Association Between Physical Activity Levels and Chemotherapy-Induced Peripheral Neuropathy Severity in Cancer Survivors

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OBJECTIVES: To evaluate for differences in demographic and clinical characteristics, as well as subjective and objective measures of chemotherapy-induced peripheral neuropathy (CIPN), among different exercise groups.

SAMPLE & SETTING: Cancer survivors (N = 290) were recruited from throughout the San Francisco Bay Area.

METHODS & VARIABLES: Based on the recommended 150 minutes or more of exercise per week, survivors were classified into the no exercise (NoEx), less exercise (LessEx), or recommended exercise (RecEx) group. Survivors completed self-report questionnaires and underwent sensory and balance testing.

RESULTS: Compared to the RecEx group, survivors in the NoEx group had less education, were less likely to be married/partnered, had a lower household income, had a higher level of comorbidity, and had poorer functional status. No differences were found among the groups in CIPN duration; pain intensity scores; or changes in light touch, cold, and pain sensations.

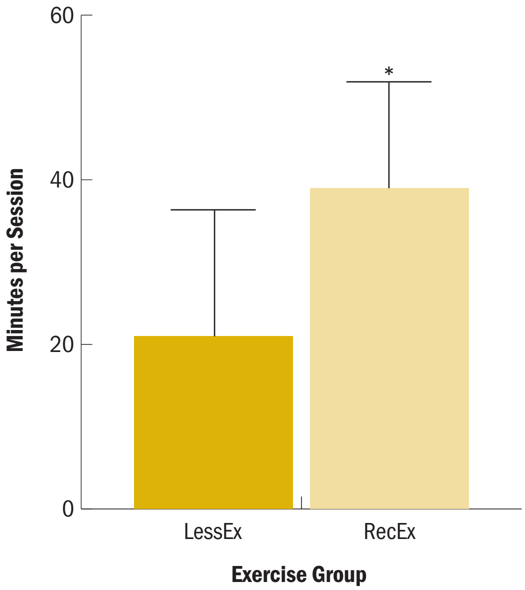
IMPLICATIONS FOR NURSING: Clinicians can recommend walking as a therapeutic option for survivors with CIPN and refer them to physical therapy.

KEYWORDS chemotherapy-induced peripheral neuropathy; exercise; chemotherapy; gait; balance
***ONF, 47*(6), 703–719.**
DOI 10.1188/20.ONF.703-719

Chemotherapy-induced peripheral neuropathy (CIPN) occurs in 30%–50% of cancer survivors (Kerckhove et al., 2017; Vollmers et al., 2018), has negative effects on patient outcomes (Chan et al., 2019; Kneis et al., 2019), and is associated with an increased risk of falls (Kneis et al., 2019). Although duloxetine is the only drug recommended to decrease CIPN pain (Hershman et al., 2014), a growing body of evidence suggests that regular physical activity is a safe and low-cost intervention to decrease the severity of CIPN symptoms (Andersen Hammond et al., 2019; Streckmann et al., 2014). The mechanisms that underlie the efficacy of exercise are not completely understood, but findings from preclinical studies suggest that physical exercise can decrease levels of proinflammatory 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 (Andersen Hammond et al., 2019; Cooper et al., 2016; Kami et al., 2017).

In terms of clinical research, only three studies have evaluated the effects of exercise on CIPN symptoms in cancer survivors (Kneis et al., 2019; McCrary et al., 2019; Wonders et al., 2013). In one study (Wonders et al., 2013), 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

FIGURE 1. Differences Between the LessEx and RecEx Groups in Minutes per Session



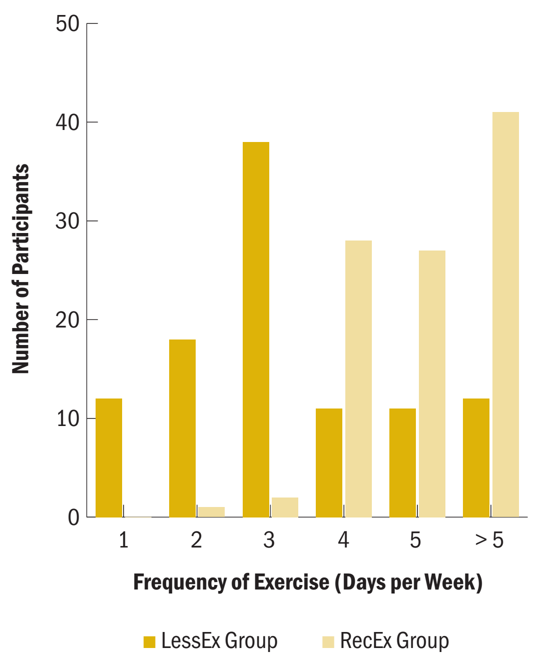
* $p < 0.001$
LessEx—patients who exercised less than 150 minutes per week; RecEx—patients who exercised for the recommended 150 minutes or more per week

study that compared endurance and balance training (n = 18) to only endurance training (n = 19) (Kneis et al., 2019), although no between-group differences were found in functional performance, both groups reported decreases in sensory, motor, and autonomic scores on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–CIPN 20-Item Scale (CIPN20) (Postma et al., 2005). In another study that evaluated the effects of an eight-week multimodal exercise intervention on CIPN symptoms and functional deficits in 29 survivors with CIPN (McCrary et al., 2019), significant improvements in dynamic balance and CIPN symptoms were found following the intervention. Although 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., 150 minutes or more per week) (Office of Disease Prevention and Health Promotion, 2018). In the first of two studies that used this approach (Wonders & Drury, 2012), 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 (Mols et al., 2015), although a definitive diagnosis of CIPN was not confirmed, in survivors who received chemotherapy (n = 506), not meeting the recommended level of physical activity was associated with increased rates of CIPN symptoms.

Although these two studies suggested positive relationships between self-reported levels of physical activity and decreases in CIPN symptoms (Mols et al., 2015; Wonders & Drury, 2012), neither study used both subjective and objective measures of CIPN. Therefore, the current 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

FIGURE 2. Differences Between the LessEx and RecEx Groups in Frequency of Exercise



LessEx—patients who exercised less than 150 minutes per week; RecEx—patients who exercised for the recommended 150 minutes or more per week and Health Promotion's (2018) Healthy People 2020 report. The authors hypothesized that lower levels of exercise would be associated with worse scores on subjective and objective measures of CIPN and more balance problems.

Methods

Sample and Setting

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 were described in detail by Miaskowski et al. (2017). Survivors were recruited from throughout the San Francisco Bay Area. Those with CIPN met the following inclusion criteria:

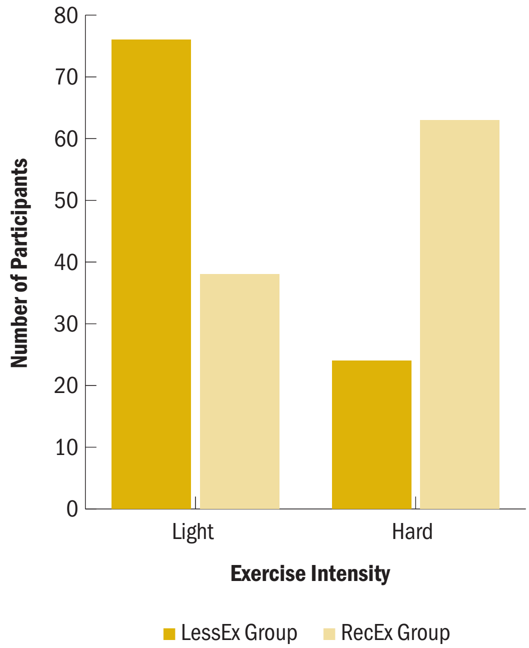
- Aged 18 years or older
- Had received a platinum and/or a taxane compound
- Had completed their course of chemotherapy three months or more prior to enrollment
- Had changes in sensation and/or pain in their feet and/or hands of three months' duration or more following the completion of chemotherapy
- Had a rating of 3 or more on a 0–10 numeric rating scale (NRS) for any one of the following sensations from the Pain Quality Assessment Scale (PQAS) (Jensen et al., 2006): numb, tender, shooting, sensitive, electrical, tingling, radiating, throbbing, cramping, itchy, or unpleasant
- If they had pain associated with CIPN, had an average pain intensity score in their feet and/or hands of 3 or greater on a 0–10 NRS
- Had a Karnofsky Performance Status (KPS) score of 50 or greater
- Were able to read, write, and understand English

Survivors were excluded if they had peripheral vascular disease, vitamin B_{12} 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 1,450 survivors who were screened, 754 were enrolled and 623 (423 with CIPN 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.

Procedure

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

FIGURE 3. Differences Between the LessEx and RecEx Groups in Exercise Intensity



LessEx—patients who exercised less than 150 minutes per week; RecEx—patients who exercised for the recommended 150 minutes or more per week

Measures

Demographic and clinical characteristics: Survivors provided information on demographic characteristics and completed the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001), the KPS scale (Karnofsky, 1977), and the Self-Administered Comorbidity Questionnaire (SCQ) (Sangha et al., 2003). The AUDIT assesses alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the past 12 months (Babor et al., 2001). The SCQ consists of 13 common medical conditions that are simplified into language that can be understood without any prior medical knowledge. Patients were asked to indicate if they had the condition, if they received treatment for it, and if it limited their activities. A patient can receive a maximum of three points for each condition. The total SCQ score can range from 0–39 (Sangha et al., 2003).

Evaluation of regular exercise: Survivors completed a six-item exercise questionnaire that asked them to report whether they exercised on a regular basis, what types of physical activity they engaged in at the present time (e.g., walking, swimming), how many days per week they exercised, how many times per day they exercised, and the duration and intensity of each session. Based on responses to this questionnaire, the following three exercise groups were created: no exercise (NoEx), less than 150 minutes per week (LessEx), and 150 or more minutes per week (RecEx).

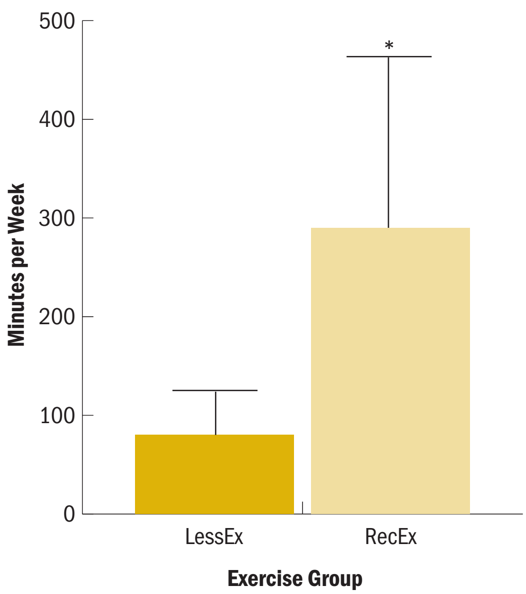
Pain questionnaires: Separate assessments were done for pain intensity and quality ratings for the hands and feet. A detailed CIPN history was obtained using a questionnaire from the authors' previous (Langford et al., 2015; Posternak et al., 2016) and ongoing studies. Information was obtained on the date of pain onset and its interference level with function. Average and worst pain intensity during the past 24 hours was assessed using an NRS ranging from 0 (no pain) to 10 (worst pain imaginable) (Downie et al., 1978).

The 20-item PQAS was used to assess the qualities associated with CIPN (Jensen et al., 2005, 2006). Sixteen items evaluated the magnitude of the different pain quality descriptors (e.g., sharp, hot, aching, cold), measured on an NRS ranging from 0 to 10. Four items evaluated global and spatial pain qualities. In studies of various types of neuropathic pain, the PQAS has well-established validity and reliability (Jensen et al., 2005, 2006).

Sensation: Light touch was evaluated with Semmes-Weinstein monofilaments (Bell-Krotoski, 2002). A Tip Therm® rod was used to evaluate cold sensation (Papanas & Ziegler, 2011; Viswanathan et al., 2002). A Neurotip™ evaluated pain sensation (Papanas & Ziegler, 2011). A biothesiometer assessed vibration threshold (Garrow & Boulton, 2006). For all measures of sensation, the upper and lower extremities on the dominant side were tested.

Balance: To assess balance, self-report questions from the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool were used (Tofthagen et al., 2011). Objective measures of balance were the Timed Up and Go (TUG) test (Mathias et al., 1986) and the Fullerton Advanced Balance (FAB) test (Hernandez & Rose, 2008; Rose et al., 2006).

FIGURE 4. Differences Between the LessEx and RecEx Groups in Minutes of Exercise per Week



* p < 0.001
LessEx—patients who exercised less than 150 minutes per week; RecEx—patients who exercised for the recommended 150 minutes or more per week

Data Analysis

Data were analyzed using IBM SPSS Statistics, version 23.0. For survivors' demographic and clinical characteristics, descriptive statistics and frequency distributions were calculated. For the four measures of sensation (light touch, cold, pain, and vibration), composite scores were created over all sites that were tested on the dominant upper and lower extremities. The number of sites with loss of each sensation was summed for light touch, cold, and pain. The mean score across the sites was calculated for vibration.

The three exercise groups were created using the survivors' responses to the exercise questionnaire. Survivors who responded "no" to the question about whether they exercised on a regular basis were assigned to the NoEX group. The remaining two groups (survivors who exercised less than 150 minutes per week [LessEx] and survivors who exercised for the recommended 150 minutes or more 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 less than 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, 21% were classified in the NoEx group, 45% in the LessEx group, and 35% in the RecEx group. As shown in Figures 1–4, compared to the RecEx group, patients in the LessEx group exercised for fewer minutes per session and for fewer total minutes per week and participated in less intense exercise and for fewer days per week (all, $p < 0.001$). Figure 5 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.

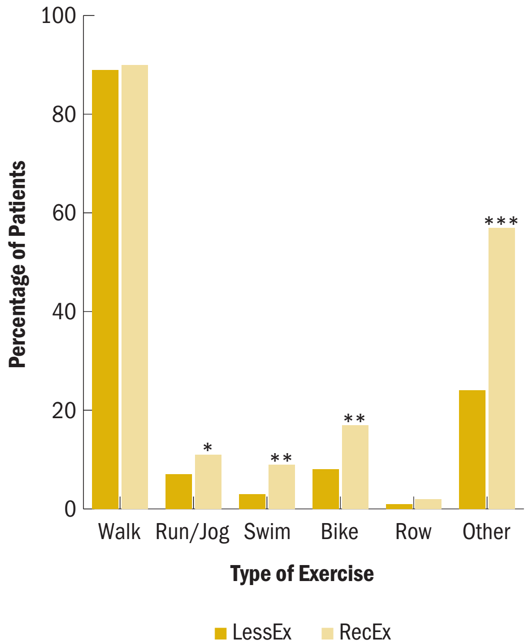
In terms of clinical characteristics (see Table 2), compared to the other two groups, survivors in the NoEx group had a significantly lower KPS score and a higher body mass index (BMI). In addition, compared to the RecEx group, survivors in the NoEx group had a significantly higher number of comorbidities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

Differences in Self-Reported Pain Characteristics

In terms of pain characteristics, 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 interference 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 extremities for throbbing and tender qualities. For the upper extremities, no significant differences were found among the three groups for any of the PQAS scores.

FIGURE 5. Differences Between the LessEx and RecEx Groups in the Types of Exercise Used



* p = 0.11; ** p = 0.001; *** p < 0.001
LessEx—patients who exercised less than 150 minutes per week; RecEx—patients who exercised for the recommended 150 minutes or more per week

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, compared with the RecEx group, survivors in the NoEx group had significantly higher TUG scores. In addition, compared

TABLE 1. Demographic Characteristics by Exercise Group

Characteristic	NoEx (N = 60)		LessEx (N = 129)		RecEx (N = 101)		Statistics
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
Age (years)	61.1	10.6	60.2	11.4	61.3	10.2	F = 0.35, p = 0.708
Education (years)	15.6	2.9	16.5	3.2	16.9	2.2	F = 3.75, p = 0.025; 1 < 3
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Gender							χ^2 = 2.87, p = 0.025
Female	48	80	112	87	90	89	
Male	12	20	17	13	11	11	
Marital status							χ^2 = 7.41, p = 0.25; 1 < 3
Not married or partnered	32	56	47	37	35	35	
Married or partnered	25	44	79	63	64	65	
Living situation							χ^2 = 4.87, p = 0.088
Lives with others	35	59	89	71	75	76	
Lives alone	24	41	36	29	24	24	
Employment status							χ^2 = 2.66, p = 0.265
Not employed	43	72	76	59	64	63	
Employed	17	28	52	41	37	37	
Childcare responsibilities							χ^2 = 2.01, p = 0.366
No	53	88	105	81	85	87	
Yes	7	12	24	19	13	13	
Adult care responsibilities							χ^2 = 6.05, p = 0.049
No	47	90	117	97	90	98	
Yes	5	10	3	3	2	2	
Ethnicity							χ^2 = 6.58, p = 0.361
White	41	68	97	75	79	78	
Hispanic, mixed, or other	11	18	11	9	10	10	
Black	5	8	9	7	4	4	
Asian/Pacific Islander	3	5	12	9	8	8	
Annual household income ($)							KW, p < 0.0001; 1 < 2 and 3
Less than 30,000	26	47	26	22	17	19	
30,000–69,999	12	21	32	27	12	13	
70,000–99,999	9	16	15	12	18	20	
100,000 or greater	9	16	47	39	45	48	

KW—Kruskal-Wallis test; LessEx—patients who exercised less than 150 minutes per week; NoEx—patients who reported they did not exercise on a regular basis; RecEx—patients who exercised for the recommended 150 minutes or more per week

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 (Kneis et al., 2019; McCrary et al., 2019; Mols et al., 2015; Wonders et al., 2013), the current findings support the authors' hypothesis that lower levels of exercise would be associated with worse scores for both subjective and

TABLE 2. Clinical Characteristics by Exercise Group

Characteristic	NoEx (N = 60)		LessEx (N = 129)		RecEx (N = 101)		Statistics
	X̄	SD	X̄	SD	X̄	SD	
KPS score	77	10.9	83.8	10.1	84.4	9.7	F = 11.65, p < 0.001; 1 < 2 and 3
Body mass index (kg/m^2)	29	6.3	26.3	6	26.2	5.1	F = 5.23, p = 0.006; 1 > 2 and 3
Number of comorbidities	2.4	1.6	2.1	1.4	1.7	1.4	F = 4.31, p = 0.014; 1 > 3
SCQ score	5.5	4.1	4.3	3.2	3.7	3.1	F = 5.22, p = 0.006; 1 > 3
AUDIT score	2.2	2.7	2.1	1.9	2.2	2.1	F = 0.78, p = 0.925
Years since cancer diagnosis	3.9	3.5	5.2	5.6	4.8	4.8	F = 1.43, p = 0.24
Number of prior cancer treatments	3	1	3.1	1	3.1	0.9	F = 0.61, p = 0.545
Number of current cancer treatments	0.3	0.5	0.4	0.6	0.4	0.6	F = 0.56, p = 0.574
Number of metastatic sites (of 7)	0.8	0.7	0.8	0.9	0.7	0.6	F = 0.19, p = 0.829
Number of metastatic sites without lymph node involvement	0.3	0.5	0.3	0.7	0.1	0.4	F = 2.35, p = 0.097
Platinum dose (mg/m^2)[a]	908.5	895.6	631.1	336.6	793.9	396	F = 1.41, p = 0.253
Taxane dose (mg/m^2)[b]	829.9	213.9	870.8	1,145.9	764.4	295.3	F = 0.22, p = 0.807
Platinum dose (mg/m^2)[c]	1,798.5	1,005	1,619.2	800.9	1747.3	485.7	F = 0.41, p = 0.663
Taxane dose (mg/m^2)[c]	1,009.9	479.6	803.6	438.7	937.6	457.3	F = 1.51, p = 0.227
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Smoking status							χ^2 = 0.26, p = 0.877
Nonsmoker	35	58	79	62	62	61	
Smoker (ever)	25	42	48	38	39	39	
Born prematurely							χ^2 = 0.62, p = 0.733
No	49	94	109	94	86	91	
Yes	3	6	7	6	8	9	
Past surgery to arms							χ^2 = 1.42, p = 0.491
No	45	75	106	82	78	78	
Yes	15	25	23	18	22	22	
Past surgery to hands							χ^2 = 2.48, p = 0.29
No	50	85	118	92	91	90	
Yes	9	15	10	8	10	10	
Past surgery to legs							χ^2 = 0.28, p = 0.871
No	47	80	98	77	74	76	
Yes	12	20	30	23	23	24	
Past surgery to feet							χ^2 = 2.91, p = 0.234
No	47	78	112	87	80	82	
Yes	13	22	16	13	18	18	

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TABLE 2. Clinical Characteristics by Exercise Group *(Continued)*

Characteristic	NoEx (N = 60)		LessEx (N = 129)		RecEx (N = 101)		Statistics
	n	%	n	%	n	%	
Past injury to arms							$\chi^2 = 0.18, p = 0.914$
No	43	74	91	72	71	71	
Yes	15	26	35	28	29	29	
Past injury to hands							$\chi^2 = 2.88, p = 0.237$
No	37	66	88	69	55	58	
Yes	19	34	40	31	40	42	
Past injury to legs							$\chi^2 = 0.53, p = 0.767$
No	48	80	105	81	75	77	
Yes	12	20	24	19	22	23	
Past injury to feet							$\chi^2 = 1.78, p = 0.411$
No	41	71	99	78	69	71	
Yes	17	29	28	22	31	29	
Metastatic disease							$\chi^2 = 3.12, p = 0.21$
Yes	40	67	72	56	65	66	
No	20	33	56	44	33	34	
Dose reduction or delay from neuropathy							$\chi^2 = 1.05, p = 0.591$
No	52	88	100	83	83	87	
Yes	7	12	20	17	12	13	
Comorbid conditions[d]							
Back pain	23	38	51	40	33	33	$\chi^2 = 1.21, p = 0.545$
Osteoarthritis	21	35	43	33	31	31	$\chi^2 = 0.35, p = 0.839$
Depression	20	33	31	24	21	21	$\chi^2 = 3.25, p = 0.197$
High blood pressure	20	33	34	26	25	25	$\chi^2 = 1.49, p = 0.475$
Anemia or blood disease	4	7	7	5	5	5	$\chi^2 = 0.22, p = 0.897$
Diabetes	4	7	5	4	5	5	$\chi^2 = 0.7, p = 0.705$
Heart disease	4	7	11	9	9	9	$\chi^2 = 0.27, p = 0.874$
Lung disease	4	7	6	5	1	1	$\chi^2 = 3.79, p = 0.15$
Liver disease	3	5	2	2	2	2	$\chi^2 = 2.19, p = 0.334$
Rheumatoid arthritis	3	5	3	2	1	1	$\chi^2 = 2.58, p = 0.276$
Kidney disease	2	3	3	2	1	1	$\chi^2 = 1.1, p = 0.578$
Ulcer or stomach disease	1	2	7	5	2	2	$\chi^2 = 2.74, p = 0.254$
Type of cancer							$\chi^2 = 7.98, p = 0.436$
Breast	29	48	71	55	53	52	
Colon	5	8	14	11	11	11	
Lung	1	2	6	5	–	–	
Ovarian	7	12	12	9	11	11	
Other	18	30	26	20	26	26	
Chemotherapy regimen							$\chi^2 = 0.84, p = 0.933$
Only a platinum compound	14	23	32	25	22	22	

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TABLE 2. Clinical Characteristics by Exercise Group *(Continued)*

Characteristic	NoEx (N = 60)		LessEx (N = 129)		RecEx (N = 101)		Statistics
	n	%	n	%	n	%	
Chemotherapy regimen *(continued)*							$\chi^2 = 0.84$, p = 0.933
Only a taxane compound	25	42	59	46	47	47	
A platinum and a taxane compound	21	35	38	29	32	32	

[a] For patients who received only a platinum
[b] For patients who received only a taxane
[c] For patients who received both a platinum and a taxane
[d] Participants could choose more than 1 response.
AUDIT—Alcohol Use Disorders Identification Test; KPS—Karnofsky Performance Status; LessEx—patients who exercised less than 150 minutes per week; NoEx—patients who reported they did not exercise on a regular basis; RecEx—patients who exercised for the recommended 150 minutes or more per week; SCQ—Self-Administered Comorbidity Questionnaire
Note. Because of rounding, percentages may not total 100.
Note. KPS scores (i.e., a measure of functional status) range from 50 ("I need a large amount of assistance and require medical care") to 100 ("I feel normal; I have no complaints or symptoms").

objective measures of CIPN, as well as more problems with balance. Compared to the survivors who met the Healthy People 2020 exercise recommendation (Office of Disease Prevention and Health Promotion, 2018), 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 and the RecEx groups, it is possible that some level of physical activity is beneficial to survivors with CIPN. However, when the authors 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 or pain interference. For TUG ($r = -0.174$, $p = 0.008$) and FAB ($r = 0.191$, $p = 0.004$) scores, although statistically significant, the correlations were extremely small. The actual amount of exercise that is sufficient to decrease CIPN signs and symptoms and improve balance remains to be determined.

In the current study, although 35% of the survivors reported that they exercised for 150 minutes or more per week, this percentage is lower than the 88% reported in a Dutch registry study (Mols et al., 2015), but higher than the 16% reported by breast cancer survivors with CIPN in the United States (Wonders & Drury, 2012). The current findings are consistent with previous studies of cancer survivors that found that self-reported rates of physical activity ranged from 30% to 37% (Beasley et al., 2012; Pinto & Ciccolo, 2011).

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. Although these characteristics were not evaluated in previous CIPN studies (Kneis et al., 2019; Mols et al., 2015; Wonders et al., 2013), evidence from the general population suggests that these same demographic characteristics are associated with lower levels of exercise (Bird et al., 2015). In several studies (AuYoung et al., 2016; Clifford et al., 2018; Hirschey et al., 2020), 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 (Beasley et al., 2012; Blanchard et al., 2010) and poorer functional status (Su et al., 2014). However, for all exercise groups, survivors' BMIs were in the overweight range (Centers for Disease Control and Prevention, 2016). In terms of functional status, the decrement found between the RecEx and NoEx groups represents not only a statistically significant but also a clinically meaningful decrease in KPS score (Cohen's $d = 0.7$). In addition, and consistent with reports from the general population (Pedersen & Saltin, 2015; Roberts et al., 2015), compared to the RecEx group, survivors in the NoEx group had a worse comorbidity profile. Although no differences were found among the exercise groups in the occurrence rates for specific comorbidities, as noted in reports regarding the need to tailor exercise regimens for various chronic conditions (Hayes et al., 2019; Pedersen & Saltin, 2015), clinicians need

TABLE 3. Pain Characteristics by Exercise Group

	NoEx (N = 60)		LessEx (N = 129)		RecEx (N = 101)		
Characteristic	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	Statistics
Pain characteristics: lower extremity							
Duration of CIPN (years)	3.5	3.4	4.2	4.9	3.8	4.2	F = 0.6, p = 0.549
Pain now	4.1	2.2	3.8	2.4	3.4	2.2	F = 1.74, p = 0.178
Average pain	4.5	2.1	4.2	2.2	3.8	2.1	F = 1.94, p = 0.145
Worst pain	6.2	2.4	6	2.6	6.1	2.6	F = 0.18, p = 0.837
Days per week in pain	4.7	3	3.6	2.9	3.7	3	F = 2.94, p = 0.055
Hours per day in pain	15.2	8.9	15.4	9.3	14.9	9.7	F = 0.08, p = 0.925
Pain characteristics: upper extremity							
Duration of CIPN (years)	3.2	3.5	4.2	5	3.2	3.4	F = 1.36, p = 0.259
Pain now	2.9	2.1	2.8	2.1	2.8	2.1	F = 0.03, p = 0.97
Average pain	3.3	2.2	3.2	2.2	3	2	F = 0.25, p = 0.778
Worst pain	4.6	2.8	4.6	2.6	4.5	2.8	F = 0.04, p = 0.961
Days per week in pain	4.1	3	3.8	3	3.5	3	F = 0.67, p = 0.513
Hours per day in pain	13.4	9.5	12.1	9.8	13.8	10.1	F = 0.61, p = 0.546
Pain Interference Scale: lower extremity							
Balance	4.9	3.2	3.8	3.1	3.3	3.1	F = 5.28, p = 0.006; 1 > 3
Walking ability	4.7	3	3.6	3.1	3.1	3	F = 4.92, p = 0.008; 1 > 3
Enjoyment of life	4.1	2.9	3	2.8	2.4	2.5	F = 6.18, p = 0.002; 1 > 2 and 3
Normal work	3.7	2.8	2.9	3	2.5	2.8	F = 3.12, p = 0.046; 1 > 3
Sleep	3.6	3.2	2.9	2.9	2.1	2.4	F = 5.3, p = 0.006; 1 > 3
General activity	3.5	2.8	2.9	2.6	2.6	2.8	F = 2.05, p = 0.13
Mood	2.8	2.5	2.6	2.6	2.5	2.6	F = 0.17, p = 0.848
Relations with other people	2.5	2.7	1.7	2.4	1.5	2.3	F = 3.03, p = 0.05
Sexual activity	1.6	2.8	0.9	2.1	0.8	1.9	F = 2.1, p = 0.125
Interference score	3.5	2.4	2.7	2.3	2.3	2.3	F = 5.06, p = 0.007; 1 > 3
Pain Interference Scale: upper extremity							
Routine activities[a]	3	3	2.7	2.8	2.3	2.6	F = 1, p = 0.373
Walking ability	0.8	2.2	0.6	1.6	0.2	0.7	F = 2.17, p = 0.117
Enjoyment of life	3.2	3.2	2.1	2.8	1.8	2.3	F = 3.98, p = 0.02; 1 > 3
Normal work	3.4	2.9	3	2.9	2.4	2.5	F = 1.98, p = 0.141
Sleep	2.5	3.1	1.4	2.5	1.3	2	F = 3.73, p = 0.026; 1 > 3
General activity	3	3.1	2.6	2.7	2.2	2.5	F = 1.27, p = 0.284
Mood	2.5	2.6	1.9	2.5	2.1	2.1	F = 1.15, p = 0.319
Relations with other people	0.9	1.6	0.8	1.8	0.8	1.6	F = 0.1, p = 0.907
Sexual activity	0.9	2.3	0.8	2.2	0.4	1.3	F = 1.26, p = 0.285
Interference score	2.3	2.3	1.8	2	1.5	1.6	F = 2.32, p = 0.101
PQAS scores: lower extremity							
Numb	5.8	3	5.5	3.1	5.1	3	F = 1.21, p = 0.299
Unpleasant	5.3	2.6	4.6	2.4	4.1	2.7	F = 3.78, p = 0.024; 1 > 3
Tingling	5.1	2.8	4.2	2.8	4	3.2	F = 2.82, p = 0.061
Intense	4.2	2.4	3.4	2.6	3	2.6	F = 3.94, p = 0.021; 1 > 3
Dull	3.7	2.7	2.6	2.5	3.2	2.8	F = 3.08, p = 0.047
Cramping	3.6	3.4	2.7	3.2	2.8	3.3	F = 1.62, p = 0.199
Electrical	2.9	3.1	2.1	2.8	2.5	3.1	F = 1.35, p = 0.262

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TABLE 3. Pain Characteristics by Exercise Group *(Continued)*

Characteristic	NoEx (N = 60)		LessEx (N = 129)		RecEx (N = 101)		Statistics
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
PQAS scores: lower extremity *(continued)*							
Shooting	3.1	3	2.2	2.9	2.2	2.8	F = 1.97, p = 0.141
Sharp	2.7	2.8	2.1	2.9	2.6	3.1	F = 0.98, p = 0.376
Aching	3.2	3.1	2.2	2.6	2	2.8	F = 3.84, p = 0.023; 1 > 3
Heavy	2.4	2.8	2.2	2.7	2	2.8	F = 0.45, p = 0.638
Cold	2.8	3.3	2.2	2.9	1.9	2.7	F = 1.88, p = 0.155
Radiating	2.7	3.1	1.8	2.5	2.1	2.9	F = 2.02, p = 0.134
Hot	2.9	3.1	2	2.7	2.1	2.8	F = 2.23, p = 0.109
Tender	2.7	2.9	1.7	2.4	2.2	2.6	F = 3.34, p = 0.037; 1 > 2
Sensitive skin	2.7	3	1.9	2.2	1.7	2.3	F = 3.03, p = 0.05
Throbbing	3	3.2	1.5	2.4	1.6	2.5	F = 6.76, p = 0.001; 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	2.8	F = 3.98, p = 0.02; 1 > 3
Intense—deep pain	3.7	2.7	3.3	2.9	3.2	2.9	F = 0.68, p = 0.508
PQAS scores: upper extremity							
Numb	3.4	2.4	4.3	2.9	3.7	2.9	F = 2.09, p = 0.126
Unpleasant	4.2	2.6	3.6	2.5	3.5	2.4	F = 1.06, p = 0.349
Tingling	3.2	2.6	3.3	2.7	3.3	3.2	F = 0.01, p = 0.987
Intense	3	2.3	2.6	2.4	2.5	2.3	F = 0.65, p = 0.523
Dull	2.7	2.6	2.3	2.5	2.1	2.3	F = 0.68, p = 0.51
Cramping	2.2	2.9	1.6	2.6	1.6	2.3	F = 0.95, p = 0.389
Electrical	1.9	2.5	1.7	2.5	2.1	3	F = 0.34, p = 0.712
Shooting	1.7	2.4	1.7	2.6	1.5	2.5	F = 0.18, p = 0.835
Sharp	1.2	2	1.3	2.3	1.5	2.2	F = 0.2, p = 0.816
Aching	2.5	3.1	1.8	2.3	1.5	2.3	F = 2.29, p = 0.104
Heavy	1.6	2.5	1.5	2.5	0.9	1.8	F = 2, p = 0.138
Cold	1.6	2.5	1.9	2.6	1.1	2.3	F = 2, p = 0.138
Radiating	1.7	2.5	1.5	2.5	1	1.9	F = 1.83, p = 0.162
Hot	1.6	2.4	1.1	2.2	0.8	1.8	F = 1.9, p = 0.152
Tender	1.7	2.4	1.6	2.3	1.6	2.3	F = 0.05, p = 0.949
Sensitive skin	1.9	2.4	1.3	2.1	1.2	2.1	F = 1.56, p = 0.212
Throbbing	1.8	2.8	1.3	2.1	1.2	2.3	F = 1.06, p = 0.347
Itchy	0.8	2	1	2	0.6	1.7	F = 0.87, p = 0.421
Intense—surface pain	3	2.8	3.1	2.5	3.1	2.7	F = 0.03, p = 0.973
Intense—deep pain	2.7	2.9	2.3	2.6	2.3	2.5	F = 0.34, p = 0.709

[a] Dressing, toileting, typing

CIPN—chemotherapy-induced peripheral neuropathy; LessEx—patients who exercised less than 150 minutes per week; NoEx—patients who reported they did not exercise on a regular basis; PQAS—Pain Quality Assessment Scale; RecEx—patients who exercised for the recommended 150 minutes or more per week

Note. Pain intensity scores range from 0 (no pain) to 10 (most pain imaginable). Pain interference scores range from 0 (no interference) to 10 (completely interferes). Pain quality scores range from 0 (no sensation) to 10 (most possible sensation).

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 also those that are required for other chronic conditions. Of note, no differences were found among the exercise groups in the types of chemotherapy regimens and doses of neurotoxic drugs the survivors received.

TABLE 4. Differences in Sensation and Balance Measures by Exercise Group

Characteristic	Site	NoEx (N = 60)		LessEx (N = 129)		RecEx (N = 101)		Statistics
		X̄	SD	X̄	SD	X̄	SD	
Sensation measures								
Light touch—UE sites (of 7)	Pad of thumb, thumb web-space, tip of index finger, tip of little finger, midway base of palm, one-third up anterior arm, two-thirds up anterior arm	0.2	0.6	0.3	1.1	0.1	0.7	F = 1.07, p = 0.345
Light touch—LE sites (of 9)	Pad of great toe, pad of third toe, pad of fifth toe, base of heel, MP joint of great toe, MP joint of third toe, MP joint of fifth toe, midway along tibia, patella	2.5	2	2.2	2.5	2	2.2	F = 0.76, p = 0.471
Cold—UE sites (of 4)	Pad of index finger, pad of little finger, dorsal MP area of the hand, wrist	1	0.8	0.8	1	0.8	1.1	F = 0.66, p = 0.515
Cold—LE sites (of 4)	Top of great toe at first MP joint, pad of great toe, dorsum of foot midpoint, medial malleolus	2.2	1.1	2.3	1.2	2.3	1.1	F = 0.24, p = 0.784
Pain—UE sites (of 7)	Pad of thumb, thumb web-space, tip of index finger, tip of little finger, midway base of palm, one-third up anterior arm, two-thirds up anterior arm	1.4	1.5	1.1	1.4	1.1	1.4	F = 0.92, p = 0.4
Pain—LE sites (of 9)	Pad of great toe, pad of third toe, pad of fifth toe, base of heel, MP joint of great toe, MP joint of third toe, MP joint of fifth toe, midway along tibia, patella	3.6	2	3.4	2.3	3.2	2.2	F = 0.89, p = 0.411
Vibration—UE sites (volts)	Dorsal IP joint of thumb, dorsal IP joint of index finger, ulnar prominence, lateral epicondyle	9.1	3.2	9.9	6	8.7	3.8	F = 1.71, p = 0.183
Vibration—LE sites (volts)	Dorsal IP joint of great toe, medial malleolus, patella	31.2	12.1	27.3	11.8	26.5	12.3	F = 3.17, p = 0.044; 1 > 3
Characteristic	**Question**	**X̄**	**SD**	**X̄**	**SD**	**X̄**	**SD**	**Statistics**
Balance measures								
Severity of balance trouble (0–10)	At its worst, how severe is the trouble with your balance? (0 = not at all severe, 10 = extremely severe)	5.4	2.6	4.7	2.7	5.3	2.6	F = 1.22, p = 0.296
Frequency of balance trouble (0–10)	How often do you have trouble with your balance? (0 = never, 10 = always)	5	2.9	4.9	3.1	4.5	2.9	F = 0.42, p = 0.656

Continued on the next page

TABLE 4. Differences in Sensation and Balance Measures by Exercise Group *(Continued)*

Characteristic	Question	NoEx (N = 60)		LessEx (N = 129)		RecEx (N = 101)		Statistics
		$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
Balance measures *(continued)*								
Distress from balance trouble (0–10)	At its worst, how distressing is the trouble with your balance? (0 = not at all distressing, 10 = extremely distressing)	5.8	2.9	5.4	2.9	5.4	3	F = 0.44, p = 0.643
TUG test (greater than 13.5 seconds equals higher risk for falls)	–	8.6	2.6	8	3.1	7.4	1.7	F = 4.4, p = 0.013; 1 > 3
FAB test (less than 25 is associated with a higher risk of falls)	–	30.3	8.26	32.7	7	34.9	4.9	F = 8.83, p < 0.001; 1 < 2 and 3; 2 < 3
Characteristic	**Question**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Balance measures								
Trouble with balance	Since your chemotherapy, have you had trouble with your balance?	49	82	84	65	65	64	χ^2 = 5.84, p = 0.054

FAB—Fullerton Advanced Balance; IP— interphalangeal; LE—lower extremity; LessEx—patients who exercised less than 150 minutes per week; MP—metacarpophalangeal; NoEx—patients who reported they did not exercise on a regular basis; RecEx—patients who exercised for the recommended 150 minutes or more per week; TUG—Timed Up and Go; UE—upper extremity
Note. When available, the clinically meaningful cut-point score is provided in parentheses next to the characteristic.
Note. Changes in sensation are reported for the dominant extremity.

This study is the first detailed examination of the associations between a comprehensive set of subjective measures of CIPN (i.e., duration, intensity, qualities, and interference) and self-reported levels of exercise. It is difficult to compare findings across previous studies of self-reported exercise (Mols et al., 2015; Wonders & Drury, 2012) because of the variability in the subjective measures that were used. Although the authors found no differences among the 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 patients with cancer (Syrjala et al., 2014) and patients with chronic pain (Geneen et al., 2017; Naugle et al., 2012) are inconsistent. For example, in two studies of patients with cancer, one found a decrease (Griffith et al., 2009) and the other found no change (Cho et al., 2012) in pain intensity. In the two reviews of the effects of exercise on chronic noncancer pain (Geneen et al., 2017; Naugle et al., 2012), the authors suggested that the effects of exercise on pain intensity were inconsistent and were dependent on the type of exercise and the type of chronic pain evaluated.

Although no differences were found among the exercise groups in any of the pain quality scores in the upper extremities, which is consistent with previous reports (Duregon et al., 2018; Kneis et al., 2019; Mols et al., 2015), compared to the RecEX group, survivors in the NoEx group reported higher scores for unpleasant, intense, aching, and throbbing sensations. The lack of effect of exercise on pain qualities in the hands may be partially explained by the fact that the most common type of exercise in the current 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. Although prior studies reported significant improvements in CIPN20 scores associated with exercise (Kneis et al., 2019; Mols et al., 2015), no studies have used the interference items from the Brief Pain Inventory (BPI). The authors 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, and typing), but 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 to the upper extremities.

Of all 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 patients with cancer randomized to either sensorimotor training or whole-body vibration training (Streckmann et al., 2019).

Although from 64% (RecEx) to 82% (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 the TUG and FAB tests. These results are consistent with the findings from a systematic review on the effects of exercise in patients with CIPN undergoing active treatment (Duregon et al., 2018), as well as findings in the geriatric literature that demonstrate that exercise decreases the risk of falls (Guirguis-Blake et al., 2018; Sherrington et al., 2017).

Limitations

Several limitations warrant consideration. In this study, because only survivors who had received platinum- and/or taxane-containing regimens were evaluated, the authors cannot determine whether these findings generalize to survivors who received other types of neurotoxic chemotherapy. The cross-sectional nature of this study limits the authors' ability to determine causal associations between various CIPN characteristics and levels of physical activity. Although levels of exercise prior to and during chemotherapy were not evaluated, findings from one study suggest that level of physical activity prior to a cancer diagnosis is a strong predictor of activity as many as 10 years postdiagnosis (Mason et al., 2013). Self-reported levels of exercise, rather than objective measures of exercise, are susceptible to recall and social desirability biases (Brenner & DeLamater, 2016), but self-reported physical activity is moderately correlated with data obtained using an accelerometer (Limb et al., 2019; Nelson et al., 2019; Sloane et al., 2009).

KNOWLEDGE TRANSLATION

- Clinicians should educate survivors about the benefits of regular exercise.
- Clinicians need to inform survivors with chemotherapy-induced peripheral neuropathy (CIPN) of the benefits of regular exercise and monitor their level of adherence with a prescribed exercise regimen.
- Information can be used to tailor exercise regimens for sedentary survivors, as well as for survivors with higher levels of comorbidity and co-occurring CIPN.

Implications for Nursing

Despite these limitations, these findings suggest that the lack of regular exercise in cancer survivors is associated with worse scores on 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 (Miller et al., 2019), as well as the lack of effective treatments for numbness, tingling, and pain associated with CIPN (Hershman et al., 2014), 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 patients and survivors can safely engage in moderate amounts of exercise during and after cancer treatment (Schmitz et al., 2019; Segal et al., 2017; Stout et al., 2017). Based on these 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 (Andersen Hammond et al., 2019; Kneis et al., 2019; McCrary et al., 2019), clinicians can recommend walking as a therapeutic option, as well as provide referrals to physical therapy for additional strength and balance training.

Conclusion

Prospective longitudinal studies are needed to determine the optimal dose and types of exercise that are necessary 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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This study was funded by the National Cancer Institute (CA151692). Miaskowski is supported by a grant from the American Cancer Society. This project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through University of California, San Francisco–Clinical and Translational Science Institute Grant Number UL1 TR000004. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Recruitment was facilitated by the Dr. Susan Love Foundation for Breast Cancer Research's Love Research Army.

Kober, Topp, Chesney, Levine, and Miaskowski contributed to the conceptualization and design. Kober, Abrams, and Miaskowski completed the data collection. Kober, Paul, and Miaskowski provided statistical support. Wilcoxon, Kober, Chesney, Conley, and Miaskowski provided analysis. Wilcoxon, Kober, Viele, Topp, Smoot, Abrams, Chesney, Conley, Levine, and Miaskowski contributed to the manuscript preparation.

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