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Effects of an Exercise Intervention on Cancer-Related Fatigue and Its Relationship to Markers of Oxidative Stress

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Abstract

Background: Although the underlying mechanisms of cancer-related fatigue (CRF) are not fully characterized, treatment-associated oxidative stress may play a role. The purpose of this study was to determine the effect of an exercise intervention on the relationship between CRF and oxidative stress. **Methods:** Upon cessation of radiation or chemotherapy, 8 cancer patients participated in a 10-week exercise intervention (EX), while 7 continued standard care (CON). Blood draws and fatigue questionnaires were administered to cancer patients before and after the intervention as well as to 7 age-matched individuals with no cancer history. Changes in plasma 8-hydroxy-deoxyguanosine (8-OHdG), protein carbonyls, antioxidant capacity, and fatigue were compared between groups. Correlations between CRF and oxidative stress were evaluated. **Results:** Mean total fatigue scores decreased significantly (5.0 ± 2.2 to 2.6 ± 1.5, $P < .05$) in EX, but not in CON. Antioxidant capacity significantly increased (+41%; $P < .05$) and protein carbonyls significantly decreased (−36%; $P < .05$) in EX, but not in CON. Increases in antioxidant capacity were significantly correlated with reductions in affective ($r = -.49$), sensory ($r = -.47$), and cognitive fatigue ($r = -.58$). Changes in total ($r = .46$) and affective ($r = .47$) fatigue exhibited significant correlations with changes in 8-OHdG over time, while behavioral ($r = .46$) and sensory ($r = .47$) fatigue changes were significantly correlated with protein carbonyls. **Conclusions:** Oxidative stress may be implicated in CRF, while improved antioxidant capacity following an exercise intervention may play a role in mitigating CRF in cancer survivors.

Keywords

exercise therapy, oxidative stress, fatigue, cancer rehabilitation, biological markers

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Introduction

Although cancer survival rates continue to improve, patients can expect to experience adverse side effects from surgery, radiation, chemotherapy, and other treatment modalities that may last for years. Cancer-related fatigue (CRF) associated with radiation, chemotherapy, and the tumor burden itself is particularly prevalent in cancer survivors and has been well documented for decades.[1,2] Up to 90% of cancer patients report experiencing fatigue following cancer treatment, and it is commonly reported as the single most problematic side effect for cancer survivors.[3] CRF, like chronic fatigue syndrome, is more severe and debilitating than standard fatigue, often leading to significant changes in behavior and demeanor.[4]

Because fatigue is both a physiological and psychological condition, it is difficult to identify a specific mechanism, but there are likely many. It has been suggested that fatigue is related to immune and inflammatory responses,[5] muscular wasting related to cachexia,[6] sleep disturbances,[7] psychological depression,[8] anemia,[9] tumor-induced metabolic imbalances, mitochondrial damage, and decreased substrate availability associated with anorexia, nausea, or vomiting.[10] Although CRF is likely a product of a combination of these factors, and may vary between individuals, oxidative stress is thought to play a pivotal role in many pathological processes associated with cancer and its treatments.[6] Oxidative

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stress is a state in which reactive oxygen species are produced at a rate that exceeds cellular protective, adaptive, and repair capacities, resulting in damage to local tissues, including lipid membranes, protein structures, and nucleic acids.[11] Cancer treatments, including but not limited to doxorubicin, tamoxifen, etoposide, 5-fluorouracil, alkylating agents, platinum coordinating complexes, and radiation, are all known to cause substantial oxidative stress, both as a side effect and antineoplastic mechanism.[12,13]

While CRF has been theoretically tied to oxidative stress, and many of the proposed mechanisms mentioned above can be driven by oxidative stress, there is a general lack of evidence explicitly relating oxidative stress to CRF. Gramignano et al[14] demonstrated that 4 weeks of antioxidant therapy in the form of L-carnitine administration simultaneously reduced fatigue and resulted in a decrease in oxidative stress in patients currently undergoing cancer treatment. Additionally, other fatigue-related conditions, such as chronic fatigue syndrome, have been associated with oxidative stress.[15] Maes et al found that 8-hydroxy-deoxyguanosine (8-OHdG), a marker of oxidative damage to DNA, was elevated in individuals suffering from both depression and chronic fatigue syndrome.[16] DNA oxidation is linked to oncogenesis, as well as atherosclerosis and neurodegeneration, factors that are associated with psychological and cognitive dysfunction. Accordingly, oxidative stress may represent a potential mechanistic link between cancer and CRF. Despite this, a review article summarizing our current understanding of the biology of CRF did not identify any published data associating oxidative stress with CRF, further highlighting the need to investigate the role of oxidative stress in this context.[5] More recently, Rodgers et al found that in school-aged children undergoing leukemia treatment, but not 3 to 6 year olds, there was a correlation between markers of oxidative stress in cerebrospinal fluid and fatigue.[17] Clearly additional research on this topic is warranted.

Until recently, oncologists and primary care physicians treating cancer patients often prescribed rest as a strategy to counteract CRF. Although it is somewhat counterintuitive, research has shown that physical activity is a more effective method of reducing acute and chronic fatigue in cancer survivors. Whereas exercise has been shown to have significant therapeutic benefit,[18,19] daytime inactivity may actually exacerbate fatigue symptoms.[20] Various methods of prescribed exercise, including resistance and aerobic exercise, both supervised and at home, have been shown to attenuate fatigue symptoms in cancer patients following treatment,[18] while improving quality of life[21] and cancer survival rates.[22]

Although exercise interventions are known to improve antioxidant capacity in healthy individuals,[23] and rodents treated with chemotherapeutic agents,[24] research on exercise-associated oxidative stress modifications in cancer patients is minimal and inconsistent. Guinan et al[25] found that while a multimodal rehabilitation program reduced inflammation in esophageal cancer survivors, there was no significant effect on oxidative stress markers. No analysis was conducted on 8-OHdG, an oxidative stress parameter, since values fell below assay detection levels, possibly due to reduced oxidative stress related to an extended time since completion of treatment (nearly 2 years since surgical treatment). Allgayer et al[26] demonstrated that 2 weeks of moderate-intensity exercise reduced urinary 8-OHdG excretion in colorectal patients following primary treatment, while 2 weeks of high-intensity exercise training resulted in a nonsignificant increase in 8-OHdG excretion. These disparate results indicate that, among other factors, exercise intensity likely plays a role in the redox balance response to exercise interventions in cancer patients. Additionally, redox signaling is plastic and time sensitive. For instance, although exercise training in rats increased left ventricular activity of the antioxidant enzyme catalase upon cessation of exercise, catalase activity returned to preexercise values within 9 days.[27] There is evidence that these effects may also be tissue specific. Parise et al found that in healthy individuals, unilateral leg exercise increased antioxidant enzyme activity in the trained leg but not the untrained leg.[28] This suggests that the exercise-associated increases in tissue antioxidant capacity are unlikely to be conveyed to cancerous tissue, but also demonstrates the importance of total body exercise interventions in cancer survivors.

It is possible that the exercise-mediated reductions in oxidative stress are, at least in part, responsible for exercise-associated decreases in CRF, but to date, this relationship is largely uncharacterized. Therefore, the purpose of this study was to investigate CRF changes in cancer patients following a whole-body exercise intervention and to examine its relationship with antioxidant capacity and oxidative stress.

Methods

Design

Fifteen cancer patients and 7 healthy age-matched individuals with no history of cancer (NC) or other chronic diseases (n = 7) participated in the study. This study consisted of a 10-week prescribed exercise intervention in cancer patients following oxidative stress-inducing cancer treatments, including radiation or chemotherapy. This study included overlapping subjects from a previously published study related to parameters of physical fitness and oxidative stress.[29] Subjects had completed radiation or chemotherapy treatment within the previous 6 weeks, with an average time out of treatment of 4 weeks. Cancer patients were admitted to either an exercise intervention group (EX; n = 8) or a standard care group (CON; n = 7) based on date of initial contact (pseudorandomization),

while NC subjects were only evaluated at baseline. Subjects were recruited from walk-in and oncologist referred patients at the the University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI). The University of Northern Colorado institutional review board approved all procedures and written informed consent forms were signed by all subjects.

Subjects

Twenty-six cancer patients made contact with the primary investigator, but exclusion criteria or attrition resulted in the loss of 11 potential subjects. All cancer diagnoses were considered for this study, but subjects 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.[12,30,31] Cancer patient inclusion criteria consisted of the following: (1) completed radiation or approved chemotherapy regimen within 6 weeks of initial blood draw, (2) currently sedentary (less than 2 days/week of 20 minutes of aerobic or resistance exercise), and (3) able to walk comfortably on a treadmill. Exclusion criteria were the following: (1) age of 85 years or older; (2) consistent dietary supplementation with antioxidants, including vitamins C and E, in the previous month; (3) any dietary antioxidant supplementation in the 72 hours prior to blood draws; and (4) tobacco smoking in the prior 2 months.

Noncancer, healthy controls (NC) were primarily recruited from among the faculty and staff at the University of Northern Colorado via campus-wide email and by word of mouth. The inclusion criterion for the NC group was a currently sedentary status (less than 2 days/week of 20 minutes of aerobic or resistance exercise). Exclusion criteria were the following (1) a history of cancer; (2) age of 85 years or older; (3) consistent dietary supplementation with antioxidants, including vitamins C and E, in the previous month; (4) any dietary antioxidant supplementation in the 72 hours prior to blood draws; and (5) tobacco smoking in the prior 2 months.

Prior to the initial blood draw, all cancer and noncancer subjects were provided with the Piper Fatigue Inventory[32] to complete within 24 hours of the initial blood draw. For 72 hours prior to the blood draw, subjects were asked to avoid exhaustive exercise and antioxidant supplementation. The day before the cancer patient's initial exercise assessment, a 12-hour fasting blood sample was obtained.

Piper Fatigue Inventory

The Piper Fatigue Inventory[32] was used to assess total CRF, as well as subscales of behavioral, affective, sensory, and cognitive/mood fatigue. The behavioral fatigue subscale assesses the impact of fatigue on school and/or work, interacting with friends, and overall interference with activities that are enjoyable. The affective fatigue subscale assesses the emotional meaning attributed to fatigue. The sensory fatigue subscale assesses the mental, physical, and emotional symptoms of fatigue. The cognitive and/or mood fatigue subscale assesses the impact of fatigue on concentration, memory, and the ability to think clearly. The average score on the 22 total questions from the subscales provides the total fatigue score. Scores on the subscales and total fatigue range from "0" to "10." A score of a "0" indicates that the cancer survivor has no fatigue; scores ranging from "1" to "3" are indicative of mild fatigue; scores "4" to "6" suggest moderate fatigue; and scores of "7" or greater indicate severe fatigue.

Exercise Intervention

Each EX subject completed a 10-week exercise intervention that was individually supervised by a certified cancer exercise specialist 3 days per week. Each 1-hour session was prescribed by the cancer exercise specialist in accordance with individual goals and results from an initial comprehensive fitness assessment. Progression was based on feedback from previous exercise sessions. Exercise sessions varied depending on the subject's health and fitness status, but typically included a 5-minute warmup, 20 minutes of aerobic exercise, 25 minutes of resistance training, and 10 minutes of flexibility and balance training. Blood pressure and heart rate were measured at the beginning and end of the exercise session, and heart rate, rating of perceived exertion (RPE), and oxygen saturation were monitored throughout. Aerobic exercise intensity was based on initial cardiorespiratory fitness, and was generally low to moderate intensity, ranging from 40% to 60% of heart rate reserve (HRR), or an RPE 4 to 5. The mode of aerobic exercise selected for each subject 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 rate of progression varied significantly by subject, cancer exercise specialists aimed to increase speed or resistance weekly, while keeping RPE values below 5 and heart rate values below 75% HRR.

At the beginning of the intervention, initial percent of maximal strength was similar to percent of HRR for the aerobic exercise component (40% to 50% for low fitness, 50% to 60% for average fitness). Cybex Eagle Selectorized Strength Machines (Cybex International Inc, Medway, MA), free weights, resistance bands, and body weight exercises were all used for the exercise intervention, depending on fitness, mobility, and comfort of the cancer patient.

Muscular endurance was emphasized over hypertrophic training, as subjects performed 8 to 15 repetitions per set and typically ended each set at muscular fatigue rather than muscle failure. Resistance was increased when 8 to 15 repetitions no longer resulted in muscular fatigue.

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

Blood Handling and Analysis

A minimum of 4 mL of blood was withdrawn into sterile tubes containing potassium-ethylenediaminetetraacetic acid and immediately put on ice. Samples were centrifuged at 3000 rpm for 10 minutes, and the plasma was separated and stored at −80°C until analysis. All samples were assayed in duplicate on the first thaw. Reactive carbonyl derivatives were measured as an indicator of oxidative protein damage. Oxidative DNA damage, as determined by plasma 8-OHdG, and protein carbonyls were measured in plasma using enzyme-linked immunosorbent assays according to the procedures recommended by the manufacturer (Cell Biolabs, Inc, San Diego, CA). This value is associated with the risk of cancer development and recurrence.[33] Antioxidant capacity was measured in plasma using the Trolox-equivalent antioxidant capacity assay using procedures outlined by the reagent provider (Sigma Chemical, St Louis, MO).

Statistical Analyses

Data are presented as means ± SD. Baseline characteristics in the 2 cancer groups (EX vs CON) and the NC group were compared using one-tailed independent *t* tests. A repeated-measures 2 (group) × 2 (pre- and postintervention) analysis of variance with Bonferroni correction was used to identify differences within (across time) and between the 2 groups related to protein and DNA oxidation, antioxidant capacity, and fatigue. 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 fatigue. Additionally, Spearman correlation coefficients were calculated to determine the relationship between postintervention changes in markers of oxidative stress and postintervention changes in fatigue. A significance level of $\alpha = .05$ was used for all statistical analyses. Statistical analyses were conducted using GraphPad Prism (Version 5; GraphPad Software, Inc, La Jolla, CA).

Results

The 2 cancer groups had statistically similar height, weight, body mass index, and time out of treatment, while no significant differences in age were found between the 3 groups (Table 1). Exit surveys in control subjects indicated that even in the absence of an exercise intervention, qualitative physical activity increased from baseline as time out of treatment resulted in greater 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 subjects reported participation in a structured exercise program. No qualitative changes in dietary habits were identified from the exit surveys in either the EX or CON group.

At baseline, total fatigue and all 4 subcategories of the Piper Fatigue Inventory were significantly elevated in the cancer population compared with NC (Table 2). The 10-week intervention resulted in significant reductions in total fatigue and all 4 fatigue subcategories in EX, while only cognitive fatigue significantly diminished in CON. No group by time interaction effects were observed between EX and CON for any fatigue parameter. Mean total fatigue in the EX group fell from 5.0 ± 2.3 to 2.6 ± 1.9 ($P < .01$), indicating a change in group mean classification from "moderate fatigue" to "mild fatigue." The only subject in this group failing to downgrade classification status was the individual with mild fatigue at baseline, who therefore had little room for improvement. Mean total fatigue in the CON group dropped from 4.6 ± 2.4 at baseline to 3.2 ± 2.4 at follow-up, but this represented neither a statistically significant change nor a change in group mean classification. Post hoc analysis revealed that behavioral and affective fatigue in the exercise group no longer statistically differed from the NC group ($P > .05$) at follow-up.

Baseline plasma antioxidant status and protein carbonyls did not differ between EX and CON, but significantly differed between NC and cancer patients ($P < .05$). Plasma 8-OHdG did not differ between any of the groups at baseline ($P > .05$). Following the intervention, antioxidant capacity (Trolox-equivalent antioxidant capacity) significantly increased, and protein carbonyls significantly decreased in EX, but not in CON. Following the 10-week study period, EX no longer differed significantly from NC for protein oxidation, and neither cancer group differed in antioxidant capacity from NC. DNA oxidation did not change significantly over time in either group, but there was a

Table 1. Subject Characteristics[a].

Characteristics	Exercise	Control	Noncancer
N	8	7	7
Age (years)	64.0 ± 10.8	62.4 ± 9.7	55.1 ± 9.7
Age range (years)	50-77	43-75	42-74
Females	7	4	5
Males	1	3	2
Height (in.)	65.4 ± 2.5	66.8 ± 4.7	66.3 ± 3.3
Weight (lbs)	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
Initial fatigue classification (number of subjects)			
No fatigue	0	0	4
Mild	3	2	3
Moderate	4	4	0
Severe	1	1	0
Primary treatment (number of subjects)			
Radiation	4	3	—
Chemotherapy	4	4	—
Cancer type	Hodgkin's lymphoma (1), pancreatic (1), ovarian (1), and breast (5)	Non-Hodgkin's lymphoma (1), leukemia (1), squamous cell carcinoma (1), uterine (1), colon (1), and breast (2)	
Days out of treatment	29.9 ± 18.6	31.4 ± 21.7	—
Exercise adherence rate (%)	83.9 ± 12.8	—	—

Abbreviation: BMI, body mass index.
[a]Data are presented as mean ± SD. No significant differences existed between the groups.

Table 2. Changes in Fatigue and Blood Parameters[a].

		EX (n = 8)		CON (n = 7)	
	NC (n = 7)	Pre	Post	Pre	Post
Fatigue parameters					
Total	1.0 ± 1.0[b]	5.0 ± 2.2	2.6 ± 1.9[c]	4.7 ± 2.5	3.2 ± 2.4
Behavioral	0.9 ± 1.3[b]	4.5 ± 3.0	1.9 ± 2.2[c]	4.2 ± 3.5	3.0 ± 3.1
Affective	0.7 ± 0.8[b]	5.7 ± 2.5	2.3 ± 2.4[c]	5.2 ± 2.5	3.6 ± 2.5
Sensory	1.4 ± 1.3[b]	5.9 ± 2.2	3.4 ± 2.3[c]	5.0 ± 2.4	3.5 ± 2.3
Cognitive	1.2 ± 1.2[b]	4.5 ± 2.3	2.7 ± 1.8[c]	5.0 ± 2.0	2.9 ± 2.1[c]
Blood parameters					
TEAC	1.0 ± 0.20[b]	0.75 ± 0.19	1.06 ± 0.13[c]	0.69 ± 0.16	0.85 ± 0.22
Protein carbonyls	1.0 ± 0.28[b]	1.46 ± 0.49	0.94 ± 0.37[c]	1.32 ± 0.48	1.26 ± 0.25
8-OHdG	1.0 ± 0.57	1.45 ± 0.96	0.88 ± 0.55[d]	1.08 ± 0.44	1.48 ± 0.66

Abbreviations: NC, noncancer baseline control group; EX, exercise cancer group; CON, cancer control group; TEAC, Trolox-equivalent antioxidant capacity.
[a]Data are presented as mean ± SD. Blood parameters expressed as arbitrary units (% of baseline control).
[b]Significantly different than cancer patients at baseline ($P < .05$).
[c]Significant change from baseline ($P < .05$).
[d]Significant time by group interaction with control group ($P < .05$).

significant interaction effect between EX and CON ($P < .05$), as EX trended downwards, and CON trended upwards.

Baseline antioxidant capacity was negatively correlated with total, affective, sensory, and cognitive fatigue ($P < .05$). All baseline fatigue parameters correlated with protein carbonyls ($P < .05$), but none correlated with 8-OHdG. Changes in antioxidant capacity had significant negative correlations with changes in affective, sensory, and cognitive fatigue, whereas changes in 8-OHdG positively correlated with total and behavioral fatigue, and protein carbonyl

Table 3. Correlations Between Oxidative Stress and Fatigue Parameters at Baseline and Over Time[a].

	Time Point	Total Fatigue	Behavioral	Affective	Sensory	Cognitive
TEAC	Baseline	−0.41*	−0.33	−0.39*	−0.40*	−0.57*
	Change	−0.37	−0.10	−0.49*	−0.47*	−0.58*
8-OHdG	Baseline	0.28	0.30	0.27	0.26	0.19
	Change	0.49*	0.62*	0.34	0.26	−0.01
Protein carbonyls	Baseline	0.56*	0.49*	0.57*	0.57*	0.47*
	Change	0.46*	0.41	0.47*	0.43	0.06

Abbreviation: TEAC, Trolox-equivalent antioxidant capacity.
[a]All values presented as Spearman's correlation coefficients (*r*).
*Indicates significant correlation between blood parameter and fatigue score ($P < .05$).

changes positively correlated with total and affective fatigue improvements (Table 3).

Adverse Events and Exercise Adherence

Despite chronic musculoskeletal limitations in several EX subjects, overall adherence was high, as subjects attended 84 ± 13% of scheduled exercise sessions. Most missed sessions were associated with preexisting conditions rather than a general exercise intolerance in this posttreatment cancer population. Other common reasons for missed sessions included scheduling conflicts, acute respiratory infections, and complications owing to non–cancer-related surgeries. Individualization of the exercise intervention allowed for completion of the intervention in all EX subjects.

Discussion

Results from this study indicate that exercise training is an effective method of reducing fatigue in cancer patients who have recently completed treatment. It appears that time out of treatment is an important variable in that it clearly has a restorative effect on its own, as cognitive fatigue was significantly reduced in the CON group and there were no significant interaction effects between EX and CON for any fatigue variable. The attenuation of only cognitive fatigue in CON may indicate that physiological components of CRF are more persistent than psychological impairments in patients who are not actively counteracting cancer treatment–induced physiological damage with physical activity. It should be noted, though, that reported increases in physical activity and activities of daily living in several CON subjects represents some degree of control group contamination. This may partially explain the universal trend of reduced fatigue in control subjects, and subsequently no significant group by time interaction effects for fatigue parameters. Nonetheless, significant correlations between antioxidant capacity and baseline fatigue, as well as antioxidant capacity and change in fatigue indicate that improved antioxidant capacity may play a role in reduced fatigue, regardless of physical activity level. Additional research on the mechanistic link between oxidative stress and fatigue is warranted, as the improvement of these parameters could conceivably be caused by independent physiological responses to exercise training. Further studies using dietary or intravenous antioxidant administration to manipulate redox status in combination with exercise may provide additional evidence of the possible mechanisms of fatigue reduction in cancer survivors.

Despite a lack of significant change in 8-OHdG over time, there was a significant group by time interaction effect between EX and CON. Matsumoto et al[34] found that hepatic cancer patients with higher 8-OHdG levels in noncancerous liver regions were more likely to experience a cancer recurrence than those with lower 8-OHdG levels ($P < .01$). Therefore, it is possible that variable 8-OHdG responses over time between the groups may be implicated in a reduced risk for cancer recurrence following the cessation of treatment in exercise subjects compared with standard care. Indeed, it has been reported that higher levels of physical activity are associated with an improved disease-free survival rate,[35] and exercise following treatment may reduce the risk of cancer recurrence.[36]

It is not entirely clear why there was a nonsignificant rise in 8-OHdG in the control group during the study period. Although the cancer treatments investigated in this study all are known to acutely introduce oxidative stress, the time frame of the persistence of markers of oxidative stress is still not entirely characterized and may be affected by an undetected cancer burden. For instance, Erhola et al[37] found that the overall response to radiation and chemotherapy ("complete or partial remission" vs "no change or progressive disease") determined whether urinary 8-OHdG concentration increased or decreased with treatment. It is therefore possible that oxidative stress may worsen for a period of time after the cessation of treatment in some cancer patients, but the effects of variable prognostic criteria and differing cancer stages, types, and treatment regimens on the timeframe of chronic oxidative stress are unknown at this time.

Limitations

Because subjects in this study represented a variety of cancer types and treatments, it is possible that undetected prolonged physiological effects of treatment and cancer type may play a role in patient response to exercise or time out of treatment. Although no subjects explicitly reported substantial dietary alterations at follow-up, diets were not controlled and food logs were not utilized to evaluate subjects' 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.

Conclusions

As expected, baseline fatigue and protein oxidation were greater, and antioxidant capacity lower, in cancer patients compared with NC. Previously, sparse data existed regarding the time course of antioxidant capacity following the cessation of treatment. The current study indicates that additional time out of treatment (in this case, from 1 month to more than 3 months) helps restore antioxidant capacity, albeit nonsignificantly. Exercise, on the other hand, resulted in a more robust, and statistically significant, increase in antioxidant capacity and decrease in protein oxidation. Moreover, significant correlations between changes in fatigue and both protein oxidation and antioxidant capacity indicate that systemic oxidative stress may be a potential mechanism for CRF, much as it has been hypothesized in chronic fatigue syndrome. Our data support the current physical activity guidelines for cancer survivors, which suggest moderate physical activity as a means to reduce treatment-associated side effects,[38] an effect that may be in part due to changes in antioxidant capacity and oxidative stress.

Declaration of Conflicting Interests

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