Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy

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ABSTRACT

SCHWARTZ, A. L., M. MORI, R. GAO, L. M. NAIL, and M. E. KING. Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. *Med. Sci. Sports Exerc.*, Vol. 33, No. 5, 2001, pp. 000–000. **Purpose:** Cancer treatment-related fatigue is the most prevalent and distressing symptom of cancer therapy. Interventions to minimize fatigue are needed. The purpose of this study was to examine the relationship between exercise and fatigue over the first three cycles of chemotherapy in women receiving either cyclophosphamide, methotrexate, and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) for breast cancer. **Methods:** Seventy-two newly diagnosed women with breast cancer were instructed in a home-based moderate-intensity exercise intervention. Measures of functional ability, energy expenditure, and fatigue were obtained at baseline and posttest. Subjects maintained daily records of four types of fatigue, and exercise duration, intensity, and type. **Results:** Exercise significantly reduced all four levels of fatigue ($P < 0.01$). As the duration of exercise increased, the intensity of fatigue declined ($P < 0.01$). There was a significant carry-over effect of exercise on fatigue, but the effect lasted only 1 d. The level of fatigue at study entry was not associated with number of days of exercise or amount of exercise a woman engaged in. **Conclusions:** The impact of exercise on fatigue was significant and suggests the effectiveness of a low- to moderate-intensity regular exercise program in maintaining functional ability and reducing fatigue in women with breast cancer receiving chemotherapy. **Key Words:** CANCER-RELATED FATIGUE, CHEMOTHERAPY, UNBALANCED REPEATED MEASURES

Everyday people experience fatigue. Fatigue is a symptom commonly associated with diseases such as depression, multiple sclerosis, arthritis and renal disease, and different medical and pharmacological treatments. Persons being treated for cancer experience a different and far more disruptive form of fatigue. Cancer treatment-related fatigue (fatigue) is the most prevalent and disturbing side effect of treatment for the majority of cancer patients (11,12,26). Fatigue leads to declines in emotional, psychosocial, and physical function (5,6,17,19,20). Fatigue is described as being relentless and intense; a type of fatigue that is more severe, unpredictable, and overwhelming than the fatigue experienced before cancer treatment (22,26).

Exercise is an intervention proposed to reduce fatigue (5,7,19,20,28,29). Exercise studies with cancer patients have reported positive effects of exercise on mood, chemotherapy side effect severity, weight gain, functional ability, and quality of life (5–7,17,19,20,26,28). However, in these studies, the conclusion that exercise decreases fatigue was based on a single composite score, which aggregated data over several days or weeks (5,7,19,20), or the method of measuring fatigue was not described (6). However, there is a dramatic day-to-day fluctuation in fatigue that is not addressed or captured using the aggregated approach (29). Understanding the relationship between exercise and fatigue within relatively brief time frames is essential in determining whether a dose of exercise could be prescribed to reduce fatigue and to determine the dose-response relationship.

The purpose of this study was to examine the relationship between exercise and fatigue over the first two cycles of chemotherapy in women receiving either cyclophosphamide, methotrexate, and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) for stage I to III ductal carcinoma of the breast. Five research questions were examined: 1) Does exercise decrease level of fatigue on the same day? 2) Does the amount of exercise correlate with fatigue level? 3) Is there a cumulative effect of exercise on fatigue level? 4) Is the effect of exercise transient or long lasting? And 5) Is there a relationship between exercise intensity and fatigue level?

METHODS

A one-group pretest-posttest design was used to examine the relationship between fatigue and exercise in women with breast cancer who participated in a home-based exercise intervention. The one-group design was selected to minimize treatment diffusion, compensatory equalization, and resentful demoralization.

Sample

Potential subjects were recruited to participate in an 8-wk home-based aerobic exercise program, from a university cancer center and private practice. All eligible subjects (chemotherapy naive, no previous radiotherapy, ambulatory with histologically documented breast cancer) were invited to participate in the study. Seventy-two women enrolled in

0195-9131/01/3305-0718/$3.00/0
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Received for publication March 2000.
Accepted for publication August 2000.

the study. Results are presented on the 61 subjects who completed the study and maintained exercise and fatigue diaries. The 11 subjects who did not complete the study either did not complete the fatigue measures ($N = 5$) were lost to follow-up ($N = 1$) or withdrew from the study ($N = 5$). No differences in age, education, ethnicity, previous exercise history, stage of disease, or type of treatment ($\chi^2 > 0.05$) were observed between those who completed the study and those who did not. Subjects ranged in age from 27 to 69 yr old (mean = 47.3 yr old, SD = 7.9). The majority of subjects were married (72%), employed (64%), Caucasian (90%), and had attended some college (79%). Most participants were being treated on a 21-d cycle of AC (61%) for stage II (54%) infiltrating ductal carcinoma of the breast. All subjects had surgery at least 21 d before beginning the study, with 74% having modified radical mastectomy with nodal dissection. None of the subjects had received radiation therapy before study entry. Fifty-eight percent of the sample did not exercise at entry into the study. The subjects who were regular exercisers at baseline (42%) reported exercising an average of 38 min, 4 $d \cdot wk^{-1}$. Walking as part of their work or housework was the primary exercise for these women. Only two of these women met the current recommendations for physical activity (24).

Measures

Demographics. Demographic variables recorded included age, ethnicity, marital status, education, and previous exercise behavior. Chart review was used to obtain clinical information such as stage of disease and chemotherapy regimen.

Functional ability. The 12-min walk is a measure of the distance in feet an individual can cover in 12-min. Baseline and posttest measures were used to assess changes in functional ability resulting from exercise. All subjects followed a measured course, received consistent instructions and were encouraged only in the last 2 min of the walk. The tests were conducted indoors in a climate-controlled environment. The 12-min walk is strongly correlated ($r = 0.9$) with oxygen consumption (3), has been successfully used in studies with women with breast cancer (19,20,28), and is used extensively in cardiopulmonary rehabilitation as a measure of functional ability (1,30). The 12-min walking distance is relevant to daily activities and the test is easily administered in a clinical setting.

Exercise intensity. Caltrac™ accelerometers (Muscle Dynamics Fitness Network, Torrence, CA) were used to record the amount of energy (calories) expended, or exercise intensity, during the 12-min walks and in each exercise session. The Caltrac has demonstrated test-retest reliability, interinstrument reliability, and strong correlations with maximum oxygen uptake and doubly labeled water (10,21,23). Reliability and validity have been demonstrated for walking, running, and cycling (9,10,23). Subjects recorded calories expended during exercise, as measured by the Caltrac™, in an exercise log that included information about type and duration of exercise.

Self-reported measures. Fatigue diaries were used to record, on four 100-mm visual analog scales (VAS-F), the level of 1) fatigue at its worst in the past 24 h, 2) fatigue at its least in the past 24 h, 3) fatigue on the average over the past 24-h, and 4) fatigue right now. For consistency of measurement, subjects were instructed to complete the diary at the same time each night before they went to bed. This helped make recording fatigue part of their nightly routine and provided consistency in women's evaluation of their fatigue. Subjects who recorded data for each day produced 56 measures each of worst, least, average, and fatigue right now. Visual analog scales have been successfully used in previous studies to measure cancer-related fatigue with reliability and validity (19,25,27).

The exercise diary was integrated into the fatigue diary. Subjects recorded exercise frequency, duration, and calories expended in the activity monitor mode of the Caltrac™ accelerometer. This mode only provides a calculation of the number of calories expended in exercise minus the basal metabolic rate (BMR).

Procedures

After written informed consent was obtained, all baseline measures were obtained before the first dose of chemotherapy. These measures included: 12-min walking distance, Caltrac™ accelerometry, and daily visual analog measures of fatigue. All women received instruction to exercise between 15 and 30 min, 3–4 $d \cdot wk^{-1}$, and to wear the Caltrac™ accelerometer with each exercise session. Women were instructed to exercise at an intensity that did not aggravate their symptoms (e.g., pain, fatigue). To improve adherence to exercise and because the benefits of aerobic exercise are not determined by type of activity as much as by exercise intensity and duration, the women were encouraged to choose an aerobic activity they enjoyed. Instruction was provided about using the Caltrac™ accelerometer. All of the women received information about contraindications to exercise and were given a 24-h contact number to call if they had questions regarding their exercise program or how to operate their Caltrac. Weekly telephone calls, conducted by a research assistant, were used to remind subjects to return their exercise and fatigue diaries and address barriers to exercise.

Data Analysis

Only for the discussion of descriptive data were women divided into two groups, exercisers and nonexercisers. Exercisers were defined as women who increased the 12-min walking distance at posttest. Nonexercisers declined in their posttest performance on the 12-min walk.

The daily fatigue data were analyzed using unbalanced repeated measures analysis (13,14). Classic analytic techniques could not be used because of missing values. This technique allows parameterization of the covariation matrix and automatically incorporates time-varying covariates and incomplete data into the model (13,14).

TABLE 1. Least squares means and standard errors for four measures of fatigue on no-exercise and exercise days.

	Worst Fatigue	Least Fatigue	Fatigue Now	Average Fatigue
Non-exercise day	50.98 (1.26)	22.81 (0.94)	47.11 (2.50)	36.90 (1.06)
Exercise day	46.01 (1.36)	18.14 (1.03)	40.66 (2.67)	31.65 (1.15)
P-value	<0.001	<0.001	<0.001	<0.001

Unbalance repeated measures allowed the inclusion of all women who recorded exercise in their exercise and fatigue diary (N = 61) regardless of their performance on the 12-min walk. Although measures of fatigue were obtained daily for 8 wk (56 d), we limited our analysis to the first 6 wk (42 d) of treatment to reflect two complete cycles of chemotherapy. Unbalance repeated measures analysis maximized the data and examined exercise in women who may not have been classified as exercisers by virtue of increasing the distance on the posttest 12-min walk. The presence or absence of exercise, number of minutes exercised, and cumulative amount of exercise were evaluated as time-dependent covariates in the analysis. This variance-covariance matrix was assumed to have a toeplitz structure with seven bands. The structure implies that the fatigued measures over 6 d are correlated, whereas the fatigue measures over more than 6 d are uncorrelated (e.g., the correlation between day 1 and day 7 is zero). Given that fatigue is a highly variable state and not a trait characteristic, this assumption seemed appropriate (22).

RESULTS

Descriptive analysis of measures. Using the criteria to categorize women as exercisers or nonexercisers, 61% (N = 37) of the women adopted the exercise program and demonstrated improvements in functional ability. The mean baseline 12-min walking distance for the group was 3449 ft (SD = 649, min·max = 1923–4990). Women who adopted the exercise program (N = 37) showed an increase in posttest 12-min walking distance (mean = 3914 ft, SD = 624, min·max = 2325–5747); demonstrating a mean increased functional ability at posttest of 15% (SD = 14.1, min·max = 1–58%, $P < 0.001$). Women who did not adopt the exercise program (N = 24) decreased the 12-min walking distance at posttest (mean = 2938 ft, SD = 679, min·max = 1763–3934); declining a mean of 16% (SD = 13% min·max = −2–48%, $P < 0.001$). Nine women who were regular exercisers at baseline did not continue to exercise during the study period. Although one of the women's functional ability declined 37% (mean = 22%, SD = 13%), five of the women showed only modest declines (mean = 4%) in functional ability. These women may have been categorized as nonexercisers by virtue of the stringent criteria used to define those women who adopted the exercise program when they really maintained an exercise program but at a lower intensity, frequency, or duration than before beginning chemotherapy. The 35 women who were nonexercisers at baseline but adopted the exercise program demonstrated improvements in functional ability (mean = 15.8%, SD = 16.4, range = 1–58%) over the study period.

Functional ability at study entry correlated with frequency (r = 0.44, P = 0.0006) and duration (r = 0.30, P = 0.023) of exercise over the study period. Functional ability at posttest also correlated with the frequency (r = 0.37, P = 0.004) and duration (r = 0.42, P = 0.001) of exercise women reported. These correlations suggest that women adopted the exercise intervention and that patients were accurately reporting their exercise.

Does exercise decrease level of fatigue on the same day? A comparison of the four measures of fatigue on nonexercise and exercise days revealed a significant effect of exercise on fatigue (Table 1). All measures of fatigue were significantly reduced on the exercise days compared with the nonexercise days. Because subjects recorded their fatigue at night, it can be assumed that the declines in fatigue on exercise days were related to exercise and not simply that people exercised because they felt better or experienced fewer symptoms. There was no interaction between exercise and time (all P-values > 0.3), suggesting that the effects of exercise are stable over time. The effects of exercise remained significant even after adjusting for baseline level of fatigue and functional ability (all P-values < 0.001).

Does the amount of exercise correlate with the fatigue level? The amount of exercise, measured as the number of minutes exercised, was significantly associated with fatigue levels (Table 2). In general, the longer a woman exercised, the less fatigue she felt on that day. The exception was for current level of fatigue (fatigue now) which increased when exercise exceeded 60-min bouts.

Is there a cumulative effect of exercise? The analysis of cumulative amount of exercise, measured by cumulative days of exercise (mean = 12.12, SD = 11.43, min·max = 0–42) and cumulative minutes of exercise (mean = 434.63, SD = 610.15, min·max = 0–1878),

TABLE 2. Least squares means and standard errors for four daily measures of fatigue by number of minutes of exercise per session.

No. Minutes/Session	Worst Fatigue	Least Fatigue	Fatigue Now	Average Fatigue
0 min	50.99 (1.24)	22.85 (0.94)	47.11 (2.50)	36.89 (1.05)
1–30 min	47.87 (1.49)	18.69 (1.14)	42.30 (2.86)	33.55 (1.25)
31–60 min	43.43 (1.83)	17.29 (1.43)	36.16 (3.39)	28.47 (1.53)
>60 min	39.79 (3.01)	14.76 (2.44)	40.33 (5.33)	26.89 (2.56)
P-value	<0.001	<0.001	<0.001	<0.001

TABLE 3. Definition of categorizations of days in terms of exercise on the current and previous day.

Group	Current Day	Previous Day	Total Number of Days in Analysis
1	No exercise	No exercise	1498
2	No exercise	Exercise	295
3	Exercise	No exercise	295
4	Exercise	Exercise	432

showed a weaker and inconsistent association with reduced fatigue levels. No significant difference was observed for current level of fatigue. However, a significant decline of over 10 points was observed between women who exercised and those who did not on level of worst, average, and least fatigue ($P < 0.05$). The effect of exercise on fatigue was greatest on the day of exercise and did not necessarily carry over to subsequent days. The trend was for fatigue to decrease as the cumulative number of min of exercise increased.

Is the effect of exercise transient or long-lasting? To evaluate whether the effects of exercise persist from one day to the next, we categorized the data according to the presence or absence of exercise on the current or previous day (Table 3). Although there was a small carry-over effect of exercise to the next day, the impact of exercise on fatigue appeared to be more immediate than long-lasting. Fatigue was lowest when a woman exercised 2 d in a row; somewhat higher when she exercised one day but not the next day; and still higher when she did not exercise at all in the 2-d period (Table 4). These results show the immediate effect of exercise and a small but significant carry-over effect of exercise on fatigue.

Is there a relationship between exercise intensity and fatigue level? Exercise intensity was measured by the number of calories expended during exercise as recorded by the Caltrac accelerometer. The effects of the number of calories expended on the level of fatigue are summarized in Table 5. In general, as caloric expenditure increased, fatigue declined. However, the effects of exercise intensity were only significant for the least fatigue ($P = 0.04$) and the average daily fatigue ($P = 0.03$). These results suggest that when a woman exercises at moderate- to high-intensity levels her perceptions of worst and current level of fatigue are not changed, possibly reflecting changes in hydration and nutritional state that could contribute to fatigue.

DISCUSSION

Although this study is limited by the single group design, results provide additional evidence that women undergoing chemotherapy for breast cancer will follow a home-based exercise intervention (19,20). The impact of exercise on all four types of fatigue was significant and reflects the effectiveness of low- to moderate-intensity regular exercise in maintaining functional ability and reducing fatigue in patients with breast cancer. Previous studies have consistently demonstrated reduced fatigue with exercise but with less frequency of measurement and longer periods of time between measures (5,7,19,20,28). The frequency of measurement used in this study provides examination of the day-to-day effect of exercise on fatigue and demonstrates remarkable magnitude of decline in all four types of fatigue by frequency and duration of exercise. Exercise reduced the intensity of fatigue between 14% and 35%, depending on type of fatigue, with the greatest declines in fatigue observed in levels of worst fatigue. Exercise was consistently associated with reducing fatigue the day of exercise and one day afterward.

The effects of exercise on current level of fatigue were somewhat inconsistent. Current level of fatigue increased when exercise exceeded 60 min. The reason for this is unclear, perhaps prolonged exercise provokes muscular fatigue and the feelings of fatigue associated with changes in nutrition and hydration states that could increase the sensation of current level of fatigue. None of these women were highly fit at study entry, so exercising beyond 60 min and continuing with their normal routine may have provoked the increase in fatigue. The inconsistent results observed in current level of fatigue may simply reflect that women recorded their fatigue at night, when one usually feels most tired.

Determining the optimal dose of exercise to reduce fatigue is elusive. Consistent with previous studies, the women in this study who exercised experienced less severe fatigue than nonexercisers (5,7,19,20,28). The somewhat inconsistent findings that there is not a cumulative effect of exercise on fatigue could lead one to speculate that daily or every-other-day exercise may be necessary to optimally reduce fatigue. As observed in Dimeo et al.'s study (7), even brief periods of exercise may be sufficient to reduce fatigue. It appears that exercising for longer duration reduces fatigue more, but providing an exercise recommendation that is realistic and achievable for women is paramount. Given the sedentary lifestyle of the majority of healthy persons, and the propensity for cancer patients to increase rest, the findings that minimal exercise reduces fatigue are encouraging (5,7,19,20,28). Breast cancer patients who begin an exercise program of regular, short bouts of low to moderate exercise and gradually increase duration as their fitness levels improve

TABLE 4. Least squares means and standard errors for four measures of fatigue by the group defined by previous and current day of exercise.

Group[a]	Worst Fatigue	Least Fatigue	Fatigue Now	Average Fatigue
1	52.92 (1.37)	24.35 (1.04)	48.93 (2.69)	38.64 (1.16)
2	47.73 (1.57)	20.16 (1.21)	44.69 (2.95)	33.933 (1.31)
3	45.35 (1.56)	17.34 (1.19)	41.19 (2.98)	30.42 (1.20)
4	43.86 (1.62)	16.75 (1.25)	27.32 (3.09)	30.27 (1.39)
P-value	$<$0.001	$<$0.001	$<$0.001	$<$0.001

[a] Groups defined in Table 5.

TABLE 5. Least squares means and standard errors for four measures of daily fatigue by caloric expenditure in each exercise session.

Caloric Expenditure/Session	Worst Fatigue	Least Fatigue	Fatigue Now	Average Fatigue
0	47.33 (2.01)	20.93 (1.41)	44.65 (4.52)	32.94 (1.58)
1–119	46.55 (1.90)	16.41 (1.34)	40.13 (4.40)	32.82 (1.50)
≥120	44.04 (2.02)	16.48 (1.42)	32.13 (4.65)	28.94 (1.59)
P-value	0.3484	0.0402	0.1009	0.0359

may reap the benefits of improved functional ability and markedly reduced fatigue.

In this study, women were instructed to exercise at an intensity that was symptom limited. Consequently, the majority of women who adopted the exercise program walked and engaged in other low- to moderate-intensity exercise. This exercise intensity was acceptable to the women, did not worsen their symptoms, and produced favorable outcomes; a finding concurrent with epidemiologic studies that have demonstrated the benefits of low- to moderate-intensity, regular exercise in promoting health and reducing morbidity (16,24).

As observed in other studies, a woman's functional ability at the beginning of chemotherapy was predictive of the amount and frequency of exercise that she would engage in over the study period (8,14). Women who are already self-motivated to exercise may be more likely to follow a home-based exercise program than women who are not physically active. Although healthier, more functionally able individuals may be more likely to adhere to a home-based exercise program. For this reason, it is important for clinicians to screen patients to identify those with low functional ability before beginning chemotherapy (14,18). Inactive women who are beginning chemotherapy may benefit from a supervised, structured exercise program that would guide them through a progressive exercise regimen designed to enhance exercise self-efficacy and promote independent exercise in a self-monitored home-based program (15).

In this study, women were asked to follow the exercise intervention but were not admonished for failing to adhere. Although all the women who enrolled in the study expressed an interest in exercise and intent to exercise, clearly not all subjects were able to comply with the exercise prescription. For the most part, the women who did not exercise had a greater body mass index and were not previous exercisers, two factors that are the strongest predictors of who will adopt an exercise program (18). Identifying characteristics of women who would succeed in and benefit from a more structured supervised exercise programs will be important to promoting exercise for all women with breast cancer. The period of breast cancer diagnosis is a time when women evaluate their lifestyles and often decide to make positive changes. Exercise rehabilitation programs could minimize the weight gain observed in breast cancer patients (2,4,27) and lower their risks for cardiovascular disease, osteoporosis, and comorbidities associated with weight gain.

The generalizability of the study is limited by the one-group design. The use of self-reported measures of exercise and fatigue, although an inherent weakness of the study, were logistically necessary. However, the correlation between duration and frequency of exercise suggests that subjects accurately reported exercise. Home-based exercise programs are more convenient and cost effective but greatly limit control over the intervention. Although the Caltrac accelerometer monitoring is not an ideal method of measuring exercise intensity, heart rate monitoring is problematic because of the anemia that is caused by chemotherapy. Similar to previous exercise studies, the sample was predominantly Caucasian, further limiting generalizability. The problem of missing data in the last 2 wk of the study may reflect excessive subject burden of daily measures of fatigue and exercise or increasing overall fatigue.

The results of this study suggest the importance of short bouts of regular low- to moderate-intensity exercise to reduce fatigue in women with breast cancer receiving adjuvant chemotherapy. Although contrary to standard practice, it appears that women with breast cancer who are regular exercisers should be encouraged to continue their exercise program and women who are not regular exercisers should be given guidance and instruction to begin an exercise program. Clearly, a randomized trial is needed to validate these results. Encouraging patients to exercise during cancer treatment to maintain and improve functional ability appears to have a positive impact on fatigue and functional ability (5,7,19,20,26,28,31). These data suggest that daily or at least every-other-day, low- to moderate-intensity, symptom-limited exercise may be optimal to reduce fatigue in women with breast cancer receiving chemotherapy.

This work was supported in part by grants from the U.S. Army Medical Research and Materiel Command under DAMD17-96-1-6171, NIH/NINRF31 NR07159, and the Oncology Nursing Foundation.

Conflict of Interest: The results of this study do not constitute endorsement of the product by the authors of ACSM. The authors have no relationships with the companies that would constitute a conflict of interest.

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