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Relationships between Physiological and Self-Reported Assessment of Cancer-Related Fatigue

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ABSTRACT

International Journal of Exercise Science 15(3): 177-190, 2022. The purpose of this study was to evaluate the relationships between subjective, self-reported cancer related fatigue (CRF) and objective measures of muscular strength and fatigability in cancer survivors. A total of 155 cancer survivors (60 ± 13 years of age) completed a questionnaire for the assessment of CRF, along with assessments of handgrip strength, quadriceps strength and fatigability (reduced force/torque). Fatigability was measured by completing 15 maximal isokinetic contractions of the knee extensors (QFI). Spearman's rho correlation coefficients were calculated as pairwise combinations of the numerical and categorical dependent measures. Categorical variables were analyzed via nonparametric means of association. This included a 4x4 chi-square to test whether cancer stage (0–4) was independent of fatigue status (none, mild, moderate, severe) and whether cancer treatment (surgery, radiation, chemotherapy, or combinations of these) was independent of fatigue status. None of the physiological strength and fatigue measures were significantly correlated to overall perceived fatigue or any of the subscales. Cancer stage and treatment type were also not significantly related to fatigue status (likelihood ratio = .225, Cramer's V = .228; likelihood ratio = .103, Cramer's V = .369, respectively). Our results show that levels of patient reported fatigue severity were not significantly related to muscular fatigability or strength. As a result, cancer patients experiencing fatigue may benefit from following the standard exercise guidelines for cancer survivors, regardless of their levels of self-reported fatigue.

KEY WORDS: Muscle fatigue, perceived fatigue, cancer survivors, fatigue assessment, muscular strength, exercise, fatigability

INTRODUCTION

Cancer-related fatigue (CRF) is a ubiquitous side effect of cancer and its treatment. It is characterized by a distressing and persistent symptom of tiredness which negatively impacts physical functioning (2). Fatigue is consistently the most frequently reported symptom in cancer survivors and can often continue for months or years following completion of treatment (20). A 2014 multicenter study found 45% prevalence of moderate to severe CRF in cancer survivors (52). However, reported prevalence measures of CRF are highly variable as rates depend on cancer type, cancer stage, treatment regimen, fatigue assessment method, along with a number of other factors (20). The extent to which CRF is elicited by cancer itself, cancer therapies, or a combination of factors has yet to be elucidated (43). Several biological mechanisms have been proposed to explain the development of CRF including anemia, cachexia, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, pro-inflammatory cytokines, and altered muscle metabolism, among others (4). Despite the biological evidence, the etiology and underlying mechanisms remain unclear as both psychological and physiological factors appear to play a role (1, 42, 43, 51).

Fatigue is also described as a reduction in the ability to produce maximal force during an exercise-related task (48). Muscular fatigue is commonly associated with exercise but is oftentimes experienced as a secondary outcome to many health conditions, disease states, and cancer (3). Several studies have indicated that a reduction in muscle mass and decreased functional capacity result from cancer and its treatment (11, 26, 53). Inactivity can be a contributing factor and may exacerbate losses of muscle mass and strength as well as increased fatigability (3). It has been hypothesized that this reduction in muscle function may contribute to CRF while the brain concomitantly functions as a key regulator of fatigue perception (19). Thus, evidence points to at least two dimensions of fatigue (46). The proposed taxonomy for describing fatigue in clinical populations includes both a dimension of perceived fatigue and performance fatigability (29). To discern between these domains the term fatigue will be used to describe subjective or perceived fatigue and fatigability to describe objective or muscular fatigue.

As with the varying definitions of fatigue there is also variation in measurement techniques. Differences in cancer type, stage, treatment, in addition to the individual and multifactorial causes of CRF make assessment difficult and no universal standard exists for assessing CRF. Because there is no objective surrogate measure of CRF, the subjective nature and severity of fatigue is assessed using a variety of self-reported questionnaires and scales as well as patient reported outcomes. These scales are well established assessments of CRF and are useful in evaluating prevalence, severity, and clinical consequences of fatigue (2, 19). While perceived fatigue is useful clinically, it is difficult to discriminate between perceived and physiological fatigue (21). Even multidimensional subjective scales are not well suited to evaluate the impact of this fatigue on functional tasks in real-world settings (34).

Based on current evidence, exercise seems to be most effective in preventing or ameliorating CRF both during and after treatment. Recent systematic reviews and meta-analyses have concluded that both aerobic and resistance exercise training are effective in reducing CRF both during and after treatment (9, 25). Proposed mechanisms by which exercise improves CRF include direct physiological and biological mechanisms, including improved muscular and cardiovascular fitness, enhanced metabolic function, and reduced inflammatory responses. Indirect mechanisms include improvements in behavioral, social, and psychological domains (33).

Current ACSM guidelines for exercise prescriptions in cancer patients suggest a potential need for reductions in exercise intensity (45-65% HR_{max}; 60% 1RM; RPE 12) and duration (30 minutes) for survivors experiencing CRF compared to those for improving physical function (60-85% HR_{max}, RPE 12-13; 60-75% 1RM, RPE 13-15; 30-60 minutes) (7). Previous CRF specific guidelines have recommended reductions in exercise intensity with increased CRF severity (33). In addition, these guidelines suggest that survivors with severe CRF may need to begin a resistance training program with only active movement, very light intensity, or reduce session volume to avoid worsening fatigue (14, 33). Yet, evidence of increased perceived exertion rate in survivors experiencing fatigue has yet to be well established (48). Prescribing a reduced exercise intensity and duration contrasts the evidence that moderate to vigorous intensity exercise and longer duration exercise are more effective at reducing CRF (7). Reductions in aerobic capacity and muscular strength are well established in cancer survivors (15, 20), but the extent to which this reduced strength relates to performance fatigability and perceptions of fatigue is unknown (48).

The literature has yet to show clear evidence of a relationship between subjective feelings of fatigue and performance fatigability, specifically in cancer survivors. Exercise guidelines for cancer survivors experiencing fatigue recommend a reduced time and intensity for exercise sessions. This recommendation led us to hypothesize that perceived fatigue would be associated with muscular strength and muscular fatigue in this population. Having more specific CRF data may better inform clinicians about the efficacy of self-reported fatigue as a parameter for altering exercise session intensity based on CRF severity. If in fact a relationship does exist between muscular fatigue and self-report assessment of CRF, reducing intensity and duration of exercise sessions for patients experiencing CRF would be supported. The absence of a significant relationship between CRF and strength/fatigability would indicate that exercise prescriptions may not need to be altered as current guidelines suggest. A better understanding of the associations between fatigue dimensions would assist clinicians in creating more precise exercise prescriptions and enhance the efficacy of exercise-based cancer rehabilitation programs. Therefore, the purpose of this study was to evaluate the relationships between subjective self-reported fatigue, strength, and objective performance fatigability in cancer survivors.

METHODS

Study procedures were approved by the University's Institutional Review Board. This research was carried out fully in accordance to the ethical standards of the International Journal of Exercise Science (35).

Participants

Participants in this study were males and females over 18 years of age who had previously been diagnosed with cancer. Participants were referred to the University of Northern Colorado Cancer Rehabilitation Institute from local oncologists as individuals who were either undergoing or who had undergone chemotherapy, radiation, surgery, hormone therapy, immunotherapy, or a combination of treatments. To evaluate relationships between strength and fatigue assessments, our group felt it important to include a broad variety of cancer patient demographics and treatments. This provided a sample of individuals experiencing a range of

CRF from no fatigue to severe fatigue which we felt more beneficial for correlational techniques and generalizability. An a priori power analysis was conducted using G*Power3 using a medium effect size (d = .35), and an alpha of 0.05. Results showed that a total sample of n = 46 was required to achieve a power of .80. A total of 155 cancer survivors (60 ± 13 years of age) completed three different assessments of strength and fatigue including measurements of subjective fatigue and muscular fatigability.

Protocol

An informed written consent was provided to each participant and signed prior to participation. Medical histories consisting of cancer type, stage, and treatments were obtained prior to assessments. Anthropometric data including age, height, weight, and body composition were collected. Body composition was determined via bioelectrical impedance analysis (InBody, Cerritos, CA). This method of body composition assessment is a non-invasive, widely used method in clinical populations and has been shown to be a valid and reliable tool for the assessment of body composition and lean body mass in adults (17, 31) and the cancer population (40).

Subjective feelings of fatigue were established via the revised Piper Fatigue Scale (PFS) which evaluates total CRF and includes subscales of fatigue including sensory, affective, behavioral, and cognitive/mood. This questionnaire asks individuals to, "best describe the fatigue you are experiencing now or for today" and is a valid and reliable measure of CRF in cancer survivors (39). The individual subscales together consist of 22 questions with the average score representing total CRF. Each of the 22 questions were scaled from 0 to 10. These scores formed categories of (a) no fatigue (0), (b) mild fatigue (1-3), (c) moderate fatigue (4-5), and (d) severe fatigue (> 7).

Following completion of the PFS, participants performed an assessment of handgrip strength using a handgrip dynamometer. The dynamometer (Lafayette/TEC, Lafayette, IN) handle was first sized to correctly fit the dominant hand of the participant, with the dominant hand being identified as the hand used for writing. Measurement was taken in a standing position, with the elbow extended and arm parallel to, but not touching, the side of the body. Handgrip strength (kg) was recorded as the highest of three ~3-s maximal efforts, separated by a 1-minute rest. Handgrip strength measures were converted to Newtons for consistency with torque units from the lower body assessment and referenced subsequently as peak hand force (PHF). Hand dynamometry is a widely accepted measure of strength and has been used in the cancer population (26, 55).

Participants then completed an assessment of strength and fatigability of the quadriceps musculature. Fatigability is defined here as a decrease in maximal force or power production in response to contractile activity (50). Torque of the dominant limb's knee extensors was measured on a Biodex© dynamometer (Biodex Medical Inc., Shirley, NY) during an isokinetic exercise protocol. Participants sat upright and were fitted to the dynamometer according to manufacturer recommendations. Participants were instructed to give maximum effort for each repetition during each set of exercises with 90 seconds of rest between sets (37). The first two sets consisted of five submaximal repetitions as a specific warm-up and to become familiar with the movement at speeds of 180°·s-1 and 120°·s-1, respectively. The third and final set was the fatigue protocol, which consisted of 15 repetitions at 60°·s-1. A familiarization session was conducted prior to the testing session to familiarize the participant to the protocol. A minimum of two rest days were given between the familiarization and testing protocols. Similar strength and performance fatigability protocols have been utilized by others (10, 28, 30, 38, 54).

A custom MATLAB® script (R2014a, Mathworks Inc., Natick, MA) was used to analyze Biodex© data output and identify peak torque (N·m) from each repetition. The highest torque was recorded as peak quadriceps force (PQF). A fatigue index was then generated using the following equation: Fatigue Index (%) = [(highest force – lowest force) / highest force] * 100 and is referenced subsequently as quadriceps fatigue index (QFI). This formula was adapted from other studies (24, 27, 28) that utilized averages of initial values and repetition values in their calculations. If peak torque on the first repetition was markedly lower than the second repetition, it was omitted from the calculation of initial peak values (18). Isokinetic dynamometry is currently considered the gold standard to evaluate strength (11) and muscular fatigue in the cancer population (28). A dynamic movement of 15 repetitions for fatigue assessment was used as it more accurately mimics exercise and normal activities of daily living than sustained isometric contractions for fatigability assessment (12).

Statistical Analysis

Spearman's rho correlation coefficients were calculated as pairwise combinations of the numerical dependent measures (i.e., FI, cancer stage, lean mass, PQF, PHF) and all scores from the PFS. A Bonferroni correction for multiple correlation tests was performed to adjust for Type I error rate. The nominal 0.05 alpha was divided by 25 correlation tests, resulting in an adjusted alpha level of 0.002 for determining statistical significance. Strength of association of categorical variables was analyzed via nonparametric means of association. This included a 4x4 Chi square test to evaluate whether cancer stage (0–4) was independent of fatigue status (none, mild, moderate, severe) and whether cancer treatment (surgery, radiation, chemotherapy, or combinations of these) was independent of fatigue status. For these nonparametric tests a Cramer's *V* effect size was presented to indicate strength of association. Alpha was adjusted for multiple chi-square tests by dividing 0.05 by 2, yielding an adjusted Type I error rate of 0.025 for these categorical tests of association. All statistical analyses were performed using IBM SPSS Statistics 20 (IBM® Armonk, NY).

RESULTS

Initial characteristics and treatment history of participants are summarized in Table 1. Table 2 provides a summary of fatigue indices, muscular strength, and lean mass for all participants. Figure 1 provides representative data of quadriceps strength and fatigue from one subject for the QFI protocol.

Table 1. Subject Characteristics (*n* = 155)

Variables	Mean ± SD		*n*	%
Age	60 ± 13			
Total Body Mass (kg)	77 ± 19			
Height (cm)	165 ± 14			
Female			97	63
Male			58	37
Cancer stage		Not Staged	3	1
		I	39	25
		II	46	30
		III	41	26
		IV	26	17
Chemotherapy		Yes	113	73
		No	42	27
Radiation		Yes	86	55
		No	69	45
Surgery		Yes	122	79
		No	33	21
In-treatment			19	12
Out of treatment			136	88
Months from treatment	12 ± 21			

Table 2. Strength, Lean Mass, and Fatigue

Variables	Mean ± SD
Lean Muscle Mass (kg)	51 ± 13
Peak Handgrip Force (N)	176 ± 69
Peak Quadriceps Force (Nm)	150 ± 53
Quadriceps Fatigue Index (%)	34 ± 10
Fatigue Classifications	
None	19
Mild	71
Moderate	55
Severe	10

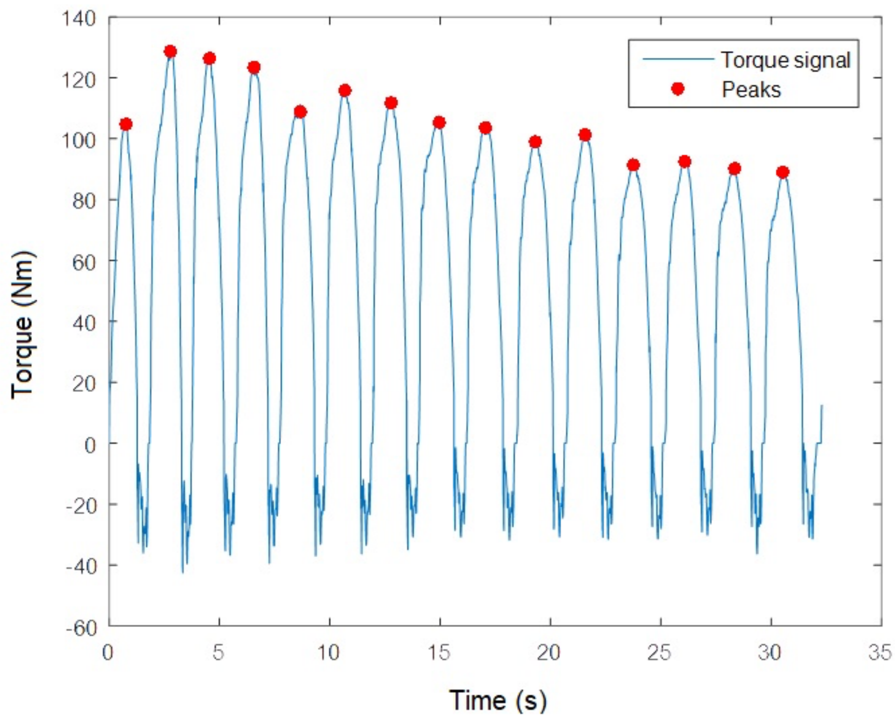

Figure 1. Representative image for quadriceps fatigue testing from a single subject.

A correlation matrix representing all pairs of dependent variables is shown in Table 3. None of the dependent physical performance variables were significantly correlated to total fatigue score or any of the subscale fatigue scores (all $p > 0.002$). Fatigue status was not significantly related to cancer stage (likelihood ratio = .225, Cramer's $V = .228$) or type of treatment (likelihood ratio = .103, Cramer's $V = .369$). A scatterplot of total perceived fatigue scores and performance fatigability scores are provided in Figure 2.

Table 3. Spearman's Correlation Matrix for Main Study Variables

	Piper Fatigue Scale Dimensions				
	Total	Behavioral	Affective	Sensory	Cognitive/Mood
Quadriceps Fatigue Index (%)	-.048	-.063	-.050	-.029	-.050
Peak Hand Force (N)	-.187	-.196	-.148	-.192	-.123
Peak Quadriceps Force (N)	-.056	-.085	-.057	-.042	-.067
Lean Muscle Mass (kg)	-.104	-.112	-.092	-.133	-.064
Cancer Stage	.061	.029	.083	.073	.055

Note. None of the correlations are significant at $p > 0.002$.

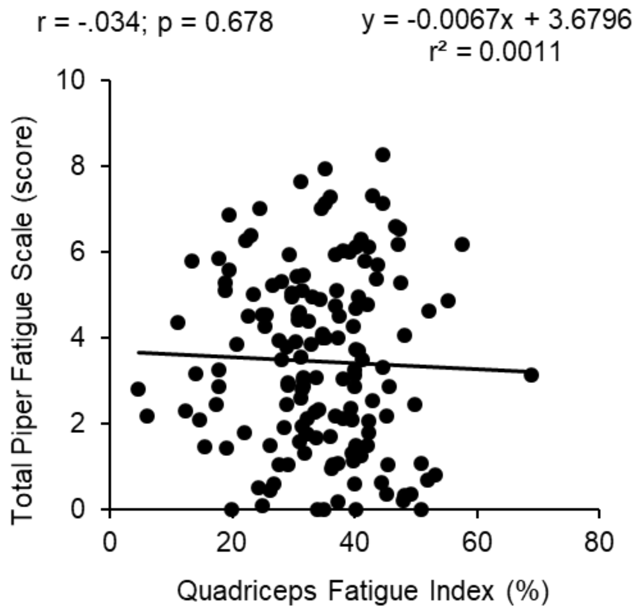

Figure 2. Quadriceps Fatigue Index plotted against total Piper Fatigue Scale Scores. Line represents the line of best fit.

DISCUSSION

The aim of the present study was to determine if objectively measured muscular strength and fatigability variables correlate with subjective fatigue assessment of CRF in cancer survivors. Furthermore, our hypothesis was that CRF would be correlated with muscular strength and fatigue. The importance of this research question is rooted in our clinical experience working with large numbers of cancer survivors in an exercise-based rehabilitation setting. While many of the participants in our program report fatigue immediately prior to prescribed exercise sessions, this fatigue varies from day-to-day and can often fluctuate widely. This prompted many questions about exercise interventions for cancer survivors, and whether individual exercise sessions should be altered or modified based on the level of subjective, self-reported fatigue for that particular day. If, in fact, a strong relationship exists between CRF and fatigability, clinicians working with cancer survivors could screen exercise participants prior to each session and modify intensity or duration to match the level of self-reported fatigue. We failed to observe a significant relationship between CRF, muscular strength, and fatigability, which suggests that cancer patients experiencing fatigue may benefit from following the standard exercise guidelines for cancer survivors, regardless of their levels of self-reported fatigue.

Results from the present study suggest handgrip strength, quadriceps strength, and fatigability are not significantly associated with subjective feelings of fatigue as assessed by the PFS. No significant relationships were observed between any of the self-reported fatigue measures and handgrip strength, quadriceps strength, or rate of quadriceps muscular fatigue during repeated knee extensions. In addition, cancer treatment type, stage, and muscle mass were not related to either subjective or local muscular fatigue measures. Several studies have reported reductions in muscle mass and function due to cancer and its treatments (11, 26, 28, 53), yet these studies do not connect perceived fatigue with any underlying functional physiology. Lower levels of lean mass have been shown to be associated with higher levels of CRF (26) which contrasts the results of the present study showing no correlation with muscle mass. The lack of a significant association between muscle mass and fatigue may also partly explain the absence of associations between perceived fatigue, strength, and fatigability in the present study.

Small correlations between isometric handgrip strength and CRF have been observed previously in the cancer population (8, 23, 26, 44) but are not in agreement with our findings or findings of others who reported no such correlation (5, 45). Previous studies have found lower levels of quadriceps strength to be associated with higher levels of CRF in cancer patients (27, 28) and those with advanced cancer (26) which are also contrary to results of the present study. We propose two possible reasons for the contrast in results between the present study and others. First, in our study the majority of cancer survivors presented with mild to moderate fatigue levels, with few experiencing no fatigue or severe fatigue. Second, the present study did not limit inclusion criteria to more advanced stages of cancer, which may present with more severe fatigue levels (1).

Similar to the results of the present study, others found comparable rates of lower body neuromuscular fatigue between fatigued and non-fatigued cancer survivors (36, 54). In contrast, Brownstein and colleagues found a higher degree of performance fatigability in cancer survivors who reported a higher degree of CRF (6). An important distinction between the present study and others is the use of an incremental cycling test (6) and isometric contractions (28, 36, 56) to evaluate performance fatigability of the lower body as opposed to the 15 isokinetic repetitions used here.

Screening, evaluation, and treatment for CRF in clinical settings remains suboptimal and current CRF assessment tools include only the perceived fatigability dimension (28). Adoption of a single scale to assess CRF in addition to a more standardized and consistent fatigability assessment that represents daily activities and exercise would assist in the evaluation of outcomes. As with subjective assessment of fatigue, methodology of assessment of neuromuscular strength, function, and fatigability is varied, limiting the ability to compare results across studies and limiting generalizability to prescriptive exercise and the rehabilitation setting (27, 56). This variability in assessment methodology may partially explain the contrasting results between the present study and others. Additional research is necessary to determine whether the lack of a significant relationship between self-reported fatigue and measured muscular fatigue is due to the selected methodology of assessment or if it is a true lack of association between these two measures of fatigue in this population.

Currently there is insufficient evidence to establish a relationship between perceived fatigue, fatigability, muscular strength, and exercise-induced fatigue in cancer survivors and further investigation is warranted (48). To our knowledge, no studies have investigated neuromuscular fatigue using whole-body, dynamic movements relevant to daily activities, rehabilitation exercises, and locomotion (48). As such, more studies are needed to determine performance fatigability with different task requirements that are functionally relevant (57). A further limitation of the current literature is a lack of understanding about whether reductions in muscular strength and increases in fatigability are related to perceived fatigue experienced in cancer survivors before, during, and after exercise (28). Rating of perceived exertion (RPE) is a common method used by exercise specialists to assess the participant's self-perceived effort during exercise and as a measure of exercise tolerance. Future investigations should evaluate relationships between exercise tolerance and fatigue severity to determine if a reduction in intensity or volume is necessary for those experiencing CRF. Continued investigation into muscular dysfunction, rate of perceived exertion, fatigability, and their relationships to CRF may assist clinicians in individualizing treatment methods and further our understating of mechanisms underlying CRF in cancer survivors.

Relationships between fatigability and subjective feelings of fatigue have received very little attention in the cancer population. Assessing both objective and subjective measures of fatigue in clinical populations may assist in determining if perceived fatigue is related to performance fatigability (32). Evaluating the relationships between neuromuscular fatigue and the chronic fatigue felt by cancer survivors has important clinical and rehabilitation implications. Fatigue can be a considerable barrier to exercise in cancer survivors, and low-to-moderate intensity exercise and shorter exercise duration have been suggested as strategies to overcome the barrier of CRF (33). Evidence supporting the role of exercise interventions in reducing subjective feelings of CRF is well substantiated (2, 7, 16, 19, 47, 49), but the impact of exercise training on objective measures of fatigue has yet to be adequately investigated in this population. A reduction in exercise tolerance may be the primary rationale for decreases in prescribed exercise intensity with increased CRF severity (7, 16, 33). However, to date, there is no physiological evidence to support this (48). Furthermore, previous studies published by our research group have found that exercise-mediated improvements in CRF and VO_2 were not affected by cancer type (41), which further strengthens the rationale that exercise prescriptions should be individually prescribed rather than dictated by cancer type, stage, or perceived fatigue.

Our study has several strengths that differentiate our findings from other similar studies. We report data on a large sample size ($n = 155$) in a diverse population of cancer survivors. The present study performed stationary isokinetic testing as an objective measure of local quadriceps strength and fatigability, which is the gold standard procedure for functional skeletal muscle assessment. Quantifying muscular fatigue over a period of cyclical contractions may better characterize the actual fatigue experienced by muscle during exercise rather than a simple maximum effort contraction or a sustained isometric action, as these are not representative of the typical muscle actions that take place during exercise or activities of daily living. For this purpose, it was intentional to use a dynamic assessment of 15 repetitions for assessing fatigability to better mirror the prescription guidelines and typical repetitions in one set during an exercise session.

A recognized limitation of the present study is the difference in isokinetic contractions used for assessment versus repeated isotonic contractions during exercise. Similar to assessment of CRF, assessment of strength and performance fatigability also bears the limitation of generalizability to rehabilitation standards, activities of daily living, as well as other clinical populations (22). In addition, while in practice the PFS is used to assess CRF across a variety of cancer types, it was originally developed and validated for breast cancer survivors. It is possible that a different subjective CRF assessment would have more closely correlated to muscular fatigue than the PFS. Despite these limitations with the PFS, it has shown to be the most widely used, comprehensive, multi-dimensional method available for use as a research instrument in the cancer population (1).

Our results suggest that there is not a significant relationship between subjective, self-reported fatigue measures and muscular fatigability in cancer survivors. As a result, self-reported fatigue may unnecessarily limit exercise in cancer survivors. This raises questions as to whether the exercise dose should be modified to accommodate CRF, and highlights the need to continue examining any role that perceived fatigue may play in determining muscular performance or rate of perceived exertion during exercise in cancer survivors. Considering the lack of an association between self-reported fatigue and fatigability, and the empirical evidence that higher intensity exercise reduces CRF, extrinsic motivation to combat perceived fatigue in order to maintain a moderate to high intensity may be more beneficial in reducing CRF than a reactionary reduction in exercise intensity in response to CRF. It should be noted that the evidence presented here supports the practice of completing the exercise intervention as prescribed based on data obtained from an accurate exercise assessment, rather that decreasing the intensity or duration below what is prescribed. As such, individuals supervising prescribed exercise for cancer patients experiencing fatigue may observe enhanced patient benefit by following the standard exercise guidelines for cancer survivors, regardless of their levels of self-reported fatigue.

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