Exercise Programs for Cancer-Related Fatigue: Evidence and Clinical Guidelines

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Abstract
This article provides an overview of the research literature and clinical recommendations on aerobic and resistance exercise programs for managing cancer-related fatigue (CRF). Current research evidence suggests that exercise improves CRF, with more recent evidence suggesting greater benefits when exercise programs are administered in the survivorship phase than in the active treatment phase. Moreover, positive changes in fitness from aerobic exercise programs have been shown to mediate the effects of exercise on CRF. Resistance exercise programs show promise in ameliorating CRF, especially in patients with prostate cancer, and should be considered a potential component of the exercise program. Future trials should examine the potential mechanisms through which exercise influences symptoms of CRF and the effect of exercise on CRF in the long-term. More research is needed evaluating exercise programs for cancer survivors with CRF, especially those with moderate-to-severe CRF. (JNCCN 2010;8:945–953)

Physical Activity and Exercise Definitions

Physical activity and exercise are terms that are often used interchangeably; however, they are not completely synonymous. Physical activity is the broader term that encompasses all forms of muscular movement that result in an increase in energy expenditure over resting levels. Exercise is a form of physical activity that is performed on a repeated basis over an extended period with the objective of improving physiologic function to enhance performance or health. Exercise is prescribed with the intent to place a demand on the body greater than that to which it is accustomed. Adaptation is the response, or improvement, in physiological functioning that results from the exercise training. An exercise training program typically includes a mode, or type of exercise (e.g., walking, swimming, weight training), volume (i.e., frequency, intensity, and duration), and setting (i.e., physical and social environment).

Exercise Participation in Cancer Survivors

Physical inactivity can have detrimental effects on cardiovascular, pulmonary, and musculoskeletal systems. The resulting decrease in functional and muscular capacity may be factors that worsen or perpetuate CRF. Several studies have examined...
the effect of cancer and its treatment on physical activity and exercise participation. These studies report that the percentage of cancer survivors who exercise regularly is as low as 16% to 20%. Moreover, cancer treatment has been found to have a negative effect on physical activity participation that may persist posttreatment. As an example, in one study of non-Hodgkin’s lymphoma survivors, only 34.3%, 6.6%, and 23.9% of survivors were meeting recommended levels of physical activity prediagnosis, during treatment, and posttreatment, respectively.

Conceptual Framework for the Study of Exercise and CRF

Because CRF is seen as a multicausal and complex problem, determining the benefits of the various types of exercise for CRF may not be straightforward or discrete. The Physical Activity and Cancer Control (PACC) framework was developed by Courneya and Friedenreich to organize and stimulate research in physical activity and cancer control. This framework considers 6 possible periods for administering an exercise intervention across the cancer continuum, including 4 postdiagnosis periods: 1) pretreatment, 2) treatment, 3) survivorship, 4) and end of life. Using the PACC framework in the context of CRF, exercise interventions conducted before or during anticancer treatment would likely be prescribed to prevent or attenuate symptoms of CRF, whereas exercise interventions in the survivorship or palliative periods would be prescribed with therapeutic intent to reduce CRF.

Figure 1 provides a conceptual framework for examining exercise and CRF. The framework is an expanded and revised version of the framework originally developed by Courneya et al. In the original framework, exercise was seen to reduce CRF through alterations in physical, behavioral, psychological, or social functioning. This expanded version incorporates the PACC framework and features of the realist review method for synthesizing research evidence. The realist review method seeks to determine the mechanisms through which complex programs work in particular contexts or settings, and is emerging as an approach to the synthesis of evidence in health care. In this revised exercise–CRF framework, aspects of the CRF context (e.g., type of cancer, extent of CRF) and PACC stage are seen as interacting with particular aspects of a specific direct mechanism (e.g., enhanced functional capacity, decreased inflammation) or indirect mechanism (e.g., improved sleep quality, decreased anxiety) that ultimately influence how exercise and its prescription factors affect the outcome of CRF. The conceptual framework may help reveal what it is about exercise that works for survivors with CRF, in what circumstances and ways it works, and why.

Research Evidence Supporting Exercise for CRF

More recently, several systematic reviews and meta-analyses examined the efficacy of exercise interventions for CRF. Kangas et al. performed a combined systematic review and meta-analysis of nonpharmacologic interventions for CRF. The systematic review included 17 exercise trials that assessed fatigue or tiredness as an outcome measure. Of these 17 trials, the authors noted that only 10 included an aim/hypothesis relating to potential effects of exercise in reducing CRF. Moreover, none of the studies had specific inclusion criteria, limiting eligibility to individuals with specific levels of CRF. In the meta-analysis, the pooled data from 16 randomized controlled trials including 1001 participants showed a clinically moderate overall effect of exercise on CRF (effect size, –0.42; 95% CI, –0.60, –0.23). The authors reported a larger effect from the pooled results of 10 studies examining exercise interventions administered during anticancer treatments (effect size, –0.57; 95% CI, –0.74, –0.40) when compared with the pooled results of 6 studies examining interventions delivered after completion of cancer treatment (effect size, –0.16; 95% CI, –0.45, –0.13).

In a Cochrane Systematic Review involving 28 studies with 2083 participants, Cramp and Daniels summarized the effects of exercise on symptoms of CRF. The authors reported that most exercise studies (n = 16) involved survivors of breast cancer and that few studies focused on CRF as the primary study outcome. In their meta-analysis of 22 comparisons involving 1662 participants, a statistically significant, clinically small benefit was found for symptoms of CRF (standardized mean difference [SMD], –0.23; 95% CI, –0.33, –0.13). In contrast to the findings of Kangas et al., Cramp and Daniells reported a slightly larger effect size when data were pooled from 9 studies delivered after completion of cancer treatment (SMD, –0.37; 95% CI, –0.55, –0.18) than when pooled from the results of 9 studies (10 com-
comorbidities, treatment side effects
Fatigue state: mild, moderate, severe
Timing: pretreatment, treatment, survivorship, end of life
Goal of exercise program (e.g., prevent, mitigate, or reduce cancer-related fatigue)
Physiologic systems and energy systems to be trained
Exercise prescription factors: mode, frequency, intensity, type and duration, exercise adherence
Environmental/social factors: supervised/self-directed, group vs. individual, location/setting, qualifications of exercise personnel

Physiologic
- Muscular strength
- Muscular endurance
- Cardiopulmonary fitness
- Body composition

Biologic/Hematologic
- Inflammatory response
- Metabolic function (insulin resistance)
- Endocrine function
- Immune function

Psychological
- Anxiety
- Depression
- Distress
- Cognition

Behavioral
- Sleep: quantity and quality
- Appetite

Social
- Social interaction
- Positive reinforcement

Fatigue Outcome
- Change in hypothesized parameters
- Effect on fatigue/components of fatigue

Figure 1  Model of exercise and cancer-related fatigue. Abbreviation: PACC, Physical Activity and Cancer Control.

Comparisons) administered during anticancer treatment (SMD, –0.18; 95% CI, –0.32, –0.05).

Recently, Speck et al.\(^6\) performed a combined systematic review and meta-analysis examining the benefit of exercise interventions for health-related outcomes, including CRF. The review focused on 2 time points along the cancer continuum: during and after cancer treatment. In their meta-analysis, the pooled results of 15 studies administered during anticancer treatment did not show a beneficial effect on
CRF (SMD, –0.01; 95% CI, –0.35, 0.33), whereas a statistically significant, clinically moderate benefit was found from the pooled results of 14 studies delivered after completion of cancer treatment (SMD, –0.54; 95% CI, –0.90, –0.19).

The reasons for the somewhat conflicting findings among these systematic reviews regarding on-treatment versus off-treatment effect sizes are unclear. However, differences in inclusion criteria and review methods probably explain the variability in findings. Within each of these reviews, significant heterogeneity was found across individual studies in the strength of the effect size. Clearly, further research is needed to elucidate whether this heterogeneity is a result of differences in the chosen study population (e.g., type of cancer, degree of CRF at study entry), in the timing of the intervention relative to cancer treatment, or in exercise prescription factors (e.g., the type, intensity, and duration). As noted in these reviews, few studies have focused on CRF as a primary outcome. Therefore, although evidence supports exercise for management of CRF, questions remain regarding the optimal type and timing of exercise, the long-term effects of exercise on CRF, and the efficacy of exercise in cancer survivors with moderate-to-severe CRF.

Potential Mechanisms of Exercise

To date, only 2 randomized controlled trials have examined potential mechanisms for the effects of exercise on CRF.21,22 In the first study, aerobic exercise was found to reduce CRF in breast cancer survivors.18 The authors found that this reduction was largely mediated by fitness changes in peak power output (e.g., the amount of power generated by pedaling) as measured in watts on a cycle ergometer (bike). The second study showed that aerobic exercise reduced CRF in lymphoma survivors on and off anticancer treatment. In this study, the improvement in peak oxygen consumption was found to be a borderline significant mediator for fatigue.22 The findings from these 2 studies suggest that positive changes related to cardiorespiratory fitness may mediate the effects of exercise on CRF.

Exercise Testing in Cancer Survivors

Exercise testing is important for evaluating the degree to which physical components, such as muscular strength and endurance, and cardiorespiratory fitness may be factors affecting CRF. Appropriate screening before exercise testing and training is necessary to ensure the safety and appropriateness of exercise. Screening should include assessment of risks inherent in the individual (e.g., presence of comorbidities, potential for cardiovascular event), those related to anticancer treatment or treatment-related side effects (e.g., anemia, cardiomyopathy), and those associated with the exercise intervention (e.g., planned intensity of exercise). The oncologist and exercise specialist can then use the information gleaned from screening to guide the need for and appropriate type of exercise test. Previously published guidelines address safety and include recommended procedures for exercise testing.23–28 Importantly, cancer survivors with CRF may require medical supervision of exercise testing and additional monitoring during exercise sessions.25 A summary of precautions and potential contraindications to exercise testing and training are provided in Table 1.23–27

Cardiorespiratory fitness can be measured in several ways; however, it is commonly assessed using the gold standard test of maximal or peak (symptom-limited) oxygen consumption (VO$_{2 \text{peak}}$).26 Several indirect measures of cardiorespiratory fitness can be used when direct measurement of maximal oxygen consumption may not be feasible or appropriate, including modified testing with submaximal tests, field tests (e.g., 2- or 6-minute walk test), or performance-based tests (e.g., Seniors Fitness Test).23

Muscular strength may be assessed using 1 repetition maximum (1RM) testing. The objective of the 1RM method is to determine the heaviest weight an individual can lift one time, with proper technique, for a given exercise or muscle group.26 If safety of the 1RM is a concern, submaximal testing such as 6, 8, or 10RM testing can be used to estimate an individual’s 1RM. Muscular endurance is often assessed using a standard load test, which determines the number of repetitions completed at a fixed submaximal load (usually a percentage of 1RM) for a particular exercise and is performed at a specific pace set by a metronome.23,26 Isokinetic dynamometers may also be used to assess strength and endurance of a muscle or muscle group, but require the use of specialized equipment.28

Whichever tests are chosen, it is important to take into account the extent of CRF and to ensure
that the mode of the exercise test matches the physiologic system of interest for evaluation and training. Moreover, the test should stress the cancer survivor to the intensity that will be prescribed in subsequent exercise sessions to ensure that any potential symptoms occur in a supervised testing situation.

### Exercise Prescription and Programming for CRF

The NCCN developed guidelines for treatment of CRF that include recommendations for activity enhancement. The recommendations suggest consideration of a moderate exercise program to improve functional capacity and activity tolerance and highlight the need for tailored exercise training programs based on the individual’s age, gender, type of cancer, and physical fitness level. Therefore, the exercise prescription for CRF may need to include one or more components of health-related fitness, such as aerobic training, muscular strength and endurance (resistance training), and flexibility training. The following section focuses on the rationale and prescription factors for aerobic and resistance training components of an exercise program for CRF based on the research evidence and the authors’ clinical experience (Table 2).

### Aerobic Exercise Interventions

Cardiorespiratory fitness is necessary to be able to perform activities for extended periods without becoming excessively fatigued or short of breath. Cardiorespiratory fitness is a strong predictor of the level of fatigue in cancer survivors and may mediate the effects of exercise on fatigue. Cardiorespiratory fitness is determined by the ability of the cardiorespiratory system to take in, extract, deliver, and use oxygen, and to remove waste products from the body tissues. Cancer treatments along with any associated reductions in physical activity will result in deconditioning of the cardiorespiratory system, which is characterized by a decrease in VO$_{2\text{max/peak}}$. Cardiorespiratory fitness is improved by aerobic activities, such as walking, swimming, and cycling, that use large muscle groups, are rhythmic, and are maintained for a prolonged period. In aerobic exercise training, normal physiologic responses to aerobic training involve improvements in peripheral (skeletal muscle and vasculature) and cardiorespiratory systems. These changes result in improvement in physical functioning and an enhancement of energy capacity.

Aerobic interval exercise training is a method that can be used to maximize improvements in car-
Cardiorespiratory fitness and is an alternative if performance of continuous exercise results in early fatigue. Interval training applies various work-to-rest intervals with periods of higher-intensity work (e.g., 15 seconds) followed by a recovery phase (e.g., 30 seconds).\(^8\,^{26}\) Interval training allows for a higher intensity and volume of exercise than would be possible with a continuous exercise protocol.

In a recent randomized controlled trial, Courneya et al.\(^{22}\) compared the effect of a 12-week supervised aerobic exercise training program versus usual care in 122 survivors of lymphoma who were on or off anticancer treatments. In the study, participants were prescribed a progressive program on a cycle ergometer 3 times per week, progressing from 15 to 20 minutes to 40 to 45 minutes per session. The exercise prescription also incorporated aerobic interval training toward the end of the training program as a way to optimize improvements in cardiorespiratory fitness. Significant benefit from exercise was found for symptoms of CRF and for cardiorespiratory fitness, lean body mass, and depression. Notably, the improvement in fatigue of 4.6 points on the Functional Assessment of Cancer Therapy–Fatigue Scale exceeded the minimal important difference of 3 points.

### Resistance Exercise Interventions

Muscular strength and endurance training are particularly important to attenuate declines in muscle mass\(^8\) that may occur as a result of inactivity or disease-related factors such as cachexia. Deficits in muscular strength and endurance will lead to early fatigue as greater effort and energy are required to perform a given activity. In survivors with marked muscle atrophy and decreased stamina, muscular strength and endurance training, with the goal of restoring skeletal muscle mass, may need to precede an aerobic training program.\(^{32}\)

Muscular strength and endurance are best en-

### Table 2: Exercise Prescription Considerations for Survivors with CRF

<table>
<thead>
<tr>
<th>Fatigue State</th>
<th>Aerobic Exercise</th>
<th>Resistance Exercise</th>
<th>Comments*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild fatigue  &lt; 3/10 VAS</td>
<td>Consider prescribing progressive aerobic exercise program; 20–30 min per session, 3–5 d/wk, at 60%–80% of maximum heart rate(^{3,22,23,35})</td>
<td>Consider prescribing 8–10 exercises for major muscle groups of upper and lower extremities and trunk(^{23,33,35}) Resistance: 60%–70% of 1RM; 8–12 repetitions, 1–2 sets, 2–3 d/wk(^{33})</td>
<td>Exercise as part of multidisciplinary approach, including counseling on energy conservation and pacing of activities</td>
</tr>
<tr>
<td>Moderate fatigue  4–6/10 VAS</td>
<td>Consider a gradual increase in volume of exercise through repeated bouts of 5–10 min per session; progress to 60%–80% heart rate(^{23,25}) Increase exercise frequency or duration before increasing intensity(^{23})</td>
<td>Consider prescribing 8–10 exercises of major muscle groups of upper and lower extremities and trunk(^{23,25}) Resistance: may need to start with lower-intensity resistance (e.g., lightest weight on rack or alternatively at 30%–50% of 1RM); 10–15 repetitions, 1–2 sets, and progress to standard prescription of 60%–70% of 1RM over time(^{23,25})</td>
<td>Assess and monitor for any acute, chronic, and long-term side effects of cancer treatment</td>
</tr>
<tr>
<td>Severe fatigue  7+/10 VAS</td>
<td>Consider prescribing frequent sessions of low intensity walking/biking of 5–10 min in duration spaced throughout the day; increase total duration of exercise as a prescription factor(^{23}) Consider modest interval training for those unable to perform continuous exercise(^{1,23})</td>
<td>Referral to physical therapy recommended/consider starting with active range of motion (gravity-only resistance) and functional activities and progress to light weights as tolerated(^{17})</td>
<td>Monitor fatigue response during and after exercise; modify program as necessary</td>
</tr>
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* Applies to the entire table, except where noted. Abbreviations: CRF, cancer-related fatigue; RM, repetition maximum; VAS, visual analog scale.
hanced by progressive resistance exercise training. Muscular strength training is performed with moderate to high intensity (e.g., at least 60% of 1RM) but fewer repetitions (e.g., 3–10), whereas muscular endurance training is performed with lower intensity (e.g., 30% 1RM) and higher number of repetitions (e.g., 10–25). An increase in muscle cross-sectional area and improvements in energy source use result from appropriately prescribed progressive resistance exercise training. These changes improve efficiency of the muscular system and allow more activity before onset of muscular fatigue.

Resistance training should include 1 to 2 sets of 8 to 10 different exercises that involve the major muscle groups, and should be performed at 60% to 70% of 1RM, 2 to 3 times per week, with a minimum of 48 hours of rest between sessions. Resistance training may need to commence with a muscular endurance focus with less resistance (e.g., lightest weight on the rack; 30% of 1RM) and more repetitions, and then progress slowly to allow adaptation and avoid secondary muscle soreness. Survivors with severe CRF may need to begin their exercise program with active movements using gravity-only resistance and then progress to light weights overtime. Initial sessions should be closely supervised to ensure movements are performed in a controlled manner with proper posture and technique. If early muscular fatigue is problematic, the target exercise volume may be divided into smaller, more frequent sessions throughout the day (2–5 sessions per day) to obtain benefit and avoid worsening fatigue.

In a 3-arm trial, Segal et al. randomized 121 men with prostate cancer who were undergoing radiotherapy to a 24-week resistance or aerobic training regimen or usual care. Participants in the resistance exercise arm of the trial performed 2 sets of 8 to 12 repetitions of 10 different exercises at 60% to 70% of their estimated 1RM. Resistance was increased by 5 pounds when participants were able to complete more than 12 repetitions. Participants in the aerobic arm of the trial exercised 3 times per week on a bike, treadmill, or elliptical trainer starting at 50% to 60% of their peak oxygen consumption, progressing to 70% to 75% by week 5. Exercise duration started at 15 minutes, and progressed by 5 minutes every few weeks to a maximum of 45 minutes. Both resistance and aerobic exercise were found to significantly attenuate the decline in CRF over the short-term. Only resistance exercise, however, was found to significantly benefit CRF in the long-term.

**Patient Education**

An important key to successful exercise programming involves counseling and educating the survivor on exercise training principles, expected physiologic responses to exercise, safety issues, and the need for a slow progression of exercise to improve physical function (Table 3). Some survivors may require help with motivation, and therefore the chosen activity, or type of exercise, should consider each individual’s lifestyle needs, goals, and preferences.

It is especially important that the prescribed exercise program result in early success to increase the likelihood of long-term adherence. General malaise or symptom flairs after exercise may be problematic for some survivors with CRF and should be avoided. To that end, the survivor must understand the important need to monitor involvement in other daily activities, and to evaluate the response during and after exercise sessions to allow for appropriate and timely modification of the exercise program. Although the survivor may continue to experience periods of increased fatigue, appropriately prescribed exercise and activity pacing should cause symptoms to occur less frequently and be less severe.

Given that CRF is a well-known barrier to exercise in cancer survivors, exercise motivation will be a particular challenge for survivors with moderate-to-severe CRF. Cancer care professionals can suggest strategies to overcome the barrier of CRF, such as low-to-moderate intensity exercise (e.g., 50%–60% of maximal capacity), shorter duration exercise (e.g., 10 minutes at a time), interval exercise (i.e., alternating exercise and rest bouts), or exercising during days (e.g., not during chemotherapy week) and times (e.g., early in the morning) when fatigue is at its lowest.

**Conclusions**

Current research evidence suggests that both aerobic and resistance exercise programs are effective in ameliorating CRF, with recent evidence suggesting greater benefits when exercise programs are administered in the survivorship phase than in the active treatment phase. NCCN has developed guidelines for CRF (in this issue; to view the most recent version of
these guidelines, visit the NCCN Web site at www.NCCN.org) that include recommendations for activity enhancement and individually tailored exercise training programs. More research is needed evaluating exercise programs for cancer survivors with CRF, especially those with moderate-to-severe CRF.

### References

Exercise and Cancer-Related Fatigue


