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PHENOTYPIC CHARACTERIZATION OF PACLITAXEL-INDUCED PERIPHERAL NEUROPATHY IN CANCER SURVIVORS

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Abstract

Context—While paclitaxel is one of the most commonly used drugs to treat breast, ovarian, and lung cancers, little is known about the impact of paclitaxel-induced peripheral neuropathy (PIPN) on cancer survivors.

Objectives—The purposes of this study were to evaluate for differences in demographic and clinical characteristics, as well as measures of sensation, balance, upper extremity function, perceived stress, symptom burden, and quality of life (QOL) between survivors who received paclitaxel and did (n=153) and did not (n=58) develop PIPN.

Methods—Pain characteristics associated with PIPN are described in detail. Both subjective and objective measures were used to evaluate the impact of PIPN.

Results—Survivors with PIPN were significantly older, had a higher BMI, and a worse comorbidity profile. The duration of PIPN was almost four years and pain scores were in the moderate range. Compared to survivors without PIPN, survivors with PIPN had a higher number of upper and lower extremity sites that had lost light touch, cold and pain sensations. Survivors with PIPN had worse upper extremity function, more problems with balance, a higher symptom burden, and higher levels of perceived stress. In addition, survivors with PIPN had worse QOL scores particularly in the domain of physical functioning.

Conclusion—The findings from this large descriptive study are the first to document the impact of PIPN on survivors' symptom burden, functional status, and QOL.

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Keywords

paclitaxel; cancer; chemotherapy; peripheral neuropathy; pain; stress; quality of life; balance; survivor

INTRODUCTION

With the establishment of its anti-tumor activity in the early 1990's, paclitaxel became one of the most commonly used drugs to treat breast, ovarian, and lung cancers.[41] Paclitaxel exerts its therapeutic effect by binding to β-tubulin which interferes with microtubule dynamics and results in microtubule stabilization, mitotic arrest, and apoptosis of cancer cells. However, microtubules are critical for axonal function and for the transport of essential organelles to distal nerve endings. Disruption of axonal transport can lead to axonal degeneration and neuropathy.[59]

Paclitaxel-induced peripheral neuropathy (PIPN) is the dose limiting toxicity of this chemotherapy (CTX) drug. Prevalence estimates for PIPN range from 59% to 87%.[37,67] PIPN is described as a distal polyneuropathy that presents with paresthesias and dysethesias in the lower extremities. Symptoms spread proximally, as well as to the upper extremities, in a "stocking-glove" distribution. The majority of the information on the characteristics and impact of PIPN comes from clinical trials of the efficacy of the drug. In general, these studies used the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) to grade the severity of PIPN. In some cases, the CTCAE were supplemented by the Functional Assessment of Cancer Therapy (FACT)-Taxane.[12]

While the evaluation of PIPN in the context of clinical trials guides treatment decisions, the long term impact of this adverse effect is critically important to cancer survivors. Only two studies were found that evaluated the prevalence, severity, and impact of long-term taxane-induced neuropathy.[34,55] In the first study,[34] PIPN was assessed using objective measures of touch perception and vibration threshold, as well as the FACT-Taxane. Participants included a cross-sectional sample of 50 consecutive patients with stage I-III breast cancer who were assessed within 6 months to 2 years after completing treatment and a prospective sample of 50 women who were initiating treatment and who were assessed prior to the initiation of CTX, at the completion of therapy, and again at 3, 6, 9 and 12 months after treatment. In the cross-sectional study, 81% of the women reported symptoms of numbness and/or discomfort. In addition, hand numbness/discomfort was associated with decrements in vibration threshold. In the prospective sample, FACT-Taxane scores decreased over time [i.e., increase in neuropathy symptoms] and reports of both hand and foot numbness were associated with decrements in vibration threshold. No significant changes were found in touch perception using von Frey filaments.

In the second study, that evaluated 69 women who received either docetaxel or paclitaxel for breast or gynecologic cancer,[55] neuropathy was evaluated using the CTCAE at 1 year to 13 years (median = 3 years) after the completion of CTX. In addition, 14 patients underwent motor and sensory nerve conduction studies. Of the 64% of survivors who reported CTX-induced peripheral neuropathy (CIPN), it was categorized as Grade 2. In terms of the nerve

conduction studies, 7 patients were normal, 5 had a sensory axonal neuropathy, and 2 had a sensory motor neuropathy. The authors concluded that while the occurrence rate for neuropathy was high, “it was extremely well tolerated” (p.1943) by these survivors.

Emerging, albeit limited, evidence suggests that cancer survivors experience multiple cooccurring symptoms that persist for years after the completion of treatment.[36,47] In addition, findings from a limited number of studies suggest that survivors with CIPN have higher levels of stress,[50,51] a higher symptom burden,[5,48,49] as well as a poorer functional status and quality of life (QOL).[22,28,48,49,53,78,79] However, no studies were found that provided detailed comparisons of subjective and objective characteristics of PIPN, as well as the impact of PIPN on important survivor outcomes. Therefore, the purposes of this study were to evaluate for differences in demographic and clinical characteristics, as well as measures of sensation, balance, upper extremity function, perceived stress, symptom burden, and QOL between survivors who received paclitaxel and did (n=153) and did not (n=58) develop PIPN. In addition, pain characteristics (e.g., severity, interference) associated with PIPN are described in detail.

METHODS

Survivors and Settings

The present analysis is part of a larger study that evaluated CIPN in cancer survivors. The methods for the larger study are described in detail elsewhere.[49] 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 ≥3 months prior to enrollment; had changes in sensation and/or pain in their feet and/or hands of ≥3 months duration following 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;[81] i.e., numb, tender, shooting, sensitive, electrical, tingling radiating, throbbing, cramping, itchy, unpleasant); if they had pain associated with the CIPN, had an average pain intensity score in their feet and/or hands 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 without CIPN were ≥18 years of age; had received a platinum and/or a taxane compound; had completed their course of CTX ≥3 months prior to enrollment; did not have persistent changes in sensation and/or pain in their hands or feet at the time of enrollment; had a KPS score of ≥50; and were able to read, write, and understand English. Survivors with and without CIPN 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 609 completed the self-report questionnaires and the study visit. For this analysis, only survivors who received paclitaxel (n=211) were included.

Study procedures

Research nurses screened and consented the survivors over the phone; sent and asked them to complete the self-report questionnaires prior to 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,[7] the Karnofsky Performance Status (KPS) scale[38,39,69] and the Self-Administered Comorbidity Questionnaire (SCQ).[9,13]

Sensation ––Light touch was evaluated using Semmes Weinstein monofilaments.[6] Cold sensation was evaluated using the Tiptherm Rod.[58,82] Pain sensation was evaluated using the Neurotip.[58] Vibration threshold was assessed using a biothesiometer.[20] For all of the measures of sensation, both the upper and lower extremities on the dominant side were tested.

Balance ––Self-report questions from the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) were used to assess balance.[80] The objective measures of balance were the timed get up and go test (TUG)[46] and the Fullerton Advanced Balance (FAB) test.[33,65]

Upper Extremity Function ––Hand grip strength was assessed using a hand dynamometer (Smedley III Analgou Grip Tester, Creative Health Products, Ann Arbor, MI). The mean force in kilograms (kg) of the three trials was calculated for each hand.[68] In addition, manual dexterity in the upper extremities was assessed using the Purdue Pegboard (Lafayette Instrument, Lafayette, IN). The number of pins placed in 30 seconds was recorded.[10,19,63]

Symptom Burden ––Survivors completed self-report questionnaires that evaluated trait and state anxiety,[74] depressive symptoms,[61] diurnal variations in fatigue and energy,[44] sleep disturbance,[43] and changes in attentional function.[14]

Stress ––Stress associated with cancer and its treatment was evaluated using the Impact of Event Scale-Revised (IES-R). A total score was created by summing the responses to the 22 IES-R items. Three subscale scores were calculated that evaluate the level of intrusion, avoidance, and hyperarousal perceived by the survivor. The total IES-R score ranges from 0 to 88. A total score of ≥37 indicates a high presence of post-traumatic symptomatology.[15,18,77] A global evaluation of perceived stress due to life circumstances was done using the Perceived Stress Scale.[16] Total PSS scores range from 0 to 56, with a higher score indicating greater stress.

QOL ––A generic evaluation of QOL was done using the Medical Outcomes Study-Short Form (SF12).[84] The disease specific measure of QOL was the Multidimensional QOL Scale-Patient Version (MQOLS-PV).[23,24,56,57]

Data Analysis

Data were analyzed using SPSS version 23.[75] Descriptive statistics and frequency distributions were calculated for survivors' demographic and clinical characteristics. For the four measures of sensation (i.e., light touch, cold, pain, vibration), composite scores, over all of 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 between the PIPN and no PINP groups in phenotypic characteristics, balance, and levels of perceived stress, symptom burden, and QOL were evaluated using Independent sample t-tests, Chi square analyses, or Mann-Whitney U tests. The specific test used for each characteristic are identified in the corresponding results Tables. Significant predictors of PIPN group membership were evaluated using logistic regression analysis. A p-value of ≤0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

In terms of demographic and clinical characteristics (Tables 1 and 2), survivors with PIPN were significantly older (p=.001); had a higher BMI (p=.009), a higher number of comorbidities (p=.002) and a worse comorbidity profile (p=.001); had a lower AUDIT score (p=.001) and a lower KPS score (p≤.001); and had received fewer cancer treatments (p=.005). In addition, survivors with PIPN were more likely to report an injury to their hands (p=.001), osteoarthritis (p=.009), high blood pressure (p=.027), and were more likely to have had a dose reduction or delay due to PIPN (p=.001). Of note, no between group differences were found in: cancer diagnoses, number of years since the cancer diagnosis, number of metastatic sites, and total dose of paclitaxel received. As shown in Supplementary Table 1, in the logistic regression analysis, the characteristics associated with PIPN group membership that were retained in the final model included: older age, a lower KPS score, and having had a fewer number of cancer treatments ($X^2 = 77.14$, p≤.001)

Pain Characteristics

Of the 153 survivors with PIPN, 4.6% had neuropathy only in their hands, 25.5% only in their feet, and 69.9% in both their hands and feet. The duration, severity, and interference associated with PIPN in the hands and the feet are summarized in Table 3. For both the hands and the feet, the pain qualities with the highest severity scores were: numb, unpleasant, and tingling.

Sensation

Survivors with PIPN had a higher number of upper and lower extremity sites with loss of light touch, cold, and pain sensations (all, p≤.015). For both the upper and lower extremities, vibration thresholds were significantly higher in the PIPN group (both, p≤.001, Table 4).

Balance

Survivors with PIPN were more likely to report trouble with balance (p≤.001) as well as higher severity (p=.042) and frequency (p=.002) scores associated with balance problems (see Table 4). In addition, these survivors reported worse TUG (p≤.001) and worse FAB (p≤.001) scores.

Upper Extremity Function

Survivors with PIPN had worse grip strength (p≤.001). In addition, they had a worse score on the Purdue Pegboard test (p≤.001, Table 4). Detailed information on differences in all of the objective measures can be found in Supplementary Tables 2 through 5.

Symptom Burden

Survivors with PIPN reported higher morning fatigue (p=.038) and sleep disturbance (p=.008) scores as well as lower morning energy scores (p=.015). No between group differences were found in trait anxiety, state anxiety, depressive symptoms, evening fatigue, evening energy, or attentional function scores (see Table 4).

Perceived Stress

Survivors with PIPN reported higher avoidance and hyperarousaI (both p≤.011) and total IES-R (p=.004) scores. No between group differences were found in the PSS score (Table 4).

QOL

For the SF-12, survivors with PIPN reported lower scores for the physical functioning, role physical, bodily pain, general health, vitality, and social functioning subscales, as well as for the PCS score (all, p≤.008). For the MQOLS-PV, survivors with PIPN reported lower scores for the physical wellbeing and psychological well-being subscales (both p≤.039; Table 4).

DISCUSSION

This study is the first to provide a detailed phenotypic characterization of PIPN and its impact on a large sample of cancer survivors who were an average of five years from their cancer diagnosis. For the survivors with PIPN, its average duration was almost four years. Consistent with previous reports,[41,42] PIPN was bilateral, occurred in a stocking-glove distribution, and was associated with reports of numbness and tingling. However, this study provides detailed information on the severity and interference associated with PIPN. Worst pain intensity scores for both the upper and lower extremities were in the moderate range and pain lasted approximately 13 hours per day. As expected, PIPN resulted in moderate levels of interference with walking (lower extremity function) and with the ability to perform routine activities (e.g., dressing; upper extremity function).

Demographic and clinical characteristics

While two studies found no age differences in the occurrence of CIPN associated with taxanes,[21,71] our finding is consistent with previous reports that reported an increase in CIPN in older patients who received a taxane compound.[70,72,73] In fact, in one study,[70] with

each decade of life the risk for taxane-induced neuropathy increased by 13%. A growing body of evidence suggests that patients with a higher BMI are at greater risk for the development of CIPN,[17,29] with one study finding that obese patients had a more than 2-fold increased risk of CIPN compared to normal weight patients.[29] In the current study, the mean weight of the survivors without PIPN was in the normal range, while those with PIPN were in the overweight range. While the exact mechanisms that underlie this association in patients with cancer are unknown, a growing body of evidence in patients with diabetes supports an association between metabolic syndrome and injury to peripheral nerves (e.g., fatty deposition in nerves, oxidative stress, mitochondrial dysfunction).[11]

While a positive association was reported in our previous analysis of the total sample,[49] as well as in patients with diabetic neuropathy,[2,66] the current study is the first to report that survivors with PIPN have a higher comorbidity burden. In terms of the specific comorbidities, patients with PIPN reported higher occurrence rates for high blood pressure and osteoarthritis. While these associations were not reported in previous investigations of CIPN, in a population-based study,[54] a positive association was found between chronic pain and hypertension. In addition, recent evidence suggests that osteoarthritis has a neuropathic component.[32,62]

While no differences were found in cancer diagnoses, years since cancer diagnosis, number of metastatic sites, or total dose of paclitaxel administered, survivors with PIPN were more likely to have had a dose reduction or delay in their treatment due to PIPN. While all of the patients in both groups completed their course of CTX, details on the exact number and duration of the delays in treatment in the PIPN group were difficult to find in the survivors' medical records. Given that PIPN is considered to be a dose-dependent neuropathy,[52,76] prospective studies are warranted that track this information on an ongoing basis.

Sensation

As expected, survivors with PIPN had significant decrements in light touch, pain, cold, and vibratory sensations in both the upper and lower extremities (for details see Supplemental Tables 1 through 4). While most clinicians use a 5.07 monofilament to evaluate for diabetic neuropathy, our findings regarding differences in light touch sensation suggest that a finer monofilament should be used to assess for changes in sensation in survivors who received paclitaxel. In addition, given that significant decrements were found in all four sensations, survivors need education on how to protect their upper and lower extremities from traumatic injuries.

Upper Extremity Function and Balance

Both measures of upper extremity function were significantly worse in the survivors with PIPN. In the one study that compared CTX naïve patients to those who received CTX, the mean grip strengths were 33.5 kg versus 30.1 kg, respectively.[30] For both groups of survivors in our study, mean grip strength was lower than for the CTX naïve patients. These findings may be attributable to age differences and/or to the fact that the survivors without PIPN did receive CTX. In terms of the Purdue Pegboard test,[60] healthy individuals between 40 and 80 years of age, using their dominant hand, typically insert 13 to 16 pins in 30

seconds.[1] While the number of pins inserted by our survivors with PIPN was lower, both groups of survivors had scores that were within the range of the healthy controls. Additional research is warranted to determine how decrements in upper extremity function correlate with survivors' ability to perform routine activities of daily living (e.g., writing, typing, using electronic devices).

Consistent with previous reports,[28,40,79] over 60% of the survivors with PIPN reported problems with balance and indicated that the frequency, severity, and distress associated with balance problems were in the moderate range. Compared to healthy controls whose average TUG scores were 5.85,[83] both groups of survivors had worse scores. However, neither group of survivors' scores were >13.5 which is the TUG score associated with an increased risk of falls.[4] In terms of the FAB scores, our findings for survivors with PIPN were similar to those reported in a previous study of patients with breast cancer who received taxanes (i.e., 33.9). In addition, the scores for our survivors without PIPN were slightly higher than those for healthy controls (i.e., 36.5).[83] Neither group of survivors had FAB scores that were below the clinically meaningful cutoff score of ≤25. Future studies need to determine if balance problems resolve, persist, or worsen in survivors with PIPN, as well as the relationship between balance problems and falls.

Symptom Burden

In our previous study that evaluated for differences in symptom burden between survivors who experienced CIPN, hearing loss, and tinnitus compared to survivors without any neurotoxicities,[48] with the exception of evening fatigue, all of the symptoms listed in Table 4 were significantly higher in the survivors with CIPN. In the current study, survivors with PIPN reported significantly higher and clinically meaningful increases in morning fatigue and sleep disturbance, as well as decrements in morning energy. From a clinical perspective, one can hypothesize that higher levels of sleep disturbance would be associated with higher levels of morning fatigue and decrements in morning energy. In fact, these three symptoms may constitute a symptom cluster that warrants ongoing assessment and management.

Stress and Quality of Life

While it is acknowledged that the diagnosis of cancer and its treatment is a stressful experience for most patients[3,8,31,64] and emerging evidence documents positive associations between long-term stress and chronic pain,[25–27,45] our previous study was the first to demonstrate associations between cancer survivors' perceptions of disease-specific stress (i.e., IES-R) and the occurrence of CIPN, hearing loss, and tinnitus.[50] The current study extends this line of inquiry and is the first to demonstrate differences in perceived stress in survivors with and without PIPN. It is interesting to note that between group differences were found only for the disease-specific measure of stress. For our survivors with and without PIPN, the subscale and total IES-R scores were similar to those reported by the total sample.[50] In the current study, survivors with PIPN reported higher avoidance, hyperarousal, and total IES-R scores. The avoidance subscale includes items related to denial of the meaning and consequences of the stress, blunted sensations, and awareness of emotional numbness.[35] In contrast, the hyperarousal subscale was added to the original version of the IES-R after the American Psychiatric Association published their diagnostic criteria for

post-traumatic stress disorder (PTSD).[85] The items included on this subscale evaluate irritability, anger, difficulty falling asleep, jumpiness, difficulty concentrating, and heightened watchfulness. Of note, for our survivors with PIPN, higher scores on the IES-R were associated with higher levels of trait anxiety (i.e., r=0.57 for hyperarousal, r=0.55 for total IES-R score; both p≤.001). While the total IES-R score did not reach the clinically meaningful cutoff score of ≥33, our findings suggest that survivors with PIPN may benefit from interventions to decrease anxiety and stress.

QOL is an extremely important outcome for cancer survivors.[36,47] While one would hypothesize that survivors with PIPN would report lower scores for all of the QOL domains, for both the generic and disease-specific measures of QOL, the significant between group differences were found primarily in the physical function subscales. In fact, all of the significant differences in these physical function scores represent not only statistically significant but clinically meaningful decrements in various aspects of physical functioning (i.e., Cohen's d = 0.4 to 1.8). In addition, for the cancer survivors with PIPN, their mean PCS score on the SF-12 (i.e., 43.14) is substantially below the normative score of 50 for the general United States population.[84]

A number of limitations warrant consideration. While paclitaxel is used for the treatment of breast, lung, and ovarian cancers, the majority of the survivors in this study had breast cancer. Therefore, the generalizability of these findings across cancer diagnoses warrants confirmation. Given the crosssectional study design, the demographic and clinical characteristics associated with PIPN warrant confirmation in a prospective longitudinal study. While the subjective measures of stress have excellent psychometric properties, future studies should examine associations between the occurrence and severity of PIPN and objective measures of stress (e.g., hair cortisol). Given that physical activity may be impacted by PIPN given the pain, future research should assess these relationships (e.g., pain and BMI). In addition, given that the total dose of paclitaxel did not differ between the two groups, future studies should evaluate for associations between genetic, gene expression, and epigenetic markers and the occurrence and severity of PIPN.

Despite these limitations, the findings from this large descriptive study are the first to document the impact of PIPN on survivors' symptom burden, functional status, and QOL. Given the relatively high levels of stress and significant decrements in physical function in these survivors, future studies are needed that evaluate the impact of stress reduction strategies and rehabilitation programs on the severity of PIPN and other patient-reported outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1 –

Differences in Demographic Characteristics Between Cancer Survivors Who Received Paclitaxel and Did and Did Not Develop Peripheral Neuropathy

Characteristic	No PIPN 27.5% (n=58)	PIPN 72.5% (n=153)	Test, p-value
	Mean (SD)	Mean (SD)	
Age (years)	53.36 (9.55)	59.59 (9.82)	t= −4.14, <.001
Education (years)	16.55 (1.95)	16.58 (2.69)	t= −0.09, .927
	% (n)	% (n)	
Female	100.0 (58)	99.3 (152)	FE, 1.000
Married/partnered (% yes)	77.6 (45)	66.0 (99)	FE, .132
Lives alone (% yes)	22.4 (13)	25.8 (39)	FE, .722
Employed (% yes)	62.1 (36)	47.7 (73)	FE, .066
Ethnicity			X^2=0.72, .870
White	79.3 (46)	75.2 (115)	
Asian/Pacific Islander	5.2 (3)	7.2 (11)	
Black	3.4 (2)	2.6 (4)	
Hispanic/Mixed/Other	12.1 (7)	15.0 (23)	
Annual household income			U, .109
<$30,000	9.4 (5)	19.3 (28)	
$30,000 - $69,999	11.3 (6)	19.3 (28)	
$70,000 - $99,999	28.3 (15)	16.6 (24)	
>$100,000	50.9 (27)	44.8 (65)	
Child care responsibilities (% yes)	23.2 (13)	16.6 (25)	FE, .313
Adult care responsibilities (% yes)	7.5 (4)	4.3 (6)	FE, .467

Abbreviations: FE = Fisher's Exact test, PIPN = paclitaxel-induced peripheral neuropathy, SD = standard deviation, U = Mann-Whitney U test

Table 2 –

Differences in Clinical Characteristics Between Cancer Survivors Who Received Paclitaxel and Did and Did Not Develop Peripheral Neuropathy

Characteristic	**No PIPN 27.5% (n=58)**	**PIPN 72.5% (n=153)**	**Test, p-value**
	Mean (SD)	**Mean (SD)**	
Karnofsky Performance Status score	92.28 (8.02)	82.73 (10.42)	t= 7.01, <.001
Body mass index (kg/m^2)	24.52 (4.55)	26.78 (5.92)	t= −2.62, .009
Number of comorbidities	1.35 (1.09)	1.93 (1.50)	t= −3.08, .002
SCO. score	2.63 (2.25)	3.99 (3.53)	t= −3.28, .001
AUDIT score	2.97 (1.96)	1.91 (1.95)	t= 3.50, .001
Years since cancer diagnosis	5.00 (4.77)	4.73 (4.63)	t= 0.38, .706
Number of prior cancer treatments	3.93 (0.73)	3.59 (0.83)	t= 2.85, .005
Number of current cancer treatments	0.74 (0.66)	0.67 (0.67)	t= 0.66, .508
Number of metastatic sites (out of 7)	0.77 (0.68)	0.72 (0.76)	MW, .388
Number of metastatic sites without lymph node involvement	0.09 (0.43)	0.12 (0.51)	MW, .727
	% (n)	% (n)	
Smoker (ever)	31.6 (18)	34.0 (51)	FE, .869
Exercise on a regular basis (% yes)	89.3 (50)	84.9 (129)	FE, .503
Born prematurely (% yes)	1.7 (1)	7.8 (11)	FE, .186
Surgery on arms (% yes)	21.1 (12)	28.5 (43)	FE, .297
Surgery on hands (% yes)	1.7 (1)	9.3 (14)	FE, .073
Surgery on legs (% yes)	17.9 (10)	22.7 (34)	FE, .567
Surgery on feet (% yes)	16.1 (9)	20.7 (31)	FE, .555
Injury to arms (% yes)	29.3 (17)	29.1 (44)	FE, 1.000
Injury to hands (% yes)	14.3 (8)	38.5 (57)	FE,.001
Injury to legs (% yes)	17.9 (10)	19.3 (29)	FE, 1.000
Injury to feet (% yes)	29.1 (16)	26.7 (39)	FE,.726
Comorbid conditions (% yes)			
Cancer	50.0 (29)	43.1 (66)	FE, .439
Osteoarthritis	13.8 (8)	31.4 (48)	FE, .009
Back pain	27.6 (16)	35.3 (54)	FE, .328
Depression	24.1 (14)	27.5 (42)	FE, .728
High blood pressure	12.1 (7)	26.8 (41)	FE, .027
Heart disease	0.0 (0)	5.9 (9)	FE, .066
Diabetes	1.7 (1)	5.2 (8)	FE, .450
Lung disease	1.7 (1)	3.9 (6)	FE, .676
Anemia or blood disease	1.7 (1)	5.9 (9)	FE, .291
Ulcer or stomach disease	0.0 (0)	4.6 (7)	FE, .194
Kidney disease	0.0 (0)	0.0 (0)	FE, 1.000

Characteristic	No PIPN 27.5% (n=58)	PIPN 72.5% (n=153)	Test, p-value
	Mean (SD)	Mean (SD)	
Liver disease	0.0 (0)	1.3 (2)	FE, 1.000
Rheumatoid arthritis	0.0 (0)	1.3 (2)	FE, 1.000
Pain not related to cancer	53.4 (31)	58.8 (90)	FE, .534
Type of cancer			X^2=5.11, .078
Breast	93.1 (54)	98.0 (150)	
Ovarian	0.0 (0)	0.7 (1)	
Other	6.9 (4)	1.3 (2)	
Any metastatic disease (% yes)	68.4 (39)	62.0 (93)	FE, .422
Dose of paclitaxel (mg/m^2)	799.98 (208.50)	851.25 (718.90)	t= −0.51, .610
Patients who had a dose reduction or delay due to neuropathy (% (n))	0.0 (0)	13.6 (20)	FE, .001

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, FE = Fisher's Exact test, kg = kilograms, m^2 = meters squared, mg = milligrams, PIPN = paclitaxel-induced peripheral neuropathy, SCQ = Self-Administered Comorbidity Questionnaire, SD = standard deviation, U = Mann Whitney U test

Table 3 –

Pain Characteristics of the Cancer Survivors Who Received Paclitaxel and Developed Peripheral Neuropathy

Characteristic	Lower Extremity (n=146)	Upper Extremity (n=114)
	Mean (SD)	Mean (SD)
Pain Characteristics		
Duration of PIPN (years)	3.87 (4.00)	3.82 (4.05)
Pain now	3.41 (2.18)	2.98 (2.22)
Average pain	3.84 (2.11)	3.17 (2.21)
Worst pain	5.92 (2.51)	4.76 (2.77)
Days per week in pain	3.66 (3.02)	3.78 (2.94)
Hours per day in pain	13.06 (9.11)	12.27 (9.24)
Pain Interference Scale		
Balance	3.46 (2.94)	
Routine activities [+]		2.67 (2.79)
Walking ability	3.42 (3.01)	0.42 (1.56)
Enjoyment of life	2.86 (2.86)	2.24 (2.78)
Normal work	2.65 (2.72)	2.79 (2.68)
Sleep	2.86 (2.96)	1.78 (2.57)
General activity	2.63 (2.59)	2.54 (2.60)
Mood	2.52 (2.55)	2.05 (2.26)
Relations with other people	1.65 (2.27)	0.90 (1.74)
Sexual activity	1.11 (2.37)	0.69 (1.96)
Mean interference score	2.59 (2.28)	1.82 (1.94)
Pain Quality Assessment Scale (PQAS) Scores		
Numb	5.32 (2.91)	4.07 (2.68)
Unpleasant	4.32 (2.43)	3.72 (2.48)
Tingling	4.01 (2.99)	3.05 (2.97)
Intense	3.34 (2.49)	2.73 (2.37)
Dull	3.02 (2.61)	2.34 (2.25)
Cramping	2.80 (3.05)	1.73 (2.63)
Electrical	2.35 (2.94)	1.93 (2.84)
Shooting	2.25 (2.72)	1.33 (2.32)
Sharp	2.19 (2.73)	1.31 (2.21)
Aching	2.28 (2.63)	1.66 (2.41)
Heavy	1.94 (2.63)	1.41 (2.40)
Cold	1.64 (2.46)	1.12 (2.10)
Radiating	2.16 (2.75)	1.48 (2.34)
Hot	1.94 (2.71)	1.08 (2.08)
Tender	1.96 (2.45)	1.60 (2.27)

Characteristic	Lower Extremity (n=146)	Upper Extremity (n=114)
	Mean (SD)	Mean (SD)
Sensitive skin	1.77 (2.22)	1.32 (2.14)
Throbbing	1.88 (2.55)	1.31 (2.21)
Itchy	1.22 (2.23)	0.60 (1.61)
Intense - surface pain	3.38 (2.71)	2.96 (2.42)
Intense - deep pain	3.18 (2.73)	2.39 (2.73)
PQAS subscale - paroxysmal	2.19 (2.21)	1.41 (1.90)
PQAS subscale - surface	2.79 (1.70)	2.02 (1.61)
PQAS subscale - deep	2.38 (1.92)	1.70 (1.88)

[+] Dressing, toileting, typing

Abbreviations: PIPN - paclitaxel-induced peripheral neuropathy, SD = standard deviation

Table 4 –

Differences in Sensation Measures, Balance Measures, Symptom Severity Scores, Stress Measures, and Quality of Life Outcomes Between Cancer Survivors Who Received Paclitaxel and Did and Did Not Develop Peripheral Neuropathy

Characteristic*	No PIPN 27.5% (n=58)	PIPN 72.5% (n=153)	Statistic; p-value
	Mean (SD)	Mean (SD)	
Sensation Measures +			
Light touch - upper extremity sites (out of 7)[a]	0.00 (0.00)	0.16 (0.70)	t= −2.88, .005
Light touch - lower extremity sites (out of 9)[b]	0.22 (0.50)	1.84 (2.18)	t= −8.53, <.001
Cold - upper extremity sites out of 4[c]	0.45 (0.78)	0.80 (0.98)	t= −2.47, .015
Cold - lower extremity sites out of 4[d]	1.60 (1.36)	2.21 (1.18)	t= −3.19, .002
Pain - upper extremity sites (out of 7)[e]	0.47 (0.75)	1.10 (1.43)	t= −4.15, <.001
Pain - lower extremity sites (out of 9)[f]	1.53 (1.48)	3.29 (2.16)	t= −6.71, <.001
Vibration - upper extremity sites (volts)[g]	16.34 (7.56)	25.19 (11.53)	t= −6.48, <.001
Vibration - lower extremity sites (volts)[h]	6.24 (1.77)	8.77 (4.41)	t= −5.93, <.001
Balance Measures			
Trouble with balance (% yes (n))[i]	10.9 (6)	61.2 (93)	FE, <.001
Severity of balance trouble (0 to 10)[j]	2.33 (1.63)	4.67 (2.74)	t= −2.06, .042
Frequency of balance trouble (0 to 10)[k]	2.17 (1.17)	4.62 (3.00)	t= −4.30, .002
Distress from balance trouble (0 to 10)[l]	3.00 (3.03)	5.10 (2.98)	t=1.67, .098
Timed get up and go test (>13.5 seconds = higher risk for falls)	6.20 (1.24)	7.85 (2.36)	t= −6.54, <.001
Fullerton Advanced Balance test (≤25 is associated with a higher risk of falls)	37.79 (3.08)	33.95 (5.88)	t=6.17, <.001
Upper Extremity Function			
Grip strength (kilograms)	27.41 (5.15)	23.68 (5.92)	t=4.23, p<.001
Number of pins in 30 seconds	15.50 (1.95)	14.25 (2.04)	t=4.02, p<.001
Symptom Severity Scores			
Trait anxiety (STAI-T score ≥31.8)	35.21 (10.59)	36.42 (9.66)	t= −0.79, .429
State anxiety (STAI-S score ≥32.2)	31.45 (10.03)	34.10 (12.07)	t= −1.48, .141
Depressive symptoms (CES-D score ≥16)	8.77 (7.99)	10.94 (9.51)	t= −1.54, .125
Morning fatigue (LFS score ≥3.2)	2.64 (1.99)	3.35 (2.27)	t= −2.09, .038
Evening fatigue (LFS score ≥5.6)	5.34 (1.84)	5.48 (1.89)	t= −0.49, .623
Morning energy (LFS score ≤6.2)	5.74 (2.23)	4.93 (2.10)	t=2.45, .015
Evening energy (LFS score ≤3.5)	3.89 (2.10)	3.42 (1.81)	t=1.61, .109
Sleep disturbance (GSDS score ≥43)	40.55 (20.55)	48.88 (20.20)	t= −2.66, .008
Attentional function (AFI score <5 is low function, 5.0 to 7.5 is moderate function, >7.5 is high function)	6.91 (1.62)	6.51 (1.67)	t= 1.54, .124

Characteristic*	No PIPN 27.5% (n=58)	PIPN 72.5% (n=153)	Statistic; p-value
	Mean (SD)	Mean (SD)	
Stress Measures			
IES-R Avoidance mean subscale score	0.53 (0.48)	0.68 (0.64)	t= −3.09, .002
IES-R Intrusion mean subscale score	0.47 (0.46)	0.74 (0.74)	t= −1.73, .085
IES-R Hyperarousal mean subscale score	0.32 (0.55)	0.56 (0.68)	t= −2.59, .011
IES-R Total score (≥33)	9.96 (8.66)	14.62 (13.63)	t= −2.91, .004
Perceived Stress Scale score	17.36 (10.11)	18.68 (9.31)	t= −0.89, .373
MOS-SF12 Scores			
Physical functioning	83.19 (25.39)	61.11 (34.76)	t= 5.06, <.001
Role physical	79.53 (24.41)	59.31 (30.06)	t= 5.02, <.001
Bodily pain	86.40 (20.08)	66.28 (28.46)	t= 5.69, <.001
General health	76.55 (17.78)	68.58 (22.89)	t= 2.67, .009
Vitality	57.46 (24.53)	47.02 (24.82)	t= 2.73, .008
Social functioning	88.16 (20.10)	76.66 (28.24)	t= 3.27, .001
Role emotional	80.92 (23.99)	76.58 (25.35)	t= 1.12, .266
Mental health	74.12 (18.28)	69.13 (19.94)	t= 1.65, .101
Physical component summary score (≥50.0)	51.33 (8.86)	43.14 (11.30)	t= 5.46, <.001
Mental component summary score (≥50.0)	49.82 (10.93)	48.93 (10.37)	t= 0.54, .589
Multidimensional Quality of Life (QOL) Scale - Cancer			
Physical well-being	7.99 (1.37)	7.33 (1.60)	t= 2.76, .006
Psychological well-being	5.79 (1.50)	5.28 (1.70)	t= 2.09, .039
Social well-being	6.34 (2.07)	5.77 (2.19)	t= 1.72, .086
Spiritual well-being	4.98 (1.96)	5.32 (2.26)	t= −1.10, .274
Total QOL score	6.18 (1.32)	5.79 (1.42)	t= 1.81, .072

*When available, the clinically meaningful cut-point score is provided in parentheses next to the characteristic.

+Changes in sensation are reported for the dominant extremity

[a]Upper extremity sites for light touch were: pad of thumb, thumb webspace, tip of index finger, tip of little finger, midway base of palm, one third up anterior arm, two thirds up anterior arm

[b]Lower extremity sites for light touch were: pad of great toe, pad of 3rd toe, pad of 5th toe, base of heel, metocarpophalangeal (MP) joint of great toe, MP joint of 3rd toe, MP joint of 5th toe, midway along tibia, patella

[c]Upper extremity sites for cold were: pad of index finger, pad of little finger, dorsal MP area of the hand, wrist

[d]Lower extremity sites for cold were: top of great toe at 1st MP joint, pad of great toe, dorsum of foot midpoint, medial malleolus

[e]Upper extremity sites for pain were: pad of thumb, thumb webspace, tip of index finger, tip of little finger, midway base of palm, one third up anterior arm, two thirds up anterior arm

[f]Lower extremity sites for pain were: pad of great toe, pad of 3rd toe, pad of 5th toe, base of heel, metocarpophalangeal (MP) joint of great toe, MP joint of 3rd toe, MP joint of 5th toe, midway along tibia, patella

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

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

[i] Since your chemotherapy, have you had trouble with your balance?

[j] At its worst, how severe is the trouble with your balance (0 = not at all severe to 10 = extremely severe)?

[k] How often do you have trouble with your balance (0 = never to 10 = always)?

[l] At its worst, how distressing is the trouble with your balance (0 = not at all distressing to 10 = extremely distressing)?

Abbreviations: AFI = Attentional Function Index, CES-D = Center for Epidemiological Studies-Depression Scale, LFS = Lee Fatigue Scale, GSDS = General Sleep Disturbance Scale, IES-R = Impact of Event Scale-Revised, MOS-SF-12 = Medical Outcomes Study-Short Form 12, PIPN = paclitaxel-induced peripheral neuropathy, QOL = quality of life, SD = standard deviation