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Impaired Postural Control and Altered Sensory Organization During Quiet Stance Following Neurotoxic Chemotherapy: A Preliminary Study

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Abstract

Individuals diagnosed with chemotherapy-induced peripheral neuropathy (CIPN) demonstrate impaired balance and carry an increased risk of falling. However, prior investigations of postural instability have only compared these individuals against healthy controls, limiting the understanding of impairments associated with CIPN. Therefore, the purpose of this study was to better isolate postural control impairments that are associated with CIPN. Twenty cancer survivors previously diagnosed with breast or colorectal cancer participated. Participants were separated into 3 groups: no prior chemotherapy exposure (CON, n = 6), and recent treatment with taxane- or oxaliplatin-based chemotherapy with no/mild symptoms of CIPN (−CIPN, n = 8) or moderate/severe symptoms of CIPN (+CIPN, n = 6). Postural control was assessed by measuring center of pressure during standing balance conditions that systematically interfered with somatosensory, visual, and/or vestibular information. The presence of CIPN sensory symptoms was associated with impaired postural control, particularly during eyes-closed balance conditions ($P < .05$). Additionally, medial-lateral postural instability was more pronounced in the +CIPN group compared with the −CIPN group and CON participants ($P < .05$). Greater postural instability during eyes-closed balance in individuals with CIPN is consistent with impaired peripheral sensation. Balance impairments in cancer survivors with CIPN demonstrate the unique challenges in this population and motivate the need for targeted efforts to mitigate postural control deficits that have previously been associated with fall risk.

Keywords

balance, center of pressure, sensory reweighting, chemotherapy-induced peripheral neuropathy, CIPN

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Introduction

The increased risk of falling in cancer survivors motivates the need for improved understanding of factors contributing to the functional impairments that challenge cancer survivorship.[1-3] Standing balance is an important risk factor for falls in this population.[3] While quantitative assessment of postural control has been widely used to elucidate novel aspects of postural instability in a number of populations, balance impairments are most often assessed via patient reports for cancer patients due to ease of collecting these data. The feasibility of collecting objective balance data in the oncology clinic has been demonstrated,[4,5] and several groups have reported balance impairments that are demonstrated in cancer patients in different stages of treatment or survivorship.[2,4,6-11] However, much is still unknown about how common neurotoxic adverse effects of treatment associate with balance impairments.

Many individuals diagnosed with cancer are treated with chemotherapy agents, such as taxanes or oxaliplatin, which can cause adverse side effects due to their neurotoxicity.

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Chemotherapy-induced peripheral neuropathy (CIPN), a prominent dose-limiting toxicity of these chemotherapy agents, in addition to causing sensory symptoms, also impairs other peripheral nerve function.[12-15] An estimated 68% of patients who receive chemotherapy develop CIPN symptoms, and these symptoms can become severe enough to cause premature cessation of chemotherapy.[14,16] Reported symptoms are most severe in sensory nerves, and they commonly include pain, tingling, and numbness.[12-15] Large myelinated afferent sensory nerve fibers are often implicated in CIPN,[13,14] suggesting that somatosensory information may be impaired. The effects of this neurotoxicity can be persistent, with 30% of patients continuing to experience symptoms 6 months or more following completion of chemotherapy.[16] The functional relevance of these symptoms is supported by CIPN being associated with an increased risk of falling.[3]

While CIPN has received increased awareness recently, the underlying mechanisms that may contribute to postural instability and an increased risk of falling in cancer survivors with CIPN remain poorly defined. Impaired balance is associated with fall history in breast cancer survivors.[2] Monfort et al previously reported on the longitudinal progression of balance impairments in breast cancer patients receiving taxane-based chemotherapy who were largely asymptomatic with respect to CIPN.[4,5] Additionally, others have reported impaired postural control in breast cancer survivors with CIPN symptoms when compared with healthy controls.[6,7] However, no previous studies have directly compared cancer survivors who are symptomatic against those who are asymptomatic for CIPN, which contributes to the existing gaps in knowledge on how balance impairments associate with specific adverse effects of treatment.

To gain insight into sensory system contributions to postural control, researchers have developed sensory organization protocols that systematically interfere with the availability or fidelity of sensory information from visual, vestibular, and somatosensory systems.[17,18] Prior use of these protocols in cancer survivors suggests that, after completing taxane-based chemotherapy, patients with CIPN demonstrate difficulty across all conditions, with the most severe deficits occurring in visually deprived conditions.[6] Large deficits during visual and somatosensory interference conditions, whereby only vestibular information is available and unaltered, also identified cancer survivors who had recently fallen.[2] Both of these findings are consistent with somatosensory and/or vestibular deficits.

While balance impairments have been reported in individuals with CIPN,[6,7] it is unknown whether these impairments exceed those that may be experienced by cancer survivors without symptoms of CIPN. Previous studies have provided valuable insight into the underexplored area of quantifying functional impairments in cancer survivors but are limited in their ability to provide insight on CIPN-associated balance deficits because they used healthy control groups for comparison,[6,7,9,11] did not assess CIPN symptoms,[2] or were restricted to largely asymptomatic cancer survivors.[4,5] Additionally, potential multifactorial sensory system contributions to postural instability in cancer survivors have not been delineated. Therefore, the purpose of this current study was to better isolate postural control impairments that are associated with CIPN from balance impairments that may exist in other cancer survivor populations. Our hypothesis was that (1) CIPN would be associated with impaired balance during quiet standing that would exceed those of asymptomatic cancer survivors and (2) balance impairments in the CIPN group would be consistent with somatosensory deficits.

Methods

Participants

Breast (stages I-III) and colorectal (stages I-IV) cancer patients were recruited from the following 3 groups: (1) had not received chemotherapy (CON), (2) had received taxane or oxaliplatin chemotherapy but had none to mild symptoms of CIPN (−CIPN), and (3) had received taxane or oxaliplatin chemotherapy with resultant moderate to severe symptoms of CIPN (+CIPN). These groups were chosen to delineate balance impairments observed in survivors with CIPN from those that may be present in asymptomatic or non–chemotherapy-treated survivors. Survivors unable to stand or walk without assistance, having a preexisting diagnosis of neuropathy of any kind, or having a prior lower extremity joint replacement were excluded from the study.

Protocol

Participants (both in the −CIPN and +CIPN groups) completed testing sessions within approximately 6 weeks of completing chemotherapy (mean = 3.8 weeks; range = 1.1-6.3 weeks). CON participants were all at least 6 weeks post-surgery. During their visits, participants completed a sensory organization balance testing protocol and patient-reported outcomes of CIPN.

Assessing Postural Control

The sensory organization protocol systematically interfered with or omitted sensory information from somatosensory, visual, and/or vestibular systems. A 6-cm thick balance pad (Airex, Airex AG, Sins, Switzerland) was used to interfere with somatosensory information by providing an unstable foam surface as opposed to a rigid surface. Having participants tilt their heads back at 45° was used to

Table 1. Sensory Organization Balance Conditions and Descriptions[a,b,c].

Condition	Symbol	Eyes	Surface	Head Orientation	Unaltered Sensory Information
ORS		Open	Rigid	Straight	Vision, somatosensation, vestibular
CRS		Closed	Rigid	Straight	Somatosensation, vestibular
OFS		Open	Foam	Straight	Vision, vestibular
CFS		Closed	Foam	Straight	Vestibular
ORT		Open	Rigid	45° tilt	Vision, somatosensation
CRT		Closed	Rigid	45° tilt	Somatosensation
CFT		Closed	Foam	45° tilt	None

[a]Task symbols adapted from van der Kooij et al.[28]
[b]A 6-cm thick Airex pad was used for the foam conditions.
[c]A goniometer was used to verify the head angle for the conditions involving a 45° head tilt.

degrade vestibular information by altering the head orientation compared with typical straight-ahead gaze.[19] A goniometer was used to verify the head angle for the conditions involving a 45° head tilt. Visual information was omitted by having participants close their eyes. The corresponding 7 balance conditions included in this study were (Table 1) the following: eyes open, rigid surface, straight ahead (ORS); eyes closed, rigid surface, straight ahead (CRS); eyes open, foam surface, straight ahead (OFS); eyes closed, foam surface, straight ahead (CFS); eyes open, rigid surface, 45° tilt (ORT); eyes closed, rigid surface, 45° tilt (CRT); and eyes closed, foam surface, 45° tilt (CFT). The order of the first 6 conditions was randomized, and the CFT condition was always performed last. Each condition was performed for three 30-second trials.

Participants' feet positions were standardized by having the medial borders of the feet separated by 5 cm and parallel to each other.[4] Participants were instructed to focus their gaze on an object in the center of their field of view during the task (or prior to closing eyes for the eyes closed conditions) and stand as still as possible during each trial. A poster was 185 cm in front of the participants for the straight-ahead conditions, while the ceiling was approximately 250 cm from the participants for the 45° head tilted conditions. Participants were instructed to stand as relaxed and as still as possible. The averages of the three 30-second trials for each condition were used as the estimates for the various balance parameters. Participants could take breaks as needed, and predetermined breaks were taken after sets of 3 conditions were performed to reduce the potential effects of physical or mental fatigue. The postural control protocol took approximately 45 minutes to complete.

Center of pressure (CoP) data were recorded at 1000 Hz using a BP5046 balance plate (Bertec Corp, Columbus, OH). The data were fourth-order Butterworth low-pass filtered at 20 Hz for calculating summary CoP measures, which included 95% confidence ellipse area (EA), medial-lateral root-mean-squared excursion (RMS_ml), planar mean velocity of the CoP (MVEL_r), and medial-lateral mean CoP velocity (MVEL_ml). Detailed descriptions of these measures and their interpretations are provided elsewhere.[4,20] Briefly, increases in these parameters are interpreted as impaired postural control either through diminished spatial control (EA and RMS_ml) or a greater degree of overcorrecting in postural adjustments (MVEL_r, MVEL_ml). These measures were chosen because they have previously been associated with falling in the elderly.[21-24] All calculations were performed using custom scripts in MATLAB (Version 2015b; MathWorks, Inc; Natick, MA).

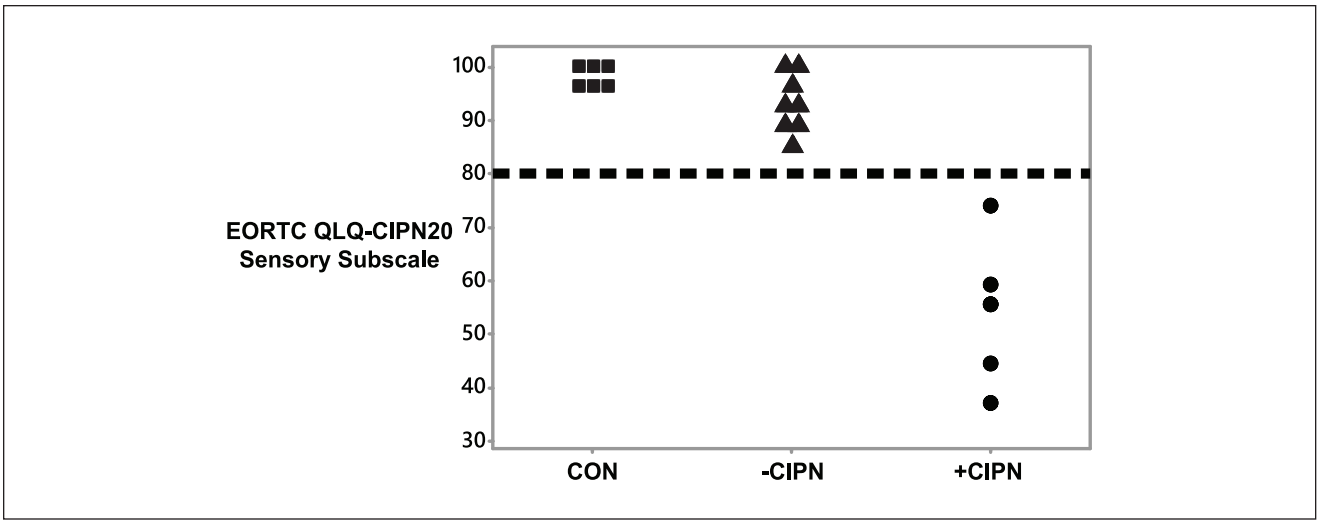

Figure 1. Distribution of EORTC QLQ-CIPN20 sensory subscale scores by study group. Dashed line indicates the cutoff score that was imposed to distinguish symptomatic (+CIPN) from asymptomatic (−CIPN) participants. Lower sensory subscale values indicate worse symptoms.

Patient-Reported Outcomes

Participants also completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20), which is a 20-item questionnaire that assesses sensory, motor, and autonomic system interference.[25,26] Subscale scores (sensory, motor, and autonomic) were transformed to a 0 to 100 scale, with lower scores indicating higher symptom severity. The sensory subscale was used to separate participants who received chemotherapy into the −CIPN and +CIPN groups. This approach was chosen due to its alignment with the common clinical practice of evaluating CIPN symptoms via verbal sensory symptom questions that ask patients if they are experiencing any pain, tingling, or numbness in their hands or feet. A cutoff of 80 for the EORTC QLQ-CIPN20 sensory subscale score at the time the balance data were collected was used to separate the 2 groups (Figure 1). Scores above 80 for this subscale previously characterized 97% of respondents from the general Dutch population, which supports that scores lower than 80 represent greater than typical symptom severity.[27]

Statistical Analysis

Kruskal-Wallis tests (nonparametric equivalent to an ANOVA [analysis of variance]) were used to identify balance conditions and interference ratios where at least one between-group difference was likely for a given balance parameter ($P < .05$). Nonparametric tests were deemed necessary because some data were not normally distributed within a group for a given balance condition. Post hoc pairwise comparisons between groups were then made with Wilcoxon rank sum tests for balance parameters with a significant Kruskal-Wallis test. These analyses were performed in SAS Workstation (Version 9.4; SAS Institute, Inc, Cary, NC). Significance for all analyses was defined at $\alpha = .05$ (2-sided). We did not correct for multiple comparisons due to the exploratory nature of this study.

Results

Participant Characteristics

Twenty individuals participated in the study after providing institutional review board–approved informed consent. Participant characteristics are provided in Table 2. Consistent with the grouping criteria, the +CIPN group had significantly worse self-reported sensory symptoms of CIPN ($P < .002$) than the other 2 groups, as well as worse motor symptoms ($P < .016$).

Sensory Organization Test Performance

Participants successfully completed all balance conditions except for one −CIPN participant who was unable to complete the CFT condition. To account for the fact that the data were not missing at random (ie, the task was attempted and failed), this participant was assigned a 10% increase from the highest recorded value across all participants for each summary CoP parameter. This decision was justified because a failed attempt of a balance condition that requires a recovery step corresponds to the CoP traveling outside the participant's boundary of support during bipedal quiet stance. As all other participants were able to maintain the CoP within their boundary of support, the loss of balance

Table 2. Patient Demographic, Treatment, and Symptom Characteristics.

	CON (n = 6)	−CIPN (n = 8)	+CIPN (n = 6)
General characteristics, mean (SD)			
Age (years)	59.3 (9.6)	55.9 (9.0)	50.0 (15.0)
Male/female	0/6	1/7	2/4
Mass (kg)	78.0 (14.1)	77.1 (11.1)	91.6 (21.6)
Height (m)	1.62 (0.05)	1.68 (0.04)	1.71 (0.06)
Cancer type, n (%)			
Breast	6 (100%)	6 (75%)	4 (67%)
Colorectal	0 (0%)	2 (25%)	2 (33%)
Cancer stage at diagnosis, n (%)			
I	4 (67%)	1 (13%)	3 (50%)
II	2 (33%)	2 (25%)	0 (0%)
III	0 (0%)	4 (50%)	3 (50%)
IV	0 (0%)	1 (13%)	0 (0%)
Chemotherapy type, n (%)			
Taxane	0 (0%)	6 (75%)	4 (67%)
Oxaliplatin	0 (0%)	2 (25%)	2 (33%)
Diagnosis and treatment timing (weeks), mean (SD)			
Time since diagnosis	111.6 (97.1)	27.7 (6.1)[a]	29.9 ± 6.7[b]
Time since completing chemotherapy	N/A	3.7 ± 1.8	3.9 ± 1.3
EORTC QLQ-CIPN20[d], mean (SD)			
Sensory	98.1 (2.0)	93.1 (5.4)	54.3 (12.7)[b,c]
Motor	95.8 (6.5)	89.1 (8.6)	69.4 (16.2)[b,c]
Autonomic	100.0 (0.0)	94.4 (7.9)	75.9 (19.1)

Abbreviation: CIPN, chemotherapy-induced peripheral neuropathy.
[a]$P < .05$ for difference between CON and −CIPN.
[b]$P < .05$ for difference between CON and +CIPN.
[c]$P < .05$ for difference between −CIPN and +CIPN.
[d]EORTC QLQ-CIPN20 subscales are on a 0 to 100 scale with lower scores representing worse symptoms.

for this one participant was assigned an added "penalty." The nonparametric analyses used in the study accommodate this approach.

The +CIPN group demonstrated significant deficits in summary CoP measures compared with the CON and −CIPN groups ($P < .05$). The majority of significant differences in balance parameters were between the +CIPN and CON groups during vision-deprived conditions (Table 3 and Supplemental Table [available online]). MVEL_ml also identified impaired CoP control in the +CIPN group compared with the −CIPN group, particularly for conditions that did not experimentally alter somatosensory information (ie, rigid surface conditions). The asymptomatic −CIPN group also demonstrated increased CoP dispersion compared with the CON group during select conditions.

Discussion

To our knowledge, this is the first study to show that balance impairments in cancer survivors with CIPN symptoms exceed those observed in asymptomatic survivors. Prior studies used healthy controls or did not characterize CIPN symptoms in their cancer survivor groups, limiting the insight that can be gained. We found that balance impairments in the +CIPN group were above and beyond those observed in asymptomatic cancer survivors who had or had not previously received chemotherapy. The findings support our hypothesis that cancer survivors with more severe symptoms of CIPN demonstrate balance deficits that are consistent with somatosensory impairment, and that these deficits exceed those in asymptomatic cancer survivors. Notably, cancer survivors who were asymptomatic for CIPN following chemotherapy also demonstrated select balance deficits compared with non-chemotherapy cancer controls. Therefore, balance deficits existed in participants who received chemotherapy regardless of perceived symptoms, with the presence of CIPN symptoms being associated with magnified balance deficits. These contributions move toward better understanding the unique challenges that burden cancer survivors with different symptomology. The previously established relevance of the postural control parameters used in this study to falls may also provide insight into these survivors' increased fall risk and warrant further investigation.[3]

Table 3. Group Differences in Postural Control Measures Across Balance Conditions[a].

Balance Condition		Group	EA	MVEL_r	MVEL_ml	RMS_ml
ORS		CON	1.9 (0.7)	11.0 (3.7)	5.3 (2.1)	2.6 (0.6)
		−CIPN	**2.9 (1.7)***	11.2 (1.7)	5.9 (2.5)	3.4 (1.1)
		+CIPN	**4.8 (4.5)**†	14.1 (10.8)	**8.4 (6.3)**†,b	4.3 (2.6)
CRS		CON	2.0 (1.2)	14.2 (5.4)	7.0 (5.9)	3.1 (0.4)
		−CIPN	3.6 (4.8)	15.0 (5.7)	7.3 (2.5)	3.7 (1.8)
		+CIPN	**10.1 (12.4)**‡	**31.0 (25.8)**†	**18.0 (9.7)**†,b	**6.3 (3.5)**‡
OFS		CON	9.1 (3.3)	26.5 (6.3)	14.2 (3.6)	6.3 (0.6)
		−CIPN	11.1 (4.7)	21.9 (7.3)	14.3 (4.8)	6.9 (2.3)
		+CIPN	14.1 (6.3)	28.9 (11.9)	19.6 (9.3)	8.2 (2.2)
CFS		CON	19.1 (7.9)	48.3 (14.4)	27.5 (9.7)	9.5 (2.6)
		−CIPN	28.8 (15.6)	53.4 (25.9)	31.3 (10.3)	12.2 (3.8)
		+CIPN	**36.7 (120.9)**‡	75.8 (116.0)	45.6 (47.8)	13.6 (16.7)
ORT		CON	2.8 (2.6)	13.0 (7.2)	5.4 (2.5)	3.3 (0.7)
		−CIPN	3.1 (2.9)	12.9 (2.1)	5.6 (0.9)	3.2 (1.1)
		+CIPN	7.2 (4.8)	18.6 (8)	**9.6 (3.5)**†,b	4.7 (3.1)
CRT		CON	2.3 (1.7)	16.0 (2.9)	6.6 (2.4)	2.9 (1.2)
		−CIPN	**4.9 (4.3)***	20.4 (9.3)	8.6 (4.0)	3.8 (1.3)
		+CIPN	**11.7 (23.9)**‡	**32.1 (39.5)**‡	**16.4 (16.6)**‡,b	**6.3 (8.2)**‡,b
CFT		CON	28.2 (9.9)	57.3 (19.9)	32.2 (9.8)	10.8 (1.4)
		−CIPN	34.7 (39.9)	65.1 (51.2)	31.1 (23.2)	11.3 (5.8)
		+CIPN	**62.0 (127.8)**‡	94.9 (97.8)	51.7 (37.5)	**16.4 (15.7)**‡

Abbreviations: IQR, interquartile range; EA, 95% confidence ellipse area in cm^2; MVEL_r, mean velocity (planar) in mm/s; MVEL_ml, mean velocity (medial-lateral) in mm/s; RMS_ml, root mean squared excursion (medial-lateral) in mm.
[a]Values presented as median (IQR).
−CIPN versus CON: *$P < .05$.
+CIPN versus CON: †$P < .05$, ‡$P < .01$.
+CIPN versus −CIPN: [b]$P < .05$.
Bold font indicates a significant difference exists ($P < .05$).

The results of this study suggest that cancer survivors with symptomatic CIPN have worse balance impairments than asymptomatic survivors. We identified that medial-lateral balance may be preferentially impaired in those with CIPN. The +CIPN group demonstrated balance deficits, particularly during conditions when somatosensation was not experimentally altered (ie, rigid surface conditions). These findings are consistent with the +CIPN group having somatosensory deficits that hinder the effective use of somatosensory information. The clinical relevance of medial-lateral balance impairments is supported by RMS_ml[22] and MVEL_ml[21] deficits during eyes closed quiet stance previously identifying individuals at an increased risk of falling.

+CIPN participants demonstrated more dispersed CoP trajectories during the CFS condition. Balance deficits in conditions that leave only vestibular information uncompromised (eg, CFS) have previously differentiated between breast cancer survivors who previously fell and nonfallers.[2] These findings may indicate the functional challenges for these individuals in real-world scenarios, such as maintaining postural control in a dark room especially while standing on a nonrigid surface (eg, soft carpet). Winters-Stone et al previously discussed the possibility that treatment-associated vestibular ototoxicity may contribute toward the impaired balance during conditions that require reliance on vestibular function.[2] Without a rigorous test of vestibular function, we are unable to isolate the source(s) of the impaired performance during the CFS condition in this study (eg, impaired vestibular sensory function, additive effects of experimental and CIPN-related degradation of somatosensory information, inappropriate weighting of sensory information, altered internal representation,[28] etc).

In addition to impaired medial-lateral balance in the +CIPN group, several other balance deficits were found. Notably, we identified balance impairments in the −CIPN group compared with the CON group in measures of planar CoP spatial control. These results suggest that chemotherapy may have detrimental effects on postural stability even in survivors without perceived symptoms of CIPN, which is

consistent with findings in a prospective breast cancer cohort.[4,5] The presence of detectable balance impairments without significant self-reported symptoms may be clinically relevant in the context of early identification of cancer survivors at an increased risk of falling. As the current study did not prospectively track falls, future research is needed to verify the extent to which fall-relevant interpretations of these CoP parameters extend to cancer survivors.

Balance parameters during the ORS (ie, baseline) balance condition of our study align well with those previously reported for a heterogeneous group of cancer survivors (mean age = 54 years).[9] This previous study identified that medial-lateral CoP measures indicated worse postural control in cancer survivors compared with a healthy control group. Our study provides a novel addition to the limited existing literature on quantitative balance impairments in cancer survivors by demonstrating worsened postural deficits in cancer survivors with symptoms of CIPN. Additionally, our asymptomatic chemotherapy group demonstrated several balance deficits when compared with survivors who did not receive chemotherapy. These findings suggest potential variability in balance function related to cancer treatment and adverse effects.

This study provides insight into postural instability in cancer survivors who receive neurotoxic chemotherapy with and without symptomatic CIPN, but there are several limitations that should be considered. The small sample sizes for the groups and nonparametric tests limit the statistical power to detect differences. Moreover, as previously mentioned, there was no correction for multiple comparisons. Therefore, caution should be taken in these findings, particularly those with marginal *P* values, as the risk of Type I error is elevated. Future studies with larger sample sizes that enable subpopulation analyses will provide further confidence in these findings and elucidate how balance deficits may differ by cancer survivor characteristics (eg, different chemotherapy agents, comorbidities, etc). An increased sample size would also allow for a more rigorous statistical approach to control for potential demographic and treatment confounding factors. Furthermore, +CIPN group assignment was based on a single questionnaire. While the EORTC QLQ-CIPN20 is a validated measure for quantifying CIPN symptoms, other instruments exist and future studies may benefit from using multiple CIPN assessments to more comprehensively characterize CIPN symptoms. Importantly, future studies that incorporate thorough assessments of neurologic function alongside patient-reported symptoms and detailed postural control testing are still needed to elucidate the underlying physiological processes of postural instability associated with CIPN. The extended time since diagnosis for the CON group may have resulted in diminished cancer diagnosis and/or treatment effects over time and should be considered when interpreting the comparisons with the other groups. Future studies of the same nature could be improved by incorporating more dynamic tasks as well as implementing dual tasks that may shed additional light into the implications of the varied adverse effects resulting from chemotherapy on patient stability and fall risk. Finally, prospective studies that utilize promising measures of postural stability and also track falls should provide a substantial step forward in the effort to reduce falls in the growing population of cancer survivors.

Conclusions

This study helps better understand aspects of impaired postural control in cancer survivors. CIPN was associated with deficits in medial-lateral postural control that have previously been associated with fall risk. These deficits exceeded those demonstrated by asymptomatic cancer survivors who had or had not previously received chemotherapy. These findings provide a step toward better understanding impaired physical function in individuals with CIPN, which may have implications for reducing the increased risk of falling in cancer survivors. Future research is warranted on the effects of interventions that target these functional impairments.

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Supplemental Material

Supplemental material for this article is available online.

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