The effects of resistance training on muscular strength and fatigue levels in breast cancer patients

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ABSTRACT

The effects of generalized exercise programs to combat cancer and cancer treatment-related side effects have been extensively reported in the literature. The purpose of this study was to examine the effects of an individualized exercise program with emphasis on resistance exercise, changes in muscular strength and fatigue in breast cancer female patients under treatment. Twenty subjects were randomly divided in two groups: an experimental (57.5 ± 23.0 years) and a control (56.6 ± 16.0 years) group. A twenty-one week intervention involving pre- and post-functional assessments, prescriptive exercise, and three moments of fatigue measures was used. The experimental group exercised at a low to moderate-intensity for sixty minutes two days a week beginning after surgery. Significant differences in overall muscular strength were observed between groups post-intervention ($p = 0.025$). Fatigue was also significantly different between groups at treatment one ($p = 0.001$), treatment two ($p = 0.005$) and post-intervention ($p = 0.001$). The results of this study suggest that an emphasis on resistance training should be utilized to combat fatigue and to increase muscular strength in breast cancer patients undergoing treatment.

Keywords: Resistance exercise. Fatigue. Cancer.

INTRODUCTION

Cancer is defined as an uncontrolled growth and spread of abnormal cells in the body. Among all cancers, breast cancer is the most frequently diagnosed cancer in women, with an estimated 211,240 new cases of invasive breast cancer expected to occur in U.S. women during 2005(1).

Common treatments used to treat breast cancer may involve one or more of the following: lumpectomy, mastectomy, radiation therapy, chemotherapy, or hormone therapy(1). Although these forms of treatments have been successful in the treatment of breast cancer, many of the side-effects produced contribute to a decline in normal functioning of many physiological systems of the patients.

Cancer treatment-related side-effects vary depending on type and intensity of treatments. Among the most frequently observed side-effects produced by cancer treatments are: nausea, loss of appetite, loss of hair, depression, weight gain, difficulty breathing, loss of muscular strength, and fatigue(1). It has been well reported that fatigue is the most common side-effect experienced by cancer patients(2). According to Dimeo(2), cancer-related fatigue may affect up to 70% of all patients that undergo chemotherapy or radiation therapy treatment. Fatigue, usually accompanied by an overall lack of energy, has been reported to last for years after treatment in at least 30% of cancer survivors(3).

The adverse effects to treatment can be acute or chronic, mild or severely debilitating. It is important to understand however that cancer-related fatigue is different from the fatigue resulting from any physical or mental exertion(4). The causes of cancer treatment-related fatigue should be seen as a multifactorial and associated with both the physical and emotional deconditioning that occurs following a cancer diagnosis and subsequent treatment(5). A decrease in physical activity is believed to worsen the side-effects, leading patients to experience a negative spiraling effect that further exacerbates the sense of fatigue. The reduction on physical activity levels associated with other side-effects, such as loss of appetite, can intensify muscular wasting and consequently loss of overall body strength. This loss of muscular strength is a further blow to a cancer patient's efforts to perform simple daily activities, significantly compromising the quality of life in patients(6).

To combat the decline in energy level and a concomitant loss of strength which lead to a significant deconditioning effect, researchers have been investigating the benefits of adding exercise to the weekly routine of cancer patients undergoing treatment. Though mostly aerobic based, researchers have seen great improvements in the quality of life and energy levels of patients. Some investigations have included the use of resistance training on resulting fatigue levels. Segal *et al.*(7) were the first to show that resistance exercise, rather than a program of purely aerobic work, reduced fatigue levels and improved quality of life for patients being treated for cancer. Recently, Roth *et al.*(8) investigation shows promise as to the influence of a multidimensional exercise program in improving muscular strength (40%) in patients with different cancer diagnosis during cancer treatment. Therefore, this study was performed to further illuminate the possible benefits that an individualized exercise program composed primarily of resistance training would have on muscular strength and fatigue levels in only breast cancer patients undergoing treatment.

METHODS

Sample

Volunteers for this study consisted of 20 females who have not participated in any regular physical activity during the last six months, ranging in ages from 40 to 70 years, who were recently diagnosed with breast cancer. Subject's characteristics are presented in table 1.

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TABLE 1
Subjects characteristics

	Age (years)		Body weight (kg)		Height (cm)		Body composition (% body fat)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Control group n = 10	56.6	16	81.7	25	169.1	10.1	29.84	14.9
Exercise group n = 10	57.5	23	77.5	27.2	168.9	10	29.13	10.1

SD = Standard deviation.

TABLE 2
Assessment timeline

Week	Exercise group
	Biopsy and diagnosis meeting Introduction to the study and informed consent signing
1	Pre-surgery assessment and randomization to groups Fatigue Assessment Fitness Assessment
2	Surgery
3	Recovery from surgery
4	Post-surgery assessment Fatigue assessment
5	
6	Exercise intervention begins
7	
8 (1st dose of chemotherapy)	1st Assessment of fatigue during treatment
9	
10 11 12	2nd Assessment of fatigue during treatment
13	
14 15 16	3rd Assessment of fatigue during treatment
17-20	
21	Final Assessment Fatigue Assessment Fitness Assessment

All subjects were recruited from oncology practices in the northern Colorado region between January 2001 and April 2003. The criteria for inclusion in the study were as follows: a) newly diagnosed with breast cancer; b) designated for definitive surgery (any type); c) designated for chemotherapy, radiation, or a combination of these treatments after surgery; d) ages ranging from 40 to 70 years at the time of the study.

The week after diagnosis and before surgery, subjects were randomly assigned to two different groups. The first group was an experimental group ("exercise") and the second group was a control group ("non-exercise"). The randomization procedure involved the drawing of numbers, which ranged from 1 to 20.

Participation in this study involved the same risks as any exercise regimen. Given the potential risks involved, patients were screened for exclusion based upon the following criteria: a) metastatic disease; b) immune deficiency; and c) cardiovascular disease, acute or chronic respiratory disease, acute or chronic bone, joint, or muscular abnormalities (unless the disease would not compromise the patient's ability to participate in the exercise rehabilitation program).

Prior to the beginning of the study, informational packets detailing all aspects of the study were provided to the physicians. Upon agreeing that they had understood the information and were interested in participating, the patients were then required to sign an informed consent form approved by the University of Northern Colorado's Internal Review Board (UNCO IRB) and the North Colorado Medical Center's Internal Review Board (NCMC IRB) outlining the purpose, procedures, benefits, risks, and voluntary nature of this investigation prior to participation in the study. All subjects recruited after April 13th of 2003 were asked to sign the Health Insurance Portability & Accountability Act of 1996 (HIPPA) authorization to use or disclosure protected health information for research form.

General procedures and assessment protocols

Fatigue assessments were completed prior to surgery, post surgery, and multiple times throughout the study (table 2). During the weeks of cancer treatment, fatigue was measured the day before subjects were to report for the next scheduled assessment/treatment.

The fitness assessments, comprised of cardiovascular endurance and muscular strength tests, were administered prior to surgery and at the end of the study (table 2) at the Rocky Mountain Cancer Rehabilitation Institute. Fitness assessment data were used to develop a prescribed exercise intervention appropriate for each subject in the exercise group. All fitness assessments were performed at the Rocky Mountain Cancer Rehabilitation Institute at the University of Northern Colorado in Greeley, CO.

Cardiovascular endurance assessments were performed using the modified Bruce treadmill protocol. The modified Bruce protocol is a submaximal protocol and is recommended for high-risk populations because less stress is imposed on the patients[9]. Muscular strength assessments involved the utilization of the following exercises: leg extension, seated leg curl, lat pull down, and seated chest press. Muscular strength assessments were performed using a submaximal muscle endurance protocol that predicts 1RM, developed for middle-aged and older women by Kuramoto and Payne[10].

Each of the two fitness assessments was standardized and followed precisely the same sequence of events and protocols. During the assessment protocol, participants were greeted and vital signs were measured (including resting heart rate, blood pressure, height, and weight). After the assessment of vital signs, the revised Piper *et al.*[11] Fatigue Scale (PFS) was administered. Following the assessment of fatigue, $\dot{V}O_2$ analyses and muscular strength were measured.

Instrumentation

Fatigue Scale

Fatigue levels were assessed using the PFS. This scale has 22 self-reported items that measures overall fatigue level on a scale of 0 to 10, as well as four domains of subjective fatigue: affective, sensory, cognitive, and behavioral, yielding a total fatigue score (TFS). In studies of patients with breast or lung cancer, the Cronbach's Alpha reliability ranged from 0.80-0.98 for the revised Piper Fatigue Scale[11]. Since the majority of cancer patients undergoing treatment experience the highest levels of fatigue approximately three days post-treatment and following recommendations from the North Colorado Medical Center oncologists, all subjects were instructed to answer the questions on the PFS during the last day of the week before reporting to the next scheduled assessment/treatment.

Fitness Assessments

The fitness level of each subject was assessed two times in the study. The first fitness assessment was administered prior to surgery and the second one at the end of the study. Each patient wore an A3 Polar heart rate monitor (Lake Success, NY) to determine resting heart rate and to monitor heart rate responses during cardiovascular assessments as well as for the control of intensity during exercise sessions. Height and body weight was assessed using a Detecto Model 437 Physician Beam Scale (Webb City, MO). Blood pressure was assessed using an ADC 922 Series aneroid sphygmomanometer (Hauppauge, NY) and a Littmann Stethoscope (St. Paul, MN). Cardiovascular endurance assessments were performed on a Quinton model 65 treadmill (Bothell, WA). Muscular strength assessments used the following exercises: leg extension, seated leg curl, lat pull down, and seated chest press. The strength assessments were performed on LifeFitness (Schiller Park, IL) and Quantum (Stafford, TX) weight training machines, as well as free weights.

The resistance exercise portion of the exercise protocol was performed using LifeFitness (Schiller Park, IL), Quantum (Stafford, TX), or Hammer Strength (Schiller Park, IL) weight training equipment with some exercise variations performed with free weights (hand dumbbells), elastic bands, and/or therapeutic balls (fit balls).

Exercise intervention protocol

The exercise intervention assigned to the exercise group started during week six of the study, approximately three weeks prior to the administration of the first cancer treatment, and lasted until week twenty. All the exercise sessions were conducted at the Rocky Mountain Cancer Rehabilitation Institute and/or at the University of Northern Colorado Campus Recreation Center at no cost to the subject. Subjects assigned to the exercise group exercised two times per week for a period no longer than 60 minutes. The rest period between exercise sessions was at least 48 hours, but no longer than 84 hours. Subjects followed an individually prescribed exercise intervention program designed in accordance with the recommendations of the American College of Sports Medicine (ACSM) exercise guidelines for special and elderly populations(12) and specific guidelines published in Exercise and Cancer Recovery(13). Because of the age range criteria for participation in the study, as well as the lack of specific guidelines for exercise in cancer patients, the above guidelines were believed to be the most appropriate for the population used in this investigation.

All subjects assigned to the exercise group performed exercises at sub-maximal intensities that were determined according to the results of their physical assessments. These subjects performed exercises with intensities varying between 40%-60% of their predicted maximum exercise capacity for each type of exercise. Each of the individualized exercise prescriptions was based on results of the fitness assessment administered at the beginning of the study. A trained cancer exercise specialist from the University of Northern Colorado School of Sport and Exercise Science (graduate and undergraduate level) monitored and conducted each exercise session with the subjects. The design of the exercise intervention included both cardiovascular and resistance training as well as flexibility training. The format for each exercise session followed an initial administration of a cardiovascular activity (approximately 6-12 minutes) that included walking on a treadmill, the use of a cycle ergometer, or elliptical equipment, followed by an entire body stretching session (5-10 minutes), resistance training (15-30 minutes), and a cool down period that included stretching activities for approximately 8 minutes.

The administration of resistance training in the design was emphasized because resistance training is the type of exercise that promotes changes in muscular strength, attenuating the loss of lean body mass, usually associated with a variety of catabolic conditions including cancer(14). Eight to twelve different types of resistance exercises that use all major muscle groups were utilized and administered from large to smaller muscle groups. The resistance exercises that were assigned to the exercise group included: 1) lateral raises, 2) frontal raise, 3) horizontal chest press, 4) lat pull down, 5) alternating biceps curls with dumbbells, 6) triceps extension, 7) leg press, 8) leg extension, 9) leg curl, 10) standing calf raise, and 11) crunches.

For the development of a training effect, the increases in load during the experiment followed the ACSM progression models(15) for resistance exercise training methods. The number of repetitions for each exercise ranged from six to twelve repetitions. During the first week of exercise, all subjects assigned to the exercise group performed only one set of each exercise prescribed for the sessions. Subjects progressively advanced to perform two to three sets for each exercise, which were administered until the end of the study. The movements for each exercise were performed at a moderate speed (three seconds of the concentric phase and three seconds of the eccentric phase of the movement during each repetition for each exercise). The rest interval period between each set, and between each exercise, varied from 60 seconds minimal to according to each subjects need.

Statistical analyses

Statistical evaluation of the data was measured using a 2 x 2 mixed model analysis of variance [time (pre and post) x group (experimental and control)] with an independent *t*-test *post-hoc* procedure for all measurements. The probability level of statistical significance was set at $P < 0.05$ in all comparisons. A Data were entered into a personal computer and statistical procedures performed using the SPSS statistical package (v. 10.0). Descriptive statistics were expressed as means ± SD.

RESULTS

Statistical analysis reported no significant difference between groups at the beginning of the study (table 1). The descriptive statistics for the analysis of the variable overall muscular strength for each group are presented in table 3.

TABLE 3
Descriptive data for overall muscular strength during the study (n = 20)

	Group	Mean (kg)	Standard deviation
Prior to surgery	Control	103.3	16.0
	Exercise	106.2	5.0
Post intervention	Control	102.7	15.2
	Exercise	116.3*	8.9

* p < 0.05 *vs* Control group.

No significant changes were observed in either group on the dependent variable overall muscular strength over the course of the study, F-value, $F(1, 18) = 2.340$ with $p = 0.144$ ($\alpha = 0.05$). The result of the ANOVA design however, presented a significant interaction effect between the variable overall muscular strength and the exercise and control groups across time ($p = 0.000$).

Post hoc analyses using independent-sample T-Tests revealed significant differences between groups at the end of the study at the final assessment ($p = 0.025$).

Significant differences in fatigue was observed in the exercise and control groups from the time of diagnosis throughout the period that encompassed the entire study, F-value, $F(1, 18) = 8.910$ with $p = 0.008$ ($\alpha = 0.05$). The results of *Post hoc* revealed significant differences in fatigue scores were between the exercise and control groups at assessment 3 (the first assessment during treatment, $p = 0.001$), assessment 4 (the second assessment during treatment, $p = 0.005$) and at the end of the study during the final assessment ($p = 0.001$). The descriptive statistics for the analysis of fatigue during the study for each group is presented in table 4.

TABLE 4
Descriptive data for fatigue during the study (n = 20)

Assessments	Group	Mean	Standard deviation
1) Pre-Surgery	Control	1.21	1.29
	Exercise	1.28	0.90
2) Post-Surgery	Control	1.39	0.83
	Exercise	2.19	1.79
3) 1st Treatment	Control	2.57	1.44
	Exercise	0.69**	0.47
4) 2nd Treatment	Control	3.95	1.66
	Exercise	1.53**	1.76
5) 3rd Treatment	Control	3.45	1.93
	Exercise	2.75	2.06
Final Assessment	Control	3.23	1.16
	Exercise	0.84**	1.13

* $p < 0.05$ *vs* Control group; ** $p < 0.01$ *vs* Control group.

Even though fatigue changes observed between groups were significant different during assessment 3 (the first assessment during treatment, p = 0.001), assessment 4 (the second assessment during treatment, p = 0.005) and at the end of the study during the final assessment, p = 0.000, with the exercise group experiencing lower levels of fatigue when compared to the control group, no significant relationship between the change in fatigue and change in overall body strength in the exercise group during the study was observed. The variables that were included in the Pearson Product-Moment correlation model were: Δ_S = Overall muscular strength final assessment – overall strength pre-surgery and Δ_F = Fatigue levels final assessment – fatigue levels pre-surgery. The results of the correlation analysis are presented in table 5.

TABLE 5
Pearson product-moment correlation between fatigue and overall muscular strength in the exercise group (n = 10)

		Change in fatigue scores
Change in Overall Strength	**Pearson Correlation**	–0.11
	P value	0.76

DISCUSSION

Fatigue has been reported by previous research to be the most common side-effect observed in cancer patients that undergo cancer treatment[6]. When fatigue in cancer patients interferes with normal daily activities, persists for many years after cancer treatment, and/or becomes severe enough that patients are forced to reduce their physical activity levels, a pathological condition has developed[6]. Decreases in physical activity levels cause further decline in key physiological and psychological facets which initiates a downward spiral into disability. To mitigate this process, exercise has been used as an adjunct therapy to prevent further disability thus helping patients to improve their quality of life[16].

One of the mechanisms believed to contribute to the development of fatigue in cancer patients is the progressive loss of muscle mass. Unfavorable prognosis and reduction in survival time as well as decreased responsiveness and tolerance to cancer treatments have been associated with significant loss of muscle mass[17,18]. This loss diminishes muscular strength, impacts metabolism negatively, and reduces the ability of patients to perform even the simplest daily living activities.

The results of the present study did not agree with previous research where significant increases in overall muscular strength in cancer patients participating in the exercise intervention were observed[19-21]. The reason for the contradictory results observed in the present study may be attributed to the small sample size, the muscular strength assessment protocol, and/or duration and intensity of the exercise protocol used in the study. In a study by Kolden *et al.*[20], forty breast cancer patients underwent an exercise intervention consisting of one hour sessions of warm-up, aerobic, resistance, and cool-down exercises three days a week for sixteen weeks. Kolden *et al.*[20] found significant changes in muscular strength in women who adhered to the exercise program during the study. The protocol of the present study was similar to Kolden *et al.*[20], however, the lower number of subjects (twenty, with ten in the exercise group and 10 in the control group), and the lower frequency of the administration of the exercise intervention of only two days a week may have been the reason for the different results among the two studies.

Adamsen *et al.*[19] examined the effects of an exercise program involving high intense training (cycling at 60-100% of age predicted maximum and three sets of five to eight repetitions at 85-95% 1 RM), three times a week for twenty-three subjects with various types of cancer. This study found significant changes in muscular strength with gains of 33% over the course of the study. The authors concluded that an exercise program involving higher intensities can be safe for cancer patients undergoing treatment, and that no physical discomfort was reported when physical training occurred the day prior, or on the day of treatment.

The overall exercise intensity used in the present study may have contributed for the non-significant changes observed in overall muscular strength in the exercise group from the period of diagnosis until the completion of the study. However, the significant differences in overall muscular strength observed between groups at the end of the study do agree with the results of previous studies where an exercise protocol involving resistance training presented overall muscular strength changes in cancer patients during treatment. At the end of the study, even though not statistically significant, the exercise group experienced an increase of approximately 10% in overall muscular strength while a slight decrease of 0.61% was observed in the control group. The reason for the small but important changes in overall muscular strength observed in both groups can be attributed to the type of muscular strength assessment protocol adopted during the study. The Kuramoto and Payne[10] submaximal protocol, designed to assess muscular strength is a protocol recommended for use in frail and elderly populations. Even though pilot data was gathered before the implementation of the protocol in the present study, to ensure the efficiency of the protocol in measuring muscular strength in breast cancer patients, some subjects after enrollment in the study were not able to perform the exercise bench press prior to surgery or at the end of the experiment. Therefore, the results of the analyses of the bench press exercise, which was included in the overall muscular strength model, may have affected the results of the analyses. Regardless of the non-statistically significant result observed for changes in overall muscular strength in either of the groups at the end of the study, the significant differences found between groups, with the increases of approximately 10% in the exercise group indicate that more research is needed to allow researchers to developed exercise assessment and protocols specifically designed for cancer patients with the goal of maximizing the benefits of resistance exercise for this population. If the present study had included a larger sample size, higher exercise intensity and duration, and an assessment protocol that would not limit the precision of the assessment of muscular strength, the results could have possibly been different.

Regarding changes in fatigue levels, the results of the present study are in agreement with many previous studies that reported significant reductions on fatigue in cancer patients that exercise while undergoing cancer treatment[5,7,16]. Courneya *et al.*[16] studied breast cancer survivors who cycled three times a week for 15 weeks on upright or recumbent bikes. Results from surveys demonstrated a lowering of fatigue levels for the exercise group after the intervention. Mock *et al.*[5] used the PFS scale, on fifty-two breast cancer patients who participated in a walking program five to six times a week for the duration of their treatment. Results showed a significant increase in fatigue scores for the low-walk group as compared to the high-walk group. Segal *et al.*[7] was one of the very few groups of researchers that explored the effect of an exercise protocol involving resistance training on changes in fatigue in men with prostate cancer. Segal *et al.*[7] used the Functional Assessment of Cancer Therapy-Fatigue survey during twelve weeks of a resistance training program. The results showed a significant decrease in fatigue for the exercise group when compared to the control group.

A significant difference observed in fatigue scores in the present study for the exercise group compared to the control group after the first and second chemotherapy treatments and at post intervention leads one to surmise that the exercise protocol emphasized with resistance training played a possible role in decreasing treatment-related fatigue. The difference in fatigue scores in this study between groups suggests that this exercise protocol, emphasizing resistance training, decreases treatment-related fatigue. After the exercise group reached the highest levels of fatigue during treatment three, the levels of fatigue returned to almost the same levels observed during treatment one while the control group kept the levels of fatigue high at the end of the experiment. The reason for this drastic increase in fatigue in both groups at treatment is difficult to explain. The accumulation of necrotic load produced by the toxicity of chemotherapy at a particular point during treatment, lead patients to reach a peak in fatigue that in this study was observed at treatment three. However, the peak in fatigue observed in the exercise group was lower than the control group.

The significant difference observed in fatigue between groups during the first treatment, may be attributed to the exercise program, since subjects in the exercise group had already begun their exercise program approximately three weeks prior to the first treatment. The exercise program administered during the weeks prior to the beginning of treatment may have elicited some early physiological adaptations contributing to the improvement in the efficiency of the cardiovascular, pulmonary, endocrine, and musculoskeletal systems. These possible early physiological adaptations may have contributed for improvements in oxygen consumption, cardiac output, and metabolic rate, all of which could have potentially influenced the decrease in fatigue. The most significant difference in fatigue levels between groups, however, was observed at the end of treatment, suggesting that all of the possible physiological adaptations caused by the prescriptive exercise intervention significantly impacted the reduction of overall fatigue levels experienced by the exercise group. Also, if the study had a longer duration, the reduction observed in the exercise group could have been even more accentuated. In agreement with the results presented by Segal *et al.*[7], an exercise protocol involving the utilization of resistance training in the design should be further explored as a possible venue in the combat of fatigue in cancer patients.

Of all the studies involving the administration of exercise with the goal of combating fatigue and improving gains in muscular strength, none attempted to correlate the two variables to determine if a relationship exists between the changes in strength and changes in fatigue. Interestingly, no significant correlations were found for either the exercise or the control groups. The results of the non-significant correlations observed in this study may be explained by the fact that cancer treatment-related fatigue is multifactorial and complex. The results of the correlation may indicate that improvements in various physiological systems in the body are necessary to offset the debilitating fatigue experienced by cancer patients during treatment. Factors such as energy imbalance, ongoing stress and pain, sedatives, and possible depression are all important factors in determining the cause of a cancer patient's fatigue.

Many studies researching fatigue in cancer patients have used aerobic only protocols, or combination exercise protocols incorporating aerobic and resistance training[5,16,22]. Most of these studies found a significant lowering of fatigue in the exercise group; leading to a conclusion that while resistance training is beneficial for the development of muscular strength, a program including both aerobic and resistance training seems to be the most appropriate protocol in reducing cancer treatment-related fatigue. In this study, the protocol emphasized with resistance training was very successful in lowering fatigue and in promoting significant differences in overall muscular strength between groups, however, the association between reduction in fatigue and muscular strength could not be established. Many limitations, such as small sample size, type of strength assessment, duration and intensity of the exercise intervention, could have possibly affected the outcome of the study. Therefore, further research is needed to explore resistance training as a possible intervention in assisting patients in the combat of fatigue. The results of this study suggests that a combination of exercises involving cardiovascular endurance, resistance training, and flexibility can be effective in reducing fatigue levels and increasing muscular strength in breast cancer patients undergoing treatment.

CONCLUSION

In conclusion, an exercise protocol emphasized with resistance training seemed to be beneficial for the increase of muscular strength and to reduce fatigue in breast cancer patients undergoing treatment. Further research is needed to explore the benefits of resistance training within the cancer population as well as to establish the most appropriate exercise protocol in the combat of fatigue and loss of muscular strength in cancer patients.

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