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Effect of Exercise on Taxane Chemotherapy–Induced Peripheral Neuropathy in Women With Breast Cancer: A Randomized Controlled Trial

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting adverse effect of taxanes used to treat breast cancer. In this proof-of-concept trial, 27 breast cancer patients were randomized to exercise during versus after taxane chemotherapy to explore the effect on CIPN and taxane treatment adherence. Our findings suggest exercise may mediate patient-reported CIPN during taxane chemotherapy, but not by the end of chemotherapy, and potentially help patients better tolerate their taxane treatment.

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting adverse effect of taxanes. We sought to evaluate the effect of exercise on taxane CIPN in women with breast cancer. **Patients and Methods:** Women (n = 27) were randomized to immediate exercise (IE, during taxane chemotherapy) or delayed exercise (DE, after chemotherapy). Supervised aerobic, resistance, and balance training was offered 3 days a week for 8-12 weeks. CIPN symptoms and quality of life were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 and CIPN20 (scored from 0 to 100). The percentage of participants reporting moderate to severe sensory symptoms ('3/4' or '4/4' for CIPN20 sensory items) was also evaluated, along with clinical sensory testing at the lower limb (vibration sense and pinprick). Taxane treatment adherence, including relative dose intensity, was extracted from patient medical records. Assessments occurred at: baseline (before taxane chemotherapy), pre-cycle 4 (before the final taxane cycle), the end of chemotherapy, and follow-up (10-15 weeks after chemotherapy). **Results:** No differences in the EORTC QLQ CIPN20 symptom scores were detected between groups at any time point. At pre-cycle 4, there was a significant difference between groups in patient-reported moderate to severe numbness in the toes or feet (IE: n = 1, 9%, DE: n = 7, 50%, $P = .04$) and impaired vibration sense in the feet (IE: n = 2, 18%, DE: n = 10, 83%, $P < .01$). Overall global health status/quality of life was higher in IE compared to DE at the end of chemotherapy ($P = .05$), yet both groups had worse CIPN20 sensory ($\Delta 24.3 \pm 4.6$, $P < .01$) and motor symptom scores ($\Delta 10.5 \pm 1.9$, $P < .01$) relative to baseline. By the end of chemotherapy, no differences between groups were found for moderate to severe numbness in the toes or feet ($P = 1.0$) or impaired vibration sense in the feet ($P = .71$). More IE participants received ≥ 85% relative dose intensity (IE: n = 12, 100%, DE: n = 10, 67%, $P < .05$). **Conclusion:** Exercise may attenuate CIPN over the course of taxane chemotherapy and possibly improve taxane adherence in women with breast cancer. These findings, as well as whether exercise can attenuate CIPN by the end of taxane chemotherapy, should be confirmed in larger trials.

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common non-hematologic adverse effect of select antineoplastic agents, including taxanes.[1,2] Taxanes, namely docetaxel and paclitaxel, are frequently prescribed as a component of modern breast cancer multi-agent chemotherapeutic regimens,[3] and up to 80% of women with breast cancer may experience CIPN symptoms up to 2 years after paclitaxel treatment.[4] CIPN from taxane-based chemotherapy is primarily sensory neuropathy, manifesting as paresthesia, numbness, or pain in the hands and feet, with the thick myelinated nerve fibers responsible for vibration sensation and sense of position being primarily affected.[2] Gait and balance issues may also occur after a single cycle of taxane treatment in breast cancer patients, which worsen with cumulative taxane exposure and are mirrored by increases in patient-reported CIPN symptoms.[5] In addition to decreasing quality of life (QoL)[6] and increasing risk of disability and future falls,[7] CIPN might affect disease outcome and survival, if symptoms progress to a point where dose reductions, cancellations, or delays in taxane treatments occur, thereby reducing the prescribed relative dose intensity (RDI).[8-10] RDI, the ratio of the delivered chemotherapy dose to the planned dose, is often used as a clinical benchmark to predict patient prognosis.[11] In women with breast cancer, an RDI of $< 85\%$ frequently significantly predicts worse patient outcomes, including progression-free and overall survival.[12,13] Thus, the inability to tolerate the full dose and duration of taxane-based chemotherapy due to CIPN is a major oncologic concern. Because there are few evidence-based prevention and treatment options for CIPN,[14] further research on supportive care strategies to manage the burden of CIPN is needed.

Exercise has been shown to play an important role in managing chemotherapy's negative side effects, such as fatigue, and improving physical fitness and QoL after a diagnosis of cancer.[15,16] Nonetheless, whether these benefits extend to taxane-specific toxicities, particularly CIPN, is an emerging area of research. A positive effect of exercise on peripheral neuropathy in non-cancer populations, predominantly adults with diabetes, has been reported.[17] Further, women treated with taxanes for breast cancer who report higher pre-treatment levels of moderate to vigorous physical activity are at a lower risk of CIPN.[18] Recent evidence from clinical trials has shown that exercise, including combinations of aerobic, resistance, and sensorimotor training, may positively influence CIPN in mixed cancer patients as well as women with breast cancer treated with neurotoxic chemotherapy.[19-25]

The primary aim of the EXercise Influence on Taxane side effects (EXIT) trial was to evaluate the effect of exercise during versus after taxane-based chemotherapy (ie, usual care during taxane treatment) on patient-reported CIPN symptoms in women with early-stage breast cancer. This study also evaluated the effect of exercise on clinical sensory tests for CIPN at the lower limb and QoL. Finally, an exploratory analysis of the effect of exercise on taxane chemotherapy adherence was conducted. We hypothesized that women randomized to exercise for the duration of their taxane-based chemotherapy (immediate exercise group) would have reduced patient-reported CIPN symptoms by the end of chemotherapy relative to women who received usual care (delayed exercise group).

Patients and Methods

Study Participants

Participants were recruited by oncologist referral, posters, and word of mouth. Inclusion criteria were women > 19 years old with stage I-III breast cancer who were scheduled to receive paclitaxel or docetaxel chemotherapy in 2- or 3-week cycles, and who were able to communicate in English. Exclusion criteria were stage IV cancer, acute or uncontrolled health conditions, diabetes, history of a neurologic disorder (eg, hereditary peripheral neuropathy), body mass index > 40 kg/m^2, chemotherapy prescribed in a weekly format, or previous receipt of treatment for a past cancer diagnosis.

Study Design and Randomization

This study was a 2-arm randomized controlled trial (Figure 1). The EXIT trial was pre-registered on ClinicalTrials.gov (NCT02473861), and ethical approval was obtained from the University of British Columbia. All participants provided informed consent.

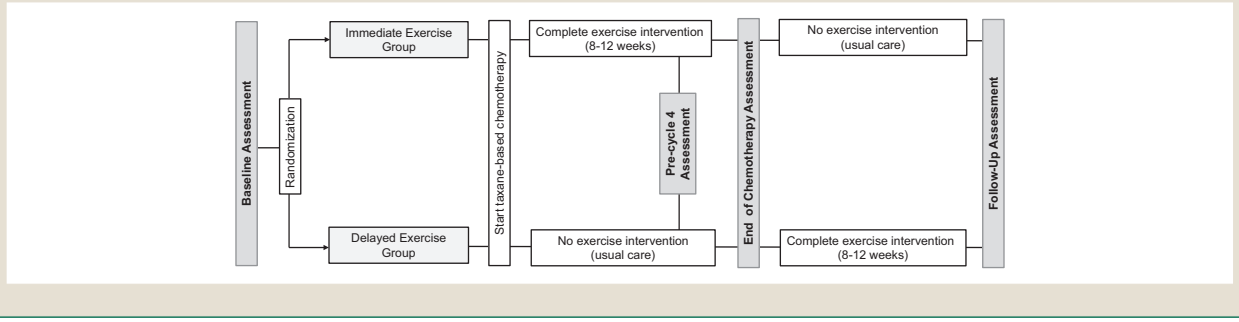
Randomization was stratified by taxane agent type to ensure an equal distribution of docetaxel- and paclitaxel-based protocols within each group, as paclitaxel is more neurotoxic than docetaxel and has been shown to be more likely to cause CIPN-related chemotherapy dose reductions.[10] Randomization occurred after baseline testing to immediate exercise (IE), where the exercise intervention occurred during taxane chemotherapy, followed by a period of no formal exercise training; or usual care during taxane chemotherapy, followed by delayed exercise (DE) of an identical exercise intervention after taxane chemotherapy. The allocation sequence was generated using a spreadsheet random function and was included in sequentially numbered opaque envelopes by a researcher different from the project coordinators who assigned participants to groups.

Exercise Intervention

The exercise intervention length matched the length of participants' taxane protocol, regardless of group assignment (typically 4 taxane cycles delivered 2-3 weeks apart). For IE, the intervention began up to 1 week before the first taxane cycle and ended 2 or 3 weeks after the last cycle. In DE, exercise commenced 2 or 3 weeks after the last taxane cycle, or after surgery in women who underwent second surgeries—for example, reconstruction or following neo-adjuvant chemotherapy. The exercise prescription included supervised multi-modal exercise 3 days a week and 2 days a week of home-based aerobic exercise. All supervised exercise took place a private facility near the cancer treatment center and was supervised by research staff with experience delivering exercise to individuals with cancer.

A "chemotherapy-periodized" exercise approach was developed for the supervised component of the intervention. Chemotherapy treatments can result in cyclical fluctuations and the accumulation of symptoms, such as fatigue[26] and elevated resting heart rate.[27] An exercise prescription that linearly increases in intensity and duration may fail to account for patient-reported and physiologic chemotherapy-related changes. Throughout our intervention, aerobic and resistance exercise progressed in volume; however, the relative intensity and duration was periodized to the chemotherapy

Figure 1 Study Design



Participants were randomized to immediate or delayed exercise. Assessments took place at: (1) baseline (0-7 days before taxane cycle 1); (2) pre-cycle 4 (0-3 days before the fourth taxane cycle); (3) end of chemotherapy (2-3 weeks after the final taxane cycle and after the intervention for the immediate exercise group); and (4) at follow-up (10-15 weeks after chemotherapy and after the intervention for the delayed exercise group).

treatment protocol. Aerobic intensity was prescribed using heart rate reserve (HRR), which was calculated using participants' resting heart rate measured during a 5-minute seated rest period before every exercise session. For the week after chemotherapy, where symptoms were expected to peak, a lower aerobic intensity was prescribed (50%-55% HRR) with increased duration (40 minutes) to maintain load. In the time after the first week of the chemotherapy cycle (1-2 weeks total), the intervention focused on progression and overload, where intensity increased to 75% HRR by week 8. Duration progressed from 25 to 35 minutes on non-chemotherapy weeks. Supervised aerobic exercise modes included the treadmill, cycle ergometer, or elliptical trainer. Despite the pre-emptive decrease in aerobic exercise intensity during chemotherapy weeks, if participants attended their exercise sessions and felt they were unable to achieve the aerobic exercise target, exercise intensity or duration were reduced as needed on the basis of the judgment of the research staff. After 3 weeks, home-based aerobic exercise was prescribed, progressing from 15 to 30 minutes at a Borg rating of perceived exertion of 12 to 14 on a scale of 6 to 20.[28] Home-based aerobic exercise could be selected on the basis of participant convenience and preference, but if patients did not have access to exercise facilities or equipment, they were encouraged to walk outside. Participants were provided with an exercise log to track their exercise at home.

Resistance exercise included 5 specific exercises using machines, free weights, or resistance bands to target the primary upper and lower body muscle groups starting at 1 set of 10 repetitions at 50% of estimated 1 repetition maximum,[29] progressing to 2 sets of 10 to 12 repetitions at 65% 1 repetition maximum. Resistance exercise was reduced to 1 set per exercise for 1 week after chemotherapy to accommodate increased treatment symptoms and to allow for the maintenance of the aerobic exercise volume. If participants were unable to complete resistance exercises at the planned intensity (eg, due to pre-existing musculoskeletal issues), specific exercises were removed from the program or the intensity was reduced. Participants also completed 2 single-leg standing balance exercises for 6 to 8 repetitions (20-30 seconds per exercise), with approximately 1 minute of rest in between exercises. Balance training progressed from being performed on a stable surface with support to being performed unsupported on an unstable surface. Hand and foot exercises that involved resistance bands and balls were performed to target these areas known to be at an increased risk of chemotherapy neurotoxic damage. Two mat exercises for abdominal strength were also prescribed. All balance, core, and hand and foot exercises are described in detail in the Supplementary Material.

Outcome Measures

All measures were performed at 4 time points in both groups (Figure 1): at baseline (before taxane cycle 1); pre-cycle 4 (after 3 taxane cycles and 0-3 days before the fourth and final taxane cycle); at the end of chemotherapy (after the intervention for IE); and at follow-up (10-15 weeks after chemotherapy or after the intervention for DE). Assessments were performed at least 2 days after the most recent supervised exercise session.

Patient-Reported CIPN Symptoms

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) CIPN20 subscale was used to evaluate patient-reported CIPN. The EORTC QLQ CIPN20 contains 20 items assessing sensory (9 items), motor (8 items), and autonomic symptoms (3 items for female subjects) on a 4-point Likert scale. In addition to looking at summary scores (on a scale from 0 to 100) for the CIPN20 subscale, the number of participants who reported experiencing symptoms "quite a bit" (3/4) or "very much" (4/4) for each individual sensory item was evaluated, given that taxane-induced peripheral neuropathy is often sensory in nature.

Non-automated Quantitative Sensory Testing

Clinical sensory testing included 2 non-automated quantitative sensory tests: vibration sensation and temporal summation of pain (pinprick) performed at the lower limb. A standard C (128 Hz) tuning fork was used to test vibration sense at 3 different landmarks.[30] The vibrating tuning fork was first placed on the superior surface of the participant's right and left great toe proximal interphalangeal with the examiner's index finger underneath the joint. With eyes closed, participants indicated when they no longer felt the vibration. The examiner then recorded whether the participant reported feeling the vibration stop at the same time as the examiner (normal) or before the examiner/not at all (impaired). The vibrating

tuning fork was also applied to the medial malleolus and inferior pole of the patella, and the participant indicated whether they sensed any vibration (recorded as present or absent).

A Neuropen peripheral neuropathy screening device and Neurotip (Owen Mumford, Brook Hill, Woodstock, Canada)[31,32] was used to standardize a pinprick force (40 *g*) applied to the distal end of the great toe 10 times at 1-second intervals. The participant was then asked to report whether the sensation of the prick stayed the same, increased, or decreased from the first to the last pinprick. This test intended to identify temporal summation, referred to as wind-up, as modestly sharp stimuli may elicit an abnormal painful sensation (mechanical hyperalgesia) when neuropathy is present.[30] Alternatively, the loss of nociceptors from neuropathy may also cause a diminished sensation of sharpness.[30]

Quality of Life

The EORTC QLQ-C30 core questionnaire was administered to evaluate QoL.[33] This questionnaire contains an overall global health status/QoL scale, 5 functional subscales, including physical, role, emotional, social, and cognitive functioning, 3 symptom subscales for pain, nausea and vomiting, and fatigue, and 6 single items evaluating dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact.

Chemotherapy Completion Rate

The number of participants who experienced a dose reduction or a complete taxane treatment cancellation was extracted from patient medical records, along with the reason (per medical oncologist notes) for the dose adjustment. RDI was also calculated for taxane-based treatments as the delivered total dose (delivered dose divided by actual time to complete chemotherapy) divided by standard total dose (planned dose divided by planned time to complete chemotherapy) multiplied by 100 to obtain a percentage.[34] The planned time to complete taxane chemotherapy was also compared between groups. The chemotherapy dose received and timing of administration extracted from patient medical records was compared against the standard dose and timing for the corresponding taxane-based protocol at the cancer center.[34]

Statistical Analyses

G*Power 3.0.10 was used to estimate a sample size of 36 participants, to achieve 80% power to detect a medium (d = 0.6) effect size in the EORTC QLQ CIPN20 subscale at an alpha of 0.05 (1 tailed). Descriptive statistics were used to characterize participant baseline demographics, medical information, and exercise intervention attendance and adherence. Any deviation from the supervised exercise intensity, duration, or sets and repetitions exactly as planned, including changes made on the day of each supervised session as judged by research staff due to participant symptoms was considered as adherence 'not met.' All exercise adherence outcomes are reported as mean ± standard deviation (SD). To evaluate the difference in mean exercise program length between groups, a 2-tailed independent *t* test was used and results are reported as mean ± SD. A generalized linear mixed model was selected to evaluate differences EORTC QLQ-C30 and CIPN20 outcomes between groups and over time. Participant was included as a random effect to account for correlations across time. For these analyses, a relationship link function and distribution that resulted in normality of residuals, or that produced the best model fit, was selected for each outcome. For the evaluation of patient-reported CIPN20 symptoms, mean RDI was included as a covariate, given that CIPN development depends on chemotherapy dose.[1,2] Hypothesized differences were investigated for significant group by time interactions using pairwise corrected contrasts (least significant difference). All generalized linear mixed model results are reported as mean ± standard error (SE). A 2-sided Fisher exact test was used to detect differences in the proportion of participants who reported experiencing moderate to severe sensory symptoms and altered versus normal sensation at the lower limb for the clinical sensory tests. A 2-tailed independent *t* test was used to assess between-group differences in RDI (reported as mean ± SD) and a Fisher exact test for the proportion of participants who received a taxane dose adjustment/cancellation, dose delay of 7 days or more, and ≥ 85% RDI. SPSS 25.0 software (IBM, Armonk, NY) was used to perform the analyses. Statistically significant outcomes were defined as $P \leq .05$.

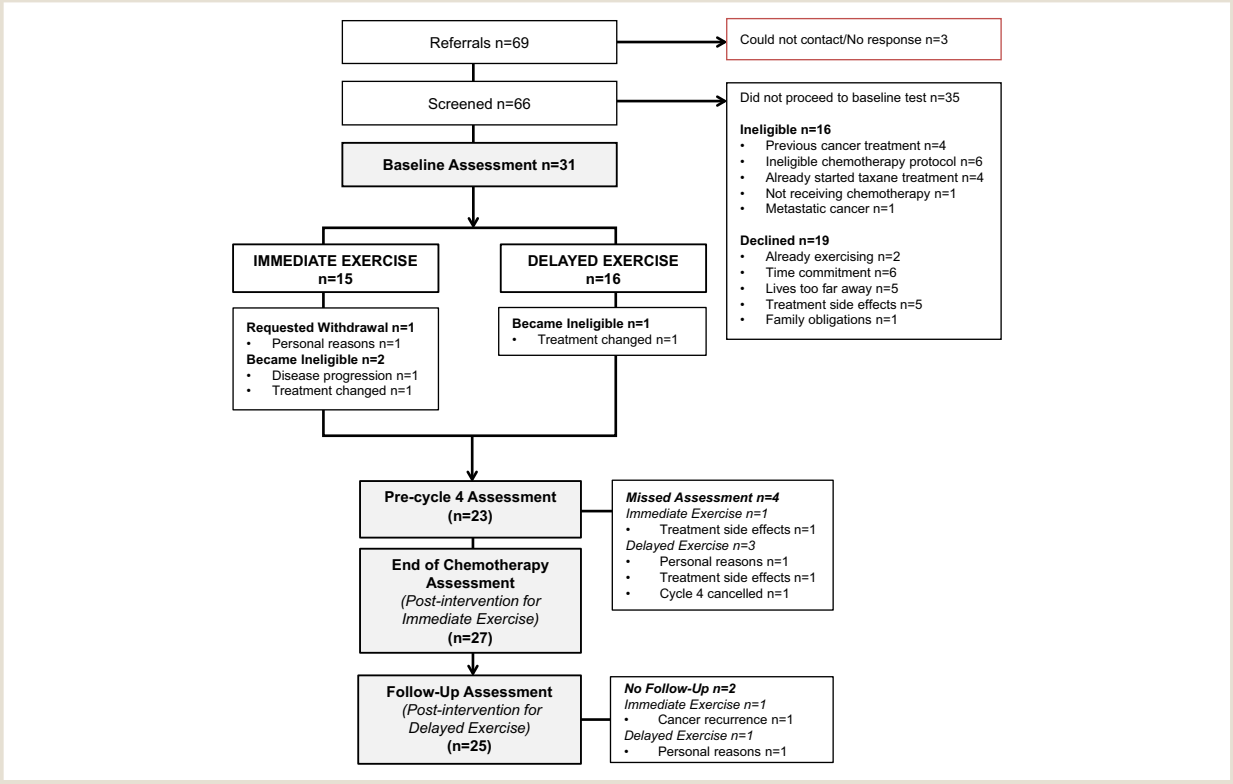
Results

Sixty-nine patients were referred to the study and 31 women enrolled, completed baseline testing, and were subsequently randomized (Figure 2). As a result of slow accrual in a 2-year recruitment period, we were unable to achieve our target sample size. Additionally, 3 participants became ineligible after randomization, and 1 requested withdrawal for personal reasons, leaving 27 women who completed the study (IE: n = 12, DE: n = 15). Baseline demographic and medical characteristics were evenly distributed between groups (Table 1). In regards to treatment for possible CIPN, 6 participants were prescribed gabapentin for pain during chemotherapy (IE: n = 2, DE: n = 4), while no participants reported receipt of duloxetine or prednisone. Nine participants reported taking over-the-counter pain medications, such as ibuprofen or aspirin (IE: n = 3, DE: n = 6). Some participants also visited health care providers for pain during and after chemotherapy, including chiropractor (DE: n = 1), massage therapist (IE: n = 1), and acupuncturist (DE: n = 2). One DE participant also reported using medicinal cannabis during chemotherapy.

Exercise Intervention Adherence

Adherence data are reported for 26 participants (IE: n = 12, DE: n = 14), as one DE participant did not complete the intervention for personal reasons but completed study assessments. Mean exercise program length was 10 weeks (IE: 10.7 ± 2.1, DE: 9.4 ± 2.1 weeks, $P = .11$). Supervised session attendance, as a mean of each participant's attendance, was 78 ± 23% for IE and 81 ± 20% for DE. Adherence to the supervised aerobic exercise intensity and duration was 77 ± 30% and 78 ± 24% for IE, and 81 ± 17% and 81 ± 21% for DE, respectively. Adherence to the resistance and balance exercise prescription, including prescribed exercises, weight, sets, and repetitions was 78 ± 37% for IE and 93 ± 6% for DE. One IE participant was unable to complete the resistance training program exactly as prescribed at the start of the intervention as a result of a pre-existing musculoskeletal injury (shoulder injury) that required specific exercises that caused discomfort to be removed from the program. Therefore, adherence to resistance exercises for her was considered 'not

Figure 2 Flow-Through Study



met.' Twenty-two women completed home-based exercise and handed in their exercise logs at the end of the intervention (IE: n = 11, DE: n = 11). Adherence to the prescribed home-based exercise session frequency was 87 ± 23% for IE and 94 ± 5% for DE and was most frequently reported as walking outside. All participants met or exceeded the prescribed home-based aerobic exercise duration. Adherence to home-based exercise intensity based on target rating of perceived exertion was 78 ± 19% for IE and 95 ± 9% for DE. No adverse events related to the exercise intervention occurred.

Patient-Reported CIPN Symptoms

The results for the EORTC QLQ CIPN20 subscales are depicted in Figure 3. No differences between groups were detected at any time point for the CIPN20 symptom scores. A main effect of time was detected for sensory and motor symptoms in both groups combined (both $P < .01$), showing that symptoms worsened with cumulative treatment doses and peaked at the end of chemotherapy. Relative to baseline, mean sensory symptoms significantly increased in both groups at pre-cycle 4 ($\Delta 16.8 \pm 3.2$, $P < .01$) and at the end of chemotherapy ($\Delta 24.3 \pm 4.6$, $P < .01$). By the end of chemotherapy, the fourth and final taxane treatment cycle resulted in a further increase in symptoms relative to the pre-cycle 4 time point ($\Delta 7.3 \pm 3.3$, $P = .04$). Sensory symptoms recovered in both groups by follow-up and were not different from baseline ($\Delta 3.0 \pm 1.9$, $P = .14$). Relative to baseline, mean motor symptoms also significantly increased in both groups, although not as much as sensory symptoms, at pre-cycle 4 ($\Delta 6.5 \pm 1.6$, $P < .01$) and at the end of chemotherapy ($\Delta 10.5 \pm 1.9$, $P < .01$). The change from pre-cycle 4 to the end of chemotherapy was also significant ($\Delta 3.9 \pm 1.6$, $P = .02$). Motor symptoms did not recover by follow-up and remained higher than baseline in both groups ($\Delta 5.3 \pm 1.9$, $P < .01$). No significant changes were detected over time for autonomic symptoms.

In both groups combined, the 3 most common patient-reported moderate to severe CIPN20 sensory items were numbness in the toes or feet, tingling in the fingers or hands, and tingling in the toes or feet (Table 2). At pre-cycle 4, the percentage of participants reporting moderate to severe numbness in the toes or feet was lower in the IE group compared to the DE group (IE: n = 1, 9%, DE: n = 7, 50%, $P = .04$). By the end of chemotherapy, the percentage of participants reporting this symptom was similar between groups (IE: n = 5, 42%; DE: n = 8, 57%, $P = 1.0$). There were no other differences between groups in patient-reported moderate to severe symptoms for the CIPN20 sensory items.

Non-automated Quantitative Sensory Testing

Results for the responses to the vibration timing test at the great toe interphalangeal joint are shown in Figure 4. At baseline, 4 participants (DE: n = 3, IE: n = 1) exhibited impaired vibration sense. At pre-cycle 4, there was a significant difference between groups in the percentage of participants exhibiting impaired vibration sense (IE: n = 2, 18%, DE: n = 10, 83%, $P < .01$), reflecting a similar trend observed for patient-reported numbness in the toes

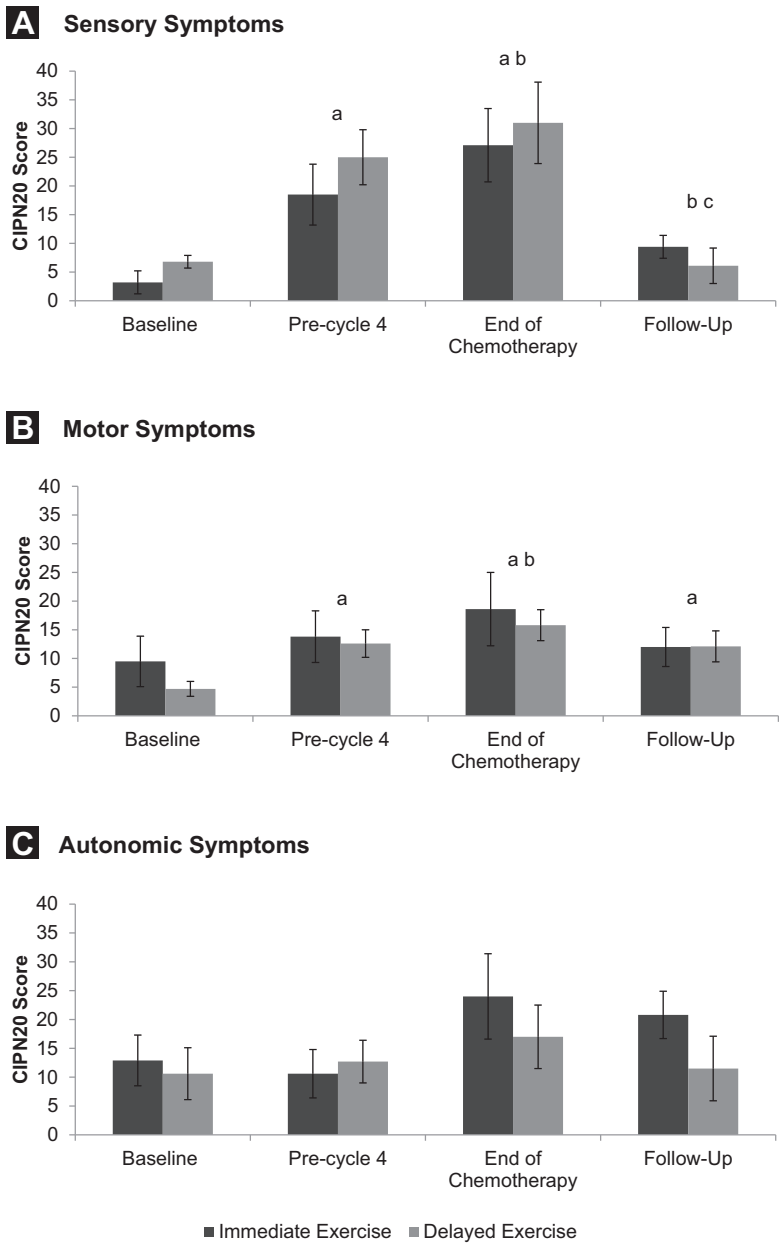
Table 1 Participant Demographic and Medical Characteristics

Characteristic	Total (N = 27)	Immediate Exercise (N = 12)	Delayed Exercise (N = 15)
Age (y), mean ± standard deviation	50.2 ± 10.2	51.0 ± 8.1	49.5 ± 11
Body mass index (kg/m^2), mean ± standard deviation	25.2 ± 5.7	26.1 ± 5.8	24.5 ± 5.3
Menopausal Status			
Premenopausal	13 (48)	5 (42)	8 (53)
Perimenopausal	3 (11)	1 (8)	2 (13)
Postmenopausal	11 (41)	6 (50)	5 (33)
Marital Status			
Married/common-law	24 (88)	10 (83)	14 (93)
Single or widowed	3 (11)	2 (17)	1 (7)
Ethnicity			
White	18 (67)	8 (67)	10 (67)
Asian	8 (30)	4 (33)	4 (31)
Other	1 (4)	0	1 (7)
Education			
Less than bachelor's degree	11 (41)	5 (42)	6 (40)
Bachelor's degree or higher	15 (56)	7 (58)	8 (53)
Prefer not to answer	1 (4)	0	1 (7)
Comorbidities			
Heart disease	3 (11)	1 (8)	2 (13)
Stroke	2 (7)	1 (8)	1 (7)
Diabetes	2 (7)	1 (8)	1 (7)
Asthma/lung disease	4 (15)	2 (17)	2 (13)
Arthritis	7 (25)	3 (25)	4 (27)
Fibromyalgia	3 (11)	2 (17)	1 (7)
Hip or joint replacement	4 (15)	2 (17)	2 (13)
Osteoporosis	1 (4)	1 (8)	0
Hypertension	3 (11)	1 (8)	2 (15)
Cancer Stage			
I	5 (19)	1 (8)	4 (27)
II	13 (48)	4 (33)	9 (60)
III	7 (26)	5 (42)	2 (13)
Unknown	2 (7)	2 (17)	0
Surgery			
Lumpectomy	11 (41)	3 (25)	8 (53)
Partial/total mastectomy	16 (59)	9 (75)	7 (47)
Chemotherapy Protocol			
Adjuvant	18 (67)	8 (67)	10 (67)
Neoadjuvant	9 (33)	4 (33)	5 (33)
Paclitaxel-based	20 (74)	8 (67)	12 (80)
Docetaxel-based	7 (26)	4 (33)	3 (20)
Other Treatment Information			
Radiotherapy[a]	23 (85)	9 (75)	14 (93)
Trastuzumab	9 (33)	4 (33)	5 (33)

Data are presented as n (%) unless otherwise indicated.
[a]Radiotherapy received at chemotherapy completion.

or feet. However, by the end of chemotherapy and at follow-up, there were no significant differences between groups (end of chemotherapy: $P = .71$, follow-up: $P = .13$). Further, no differences between groups were found for vibration sense abnormalities at the medial malleolus and patella or for the summation of multiple pinprick test at any time point.

Figure 3 EORTC QLQ CIPN20 Subscale Scores. (A) Significant Main Effect of Time ($P < .01$). (B) Significant Main Effect of Time ($P < .01$). (C) No Significant Main Effects or Group by Time Interaction



Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; QLQ = Quality of Life Questionnaire. Participants used a Likert scale to indicate the level at which they were experiencing symptoms within the past week (1= "not at all" to 4 = "very much"). All scale scores were linearly converted to a 0 to 100 scale; higher scores indicate greater symptom burden. Data are presented as mean ± standard error. [a]Significant difference compared to baseline in both groups combined ($P < .01$). [b]Significant difference compared to pre-cycle 4 in both groups combined ($P < .05$). [c]Significant difference compared to end of chemotherapy in both groups combined ($P < .01$).

Quality of Life

There was a significant interaction between group and time for the EORTC QLQ-C30 overall global health status/QoL ($P = .01$), as shown in Figure 5. By the end of chemotherapy, overall QoL was higher in the IE group relative to the DE group (mean difference = 11.9, $P = .05$). Upon completion of the exercise intervention following chemotherapy, overall QoL increased by a mean of 18.5 points in the DE group, while QoL was maintained in the IE group. Consequently, no significant difference between groups was observed at follow-up ($P = .29$). No other significant group by time interactions were detected for the remaining functional or symptom subscales. There were significant main effects of time for physical

Table 2 EORTC QLQ-C30 CIPN20 Sensory Subscale Items

Sensory Item	Immediate Exercise				Delayed Exercise			
	Baseline (N = 12)	Pre-cycle 4 (N = 11)	End of Chemotherapy (N = 12)	Follow-Up (N = 11)	Baseline (N = 14)	Pre-cycle 4 (N = 14)	End of Chemotherapy (N = 14)	Follow-Up (N = 14)
Numbness in toes or feet	0	1 (9)[a]	5 (42)	1 (9)	0	7 (50)[a]	8 (57)	0
Tingling in fingers or hands	0	4 (36)	2 (17)	2 (18)	0	5 (36)	4 (29)	0
Tingling in toes or feet	0	1 (9)	4 (33)	1 (9)	0	6 (43)	4 (28)	0
Numbness in fingers or hands	0	2 (18)	3 (25)	0	0	4 (29)	5 (36)	0
Problems walking because of difficulty feeling ground under feet	0	0	2 (17)	0	1 (7)	0	2 (14)	0
Shooting or burning pain in fingers or hands	0	1 (9)	1 (8)	0	0	1 (7)	1 (7)	0
Shooting or burning pain in toes or feet	0	0	1 (8)	0	0	1 (7)	2 (14)	0
Difficulty distinguishing between hot and cold	0	0	0	0	0	1 (7)	1 (7)	0
Difficulty hearing	0	0	1 (8)	0	0	0	0	0

Data are presented as n (%). Summary of participants who reported experiencing symptoms "quite a bit" (3/4) or "very much" (4/4) on the EORTC QLQ-C30 CIPN20 subscale. Items are ordered from most common to least common symptom.
Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; QLQ = Quality of Life Questionnaire.
[a]Significant difference between groups ($P = .04$).

function, cognitive function, and emotional function (all $P < 0.05$). After pairwise contrasts, significant changes across time points in both groups combined were found for overall QoL and cognitive function (all $P < 0.01$).

Chemotherapy Completion Rate

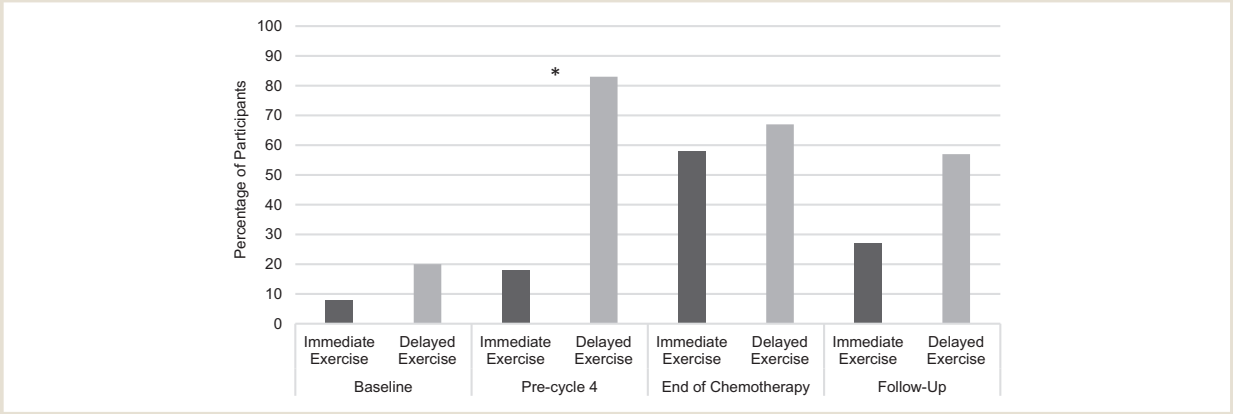
In total, 10 participants experienced a taxane dose reduction of at least 10% or a complete dose cancellation for one or more of their treatments (IE: n = 2, 20%; DE: n = 8, 53%, $P = .06$). Of these participants, one DE participant had dose reductions for her second, third, and fourth taxane treatments due to both general toxicity and CIPN. Four participants had dose reductions for their third and fourth taxane treatments for general toxicity (IE: n = 1, DE: n = 1), CIPN (DE: n = 1), or the reason was not recorded (DE: n = 1). Five participants had dose reductions or cancellations for their last taxane treatment only due to general toxicity (DE: n = 1), liver toxicity (DE: n = 1), CIPN (IE: n = 1, DE: n = 1), or the reason was not recorded (DE: n = 1). Only 3 participants did not complete their taxane treatment within the planned time frameand and were delayed by 1 week (IE: n = 1, 8%, DE: n = 2, 13%, $P = 1.0$). Mean RDI for taxane-based chemotherapy did not significantly differ between groups (IE: 95.9 ± 6.1%, DE: 92.2 ± 11.0%, $P = .31$). However, all IE participants received at least the clinically relevant threshold of 85% RDI, while fewer DE participants achieved this threshold (IE: n = 12, 100%, DE: n = 10, 67%, $P < .05$).

Discussion

CIPN can become a significant burden for patients undergoing neurotoxic chemotherapy regimens. The EXIT trial aimed to investigate the effect of a combined supervised and home-based exercise intervention on CIPN associated specifically with taxane-based chemotherapy, namely docetaxel and paclitaxel, in women with early-stage breast cancer. Exercise did not influence our primary outcome of patient-reported CIPN symptoms assessed using the EORTC QLQ CIPN20 subscale. Exercise during chemotherapy did appear to attenuate the progression in specific CIPN symptom severity after 3 taxane treatment cycles, namely moderate to severe numbness in the toes and feet, and clinically measured vibration sensation. After the fourth and final taxane cycle, the accumulating treatment toxicity may have blunted the effect of exercise on CIPN, resulting in equally severe symptoms in both groups by the end of chemotherapy. This dose–response relationship between neurotoxic agents and neuropathy development is well established.[1] We also observed that exercise during taxane-based chemotherapy may result in maintained overall QoL and a greater tolerance of taxane treatment, including a trend toward fewer taxane dose reductions or cancellations, and the achievement of RDI ≥ 85% despite increasing CIPN symptoms relative to usual care.

The most widely used approach to manage CIPN includes chemotherapy dose reductions, limiting the total dose, or cancelling the therapy.[9,14] These adjustments frequently depend on patient-reported neuropathy symptoms and limitations. Chemotherapy dose adjustments due to CIPN have unfavorable clinical implications when treatment efficacy and patient prognosis depend on chemotherapy dose intensity. Evidence favoring the use of pharmacologic agents or alternative therapies for taxane-related CIPN is scarce and resultantly, there is no treatment currently recommended

Figure 4 Vibration Threshold Test



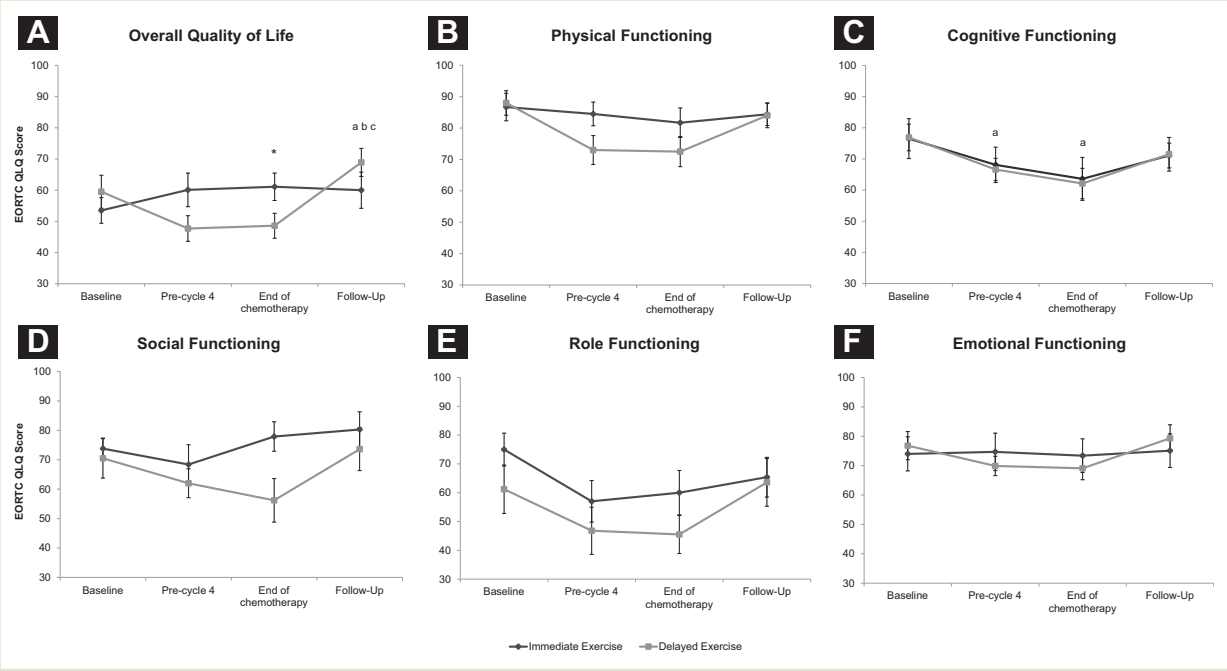
Percentage of individuals in each group who reported altered response to vibration threshold testing. *Significant difference between groups ($P < .01$).

for standard clinical use.[14] In a previous randomized controlled trial, CIPN was reported as the top reason for a disruption in chemotherapy treatments in women with early-stage breast cancer.[35] That same trial also reported that randomization to an exercise intervention versus usual care resulted in a lower average chemotherapy dose reduction. Although preliminary, this finding supports a developing body of evidence that suggests there may be a positive effect of exercise on chemotherapy completion rate;[36] and the attenuation of CIPN is a possible underlying reason for this benefit. Taken together, findings from the EXIT trial help support the hypothesis that exercise may mediate CIPN symptoms just enough over the course of taxane-based chemotherapy to allow patients to better adhere to their prescribed treatment protocol.

Prescribing exercise to manage CIPN and its related impairments is increasingly supported by evidence to-date.[19-25] However, trials have included varying cancer populations and chemotherapy treatment protocols, as well as different CIPN outcome measures and intervention designs. In one of the first randomized controlled trials evaluating exercise for CIPN, Streckmann et al[37] reported that 36 weeks of multi-modal supervised exercise during chemotherapy for lymphoma significantly improved peripheral deep sensitivity and balance control among patients randomized to exercise (n = 30) versus usual care (n = 31), although patient-reported CIPN symptoms were not specifically evaluated. More recently, Zimmer et al[21] reported that an 8-week multi-modal supervised exercise intervention (n = 17) prevented the worsening of patient-reported CIPN symptoms and improved balance and strength in patients with advanced colorectal cancer who were prescribed vinca alkaloids relative to usual care (n = 13). Dhawan et al[23] enrolled patients with pre-existing CIPN (n = 45), and randomization to a home-based strength and balance intervention for 10 weeks resulted in a significant reduction in patient-reported pain, CIPN symptom experience, and improved QoL relative to usual care. In a trial of 355 cancer patients (79% women with breast cancer), Kleckner et al[20] reported significantly attenuated patient-reported hotness and coldness in the hands and feet, and a trend toward attenuated numbness and tingling among participants randomized to a home-based walking and resistance exercise intervention versus usual care. However, these outcomes were part of a secondary analysis and only included single-item questions evaluated on a scale of 0 to 10. Sensorimotor training alone has also been shown to significantly improve postural stability, specifically in women with breast cancer undergoing paclitaxel therapy,[24] as well as to improve tendon reflexes, peripheral deep sensitivity, and pain in mixed cancer patients with self-reported CIPN symptoms.[25] Improved patient-reported CIPN symptoms, however, with these sensorimotor-only interventions were not reported.[24,25] Evidently, key research questions need to be answered to strengthen the argument for exercise for CIPN. Notably, in the current trial, there was no observed impact on the CIPN20 subscale, or CIPN symptoms by the end of chemotherapy, only following 3 taxane cycles. Understanding why this may be and whether adjustments to the intervention are needed should be further explored. Overall, future investigations to help identify the optimal type of exercise for CIPN, the specific aspects of CIPN exercise may affect, and the most appropriate timing of exercise program delivery relative to the receipt of neurotoxic therapies are needed.

Although the pathophysiology of taxane-induced peripheral neuropathy has not been fully elucidated, impaired mitochondrial function, altered peripheral vascularization, and inflammation phenomena, such as an increase in Langerhans cells, up-regulation of proinflammatory cytokines, macrophage accumulation, and microglia activation, may be linked to taxane-related peripheral nerve damage.[38,39] Exercise may counteract this CIPN by improving vascular function and metabolic activity at the level of the peripheral nerves, up-regulating protective neurotrophic factors,[40] or reducing inflammation.[41] Endurance or aerobic exercise can greatly improve mitochondrial function in skeletal muscle,[42] and there is some evidence suggesting a similar positive influence on mitochondria in nerve cells.[43] Exercise may also up-regulate protective neurotrophic factors, including glial-derived neurotrophic factor, brain-derived neurotrophic factor, and insulin-like growth factor, which are biomolecules that promote the growth, survival, and differentiation of both mature and developing

Figure 5 Change in EORTC QLQ-C30 QoL and Functional Subscale Scores. (A) Significant Main Effect of Time ($P < .05$) and Group by Time Interaction ($P < .01$). (B) Significant Main Effect of Time ($P < .05$). (C) Significant Main Effect of Time ($P < .05$). (D and E) No Significant Interaction or Main Effects. (F) Significant Main Effect of Time ($P < .05$)



Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; QLQ = Quality of Life Questionnaire; QoL = quality of life. Data are presented as mean ± standard error. *Significant difference between groups ($P = .05$). Participants used a Likert scale from 1= "not at all" to 4= "very much", except for overall global health status/QoL scale, which was from 1= "very poor" to 7= "excellent." All scores were linearly converted to a 0 to 100 scale. Higher scores indicate better functioning and QoL. [a]Significant difference compared to baseline in both groups combined ($P < .01$). [b]Significant difference compared to pre-cycle 4 in both groups combined ($P < .01$). [c]Significant difference compared to end of chemotherapy in both groups combined ($P < .01$).

neurons.[40,44] Sensorimotor or balance training may also independently play a key role in neuromuscular adaptations and enhanced proprioception,[45] and thus improved coordination, strength, and balance control.[46,47] Thus, it stands to reason that multi-modal exercise interventions may have the greatest potential to attenuate CIPN and its adverse effects. These existing mechanistic explanations supporting exercise for CIPN further strengthen the rationale for continued research in this area.

Finally, another important finding from this trial is the benefit of exercise on patient-reported QoL both during and after taxane-based chemotherapy. We found that 8 to 12 weeks of our prescribed intervention during taxane treatment prevented a decline in QoL by a clinically meaningful amount relative to usual care.[48] This is notable given the potential impact of taxanes and CIPN symptoms on patient QoL. Our results also suggest that if women are unable to engage in exercise training while actively undergoing chemotherapy, completing a similar program after chemotherapy still offers QoL benefits. In particular, our DE intervention ameliorated the detrimental chemotherapy effects on QoL. Specifically, there was a larger magnitude of improvement over time in QoL with an identical exercise program initiated after chemotherapy compared to during chemotherapy. Thus, it is never too late to exercise and QoL benefits are achievable at different time points along the cancer treatment continuum.

This trial has several limitations. We prescribed a multi-modal intervention to optimize the potential impact on CIPN development and to provide the greatest overall benefit to participants.[19] Our intervention included a combination of aerobic and resistance training, which is currently recommended for cancer patients,[49] in addition to specific balance and hand and foot exercises that we thought may be especially important for individuals at risk of developing CIPN. A limitation of this design, is the inability to control for differences in individual effects of each intervention component. Further, we did not control for potential physical activity that both groups may have been engaging in outside of the intervention, including the DE group during chemotherapy. Our lack of statistically significant differences may also be due to our small sample size. This small sample size was in large part due to a slow referral rate from a single cancer treatment center. This is an important consideration for all exercise oncology trials with relatively strict inclusion criteria needed to target specific primary outcomes. However, effect sizes from the current trial could be used to plan adequate sample sizes for future trials. Because of limited resources, blinding of outcome assessments and personnel was also not feasible. This produces an inherent bias for some outcome measures, specifically our clinical sensory tests, and results should therefore be interpreted with caution. However, trends observed for our clinical sensory tests, specifically vibration threshold testing, appeared to match trends observed for patient-reported symptoms.

Some women in this trial also received 3 to 4 cycles of non-taxane chemotherapy, specifically doxorubicin and cyclophosphamide, before enrollment into the current trial. As a result, baseline values were not true pre-chemotherapy values for approximately three quarters of our sample.

Conclusion

CIPN is a frequent and significant adverse effect of taxane-based chemotherapy and there are few treatment options to prevent and manage symptoms. The benefits of exercise during chemotherapy for breast cancer are extensive, yet there is a lack of evidence on the impact of exercise on CIPN in this population. We found that exercise may partially mitigate the progression of CIPN symptoms and maintain QoL, while allowing more patients to possibly receive an adequate taxane RDI. Results from the current trial remain preliminary and are hypothesis-generating for future research investigations on this topic.

Clinical Practice Points

- Managing CIPN in women prescribed taxane agents for breast cancer remains a clinical priority, especially given its relationship to patients' ability to complete their planned taxane treatment.
- There are few effective medical and pharmaceutical CIPN prevention and treatment strategies; thus, understanding the role of lifestyle interventions for CIPN is a growing area of interest.
- Previous research has indicated that exercise is a feasible and promising strategy to attenuate CIPN symptoms in cancer populations, including women with breast cancer.
- We demonstrated that a supervised, structured exercise program concurrent with taxane chemotherapy is feasible among women with breast cancer and may potentially mitigate CIPN symptoms enough to allow patients to better tolerate the planned dose and duration of their taxane chemotherapy. We also found a positive effect of our exercise intervention on quality of life.
- Exercise may be a possible adjunct therapy that can be prescribed to support patients undergoing taxane chemotherapy who are at risk of CIPN.
- Combined with the knowledge that exercise consistently appears to provide a wide range of physical and psychosocial benefits among women with breast cancer, identifying strategies that support increasing physical activity and regular exercise within this population is encouraged.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

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References

1. Argyriou AA, Kyritsis AP, Makatsoris T, Kalofonos HP. Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature. *Cancer Manag Res* 2014; 6:135-47.
2. Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. *J Neurol* 2002; 249:9-17.
3. Ghersi D, Willson ML, Chan MM, Simes J, Donoghue E, Wilcken N. Taxane-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev* 2015: CD003366.
4. Hershman DL, Weimer LH, Wang A, et al. Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast Cancer Res Treat* 2011; 125:767-74.
5. Monfort SM, Pan X, Patrick R, et al. Gait, balance, and patient-reported outcomes during taxane-based chemotherapy in early-stage breast cancer patients. *Breast Cancer Res Treat* 2017; 164:69-77.
6. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. *Support Care Cancer* 2014; 22:2261-9.
7. Winters-Stone KM, Horak F, Jacobs PG, et al. Falls, functioning, and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. *J Clin Oncol* 2017; 35:2604-12.
8. Speck RM, Sammel MD, Farrar JT, et al. Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. *J Oncol Pract* 2013; 9:e234-40.
9. Kim JH, Dougherty PM, Abdi S. Basic science and clinical management of painful and non-painful chemotherapy-related neuropathy. *Gynecol Oncol* 2015; 136:453-9.
10. Bhatnagar B, Gilmore S, Goloubeva O, et al. Chemotherapy dose reduction due to chemotherapy induced peripheral neuropathy in breast cancer patients receiving chemotherapy in the neoadjuvant or adjuvant settings: a single-center experience. *Springerplus* 2014; 3:366.
11. Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. *J Natl Compr Canc Netw* 2009; 7:99-108.
12. Wildiers H, Reiser M. Relative dose intensity of chemotherapy and its impact on outcomes in patients with early breast cancer or aggressive lymphoma. *Crit Rev Oncol Hematol* 2011; 77:221-40.
13. Loibl S, Skacel T, Nekljudova V, et al. Evaluating the impact of Relative Total Dose Intensity (RTDI) on patients' short and long-term outcome in taxane- and anthracycline-based chemotherapy of metastatic breast cancer- a pooled analysis. *BMC Cancer* 2011; 11:131.
14. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014; 32:1941-67.
15. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ* 2012; 344:e70.
16. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2010; 4:87-100.
17. Streckmann F, Zopf EM, Lehmann HC, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. *Sports Med* 2014; 44: 1289-304.
18. Greenlee H, Hershman DL, Shi Z, et al. BMI, lifestyle factors and taxane-induced neuropathy in breast cancer patients: the Pathways study. *J Natl Cancer Inst* 2016; 109:djw206.
19. Duregon F, Vendramin B, Bullo V, et al. Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: a systematic review. *Crit Rev Oncol Hematol* 2018; 121:90-100.
20. Kleckner IR, Kamen C, Gewandter JS, et al. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. *Support Care Cancer* 2018; 26:1019-28.
21. Zimmer P, Trebing S, Timmers-Trebing U, et al. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. *Support Care Cancer* 2018; 26:615-24.
22. McCrary JM, Goldstein D, Sandler CX, et al. Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy [e-pub ahead of print], *Support Care Cancer*, https://doi.org/10.1007/s00520-019-04680-w. accessed May 1, 2019.
23. Dhawan S, Andrews R, Kumar L, Wadhwa S, Shukla G. A randomized controlled trial to assess the effectiveness of muscle strengthening and balancing exercises on chemotherapy-induced peripheral neuropathic pain and quality of life among cancer patients [e-pub ahead of print], *Cancer Nurs*, https://doi.org/10.1097/NCC.0000000000000693. accessed May 1, 2019.
24. Vollmers PL, Mundhenke C, Maass N, et al. Evaluation of the effects of sensorimotor exercise on physical and psychological parameters in breast cancer patients undergoing neurotoxic chemotherapy. *J Cancer Res Clin Oncol* 2018; 144:1785-92.
25. Streckmann F, Lehmann HC, Balke M, et al. Sensorimotor training and whole-body vibration training have the potential to reduce motor and sensory symptoms of chemotherapy-induced peripheral neuropathy-a randomized controlled pilot trial. *Support Care Cancer* 2019; 27:2471-8.
26. Richardson A, Ream E, Wilson-Barnett J. Fatigue in patients receiving chemotherapy: patterns of change. *Cancer Nurs* 1998; 21:17-30.

27. Kirkham AA, Lloyd MG, Claydon VE, Gelmon KA, McKenzie DC, Campbell KL. A longitudinal study of the Association of Clinical Indices of Cardiovascular Autonomic Function With Breast Cancer Treatment and Exercise Training. *Oncologist* 2019; 24:273-84.
28. Borg G. *Borg's Perceived Exertion and Pain Scales*. Champaign, IL: Human Kinetics; 1998.
29. Knutzen KM, Brilla LR, Caine D. Validity of 1RM prediction equations for older adults. *J Strength Cond Res* 1999; 13:242-6.
30. Walk D, Sehgal N, Moeller-Bertram T, et al. Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. *Clin J Pain* 2009; 25:632-40.
31. Booth J, Young MJ. Differences in the performance of commercially available 10-g monofilaments. *Diabetes Care* 2000; 23:984-8.
32. Paisley A, Abbott C, van Schie C, Boulton A. A comparison of the Neuropen against standard quantitative sensory-threshold measures for assessing peripheral nerve function. *Diabet Med* 2002; 19:400-5.
33. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85:365-76.
34. Weycker D, Barron R, Edelsberg J, Kartashov A, Lyman GH. Incidence of reduced chemotherapy relative dose intensity among women with early stage breast cancer in US clinical practice. *Breast Cancer Res Treat* 2012; 133:301-10.
35. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. *J Clin Oncol* 2015; 33:1918-27.
36. Bland KA, Zadravec K, Landry T, Weller S, Meyers L, Campbell KL. Impact of exercise on chemotherapy completion rate: a systematic review of the evidence and recommendations for future exercise oncology research. *Crit Rev Oncol Hematol* 2019; 136:79-85.
37. Streckmann F, Kneis S, Leifert JA, et al. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Ann Oncol* 2014; 25:493-9.
38. Carozzi VA, Canta A, Chiorazzi A. Chemotherapy-induced peripheral neuropathy: what do we know about mechanisms? *Neurosci Lett* 2015; 596: 90-107.
39. De Iuliis F, Taglieri L, Salerno G, Lanza R, Scarpa S. Taxane induced neuropathy in patients affected by breast cancer: literature review. *Crit Rev Oncol Hematol* 2015; 96:34-45.
40. Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J Psychiatr Res* 2015; 60:56-64.
41. Meneses-Echavez JF, Correa-Bautista JE, Gonzalez-Jimenez E, et al. The effect of exercise training on mediators of inflammation in breast cancer survivors: a systematic review with meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2016; 25: 1009-17.
42. Hoppeler H, Fluck M. Plasticity of skeletal muscle mitochondria: structure and function. *Med Sci Sports Exerc* 2003; 35:95-104.
43. Steib K, Schaffner I, Jagasia R, Ebert B, Lie DC. Mitochondria modify exercise-induced development of stem cell–derived neurons in the adult brain. *J Neurosci* 2014; 34:6624-33.
44. Park JS, Hoke A. Treadmill exercise induced functional recovery after peripheral nerve repair is associated with increased levels of neurotrophic factors. *PLoS One* 2014; 9:e90245.
45. Gruber M, Gruber SB, Taube W, Schubert M, Beck SC, Gollhofer A. Differential effects of ballistic versus sensorimotor training on rate of force development and neural activation in humans. *J Strength Cond Res* 2007; 21:274-82.
46. Heitkamp HC, Horstmann T, Mayer F, Weller J, Dickhuth HH. Gain in strength and muscular balance after balance training. *Int J Sports Med* 2001; 22:285-90.
47. Granacher U, Gollhofer A, Strass D. Training induced adaptations in characteristics of postural reflexes in elderly men. *Gait Posture* 2006; 24:459-66.
48. Maringwa J, Quinten C, King M, et al. Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. *Ann Oncol* 2011; 22:2107-12.
49. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010; 42:1409-26.