Title
Lower Levels of Physical Activity Are Associated with Increased Severity of Chemotherapy-Induced Peripheral Neuropathy in Cancer Survivors

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Lower Levels of Physical Activity Are Associated with Increased Severity of Chemotherapy-Induced Peripheral Neuropathy in Cancer Survivors

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Dedication

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Abstract

Lower Levels of Physical Activity Are Associated with Increased Severity of Chemotherapy-Induced Peripheral Neuropathy in Cancer Survivors

By Anna Wilcoxon

Limited information exists on the effects of self-reported exercise on subjective and objective measures of chemotherapy-induced peripheral neuropathy (CIPN). In this study, we evaluated for differences in demographic and clinical characteristics, as well as subjective and objective measures of CIPN and balance among 290 cancer survivors with CIPN who were classified into one of three exercise (Ex) groups (i.e., NoEx, LessEx, RecEX) based on the recommended level of >150 minutes per week. Survivors completed self-report questionnaires and underwent a sensory examination and balance testing. Compared to RecEx group (34.8%), survivors in the NoEx group (20.7%) had less education, were less likely to be married/partnered, had a lower household income, a higher level of comorbidity, and a poorer functional status. No differences were found among the three exercise groups in duration of CIPN, pain intensity scores, or changes in light touch, cold and pain sensations. However, compared to the RecEx group, survivors in the NoEx group had higher vibratory thresholds and worse scores on objective measures of balance. Based on our “real world” findings, clinicians can recommend walking as a therapeutic option, as well as referrals to physical therapy for additional balance and strength training in survivors with CIPN.

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) occurs in 30% to 50% of cancer survivors[28,61] has negative effects on patient outcomes,[10,29] and is associated with an increased risks of falls.[29] While duloxetine is the only drug recommended to decrease CIPN pain,[22] a growing body of evidence suggests that regular physical activity is a safe and low cost intervention to decrease the severity of CIPN symptoms.[1,56] While the mechanisms that underlie the efficacy of exercise are not completely understood, findings from preclinical studies suggest that physical exercise can decrease levels of pro-inflammatory cytokines and neurotrophins; increase GABAergic inhibition; increase the upregulation of analgesic factors; activate the descending serotonin inhibitory pathway; and increase the release of endogenous opioids.[1,13,26]

In terms of clinical research, only three studies have evaluated the effects of exercise on CIPN symptoms in cancer survivors.[29,34,63] In one study,[63] breast cancer survivors with CIPN (n=20) were asked to follow a 10-week home-based exercise program that included walking and resistance exercises. The number of survivors who reported unpleasant skin sensations, abnormal sensitivity to touch, and sudden bursts of pain decreased following the intervention. In the second 12-week study that compared endurance and balance training (n=18) to only endurance training (n=19),[29] while no between group differences were found in functional performance, both groups reported decreases in sensory, motor, and autonomic scores on the CIPN20.[44] In another study that evaluated the effects of an 8-week multimodal exercise intervention on CIPN symptoms and functional deficits in 29 survivors with CIPN,[34] significant improvements in dynamic balance and CIPN20 symptoms were found following the intervention. While sample sizes were small and the exercise interventions were diverse, these findings provide preliminary evidence of the beneficial effects of exercise for CIPN.

Another approach to determine the efficacy of exercise is to evaluate for differences in CIPN characteristics in survivors who self-report that they do or do not meet the minimum recommended levels of physical exercise (i.e., $\geq$150 minutes per week).[36] In the first of two

studies that used this approach,[62] of the 134 women with breast cancer and CIPN, only 15.6% reported meeting the physical exercise recommendation. Of note, only 15% of the patients who exercised reported experiencing pain compared to 72% of the sedentary patients. In another study of colorectal cancer survivors,[37] while a definitive diagnosis of CIPN was not confirmed, in those survivors who received chemotherapy (CTX; n=506), not meeting the recommended level of physical activity was associated with increased rates of CIPN symptoms.

While these two studies suggested positive relationships between self-reported levels of physical activity and decreases in CIPN symptoms,[37,62] neither study used both subjective and objective measures of CIPN. Therefore, our study aimed to evaluate for differences in demographic and clinical characteristics, subjective and objective measures of CIPN, and measures of balance among a sample of 290 cancer survivors with CIPN who were classified into one of three exercise groups using the recommendation for physical activity from the Office of Disease Prevention and Health Promotion's Healthy People 2020 report.[45] We hypothesized that lower levels of exercise would be associated with worse scores on subjective and objective measures of CIPN and more balance problems.

Methods

Survivors and settings

The current analysis is part of a larger study, funded by the National Cancer Institute, that evaluated CIPN in cancer survivors. The methods for the parent study are described in detail elsewhere.[35] In brief, survivors were recruited from throughout the San Francisco Bay area. Survivors with CIPN met the following inclusion criteria: were $\geq$18 years of age; had received a platinum and/or a taxane compound; had completed their course of CTX $\geq$3 months prior to enrollment; had changes in sensation and/or pain in their feet and/or hands of $\geq$3 months duration following the completion of CTX; had a rating of $\geq$3 on a 0 to 10 numeric rating scale (NRS) for any one of the following sensations from the Pain Quality Assessment Scale (PQAS;[25] i.e., numb, tender, shooting, sensitive, electrical, tingling, radiating, throbbing,

cramping, itchy, unpleasant); if they had pain associated with CIPN, had an average pain intensity score in their feet and/or hands of ≥3 on a 0 to 10 NRS; had a Karnofsky Performance Status (KPS) score of ≥50; and were able to read, write, and understand English. Survivors were excluded if they had: peripheral vascular disease, vitamin B12 deficiency, thyroid dysfunction, HIV neuropathy, another painful condition that was difficult for them to distinguish from their CIPN, a hereditary sensory or autonomic neuropathy, and/or a hereditary mitochondrial disorder. Of the 1450 survivors who were screened, 754 were enrolled, and 623 (i.e., 423 with and 200 without CIPN) completed the self-report questionnaires and the study visit. For this analysis, complete data on regular exercise were available from 290 survivors with CIPN.

Study procedures

Research nurses screened and consented the survivors over the phone; sent and asked them to complete the self-report questionnaires prior to their study visit; and scheduled the in person assessment. At this assessment, written informed consent was obtained, questionnaires were reviewed for completeness, and objective measurements were done.

Study Measures

Demographic and clinical characteristics – Survivors provided information on demographic characteristics and completed the Alcohol Use Disorders Identification Test,[3] the KPS scale,[27] and the Self-Administered Comorbidity Questionnaire (SCQ).[48]

Evaluation of regular exercise Survivors completed a 6-item exercise questionnaire that asked them to report whether or not they exercised on a regular basis; what types of physical activity they engaged in at the present time (e.g., walk, swim); how many days per week they exercised; how many times per day they exercised; as well as the duration and intensity of each session. Based on responses to this questionnaire, three exercise groups were created (i.e., no exercise (NoEx); <150 minutes per week (LessEx); ≥150 minutes per week (RecEx)).

Pain questionnaires – Separate assessments were completed for pain intensity and quality ratings for the hands and feet. A detailed history of CIPN was obtained using a questionnaire from our previous[30,43] and ongoing studies. Information was obtained on the date of onset of pain and its level of interference with function. Average and worst pain intensity over the past 24 hours were assessed using 0 (no pain) to 10 (worst pain imaginable) NRS.[14]

The 20-item PQAS was used to assess the qualities associated with CIPN.[24,25] Sixteen items evaluated the magnitude of the different pain quality descriptors (e.g., sharp, hot, aching, cold) measured on a 0 to 10 NRS. Four items evaluated global and spatial qualities of pain. The PQAS has well established validity and reliability in studies of various types of neuropathic pain.[24,25]

Sensation – Light touch was evaluated using Semmes Weinstein monofilaments.[5] Cold sensation was evaluated using the Tiptherm Rod.[40,60] Pain sensation was evaluated using the Neurotip.[40] Vibration threshold was assessed using a biothesiometer.[16] For all of the measures of sensation, both the upper and lower extremities on the dominant side were tested.

Balance – Self-report questions from the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) were used to assess balance.[59] The objective measures of balance were the Timed Get Up and Go test (TUG)[33] and the Fullerton Advanced Balance (FAB) test.[21,47]

Data analysis

Data were analyzed using SPSS version 23.[53] Descriptive statistics and frequency distributions were calculated for survivors' demographic and clinical characteristics. For the four measures of sensation (i.e., light touch, cold, pain, vibration), composite scores, over all of the sites that were tested on the dominant upper and lower extremities, were created. For light touch, cold, and pain, the number of sites with loss of each sensation were summed. For vibration, the mean score across the sites was calculated.

The three exercise groups were created using the survivors' responses to the exercise questionnaire. Survivors who responded no to the question about whether or not they exercised on a regular basis were assigned to the NoEX group. The remaining two groups (i.e., survivors who exercised <150 minutes per week (LessEx) and survivors who exercised for the recommended ≥150 minutes per week (RecEx)) were assigned based on a calculation of the number of times they exercised per week, the number of times per day that they exercised, and the duration of the exercise sessions.

Differences among the three exercise groups in demographic and clinical characteristics, as well as subjective and objective measures of CIPN, were evaluated using analyses of variance, Chi square analyses, or Kruskal-Wallis tests. For the Bonferroni corrected post hoc contrasts, a p-value of <0.0167 (i.e., 0.05/3) was considered statistically significant.

Results

Classification of the Exercise Groups

Of the 290 survivors with CIPN who completed the exercise questionnaire, 20.7% were classified in the NoEx group, 44.5% in the LessEx group, and 34.8% in the RecEx group. As shown in Figures 1A to ID, compared to the RecEx group, patients in the LessEx group, exercised for fewer minutes per session as well as for fewer total minutes per week and participated in less intense exercise and for fewer days per week (all, p<.001). Figure 2 illustrates the differences in the percentages of patients in the two exercise groups who engaged in different types of exercise.

Differences in Demographic and Clinical Characteristics

As shown in Table 1, compared with the RecEx group, survivors in the NoEx group had completed significantly fewer years of education and were less likely to be married or partnered. In addition, compared to the other two exercise groups, survivors in the NoEx group had significantly lower annual household incomes.

In terms of clinical characteristics (Table 2), compared to the other two groups, survivors in the NoEx group had a significantly lower KPS score and a higher BMI. In addition, compared to the RecEx group, survivors in the NoEx group had a significantly higher number of comorbidities and a higher SCQ score.

Differences in Self-Reported Pain Characteristics

In terms of pain characteristics (Table 3), no differences were found among the exercise groups in terms of duration of CIPN and pain intensity scores. However, in terms of interference scores in the lower extremities, compared to the RecEx group, survivors in the NoEx group reported significantly higher interference scores for balance, walking ability, normal work, sleep, and overall interference. In addition, compared to the other two groups, survivors in the NoEx group reported significantly higher interference scores for enjoyment of life. In terms of pain interference scores in the upper extremities, compared to the RecEx group, survivors in the NoEx group reported significantly higher interferences scores for enjoyment of life and sleep.

Table 3 summarizes the differences among the three exercise groups in pain quality scores in the upper and lower extremities. In terms of the lower extremities, compared to the RecEx group, survivors in the NoEx group reported significantly higher PQAS scores for the following qualities: unpleasant, intense, aching, throbbing, and intense surface pain. Compared with the LessEx group, the NoEx group reported significantly higher PQAS scores in the lower extremity for throbbing and tender qualities. For the upper extremities, no significant differences were found among the three groups for any of the PQAS scores.

Differences in Objective Measures of Sensation

As shown in Table 4, compared to the RecEx group, survivors in the NoEx group had significantly higher vibration scores in the lower extremities. No statistically significant differences were found among the three exercise groups for any of the other objective measures of sensation.

Differences in balance

In terms of objective measures of balance (Table 4), compared with the RecEx group, survivors in the NoEx group had significantly higher TUG scores. In addition, compared to the other two groups, survivors in the NoEx group had significantly lower FAB scores. Compared to survivors in the RecEx groups, survivors in the LessEx group had significantly lower FAB scores.

Discussion

This study is the first to evaluate for differences in demographic and clinical characteristics, subjective and objective measures of CIPN, and measures of balance among cancer survivors with CIPN who were categorized using self-reported levels of exercise. Consistent with prior reports,[29,34,37,63] our findings support our hypothesis that lower levels of exercise would be associated with worse scores for both subjective and objective measures of CIPN, as well as more problems with balance. Compared to the survivors who met the Healthy People 2020 exercise recommendation,[45] survivors in the NoEx group had worse scores for the majority of the measures.

Given that the majority of the differences were found between the NoEx versus the RecEx, it is possible that some level of physical activity is beneficial to survivors with CIPN. However, when we evaluated, using data from the LessEx and RecEx groups, the relationships between the total number of minutes of exercise and worst pain intensity, pain interference, TUG, and FAB scores, no “dose response” effect was found for worst pain (Supplemental Figure 3A) or pain interference (Supplemental Figure 3B). For TUG (r=-.174, p=.008; Supplemental Figure 3C) and FAB (r=.191, p=.004, Supplemental Figure 3D) scores, while statistically significant, the correlations were extremely small. The actual “dose” of exercise that is sufficient to decrease CIPN signs and symptoms and improve balance remains to be determined.

In our study, while 34.8% of the survivors reported that they exercised for ≥150 minutes per week, this percentage is lower than the 87.7% reported in a Dutch registry study,[37] but higher than the 15.7% reported by breast cancer survivors with CIPN in the United States.[62] Our findings are consistent with previous studies of cancer survivors that found that self-reported rates of physical activity ranged from 30% to 37%.[4,42]

Compared to the RecEx group, survivors in the NoEx group had fewer years of education, were less likely to be married or partnered, and reported a lower annual household income. While these characteristics were not evaluated in previous CIPN studies,[29,37,63] evidence from the general population suggests that these same demographic characteristics are associated with lower levels of exercise.[6] In several studies,[2,12,23] lacking someone to help motivate an individual to exercise and not having sufficient resources to join a gym or exercise group, as well as lack of time were cited as significant barriers to increasing physical activity.

Consistent with previous studies, compared to the other two exercise groups, survivors in the NoEx group had a higher BMI[4,7] and poorer functional status.[57] However, for all of our exercise groups, their BMIs were in the overweight range.[9] In terms of functional status, the decrement found between the RecEx and NoEx groups represents not only a statistically significant but a clinically meaningful decrease in KPS score (i.e., Cohen's d=0.7). In addition, and consistent with reports from the general population,[41,46] compared to the RecEx group, survivors in the NoEx group had a worse comorbidity profile. While no differences were found among our exercise groups in the occurrence rates for specific comorbidities, as noted in recent reports regarding the need to tailor exercise regimens for various chronic conditions,[20,41] clinicians need to identify survivors who warrant referrals to physical therapy. These therapists can develop exercise interventions that accommodate not only the deficits associated with CIPN but those that are required for other chronic conditions. It should be noted that no differences were found among our exercise groups in the types of CTX regimens and doses of neurotoxic drugs the survivors received.

This study is the first detailed examination of the associations between a comprehensive set of subjective measures of CIPN (i.e., duration, intensity, qualities, interference) and self-reported levels of exercise. It is difficult to compare findings across previous studies of self-reported exercise[37,62] because of the variability in the subjective measures that were used. While we found no differences among our exercise groups in the duration of CIPN and the severity of upper and lower extremity pain, these findings require confirmation because none of the previous studies reported on differences in either of these characteristics. Findings regarding the effects of exercise on pain intensity in oncology patients[58] and patients with chronic pain[17,38] are inconsistent. For example, in two studies of oncology patients, one found a decrease[18] while the other found no change[11] in pain intensity. In the two reviews of the effects of exercise on chronic non-cancer pain,[17,38] the authors suggested that the effects of exercise on pain intensity were inconsistent and were dependent on both the type of exercise and the type of chronic pain evaluated.

While no differences were found among the exercise groups in any of the pain quality scores in the upper extremities, consistent with previous reports,[15,29,37] compared to the RecEX group, survivors in the NoEx group reported higher scores for unpleasant, intense, aching, and throbbing. The lack of effect of exercise on pain qualities in the hands may be partially explained by the fact that the most common type exercise in our study was walking which is not likely to have an effect on symptoms in the upper extremities.

Compared to the RecEX group, survivors in the NoEX group reported higher pain interference scores in their lower extremities for sleep, enjoyment of life, normal work, walking ability, and balance and in their upper extremities for enjoyment of life and sleep. While prior studies reported significant improvements in CIPN20 scores associated with exercise,[29,37] no studies have used the interference items from the Brief Pain Inventory (BPI). While we adapted one of the BPI items to assess the effects of CIPN on upper extremity function (i.e., interference with routine activities like dressing, toileting, typing), additional research is needed using items

that are more specific to hand- and arm-related activities (e.g., manipulation of small objects), as well as exercises that are tailored for the upper extremities.

Of all of the objective measures of sensation that were evaluated, vibration was the only one that demonstrated significant between group differences. Compared to the RecEx group, survivors in the NoEx group had higher vibration thresholds in the lower extremities. These findings are consistent with a pilot study that found significant improvements in vibration thresholds but no differences in light touch sensation in oncology patients randomized to either sensorimotor training or whole body vibration training.[55]

While between 64.4% (RecEx) and 81.7% (NoEx) of the survivors reported balance problems that were moderately severe, frequent, and distressing, no differences were found among the exercise groups in their self-reports of balance problems. However, compared to the RecEX group, survivors in the NoEx group had worse scores on both the TUG and FAB tests. Our results are consistent with the findings from a systematic review on the effects of exercise in patients with CIPN undergoing active treatment,[15] as well as findings in the geriatric literature that demonstrate that exercise decreases the risk of falls.[19,51]

Limitations

Several limitations warrant consideration. In this study, because only survivors who had received platinum- and/or taxane-containing regimens were evaluated, we cannot determine whether these findings generalize to survivors who received other types of neurotoxic CTX. The cross-sectional nature of this study limits our ability to determine causal associations between various CIPN characteristics and levels of physical activity. While levels of exercise prior to and during CTX were not evaluated, findings from one study suggest that level of physical activity prior to a cancer diagnosis is a strong predictor of activity up to 10 years post-diagnosis.[32] While self-reported levels of exercise, rather than objective measures of exercise, are susceptible to recall and social desirability biases,[8] self-reported physical activity is moderately correlated with data obtained using an accelerometer.[31,39,52]

Conclusions

Despite these limitations, our findings suggest that the lack of regular exercise in cancer survivors is associated with worse scores on both subjective and objective measures of CIPN and objective balance scores. With the projected increase in the number of cancer survivors in the United States to 20 million by 2026,[36] as well as the lack of effective treatments for numbness, tingling, and pain associated with CIPN,[22] it is critical to evaluate cost effective and readily available strategies (e.g., walking) to improve CIPN symptoms and balance problems. A growing body of evidence suggests that both patients and survivors can safely engage in moderate amounts of exercise during and after cancer treatment.[49,50,54] Based on our "real world findings", as well as the findings from a limited number of studies on the efficacy of exercise for CIPN symptoms and balance problems that suggest benefits,[1,29,34] clinicians can recommend walking as a therapeutic option, as well as provide referrals to physical therapy for additional strength and balance training. Prospective longitudinal studies are needed to determine the "optimal dose" and types of exercise that are needed to prevent and treat CIPN symptoms and balance problems. In addition, preclinical and clinical studies are warranted to determine the mechanisms that underlie the therapeutic benefits of exercise for CIPN.

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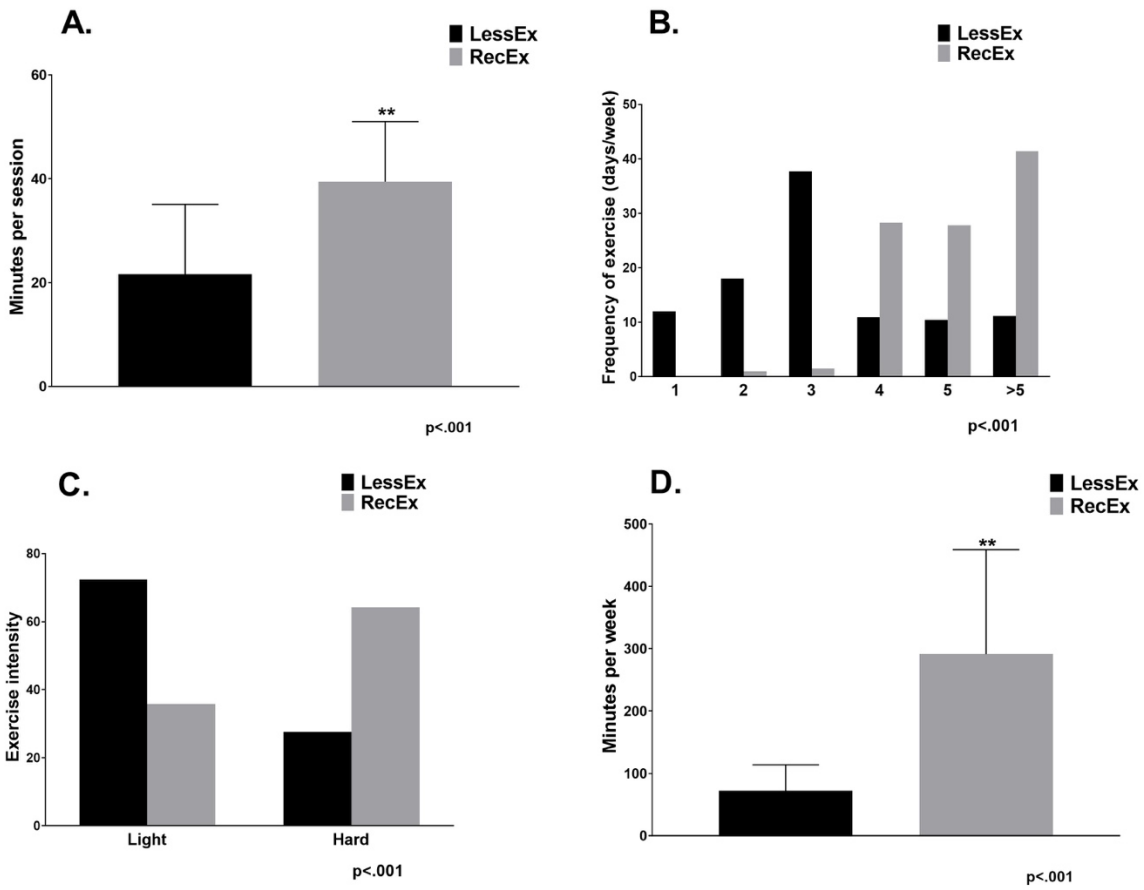


Figure 1 – Differences between the <150 minutes per week (LessEx) and ≥150 minutes per week (RecEx) of recommended exercise groups in minutes per session (A), frequency of exercise (B), exercise intensity (C), and minutes of exercise per week (D).

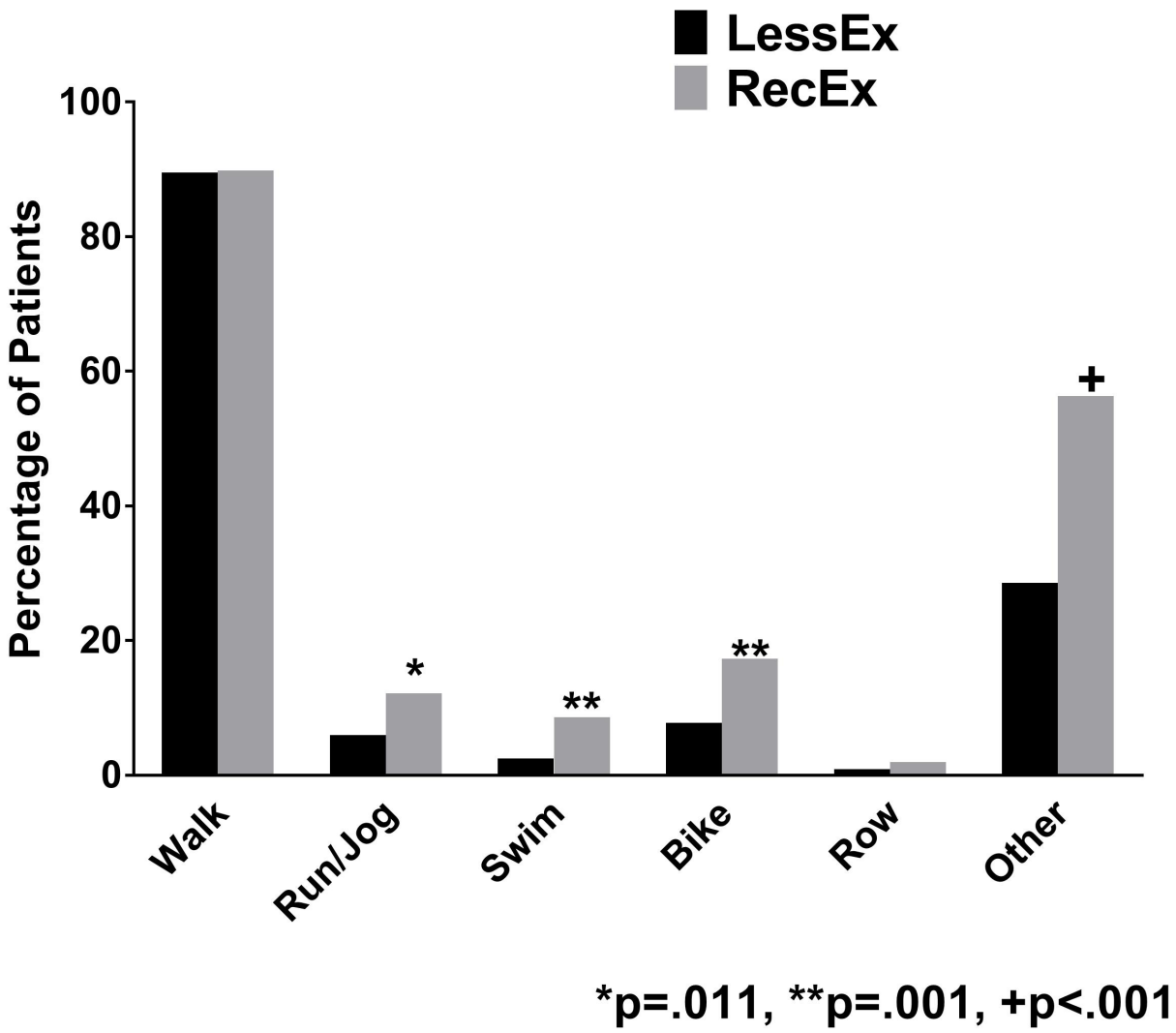
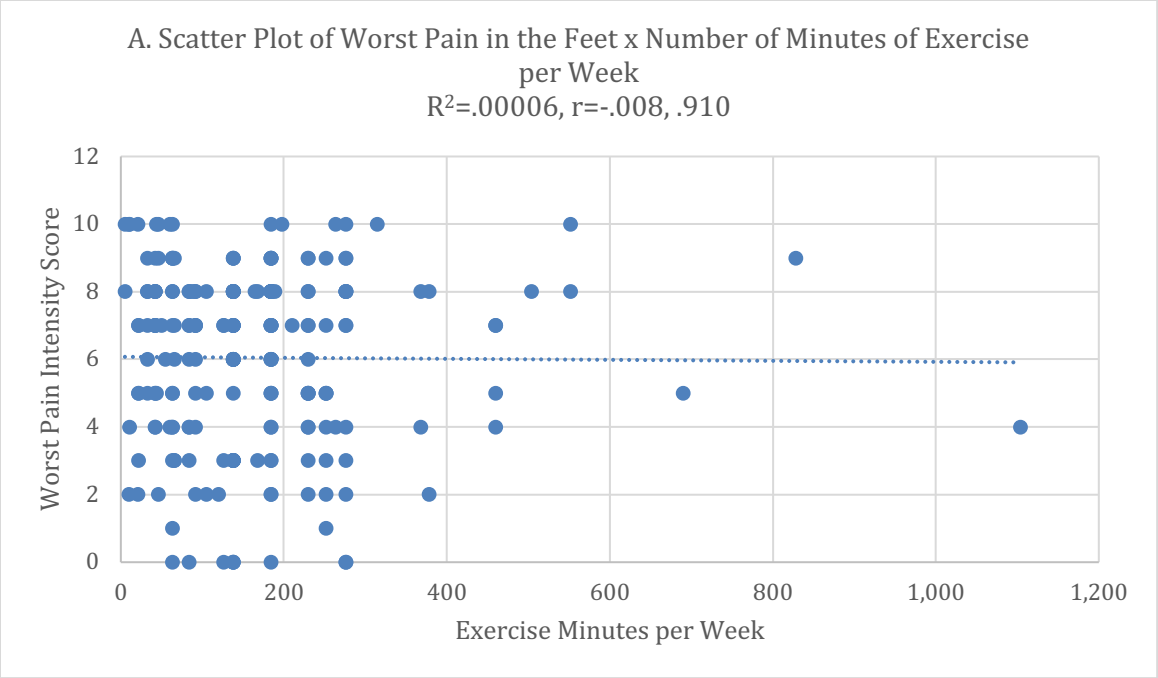
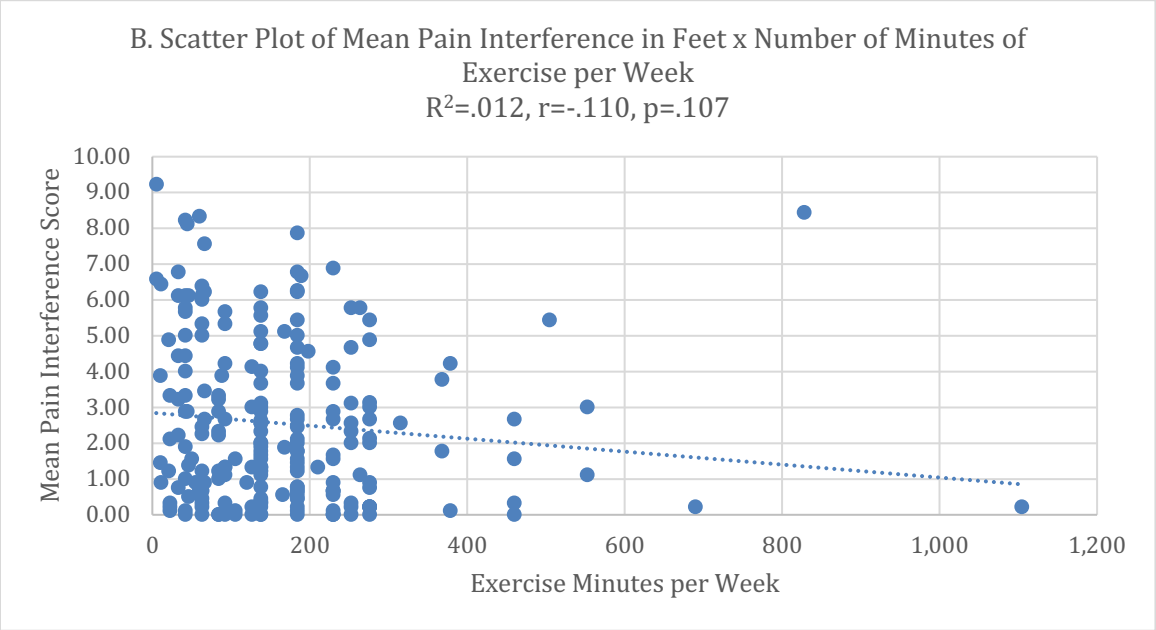


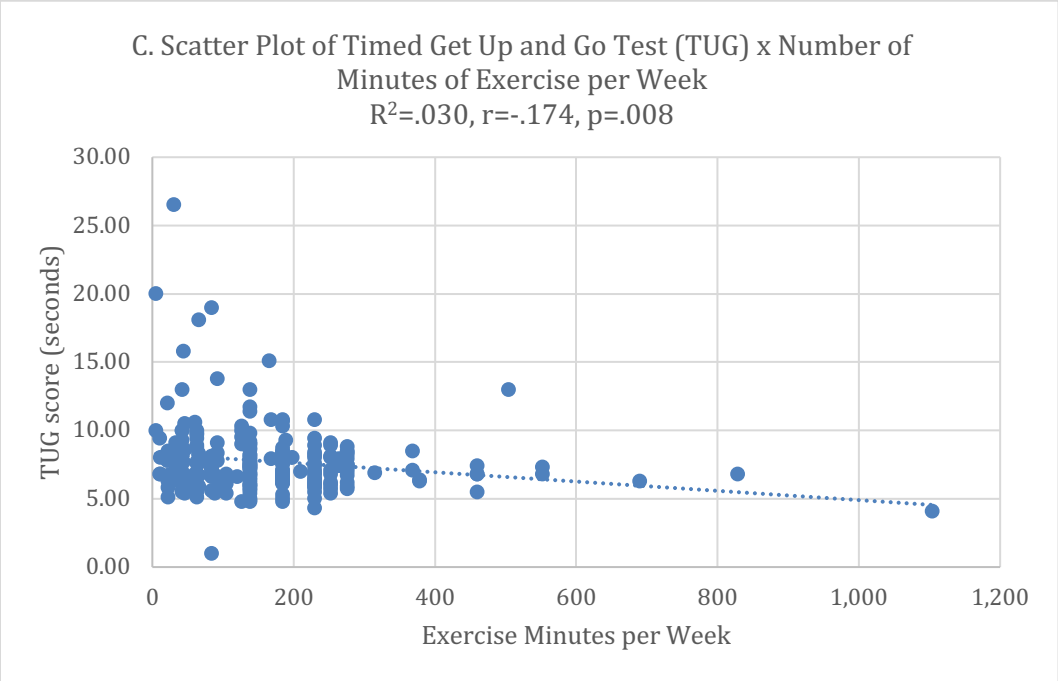
Figure 2 – Differences between the <150 minutes per week (LessEx) and ≥150 minutes per week (RecEx) of recommended exercise groups in the types of exercise used.



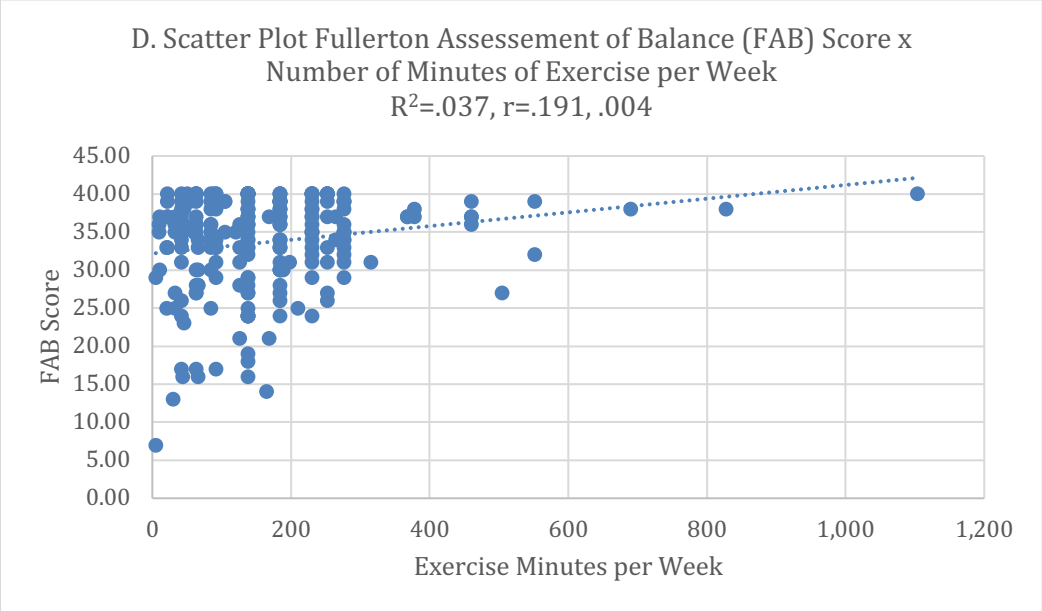
Supplemental Figure 3A



Supplemental Figure 3B



Supplemental Figure 3C



Supplemental Figure 3D

Table 1 – Differences in Demographic Characteristics Among the Exercise Groups[a]

Characteristic	NoEx (1) 20.7% (n=60)	LessEx (2) 44.5% (n=129)	RecEx (3) 34.8% (n=101)	Test, p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	61.1 (10.6)	60.2 (11.4)	61.3 (10.2)	F = 0.35, p = .708
Education (years)	15.6 (2.9)	16.5 (3.2)	16.9 (2.2)	F = 3.75, p = .025 1<3
	% (n)	% (n)	% (n)	
Female	80.0 (48)	87.5 (112)	89.1 (90)	X_2 = 2.87, p = .238
Married/partnered	43.9 (25)	62.7 (79)	64.6 (64)	X_2 = 7.41, p = .025 1<3
Lives alone	40.7 (24)	28.8 (36)	24.2 (24)	X_2 = 4.87, p = .088
Employed	28.3 (17)	40.6 (52)	36.6 (37)	X_2 = 2.66, p = .265
Ethnicity White Asian/Pacific Islander Black Hispanic/Mixed/Other	 68.3 (41) 5.0 (3) 8.3 (5) 18.3 (11)	 75.2 (97) 9.3 (12) 7.0 (9) 8.5 (11)	 78.2 (79) 7.9 (8) 4.0 (4) 9.9 (10)	X_2 = 6.58, p = .361
Annual household income <$30,000 $30,000 - $69,999 $70,000 - $99,999 >$100,000	 46.4 (26) 21.4 (12) 16.1 (9) 16.1 (9)	 21.7 (26) 26.7 (32) 12.5 (15) 39.2 (47)	 18.5 (17) 13.0 (12) 19.6 (18) 48.9 (45)	KW, p < .0001 1<2 and 3
Child care responsibilities (% yes)	11.7 (7)	18.6 (24)	13.3 (13)	X_2 = 2.01, p = .366
Adult care responsibilities (% yes)	9.6 (5)	2.5 (3)	2.2 (2)	X_2 = 6.05, p = .049 No significant pairwise comparison

Abbreviations: KW = Kruskal Wallis test, SD = standard deviation

[a]Exercise groups = NoEx – patients who reported that they did not exercise on a regular basis; LessEx = patients who exercised <150 minutes per week; RecEx – patients who exercised for the recommended ≥150 minutes per week

Table 2 – Differences in Clinical Characteristics Among the Exercise Groups[a]

Characteristic	NoEx (1) 20.7% (n=60)	LessEx 44.5% (n=129)	RecEx(3) 34.8% (n=101)	Test, p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Karnofsky Performance Status score	77.0 (10.9)	83.8 (10.1)	84.4 (9.7)	F = 11.65, p <.001 1<2 and 3
Body mass index (kg/m_2)	29.0 (6.3)	26.3 (6.0)	26.2 (5.1)	F = 5.23, p = .006 1>2 and 3
Number of comorbidities	2.4 (1.6)	2.1 (1.4)	1.7 (1.4)	F = 4.31, p = .014 1>3
Self-Administered Comorbidity Questionnaire score	5.5 (4.1)	4.3 (3.2)	3.7 (3.1)	F = 5.22, p = .006 1>3
Alcohol Use Disorders Identification Test score	2.2 (2.7)	2.1 (1.9)	2.2 (2.1)	F = 0.78, p = .925
Years since cancer diagnosis	3.9 (3.5)	5.2 (5.6)	4.8 (4.8)	F = 1.43, p = .240
Number of prior cancer treatments	3.0 (1.0)	3.1 (1.0)	3.1 (0.9)	F = 0.61, p = .545
Number of current cancer treatments	0.3 (0.5)	0.4 (0.6)	0.4 (0.6)	F = 0.56, p = .574
Number of metastatic sites (out of 7)	0.8 (0.7)	0.8 (0.9)	0.7 (0.6)	F = 0.19, p = .829
Number of metastatic sites without lymph node involvement	0.3 (0.5)	0.3 (0.7)	0.1 (0.4)	F = 2.35, p = .097
	% (n)	% (n)	% (n)	
Smoker (ever)	41.7 (25)	37.8 (48)	38.6 (39)	X_2 = 0.26, p = .877
Born prematurely (% yes)	5.8 (3)	6.0 (7)	8.5 (8)	X_2 = 0.62, p = .733
Surgery on arms (% yes)	25.0 (15)	17.8 (23)	22.0 (22)	X_2 = 1.42, p = .491
Surgery on hands (% yes)	15.3 (9)	7.8 (10)	9.9 (10)	X_2 = 2.48, p = .290
Surgery on legs (% yes)	20.3 (12)	23.4 (30)	23.7 (23)	X_2 = 0.28, p = .871
Surgery on feet (% yes)	21.7 (13)	12.5 (16)	18.4 (18)	X_2 = 2.91, p = .234
Injury to arms (% yes)	25.9 (15)	27.8 (35)	29.0 (29)	X_2 = 0.18, p = .914
Injury to hands (% yes)	33.9 (19)	31.3 (40)	42.1 (40)	X_2 = 2.88, p = .237
Injury to legs (% yes)	20.0 (12)	18.8 (24)	22.7 (22)	X_2 = 0.53, p = .767
Injury to feet (% yes)	29.3 (17)	22.0 (28)	28.9 (28)	X_2 = 1.78, p = .411
Comorbid conditions (% yes)				
Osteoarthritis	35.0 (21)	33.3 (43)	30.7 (31)	X_2 = 0.35, p = .839
Back pain	38.3 (23)	39.5 (51)	32.7 (33)	X_2 = 1.21, p = .545
Depression	33.3 (20)	24.0 (31)	20.8 (21)	X_2 = 3.25, p = .197
High blood pressure	33.3 (20)	26.4 (34)	24.8 (25)	X_2 = 1.49, p = .475
Heart disease	6.7 (4)	8.5 (11)	8.9 (9)	X_2 = 0.27, p = .874
Diabetes	6.7 (4)	3.9 (5)	5.0 (5)	X_2 = 0.70, p = .705
Lung disease	6.7 (4)	4.7 (6)	1.0 (1)	X_2 = 3.79, p = .150
Anemia or blood disease	6.7 (4)	5.4 (7)	5.0 (5)	X_2 = 0.22, p = .897
Ulcer or stomach disease	1.7 (1)	5.4 (7)	2.0 (2)	X_2 = 2.74, p = .254
Kidney disease	3.3 (2)	2.3 (3)	1.0 (1)	X_2 = 1.10, p = .578
Liver disease	5.0 (3)	1.6 (2)	2.0 (2)	X_2 = 2.19, p = .334
Rheumatoid arthritis	5.0 (3)	2.3 (3)	1.0 (1)	X_2 = 2.58, p = .276
Type of cancer				
Breast	48.3 (29)	55.0 (71)	52.5 (53)	
Colon	8.3 (5)	10.9 (14)	10.9 (11)	
Lung	1.7 (1)	4.7 (6)	0.0 (0)	X_2 = 7.98, p = .436
Ovarian	11.7 (7)	9.3 (12)	10.9 (11)	
Other	30.0 (18)	20.2 (26)	25.7 (26)	
Any metastatic disease	66.7 (40)	56.3 (72)	66.3 (65)	X_2 = 3.12, p = .210
Chemotherapy regimen				
Only a platinum compound	23.3 (14)	24.8 (32)	21.8 (22)	
Only a taxane compound	41.7 (25)	45.7 (59)	46.5 (47)	X_2 = 0.84, p = .933
Both a platinum and a taxane compound	35.0 (21)	29.5 (38)	31.7 (32)	
Dose of platinum compound for patients who received only a platinum (mg/m_2)	908.5 (895.6)	631.1 (336.6)	793.9 (396.0)	F = 1.41, p = .253
Dose of taxane compound for patients who received only a taxane (mg/m_2)	829.9 (213.9)	870.8 (1145.9)	764.4 (295.3)	F = 0.22, p =.807
Dose of drugs for patients who received both a platinum and a taxane compound				
Platinum dose (mg/m_2)	1798.5 (1005.0)	1619.2 (800.9)	1747.3 (485.7)	F = 0.41, p = .663
Taxane dose (mg/m_2)	1009.9 (479.6)	803.6 (438.7)	937.6 (457.3)	F = 1.51, p =.227
Patients who had a dose reduction or delay due to neuropathy (% (n))	11.9 (7)	16.7 (20)	12.6 (12)	X_2 = 1.05, p = .591

Abbreviations: kg = kilograms, m_2 = meters squared, mg = milligrams, SD = standard deviation

[a]Exercise groups = NoEx – patients who reported that they did not exercise on a regular basis; LessEx = patients who exercised <150 minutes per week; RecEx – patients who exercised for the recommended ≥150 minutes per week

Table 3 – Differences in Pain Characteristics Among the Exercise Groups[a]

Characteristic	NoEx (1) 20.7% (n=60)	LessEx (2) 44.5% (n=129)	RecEx (3) 38.4% (n=101)	Test, p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Pain Characteristics – Lower Extremity				
Duration of CIPN (years)	3.5 (3.4)	4.2 (4.9)	3.8 (4.2)	F = 0.60, p = .549
Pain now	4.1 (2.2)	3.8 (2.4)	3.4 (2.2)	F = 1.74, p = .178
Average pain	4.5 (2.1)	4.2 (2.2)	3.8 (2.1)	F = 1.94, p = .145
Worst pain	6.2 (2.4)	6.0 (2.6)	6.1 (2.6)	F = 0.18, p = .837
Days per week in pain	4.7 (3.0)	3.6 (2.9)	3.7 (3.0)	F = 2.94, p = .055
Hours per day in pain	15.2 (8.9)	15.4 (9.3)	14.9 (9.7)	F = 0.08, p = .925
Pain Characteristics – Upper Extremity				
Duration of CIPN (years)	3.2 (3.5)	4.2 (5.0)	3.2 (3.4)	F = 1.36, p = .259
Pain now	2.9 (2.1)	2.8 (2.1)	2.8 (2.1)	F = 0.03, p = .970
Average pain	3.3 (2.2)	3.2 (2.2)	3.0 (2.0)	F = 0.25, p = .778
Worst pain	4.6 (2.8)	4.6 (2.6)	4.5 (2.8)	F = 0.04, p = .961
Days per week in pain	4.1 (3.0)	3.8 (3.0)	3.5 (3.0)	F = 0.67, p = .513
Hours per day in pain	13.4 (9.5)	12.1 (9.8)	13.8 (10.1)	F = 0.61, p = .546
Pain Interference Scale – Lower Extremity				
Balance	4.9 (3.2)	3.8 (3.1)	3.3 (3.1)	F = 5.28, p = .006 1>3
Walking ability	4.7 (3.0)	3.6 (3.1)	3.1 (3.0)	F = 4.92, p = .008 1>3
Enjoyment of life	4.1 (2.9)	3.0 (2.8)	2.4 (2.5)	F = 6.18, p = .002 1> 2 and 3
Normal work	3.7 (2.8)	2.9 (3.0)	2.5 (2.8)	F = 3.12, p = .046 1>3
Sleep	3.6 (3.2)	2.9 (2.9)	2.1 (2.4)	F = 5.30, p = .006 1>3
General activity	3.5 (2.8)	2.9 (2.6)	2.6 (2.8)	F = 2.05, p = .130
Mood	2.8 (2.5)	2.6 (2.6)	2.5 (2.6)	F = 0.17, p = .848
Relations with other people	2.5 (2.7)	1.7 (2.4)	1.5 (2.3)	F = 3.03, p = .050
Sexual activity	1.6 (2.8)	0.9 (2.1)	0.8 (1.9)	F = 2.10, p = .125
Mean interference score	3.5 (2.4)	2.7 (2.3)	2.3 (2.3)	F = 5.06, p = .007 1 > 3
Pain Interference Scale – Upper Extremity				
Routine activities+	3.0 (3.0)	2.7 (2.8)	2.3 (2.6)	F = 1.00, p = .373
Walking ability	0.8 (2.2)	0.6 (1.6)	0.2 (0.7)	F = 2.17, p = .117
Enjoyment of life	3.2 (3.2)	2.1 (2.8)	1.8 (2.3)	F = 3.98, p = .020 1>3
Normal work	3.4 (2.9)	3.0 (2.9)	2.4 (2.5)	F = 1.98, p = .141
Sleep	2.5 (3.1)	1.4 (2.5)	1.3 (2.0)	F = 3.73, p = .026 1>3
General activity	3.0 (3.1)	2.6 (2.7)	2.2 (2.5)	F = 1.27, p = .284
Mood	2.5 (2.6)	1.9 (2.5)	2.1 (2.1)	F = 1.15, p = .319
Relations with other people	0.9 (1.6)	0.8 (1.8)	0.8 (1.6)	F = 0.10, p = .907
Sexual activity	0.9 (2.3)	0.8 (2.2)	0.4 (1.3)	F = 1.26, p = .285
Mean interference score	2.3 (2.3)	1.8 (2.0)	1.5 (1.6)	F = 2.32, p = .101
Pain Qualities Assessment Scale Scores – Lower Extremity				
Numb	5.8 (3.0)	5.5 (3.1)	5.1 (3.0)	F = 1.21, p = .299
Unpleasant	5.3 (2.6)	4.6 (2.4)	4.1 (2.7)	F = 3.78, p = .024 1>3
Tingling	5.1 (2.8)	4.2 (2.8)	4.0 (3.2)	F = 2.82, p = .061
Intense	4.2 (2.4)	3.4 (2.6)	3.0 (2.6)	F = 3.94, p = .021 1>3
Dull	3.7 (2.7)	2.6 (2.5)	3.2 (2.8)	F = 3.08, p = .047
Cramping	3.6 (3.4)	2.7 (3.2)	2.8 (3.3)	F = 1.62, p = .199
Electrical	2.9 (3.1)	2.1 (2.8)	2.5 (3.1)	F = 1.35, p = .262
Shooting	3.1 (3.0)	2.2 (2.9)	2.2 (2.8)	F = 1.97, p = .141
Sharp	2.7 (2.8)	2.1 (2.9)	2.6 (3.1)	F = 0.98, p = .376
Aching	3.2 (3.1)	2.2 (2.6)	2.0 (2.8)	F = 3.84, p = .023 1>3
Heavy	2.4 (2.8)	2.2 (2.7)	2.0 (2.8)	F = 0.45, p = .638
Cold	2.8 (3.3)	2.2 (2.9)	1.9 (2.7)	F = 1.88, p = .155
Radiating	2.7 (3.1)	1.8 (2.5)	2.1 (2.9)	F = 2.02, p = .134
Hot	2.9 (3.1)	2.0 (2.7)	2.1 (2.8)	F = 2.23, p = .109
Tender	2.7 (2.9)	1.7 (2.4)	2.2 (2.6)	F = 3.34, p = .037 1>2
Sensitive skin	2.7 (3.0)	1.9 (2.2)	1.7 (2.3)	F = 3.03, p = .050
Throbbing	3.0 (3.2)	1.5 (2.4)	1.6 (2.5)	F = 6.76, p = .001 1> 2 and 3
Itchy	1.1 (2.1)	1.3 (2.4)	0.8 (1.9)	F = 1.04, p = .356
Intense – surface pain	4.3 (2.8)	3.3 (2.7)	3.0 (2.8)	F = 3.98, p = .020 1>3
Intense – deep pain	3.7 (2.7)	3.3 (2.9)	3.2 (2.9)	F = 0.68, p = .508
Pain Qualities Assessment Scale Scores – Upper Extremity				
Numb	3.4 (2.4)	4.3 (2.9)	3.7 (2.9)	F = 2.09, p = .126

Table 3 – Differences in Pain Characteristics Among the Exercise Groups[a]

Characteristic	NoEx (1) 20.7% (n=60)	LessEx (2) 44.5% (n=129)	RecEx (3) 38.4% (n=101)	Test, p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Unpleasant	4.2 (2.6)	3.6 (2.5)	3.5 (2.4)	F = 1.06, p = .349
Tingling	3.2 (2.6)	3.3 (2.7)	3.3 (3.2)	F = 0.01, p = .987
Intense	3.0 (2.3)	2.6 (2.4)	2.5 (2.3)	F = 0.65, p = .523
Dull	2.7 (2.6)	2.3 (2.5)	2.1 (2.3)	F = 0.68, p = .510
Cramping	2.2 (2.9)	1.6 (2.6)	1.6 (2.3)	F = 0.95, p = .389
Electrical	1.9 (2.5)	1.7 (2.5)	2.1 (3.0)	F = 0.34, p = .712
Shooting	1.7 (2.4)	1.7 (2.6)	1.5 (2.5)	F = 0.18, p = .835
Sharp	1.2 (2.0)	1.3 (2.3)	1.5 (2.2)	F = 0.20, p = .816
Aching	2.5 (3.1)	1.8 (2.3)	1.5 (2.3)	F = 2.29, p = .104
Heavy	1.6 (2.5)	1.5 (2.5)	0.9 (1.8)	F = 2.00, p = .138
Cold	1.6 (2.5)	1.9 (2.6)	1.1 (2.3)	F = 2.00, p = .138
Radiating	1.7 (2.5)	1.5 (2.5)	1.0 (1.9)	F = 1.83, p = .162
Hot	1.6 (2.4)	1.1 (2.2)	0.8 (1.8)	F = 1.90, p = .152
Tender	1.7 (2.4)	1.6 (2.3)	1.6 (2.3)	F = 0.05, p = .949
Sensitive skin	1.9 (2.4)	1.3 (2.1)	1.2 (2.1)	F = 1.56, p = .212
Throbbing	1.8 (2.8)	1.3 (2.1)	1.2 (2.3)	F = 1.06, p = .347
Itchy	0.8 (2.0)	1.0 (2.0)	0.6 (1.7)	F = 0.87, p = .421
Intense – surface pain	3.0 (2.8)	3.1 (2.5)	3.1 (2.7)	F = 0.03, p = .973
Intense – deep pain	2.7 (2.9)	2.3 (2.6)	2.3 (2.5)	F = 0.34, p = .709

+Dressing, toileting, typing

Abbreviations: CIPN = chemotherapy-induced peripheral neuropathy, SD = standard deviation

[a]Exercise groups = NoEx – patients who reported that they did not exercise on a regular basis; LessEx = patients who exercised <150 minutes per week; RecEx – patients who exercised for the recommended ≥150 minutes per week

Table 4 – Differences in Sensation and Balance Measures Among the Exercise Groups+

Characteristic*	NoEx (1) 20.7% (N=60)	LessEx (2) 44.5% (N=129)	RecEx (3) 38.4% (N=101)	Statistic; p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Sensation Measures+				
Light touch – upper extremity sites (out of 7)a	0.2 (0.6)	0.3 (1.1)	0.1 (0.7)	F = 1.07, p = .345
Light touch – lower extremity sites (out of 9)b	2.5 (2.0)	2.2 (2.5)	2.0 (2.2)	F = 0.76, p = .471
Cold – upper extremity sites out of 4c	1.0 (0.8)	0.8 (1.0)	0.8 (1.1)	F = 0.66, p = .515
Cold – lower extremity sites out of 4d	2.2 (1.1)	2.3 (1.2)	2.3 (1.1)	F = 0.24, p = .784
Pain – upper extremity sites (out of 7)e	1.4 (1.5)	1.1 (1.4)	1.1 (1.4)	F = 0.92, p = .400
Pain – lower extremity sites (out of 9)f	3.6 (2.0)	3.4 (2.3)	3.2 (2.2)	F = 0.89, p = .411
Vibration – upper extremity sites (volts)g	9.1 (3.2)	9.9 (6.0)	8.7 (3.8)	F = 1.71, p = .183
Vibration – lower extremity sites (volts)h	31.2 (12.1)	27.3 (11.8)	26.5 (12.3)	F = 3.17, p = .044 1>3
Balance Measures				
Trouble with balance (% yes (n))i	81.7 (49)	66.7 (84)	64.4 (65)	X_2 = 5.84, p = .054
Severity of balance trouble (0 to 10)j	5.4 (2.6)	4.7 (2.7)	5.3 (2.6)	F = 1.22, p = .296
Frequency of balance trouble (0 to 10)k	5.0 (2.9)	4.9 (3.1)	4.5 (2.9)	F = 0.42, p = .656
Distress from balance trouble (0 to 10)l	5.8 (2.9)	5.4 (2.9)	5.4 (3.0)	F = 0.44, p = .643
Timed get up and go test (>13.5 seconds = higher risk for falls)	8.6 (2.6)	8.0 (3.1)	7.4 (1.7)	F = 4.40, p = .013 1>3
Fullerton Advanced Balance test (≤25 is associated with a higher risk of falls)	30.3 (8.26)	32.7 (7.0)	34.9 (4.9)	F = 8.83, p <.001 1<2 and 3; 2<3

*When available, the clinically meaningful cut-point score is provided in parentheses next to the characteristic.

+Exercise groups = NoEx – patients who reported that they did not exercise on a regular basis; LessEx = patients who exercised <150 minutes per week; RecEx – patients who exercised for the recommended ≥150 minutes per week

Changes in sensation are reported for the dominant extremity

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