Supportive Care in Cancer (2019) 27:3905–3912
https://doi.org/10.1007/s00520-019-04695-3

ORIGINAL ARTICLE

Age-related differences in patient-reported and objective measures of chemotherapy-induced peripheral neuropathy among cancer survivors

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Received: 29 October 2018 / Accepted: 7 February 2019 / Published online: 15 February 2019

Abstract

Purpose While older adults with cancer are more likely to develop chemotherapy-induced peripheral neuropathy (CIPN), the study aimed to determine if patient-reported and objective measures of CIPN differ by age among cancer survivors.

Methods Cancer survivors with persistent CIPN after completion of platinum and/or taxane chemotherapy completed CIPN questionnaires (severity, interference with activities, sensory, and motor symptoms) and objective testing (light touch, vibration, pain, cold sensation). CIPN measures were compared by age group (< 65 $n = 260$ versus ≥ 65 $n = 165$) using parametric and nonparametric tests.

Results Among 425 cancer survivors with CIPN, mean age was 60.9 (SD 10.5). CIPN location did not differ by age (overall 68% hands and feet, 27% only feet, 5% only hands). For patient-reported measures, older survivors reported less severe pain in the hands and feet than younger survivors. In addition, older survivors reported lower interference with general activity, routine activities, normal work, enjoyment of life, sleep, mood, relations with other people, and sexual activity. No age differences in sensory and motor symptom scores were found. In contrast, for objective measures, older survivors had worse light touch and cold sensations in their feet and worse vibration detection in their hands and feet.

Conclusions Despite having worse light touch, cold, and vibration sensations, older cancer survivors with CIPN reported less severe pain and interference with activities. This discordance highlights the importance of including both patient-reported and objective measures to assess CIPN in cancer survivors to better evaluate this clinical condition.

Keywords Chemotherapy-induced peripheral neuropathy · Age · Cancer survivor · Chemotherapy · Patient-reported outcomes

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Introduction

As the incidence of cancer among adults age ≥ 65 increases to 2.3 million by 2030 [1], the number of cancer survivors who are age ≥ 65 will increase to 19.1 million by 2040 [2]. As a result, it is critically important to characterize the symptom experience of older cancer survivors, particularly persistent treatment toxicities. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most prevalent neurologic complications of cancer treatment and can persist for more than 10 years after completion of chemotherapy (CTX) [3, 4]. CIPN can precipitate functional decline, falls, and decreased quality of life [5, 6], particularly in older cancer survivors who have pre-existing functional impairments.

Retrospective pooled analyses of cancer clinical trials found that older age is associated with an increased risk of developing moderate to severe CIPN [7, 8]. However, these studies relied on clinician-reported CIPN severity and did not include patient-reported (e.g., pain intensity, interference with activities) or objective (e.g., light touch, vibration) measures of CIPN. While a small prospective study of patients diagnosed with lung or breast cancer included both patient-reported and objective measures of CIPN [9], this study included only 17 older patients. With the increasing recognition of clinically meaningful differences between clinician- and patient-reported outcomes [10, 11] and the clinical benefit of using patient-reported outcomes to identify treatment toxicities sooner [12], it is important to characterize CIPN using both patient-reported and objective measures.

Therefore, the objective of this study was to compare patient-reported and objective measures of CIPN in younger (age < 65) and older (age ≥ 65) cancer survivors with persistent CIPN in the hands and/or feet at least 3 months after completion of platinum and/or taxane CTX.

Methods

Patients and settings

This analysis is part of a larger study, funded by the National Cancer Institute, that evaluated cancer survivors with and without CIPN. The methods for the larger study are described in detail elsewhere [13]. In brief, cancer survivors were recruited from throughout the San Francisco Bay area. Survivors with CIPN met the following criteria: age ≥ 18 years; completed platinum and/or taxane CTX ≥ 3 months prior to enrollment; had changes in sensation and/or pain in their hands and/or feet of ≥ 3 months duration after completion of CTX; had a rating of ≥ 3 on a 0 to 10 numeric rating scale (NRS) for any of the Pain Quality Assessment Scale sensations (i.e., numb, tender, shooting, sensitive, electrical, tingling, radiating, throbbing, cramping, itchy, unpleasant) [14]; if they had pain associated with CIPN; had an average pain intensity score in their hands and/or feet of ≥ 3 on a 0 to 10 NRS; had a Karnofsky Performance Status (KPS) score of ≥ 50; and were able to read, write, and understand English.

Survivors were excluded if they had diabetic neuropathy, peripheral vascular disease, vitamin B12 deficiency, thyroid dysfunction, HIV neuropathy, another painful condition that was difficult for them to distinguish from their CIPN, a hereditary sensory or autonomic neuropathy, and/or a hereditary mitochondrial disorder. Of the 1450 survivors who were screened, 754 were enrolled, and 623 completed the self-report questionnaires and the study visit. For this analysis, only survivors with CIPN ($n = 425$) were included.

Study procedures

Research nurses screened and consented the survivors by phone. Survivors completed questionnaires prior to their study visit. At the in-person visit, written informed consent was obtained, questionnaires were reviewed for completeness, and objective measurements were performed.

Study measures

Demographic and clinical characteristics

Survivors provided demographic information and completed the KPS scale [15] and Self-Administered Comorbidity Questionnaire [16]. Clinical information including cancer diagnosis, CTX regimen and doses, and time since CTX completion were obtained through medical record review.

Subjective measures

A detailed history of CIPN in the hands and/or feet was obtained using a pain questionnaire that was used in our previous [17, 18] and ongoing studies. This questionnaire obtained information on duration of CIPN and current, average daily, and worst amount of pain or changes in sensation using 0 (none) to 10 (excruciating) NRSs.

Sensory, motor, and autonomic CIPN symptom severity was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN-20 (EORTC QLQ CIPN-20) [19]. Each item was measured on a 1 (not at all) to 4 (very much) Likert scale. The sensory, motor, and autonomic neuropathy subscales are the cumulative scores for nine sensory, eight motor, and three autonomic items, respectively.

The Brief Pain Inventory Pain Interference Scale [20] was used to assess how CIPN interfered with activities (e.g., walking, work, sleep) during the past week. For our study, we

Table 1 Differences in demographic and clinical characteristics among cancer survivors with CIPN by age group ($N = 425$)

Characteristic	Age < 65 ($n = 260$, 61.0%) (1) Mean (SD)	Age ≥ 65 ($n = 165$, 39.0%) (2) Mean (SD)	P^a
Age (years)	54.52 (8.01)	70.90 (4.48)	< 0.0001
Education (years)	16.07 (3.27)	16.32 (3.41)	0.47
Body mass index (kg/m^2)	26.54 (5.61)	26.49 (5.34)	0.93
Karnofsky performance status score	80.10 (15.38)	83.18 (17.43)	0.06
Number of comorbidities	1.90 (1.47)	2.07 (1.91)	0.31
Self-Administered Comorbidity Questionnaire score	4.07 (3.41)	4.24 (3.65)	0.64
Years since cancer diagnosis	4.27 (4.61)	5.72 (5.07)	0.003
Number of prior cancer treatments	3.18 (0.98)	3.02 (0.94)	0.11
Dose of platinum for patients who received only a platinum (mg/m^2)	704.83 (556.52)	705.03 (388.64)	1.00
Dose of taxane for patients who received only a taxane (mg/m^2)	738.28 (290.96)	805.02 (1090.65)	0.53
Doses for patients who received both a platinum and a taxane compound			
Platinum dose (mg/m^2)	1715.22 (788.25)	1882.87 (793.25)	0.25
Taxane dose (mg/m^2)	818.21 (459.00)	995.00 (447.69)	0.04
	n (%)	*n* (%)	
Female	226 (87.3)	141 (85.5)	0.60
Race/ethnicity			0.001
White	184 (70.8)	145 (87.9)	1 < 2
Asian/Pacific Islander	23 (8.9)	7 (4.2)	
Black	17 (6.5)	5 (3.0)	
Hispanic/mixed/other	36 (13.9)	8 (4.9)	1 > 2
Married/partnered	154 (61.4)	98 (60.5)	0.86
Lives alone	64 (25.3)	58 (35.4)	0.03
Employed	141 (54.2)	38 (23.2)	< 0.0001
Annual household income			
<$30,000	57 (23.4)	34 (22.7)	
$30,000–$69,999	47 (19.3)	36 (24.0)	
$70,000–$99,999	38 (15.6)	26 (17.3)	
> $100,000	102 (41.8)	54 (36.0)	0.44
Ever smoker	83 (32.1)	77 (47.2)	0.002
Type of cancer			0.04
Breast	158 (60.8)	75 (45.5)	1 > 2
Colon	22 (8.5)	21 (12.7)	
Lung	4 (1.5)	4 (2.4)	
Ovarian	26 (10.0)	24 (14.6)	
Other	50 (19.2)	41 (24.9)	
Metastatic disease	149 (58.0)	103 (63.6)	0.25
Prior surgery	238 (91.5)	156 (95.1)	0.16
Prior radiation	156 (60.2)	94 (57.7)	0.60
Chemotherapy regimen			
Only a platinum compound	55 (21.2)	40 (24.2)	
Only a taxane compound	131 (50.4)	68 (41.2)	
Both a platinum and a taxane compound	74 (28.5)	57 (34.6)	0.18
Patients who had a dose reduction or delay due to neuropathy	35 (14.0)	20 (13.0)	0.77
CIPN in both hands and feet	184 (70.8)	105 (63.6)	
CIPN in only feet	61 (23.5)	54 (32.7)	
CIPN in only hands	15 (5.8)	6 (3.6)	0.09

CIPN chemotherapy-induced peripheral neuropathy, *kg* kilogram, *mg* milligram, m^2 square meter, *SD* standard deviation

[a] *P* values were calculated using *t* tests (continuous variables), chi-squared tests (categorical variables), and Mann-Whitney *U* test (ordinal household income variable)

added items on interference with routine activities (e.g., dressing, toileting, typing) to assess upper extremity interference from CIPN, balance to assess lower extremity interference from CIPN, and sexual activity given the prevalence of problems with sexual interest or activity in cancer survivors [21]. Interference with routine activities was assessed separately for CIPN in the hands and feet using 0 (does not interfere) to 10 (completely interferes) NRSs.

Objective measures

Details for each objective measure are described elsewhere [13]. Light touch was evaluated using Semmes Weinstein monofilaments [22]. Vibration threshold was assessed using a biothesiometer [23]. Pain sensation was evaluated using the Neurotip [24]. Cold sensation was evaluated using the Tiptherm Rod [25]. For all objective measures of sensation,

both the upper and lower extremities on the dominant side were tested.

Data analysis

Descriptive statistics and frequency distributions were calculated for survivors' demographic and clinical characteristics; CIPN pain characteristics; EORTC QLQ CIPN-20 sensory, motor, and autonomic subscales; and pain interference scores. For the four objective measures of sensation, composite scores were created to summarize results from all tested sites on the dominant upper and lower extremities. For light touch, pain, and cold sensations, the number of sites with loss of each sensation was summed. For light touch, loss of protective sensation was defined as the inability to feel the 4.56 size monofilament (4 g) in each of the upper extremity and 5.07 size monofilament (10 g) in each of the lower extremity locations [22]. For vibration, the mean vibration threshold across the sites was calculated. Differences between age groups (i.e., age < 65 versus ≥ 65) in demographic and clinical characteristics and subjective and objective measures of CIPN were evaluated using independent sample *t* tests, chi-squared analyses, and Mann-Whitney *U* tests. A *P* value of < 0.05 was considered statistically significant. Data were analyzed using Stata/SE 15.1 (College Station, TX).

Results

Demographic and clinical characteristics

As shown in Table 1, 39.0% of our cancer survivors were age ≥ 65. Older survivors with CIPN were more likely to be white, live alone, and have a history of ever smoking. Older cancer survivors were less likely to be employed or have breast cancer. Among patients who received both platinum and taxane CTX, older survivors received a higher mean cumulative taxane dose than younger survivors ($P = 0.04$). Mean time since cancer diagnosis was 5.72 years (SD 5.07) among the older survivors compared to 4.27 years (SD 4.61) among the younger survivors ($P = 0.003$). No significant differences were found in KPS score, comorbidity score, receipt of prior surgery or radiation, type of CTX regimen received, dose reduction or delay due to neuropathy, or locations of CIPN. The most common location for CIPN was in both the hands and feet (63.6% among older survivors, 70.8% among younger survivors).

Table 2 Differences in CIPN pain characteristics of cancer survivors by age group ($N = 465$)

Characteristic	Age < 65 ($n = 260$, 61.0%) Mean (SD)	Age ≥ 65 ($n = 165$, 39.0%) Mean (SD)	P[a]
Pain characteristics—upper extremity			
Duration of CIPN (years)	3.30 (3.86)	4.23 (4.41)	0.06
Pain now	2.88 (2.18)	2.56 (1.83)	0.20
Average pain	3.17 (2.19)	2.99 (2.05)	0.48
Worst pain	4.90 (2.78)	4.20 (2.37)	0.03
Days per week in pain	3.78 (2.93)	3.28 (3.14)	0.17
Hours per day in pain	12.30 (9.84)	14.14 (9.77)	0.14
Pain characteristics—lower extremity			
Duration of CIPN (years)	3.37 (3.83)	4.85 (4.69)	0.0006
Pain now	3.69 (2.33)	3.46 (2.18)	0.31
Average pain	4.07 (2.17)	3.84 (2.02)	0.28
Worst pain	6.31 (2.52)	5.62 (2.53)	0.008
Days per week in pain	3.78 (2.96)	3.37 (3.12)	0.19
Hours per day in pain	14.45 (9.72)	15.77 (9.02)	0.18
EORTC QLQ CIPN-20			
Sensory score	33.1 (18.5)	34.1 (16.9)	0.60
Motor score	23.0 (18.7)	20.9 (15.7)	0.25
Autonomic score	16.4 (20.0)	13.0 (16.7)	0.07

CIPN chemotherapy-induced peripheral neuropathy, *EORTC QLQ* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *SD* standard deviation

[a] *P* values were calculated using *t* tests

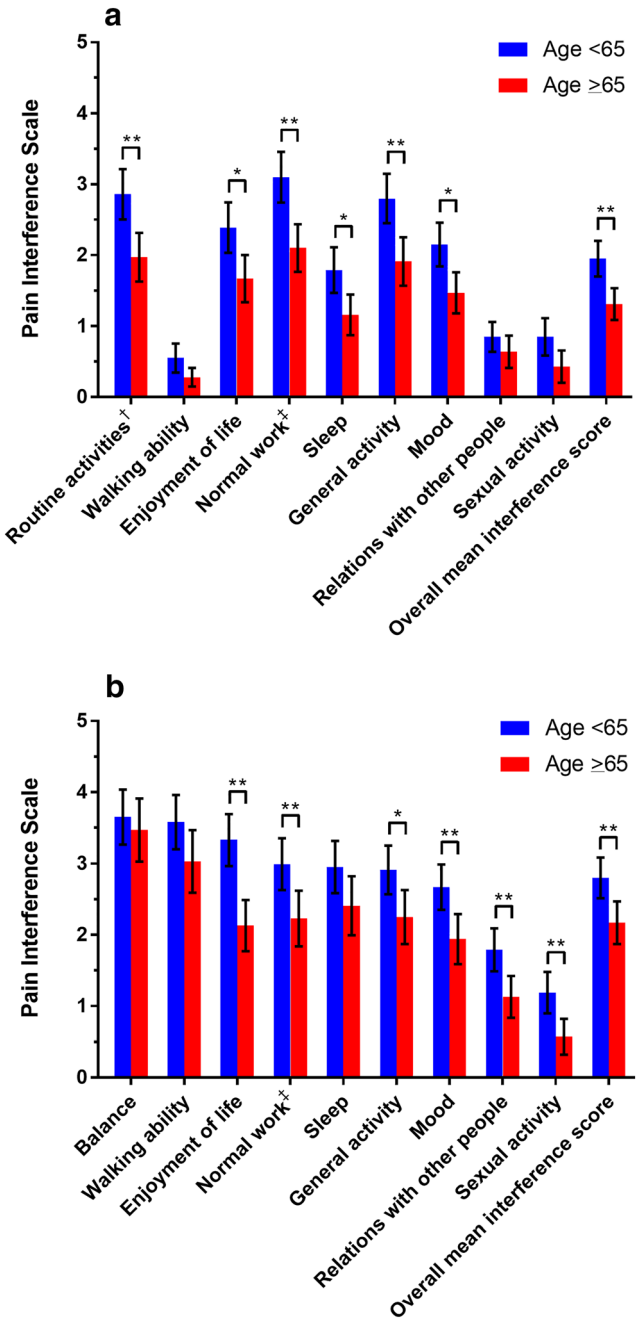

Fig. 1 Mean pain interference scores with 95% confidence intervals for chemotherapy-induced peripheral neuropathy in the **a** upper and **b** lower extremities according to age group. *$P < 0.05$. **$P < 0.01$. Dagger symbol indicates routine activities such as dressing, toileting, and typing. Double dagger indicates normal work that includes both work outside the home and housework

Patient-reported CIPN pain characteristics

Older cancer survivors reported a longer duration of CIPN in the lower extremity compared to younger survivors (4.85 vs 3.37 years, $P = 0.0006$) but not in the upper extremity (Table 2). In both the hands and feet, older survivors reported lower mean scores for their current pain at its worst compared to younger survivors. No age-related differences were found in the patient-reported days per week or hours per day in pain. No age-related differences were found in the mean sensory, motor, or autonomic subscale scores of the EORTC QLQ CIPN-20 (Table 2).

Older survivors consistently reported lower overall mean CIPN interference scores in both the hands (Fig. 1a, mean 1.31 [SD 1.44] vs 1.95 [SD 2.06]; $P = 0.004$) and feet (Fig. 1b, mean 2.17 [SD 1.95] vs 2.80 [SD 2.35]; $P = 0.005$). In both the hands and feet, older age was associated with lower mean interference scores for enjoyment of life, normal work (includes both work outside the home and housework), general activity, and mood. In the hands only, older age was associated with lower mean interference scores for routine activities (e.g., dressing, toileting, typing) and sleep. In the feet only, older age was associated with lower mean interference for relations with other people and sexual activity.

Objective sensory measures of CIPN

For light touch, no age-related differences were found in the mean number of upper extremity sites with loss of protective sensation (Table 3). However, in the lower extremity, older survivors had loss of protective sensation in an average 2.95 (SD 2.50) lower extremity sites out of 9 compared to 1.63 (SD 1.99) sites among younger survivors ($P < 0.0001$). For vibration, the mean detection threshold was higher in both the upper and lower extremities for older survivors. To illustrate, in the four upper extremity sites, older survivors detected vibration at an average threshold of 9.95 V (SD 4.20) while younger survivors detected vibration at an average threshold of 8.48 V (SD 4.63), $P < 0.0001$. In the three lower extremity sites, older survivors detected vibration at an average threshold of 32.44 V (SD 11.47), while younger survivors detected vibration at an average threshold of 23.33 V (10.82), $P < 0.0001$. For cold sensation, older survivors had loss of cold sensation in more upper ($P = 0.03$) and lower extremity sites ($P < 0.0001$) than younger survivors. No age-related differences in pain sensation were found in the upper or lower extremities.

Discussion

This study is the first to evaluate for age-related differences in CIPN using both detailed patient-reported and objective measures. Despite having worse objective light touch and cold sensations in the lower extremities and worse vibration sensation in the upper and lower extremities, older cancer survivors reported lower pain severity scores and less interference with common activities. This discordance highlights the importance of using both patient-reported and

Table 3 Differences in objective sensation measures of CIPN in cancer survivors by age group ($N = 422$)

Characteristic	Age < 65 ($n = 258$, 61.1%) Mean (SD)	Age ≥ 65 ($n = 164$, 38.9%) Mean (SD)	P[a]
Light touch			
No. of upper extremity sites (out of 7)[b] with loss of protective sensation	0.17 (0.77)	0.23 (0.84)	0.18
No. of lower extremity sites (out of 9)[c] with loss of protective sensation	1.63 (1.99)	2.95 (2.50)	< 0.0001
Vibration			
Mean vibration threshold (in volts) at 4 upper extremity sites[d]	8.48 (4.63)	9.95 (4.20)	< 0.0001
Mean vibration threshold (in volts) at 3 lower extremity sites[e]	23.33 (10.82)	32.44 (11.47)	< 0.0001
Pain sensation			
No. of upper extremity sites (out of 7)[b] with loss of pain sensation	1.16 (1.45)	1.15 (1.43)	0.87
No. of lower extremity sites (out of 9)[c] with loss of pain sensation	3.23 (2.10)	3.71 (2.24)	0.06
Cold sensation			
No. of upper extremity sites (out of 4)[d] with loss of cold sensation	0.75 (0.96)	0.94 (1.01)	0.03
No. of lower extremity sites (out of 4)[g] with loss of cold sensation	2.05 (1.17)	2.58 (1.18)	< 0.0001

Changes in sensation are reported for the dominant extremity. Three cancer survivors (two age < 65, one age ≥ 65) did not have the objective measures of CIPN and were not included in this analysis

CIPN chemotherapy-induced peripheral neuropathy, *No.* number, *SD* standard deviation

[a] Mann-Whitney *U* test

[b] Upper extremity sites for light touch and pain were pad of thumb, thumb web space, tip of index finger, tip of little finger, midway base of palm, one third up anterior arm, and two thirds up anterior arm

[c] Lower extremity sites for light touch and pain were pad of great toe, pad of third toe, pad of fifth toe, base of heel, metatarsophalangeal (MP) joint of great toe, MP joint of third toe, MP joint of fifth toe, midway along tibia, and patella

[d] Upper extremity sites for vibration were dorsal interphalangeal (IP) joint of thumb, dorsal IP joint of index finger, ulnar prominence, and lateral epicondyle

[e] Lower extremity sites for vibration were dorsal IP joint of great toe, medial malleolus, and patella

[f] Upper extremity sites for cold were pad of index finger, pad of fifth finger, dorsal metacarpal area of the hand, and dorsal wrist

[g] Lower extremity sites for cold were top of great toe at first MP joint, pad of great toe, dorsum of foot midpoint, and medial malleolus

objective measures to assess CIPN. Using both types of measures may capture older survivors who may have more loss of sensation in their hands and feet than their descriptions suggest as well as younger survivors who may experience more interference with activities than their objective sensory losses suggest.

While older adults with cancer have a higher risk of developing CIPN [7, 8], our findings suggest that among those who developed CIPN, older survivors experienced less pain at its worst than younger survivors. This difference in CIPN pain was found in both the hands and feet. Our findings are consistent with previous reports that found that older cancer patients on average report less pain than younger patients [26–28]. Reports of decreased pain intensity among older cancer patients may be due to age-related differences in how cancer treatment is adjusted in response to increasing symptoms. However, in our study, no differences in CTX dose reductions or delays due to CIPN were found between older and younger survivors that could account for the differences in pain intensity scores. Age differences may be related to how patients adapt to cancer-related pain and how patients perceive symptoms, often referred to as a response shift [29]. For example, in a mixed methods study of cancer-related pain [30], older patients were "living despite pain," more accepting of pain, and modified activities to maximize their participation. In contrast, younger patients were more likely to be "waiting to live" with their lives and activities on hold until complete pain relief was achieved [30].

Overall, in both age groups, CIPN in the feet interfered with activities more than CIPN in the hands. Consistent with reports of an increased risk of falls in cancer patients with CIPN [5, 31, 32], the worst interference scores were for balance and walking ability. However, no age-related differences were found with this outcome. While in one study CIPN and older age were both independent risk factors for falls [32], our findings suggest that both age groups experience problems with balance and walking ability. Future studies need to evaluate for age differences in objective measures of balance.

Among the other activities assessed, older survivors consistently reported less interference from CIPN. While prior studies have evaluated how CIPN interferes with common activities [33, 34], none have examined age differences. Our finding that younger survivors report more interference with activities from CIPN identifies a potential opportunity to study interventions to minimize the impact of CIPN on common activities in this population.

A major strength of our study is that we assessed CIPN using objective measures of sensation in addition to patient-reported outcomes. Of note, older survivors on average had greater loss of protective sensations in the hands and feet than their descriptions suggested. In contrast to guideline-recommended care for patients at risk of diabetic neuropathy [35], the assessment of patients receiving neurotoxic CTX does not routinely include objective measures of sensation. Our findings suggest that monofilament testing be used to assess patients at risk for CIPN to detect loss of protective sensation that may not be recognized based on patient-report alone [36–38]. Future studies need to assess for additional adverse effects associated with neurotoxic CTX (e.g., audiovestibular).

Several limitations warrant consideration. Given the cross-sectional design of our study, prospective longitudinal studies that assess CIPN during and after completion of cancer treatment are warranted to characterize how different measures of CIPN change over time among older and younger survivors. In addition, our study included only cancer survivors who received platinum and/or taxane CTX, so our results may not generalize to survivors with CIPN from other neurotoxic cancer treatments. Finally, detailed information was not obtained on the survivors' use of supportive care strategies over the duration of their CIPN.

In summary, our study identified age-related differences in CIPN with older cancer survivors reporting less pain and interference with activities while having objectively worse measures of sensation. This information can enhance patient education with careful attention to interference with activities if CIPN develops. Furthermore, this information can help clinicians more thoroughly evaluate CIPN severity among older survivors who may report moderate CIPN symptoms and better support younger survivors who may be experiencing significant interference with activities.

Acknowledgements Dr. Miaskowski is supported by the American Cancer Society and NCI (CA168960). Dr. Wong is supported by the Conquer Cancer Foundation of the American Society of Clinical Oncology (ASCO)/Vicky Merryman Women Who Conquer Cancer Young Investigator Award, National Institute on Aging (AG044281), and National Center for Advancing Translational Sciences (NCATS, KL2TR001870). This project was supported by NCATS through UCSF Clinical and Transformational Science Institute (CTSI) (UL1TR000004). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Recruitment was facilitated by Dr. Susan Love Research Foundation's Army of Women Program.

Funding information This study was funded by the National Cancer Institute (NCI, CA151692).

Compliance with ethical standards

Conflict of interest Dr. Wong has reported a conflict of interest outside of the submitted work (immediate family member is an employee of Genentech with stock ownership). The remaining authors have no conflicts to report.

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