pro-inflammatory transcription factor nuclear factor (NF)-κB in fatigued versus non-fatigued breast cancer survivors [47].

Although the available evidence is limited, there are also indications that physical activity levels may influence the inflammatory response. Observational studies in the general population have observed that more physical activity and less sedentary behaviour are associated with lower levels of pro-inflammatory markers such as CRP, leptin, IL-6, and tumour necrosis factor-α (TNF-α) [48, 49]. In cancer survivors, there is evidence from randomised controlled trials (RCTs) that exercise can have beneficial effects on circulating inflammatory factors, with the majority of research being done in breast

cancer survivors. A meta-analysis conducted by Meneses-Echávez et al. including eight RCTs in breast cancer patients showed that aerobic and/or resistance exercise can reduce serum concentrations of IL-6, TNF-α, and IL-2, although no differences were found in serum CRP or IL-10 [50]. In prostate cancer patients undergoing androgen suppression therapy, a combined aerobic and resistance exercise programme was found to be associated with decreases in CRP levels [51], and in one trial in colorectal cancer survivors, it was found that an increase in physical activity due to a home-based physical activity intervention was associated with significantly reduced levels of TNF-α [52].

Hypothalamic–Pituitary–Adrenal Axis and Circadian Rhythm Dysregulation

There is evidence that a disruption of circadian rhythms and the hypothalamic–pituitary–adrenal axis (HPA axis) may also play an important role in causing persistent fatigue after cancer [53, 54]. In particular, disrupted accelerometer-assessed daily rest-activity rhythms, indicating circadian system dysfunction, have been associated with more fatigue in breast cancer [55–57] and colorectal cancer survivors [58]. The disruption of arousal and sleep patterns may be caused by a dysregulation of the HPA axis [53, 59]. The HPA axis regulates the release of the stress hormone cortisol [53, 54], which shows a diurnal pattern with highest levels around awakening and lowest levels during bedtime [60]. Fatigued breast and ovarian cancer survivors have less cortisol decline during the day and higher evening cortisol levels than non-fatigued survivors [46, 59, 61–63], and longitudinal reductions in evening cortisol have been associated with reductions in fatigue over time [46, 62]. Evidence that physical activity may influence the HPA axis was found in an RCT in breast cancer patients, where it was observed that an exercise intervention normalised HPA axis function, by influencing diurnal salivary cortisol rhythm [64].

Serotonin Dysregulation

Another hypothesised mechanism of the development of post-cancer fatigue is that increased activity of pro-inflammatory cytokines such as interleukins and TNF-α, caused by the tumour and/or its treatment (see above), leads to increased levels of 5-hydroxytryptamine (5-HT; serotonin) and an upregulation of 5-HT receptors in the brain which results in a sensation of fatigue [53, 54]. An animal study demonstrated that 5-HT levels in the brain increase during sustained exercise and that fatigue is observed at the highest level of 5-HT [65]. There are also indications from studies in chronic fatigue syndrome patients that 5-HT dysregulation may be an important mechanism in the development of fatigue, indicating that this mechanism may also play a role in cancer survivors [53, 54].

Two clinical trials in fatigued cancer patients undergoing chemotherapy who received a selective serotonin uptake inhibitor or placebo reported no improvement in fatigue complaints, but no other studies of this nature have been conducted in cancer survivors to date. In addition, although there is evidence that exercise leads to a short-term increase in 5-HT associated with higher fatigue complaints [54], it is unknown whether in the long term exercise may normalise serotonin metabolism and thus reduce chronic fatigue after cancer.

Alterations in ATP and Muscle Metabolism

Next to the abovementioned more central mechanisms, persistent fatigue in cancer survivors has also been hypothesised to be caused by impairment of peripheral muscle metabolism and function [53, 54]. Greater muscle strength has been associated with less fatigue in cancer survivors [66], and fatigued cancer patients have a lower endurance time when performing a sustained muscle contraction to task failure, compared with healthy controls [67, 68]. Cancer and/or its treatment can reduce muscle oxidative capacity, specifically the ability to regenerate adenosine triphosphate (ATP), and cause higher vulnerability to muscle fatigue [54, 69]. An RCT with ATP infusions in lung cancer patients showed beneficial effects on muscle strength and fatigue [70]. Importantly, exercise interventions have been found to improve muscle strength and function in cancer survivors [16•, 71], indicating that physical activity can influence this hypothesised mechanism of cancer-related fatigue.

Together, these hypothesised mechanisms of cancer-related fatigue may potentially mediate associations of physical activity with fatigue in cancer survivors, with most evidence up until now for the role of inflammation. The exact causal pathways will be complex, and the mechanisms involved interrelated. For example, the HPA axis plays an important role in the regulation of cytokine production and can influence the inflammatory response [72], and disturbances in circadian rhythms have been associated with muscle metabolism aberrations [60, 73, 74]. More mechanistic research will be necessary to determine the importance of individual hypothesised mechanisms and their inter-relations in causing fatigue and being influenced by physical activity. In addition, further research will be necessary into more recently hypothesised mechanisms of cancer-related fatigue, including cellular immune system dysregulation and reactivation of latent viruses, as well as alterations in the autonomic nervous system as indicated by levels of noradrenaline and heart rate variability [1••].

Implications and Directions for Future Research

There is a clear need for further research with rigorous inclusion criteria, adequate sample size, multicentre design, and

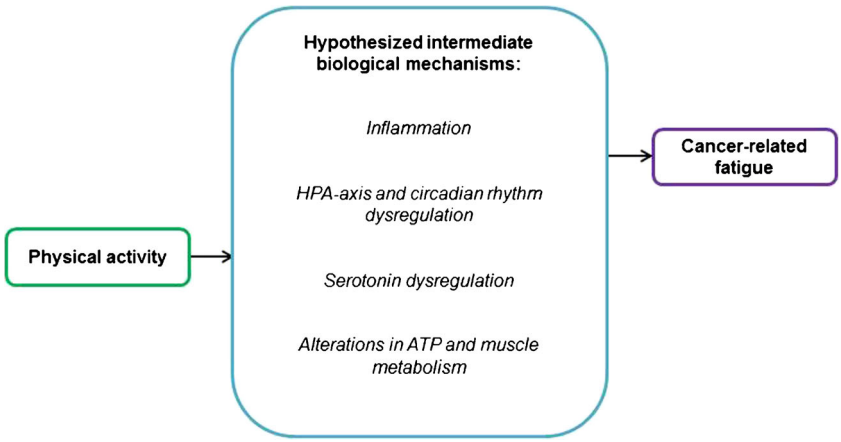

Fig. 1 Hypothesised biological mechanisms by which physical activity may decrease cancer-related fatigue

well-defined control conditions in order to better understand how physical activity reduces cancer-related fatigue. Specific cancer survivor populations that warrant additional research include less commonly studied sites, including lung, melanoma, kidney, bladder, and haematological cancers; older (≥ 80 years) cancer survivors; and survivors with advanced disease. Screening potential participants for fatigue prior to enrolment, and only including fatigued cancer survivors, may avoid dilution of intervention effect due to a ceiling effect. Studies comparing the type, dose, delivery, and timing of physical activity interventions are required to help elucidate optimal prescriptions for specific populations. Future research should also investigate how physical activity affects different subtypes of cancer-related fatigue.

There is also a need to research to identify ways to improve adherence, and support survivors to maintain physical activity on an ongoing basis. Translational approaches are required to help transition survivors from supported environments with supervised delivery of physical activity interventions to community-based approaches. Emerging e- and m-health approaches may be particularly helpful in this regard [75, 76].

Mechanistic Research

We recommend that future studies apply more agnostic approaches to identify new intermediate biomarkers and thereby discover novel potential mechanisms involved, by applying omics technologies. There are also opportunities to apply recently developed methods for longitudinal mediation analysis [79] to investigate potential intermediate mechanisms in molecular epidemiological studies. As most of the mechanistic research to date has been done in breast cancer survivors, it is essential to conduct more studies in other cancer populations. Finally, we recommend that future studies investigate how the mechanisms involved are influenced by other individual factors such as treatment received, sex, body mass index, and physical function. Such knowledge will be essential for the development of mechanism-tailored physical activity interventions to prevent or treat cancer-related fatigue.

Conclusions

As world-wide trends in population ageing continue, the number of adults diagnosed with, and surviving, cancer is projected to increase significantly [77]. Cancer survival is associated with ongoing physical and psychological adverse effects and comorbid conditions. Cancer-related fatigue is one of the most common and distressing side effects of cancer and cancer therapy [31]. Thus, cancer-related fatigue is a significant and growing public health concern and should be a high priority for both research and clinical intervention.

Available evidence suggests that physical activity can attenuate the fatigue experienced by cancer survivors. Aerobic and combination exercise may be the most helpful, while resistance training alone is less efficacious. However, the overall quality of research to date has been low, and further studies are necessary to elucidate which kinds of physical activity interventions work best for different clinical populations. There is also a pressing need to establish methods of sustaining physical activity on an ongoing basis, as the beneficial effects on fatigue quickly diminish after interventions are withdrawn.

The main biological mechanisms hypothesised to underpin the physical activity and cancer-related fatigue relationship include inflammation; the hypothalamic–pituitary–adrenal (HPA) axis and circadian rhythm dysregulation; serotonin dysregulation; and alterations in ATP and muscle metabolism. A clearer understanding of the underlying biological mechanisms linking physical activity with reduced fatigue may inform screening strategies for identifying at-risk individuals and provide additional insights into how to tailor physical activity interventions in order to optimise fatigue prevention or treatment.

Guidelines from cancer control agencies recommend at least 150 min of moderate-intensity or 75 min of vigorous-

intensity activity each week for cancer survivors. For cancer-related fatigue, the evidence suggests that even light-intensity physical activity may be beneficial. For survivors who may be struggling to adhere to recommended or prescribed physical activity levels, it is important to recognise that any activity is beneficial.

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Compliance with Ethics Guidelines

Conflict of Interest Bernat-Carles Serdà i Ferrer, Eline van Roekel, and Brigid M. Lynch declare they have 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.

Appendix

Aim

Search for systematic reviews and meta-analyses focused on physical activity (exposure or intervention) and cancer-related fatigue (outcome) in adults diagnosed with any stage of cancer, at any time post-diagnosis (including palliative care).

Data Sources and Search Strategy

The search was focused on systematic reviews and meta-analyses published from January 2013 to May of 2018 and updated to Jun 2018. The literature search was performed using MEDLINE and PsycINFO. All searches were conducted by one author [BCSF]. All references were imported into EndNote X5.

Eligibility Criteria

Inclusion criteria:

- Fatigue as a main outcome.
- Physical activity intervention.
- Primary participants had a diagnosis of cancer.
- Reviews and/or meta-analysis.
- Studies written in Spanish, English, or French.

Exclusion criteria:

- Other chronic diseases.
- Not using physical activity as primary intervention.

PubMed Search

The search strategy for identification of the studies included Medical Subject Heading terms combined with the Boolean terms as follows:

'Exercise' [Mesh] OR 'Exercise Therapy' [Mesh] OR 'Resistance Training' [Mesh] OR 'Sports' [Mesh] OR 'Yoga' [Mesh] AND 'Neoplasms' [Mesh] AND 'Fatigue' [Mesh]

Filters: Meta-Analysis, Review; From 01/01/2013 to 12/06/2018. The search identified 58 potentially relevant reviews.

PsycINFO

The search strategy implemented were 'Cancer' 'Exercise' OR 'Physical activity' AND 'Cancer-related Fatigue' AND Methodology Systematic Review OR Meta Analysis AND Peer-Reviewed Journals Only AND Year: 2013 to 2018 and identified 90 potentially relevant reviews.

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

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