Evidence-Based Practice for Fatigue Management in Adults With Cancer: Exercise as an Intervention

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Purpose/Objectives: To review and summarize the current state of the evidence for exercise as an intervention for cancer-related fatigue and to facilitate application to clinical practice.

Data Sources: Articles, abstracts, and practice guidelines published through October 2003.

Data Synthesis: The strength of the evidence of effectiveness of exercise in managing cancer-related fatigue is growing.

Conclusions: All patients with cancer should be encouraged to maintain an optimum level of physical activity during and following cancer treatment. Patients with breast cancer and other selected patients should receive recommendations for moderate exercise programs. Referrals to physical therapy and/or rehabilitation may benefit certain patients, including those with comorbidities or deconditioning. Published multidisciplinary evidence-based guidelines for exercise programs involving patients with cancer are needed.

Implications for Nursing: Nurses may participate in implementing exercise interventions with patients with cancer in various roles depending on skill and knowledge—from encouraging physical activity to referring patients to physical therapy and/or rehabilitation programs to prescribing and monitoring exercise in certain patient populations.

Key Points . . .

- ➤ Exercise has been shown to be the most effective nonpharmacologic intervention for cancer-related fatigue (CRF).
- ➤ Home-based aerobic exercise programs, including walking, are feasible and effective for CRF in diverse patients with cancer undergoing treatment.
- ➤ Oncology nurses have a responsibility to apply the knowledge of exercise for CRF to practice through education, limited exercise prescription, and referral.

Goal for CE Enrollees:

To enhance nurses' knowledge about current evidence related to exercise as an intervention for cancer-related fatigue.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Describe the theoretical basis for the use of exercise in the management of fatigue in people with cancer.
2. Outline the evidence currently available related to the use of exercise in the management of cancer-related fatigue.
3. Discuss the clinical and research implications of exercise in the management of fatigue in people with cancer.

Cancer-related fatigue (CRF) is the most common and distressing side effect of cancer treatment. This fatigue has a profound effect on patients' ability to perform activities of daily living. As the evidence for exercise in the prevention and management of CRF has grown since the 1990s, oncology nurses and healthcare professionals are challenged to integrate exercise interventions for patients with cancer. Effective management of CRF through strategies such as exercise can affect the multidimensional experience of fatigue and improve patients' functional status and quality of life (QOL). This article is a review and summary of the current state of the evidence on exercise as an intervention for CRF. This clinically relevant synthesis facilitates application to nursing practice and identifies directions for future research needed to address gaps in current knowledge.

Definitions

CRF is a multidimensional phenomenon influenced by physical, psychological, and other diverse factors. CRF is defined by the National Comprehensive Cancer Network (NCCN) as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" (Mock

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et al., 2003, p. 310). Although knowledge about CRF is evolving, the NCCN definition is used for the purposes of this review. Patients with cancer consistently have reported fatigue as the most common and distressing symptom experienced during cancer and its treatment (Curt et al., 2000; Greene, Nail, Fieler, Dudgeon, & Jones, 1994; Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Jacobsen et al., 1999; Piper, Lindsey, & Dodd, 1987). The prevalence of fatigue is reported as high as 61%–100% in studies of patients with cancer, and in one study, patients reported that fatigue was three times more distressing than pain (Piper et al.). More than 75% of patients with metastatic disease have reported CRF, and even cancer survivors report fatigue as a disruptive symptom months or years after treatment ends (Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998).

Exercise is planned, structured, and repetitive bodily movement performed with the intent of improving or maintaining one or more components of physical fitness (Brooks & Fahey, 2000). NCCN recently revised its guidelines for fatigue management developed by a multidisciplinary national panel of experts (Mock et al., 2003) and recognized exercise as the nonpharmacologic intervention with the strongest evidence of effectiveness in managing CRF.

A growing demand to integrate contemporary evidence into clinical practice is facing oncology nurses (Stricker & Sullivan, 2003). This process is known as evidence-based practice (EBP). EBP is characterized by the critical review and purposeful integration of various types of evidence, including research, theory, clinical expertise, and patient preferences regarding patient care and decision making (Rutledge & Grant, 2002).

Systematic Review of the Evidence

Identification of Evidence

A literature search was conducted in January 2002, and repeated in October 2003, of the CINAHL® and MEDLINE® databases and Database of Abstracts of Reviews Effects using the terms "fatigue," "cancer," and "exercise." Forty-two articles were identified in English, of which 21 were selected for review. In addition, 13 research studies were identified and obtained based on a book chapter by Mock (2003), most of which were represented in the literature search. Proceedings of the annual meetings of the American Society of Clinical Oncology, American College of Sports Medicine (ACSM), and Oncology Nursing Society, as well as the Seventh National Conference on Cancer Nursing Research, also were searched at these times to identify published abstracts on this topic; the authors added three abstracts from these meetings to this review (Headley, 2003; John, 2003; Poniatowski, Mock, & Cohen, 2001).

Selection of Study Reports

All identified research reports and case studies, regardless of date, as well as review articles and reports of practice guidelines from 1995 to October 2003 were included in this systematic review, provided that exercise was identified as an intervention and fatigue as an outcome variable. Nonexperimental research studies that included physical activity or exercise as the primary independent variable and fatigue as a primary outcome variable also were included. The Priority Symptom Management (PRISM) system for leveling evidence (Ropka & Spencer-Cisek, 2001) was selected to rate the levels of evidence for each of the articles (see Table 1). This system is based on three broad PRISM levels (I, II, and III) that are subdivided into eight specific levels of evidence (1–8). Throughout this article, sources of evidence are rated according to the Arabic numbered levels of evidence from this model. Study designs are based on the definitions and descriptions by Cook and Campbell (1979).

Critical Appraisal of the Evidence

Theoretical Background on Exercise as an Intervention

The use of theory is a critical component of EBP (Rutledge & Grant, 2002). Conceptual models and theories have been developed to advance the understanding of CRF and provide theoretical evidence to support the role of exercise in managing CRF. A common conceptual theme of CRF is the multidimensionality of the phenomenon. Ream and Richardson (1999) reviewed five theories used in the development and testing of fatigue interventions. The Winningham Psychobiologic Entropy Model and a physiologic model by Dimeo contributed to understanding the role of exercise in managing CRF.

Maryl Winningham, a pioneer of exercise prescription during cancer treatment, developed a model that built on the prior work of exercise physiologists with other chronic disease populations. The Winningham Psychobiologic Entropy Model provided a framework for research investigating the impact of aerobic interval training on fatigue and other outcomes in patients with cancer during treatment (Winningham, 1996). A major hypothesis of the model is that reductions in physical activity lead to reduced energy capacity and subsequently to fatigue and decreased functional status. This self-perpetuating cycle may result in disability and occur regardless of whether the decrease in physical activity is the result of treatment-related symptoms, fatigue as a primary symptom, or a multitude of other factors (Nail & Winningham, 1993). The model emphasizes the importance of maintaining a balance between activity and rest. Winningham (2001) concluded that individualized activity and exercise programs ameliorate fatigue through preservation of energy efficiency.

Dimeo, Rumberger, and Keul (1998) provided a more detailed physiologic explanation for the relationship between activity and CRF. Using complex propositions to describe etiologic mechanisms and consequences of fatigue, Dimeo (2001) posited that fatigue is caused partially by declines in neuromuscular efficiency resulting from metabolic and cellular mechanisms altered by cancer and its treatment. Subsequent physical inactivity further exacerbates fatigue by inducing muscular catabolism, leading to a cycle of further decline in performance, reduction in activity, and easy fatigability. Exercise alters the cycle of fatigue by improving neuromuscular efficiency.

Because patients with cancer have reported high levels of fatigue during the first 72 hours following the initial dose of chemotherapy, inactivity and deconditioning clearly are not the sole primary causes of CRF. CRF probably is caused by a combination of changes in physiology initiated by disease, treatment, and inactivity and is influenced further by psychological factors, alterations in nutritional status, and sleep patterns (Mock et al., 2003). Winningham's and Dimeo's models

Table 1. Priority Symptom Management (PRISM) Levels of Evidence

PRISM Level	Level of Evidence[a]	Evidence Source
I	1	Qualitative systematic review (also called "integrative review") or quantitative systematic review (also called "meta-analysis") of multiple, well-designed, randomized, controlled trials of adequate quality
	2	At least one properly designed, randomized, controlled trial of appropriate size (record if multisite and over 100 subjects, but not required)
	3	Well-designed trial without randomization (e.g., single group pre/post, cohort, time series, meta-analysis of cohort studies)
II	4	Well-conducted, qualitative, systematic review of nonexperimental design studies
	5	Well-conducted case-control study
	6	Poorly controlled study (e.g., randomized controlled trial with major flaws) or uncontrolled studies (e.g., correlational descriptive study, case series)
	7	Conflicting evidence with the weight of evidence supporting the recommendation or meta-analysis showing a trend that did not reach statistical significance
		National Institutes of Health Consensus Reports
		Published practice guidelines, for example, from professional organizations (e.g., Oncology Nursing Society, American Society of Clinical Oncology), healthcare organizations (e.g., American Cancer Society), or federal agencies (e.g., National Cancer Institute, Centers for Disease Control and Prevention)
III	8	Qualitative designs
		Case studies; opinions from expert authorities, agencies, or committees

[a] Levels of evidence range from the strongest evidence at the top to the weakest level of evidence at the bottom.

Note. From "Rating the Quality of Evidence for Clinical Practice Guidelines" by D.C. Hadorn, D. Baker, J.S. Hodges, & N. Hicks, 1996, *Journal of Clinical Epidemiology, 49,* 750. Copyright 1996 by Elsevier Inc. Adapted with permission in "PRISM: Priority Symptom Management Project Phase I: Assessment" by M.E. Ropka & P. Spencer-Cisek, 2001, *Oncology Nursing Forum, 28,* 1589. Copyright 2001 by the Oncology Nursing Society. Reprinted with permission.

provide relevant frameworks to explain the roles of exercise in reducing CRF.

Research-Based Evidence

Descriptive and correlational studies: To better describe the patterns and correlates of CRF, researchers have conducted descriptive studies of patients with cancer and cancer survivors. In populations of women receiving adjuvant chemotherapy for breast cancer, Berger (1995, 1998), Berger and Farr (1999), and Berger and Higginbotham (2000) identified an inverse relationship between activity level and fatigue and positive relationships among fatigue and sleep disturbance, daytime naps, and symptom distress. One study (Berger, 1998) used wrist actigraphs to measure activity and rest cycles in women with breast cancer. These descriptive studies provided support for the hypothesis that fatigue is related to reduced activity levels and exercise may be an effective intervention for CRF by increasing individuals' activity levels. In addition, exercise has been shown previously to positively affect intermediary variables, such as sleep, that are identified as influencing the experience of CRF (Poniatowski et al., 2001).

Two additional descriptive studies provide further support for exercise as an intervention for CRF. In a landmark retrospective study of 71 breast cancer survivors, Young-McCaughan and Sexton (1991) reported significantly higher perceived QOL among women who had exercised during treatment compared to those who had not. The QOL tool employed in this study included an item about tiring easily. Schwartz (1998) studied 219 cancer survivors who had high levels of prediagnosis physical activity and maintained their activity to varying degrees during treatment. Although overall exercise intensity, duration, and frequency were decreased in individuals compared to their baseline, the participants reported using moderate exercise to reduce CRF during treatment.

Experimental and quasi-experimental studies: Twenty experimental research articles evaluated in this article provide strong support for exercise as an intervention for CRF (see Table 2). All of these studies reported positive effects of exercise, either through reduction in levels of fatigue in participants who exercised as compared to those who did not or by documenting a decrease—or in hospice patients, a stabilization—in fatigue experienced by exercising participants from baseline to end of participation in a structured exercise program. Nine randomized clinical trials and 11 quasi-experimental studies were evaluated, all of which used a pretest/post-test design. Three of the quasi-experimental studies included a concurrent control group; Schwartz, Thompson, and Masood (2002) used historical controls. The remainder evaluated the efficacy of the exercise intervention by measuring fatigue outcomes in one treatment group before and after participation in a structured exercise program.

To date, the vast majority of research investigating the efficacy of exercise as an intervention for CRF has been conducted with patients undergoing active cancer treatments such as chemotherapy, radiation therapy, and stem cell transplant. Women with breast cancer represent the largest group of participants in these studies, although investigators are broadening their focus to include mixed cancer populations and individuals with advanced disease. All exercise interventions were

Table 2. Exercise as an Intervention for Cancer-Related Fatigue: Experimental and Quasi-Experimental Studies

Author and Year	Sample[a] (N)	Diagnosis and Treatment	Design	Exercise Intervention	Results	Level of Evidence
MacVicar & Winningham, 1986	10	Breast cancer (CA) treated with chemotherapy (CT)	Quasi-experimental, three group	Cycle ergometry (institution based [I], interval training [IT]) for 20–30 minutes, three times per week, for 10 weeks; 60%–85% maximum heart rate (HR max)	Fatigue decreased in exercising patients and nonpatients.	3
Mock et al., 1994	14	Breast CA with CT	Randomized clinical trial	Walking program (continuous [C], home based [H]) for 30 minutes, four to five times weekly, and support group for 90 minutes every two weeks (Duration of both was four to six months.)	Fatigue decreased during and after CT in exercisers.	2
Dimeo et al., 1997	32	Mixed solid tumor and non-Hodgkin lymphoma with peripheral blood stem cell transplantation (PBSCT), immediately after discharge	Pretest/post-test with untreated control group	Treadmill aerobic walking (I, IT) daily for 15–30 minutes for six weeks; 80% HR max	No reports of fatigue in exercise group; four controls (25%) reported fatigue.	3
Mock, Dow, et al., 1997	46	Breast CA with radiation therapy (RT)	Randomized clinical trial	Walking program (H, C) for 30 minutes, four to five times weekly, for six weeks; intensity was self-determined.	Fatigue was lower in exercisers versus controls and decreased from pre- to post-test in exercisers.	2
Dimeo et al., 1998	5; 2 were post treatment by 9 and 18 months	Patients had severe baseline fatigue and were treated with CT, RT, or PBSCT.	One-group, pretest/post-test	Treadmill aerobic walking (I, IT) for 15–35 minutes, five times weekly, for six weeks; 80% HR max	Three people reported no more fatigue with daily activities; two resumed work.	6 (Case series)
Dimeo et al., 1999	59	PBSCT	Pretest/post-test with untreated control group	Supine bicycle ergometry, aerobic (I, IT); 30 minutes daily during hospitalization	No significant change in fatigue over time in exercisers; fatigue increased in controls.	3
Schwartz, 1999, 2000a	27	Breast CA with CT	One group pretest/post-test	Aerobic exercise of choice (H, C) for 15–30 minutes, three to four times weekly, for eight weeks	Decreased fatigue in exercisers; fatigue mediates increased quality of life in exercisers. Peak, average, and worst fatigue levels decreased over time in exercisers.	3
Porock et al., 2000	9	Advanced CA with mixed diagnoses; patients received hospice, RT = 1, or CT = 2	One group, pretest/post-test; case studies also reported	Duke Energizing Exercise Program (H, IT) for two to four weeks; range of activities (walking, treadmill, chair or bed exercises)	Fatigue stabilized.	6
Schwartz, 2000b	71	Breast CA with CT	One group, pretest/post-test	Aerobic exercise of choice (H, C) for 15–30 minutes, four times weekly, for eight weeks	Fatigue was lower in exercise adherers versus nonadherers.	3
Mock et al., 2001	48	Breast CA with CT (36%) or RT (64%)	Randomized clinical trial, multi-institutional	Walking program (H, C) starting for 10–30 minutes, five to six times weekly, for six weeks (with RT) or four to five months (with CT)	Fatigue decreased in exercisers ("high walkers") and increased in "low-walkers."	2

(Continued on next page)

[a] N is the actual number of subjects completing the study for whom data are reported, unless otherwise indicated.

Table 2. Exercise as an Intervention for Cancer-Related Fatigue: Experimental and Quasi-Experimental Studies *(continued)*

Author and Year	Sample[a] (N)	Diagnosis and Treatment	Design	Exercise Intervention	Results	Level of Evidence
Schwartz et al., 2001	61	Breast CA with CT	One group, pretest/post-test	Aerobic exercise of choice (H, C) for 15–30 minutes, four times weekly, for eight weeks	Fatigue was lower on exercise days versus nonexercise days and amount of exercise was correlated with cancer-related fatigue.	3
Burnham & Wilcox, 2002	18	Breast and colon CA survivors (n = 15, 3) who were 9.0–10.3 months post-treatment with CT, RT, or surgery	Randomized clinical trial; matched for baseline functional capacity	Aerobic exercise, three modality (treadmill, stationary bicycle, stair-climbing machine), for 14- to 32-minute sessions, three times per week, for 10 weeks at low to moderate intensity (25%–35% or 40%–50% heart rate reserve)	Fatigue linear analog scale assessment (LASA) significantly decreased from pre- to post-test in exercisers. Energy (LASA) significantly increased compared to controls.	2
Schwartz et al., 2002	12	Malignant melanoma	One group pre/post-treatment compared to historical controls Two-group breakdown (retrospectively) 1. Exercise only 2. Exercise/methylphenidate	Methylphenidate 20 mg sustained release every morning; aerobic exercise of choice at home for 15–30 minutes, four days per week for four months; symptom limited, moderate intensity, mostly walking	Fatigue was less in exercise and exercise/methylphenidate compared to historical controls.	3
Adamsen et al., 2003	23	Mixed CA diagnoses with CT	One group, pretest/post-test	Aerobic interval and strength-resistance training group (supervised [S], I) 1.5-hour exercise (part of three-hour multicomponent sessions) three times per week for six weeks	Nonsignificant decrease in fatigue from pre- to post-test.	3
Coleman et al., 2003	24 (14 in analysis)	Multiple myeloma with CT	Randomized clinical trial	Aerobic and strength resistance training (H) using stretch bands for six month duration	Nonsignificant decrease in fatigue and sleep improved in exercisers compared to controls.	2
Courneya, Friedenreich, et al., 2003	96	Mixed CA diagnoses; $\overline{X}$ = 16.28 months since diagnosis; 44% actively on CT or RT	Randomized clinical trial of group psychotherapy (GP) alone versus GP plus exercise	Aerobic exercise of choice (H) (95% walking) for 20–30 minutes, three to five times per week, for 10 weeks; 65%–75% HR max	GP plus exercise had decreased fatigue compared to controls (GP alone).	2
Courneya, Mackey, et al., 2003	52	Breast CA survivors; $\overline{X}$ = 14 months post-treatment	Randomized clinical trial	Bicycle ergometer (C, I, S) for 15–35 minutes, three times weekly, for 15 weeks; 70%–75% maximal oxygen consumption	Fatigue significantly decreased from pre- to post-test in exercisers.	2
Mock et al., in press	111	Breast CA with CT and RT	Randomized clinical trial, multi-institutional	Walking program (H) four to five times per week for 30 minutes during CT and RT	Fatigue decreased compared to controls.	2
Oldervoll et al., 2003	9	Hodgkin disease survivors	One group, pretest/post-test	Aerobic exercise of choice (H) for 40–60 minutes, three times weekly, for 20 weeks; 60%–85% HR max	Fatigue decreased from pre- to post-test.	6 Oldervoll et al. (2003)
Segal et al., 2003	155 (135 in analysis)	Prostate CA with androgen deprivation therapy	Randomized clinical trial at two sites	Resistance exercise (C, I, S) three times weekly for 12 weeks (16–24 repetitions of nine strength-training exercises)	Fatigue decreased compared to controls.	2

[a] N is the actual number of subjects completing the study for whom data are reported, unless otherwise indicated.

individually based except for Adamsen et al.'s (2003) trial of group exercise as part of a multimodality intervention.

Women who exercise while undergoing adjuvant therapy for early-stage breast cancer experience less fatigue than their counterparts who do not exercise, based on PRISM level 2 and 3 evidence. Seven studies employed home-based aerobic exercise interventions in this population. Aerobic exercise enhances the oxygen-carrying capacity of the cardiovascular system through the prolonged rhythmical contraction and relaxation of large muscle masses (Dimeo et al., 1998). Most women in these studies were young, married, college-educated Caucasians; employed while undergoing cancer treatment; and were a mean of 44–49 years of age (Mock et al., 1994, 2001, in press; Mock, Dow, et al., 1997; Schwartz, 1999, 2000a, 2000b; Schwartz, Mori, Gao, Nail, & King, 2001). All of the women with breast cancer were undergoing either chemotherapy (Mock et al., 1994, 2001, in press; Schwartz, 1999, 2000a, 2000b; Schwartz et al., 2001) or radiation therapy (Mock et al., 2001, in press; Mock, Dow, et al.) as adjuvant treatment. In all of these studies, exercise had a statistically significant effect in decreasing fatigue and improving functional ability during treatment.

Exercise also decreases CRF during and immediately following peripheral blood stem cell transplantation (PBSCT), supported by PRISM level 3 evidence (Dimeo et al., 1997; Dimeo, Stieglitz, Novelli-Fischer, Fletcher, & Keul, 1999). Patients undergoing PBSCT are the second-largest group in whom exercise has been studied. Aerobic interval training patterns were used in Dimeo et al.'s (1997, 1998, 1999) work. Interval training is characterized by alternating brief periods of moderate- to high-intensity exercise with brief periods of low-intensity (often half-speed) exercise. In Dimeo et al.'s (1997, 1998, 1999) research, participants ranged in age from 32–42; had a diagnosis of lymphoma or a solid tumor, including lung cancer and seminoma; and were comprised of nearly twice as many female as male participants. All three studies demonstrated either less fatigue in exercisers versus controls or a decrease in fatigue from pre- to post-test in exercising participants. However, in Dimeo et al.'s (1999) study of supine bicycle ergometry (simulated biking) during hospitalization for PBSCT, a close examination of the actual mean fatigue scores on the Profile of Mood States challenges the clinical significance of these findings. Although controls demonstrated statistically significant increases in fatigue during hospitalization whereas exercisers did not, the mean fatigue scores increased in both groups from pre- to post-test to a clinically similar degree (2.1 versus 2.3 points). Exercise may have ameliorated fatigue associated with treatment only slightly.

One PRISM level 6 study supported the efficacy of exercise in managing preexisting severe fatigue in PBSCT survivors. Dimeo et al. (1998) evaluated three individuals undergoing and two after PBSCT (one 9 months and another 18 months after PBSCT); all five had severe fatigue at study entry. After six weeks of aerobic treadmill walking, three reported resolution of fatigue with daily activities. This study is limited by its small sample size, lack of a control group, and lack of a standardized measure of CRF; nonetheless, it provides beginning evidence for the ability of exercise to resolve fatigue and improve function in individuals with preexisting severe fatigue related to cancer and its treatment.

Recently, the role of exercise in decreasing fatigue in other groups of patients with cancer has been supported by growing PRISM level 2 and 3 evidence in studies of individuals undergoing treatment for a variety of solid tumors and hematologic malignancies (Adamsen et al., 2003; Coleman et al., 2003; Courneya, Friedenreich, et al., 2003; Schwartz et al., 2002; Segal et al., 2003). Schwartz et al. (2002) reported the effects of an exercise intervention combined with or without methylphenidate on the prevention and amelioration of fatigue in patients with melanoma receiving interferon therapy. All 12 participants adhered to the exercise intervention for the study duration of four months, and eight participants also took methylphenidate during this time period. Despite the fact that all participants had modest increases in fatigue over the course of the study, both the exercise and the exercise with methylphenidate groups demonstrated reduced fatigue scores and a less chaotic pattern of fatigue compared to historical controls. Although the sample size is small, the clinical findings are noteworthy, because fatigue is reported to be a dose- and treatment-limiting side effect of interferon therapy.

Segal et al. (2003) conducted a randomized clinical trial in men with prostate cancer receiving androgen deprivation therapy. They published the first study to demonstrate the positive effects of resistance exercise training on CRF. Segal et al. defined resistance exercise as requiring the body's musculature to move against some type of opposition, and they tested a repetitive upper- and lower-body strength-training program in these individuals. Exercisers demonstrated a significantly greater reduction in fatigue from baseline to post-test. These results were statistically and clinically significant, as demonstrated by a three-point difference in scores on the Functional Assessment of Cancer Therapy–Fatigue (FACT-F) between the two groups—a magnitude of improvement comparable to individuals who receive treatment for cancer-related anemia.

Also in 2003, Coleman et al. reported the results of a randomized pilot study of exercise in 24 individuals with multiple myeloma who were not at high risk for pathologic fracture. To combat the common occurrence of dexamethasone-induced skeletal muscle wasting, a strength-resistance training program was combined with aerobic exercise for the individuals randomized to the exercise intervention. Fatigue decreased and sleep outcomes (total sleep, sleep efficiency) improved in the exercise group as compared to controls. These findings, however, were not statistically significant, in part because of the small sample size and high attrition rate, with only 14 participants included in the change-over-time analyses. This study represented the first known exercise trial to include individuals with bone metastases, and no participants were injured during the course of the study.

In 2003, two additional studies were published that highlight the expansion of exercise research to more diverse patient populations. One large randomized clinical trial (Courneya, Friedenreich, et al., 2003) and one small quasi-experimental study (Adamsen et al., 2003) reported positive effects of exercise on fatigue in individuals with a diversity of solid tumors and hematologic malignancies. Participant diagnoses included colon cancer, lung cancer, testicular carcinoma, and Hodgkin and non-Hodgkin lymphoma, and all stages of disease were represented.

Each of the 23 participants in Adamsen et al.'s (2003) study was undergoing chemotherapy and participated in group-based aerobic interval training and strength-resistance training for 1.5 hours three times weekly. The exercise sessions were part of a multimodality intervention (including massage, relaxation, and body-awareness training) offered for a total time of nine hours each week for a duration of six weeks. A trend of improvement in fatigue was reported as measured by the European Organization for Research and Treatment of Cancer QOL Questionnaire C-30. In a larger clinical trial, Courneya, Friedenreich, et al. (2003) reported a statistically significant improvement in fatigue, as measured by the FACT-F, in individuals with mixed cancer diagnoses randomized to home-based aerobic exercise (95% of participants walked) in combination with group psychotherapy, as compared to group psychotherapy alone. Although participants were an average of 16.28 months from their initial cancer diagnosis, 44% were undergoing chemotherapy or radiation therapy during the trial.

The effectiveness and safety of exercise in palliative care only have begun to be evaluated, with one PRISM level 6 study to support its use in this setting (Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000). In their study of a home-based exercise program for patients with advanced cancer enrolled in hospice programs, Porock et al. contributed to the evidence base for the utility and feasibility of exercise in patients with preexisting fatigue. Nine participants with mixed solid tumor diagnoses and moderate to high baseline levels of fatigue were evaluated. Three participants received chemotherapy or radiation therapy during the 14- to 28-day exercise program. The exercise interventions were prescribed individually by an exercise physiotherapist familiar with the Duke Energizing Exercise Program, in which patients are instructed to perform periods of exercise, such as dancing, stretches, and chair or bed exercises, several times daily at an intensity and duration equaling half of what they could comfortably perform. The small sample size precluded meaningful statistical analyses; nonetheless, fatigue scores essentially remained stable across the study period. The authors concluded that their findings were clinically significant because participants became more active, without increased fatigue, despite advanced disease. Case studies of three participants suggested that individuals with the most severe fatigue benefited the most from exercise. Although promising, further research with larger sample sizes and comparison groups is needed.

In 2002 and 2003, researchers reported on studies of exercise and fatigue in cancer survivors who have completed treatment. Within the six-month period from December 2002 to May 2003, three articles (two PRISM level 2 randomized clinical trials and one PRISM level 6 pilot study) were published that support the efficacy of exercise to reduce fatigue and improve QOL in cancer survivors. Oldervoll, Kaasa, Knobel, and Loge (2003) reported a positive effect of aerobic exercise on chronic fatigue in a pilot study of nine Hodgkin disease survivors. Two randomized clinical trials by Courneya, Mackey, et al. (2003) and Burnham and Wilcox (2002) evaluated fatigue as a secondary outcome in predominantly breast cancer survivors, with Burnham and Wilcox including three colon cancer survivors. These cancer survivors were a mean of 9 and 14 months, respectively, after cancer treatment (Burnham & Wilcox; Courneya, Mackey, et al.). Both randomized clinical trials reported the positive benefits of exercise in reducing fatigue in cancer survivors.

Researchers continue to broaden the knowledge base related to exercise and CRF by testing novel exercise interventions in previously unstudied populations of patients with cancer. Preliminary findings have been presented from two studies testing seated exercise programs on fatigue and QOL in patients with lung cancer receiving chemotherapy (John, 2003) and in patients with metastatic breast cancer (Headley, 2003). Interest also is growing among nononcology healthcare professional groups. Since the 2002 meeting of ACSM, sessions have been dedicated annually to exercise in patients with cancer.

Additional Evidence

Nursing scientists, exercise physiologists, clinicians, and educators have contributed to the understanding of CRF. The significance of the problem of fatigue for patients with cancer has become an important focus of review articles and clinical practice guidelines. These strengthen the base of evidence supporting exercise as an intervention for CRF.

Qualitative review articles: Two comprehensive systematic qualitative reviews support the research-based conclusions that exercise is an effective intervention for CRF. Friedenreich and Courneya (1996) summarized nine research studies conducted through 1994 on the topic of exercise and rehabilitation of patients with cancer and identified the needs and proposed directions for further research. Based on existing research at the time of publication, these authors recommended exercise as an innovative, inexpensive, and timely intervention for rehabilitation. Ream and Richardson's (1999) review of interventions for fatigue also supported the positive impact of exercise on CRF. In addition, a recent review of the state of the knowledge of CRF was published in a leading medical journal and included an evaluation of the evidence to support interventions (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003). Exercise was determined to have the highest level of evidence of efficacy.

Clinical Practice Guidelines

The 2003 NCCN *Revised Guidelines for the Management of Fatigue* summarized the standards of care for fatigue management that were developed by a multidisciplinary national panel of experts and also supported the efficacy and utility of exercise for management of CRF (Mock et al., 2003). Guidelines for evaluating and treating CRF are presented in an algorithm categorizing interventions for fatigue into coping strategies and cause-specific, nonpharmacologic, and pharmacologic interventions. After reviewing research and nonresearch evidence addressing interventions for CRF, the panel recommended exercise as the most effective nonpharmacologic intervention. Exercise training at moderate levels was reported to improve adaptive cardiorespiratory responses, increase cardiac output, lower heart rate, decrease fatigue, and improve mood state and sleep quality.

Strength of the Evidence

Determination of the strength of the evidence in support of a specific intervention relates to the number of studies testing the intervention, the scientific rigor of study designs and execution, and the size and consistency of reported effects (Briss et al., 2000). When using these well-accepted criteria, the strength of the evidence of effectiveness of exercise in managing CRF must be characterized as strong.

At least 20 studies have been conducted focusing on the effects of exercise on CRF. Most included control or comparison groups and prospective measurement of exposure to the intervention and of study outcomes. The strongest evidence, in the form of four randomized clinical trials and four quasi-experimental studies, exists for home-based exercise programs performed by middle-aged women undergoing adjuvant chemotherapy or radiation therapy treatments for nonmetastatic breast cancer (Mock et al., 1994, 2001; Mock, Dow, et al., 1997; Mock, McCorkle, Ropka, & Pickett, 2002; Schwartz, 1999, 2000a, 2000b; Schwartz et al., 2001). Solitary trials evaluating exercise in individuals with multiple myeloma, melanoma, and prostate cancer offer promise that exercise may be equally beneficial in other cancer populations (Coleman et al., 2003; Schwartz et al., 2002; Segal et al., 2003), as do recent PRISM level 2 and 3 trials in individuals with mixed solid tumor and hematologic malignancies (Adamsen et al., 2003; Courneya, Friedenreich, et al., 2003). In addition, growing PRISM level 2 and 3 evidence supports the efficacy of exercise in reducing fatigue in cancer survivors (Courneya, Friedenreich, et al.; Oldervoll et al., 2003; Segal et al.). Consistent but less robust (PRISM level 3 and 6) evidence supports the efficacy of aerobic laboratory-based interval training in individuals receiving PBSCT (Dimeo et al., 1997, 1998, 1999).

Although scientific rigor was adequate overall, each of the 20 exercise intervention studies had some design limitations. For example, most of the studies used valid and reliable fatigue instruments previously tested in cancer populations, and many added laboratory measures of functional capacity or exercise tolerance to correlate objective physical functioning outcomes with patient-reported fatigue levels. However, four of the reviewed studies did not evaluate fatigue as a primary outcome, and two others did not use a standardized fatigue measure. Several studies were pilot projects with small sample sizes. Others had no comparison group. In still others, participants were not assigned randomly to treatment or control conditions. In two of the home-based programs, participants randomized to usual care exercised during the study in a diffusion-of-treatment effect that complicated the analysis of intervention effects. Additional elements not controlled in the studies included the reporting of anemia levels, intensity of chemotherapy or other cancer treatment across study groups, and timing of the measures in relation to chemotherapy doses.

Although several forms of exercise were tested in the studies, all but two (Porock et al., 2000; Segal et al., 2003) were considered aerobic and all were performed at a level of intensity found effective in other chronic disease populations. Two research teams (Adamsen et al., 2003; Coleman et al., 2003) added strength resistance training to aerobic exercise interventions. Differing operational definitions of exercise and adherence make clearly defining the necessary dose (intensity, frequency, and duration) of exercise to achieve the desired reduction in CRF difficult. Nonetheless, at least 15 minutes of exercise three to five times weekly, either for the duration of hospitalization or for a minimum of six weeks in outpatients, seems necessary to achieve a reduction or stabilization in fatigue levels in patients with cancer undergoing active treatment. Adherence to the exercise intervention was 60%–100%, a surprisingly high rate when compared to the 50% rate for healthy individuals beginning an exercise program (Dishman, 1998).

Although the generalizability of findings is improving as study samples grow in diversity, key limitations remain. Initial studies focused primarily on patients with breast cancer aged 40–50 years, but more recent studies have broadened the focus to include patients with other solid tumors or hematologic malignancies. Few allowed adults older than 65, and only Porock et al. (2000) included patients with notable comorbidities.

Effect sizes were moderate to large across studies, and study results were very consistent. All of the studies demonstrated significantly lower levels of fatigue in groups of participants who exercised regularly during the study, except for two small pilot studies that demonstrated trends toward improvement in fatigue (Adamsen et al., 2003; Coleman et al., 2003). In summary, the strength of the evidence supporting exercise as an intervention to manage CRF is a result of the large number of studies conducted, the moderate-to-good overall quality of the designs and study methods, the large effect size of the intervention, and the absolute consistency of results across all studies in this review.

Implications for Clinical Practice, Research, and Nursing Education

Adequate evidence exists to support the efficacy of exercise as an intervention for CRF in patients with cancer and cancer survivors. Oncology nurses have a responsibility to apply this evidence to clinical practice, research, and education. Specific challenges include safely and effectively integrating the available evidence into care of individual patients, identifying and pursuing research that will answer remaining questions related to exercise and CRF, and using current knowledge, including theories, to educate nurses about CRF.

Oncology clinicians must consider a number of issues related to exercise prescription. These include, but are not limited to, the type and dosage (intensity, frequency, and progression) of exercise, baseline screening of individuals, a monitoring plan to ensure the safety and efficacy of the program, adherence to the exercise regimen, and use of available guidelines. Clinicians must self-assess their own ability to safely develop an exercise prescription and must collaborate with other disciplines where appropriate. Evidence-based guidelines are needed to assist clinicians in teaching, prescribing, and monitoring exercise for specific groups of patients such as those in active cancer treatment, in disease-free follow-up, and those receiving palliative care. The guidelines should provide specific information, based on research, for tailoring exercise programs for children and older adults, patients with comorbidities, and individuals who have been sedentary prior to the cancer diagnosis. In the absence of such guidelines, contemporary evidence helps to guide practice.

In the available studies, various types of exercise were tested and can be considered for application to clinical practice. These can be categorized into five exercise subgroups based on intensity: (a) comfort- or symptom-limited, low-intensity exercise, (b) aerobic interval-training programs, (c) low- to moderate-intensity aerobic exercise programs (sometimes classified as symptom limited), (d) high-intensity continuous exercise, and (e) resistance exercise. Aerobic interval training and low- to moderate-intensity aerobic exercise programs are best supported by the current available evidence for application to diverse oncology populations.

Based on current PRISM level 6 evidence, low-intensity exercise individualized to patient comfort is the only type of exercise that can be considered safely for patients in palliative care settings whose activity often is limited by a number of distressing symptoms, including pain and fatigue. Porock et al.'s (2000) study used the Duke Energizing Exercise Program, in which an individual determines the preference for type of exercise and regulates the intensity and duration based on comfort. A significant limitation to the broad clinical application of such exercise programs is the level of professional training necessary for implementation. Experienced physical therapists, exercise physiologists, or rehabilitation consultation should guide individualized, comfort-based exercise programs to stabilize fatigue levels.

Aerobic interval-training programs may be considered for use in individuals with breast cancer as well as individuals undergoing PBSCT, with appropriate monitoring by physical therapists or exercise physiologists. This recommendation is supported by PRISM level 3 and 6 evidence. MacVicar and Winningham (1986) first tested the Winningham Aerobic Interval Training Program in women receiving adjuvant therapy for breast cancer. This program consisted of a progressive cycle ergometry protocol performed three times weekly. Aerobic interval training on treadmills and supine cycle ergometers subsequently has been evaluated more extensively in individuals undergoing and following PBSCT for a variety of both solid tumor and hematologic malignancies. Individuals in these studies performed aerobic interval training for 15–30 minutes daily, five to seven days per week, at a moderate intensity corresponding to 80% of the maximal heart rate or 50% of the heart rate reserve (Dimeo et al., 1997, 1998, 1999). Even during hematologic nadir, a program of bed- or chair-based bicycle ergometer pedaling was found to be safe and effective in reducing fatigue in hospitalized patients undergoing PBSCT (Dimeo et al., 1999). Exercise was withheld only for platelet counts less than 20,000/ mm^3, fever, uncontrolled infection, or multiple complications.

Home-based, moderate-intensity aerobic exercise programs for individuals during and following radiation and chemotherapy are supported by the most robust available evidence (PRISM level 2 and 3). Individuals with a wide variety of solid tumors and hematologic malignancies have participated in this research, although women with breast cancer comprise the majority of participants. Home-based exercise programs are convenient for implementation in clinical practice because they are low risk, require minimal baseline evaluation and ongoing monitoring, and can be performed by patients in their own homes or community environments.

Prescription of dose and intensity for home-based exercise programs may be guided by available research. Studies by Mock's research team (Mock et al., 1994, 2001, in press; Mock, Dow, et al., 1997) encouraged participants to walk at a moderate intensity for 15–45 minutes, four to five times weekly, with an additional five-minute warm-up and cooldown, and to increase the duration of exercise by approximately two to three minutes every one to two weeks. Individuals deconditioned at baseline were advised to start as low as five minutes of brisk walking twice daily. Similarly, participants in studies by Schwartz's research team (Schwartz, 1999, 2000a, 2000b; Schwartz et al., 2001, 2002) were instructed to exercise for 15–30 minutes, three to four times weekly, to a maximal intensity that did not provoke symptoms. Participants chose the type of exercise, and most participated in walking. In one study, participants who exercised more than 60 minutes per session were more likely to report increased levels of fatigue, suggesting a maximum effective dose (Schwartz et al., 2001).

In some studies, patients were given written instructions regarding safety and monitoring issues related to exercise performance at home (Mock et al., 1994, in press; Mock, Dow, et al., 1997; Schwartz, 1999, 2000a, 2000b; Schwartz et al., 2001, 2002). A patient education booklet (Mock, Cameron, Tompkins, Lin, & Stewart, 1997) that was developed by a multidisciplinary team of healthcare providers, including an exercise physiologist, is available from the Johns Hopkins University Press and was used in the Mock studies. This booklet provides basic exercise and safety guidelines and strategies for adherence to and progression of the exercise plan and includes instructions on moderating the level of intensity of exercise. A similar walking program is described in detail by Winningham (1991) and includes precautions, screening, and monitoring.

Continuous high-intensity aerobic exercise has been evaluated only in breast cancer survivors who were, on average, more than one year after cancer treatment (Courneya, Mackey, et al., 2003). Exercise bicycling was performed continuously under supervision at 70%–75% maximal oxygen consumption for 15- to 35-minute sessions. Based on limited evidence (one PRISM level 2 trial), high-intensity exercise should be considered only in otherwise healthy individuals who have recovered from cancer therapy.

Finally, strength-resistance training exercise has received limited evaluation in patients with prostate cancer undergoing androgen deprivation therapy (Segal et al., 2003), as well as in combination with aerobic exercise in patients with multiple myeloma receiving aggressive chemotherapy and PBSCT (Coleman et al., 2003). Supervised resistance training was evaluated in patients with prostate cancer. Stretch bands were used at home by patients with multiple myeloma, and their exercise prescriptions were adapted continuously based on their individual clinical status. Based on these two PRISM level 2 trials, nurses may consider referring individuals at risk for skeletal muscle wasting to physical therapists or other qualified professionals for resistance training, either alone or in combination with aerobic exercise.

The ACSM has published recommendations for baseline testing and exercise prescription in a number of populations such as patients with cardiac and diabetic diseases. However, no guidelines for patients with cancer currently exist, including which, if any, baseline testing should occur prior to initiation of exercise. Consideration of health status, current and anticipated illness, disability and impairments, and previous exercise level and necessary precautions are needed prior to exercise prescription. Winningham (1991) suggested additional screening related to cancer and treatment-specific factors such as cancer diagnosis, type and timing of cancer therapy and related side effects, and psychological status.

Once the exercise program has begun, regular evaluation of motivation and adherence, as well as assessment of risks and benefits, can optimize exercise prescription and modification. All of the research studies reported here used some form of regular monitoring, ranging from weekly telephone calls or review of participant daily diaries to facility-based supervision. At a minimum, patients should be educated about symptoms to report to care providers and should be queried as to adverse reactions related to exercise participation.

Adherence to exercise programs is a crucial component about which little is known, particularly in patients with cancer, and is an area in great need of further research. Identification of motivators and barriers is essential in facilitating the acceptance and regular implementation of exercise. Methods of providing safety for high-risk patients who exercise also are needed. Researchers must target more diverse populations with a variety of ages, socioeconomic levels, and cultural backgrounds so that research findings may be generalized to less commonly studied patients with cancer. Exercise interventions must be studied in patients with other types of cancer receiving a variety of cancer therapies. More rigorous experimental designs with larger sample sizes would facilitate development of the science. Instruments should include a combination of objective physiologic measures of exercise and CRF as well as patient reported outcomes to enhance reliability and validity. Use of a consistent set of high-quality measures would permit comparison of outcomes across studies.

With respect to nursing education, theories explaining CRF can be applied in the classroom, particularly for understanding CRF assessment and management. Frequent literature searches of published studies and review articles are required to keep pace with the expanding knowledge on the topic of exercise in patients with cancer. Since the 1990s, six major review articles have included summaries of fatigue and exercise and provided a strong foundation for advanced cancer nursing education. Winningham et al.'s (1994) comprehensive summary of fatigue in cancer was an important early description of the problem of CRF. Helpful tables list extensive questions and recommendations for clinical practice and research that can be useful in guiding classroom discussion or topics to be developed in lectures for advanced practice nurses. Ream and Richardson's (1999) review of interventions to decrease CRF highlighted useful conceptual models, in addition to extensively discussing nursing theories relevant to clinical practice and nursing research. Their article provides an opportunity to educate advanced practice nurses in the importance of theoretical applications. The review by Ahlberg et al. (2003) included a discussion of assessment and measurement of CRF as well as information on pathophysiologic mechanisms.

A structural framework used for analysis and critique of the review articles was adapted from Meleis' (1997) critical evaluation of nursing theories. The adapted framework was used to organize the review of each article and is summarized in Table 3. The usefulness and relevance of the articles for advanced cancer nursing education have been evaluated based on the concepts discussed, the extent of supporting evidence, and the review method and logical explanation of CRF and exercise.

Conclusions

Despite the noted limitations in the research to date, the cumulative evidence is strong in support of exercise as an intervention to manage CRF in selected patients. The following conclusions can be made based on the available evidence. All

Table 3. Summary of Fatigue and Exercise Review Articles for Advanced Cancer Nursing Education

Author and Background	Concepts and Level of Evidence	Review Method and Logical Explanation	Usefulness and Relevance	Comments
Winningham et al., 1994; pioneer nurse researcher in field; panel of nursing experts	Thorough review of causes, indicators, and effects of fatigue; cites references and interventions with relevant theoretical background	Superior rationale and organization; wide scope and goal oriented; interesting visuals	Relevant to nursing education, practice, research, and other professions (e.g., sports medicine, physical therapy, and exercise physiology)	Important summary of fatigue and exercise, with guidelines for practice and strategies for research
Friedenreich & Courneya, 1996; Canadian kinesiologist and epidemiologist	Cancer rehabilitation treatment and exercise are defined and developed; cancer-related fatigue (CRF) is not defined.	Extensive review with good table of references for quality of life and exercise; interesting discussion of "exercise is good for you"	Useful information for research and education and helpful for nononcology professionals	Informative review of exercise in the cancer literature
Ream & Richardson, 1999; British nurse researchers; university based	Assumes a limited understanding of CRF; relevant references are cited and reviewed.	Review of nursing (only) practice, theory, and research literature	No empirical evidence to substantiate practice recommendations of holistic approach for fatigue management; interesting discussion for research and education	Informative tables. Author opinion is given without empirical evidence (e.g., "single intervention can only provide partial relief").
Dimeo, 2001; physician in Germany at sports medicine institute	Well-defined etiologic mechanisms and consequences of fatigue and muscular energetic systems	References cited with development of complex propositions; no tables	Congruent with nursing science, but not instructive to practice; applicable to research and education	Interesting lecture presentation; brief review of the literature
Mock et al., 2001; nurse researcher; leader in CRF research	Patterns of CRF and mechanisms are discussed and developed.	Cited and discussed relevant references; had helpful tables of references and standards.	Useful summary guidelines for oncology practice and education standards	Instructive to nurses and disciplines other than nursing science
Ahlberg et al., 2003; Swedish nurse researcher with international team	Understanding of CRF is grounded in evidence-based review of contributing factors as well as patient perspective.	Review of multidisciplinary research literature and guidelines; logical flow of clinical and research implications	Thorough evidence-based review of fatigue assessment and management facilitates application to practice.	Highlights areas in need of further CRF research; useful review of fatigue measurement tools

Note. Based on information from Meleis, 1997.

patients should be encouraged to maintain an optimum level of activity or exercise to manage CRF during and following cancer treatment. Patients who become weak or deconditioned—or those with comorbidities—can benefit from referrals to physical therapy, physical medicine, or rehabilitation programs to maximize functional status and decrease CRF and other symptoms. Patients with breast cancer and other selected patients should receive recommendations for a moderate exercise program during and following chemotherapy and radiation therapy. Patients undergoing and recovering from PBSCT can benefit from supervised progressive exercise. High-intensity exercise can be considered for otherwise healthy individuals who have recovered from cancer therapy. Patients with progressive disease can maximize their activity level through supervised programs adapted for individual safety. Exercise for individuals at risk for skeletal muscle weakness should include strength training. Overall, exercise interventions should be tailored to an individual's specific disease and treatment characteristics and health status.

The exercise programs tested in the studies reviewed in this article were taught and monitored by oncology nurses or exercise physiologists trained to conduct exercise programs. ACSM offers certification for clinical health and fitness professionals. Although ACSM does not certify for exercise prescription in patients with cancer, collaboration among ACSM-certified specialists and oncology healthcare clinicians, researchers, and educators can benefit individual patients and advance the science of exercise prescription for patients with cancer. Published multidisciplinary evidence-based guidelines for exercise programs and the multidisciplinary development of a related professional curriculum in exercise prescription for patients would facilitate application to clinical practice.

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For more information . . .

- CancerSymptoms: Fatigue
  www.cancersymptoms.org/symptoms/fatigue
- Mayo Clinic: Fatigue: Cancer-Related Causes and How to Cope
  www.mayoclinic.com/invoke.cfm?id=CA00032
- MedlinePlus: Fatigue
  www.nlm.nih.gov/medlineplus/ency/article/003088.htm

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