Original Article

Deleterious Effects of Higher Body Mass Index on Subjective and Objective Measures of Chemotherapy-Induced Peripheral Neuropathy in Cancer Survivors

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Abstract

Context. Recent, albeit, limited evidence suggests that body mass index (BMI) may be a modifiable risk factor to reduce the deleterious effects of chemotherapy-induced peripheral neuropathy (CIPN) in cancer survivors.

Objectives. To evaluate for differences in demographic, clinical, pain, sensation, and balance characteristics among three BMI groups. We hypothesized that as BMI increased, survivors would report higher pain intensity scores and have significant decrements in measures of sensation and balance.

Methods. A total of 416 survivors with CIPN were evaluated using subjective and objective measures of CIPN. Survivors were divided into three BMI groups (i.e., normal weight, overweight, and obese). Differences among the BMI groups were evaluated using parametric and nonparametric statistics.

Results. Of the 416 survivors, 45.4% were normal weight, 32.5% were overweight, and 22.1% were obese. Compared with the normal-weight group, survivors in the other two groups had lower functional status scores, a higher comorbidity burden, higher pain intensity scores, and higher interference scores. In addition, compared with the normal-weight group, survivors in the other two BMI groups had significantly worse balance scores.

Conclusion. Our findings support the hypothesis that as BMI increased, pain sensation and balance characteristics worsened. Our findings suggest that nutritional counseling as well as exercise and weight management programs in survivors with CIPN may improve these clinically important problems. J Pain Symptom Manage 2019;58:252–263. © *2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words
Chemotherapy, peripheral neuropathy, body mass index, taxane, platinum, cancer survivor, balance

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common problem in cancer survivors with prevalence rates ranging from 38% to 90%.[1] CIPN is associated with dose reductions of potentially curative chemotherapy (CTX), functional decline and decreases in quality of life, and increases in health care costs.[2,3] In a recent study of cancer survivors who had completed CTX five years ago, 58.4% reported CIPN and nearly half reported moderate to severe symptoms.[4] In fact, CIPN is a chronic problem for many survivors, lasting months to years after CTX is completed.[5] Currently, no treatments are available

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to prevent CIPN and duloxetine is the only drug recommended for the management of pain associated CIPN.[6]

An important area for research is the identification of modifiable characteristics that are associated with deleterious effects in cancer survivors with CIPN. Recent, albeit, limited evidence suggests that a higher body mass index (BMI) is one such characteristic. For example, in one study of breast cancer survivors,[4] women who were obese (i.e., BMI > 30) were 1.94 times more likely to develop CIPN than women whose BMI was <25. In another study that evaluated for differences in pain and symptom burden between obese (BMI >30) and nonobese (BMI <30) cancer survivors,[7] obese patients reported a significantly higher number of pain descriptors. In addition, obesity was associated with a higher symptom burden. In a study of 1237 breast cancer survivors who received taxanes,[8] differences in Functional Assessment of Cancer Therapy−Taxane Neurotoxicity scores among women with normal (<25), overweight (>25 to <30), and obese (>30) BMIs at the initiation of treatment were evaluated. Compared with normal-weight patients, patients who were overweight or obese were more likely to report an increase in Functional Assessment of Cancer Therapy−Taxane Neurotoxicity scores of >10% at 24 months after the initiation of CTX.

Although these studies provide evidence of an association between BMI and CIPN, several limitations warrant consideration. All three studies used only subjective data on CIPN to examine this association. In addition, two of these studies focused only on breast cancer survivors who received a taxane.[7,8] No studies were found that evaluated for associations between both subjective and objective measures of CIPN and BMI. Therefore, the purpose of this study, in a sample of survivors with CIPN ($n = 416$), was to evaluate for differences in demographic, clinical, pain, sensation, and balance characteristics among three BMI groups (i.e., normal weight, overweight, and obese) using subjective and objective measures of CIPN. We hypothesized that as BMI increased, survivors would report higher pain intensity scores and have significant decrements in measures of sensation and balance.

Methods

Survivors and Settings

The current analysis is part of a larger study, funded by the National Cancer Institute, that evaluated CIPN in cancer survivors. The methods for the larger study are described in detail elsewhere.[9] In brief, survivors were recruited from throughout the San Francisco Bay area. Survivors with CIPN met the following inclusion criteria: were >18 years of age; had received a platinum and/or a taxane compound; had completed their course of CTX three months before enrollment; had changes in sensation and/or pain in their feet and/or hands for more than three months after the completion of CTX; had a rating of >3 on a 0 to 10 numeric rating scale (NRS) for any one of the following sensations from the Pain Quality Assessment Scale (PQAS[10]; numb, tender, shooting, sensitive, electrical, tingling, radiating, throbbing, cramping, itchy, and unpleasant); if they had pain associated with CIPN, had an average pain intensity score of >3 on a 0 to 10 NRS for their feet and/or hands, had a Karnofsky Performance Status (KPS) score of >50, and were able to read, write, and understand English. Survivors were excluded if they had peripheral vascular disease, vitamin B12 deficiency, thyroid dysfunction, HIV neuropathy, another painful condition that was difficult for them to distinguish from their CIPN, a hereditary sensory or autonomic neuropathy, and/or a hereditary mitochondrial disorder. Of the 1450 survivors who were screened, 754 were enrolled, and 623 completed the self-report questionnaires and the study visit. For this analysis, only survivors with CIPN ($n = 416$) were included.

Study Procedures

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

Study Measures

Demographic and Clinical Characteristics. Survivors provided information on demographic characteristics and completed the Alcohol Use Disorders Identification Test,[11] the KPS scale,[12] and the Self-Administered Comorbidity Questionnaire.[13]

Pain Questionnaires. Separate assessments were completed for pain intensity and quality ratings for the hands and feet. A detailed history of CIPN was obtained using a questionnaire from our previous[14,15] and ongoing studies. Information was obtained on the date of onset of pain and its level of interference with function. Average and worst pain intensity over the past 24 hours were assessed using a 0 (no pain) to 10 (worst pain imaginable) NRS.[16]

The 20-item PQAS was used to assess the qualities associated with CIPN.[10,17] Sixteen items evaluated the magnitude of the different pain quality descriptors

Table 1
Differences in Demographic Characteristics Among the Body Mass Index Groups

Characteristic	Normal Weight (0), 45.4% ($n = 189$) Mean (SD)	Overweight (1), 32.5% ($n = 135$) Mean (SD)	Obese (2), 22.1% ($n = 92$) Mean (SD)	Test, *P*-value
Age (yrs)	60.56 (11.42)	61.00 (10.26)	61.15 (9.41)	$F = 0.12$, $P = 0.884$
Education (yrs)	16.57 (2.53)	16.56 (2.90)	15.70 (2.92)	$F = 3.50$, $P = 0.031$ $0 > 2$
	% (*n*)	% (*n*)	% (*n*)	
Female	88.8 (167)	80.0 (108)	91.3 (84)	$X^2 = 7.58$, $P = 0.023$; No significant pairwise contrasts
Married/partnered (% yes)	61.3 (114)	63.8 (83)	55.7 (49)	$X^2 = 1.49$, $P = 0.474$
Lives alone (% yes)	26.7 (50)	24.2 (32)	40.4 (36)	$X^2 = 7.59$, $P = 0.022$; $1 < 2$
Employed (% yes)	45.0 (85)	42.2 (57)	37.4 (34)	$X^2 = 1.46$, $P = 0.482$
Ethnicity				
White	77.8 (147)	79.3 (107)	71.7 (66)	
Asian/Pacific Islander	9.0 (17)	6.7 (9)	3.3 (3)	
Black	4.2 (8)	3.7 (5)	9.8 (9)	
Hispanic/mixed/other	9.0 (12)	10.4 (14)	15.2 (14)	$X^2 = 10.19$, $P = 0.117$
Annual household income				
<$30,000	20.5 (35)	23.1 (30)	29.4 (25)	KW = 0.035
$30,000 - $69,999	19.9 (34)	19.2 (25)	25.9 (22)	
$70,000 - $99,999	14.6 (25)	17.7 (23)	16.5 (14)	
>$100,000	45.0 (77)	40.0 (52)	28.2 (24)	$0 > 2$
Childcare responsibilities (% yes)	16.1 (30)	13.5 (18)	8.7 (8)	$X^2 = 2.89$, $P = 0.236$
Adult care responsibilities (% yes)	3.5 (6)	4.0 (5)	4.8 (4)	$X^2 = 0.24$, $P = 0.885$

KW = Kruskal-Wallis test; SD = standard deviation.

(e.g., sharp, hot, aching, cold) measured on a 0 to 10 NRS. Four items evaluated global and spatial qualities of pain. Three subscale scores were calculated (i.e., paroxysmal pain [shooting, sharp, electrical, hot, radiating], surface pain [itchy, cold, numb, sensitive, tingling], and deep pain [aching, heavy, dull, cramping, throbbing, tender]). The PQAS has well-established validity and reliability in studies of various types of neuropathic pain.[10,17]

Sensation. Light touch was evaluated using Semmes Weinstein monofilaments.[18] Cold sensation was evaluated using the Tiptherm rod.[19,20] Pain sensation was evaluated using the Neurotip.[19] Vibration threshold was assessed using a biothesiometer.[21] For all the measures of sensation, both the upper and lower extremities on the dominant side were tested.

Balance. Self-report questions from the CIPN Assessment Tool were used to assess balance.[22] The objective measures of balance were the Timed Get Up and Go test[23] and the Fullerton Advanced Balance test.[24,25]

Data Analysis

Data were analyzed using SPSS, version 23.[26] Descriptive statistics and frequency distributions were calculated for survivors' demographic and clinical characteristics. Three BMI groups were created (i.e., normal weight [i.e., BMI <25 kg/m^2], overweight [i.e., BMI of 25 to 30 kg/m^2], and obese [i.e., BMI >30 kg/m^2]) using cutoffs established by the Centers for Disease Control.[27] For the four measures of sensation (i.e., light touch, cold, pain, and vibration), composite scores, over all the sites that were tested on the dominant upper and lower extremities, were created. For light touch, cold, and pain, the number of sites with loss of each sensation were summed. For vibration, the mean score across the sites was calculated. Differences among the three BMI groups in demographic and clinical characteristics, as well as subjective and objective measures of CIPN, were evaluated using analysis of variance, chi-squared analyses, or Kruskal-Wallis tests with Bonferroni corrected post hoc contrasts. A *P*-value of <0.0167 (i.e., 0.05/3) was considered statistically significant.

Results

Differences in Demographic and Clinical Characteristics

As shown in Table 1, compared with normal-weight survivors, obese survivors had fewer years of education. When compared with overweight survivors, obese survivors were more likely to live alone.

In terms of clinical characteristics (Table 2), compared with normal-weight survivors, survivors in

Table 2
Differences in Clinical Characteristics Among the Body Mass Index Groups

Characteristic	Normal Weight (0); 45.4% ($n = 189$)	Overweight (1); 32.5% ($n = 135$)	Obese (2); 22.1% ($n = 92$)	Test, *P*-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Karnofsky Performance Status score	85.52 (9.39)	81.65 (10.31)	81.20 (10.78)	$F = 8.28$, $P < .001$; 0 > 1 and 2
Body mass index (kg/m^2)	22.21 (1.78)	27.10 (1.44)	34.70 (4.89)	$F = 659.20$, $P < 0.001$; 0 < 1 < 2
Number of comorbidities	1.63 (1.32)	2.05 (1.45)	2.73 (1.57)	$F = 18.55$, $P < 0.001$; 0 < 1 < 2
Self-Administered Comorbidity Questionnaire score	3.31 (3.17)	4.35 (3.25)	5.68 (3.54)	$F = 16.49$, $P < 0.001$; 0 < 1 < 2
Alcohol Use Disorders Identification Test score	2.44 (2.28)	2.24 (2.29)	1.88 (1.90)	$F = 1.96$, $P = 0.142$
Years since cancer diagnosis	4.53 (5.01)	4.69 (4.53)	5.18 (4.59)	$F = 0.58$, $P = 0.560$
Number of prior cancer treatments	3.10 (0.97)	3.11 (1.00)	3.15 (0.96)	$F = 0.09$, $P = 0.915$
Number of current cancer treatments	0.41 (0.64)	0.43 (0.57)	0.39 (0.53)	$F = 0.12$, $P = 0.891$
Number of metastatic sites (of seven sites)	0.74 (0.83)	0.81 (0.75)	0.70 (0.75)	$F = 0.71$, $P = 0.492$
Number of metastatic sites without lymph node involvement	0.24 (0.58)	0.19 (0.57)	0.23 (0.56)	$F = 0.32$, $P = 0.728$
	% (n)	% (n)	% (n)	
Smoker (ever)	31.6 (59)	42.5 (57)	42.4 (39)	$X^2 = 5.21$, $P = 0.074$
Exercise on a regular basis (% yes)	92.6 (175)	82.2 (111)	75.8 (69)	$X^2 = 15.75$, $P < .001$; 0 > 1 and 2
Born prematurely (% yes)	8.7 (15)	4.2 (5)	6.8 (6)	$X^2 = 2.26$, $P = 0.323$
Surgery on arms (% yes)	20.1 (38)	21.8 (29)	22.8 (21)	$X^2 = 0.31$, $P = 0.857$
Surgery on hands (% yes)	10.1 (19)	8.1 (11)	13.2 (12)	$X^2 = 1.51$, $P = 0.469$
Surgery on legs (% yes)	25.8 (48)	22.9 (30)	26.7 (24)	$X^2 = 0.50$, $P = 0.777$
Surgery on feet (% yes)	12.9 (24)	22.0 (29)	16.7 (15)	$X^2 = 4.57$, $P = 0.102$
Injury to arms (% yes)	23.8 (44)	30.1 (40)	24.2 (22)	$X^2 = 1.78$, $P = 0.411$
Injury to hands (% yes)	30.4 (55)	37.7 (49)	36.3 (33)	$X^2 = 2.05$, $P = 0.359$
Injury to legs (% yes)	16.8 (31)	31.3 (41)	20.9 (19)	$X^2 = 9.35$, $P = 0.009$; 0 < 1
Injury to feet (% yes)	24.2 (44)	30.8 (40)	30.0 (27)	$X^2 = 1.98$, $P = 0.372$
Comorbid conditions (% yes)				
Osteoarthritis	23.3 (44)	28.9 (39)	46.7 (43)	$X^2 = 16.31$, $P < 0.001$; 0 and 1 < 2
Back pain	31.2 (59)	37.0 (50)	35.9 (33)	$X^2 = 1.35$, $P = 0.511$
Depression	19.0 (36)	26.7 (36)	30.4 (28)	$X^2 = 5.15$, $P = 0.076$
High blood pressure	12.7 (24)	26.7 (36)	53.3 (49)	$X^2 = 52.67$, $P < 0.001$; 0 < 1 and 2, 1 < 2
Heart disease	6.3 (12)	8.9 (12)	7.6 (7)	$X^2 = 0.74$, $P = 0.690$
Diabetes	1.6 (3)	3.7 (5)	16.3 (15)	$X^2 = 26.9$, $P < 0.001$; 0 and 1 < 2
Lung disease	3.2 (6)	4.4 (6)	6.5 (6)	$X^2 = 1.68$, $P = 0.431$
Anemia or blood disease	4.2 (8)	5.9 (8)	8.7 (8)	$X^2 = 2.28$, $P = 0.320$
Ulcer or stomach disease	5.3 (10)	3.0 (4)	2.2 (2)	$X^2 = 2.05$, $P = 0.359$
Kidney disease	0.5 (1)	3.0 (4)	5.4 (5)	$X^2 = 6.16$, $P = 0.037$; 0 < 2
Liver disease	3.7 (7)	3.7 (5)	2.2 (2)	$X^2 = 0.52$, $P = 0.773$
Rheumatoid arthritis	1.6 (3)	3.7 (5)	4.3 (4)	$X^2 = 2.16$, $P = 0.339$
Pain not related to cancer	48.7 (92)	61.9 (83)	70.3 (64)	$X^2 = 13.24$, $P = 0.001$; 0 < 2
Type of cancer				
Breast	54.5 (103)	49.6 (67)	62.0 (57)	$X^2 = 5.58$, $P = 0.694$
Colon	11.1 (21)	8.9 (12)	8.7 (8)	
Lung	1.6 (3)	2.2 (3)	2.2 (2)	
Ovarian	11.6 (22)	11.1 (15)	7.6 (7)	
Other	21.2 (40)	28.1 (38)	19.6 (18)	
Any metastatic disease	56.2 (104)	69.2 (92)	56.5 (52)	$X^2 = 6.22$, $P = 0.045$ No significant pairwise contrasts
Chemotherapy regimen				
Only a platinum compound	23.8 (45)	25.2 (34)	16.3 (15)	$X^2 = 2.84$, $P = 0.585$
Only a taxane compound	45.5 (86)	45.9 (62)	50.0 (46)	
Both a platinum and a taxane compound	30.7 (58)	28.9 (39)	33.7 (31)	
Dose of platinum compound for patients who received only a platinum (mg/m^2)	688.87 (389.92)	795.62 (649.72)	546.89 (295.75)	$F = 1.30$, $P = 0.277$
Dose of taxane compound for patients who received only a taxane (mg/m^2)	863.44 (963.09)	674.32 (281.56)	693.11 (288.51)	$F = 1.62$, $P = 0.201$

(*Continued*)

Table 2
Continued

Characteristic	Normal Weight (0); 45.4% ($n = 189$) Mean (SD)	Overweight (1); 32.5% ($n = 135$) Mean (SD)	Obese (2); 22.1% ($n = 92$) Mean (SD)	Test, *P*-value
Dose of drugs for patients who received both a platinum and a taxane compound				
Platinum dose (mg/m^2)	1696.95 (918.62)	1894.09 (659.07)	1815.46 (693.92)	$F = 0.71$, $P = 0.492$
Taxane dose (mg/m^2)	831.16 (522.43)	935.77 (372.18)	962.71 (439.21)	$F = 0.99$, $P = 0.375$
Patients who had a dose reduction or delay due to neuropathy, % (n)	14.5 (26)	15.4 (20)	11.4 (10)	$X^2 = 0.75$, $P = 0.688$

kg = kilograms; m^2 = meters squared; mg = milligrams; SD = standard deviation.

the other two groups had lower KPS scores and were less likely to exercise on a regular basis. In terms of number and burden of comorbidities, the differences were as follows: normal weight < overweight < obese. Of these comorbidities, obese survivors were more likely to report osteoarthritis, diabetes, and high blood pressure. In addition, compared with normal-weight survivors, obese survivors were more likely to report kidney disease and pain not related to cancer. Compared with normal-weight survivors, overweight survivors were more likely to report an injury to their legs.

Of note, no differences were found among the three groups in cancer diagnoses, number of cancer treatments, number of metastatic sites or presence of metastatic disease, surgery to the upper or lower extremities, CTX regimens, doses of CTX drugs received, and number of dose reductions or delays due to CIPN.

Differences in Pain Characteristics

As shown in Table 3, for both the upper and lower extremities, compared with normal-weight survivors, overweight and obese survivors reported higher current pain, average pain, and worst pain scores, as well as a higher number of days per week in pain. Of note, no differences were found among the three groups in the duration of CIPN in either the upper or lower extremities.

In terms of pain interference in the lower extremities, compared with normal-weight survivors, overweight and obese survivors reported high interference scores for balance, walking ability, enjoyment of life, normal work, sleep, general activity, and relationships with other people, as well as a higher total interference score. In addition, compared with normal-weight survivors, overweight survivors reported higher interference scores for mood and sexual activity.

In terms of pain interference in the upper extremities, compared with normal-weight survivors, obese and overweight survivors reported higher interference scores for routine activities (i.e., dressing, toileting, typing), enjoyment of life, normal work, sleep, general activity, mood, relations with other people, and total interference scores. In addition, compared with normal-weight survivors, overweight survivors reported higher interference scores for sexual activity.

In terms of self-reported pain qualities, for both the upper and lower extremities, compared with normal-weight survivors, survivors who were overweight or obese reported higher scores for the following pain qualities: unpleasant, intense, hot, throbbing, and intense deep, as well as for the PQAS subscales of paroxysmal and surface pain. For this between-group comparison, quality scores that were significantly higher only in the feet included electrical, shooting, and sharp. For this between-group comparison, quality scores that were significantly higher only in the hands included dull, cramping, aching, heavy, and tender and the PQAS subscale score of deep.

Compared with the normal-weight group, survivors who were overweight reported higher tingling scores in both their hands and their feet. For this comparison, quality scores that were significantly higher only in the feet included dull, cramping, tender, and intense surface and the PQAS subscale score of deep. For this between-group comparison, quality scores that were significantly higher only in the hands included electrical, shooting, and radiating.

Compared with the normal-weight group, survivors in the obese group reported higher scores for numb and sensitive skin in their feet and higher scores for sharp in their hands.

Differences in Sensation

As summarized in Table 4, compared with the normal-weight group, both the overweight and obese survivors had a higher number of sites in their lower extremities that did not feel pain. No statistically significant differences were found among the three

Table 3
Differences in Pain Characteristics Among the Body Mass Index Groups

Characteristic	Normal Weight (0); 45.4% ($n = 189$) Mean (SD)	Overweight (1); 32.5% ($n = 135$) Mean (SD)	Obese (2); 22.1% ($n = 92$) Mean (SD)	Test, *P*-value
Pain characteristics—Lower extremity				
Duration of CIPN (yrs)	3.56 (4.10)	4.09 (4.35)	4.09 (3.88)	F = 0.81, $P = 0.448$
Pain now	3.21 (2.14)	3.88 (2.25)	4.04 (2.42)	F = 5.35, $P = 0.005$ 0 < 1 and 2
Average pain	3.52 (2.00)	4.34 (2.17)	4.37 (2.04)	F = 7.79, $P < 0.001$ 0 < 1 and 2
Worst pain	5.50 (2.56)	6.46 (2.37)	6.57 (2.49)	F = 7.98, $P < 0.001$ 0 < 1 and 2
Days per week in pain	2.83 (2.98)	4.23 (2.95)	4.22 (2.89)	F = 10.75, $P < 0.001$ 0 < 1 and 2
Hours per day in pain	14.35 (9.55)	15.83 (9.44)	14.66 (9.25)	F = 0.92, $P = 0.401$
Pain characteristics—Upper extremity				
Duration of CIPN (yrs)	3.18 (3.90)	3.97 (4.60)	3.73 (3.67)	F = 1.15, $P = 0.318$
Pain now	2.27 (1.89)	3.17 (2.04)	3.27 (2.32)	F = 8.01, $P < 0.001$ 0 < 1 and 2
Average pain	2.53 (1.89)	3.47 (2.03)	3.79 (2.43)	F = 10.52, $P < 0.001$ 0 < 1 and 2
Worst pain	4.02 (2.41)	4.99 (2.68)	5.39 (2.79)	F = 7.50, $P = 0.001$ 0 < 1 and 2
Days per week in pain	2.83 (2.99)	4.34 (2.85)	3.90 (2.93)	F = 7.85, $P < 0.001$ 0 < 1 and 2
Hours per day in pain	11.41 (9.87)	14.55 (9.65)	12.79 (9.69)	F = 2.68 $P = 0.071$
Pain Interference Scale—Lower extremity				
Balance	2.77 (2.83)	4.12 (2.92)	4.35 (3.24)	F = 11.56, $P < 0.001$ 0 < 1 and 2
Walking ability	2.32 (2.56)	4.15 (3.00)	4.30 (3.23)	F = 20.92, $P < 0.001$ 0 < 1 and 2
Enjoyment of life	2.17 (2.44)	3.32 (2.85)	3.54 (3.04)	F = 10.25, $P < 0.001$ 0 < 1 and 2
Normal work	1.84 (2.43)	3.30 (2.94)	3.43 (2.88)	F = 14.95, $P < 0.001$ 0 < 1 and 2
Sleep	2.20 (2.67)	3.12 (3.00)	3.25 (2.93)	F = 5.64, $P = 0.004$ 0 < 1 and 2
General activity	1.87 (2.21)	3.22 (2.92)	3.34 (2.76)	F = 14.18, $P < 0.001$ 0 < 1 and 2
Mood	1.98 (2.28)	2.77 (2.68)	2.64 (2.57)	F = 4.32, $P = 0.014$ 0 < 1
Relations with other people	1.04 (1.77)	2.01 (2.52)	1.81 (2.60)	F = 7.78, $P < 0.001$ 0 < 1 and 2
Sexual activity	0.47 (1.28)	1.53 (2.72)	1.11 (2.40)	F = 8.68, $P < 0.001$ 0 < 1
Mean interference score	1.89 (1.83)	3.07 (2.29)	3.11 (2.40)	F = 15.37, $P < 0.001$ 0 < 1 and 2
Pain Interference Scale—Upper extremity				
Routine activities[a]	1.84 (2.31)	3.08 (2.79)	2.97 (2.91)	F = 7.59, $P = 0.001$ 0 < 1 and 2
Walking ability	0.23 (0.80)	0.49 (1.54)	0.67 (1.86)	F = 2.60, $P = 0.076$
Enjoyment of life	1.37 (2.07)	2.63 (2.71)	2.78 (3.13)	F = 9.89, $P < 0.001$ 0 < 1 and 2
Normal work	2.07 (2.43)	3.25 (2.77)	3.24 (2.87)	F = 7.21, $P = 0.001$ 0 < 1 and 2
Sleep	1.01 (1.76)	2.09 (2.70)	1.96 (2.72)	F = 7.18, $P = 0.001$ 0 < 1 and 2
General activity	1.72 (2.37)	3.05 (2.74)	3.07 (2.78)	F = 9.78, $P < 0.001$ 0 < 1 and 2
Mood	1.27 (1.85)	2.41 (2.30)	2.39 (2.70)	F = 9.53, $P < 0.001$ 0 < 1 and 2
Relations with other people	0.43 (1.05)	1.01 (1.72)	1.03 (2.10)	F = 5.14, $P = 0.006$ 0 < 1 and 2
Sexual activity	0.27 (0.94)	1.15 (2.45)	0.97 (2.51)	F = 5.92, $P = 0.003$ 0 < 1
Mean interference score	1.17 (1.38)	2.13 (1.92)	2.16 (2.22)	F = 11.06, $P < 0.001$ 0 < 1 and 2
Pain Quality Assessment Scale Scores—Lower extremity				
Numb	4.94 (3.06)	5.67 (2.99)	6.03 (2.85)	F = 4.54, $P = 0.011$ 0 < 2

(*Continued*)

Table 3
Continued

Characteristic	Normal Weight (0); 45.4% ($n = 189$) Mean (SD)	Overweight (1); 32.5% ($n = 135$) Mean (SD)	Obese (2); 22.1% ($n = 92$) Mean (SD)	Test, *P*-value
Unpleasant	3.88 (2.23)	4.90 (2.49)	5.10 (2.52)	F = 10.58, $P < 0.001$ 0 < 1 and 2
Tingling	3.91 (3.06)	4.88 (3.01)	4.25 (7.85)	F = 3.86, $P = 0.022$ 0 < 1
Intense	2.71 (2.27)	3.60 (2.50)	3.80 (2.70)	F = 7.76, $P < 0.001$ 0 < 1 and 2
Dull	2.82 (2.72)	3.67 (2.83)	3.03 (2.62)	F = 3.66, $P = 0.027$ 0 < 1
Cramping	2.51 (2.99)	3.48 (3.39)	2.60 (3.15)	F = 3.85, $P = 0.022$ 0 < 1
Electrical	1.86 (2.64)	3.04 (3.37)	3.10 (3.16)	F = 7.66, $P = 0.001$ 0 < 1 and 2
Shooting	1.70 (2.46)	3.07 (3.11)	3.08 (3.15)	F = 11.29, $P < 0.001$ 0 < 1 and 2
Sharp	1.71 (2.41)	2.67 (3.07)	3.03 (3.22)	F = 7.78, $P < 0.001$ 0 < 1 and 2
Aching	1.85 (2.51)	2.56 (2.92)	2.48 (2.86)	F = 3.02, $P = 0.050$
Heavy	1.78 (2.44)	2.40 (2.93)	2.43 (3.01)	F = 2.56, $P = 0.079$
Cold	1.82 (2.61)	2.22 (3.05)	2.32 (2.84)	F = 1.20, $P = 0.302$
Radiating	1.74 (2.61)	2.47 (2.98)	2.05 (2.47)	F = 2.74, $P = 0.066$
Hot	1.43 (2.28)	2.39 (2.82)	2.53 (3.06)	F = 7.19, $P = 0.001$ 0 < 1 and 2
Tender	1.46 (2.13)	2.45 (2.75)	2.17 (2.67)	F = 6.41, $P = 0.002$ 0 < 1
Sensitive skin	1.47 (2.05)	2.08 (2.57)	2.21 (2.45)	F = 4.05, $P = 0.018$ 0 < 2
Throbbing	1.22 (2.12)	2.11 (2.77)	2.33 (3.03)	F = 7.30, $P = 0.001$ 0 < 1 and 2
Itchy	0.78 (1.79)	1.22 (2.16)	1.25 (2.20)	F = 2.45, $P = 0.088$
Intense—surface pain	2.86 (2.66)	3.65 (2.65)	3.51 (2.70)	F = 3.71, $P = 0.025$ 0 < 1
Intense—deep pain	2.68 (2.64)	3.66 (2.81)	3.94 (2.99)	F = 7.66, $P = 0.001$ 0 < 1 and 2
Pain Quality Assessment Scale—Subscale scores—Lower extremity				
Paroxysmal	1.69 (1.90)	2.75 (2.40)	2.78 (2.43)	F = 11.33, $P < 0.001$ 0 < 1 and 2
Surface	2.58 (1.61)	3.22 (1.80)	3.22 (1.68)	F = 6.98, $P = 0.001$ 0 < 1 and 2
Deep	2.02 (1.85)	2.86 (2.22)	2.56 (2.05)	F = 6.52, $P = 0.002$ 0 < 1
Pain Quality Assessment Scale scores—Upper extremity				
Numb	3.46 (2.75)	4.03 (2.97)	4.44 (2.90)	F = 2.99, $P = 0.052$
Unpleasant	3.02 (2.16)	4.06 (2.60)	4.18 (2.74)	F = 7.39, $P = 0.001$ 0 < 1 and 2
Tingling	2.67 (2.58)	3.73 (2.91)	3.42 (3.11)	F = 4.19, $P = 0.016$ 0 < 1
Intense	1.89 (1.90)	3.19 (2.30)	3.29 (2.66)	F = 13.53, $P < 0.001$ 0 < 1 and 2
Dull	1.79 (2.11)	2.80 (2.52)	2.89 (2.80)	F = 6.94, $P = 0.001$ 0 < 1 and 2
Cramping	1.23 (2.01)	2.07 (2.86)	2.53 (3.17)	F = 6.57, $P = 0.002$ 0 < 1 and 2
Electrical	1.29 (2.16)	2.40 (3.01)	2.10 (2.85)	F = 5.30, $P = 0.005$ 0 < 1
Shooting	1.20 (2.06)	2.04 (2.87)	1.78 (2.55)	F = 3.51, $P = 0.031$ 0 < 1
Sharp	0.97 (1.79)	1.63 (2.45)	1.82 (2.77)	F = 4.05, $P = 0.018$ 0 < 2
Aching	1.30 (2.14)	2.18 (2.64)	2.42 (2.92)	F = 5.90, $P = 0.003$ 0 < 1 and 2
Heavy	0.86 (1.73)	1.66 (2.59)	1.71 (2.71)	F = 4.82, $P = 0.009$ 0 < 1 and 2
Cold	1.17 (1.91)	1.57 (2.70)	1.85 (2.64)	F = 2.03, $P = 0.133$
Radiating	0.74 (1.60)	1.93 (2.61)	1.50 (2.56)	F = 8.46, $P < 0.001$ 0 < 1

(*Continued*)

Table 3
Continued

Characteristic	Normal Weight (0); 45.4% ($n = 189$) Mean (SD)	Overweight (1); 32.5% ($n = 135$) Mean (SD)	Obese (2); 22.1% ($n = 92$) Mean (SD)	Test, *P*-value
Hot	0.53 (1.25)	1.32 (2.18)	1.51 (2.46)	$F = 8.04$, $P < 0.001$ 0 < 1 and 2
Tender	1.08 (1.76)	1.95 (2.48)	2.13 (2.76)	$F = 6.59$, $P = 0.002$ 0 < 1 and 2
Sensitive skin	1.04 (1.73)	1.59 (2.35)	1.71 (2.50)	$F = 2.97$, $P = 0.053$
Throbbing	0.86 (1.88)	1.62 (2.37)	1.76 (2.65)	$F = 5.07$, $P = 0.007$ 0 < 1 and 2
Itchy	0.51 (1.47)	1.00 (1.99)	1.13 (2.33)	$F = 3.20$, $P = 0.042$ no significant pairwise contrasts
Intense—surface pain	2.55 (2.52)	3.16 (2.52)	3.39 (2.64)	$F = 3.00$, $P = 0.052$
Intense—deep pain	1.63 (2.05)	2.97 (2.77)	3.14 (3.11)	$F = 11.11$, $P < 0.001$ 0 < 1 and 2
Pain Quality Assessment Scale—Subscale scores—Upper Extremity				
Paroxysmal	0.92 (1.24)	1.85 (2.12)	1.74 (2.13)	$F = 9.05$, $P < 0.001$ 0 < 1 and 2
Surface	1.74 (1.42)	2.38 (1.83)	2.51 (1.75)	$F = 6.66$, $P = 0.001$ 0 < 1 and 2
Deep	1.21 (1.49)	2.07 (2.02)	2.26 (2.33)	$F = 9.31$, $P < 0.001$ 0 < 1 and 2

CIPN = chemotherapy-induced neuropathy; SD = standard deviation.
[a]Routine activities such as dressing, toileting, and typing.

groups in the sensations of light touch, cold, or vibration in either the upper or lower extremities.

Differences in Balance

Compared with the normal-weight group, both overweight and obese survivors had higher scores for the self-reported severity of and frequency of balance problems (Table 4). In terms of objective measures of balance, compared with the normal-weight group, obese survivors had higher Timed Get Up and Go test scores. In addition, compared with the normal-weight and overweight groups, the obese group had lower Fullerton Advanced Balance test scores.

Discussion

This study is the first to evaluate for differences in demographic and clinical characteristics as well as subjective and objective measures of CIPN among normal-weight, overweight, and obese cancer survivors who received platinum and/or taxane chemotherapeutic compounds. Our findings are congruent with previous reports[4,7,28] and support our hypothesis that as BMI increased, pain, sensation, and balance characteristics worsened. However, it should be noted that not all the differences occurred in a linear fashion (i.e., normal weight < overweight < obese).

In terms of BMI distributions, our sample had the highest percentage of normal-weight survivors (i.e., 45.4% vs. 32.2%[4] and 33.7%[8]) compared with previous reports. Although the percentages of overweight survivors were comparable across studies (i.e., 32.5% vs. 36.4%[4] and 31.9%[8]), higher percentages of obese individuals were evaluated in previous studies (i.e., 31.4%[4] and 34.4%[8] vs. our 22.1%). Reasons for these differences in BMI distributions are not readily apparent.

In terms of regular exercise, although the President's Council on Sports, Fitness, and Nutrition reported that less than 5% of adults participate in 30 minutes of physical activity per day,[29] comparable data on cancer survivors are not available. As expected, compared with the normal-weight group, a significantly lower percentage of overweight and obese survivors exercised on a regular basis. Given the growing body of evidence on the beneficial effects of exercise on CIPN symptoms,[30–33] the relative contribution of lack of exercise in the overweight and obese patients increased symptoms and decrements in sensation and balance warrant consideration.

In our study, compared with normal-weight survivors, obese survivors had fewer years of education and a lower annual household income. These characteristics were not evaluated in previous studies that examined the association between BMI and CIPN. However, although the relationships among the social determinants of health are complex, recent evidence suggests that in the general population, less education[34] and lower income[35] are associated with an increased likelihood of obesity.

Consistent with our previous report that compared survivors with and without CIPN,[9] we observed a "dose response" effect for the number and impact

Table 4
Differences in Sensation Measures and Balance Measures Among the Body Mass Index Groups

Characteristic[a]	Normal Weight (0); 45.4% ($n = 189$) Mean (SD)	Overweight (1); 32.5% ($n = 135$) Mean (SD)	Obese (2); 22.1% ($n = 92$) Mean (SD)	Statistic; *P*-value
Sensation measures[b]				
Light touch—upper extremity sites (of seven sites)[c]	0.12 (0.60)	0.23 (0.87)	0.30 (1.01)	F = 1.78, $P = 1.69$
Light touch—lower extremity sites (of nine sites)[d]	2.00 (2.33)	2.07 (2.06)	2.50 (2.54)	F = 1.55, $P = 0.214$
Cold—upper extremity sites (of four sites)[e]	0.77 (0.98)	0.83 (0.98)	0.91 (0.99)	F = 0.64, $P = 0.529$
Cold—lower extremity sites (of four sites)[f]	2.26 (1.20)	2.30 (1.17)	2.18 (1.25)	F = 0.24, $P = 0.788$
Pain—upper extremity sites (of seven sites)[g]	1.09 (1.35)	1.29 (1.50)	1.11 (1.55)	F = 0.81, $P = 0.446$
Pain—lower extremity sites (of nine sites)[h]	3.01 (2.05)	3.67 (2.06)	3.87 (2.44)	F = 6.46, $P = 0.002$ 0 < 1 and 2
Vibration—upper extremity sites (volts)[i]	7.39 (4.03)	8.32 (4.79)	8.12 (4.30)	F = 2.02, $P = 0.134$
Vibration—lower extremity sites (volts)[j]	8.50 (4.24)	9.69 (5.06)	9.29 (4.20)	F = 2.87, $P = 0.058$
Balance measures				
Trouble with balance, % yes (n)[k]	62.8 (118)	71.6 (96)	70.3 (64)	$X^2 = 3.28$, $P = 0.194$
Severity of balance trouble, (0 to 10)[l]	4.09 (2.57)	5.33 (2.65)	5.31 (2.64)	F = 7.36, $P = 0.001$ 0 < 1 and 2
Frequency of balance trouble (0 to 10)[m]	3.78 (2.66)	5.11 (2.97)	4.89 (2.98)	F = 6.58, $P = 0.002$ 0 < 1 and 2
Distress from balance trouble (0 to 10)[n]	4.71 (2.98)	5.60 (2.92)	5.47 (2.74)	F = 2.82, $P = 0.061$
Timed Get Up and Go test (>13.5 seconds = higher risk for falls)	7.45 (2.50)	7.69 (2.00)	8.47 (3.02)	F = 5.23, $P = 0.006$ 0 < 2
Fullerton Advanced Balance test (≤25 is associated with a higher risk of falls)	34.68 (5.75)	33.52 (5.80)	29.75 (8.52)	F = 18.03, $P < 0.001$ 0 and 1 < 2

SD = standard deviation; MP = metacarpophalangeal; IP = interphalangeal.
[a]When available, the clinically meaningful cutpoint score is provided in parentheses next to the characteristic.
[b]Changes in sensation are reported for the dominant extremity.
[c]Upper extremity sites for light touch 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.
[d]Lower extremity sites for light touch were pad of great toe, pad of third toe, pad of fifth toe, base of heel, MP joint of great toe, MP joint of third toe, MP joint of fifth toe, midway along tibia, and patella.
[e]Upper extremity sites for cold were pad of index finger, pad of little finger, dorsal MP area of the hand, and wrist.
[f]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.
[g]Upper extremity sites for 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.
[h]Lower extremity sites for pain were pad of great toe, pad of third toe, pad of fifth toe, base of heel, MP joint of great toe, MP joint of third toe, MP joint of fifth toe, midway along tibia, and patella.
[i]Upper extremity sites for vibration were dorsal IP joint of thumb, dorsal IP joint of index finger, ulnar prominence, and lateral epicondyle.
[j]Lower extremity sites for vibration were dorsal IP joint of great toe, medial malleolus, and patella.
[k]Since your chemotherapy, have you had trouble with your balance?
[l]At its worst, how severe is the trouble with your balance (0 = not at all severe to 10 = extremely severe)?
[m]How often do you have trouble with your balance (0 = never to 10 = always)?
[n]At its worst, how distressing is the trouble with your balance (0 = not at all distressing to 10 = extremely distressing)?

of comorbidities across the BMI groups. In terms of specific comorbidities, compared with the normal-weight and overweight groups, survivors in the obese group reported higher occurrence rates for osteoarthritis, high blood pressure, and diabetes. The co-occurrence of these chronic conditions needs to be considered in the evaluation of differences, among the BMI groups, in our subjective and objective measures of CIPN.

Although findings from two previous studies suggest that a higher BMI is associated with worse CIPN,[4,7] specific details on pain intensity, pain qualities, and pain interferences were not reported. In our study, no differences were found among the BMI groups in the duration of CIPN. For both the upper and lower extremities, compared with the normal-weight group, the overweight and obese survivors reported significantly higher pain intensity scores. A similar pattern was found for our survivors' pain interference and quality scores. These findings are consistent with studies of individuals with noncancer pain, in that a higher BMI was associated with higher levels of pain interference[36,37] and that weight loss was associated with a reduction in pain interference.[38]

In contrast to the subjective measures, loss of pain sensation in the lower extremities was the only objective measure that differentiated the normal-weight from the overweight and obese survivors. A limited body of evidence suggests that compared with normal-weight individuals, obese individuals in the general population[39,40] and those with diabetes[41] have higher pain thresholds. Although controversy exists on the relative contribution of alterations in small- and large-diameter fibers in the development of CIPN,[42–44] our finding regarding changes in only pain sensations in the lower extremity suggests that

obesity may have differential effects on small-diameter fibers in cancer survivors who received neurotoxic CTX.

One of the most important findings in our study is the deleterious effect that being overweight or obese had on survivors' balance. Although the self-reported occurrence rates for and distress from balance problems did not differ among the three BMI groups, overweight and obese survivors reported higher severity and frequency scores for balance problems. In addition, compared with the normal-weight group, survivors who were obese had significantly worse scores on both objective measures of balance. Although a recent study of obese community-dwelling older adults identified an association between a higher BMI and balance problems,[45] recent data suggest that survivors with CIPN are at increased risk for balance problems and are 1.8 times more likely to fall than survivors without CIPN.[3,46,47]

Several limitations warrant consideration. Because our study recruited only survivors who had received a platinum- and/or a taxane-containing regimen, these findings may not generalize to survivors who received other types of neurotoxic CTX. However, it should be noted that no differences were found among the three groups in the types of CTX regimens (i.e., only platinum, only taxane, or both) or in the doses of the platinum and/or taxanes they received. Because pretreatment weight and changes in weight during CTX were not available, these relationships need to be evaluated in future studies.

Despite these limitations, our findings suggest that compared with normal-weight survivors, overweight and obese survivors have more severe pain, as well as higher pain interference scores and balance problems. These differences could be explained by two potential mechanisms. Given the deleterious effects of an increased BMI on lower extremity sensations and function, our weight-group differences in the subjective and objective measures of pain may be related to increased mechanical force on the weight-bearing joints. In addition, compared with the normal-weight (23.3%) and overweight (28.9%) groups, a higher percentage of obese survivors (46.7%) reported osteoarthritis, which may contribute to lower extremity pain.[48–50] However, this mechanism does not explain the higher pain and interference scores in the upper extremities reported by overweight and obese individuals. An alternative explanation for both the upper and lower extremity findings is chronic inflammation. It is well documented that obesity is associated with chronic inflammation.[51,52] In addition, one of the underlying mechanisms for CIPN is neuroinflammation.[53–55] To determine the causal relationships between increasing weight and CIPN characteristics, prospective longitudinal studies are needed that evaluate these relationships and underlying mechanisms. In terms of clinical practice, our findings suggest that nutritional counseling, as well as exercise and weight management programs, for survivors with CIPN may decrease pain, improve balance, and reduce the risk of falls.

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