Oxidative Stress and Fitness Changes in Cancer Patients after Exercise Training

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ABSTRACT

REPKA, C. P., and R. HAYWARD. Oxidative Stress and Fitness Changes in Cancer Patients after Exercise Training. *Med. Sci. Sports Exerc.*, Vol. 48, No. 4, pp. 607–614, 2016. **Introduction**: The purpose of this study was to determine the effect of an exercise intervention (EX) on muscular strength, cardiorespiratory fitness (CRF), and oxidative stress in cancer survivors compared with a nonexercising cancer control group (CON). **Methods**: Fifteen cancer patients and seven age-matched individuals with no history of cancer (NC) participated in this study. A blood draw and assessments of muscular strength and CRF were administered to cancer survivors within 6 wk of completing radiation or chemotherapy, and again 10 wk later. Eight cancer patients completed a 10-wk supervised exercise intervention, whereas seven continued standard care. Baseline oxidative stress was compared between cancer patients and the NC group. Changes in plasma protein carbonyls, 8-OHdG, and Trolox equivalent antioxidant capacity were compared between groups using repeated-measures ANOVA, and correlations between fitness and oxidative stress changes were evaluated. **Results**: Baseline antioxidant capacity was significantly lower, and plasma protein carbonyls were significantly higher in cancer patients compared with NC ($P = 0.001$). EX had a significant increase in antioxidant capacity ($P < 0.001$) and decrease in protein carbonyls ($P = 0.023$), whereas CON did not. Improvements in composite arm (41%, $P = 0.002$) and leg strength (34%, $P = 0.008$), isometric handgrip strength (11%, $P = 0.015$), and $\dot{V}O_{2peak}$ (16%, $P = 0.018$) were significant in EX but not in CON. 8-OHdG changes were significantly correlated with changes in $\dot{V}O_{2peak}$ ($r = -0.89$, $P < 0.001$), arm strength ($r = -0.67$, $P = 0.004$), and leg strength ($r = -0.56$, $P = 0.019$). **Conclusion**: A whole-body exercise intervention for cancer survivors may be an effective method of concurrently increasing muscular strength, CRF, and antioxidant capacity while decreasing markers of oxidative stress. **Key Words:** CANCER REHABILITATION, ANTIOXIDANT CAPACITY, MUSCULAR STRENGTH, CARDIORESPIRATORY FITNESS

Between 1990 and 2010, cancer-related mortality dropped from 215 to 172 deaths per 100,000 persons, demonstrating improved efficacy of cancer treatment methods (18). Although this is an encouraging trend, the adverse side effects of surgery, radiation, chemotherapy, and other treatment modalities are associated with severe physiological side effects that may last for years. Typical side effects include muscle dysfunction (9) and reduced cardiorespiratory fitness (CRF) (6). Although these decrements are multicausal and multifactorial, oxidative stress is thought to play a pivotal role in many pathological processes associated with cancer and its treatments (1,26,43,45).

Oxidative stress is a state in which reactive oxygen species (ROS) are produced at a rate that exceeds cellular adaptive and repair capacities. The interrelationship between oxidative stress and cancer is complex. The development and progression of cancer is associated with high levels of oxidative stress-induced DNA modification (43), but cancer cells themselves can produce increased levels of ROS, perpetuating dysfunction and cancer growth (16). In certain cancers, this allows for therapeutic selectivity, and many modes of cancer treatment depend on extremely high doses of ROS as a mechanism of cancer killing, including radiation and several chemotherapy regimens (24).

Unfortunately, treatment-associated oxidative stress typically affects healthy tissue in addition to malignant tissue, resulting in both acute and chronic side effects (8,25). Doxorubicin (DOX), for instance, is a highly effective antineoplastic agent used for treatment of various cancers, yet causes a dose-dependent cardiotoxicity associated with oxidative stress (7,23). Similarly, DOX has been shown to elicit a similar degree of dysfunction in skeletal, smooth, and cardiac muscle tissues (15). Although the primary antineoplastic mechanisms of DOX are inhibition of topoisomerase II and intercalation in DNA (8), resulting in inhibition of DNA replication and RNA transcription, the induction of ROS may contribute to antitumor activity (42). Other common chemotherapy drugs, including tamoxifen, etoposide, 5-fluorouracil, alkylating agents, and platinum coordinating complexes, are known to induce significant oxidative stress,

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either as an antineoplastic mechanism or as a side effect (8,10). For example, 5-fluorouracil generates p53 pathway-derived mitochondrial ROS (19), whereas mitochondrial nitric oxide synthase is responsible for tamoxifen-induced oxidative stress and mitochondrial apoptosis (29). Radiation, by nature, is characterized by ROS production and exerts its physiological effects, both beneficial and harmful, via this mechanism (4). Muscular dysfunction in cancer patients is likely caused by numerous factors, including physical inactivity, malnutrition, inflammatory cytokines, oxidative stress, and advanced age (9). Numerous studies link cancer and treatment-related ROS production with cachexia, among other potential mechanisms (25,27).

Exercise has been shown to attenuate many side effects of cancer treatment, including chemotherapy and radiation-induced reductions in CRF (22,39) and muscular strength (37,38). Exercise may, in part, show its rehabilitative effects by preferentially increasing antioxidant capacity in the tissues that are stressed by exercise. For instance, in healthy individuals, unilateral leg exercise resulted in increased antioxidant enzyme activity in the trained leg but not the untrained leg (31). Because of these localized changes, it may be surmised that antioxidant capacity should increase in active tissue, but not in cancer cells.

Minimal research has been published regarding exercise-associated changes in oxidative stress in cancer patients. The existing studies investigating this relationship in human cancer populations are not in agreement, because both increases and decreases in oxidative stress have been reported (2,21). Animal models provide us with more compelling evidence that exercise-induced alterations in oxidative stress can influence CRF and muscular strength improvements after cancer treatments. Kanter et al. (23) found that a swim-training protocol in rats improved antioxidant capacity and counteracted DOX-mediated cardiotoxicity. Ascensão et al. (3) mirrored these results and also found that cardiac damage, evaluated by cardiac troponin I presence in the plasma, and cardiac muscle protein carbonyls were significantly lower in exercise-trained mice treated with DOX than non–exercise-trained mice treated with DOX. More recently, Smuder et al. (41) found that exercise training in rats protects against DOX-associated increases in both protein carbonyls and proteolysis in skeletal muscle tissue. Although research on the protective mechanisms of exercise against chemotherapy-induced oxidative stress has decidedly been focused on DOX, there is recent evidence that exercise elicits similar protective benefits in cancer patients treated with cisplatin (17), and in an animal model, reduced cisplatin toxicity was associated with improved antioxidant capacity (44). Similarly, in mice, exercise preconditioning improved the antioxidant response to radiation exposure (13), but this effect has not been sufficiently investigated in humans. To address the lack of human research on the potential role that oxidative stress has in the restorative effects of exercise after cancer treatment, this study sought to investigate the effects of a 10-wk exercise intervention on CRF, muscular strength, and plasma markers of protein oxidation, DNA oxidation, and antioxidant capacity.

METHODS

Fifteen cancer patients and seven healthy age-matched individuals with no history of cancer or other chronic diseases participated in the study. This study consisted of a 10-wk prescribed exercise intervention in an exercise group (EX, $n = 8$), whereas a control group (CON, $n = 7$) had standard care for the study period. Noncancer healthy controls (NC, $n = 7$) had a single baseline blood draw taken, because this group represented a healthy population control of oxidative stress values, whereas cancer patients had pre- and postintervention blood draws taken. Cancer patients had completed cancer treatments that have previously been shown to induce oxidative stress, namely, radiation or chemotherapy treatment, within the previous 6 wk, with an average time out of treatment of 4 wk. Participants were recruited from walk-in and oncologist-referred patients at the Rocky Mountain Cancer Rehabilitation Institute at the University of Northern Colorado (UNC) in Greeley, CO, and were admitted to study groups based on the date of initial contact (pseudo-randomization). The UNC Institutional Review Board approved all procedures, and written informed consent forms were signed by all participants.

Twenty-six cancer patients made contact with the primary investigator, but exclusion criteria or attrition resulted in the loss of 11 potential participants. Four patients failed to schedule future appointments after initial contact or appointment, four patients were unwilling to participate after initial contact, one patient was diagnosed with brain metastasis after initial blood draw but before initial assessment, one patient returned to chemotherapy 4 wk into the exercise intervention, and one patient was excluded after initial contact because she did not meet the inclusion criteria (too physically active). All cancer diagnoses were considered for this study, but participants were required to have undergone radiation or a chemotherapy treatment explicitly known to elicit oxidative stress, either as a side effect or as an antineoplastic mechanism. Chemotherapy agents included antineoplastic antibiotics, alkylating agents, platinum coordinating complexes, epipodophyllotoxins, fluorouracil, and tamoxifen (8,11,26). Cancer patient inclusion criteria consisted of the following: 1) completed radiation or approved cancer therapy regimen within 6 wk of initial blood draw; 2) currently sedentary (less than 2 $d \cdot wk^{-1}$ of 20 min of aerobic or resistance exercise); 3) have not been consistently supplemented with dietary antioxidants, including vitamins C and E, in the previous month, with no supplementation in the 72 h before blood draws; 4) nonsmoker for at least 2 months; and 5) were able to walk comfortably on a treadmill.

NC participants were primarily recruited from among the faculty and staff at the UNC via campus-wide email and by word of mouth. Inclusion criteria for the noncancer group

consisted of the following: 1) currently sedentary; 2) no history of cancer or other major chronic diseases; 3) have not been consistently supplemented with dietary antioxidants in the previous month, with no supplementation in the 72 h before blood draws; and 4) nonsmoker.

The day before the cancer patient's initial exercise assessment, a 12-h fasting blood sample was taken by the primary investigator or an otherwise experienced phlebotomist. For all three groups, participants were asked to avoid exhaustive exercise and antioxidant supplementation 72 h before all blood draws.

Maximal treadmill testing. An internally validated multistage graded exercise test developed specifically for cancer patients was administered to each participant before and after the 10-wk intervention to evaluate CRF. This protocol starts at 1.0 mph and 0% grade, and the workload increased by approximately 0.5 metabolic equivalents (METs) every minute throughout the test. Instructions regarding the specific changes in speed and grade during each 1-min stage were given, and the participant was encouraged to walk or run until exhaustion or volitional fatigue (to $\dot{V}O_{2peak}$). Before each incremental treadmill test, participants were fitted with a heart rate (HR) monitor (Polar Inc., Lake Success, NY). Blood pressure was assessed at rest, every 3 min during exercise, immediately postexercise, and after 3 min of recovery (slow walking). RPE was assessed every 3 min of exercise, according to Borg's 1–10 scale. HR and oxygen saturation SaO_2 were assessed at the end of every 1-min stage. Participants were asked to use handrails only if it was required for balance support. If handrails were required for support, participants were asked to use them throughout the test. American College of Sports Medicine metabolic equations were used to quantify $\dot{V}O_{2peak}$ at time of volitional fatigue (33).

Muscular strength assessment. The Brzycki equation [one-repetition maximum (1RM) = weight lifted (lb)/ 1.0278 − (repetitions to failure × 0.0278)] was used to estimate 1RM using the number of repetitions of a given submaximal load to fatigue, provided that the repetitions do not exceed 10 (5). Muscular strength was assessed using the lat pull-down, shoulder press, chest press, seated row, leg press, leg extension, and leg curl exercises, using Cybex® resistance training equipment (Cybex International, Medford, MA). The goal was to choose a weight that elicited muscle failure in four to six repetitions. Repetitions were performed without resting until muscle failure, or until the participant's form deteriorated. If the participant exceeded 10 repetitions for any exercise, after an approximately 3-min rest period, the resistance was increased to a weight that could elicit muscle failure in less than 10 repetitions. For the purposes of data analysis, a composite score (sum of weight lifted) was used for upper body strength (lat pull-down, shoulder press, chest press, and seated row) and lower body strength (leg press, leg extension, and leg curl). After the predicted 1RM testing, a Takei TKK 5101 handgrip dynamometer (Takei Scientific Instruments, Tokyo, Japan) was used to evaluate maximal isometric handgrip strength in both hands.

Exercise intervention. Each EX participant completed a 10-wk exercise intervention that was individually supervised by a cancer exercise specialist 3 $d \cdot wk^{-1}$. Each 1-h session was prescribed by the cancer exercise specialist in accordance with the participant's assessment results and goals, and progression was based on feedback from previous exercise sessions. Exercise sessions varied depending on the participant's health and fitness status, but typically included a 5-min warm-up, 25 min of aerobic exercise, 25 min of resistance training, and 5 min of flexibility and balance training. Blood pressure and HR were measured at the beginning and end of the exercise session, and HR, RPE, and SaO_2 were monitored throughout. Initial aerobic exercise intensity was based on the HR and $\dot{V}O_{2peak}$ results from the initial graded exercise test and was at a generally low to moderate intensity, ranging from 40% to 60% of HR reserve (HRR), or an RPE 4–5. The Karvonen method was used to determine target exercise HR intensity using the formula [(220 − age) − resting HR] × percent of exercise intensity + resting HR]. The mode of aerobic exercise selected for each participant was based on the mode offering the greatest anticipated benefit based on participant goals and physiological limitations. Options included outdoor or treadmill walking, stationary cycling, or recumbent stepping. Although the rate of progression varied significantly by participant, cancer exercise specialists aimed to increase speed or resistance weekly, while keeping HR values below 75% HRR.

At the beginning of the intervention, the initial percent of 1RM corresponded with the percent of HRR values for aerobic exercise, based on the initial health and fitness status (40%–50% 1RM for low fitness, 50%–60% for average fitness). Cybex Eagle Selectorized Strength Machines© (Cybex International Inc.), free weights, resistance bands, and body weight exercises were all used for the exercise intervention, depending upon fitness, mobility, and comfort of the participant. Muscular endurance was emphasized over hypertrophic training because participants performed 8–15 repetitions per set and typically ended each set at muscular fatigue rather than muscle failure. Resistance was increased when 8–15 repetitions no longer resulted in muscular fatigue.

All participants were asked to avoid any substantial changes in their diet, assuming a physician or nutritionist did not prescribe a change in eating habits. Participants in the standard care control group were asked to maintain their exercise habits during the 10-wk study period. Although standard care cannot be "standardized" between hospitals and patients, it did not involve routine systematic exercises. Control participants were asked to complete an exit survey inquiring about any changes in physical activity, dietary habits, medications, and medical procedures. After the 10-wk study period, control participants had the opportunity to enroll in the exercise-based cancer rehabilitation program at Rocky Mountain Cancer Rehabilitation Institute for 3 months at no cost.

Blood handling and analysis. A minimum of 4 mL of blood was withdrawn into sterile tubes containing potassium-EDTA and immediately put on ice. Samples were centrifuged

at 3000 rpm for 10 min, and the plasma was separated and stored at −80°C until analysis. All samples were assayed in duplicate on the first thaw. Oxidative protein and DNA damage, as determined by reactive carbonyl derivative and 8-OHdG, respectively, were measured in plasma using an enzyme-linked immunosorbent assays according to the procedures recommended by the manufacturer (Cell Biolabs, Inc., San Diego, CA). Antioxidant capacity was measured in plasma using the Trolox equivalent antioxidant capacity assay performing procedures outlined by the reagent provider (Sigma Chemical, St. Louis, MO).

Statistical analyses. Data are presented as means ± SD. Participants' baseline characteristics in the two cancer groups (EX versus CON) and the NC group were compared using independent *t*-tests. A repeated-measures 2 (group) × 2 (pre- and postintervention) ANOVA with Bonferroni *post hoc* test was used to identify differences within (across time) and between the two groups related to protein and DNA oxidation, antioxidant capacity, $\dot{V}O_{2peak}$, and muscular strength. A Kolmogorov–Smirnov test was used to ensure that the normality assumption was met for this data set. Spearman correlation coefficients were calculated to determine associations between baseline markers of oxidative stress and baseline CRF and muscular strength. Additionally, Spearman correlation coefficients were calculated to determine the relationship between postintervention changes in markers of oxidative stress and postintervention changes in CRF and muscular strength. A significance level of $\alpha = 0.05$ was used for all statistical analyses. Statistical analyses were conducted using GraphPad Prism (Version 5; GraphPad Software, Inc, La Jolla, CA).

RESULTS

Baseline participant characteristics for the EX, CON, and NC groups are summarized in Table 1. The two cancer groups had statistically similar height, weight, body mass index (BMI), and time out of treatment, and no significant differences in age or body composition were found between the three groups. Although exit surveys in control participants indicated no notable changes in dietary habits, qualitative physical activity in this group increased from baseline because, even in the absence of an exercise intervention, time out of treatment resulted in more vigor for activities of daily living and leisure time activity. Increases in housework, light yard work, and walking were most commonly reported, but no control participants reported participation in a structured exercise program. One male control participant failed to complete a reassessment of fitness despite completing both blood draws.

Data for muscular strength, CRF, protein carbonyls, 8-OHdG, and antioxidant capacity are found in Table 2. At baseline, the plasma antioxidant status did not differ between EX and CON but was significantly lower in cancer patients compared with NC ($P = 0.001$). Similarly, plasma protein carbonyl concentrations did not differ between cancer groups but were significantly higher in cancer patients than NC ($P = 0.027$). 8-OHdG did not differ between any of the three groups at baseline. Neither EX or CON demonstrated changes in body weight or BMI at reassessment.

TABLE 1. Subject characteristics.

	Exercise	Control	Noncancer
N	8	7	7
Age (yr)	64.0 ± 10.8	62.4 ± 9.7	55.1 ± 9.7
Females	7	4	5
Males	1	3	2
Height (inches)	65.4 ± 2.5	66.8 ± 4.7	66.3 ± 3.3
Weight (lb)	174.0 ± 32.3	179.5 ± 40.8	171.0 ± 21.5
BMI	28.4 ± 4.3	28.1 ± 3.8	27.4 ± 3.4
Primary treatment			
Radiation	4	4	—
Chemotherapy	3	4	—
Cancer type	Hodgkin's lymphoma (1), pancreatic (1), ovarian (1), breast (5)	Non-Hodgkin's lymphoma (1), leukemia (1), squamous cell carcinoma (1), uterine (1), colon (1), breast (2)	
Days out of treatment	29.9 ± 18.6	31.4 ± 21.7	—
Adherence rate (%)	83.9 ± 12.8	NA	—

Data are presented as mean ± SD. No significant differences existed between the groups.

Pre- to postintervention increases in antioxidant capacity were significant in EX (+39%, $P < 0.001$) but not in CON (+23%). Protein oxidation was significantly diminished over time in EX (−35%, $P = 0.023$), whereas no such response was apparent in CON (−5%). Although no significant within-group changes in 8-OHdG occurred over time in EX or CON, an interaction effect between the two groups was detected ($P = 0.023$), because values decreased 38% in EX and increased 40% in CON. After the 10-wk study period, EX no longer differed significantly from NC for protein oxidation ($P = 0.372$), and neither EX ($P = 0.248$) nor CON ($P = 0.111$) differed in antioxidant capacity from NC.

Strength parameters did not significantly correlate with antioxidant capacity, protein oxidation, or 8-OHdG at baseline. Both composite arm ($P = 0.002$) and leg ($P = 0.008$) strength improved significantly in EX, with 41% and 34% increases, respectively. There were essentially no changes in arm (+3%) or leg strength (−0.3%) in the control group. Accordingly, a significant time–group interaction effect was present for both arm ($P = 0.005$) and leg ($P = 0.009$) strength. Handgrip strength gains in EX (+11%) were less compelling, but this change was significant nonetheless ($P = 0.015$). Although CON exhibited a 6% mean increase in handgrip strength, this result was not statistically significant. An analysis of individual strength exercises revealed significant increases in all exercises other than the leg curl in the EX group, but no significant changes in the CON group. Furthermore, a significant interaction effect between CON and EX was apparent in all exercises other than leg curl and seated row. Initial $\dot{V}O_{2peak}$ exhibited a significant negative correlation ($r = -0.71$) with baseline antioxidant

TABLE 2. Changes in fitness and blood parameters.

	NC (N = 7)	EX (N = 8)		CON (N = 6)	
		Pre	Post	Pre	Post
Fitness parameters					
Composite arm strength (lb)	—	230.4 ± 91.4	324.4 ± 125.2[a,c]	273.3 ± 148.1	280.1 ± 165.7
Lat pull-down	—	75.1 ± 13.4	102.6 ± 15.5[a,c]	90.4 ± 39.4	89.9 ± 40.3
Shoulder press	—	34.0 ± 14.7	53.7 ± 18.6[a,c]	46.6 ± 29.2	48.3 ± 33.4
Chest press	—	51.3 ± 24.6	77.8 ± 31.4[a,c]	62.5 ± 46.8	68.6 ± 50.6
Seated row	—	69.9 ± 8.5	90.2 ± 8.3[b]	73.2 ± 36.5	73.6 ± 44.4
Composite leg strength (lb)	—	332.3 ± 130.9	445.5 ± 157.2[a,c]	348.1 ± 166.3	346.9 ± 164.4
Leg curl	—	74.1 ± 16.7	89.2 ± 10.1	82.3 ± 36.8	82.8 ± 40.4
Leg extension	—	81.3 ± 26.5	113.8 ± 22.0[b,c]	88.9 ± 48.1	73.3 ± 61.6
Leg press	—	176.9 ± 39.2	242.6 ± 33.5[a,c]	177.0 ± 84.9	172.5 ± 69.9
Handgrip strength (lb)	—	25.8 ± 4.8	28.6 ± 6.0[b]	25.6 ± 9.7	26.8 ± 10.0
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	—	20.1 ± 9.7	23.4 ± 10.9[b]	18.1 ± 4.4	18.8 ± 6.1
Blood parameters					
Trolox equivalent antioxidant capacity (mM Trolox)	0.37 ± 0.07	0.28 ± 0.07[d]	0.39 ± 0.05[a]	0.26 ± 0.05[d]	0.32 ± 0.08
Protein carbonyls ($nmol \cdot mg^{-1}$)	0.89 ± 0.25	1.30 ± 0.44[e]	0.84 ± 0.33[b]	1.18 ± 0.42[e]	1.12 ± 0.22[e]
8-OHdG ($ng \cdot mL^{-1}$)	0.33 ± 0.18	0.47 ± 0.33	0.29 ± 0.18[c]	0.35 ± 0.14	0.49 ± 0.22

Data are presented as mean ± SD.
[a]Significantly higher than the baseline ($P < 0.01$).
[b]Significantly higher than the baseline ($P < 0.05$).
[c]Significant time–group interaction with the control group ($P < 0.05$).
[d]Significantly lower than NC ($P < 0.01$).
[e]Significantly greater than NC ($P < 0.05$).

capacity ($P = 0.001$), but not with baseline protein carbonyls ($P = 0.101$), or 8-OHdG ($P = 0.422$). Predicted $\dot{V}O_{2peak}$ increased 16% in EX, representing a significant increase over time ($P = 0.018$), whereas this parameter remained constant (+3.9%) in CON ($P = 0.365$). There was no significant time–group interaction between these two groups. At reassessment, significant negative correlations between changes in 8-OHdG and $\dot{V}O_{2peak}$ ($r = -0.89$, $P < 0.001$), arm strength ($r = -0.67$, $P = 0.004$), and leg strength were revealed ($r = -0.56$, $P = 0.019$). No significant correlations were found between changes in fitness parameters and changes in protein carbonyls or antioxidant capacity.

Adverse events and exercise adherence. Several EX participants exhibited chronic musculoskeletal limitations at baseline, including osteoarthritis, rheumatoid arthritis, and complications associated with previous surgery (including knee surgery, hip replacement, double mastectomy, wrist surgery, lumbar fusion, and Whipple procedure for pancreatic cancer). Because of the individualized nature of the exercise intervention, modification of the exercise program was sufficient to allow for continued exercise participation and completion of the intervention in all EX participants. Overall, exercise adherence was high, with participants attending 84% ± 13% of the scheduled sessions. One participant missed three sessions during the intervention because of hip pain associated with a previously failed hip replacement, and another missed two sessions because of complications with a breast expander placed after double mastectomy. Otherwise, scheduling conflicts and acute respiratory infections accounted for most missed training sessions.

DISCUSSION

The present study demonstrates that an exercise intervention in cancer patients after treatment increased muscular strength, CRF, and antioxidant capacity, and simultaneously decreased protein and DNA oxidation. Furthermore, these data indicate that time out of treatment alone did not significantly alter these variables. Few prior studies have investigated oxidative stress changes in response to exercise in cancer patients, and results have varied widely across those studies. Our results are most consistent with Allgayer et al. (2) who found that 2 wk of moderate-intensity exercise decreased oxidative stress, whereas a high-intensity exercise protocol resulted in nonsignificant increases in oxidative stress. More recently, a 14-wk high-intensity exercise intervention, which included 25-min sessions at ventilatory threshold and 60-s interval bouts at peak workload (21), increased urinary markers of oxidative stress in lung cancer patients. The positive outcomes of our current study supports the practice of an individualized low- to moderate-intensity exercise intervention as opposed to high-intensity exercise in the rehabilitation of cancer patients.

Although baseline CRF unexpectedly exhibited a negative correlation with antioxidant capacity ($r = -0.71$), this relationship trended toward positive at follow-up ($r = 0.35$). Because muscular strength and CRF are strongly influenced by age, gender, body composition, and lifetime physical activity, it is difficult to quantify cancer treatment-associated muscle damage and fitness decrements based solely on posttreatment fitness assessment. Therefore, it was not surprising that oxidative stress was not correlated with baseline strength values within a population of cancer survivors of this size. Because pretreatment muscular strength was not known, we cannot exclude the possibility that oxidative stress contributed to muscle wasting, as has been suggested in the literature (27,28).

Currently, an adequate characterization of the time course of the chronic oxidative stress status after the end of cancer chemotherapy or radiation does not exist. In mice,

extracellular malondialdehyde levels remained elevated 1 wk after chemotherapy, and oxidized glutathione was significantly higher than controls 6 wk after treatment (1), demonstrating prolonged depletion of antioxidant capacity after treatment. In rats, oxidative stress persisted a full 2 months after the cessation of DOX (35), but unfortunately, it is difficult to extrapolate these data to humans because of varying lifespans. Sabuncuoğlu et al. (36) showed that cancer patients had significantly elevated plasma carbonyl levels 14 and 28 d after chemotherapy and stem cell transplantation compared with immediately after (day 0) or 7 d after chemotherapy, but further research on the persistence of oxidative stress after cessation of treatment is sparse. Data presented here suggests that approximately 4 wk out of treatment, cancer patients have persistent elevations in protein oxidation, and this level remained elevated in CON participants 10 wk later. Interestingly, although 8-OHdG was not significantly elevated in CON or EX compared with NC at baseline, there was a divergent response over the 10 wk, because 8-OHdG levels were elevated in CON, resulting in an interaction effect. Although the change in antioxidant capacity during the intervention was not significant in CON, this variable no longer significantly differed from NC at follow-up, suggesting some degree of normalization as time out of treatment progressed.

Improved arm (+41%) and leg (+34%) strength in our EX participants is similar to the results of a multicenter randomized controlled study conducted by Courneya et al. (12), which demonstrated that an isolated resistance exercise training program increased muscular strength 25% to 35% in breast cancer patients receiving chemotherapy. The 3.3 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement in $\dot{V}O_{2peak}$ in our exercise group compared favorably with the 2.9 $mL \cdot kg^{-1} \cdot min^{-1}$ increase identified in a meta-analysis of six randomized controlled trials encompassing 344 cancer patients after various exercise interventions (22). Despite significant improvements, CRF was still classified as poor in EX after the exercise intervention, which highlights the need for normative data in cancer survivor populations (32,40). Regardless, this approximately 1 MET (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) mean improvement is clinically relevant. Gulati et al. (14) found that in apparently healthy individuals, for every 1 MET increase in aerobic capacity, there was an associated reduction in a mortality rate of 12% in men and 17% in women. Although such a relationship has yet to be revealed in cancer populations, a clinical lower limit of 15.4 $mL \cdot kg^{-1} \cdot min^{-1}$ has been proposed for full independent living of cancer patients (20). In the same study, patients with an absolute $\dot{V}O_{2peak}$ higher than 1.09 $L \cdot min^{-1}$ had an adjusted hazard ratio for death of 0.32 compared with patients with aerobic capacity values below 1.09 $L \cdot min^{-1}$. Two EX participants in the current study were below this threshold at baseline, but both surpassed it during the intervention, representing a meaningful clinical outcome.

One control participant demonstrated an impressive 30% increase in $\dot{V}O_{2peak}$, representing an outlier in this group. This participant had the largest increase in antioxidant capacity in the control group, more in line with changes found in the exercise group. When excluding this participant, $\dot{V}O_{2peak}$ in the control group actually decreased by 2.3%. Despite the increased time out of treatment and improved familiarity with the treadmill protocol, three control participants had diminished CRF at follow-up, which may have been associated with prolonged sedentary activity or persistent oxidative stress, resulting in continued skeletal and cardiac muscle tissue degradation (34,41). For instance, the participant with the greatest reduction in CRF (-2.0 $mL \cdot kg^{-1} \cdot min^{-1}$) also was the only participant in the study to experience a reduction in antioxidant capacity. Nishiyama et al. (30) demonstrated that oxidative stress may be associated with exercise intolerance in clinical populations, because a significant negative correlation between exercise-induced malondialdehyde production and $\dot{V}O_{2peak}$ was present in cardiac patients, whereas no such relationship existed in healthy individuals.

This study had some limitations worth noting. Because participants in this study represented a variety of cancer types and treatments, it is possible that undetected prolonged physiological effects of treatment and the cancer type may play a role in patient response to exercise or time out of treatment. Although no participants explicitly reported substantial dietary alterations at follow-up, diets were not controlled and food logs were not used to evaluate participants' consumption of antioxidant-containing foods. Whole foods containing variable antioxidant compositions may have affected plasma antioxidant capacity or oxidative stress at either baseline or follow-up. Finally, although exercise interventions were similar, individualization of exercise regimens for each cancer patient based on specific needs may have affected the biochemical and fitness responses to exercise.

CONCLUSIONS

Cancer patients exhibited decrements in antioxidant capacity and increased protein and DNA oxidation compared with healthy age-matched individuals. To counteract these effects, a prescribed whole-body exercise intervention may be an effective strategy to concurrently increase muscular strength, CRF, and antioxidant capacity and decrease markers of protein and DNA oxidation compared with a nonexercise group. Therefore, it may be possible that oxidative stress contributes to strength and cardiorespiratory decrements in cancer patients after cancer treatment, and an improvement in antioxidant capacity may play a role in the exercise-mediated benefits of cancer rehabilitation.

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