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Structured Exercise in Cancer Survivors: Is it Enough for Neural, Mental Health and Well-being?

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ABSTRACT

International Journal of Exercise Science 14(3): 162-176, 2021. The purpose of this cross-sectional study was to explore physical activity, depression, fatigue, and quality of life (QOL), and their relationship to brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in cancer survivors enrolled in a structured exercise program. Participants were recruited into two groups: in-treatment (IT), currently receiving chemotherapy and/or radiotherapy, and out of treatment (OT), not undergoing therapy. Participants wore accelerometers for 7 days and completed cardiorespiratory fitness, muscular strength, and depression, fatigue, and QOL assessments. Circulating BDNF and NGF concentrations were obtained using enzyme-linked immunosorbent assays. Thirty-two participants (IT: n = 13, OT: n = 19) with an average age of 63 years and BMI of 27.5, spent 78% of their waking hours engaged in sedentary behavior outside of exercise training. Significant correlations were observed between light physical activity (LPA) outside of exercise training and QOL in IT (r = 0.626, p = 0.030), and fatigue in OT (r = 0.553, p = 0.021). Moderate to vigorous physical activity (MVPA) outside of exercise training significantly correlated with leg press strength (r = 0.700, p = 0.008) in IT, and cardiorespiratory fitness (r = 0.440, p = 0.013) when groups were combined. Concentrations of NGF did not differ between groups, and in IT, BDNF was positively related to LPA outside of training and was significantly lower (87 ± 28.5 pg/mL) than in OT (137 ± 54 pg/mL; p=0.010). While structured exercise programs should focus on improving cardiorespiratory fitness and muscular strength during exercise training, these programs should consider physical activity outside of training, if well-tolerated, to potentially further lower fatigue and improve QOL in cancer survivors.

KEY WORDS: Physical activity behavior, disease population, exercise-based rehabilitation

INTRODUCTION

Cancer is the second leading cause of death in the United States. Although cancer treatments have reduced cancer prevalence and mortality rates, by the year 2030, approximately 22.1 million individuals will be living with a history of cancer (38). Despite improvements in survival beyond the initial cancer diagnosis, the risk of developing additional comorbidities such as type 2 diabetes and other chronic diseases can be as high as 18.5 times greater in cancer survivors (9,

23). Furthermore, cancer survivors have up to a 3.6 times greater chance of dying from cardiovascular disease when compared to non-cancer populations (9, 23).

In addition to these long-term health risks, which may be related to side effects from surgery, radiation, or chemotherapy, cancer survivor motivation for physical activity and exercise is reduced (8). Only 30% of cancer survivors are physically active, with the other 70% achieving less than the recommended 150 minutes of physical activity per week set forth by the American College of Sports Medicine (ACSM) (7, 50).

The benefits of regular, structured exercise may help offset the risks of chronic physical inactivity, help cancer survivors overcome feelings related to fatigue (20, 35), and significantly reduce the risk of other chronic diseases (31). Consequently, structured exercise programs aimed at reducing physical inactivity and improving quality of life (QOL) are becoming more common (15). These programs are associated with improvements in body composition, cardiorespiratory fitness, muscular strength and endurance, QOL, cancer-related fatigue, sleep disturbances, and anxiety and depression in individuals with a variety of cancers (31). However, it is important to note that achieving the recommended 150 minutes of physical activity per week through a structured exercise program may not be enough to improve all aspects of well-being. In fact, individuals enrolled in structured exercise programs tend to be physically active during training but may be unaware of time spent in sedentary behavior such as long periods of sitting and/or idleness outside of their training (52).

The mechanisms associated with improvements in physical fitness as the result of exercise have been identified (11); however, much less is known about the effects of exercise on neural health. Brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), proteins responsible for brain plasticity, regulate the degree of neurogenesis and subsequent changes in cognition and emotion from exercise (33). Higher concentrations of BDNF are associated with improved cognition and mood (24, 27), while lower concentrations are associated with the presence of clinical depression (29, 43). In clinically depressed and cancer populations, both chronic aerobic and resistance training increase BDNF concentrations (29), and reduce depression-like symptoms (28). Additionally, patients with neurodegenerative disorders have low concentrations of NGF, which is correlated with reduced neurogenic inflammation, a necessary response to initiate neurogenesis (32). Some evidence suggests exercise interventions significantly increase concentrations of NGF to aid in neuronal turnover in healthy populations, but diseased populations with multiple sclerosis and autism do not experience a significant change (32). In those with metabolic disorders, exercise increases NGF concentrations (2, 10). However, these studies did not include cancer survivors, nor do they measure total physical activity defined as the sum of daily activities and structured exercise (10, 32). Completing 360 minutes or more of physical activity per week is inversely related to cancer-specific and all-cause mortality risk in long-term cancer survivors, while lower levels of less than 150 minutes and 150 to 359 minutes per week are inversely related to all-cause mortality only (18). Higher physical activity levels correlate with reduced cognitive impairment (55). Depending on cancer and treatment type, 35% of cancer survivors will continue to experience cognitive impairment years following treatment (25), suggesting the need for more physical activity. However, no studies

have examined the relationship between physical activity outside training in combination with an exercise intervention for cancer survivors on BDNF and NGF concentrations.

The purpose of the present study was to examine the potential importance of physical activity behaviors outside of structured exercise training in cancer survivors either in treatment (IT) or out of treatment (OT), and whether these behaviors were related to depression, fatigue, and QOL. Due to the significant physiological, psychological, and cognitive effects of radiation and/or chemotherapy (1), cancer survivors receiving treatment were separated into IT and OT groups. This study also explored whether concentrations of BDNF and NGF differed between IT and OT, and the relationships of these biomarkers with physical activity intensity, depression, fatigue, and QOL. It was hypothesized that IT will be less physically active outside of training. It was hypothesized that physical activity, as well as concentrations of BDNF and NGF, will negatively correlate with depression, fatigue, and QOL in both IT and OT groups. It was also hypothesized that BDNF and NGF will be positively correlated with physical activity.

METHODS

Participants

Participants in this study were cancer survivors enrolled in a progressive phase program at the University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI). This program consists of an individualized exercise prescription specific to each cancer survivor, based on diagnosis, stage, and treatment, with the details of the program described elsewhere (5). All participants engaged in a 60-minute supervised exercise session 3 days per week for the duration of the study. Once agreeing to participate, individuals were separated into two groups; IT consisted of individuals currently receiving chemotherapy and/or radiotherapy, and OT consisted of individuals that were no longer receiving or had not received chemotherapy and/or radiotherapy. Due to the cross-sectional design of this study, all participants completed assessments, accelerometry, and blood draws during the last week of their training program. All recruitment and assessments were performed over the course of 6 months. Participants were excluded if they had chronically high blood pressure, defined as systolic blood pressure greater than 160 mmHg, and diastolic blood pressure greater than 100 mmHg, and significant cardiovascular disorders including but not limited to serious arrhythmias, cardiomyopathy, congestive heart failure, stroke or transient ischemic attacks, peripheral vascular disease with intermittent claudication, and acute, chronic, or recurrent thrombophlebitis. Before the 7-day accelerometer wear time, participants completed body composition, cardiorespiratory fitness, and muscular strength assessments, and after the 7-day period, a blood draw was performed. All exercise training and assessments were conducted by Clinical Cancer Exercise Specialists and were approved by the University of Northern Colorado Institutional Review Board. Informed consent was obtained from all participants. This research was carried out fully in accordance with the ethical standards of the International Journal of Exercise Science (39).

Protocol

Body Size and Composition Measurements: Participants completed body size and composition assessments. Height was measured using a stadiometer (BSM170, Cerritos, CA) and body mass was measured using an InBody scale (InBody Scale, Cerritos, CA). Body mass index (BMI) was calculated using mass (kg) / height $(m)^2$. Percent of body fat was measured using an InBody scale equipped with an 8-point electrode body composition analyzer (InBodyUSA Cerritos, CA).

Cardiorespiratory Fitness and Strength Assessments: Cardiorespiratory fitness (VO_2peak) was measured using the UNCCRI treadmill protocol, a graded protocol specifically designed for individuals with a history of cancer (48). Muscular strength measures were obtained for the lat-pull down, chest press, and leg press exercises. Briefly, all participants completed a warm-up set consisting of 1 to 5 repetitions for each strength exercise. After 2 minutes of rest, the participant was asked to perform the strength exercise to failure. If the load performed was too light, they were asked to rest for 2 minutes and repeat the exercise with an increased load until failure occurred between 1 to 10 reps. The estimated one-repetition maximum (1RM) for each exercise was determined using the Bryzcki equation which estimates 1RM to failure that must occur between 1-10 repetitions (6).

Accelerometry: Movement behaviors were evaluated for in-training and non-training times with a fitted-accelerometer (Actigraph, WGT3X-BT) worn around the participant's waist for 7 days during the last week of their progressive phase program, with epoch intervals of 10 seconds. All accelerometer data were analyzed using Actilife software (Actigraph, Pensacola, FL) with Freedson cut-points which included less than 1952 accelerometer counts/min for light intensity, 1952-5724 accelerometer counts/min for moderate intensity, 5725-9498 accelerometer counts/min for hard intensity, and more than 9498 accelerometer counts/min for very hard intensity (14). Data were separated into different periods based on times during and outside of exercise training. In-training sessions included physical activity during the three supervised one-hour exercise sessions per week. Non-training time included all waking hours outside of the three training sessions per week.

Depression, Fatigue, and QOL Assessments: Participants were asked to complete three paper-based questionnaires evaluating depression, fatigue, and QOL at the end of their progressive phase program and before accelerometer and fitness assessments. The Beck Depression Inventory consisted of 21 questions that measured intensity, severity, and depth of depression in a score range of 1 to over 40, with scores of 17 or above indicating a possible need for professional treatment (3). The inventory is an accurate self-report measure for the evaluation of depressive symptoms in an oncology setting (4). The Revised Piper Fatigue Scale measured behavioral, affective, sensory, and cognitive/mood attributes of fatigue on a 0 to 10-point scale, with higher values corresponding to severity of fatigue (44). The scale is recognized as an appropriate measure for fatigue in cancer patients (44). The modified Ferrans and Powers QOL Index Cancer Version III measures satisfaction with health and functioning, psychological aspects, spiritual aspects, social and economic aspects, and family aspects. This survey is specifically designed for the cancer population and scores range from 0 to 30, with higher values corresponding to greater satisfaction (12, 13).

Biomarkers of Neural Health: Blood samples were collected following an 8 hour fast in ethylenediaminetetraacetic acid vacutainer tubes (Becton, Dickenson and Company, NJ). Samples were centrifuged at 2000 g for 11 minutes at room temperature and stored at -80°C. Blood plasma was analyzed for concentrations of BDNF and NGF enzyme-linked immunosorbent assays (RayBiotech Life, Peachtree Corners, GA) and a plate reader (BioTek Instruments, Inc., Winooski, VT).

Statistical Analysis

Descriptive statistics are reported for all outcome variables and are reported as mean ± standard deviation (SD). Unpaired T-tests were performed to evaluate whether differences existed between IT and OT with respect to measures of body size, body composition, cardiorespiratory fitness, muscular strength, movement behaviors, depression, fatigue, QOL, and concentrations of BDNF and NGF. To evaluate effect size between groups, Cohen's D was used for body composition, cardiorespiratory fitness, and muscular strength, as well as the percentage of time spent engaged in sedentary behavior, or light, moderate, vigorous, very vigorous physical activity, and MVPA during the 7-day wear time. Pearson's *r* was used to explore relationships between body size, body composition, cardiorespiratory fitness, muscular strength, in-training and non-training movement behavior (% sedentary, % light, % moderate, % vigorous, %very vigorous, and % MVPA), depression, fatigue, QOL, and concentrations of BDNF and NGF within and between groups. All analyses were performed with GraphPad statistical software (GraphPad Software, San Diego, CA), and alpha was set at 0.05.

RESULTS

Participants (N = 32) were between 21 and 86 years of age with an average age of 63 ± 14 years (Table 1). The IT group (n = 13) consisted of 10 females and 3 males between the ages of 36 and 77 years, and OT (n = 19) consisted of 9 females and 10 males between the ages of 21 and 86 years old. Cancers consisted of breast ((n = 11; stage 1 (n = 6), stage 2 (n = 3), and stage 3 (n = 2)), prostate cancer ((n = 4; Gleason scale stage 1 (n = 1), stage 3 (n = 1), stage 7 (n = 1), and stage 8 (n = 1)), lymphomas ((n = 4; stage 2 (n = 2), stage 3 (n = 1), and liquid unstaged (n = 1)), lung (n = 3; stage 4), carcinoma ((n = 2; stage 3 (n = 1) and stage 4 (n = 1)), esophageal (n = 1; stage 2), hypopharynx (n = 1; stage 2), peritoneal (n = 1; stage 3), endometrial (n = 1; stage 3), multiple myeloma (n = 1; un-staged), leukemia (n = 1; stage 2), and sarcoma (n = 1; stage 3).

Table 1. Characteristics of participants.

Characteristics	IT (n = 13) Mean ± SD	OT (n = 19) Mean ± SD	p-value	Effect Size
Age, years	62.9 ± 1	63.6 ± 16.5	0.89	0.05
Height, inch	65.3 ± 2.7	67.0 ± 3.6	0.17	0.52
Weight, kg	74.2 ± 16.3	67.0 ± 22.4	0.33	0.37
BMI, kg/m^2	26.9 ± 5.3	28.0 ± 6.7	0.62	0.19
Body Fat, %	35.7 ± 11.5	33.9 ± 9.2	0.62	0.18

Note: standard deviation (SD); In-treatment group (IT); Out of treatment (OT); Body mass index (BMI).
No significant differences between groups.

Body Size and Composition: When groups were combined, body weight ranged from 42.5 kg to 141.6 kg with an average weight of 73.1 ± 44.6 kg, and BMI averaged 27.5 ± 6.1 kg/m^2 and ranged from 16.1 to 46 kg/m^2. Body fat percentage, when both groups were combined, ranged from 14.0 to 52.8% with an average of 34.7 ± 10.1%. There were no significant differences between IT and OT with respect to any measure of body size or composition. Although significantly greater height (p = 0.001) and less body fat percent (p = 0.0064) were observed in males compared to females, there were no other sex differences within IT and OT and when groups were combined (Table 1).

Cardiorespiratory Fitness and Muscular Strength: The average VO_2peak for all participants was 25.7 ± 8.1 mL/kg and ranged from 11.2 to 38.2 mL/kg, and there were no significant differences between groups (Table 2). No VO_2peak differences between sexes were observed and there were no significant correlations between age and VO_2peak. There were no differences between IT and OT for all strength measures except for the lat-pull down, where OT values were higher than IT values (p = 0.048, d = 0.77; Table 2). There was also a difference between sexes with chest press strength (p = 0.0004) and lat-pull down strength (p = 0.001).

Table 2. Cardiorespiratory fitness and muscular strength measures of participants.

Measure	IT (n = 13) Mean ± SD	OT (n = 19) Mean ± SD	p-value	Effect Size
VO_2peak, mL/kg/min	26.3 ± 8.6	25.3 ± 8.0	0.74	0.12
Lat-Pulldown, kg	44.1 ± 15.1	58.0± 20.8	0.048	0.77
Chest Press, kg	34.7± 18.7	41.6 ± 15.0	0.25	0.41
Leg Press, kg	98.2 ± 45.9	107.6 ± 49.7	0.59	0.04

Note: Standard deviation (SD); In-treatment (IT); Out of treatment (OT); OT Lat-pull down = significantly higher than IT (p = 0.048).

In-Training Physical Activity: Participant training programs consisted of 60-minutes of supervised exercise sessions 3 days per week, totaling 180 minutes of structured exercise. When groups were combined, participants performed an average of 25.0 ± 10.6% light, 7.8 ± 8.2% moderate, 1.2 ± 4.7% vigorous, and 0.04 ± 0.13% very vigorous physical activity, and 9.5 ± 11.9% MVPA in their respective training sessions. There were no significant differences between groups with respect to physical activity during training times. However, there was a medium effect size between IT and OT in the percentage of time spent in sedentary and moderate activities (Table 3). There were no differences between sexes either between or within groups. When groups were combined, moderate physical activity correlated with the leg curl (r = 0.382, N = 29, p = 0.041). However, in IT, there were strong positive relationships with respect to moderate physical activity and the leg curl (r = 0.689, N = 13, p = 0.009), leg extension (r = 0.560, N = 13, p = 0.046), and leg press (r = 0.745, N = 13, p = 0.003), very vigorous physical activity and lat-pull down (r = 0.746, N = 13, p = 0.003), chest press (r = 0.753, N = 13, p = 0.003), row (r = 0.715, N = 13, p = 0.006), and leg press (r = 0.702, N = 13, p = 0.007), and MVPA and the leg curl (r = 0.602, N = 13, p = 0.029) and leg press (r = 0.660, N = 13, p = 0.014), and in OT, very vigorous physical and chest press (r = 0.381, N = 30, p = 0.038).

Table 3. In training physical activity of participants.

Physical Activity	IT (n = 13) Mean ± SD	OT (n = 19) Mean ± SD	p-value	Effect Size
Sedentary, %	70.5 ± 16.5	61.3 ± 17.8	0.16	0.53
Light, %	22.7 ± 10.0	26.6 ± 11.1	0.33	0.37
Moderate, %	5.2 ± 6.0	9.7 ± 9.2	0.13	0.59
Vigorous, %	0.9 ± 1.8	2.0 ± 6.0	0.36	0.25
Very Vigorous, %	0.04 ± 0.1	0.05 ± 0.1	0.78	0.07
MVPA, %	6.9 ± 10.0	11.7 ± 13.2	0.29	0.07

Note: Standard deviation (SD); In-treatment (IT); Out of treatment (OT); Moderate to vigorous physical activity (MVPA). There were no significant differences between the groups.

Non-Training Physical Activity: Both groups spent most of their time engaged in sedentary behavior during non-training times (Table 4). The portion of time spent engaged in sedentary behaviors when groups were combined averaged 78.0 ± 10.0% and ranged from 59.7% to 94.6%, which translates to a range of 4,014 to 6,358 minutes out of the average 6,720 minutes spent awake outside of the training sessions. Additionally, there were no significant differences between groups for any measure of physical activity during non-training times. Both groups combined, spent an average of 19.6 ± 9.1% in light physical activity (LPA), 2.3 ± 1.7% in moderate physical activity, 0.09 ±0.17% in vigorous physical activity, 0.0 ± 0.008 % in very vigorous physical activity, and 2.4 ± 1.8% in MVPA (Table 4). No sex differences were observed in IT for non-training movement behavior. Within OT, a difference between the sexes was observed for the total time spent engaged in vigorous physical activity; females performed on average 4 minutes more vigorous activity than males, but no sex differences were observed between groups. Additionally, no differences were observed between sexes in any other physical activity category in OT.

When groups were combined, there were moderate correlations with VO_2peak and both moderate physical activity (r = 0.420, N = 32, p = 0.017) and MVPA (r = 0.440, N = 32, p = 0.013). There were no significant correlations between strength measures and physical activity when groups were combined. However, there were strong positive correlations between leg press and moderate physical activity (r = 0.690, N = 32, p = 0.009), and leg press and MVPA (r = 0.700, N = 32, p = 0.008) in IT outside of their structured exercise program. Conversely, OT had no significant relationships between strength measures and physical activity outside of training time.

Table 4. Non-training physical activity of participants.

Physical Activity	IT (n = 13) Mean ± SD	OT (n = 19) Mean ± SD	p-value	Effect Size
Sedentary, %	79.35 ± 7.94	77.07 ± 11.34	0.54	0.23
Light, %	17.83 ± 7.38	20.94 ± 10.15	0.36	0.35
Moderate, %	2.49 ± 1.91	2.23 ± 1.61	0.69	0.15
Vigorous, %	0.10 ± 0.15	0.09 ± 0.19	0.79	0.06
Very Vigorous, %	0.00 ± 0.01	0.00 ± 0.01	0.76	0.00
MVPA, %	2.59 ± 1.99	2.32 ± 1.73	0.69	0.14

Note: Standard deviation (SD). In-treatment (IT); Out of treatment (OT); Moderate to vigorous physical activity (MVPA). There were no significant differences between the groups. There were no differences between sexes.

Depression, Fatigue, and QOL: When both groups were combined, average Beck, Piper, and QOL scores were 6.2, 3.0, and 23.4, and ranged from 0 to 21, 0 to 6.6, and 11 to 28.4, respectively, and there were no differences between groups. However, there was a strong positive correlation between depression and fatigue (R = 0.620, N = 19, p = 0.005) and a strong negative correlation between depression and QOL (R = -0.889, N = 18, p < 0.0001) in OT, while no significant correlations were observed in IT. When groups were combined, a positive correlation was observed between depression and fatigue (r = 0.529, N = 32, p = 0.002), and strong negative correlations were observed between depression and QOL (r = -0.796, N = 30, p < 0.0001) and fatigue and QOL (r = -0.563, N = 30, p = 0.001).

Strong negative correlations were also observed between fatigue and VO_2peak in IT (r = -0.755, N = 13, p = 0.003) and when groups were combined (r = -0.438, N = 32, p = 0.012). Quality of life and lat-pull down strength were also positively correlated when groups were combined (r = 0.364, N = 30, p = 0.048). However, no significant correlations with respect to depression, VO_2peak, and other strength measures were observed. There were moderate positive correlations between LPA and QOL in IT (r = 0.626, N = 12, p = 0.030), LPA and fatigue in OT (r = 0.553, N = 17, p = 0.021), and LPA and QOL when groups were combined (r = 0.580, N = 29, p = 0.001) outside training times. Light physical activity was also negatively correlated with depression when groups were combined (r = -0.380, N = 29, p = 0.001). Moreover, there were no significant correlations between moderate, vigorous, and MVPA with depression, fatigue, and QOL during training times.

Biomarkers of Neural Health: Average BDNF concentrations in IT (87.0 ± 28.5 pg/mL) were significantly less than the average concentrations of BDNF in OT (137.1 ± 54.1 pg/mL; p = 0.010) (Figure 1). Plasma BDNF concentrations ranged from 42.4 pg/mL to 131.2 pg/mL in IT, and 62.3 pg/mL to 247.2 pg/mL in OT. Average NGF concentrations were 4.8 ± 0.5 pg/mL in IT, and 5.3 ± 1.0 pg/mL in OT (Figure 2), and there was no significant difference between groups (p = 0.26). Concentrations of NGF ranged from 4.1 pg/mL to 5.4 pg/mL in IT, and 3.9 pg/mL and 7.7 pg/mL in OT. There were no significant relationships between concentrations of BDNF and NGF with respect to any of the health-related fitness measures when IT and OT groups were combined.

The IT group had strong positive correlations between LPA and BDNF concentrations (r = 0.673, N = 11, p = 0.023) outside of training time, and LPA and BDNF concentrations (r = 0.669, N = 11, p = 0.025) during total training time. However, there was a strong negative correlation between LPA and NGF concentrations (r = -0.705, N = 10, p = 0.022) during training time. There was also a moderate negative correlation between total time spent in vigorous physical activity and NGF concentrations (r = -0.538, N = 19, p = 0.018) when groups were combined.

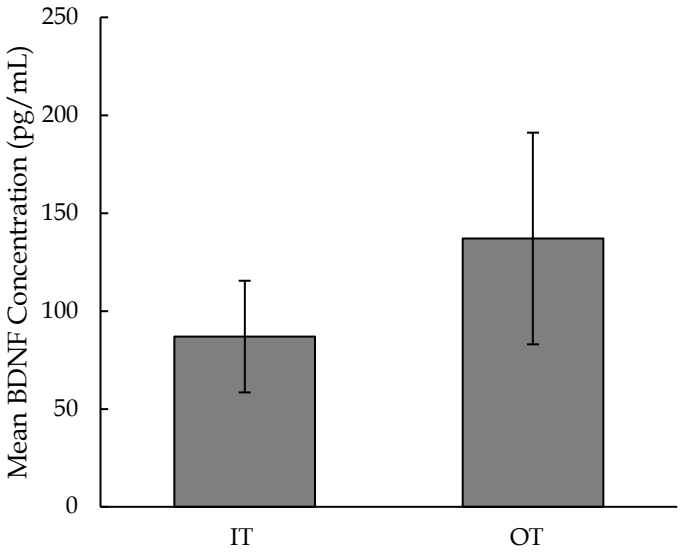

Figure 1. Mean BDNF concentrations of participants (*N* = 32). The vertical axes represent the mean concentration of brain-derived neurotrophic factor (BDNF). The horizontal axes represent each group. IT = In treatment, OT = out of treatment. The * denotes the significant decrease in BDNF of the IT group compared to the OT group, p = 0.010.

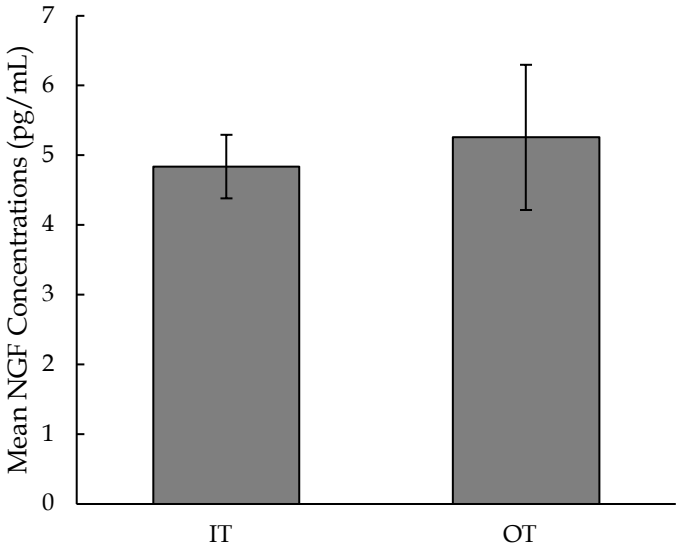

Figure 2. Mean NGF concentrations of participants (*N* = 32). The vertical axes represent the mean concentration of nerve-growth factor (NGF). The horizontal axes represent each group. IT = In treatment, OT = out of treatment. No significant differences were found between groups.

DISCUSSION

In the present study, physical activity outside of structured exercise was significantly correlated to neural health, fatigue, and QOL in cancer survivors. Concentrations of BDNF were significantly higher in the OT group and significantly correlated to LPA in the IT group. Additionally, only higher amounts of LPA outside of structured exercise was significantly correlated with fatigue and QOL in both groups.

Mean plasma BDNF concentrations were 36% higher in the OT group who were, on average, 8 months removed from cancer treatment, and engaged in 3.1% more LPA than IT. Total mean BDNF concentration in the present study was 116 pg/mL, which is 50% lower than mean concentrations in healthy older, physically active adults (30), and 211% higher than patients with advanced metastatic cancers (26). The discrepancy in BDNF concentration is most likely explained by the lingering effects of cancer treatment. Serum BDNF concentration significantly decreases in non-active, early-stage breast cancer patients before, during, and after chemotherapy (5,423, 5,313, and 4,050 pg/mL, respectively) (41), and before and after breast cancer surgery (25,523 and 21,551 pg/mL, respectively) (56). It should be noted that although serum BDNF concentration is on average 14 times greater than plasma BDNF, changes in serum positively correlate with changes in plasma BDNF (16, 53).

Interestingly, BDNF concentrations were positively correlated with LPA outside of training time in IT. This finding is similar to a report demonstrating BDNF concentration is improved with gross motor activity involving dynamic stretching, walking through obstacles, and slow breathing compared to combined resistance and aerobic training in healthy older adults 60 to 85 years old (17). The IT group spent about 18% of their outside training time engaged in LPA which may have included walking, stretching, or home-based activities. This suggests that low intensity exercise may be enough to assist with neural health and well-being in cancer survivors receiving cancer treatment and that LPA consisting of a wide variety of activities should be encouraged outside of training times. Similarly, a 6-week home-based program demonstrated that low to moderate-intensity exercise significantly can improve anxiety and mood in patients receiving chemotherapy (34). It is important to note that in healthy men, BDNF concentrations do not increase with exhaustive exercise when compared to submaximal exercise (16). Given the integral role of BDNF and its neuroprotective effects, it is possible LPA may be more beneficial for the psychological well-being of cancer patients receiving treatment compared to MVPA and may have added benefits when combined with a structured exercise program.

Plasma NGF concentrations were not different between groups and were negatively correlated with LPA during training and vigorous physical activity when training times were combined. This relationship suggests circulating concentrations of NGF may not be dependent on high levels of exercise intensity. Exercise-related increases in NGF are associated with improved spatial memory through cholinergic signaling pathways (19). In preclinical studies, NGF is sequestered into the hippocampus following exercise to aid in recovery (19). It is possible that exercise-induced NGF production amidst the effects of cancer treatment may have been utilized in a cholinergic recovery mechanism and resulted in an undetectable change (19).

Though the cancer survivors in the present study spent a minimal amount of their waking hours engaged in activity outside of training sessions, it was significantly, negatively correlated with fatigue, and significantly, positively correlated with QOL. Depression and QOL correlated with LPA outside of training times when both groups were combined, affirming the positive relationship between low-moderate physical activity and emotional well-being while receiving therapy (34), and moderate physical activity and QOL in cancer survivors removed from

treatment (50). Overall, mean total depression, fatigue, and QOL scores and associations are similar to previously reported scores from cancer survivors participating in exercise interventions. Mean total depression scores were within the "normal" range of 1-10 (3) and were 26% lower than depression scores reported from 120 cancer survivors after completing a 3-month intervention (36). Mean total fatigue fell within the "mild" range of 1-3 (44) and was 50% lower than fatigue scores reported in the aforementioned study (36), and 15% lower than scores reported from 8 cancer survivors after 10 weeks of the same structured exercise program in the present study (45). The variance in fatigue suggests treatment side effects significantly affect well-being within the first year of survivorship. In previous studies, cancer survivors were, on average, within 30 days of treatment (45), currently receiving chemotherapy and/or radiation (36), or within 6 months of completing treatment (36), while the present study assessed cancer survivors in and out of treatment. Mean total QOL was 23.4 and similar to a reported mean of 21.2 in breast cancer survivors one year after treatment (47).

These findings are intriguing especially because cancer survivors in the present study spent 78% of their days, including both training and non-training periods, engaged in sedentary behavior, and 3% of their waking hours engaged in MVPA. These results are very similar to previous reports examining movement behaviors in cancer survivors, in which 78% of waking hours were spent engaged in sedentary behavior, and less than 2% was spent engaged in MVPA (46). Significantly more sedentary behavior was expected in IT (40); however, despite a moderate effect size (d = 0.53), there were no significant differences between groups. The average overall time spent in sedentary behavior was also expected to be lower in OT. It is possible that long term fatigue, induced by cancer, cancer treatments, training sessions, or a combination of these factors, may play a role in the prevalence of sedentary behavior observed throughout the continuum of survivorship in the current study. Another possible explanation for this lack of activity increase is that cancer survivors may be developing a propensity for sedentary behavior during treatment, which persists in subsequent years. A study examining movement behaviors of breast cancer survivors for one year following treatment suggested that sedentary time is high (78%) but stable after treatment; however, it is important to note that MVPA decreased significantly in the year following treatment (46).

The participants of this study completed 180 minutes of structured exercise training, and both groups spent an average of 35% (63 minutes) performing physical activity, with 27% (17.2 minutes) of the 63 minutes in MVPA. When training times and non-training times were combined for both groups, the average MVPA was 2.7% of their waking hours, which translates to 179.2 ± 135.4 minutes and is 20% more MVPA than recommended per week (54). Furthermore, 8 out of 13 (62%) subjects in IT and 11 out of 19 (58%) subjects in OT reached the recommended 150 minutes of MVPA per week. Nonetheless, research suggests that just meeting the current MVPA recommendation may not be adequate to counteract the effects of a sedentary lifestyle (21). Increased risk related to cancer, treatments, and a sedentary lifestyle, may have a combinatorial effect resulting in an increased risk for disease. Some studies suggest this may require a higher recommendation for MVPA per week (21). Although participants in the present study were idle for the majority of their waking hours during the 7-day period, they still engaged in 162 ± 132 minutes of MVPA outside of training times which is 8% more than the

recommended 150 minutes of MVPA per week (54). Participants in this study were also similar in fitness and strength. There was a moderate relationship between VO_2peak and both moderate physical activity and MVPA outside of training. This positive relationship has been observed in many different populations (49), suggesting that emphasis on improving one or both of these components may be helpful for program goals.

There are a few noteworthy strengths and limitations in this study. The main strength of this study is that it explores physical activity both during and outside of a structured exercise program and the relationship that physical activity in these time periods may have to neural health in these cancer survivors. Data show that despite being enrolled in an exercise program, the propensity for sedentary behavior is high; however, increasing overall light physical activity may improve concentrations of BDNF more than high intensity physical activity. A limitation of this study is the small sample size that consisted of a variety of cancer types, stages, and treatments. However, this limitation may also be a strength because it provides a realistic representation of cancer survivors currently enrolled in rehabilitation programs. Additionally, during training sessions, participants spent the most time in sedentary (or in sitting) behaviors. The Actigraph accelerometer worn around the waist is limited in its ability to capture movement performed while in a seated or lying down position, such as a leg press or chest press (51).

In conclusion, this study showed that cancer survivors, both in and out of treatment, are spending nearly 78% of their waking hours in sedentary behavior even while participating in a structured, supervised exercise intervention. This is in stark contrast to the normal healthy population which spends on average 55% of their waking hours in sedentary behavior (37). With sedentary behavior now considered a health risk, this may be a cause for concern in the cancer survivor population as this could lead to the development of secondary diseases including cardiovascular and metabolic disease (9, 21-23, 42). Our results suggest that structured exercise programs for cancer survivors should encourage participants to engage in a range of additional activities outside of training times to promote the full range of health benefits associated with regular physical activity. Additionally, the neuroprotective effect of BDNF may be enhanced with LPA which may be more beneficial for the psychological well-being of cancer patients receiving treatment compared to MVPA.

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