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Chemotherapy-Induced Neuropathy in Cancer Survivors

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Abstract

Context—Evidence suggests that chemotherapy-induced neuropathy (CIN) is a significant problem for cancer survivors. However, a detailed phenotypic characterization of CIN in cancer survivors is not available.

Objectives—To evaluate between group differences in demographic and clinical characteristics, as well as in measures of sensation, function, and postural control, in a sample of cancer survivors who received a platinum and/or a taxane-based CTX regimen and did (n=426) and did not (n=197) develop CIN.

Methods—Survivors completed self-report questionnaires and underwent objective testing (i.e., light touch, pain sensation, cold sensation, vibration, muscle strength, grip strength, Purdue Pegboard test, Timed Get Up and Go Test, Fullerton Advanced Balance test). Parametric and non-parametric statistics were used to compare between group differences in study outcomes.

Results—Of the 426 survivors with CIN, 4.9% had CIN only in their upper extremities, 27.0% only in their lower extremities, and 68.1% in both their upper and lower extremities. Demographic and clinical characteristics associated with CIN included: older age, lower annual income, higher body mass index, a higher level of comorbidity, being born prematurely, receipt of a higher cumulative dose of chemotherapy, and a poorer functional status. Survivors with CIN had worse outcomes for all of the following objective measures: light touch, pain, temperature, vibration, upper and lower extremity function and balance.

Conclusions—This study is the first to provide a detailed phenotypic characterization of CIN in cancer survivors who received a platinum and/or a taxane compound. These data can serve as a benchmark for future studies of CIN in cancer survivors.

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Keywords

chemotherapy-induced neuropathy; cancer; chemotherapy; pain; pain qualities; gait; balance; sensations; vibration

INTRODUCTION

More than 14 million cancer survivors are living in the United States; a number that is expected to double in the next decade.¹ This increase in cancer survivors mandates that greater emphasis be placed on the assessment and management of persistent adverse effects associated with cancer treatment.^{2,3} Among these adverse events, chemotherapy-induced neuropathy (CIN) can be particularly severe and long-lasting.^{4,5} While CIN was described initially as a predominantly reversible condition that produced its effects within the peripheral nervous system, a growing body of evidence suggests that it persists long into survivorship⁶ and that the neurotoxic effects can occur within the central nervous system.⁷⁻⁹ Therefore, in this paper the abbreviation CIN was used instead of CIPN to describe this condition. Of note, in 2014, CIN was added to the National Comprehensive Cancer Center (NCCN) Clinical Practice Guideline for Survivorship^{2,10} and the American Society of Clinical Oncology published a guideline on the prevention and management of CIN in cancer survivors.³

While the exact prevalence of CIN in cancer survivors is unknown, findings from cross-sectional and cancer registry studies suggest that between 10% and 60% of survivors have CIN.¹¹⁻¹⁵ Self-report data from one of these studies, collected using the Quality of Life Questionnaire – CIPN20 (CIPN20),¹⁵ found that the most common symptoms were tingling in the hands and feet (30%), numbness in the toes and feet (19%), tingling in hands or fingers (15%), and burning or shooting pain in the toes or feet (13%).¹⁶ Of note, survivors reported symptoms for up to 11 years following the completion of chemotherapy (CTX).¹⁶ Equally important, recent findings suggest that CIN has a negative impact on survivors' functional status and quality of life (QOL).^{12,17-20} While all of these studies provide information on the extent and impact of CIN in cancer survivors, none have provided a detailed phenotypic description of this clinical condition.

Given the significant impact of CIN and the paucity of research on this condition in cancer survivors, we evaluated between group differences in demographic and clinical characteristics, as well as in measures of sensation, function, and postural control, in a sample of cancer survivors who received a platinum and/or a taxane-based CTX regimen and did (n=426) and did not (n=197) develop CIN.

METHODS

Survivors and Settings

Survivors were recruited from throughout the San Francisco Bay area using the following strategies: direct referral from clinicians; direct mailing to survivors who were identified through targeted searches of our medical center's electronic health record; newspaper advertisements; emails to participants in the Dr. Susan Love Research Foundation's Army of

Women[®] Program; emails to support group members; postings on survivorship websites; postings on [ClinicalTrials.gov](https://www.clinicaltrials.gov); presentations at support group meetings; and snowball sampling through referrals from survivors. The National Coalition for Cancer Survivorship's (NCCS) definition of cancer survivor was used in this study (i.e., NCCS considers a person a cancer survivor from the moment of diagnosis through the balance of life. Whether treatment is being received or has been completed anyone who has received a diagnosis is a survivor).²¹

Survivors with CIN 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 Qualities Assessment Scale (i.e., numb, tender, shooting, sensitive, electrical, tingling radiating, throbbing, cramping, itchy, unpleasant)²²; if they had pain associated with the CIN, 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.²³

Survivors without CIN 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; 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 CIN 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 CIN, a hereditary sensory or autonomic neuropathy,²⁴ and/or a hereditary mitochondrial disorder.²⁵ A detailed patient history was obtained to evaluate for the presence of these conditions. Of the 1450 survivors who were screened, 754 were enrolled, and 623 completed the self-report questionnaires and the study visit.

Study procedures

Survivors communicated their willingness to participate in our study by phone, email, or completion of an online screening questionnaire. Research nurses phoned survivors who expressed interest and determined their eligibility to participate. For survivors who met the study's inclusion criteria, the research nurses obtained consent over the phone; sent and asked the survivors to complete the self-report questionnaires prior to their study visit; and scheduled the survivors' study visit. During the study visit, the research nurse obtained written informed consent, reviewed the study questionnaires for completeness, and performed the objective measures.

Subjective Measures

Demographic and Clinical Characteristics—Survivors completed a demographic questionnaire that obtained information on age, gender, race/ethnicity, living arrangements, marital status, education, and employment. Survivors were interviewed to obtain information on their cancer diagnosis, previous and current cancer treatments, CTX regimens, prior hand and foot surgeries, and concurrent medications. Medical records were reviewed for detailed information on cancer diagnosis, previous cancer treatments, and CTX regimens.

The Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in cancer survivors and has well established validity and reliability.²⁶ Survivors rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).^{26–28}

The Self-Administered Comorbidity Questionnaire (SCQ) consists of 13 common medical conditions.²⁹ Survivors were asked to indicate if they had the condition; if they received treatment for it (proxy for disease severity); and if it limited their activities (indication of functional limitations). The total SCQ score can range from 0 to 39. The SCQ has well-established validity and reliability and has been used in studies of survivors with a variety of chronic conditions.^{30,31}

The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire that assesses alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the last 12 months. The AUDIT gives a total score that ranges from 0 to 40. Scores of 8 are defined as hazardous use and scores of 16 are defined as use of alcohol that is likely to be harmful to health.^{32,33} The AUDIT has well established validity and reliability.^{34–36}

Pain questionnaires—For survivors with CIN, separate assessments were done for pain intensity and pain quality ratings for the hands and feet. A detailed history of the CIN was obtained using a pain questionnaire that was used in our previous^{37,38} and ongoing studies. This questionnaire obtained information on date of onset of pain, duration, location(s), aggravating and relieving factors, level of interference with function, as well as previous and current treatments and their effectiveness. Average and worst pain intensity over the past 24 hours was assessed using 0 (no pain) to 10 (worst pain imaginable) NRSs.^{39,40}

The Pain Qualities Assessment Scale (PQAS) was used to assess the qualities associated with CIN.^{22,41} The 20-item PQAS is an adaptation of the Neuropathic Pain Scale developed by Galer and Jensen.²² Sixteen items evaluate the magnitude of the different pain quality descriptors (e.g., sharp, hot, aching, cold) measured with an NRS. Four items evaluate global and spatial qualities of pain. Three subscale scores were calculated (i.e., paroxysmal pain [shooting, sharp, electric, hot, radiating], surface pain [itchy, cold, numb, sensitive, tingling], deep pain [aching, heavy, dull, cramping, throbbing, tender]). The PQAS has well established validity and reliability in studies of various types of neuropathic pain.^{22,41–44}

Objective Measures

Objective measures of sensation included: light touch, pain, cold, and vibration. Objective measures of motor function included: muscle strength, grip strength, manual dexterity, heel

lift, and Achilles deep tendon reflex. Balance and postural control were evaluated using the Timed Get Up and Go test (TUG) and the Fullerton Advanced Balance (FAB) test. All of the objective measures were done in survivors with and without CIN.

Light touch sensation—Semmes-Weinstein monofilaments (SWM; North Coast Medical, Inc., Morgan Hill, CA) were used to test light touch sensation in the upper and lower extremities following the procedure of Bell-Krotoski.⁴⁵ Each upper extremity was evaluated at 7 locations: the pad of the thumb, thumb webspace, tip of the index finger, tip of the little finger, midway up the base of the palm, one third up the anterior arm, and two thirds up the anterior arm. Each lower extremity was evaluated at 14 locations: pad of the great, 3rd, and 5th toes; plantar surface of the great, 3rd, and 5th toe at the metacarpophalangeal (MP) joint; plantar medial arch; base of the heel; dorsal surface of the MP joint of the great, 3rd, and 5th toes; dorsum medial navicular; midway along the anterior surface of the tibia, and the patella. These locations were tested in random order.

SWM sizes used for the upper extremities were: 3.61 (0.4 grams (g)), 4.31 (2 g), 4.56 (4 g), 5.07 (10 g), and 6.65 (300 g). SWM used for the lower extremities were: 4.31, 4.56, 5.07, and 6.65. Before testing began, survivors were familiarized with the filament being used and the expected sensation was demonstrated. Then with the survivors' eyes closed, starting with the smallest, filaments were applied in ascending order at each site. The filaments were applied perpendicular to the skin and pressed until the filament bowed for 1.5 seconds. The survivor was asked to respond to the stimulus by stating the location of the light touch sensation. In contrast to Bell-Krotoski's recommendation, two correct responses out of three rather than one out of three at each location were considered a positive response, as the survivor could make one correct response by guessing.⁴⁶ At each location, once a positive response was identified, the next location was tested in random order. SWM measurements have good inter- and intrarater reliability and validity when calibrated and applied correctly.^{45,47,48} For each location, the smallest SWM that the survivor sensed was used in the statistical analyses.

Pain sensation—Pain sensation was tested using the Neurotip (MedExSupply Medical Supplies, NY) which has a spring mechanism that is calibrated to exert a force of 40 grams.⁴⁹ Each upper and lower extremity was evaluated once in each of the same locations as the SWM measurements. Survivors were familiarized with the device and the expected sensations were demonstrated on skin in an unaffected region. Then with their eyes closed, the survivor was asked to indicate "sharp" or "dull" when the applicator stick was applied to each location in random order. At each site, pain response was coded as present or absent for use in the statistical analyses.

Cold sensation—Cold sensation was evaluated using the Tiptherm rod (Bailey Instruments; Trafford Park, United Kingdom). This pen like device consists of a polymer cylinder at one end and a cool metal cylinder at the other end. The device provides a constant temperature that is applied to the skin. After familiarizing the survivors with the two sensations, the research nurse applied each side of the device at each location stating "one" and "two". The survivor was asked to indicate which application (i.e. "one" or "two") felt colder. Each upper extremity was evaluated at four locations: pad of the index finger,

pad of the little finger, dorsal metacarpal area of the hand, and the dorsal side of the wrist. Each lower extremity was evaluated at four locations: top of great toe at the 1st MP joint, pad of great toe, dorsum of the foot at the midpoint, and medial malleolus. Cold sensation sites were tested in random order up to three times and scored as impaired if the survivor had two incorrect responses.⁴⁹ The Tipterm has high specificity (100%) and sensitivity (97.3%) in diagnosing diabetic peripheral neuropathy.⁵⁰

Vibration threshold—Vibration threshold was tested using a Biothesiometer (Bio-Medical Instrument Company; Newbury, OH). After familiarizing survivors with the sensation, vibration thresholds were tested at four sites in the upper extremities (i.e., dorsal interphalangeal (IP) joint of the thumb and index finger, ulnar prominence of the wrist, lateral epicondyle) and three sites in the lower extremities (i.e., dorsal IP joint of the great toe, medial malleolus, patella). Following the manufacturer's instructions, the Biothesiometer was placed on the skin over the bone at each location. Beginning at zero, the amplitude of the vibration was increased until the survivor reported feeling vibration (i.e., vibration perception threshold). Then the amplitude was turned down to zero and the procedure was repeated, increasing the intensity more slowly as the initial value was approached. The survivor reported the perception of the sensation of vibration by saying, "NOW." Each site was tested three times and the mean score was used in the statistical analyses.

Muscle strength—For each movement tested, muscle strength was assessed once in the upper (i.e., abduction of the little finger, opposition of the thumb and little finger, wrist extension) and lower (i.e., extension of the great toe, dorsiflexion of the foot, plantar flexion of the foot) extremities using the Medical Research Council Scale (i.e., 0 = no visible contraction to 5 = normal strength).⁵¹

Grip strength—Hand grip strength was assessed using a hand dynamometer (Smedley III Anlgou Grip Tester, Creative Health Products, Ann Arbor, MI). Survivors stood upright with their weight evenly distributed on both feet. The grip size was adjusted for each individual survivor and both arms were extended downward. Survivors were coached to squeeze the hand dynamometer with as much force as possible. The survivor performed the test three times on each hand, alternating sides. Fifteen seconds separated each trial. The mean force in kilograms (kg) of the three trials was calculated for each hand.⁵²

Pegboard test—Manual dexterity in the upper extremities was assessed using the Purdue Pegboard (Lafayette Instrument, Lafayette, IN). Survivors were seated at a desk and the Purdue Pegboard was placed in front of them. Each upper extremity was tested separately. Survivors were instructed to place as many pins in the column of the pegboard that corresponded to their right or left hand, until they were told to stop. The number of pins placed in 30 seconds was recorded. Each upper extremity was tested twice and a mean score for each extremity was calculated.⁵³⁻⁵⁵

Heel lift—Lower extremity strength was evaluated using the heel lift test.^{56,57} Survivors were instructed to stand on the floor with one leg using the wall for balance and lift their

heel for a maximum of 15 seconds. Each lower extremity was tested once. The amount of time the survivor stood with the heel lifted was recorded.

Achilles tendon reflex—Achilles tendon reflex was tested with a Taylor Percussion Hammer (Prestige Medical, Los Angeles, CA). The response was coded as present or absent.

Timed get up and go test (TUG)—The TUG test is a timed test of a person's ability to stand from an armed chair, walk 10 feet, turn, and return to a seated position.⁵⁸ Survivors were instructed to walk as quickly as possible, without running. The time needed to perform the test was recorded.

Fullerton Advanced Balance (FAB) test—The FAB is a measure of balance that includes ten tasks: standing with feet together and eyes closed, reaching forward to retrieve a pencil held at shoulder height, turning 360° in a right then in a left direction, stepping up and over a 15.2 cm (6 in) bench, tandem walking, standing on one leg, standing on foam with eyes closed, 2-footed jumping for a distance, walking with head turns, and responding to an unexpected trunk perturbation.^{59,60} The FAB was chosen because the tasks challenge the sensory systems (i.e., visual, somatosensory, vestibular) used for postural control that may be more sensitive to balance problems in individuals with CIN, a primary sensory neuropathy. The quality of the performance of each task is scored using standardized ordinal scoring criteria. Total scores can range from 0 to 40. Higher scores indicate a better performance.

Reliability assessments of the study nurses—A neurologist and a physical therapist taught the research nurses how to perform all of the objective measures and determined their inter-rater reliability. Every 6 months, these reliability assessments were done. Measures were repeated until an inter-rater reliability of 0.80 was achieved among all of the research nurses.

Data Analysis

Data were analyzed using SPSS version 23.⁶¹ Descriptive statistics and frequency distributions were calculated for survivors' demographic and clinical characteristics. Differences between the CIN and no CIN groups on demographic and clinical characteristics, as well as objective measures were evaluated using independent sample t-tests, Chi square analyses, and Mann Whitney U tests. A p-value of <0.05 was considered statistically significant.

RESULTS

Differences in Demographic and Clinical Characteristics

As shown in Table 1, for the majority of the demographic characteristics, no differences were found between the CIN and no CIN groups. However, survivors with CIN were older (60.90 (\pm 10.52) versus 58.38 (\pm 12.27), $p=.013$) and were more likely to have a lower annual household income ($p=.031$).

As shown in Table 2, compared to survivors without CIN, survivors with CIN had a higher body mass index (BMI; $p < .001$), a lower AUDIT score ($p = .002$), a higher number of comorbidities ($p < .001$), a higher SCQ score ($p < .001$), a lower number of previous cancer treatments ($p = .018$), and a lower KPS score ($p < .001$). In addition, a significantly higher percentage of survivors in the CIN group were born prematurely (6.6% versus 1.1%, $p = .002$); reported a previous injury to their hands (34.7% versus 23.7%, $p = .008$); and reported higher occurrence rates for osteoarthritis (30.3% versus 16.8%, $p < .001$), back pain (34.7% versus 23.9%, $p = .007$), kidney disease (2.3% versus 0.0%, $p = .035$), and liver disease (3.3% versus 0.0%, $p = .007$).

In terms of cancer diagnosis, post hoc contrasts demonstrated that while no between group differences were found in the percentage of survivors with breast cancer, a higher percentage of survivors with CIN had a diagnosis of colon ($p = .038$) or ovarian cancer ($p = .014$) and a lower percentage had a diagnosis of lung cancer ($p = .021$). A higher percentage of survivors with CIN received a combination of a platinum and taxane CTX regimen ($p = .007$) and had received a dose reduction or delay in their CTX treatment due to CIN ($p < .001$). When doses of single agents were compared, patients with CIN received a higher cumulative dose of either a platinum ($p < .001$) or a taxane ($p = .010$) (Table 2).

Self-reported Pain Characteristics of Survivors with CIN

Table 3 summarizes pain intensity, pain interference, and pain quality scores for the upper and lower extremities for the survivors with CIN. Of the 426 survivors with CIN, 4.9% had CIN only in their upper extremities, 27.0% only in their lower extremities, and 68.1% in both their upper and lower extremities. The average duration of CIN was 3.62 (± 4.08) years in the upper extremities and 3.94 (± 4.24) years in the lower extremities. For the majority of the pain intensity, interference, and quality items, the scores were higher in the lower extremities compared to the upper extremities.

Differences in Objective Measures of Sensation

In terms of light touch sensation, for every site that was tested in the upper (Figure 1) and lower (Figures 2 and 3) extremities, the percentage of survivors with CIN who felt the smallest monofilament (i.e., 3.61 in the upper extremity, 4.31 in the lower extremity) was significantly lower (all, $p < .001$) and the mean monofilament score was significantly higher (all, $p < .001$; see Supplementary Table 1) compared to survivors without CIN. Except for one site in the lower extremities (i.e., dorsum medial navicular) and three sites in the upper extremities (i.e., midway up the base of the palm, one third and two thirds up the anterior arm), a significantly higher percentage of survivors with CIN did not feel pain at each of the sites tested using the Neurotip (see Table 4). In terms of cold sensation, a significantly higher percentage of survivors with CIN did not feel the Tiptherm device in all of the lower extremity sites tested, as well as in the pad of the index and little finger (see Table 5). For all of the sites tested in the upper and lower extremities, survivors with CIN had significantly higher vibration thresholds (Table 6).

Differences in Measures of Motor Function

As shown in Table 6, the measures of upper extremity strength and dexterity were significantly worse in the survivors with CIN. In the lower extremities, survivors with CIN had a significantly shorter heel lift time and were more likely to have lost their Achilles reflex. Finally, as shown in Table 7, for every site tested in the upper and lower extremities, a higher percentage of survivors with CIN had decreases in muscle strength.

Differences in Balance and Postural Control

As shown in Table 6, survivors with CIN had a significantly longer TUG test ($p < .001$) and a significantly lower FAB score ($p < .001$).

DISCUSSION

This study is the first to perform a detailed characterization of CIN in cancer survivors. In our study, enrollment was restricted to platinum and/or taxane-based regimens because these two classes of neurotoxic drugs are used to treat the most commonly occurring cancers. Of note, this study is the first to report on the occurrence rates for CIN in both the upper and lower extremities. While our findings confirm the clinical impression that most survivors have CIN in both their upper and lower extremities, 4.9% had CIN only in their upper extremities and 27.0% only in their lower extremities.

The higher percentage of patients with CIN in the lower extremities is expected given that this condition is characterized as a length dependent neuropathy.^{62,63} When the percentages of survivors, in our study, with only upper extremity CIN who had hand (14.3%) or arm (23.8%) surgery were compared to survivors with both upper and lower extremity CIN who had hand (9.7%) or arm (21.8%) surgery, no significant differences were found. However, compared to survivors with both upper and lower extremity CIN (34.4% and 25.1%, respectively), a significantly higher percentage of survivors with only upper extremity CIN reported injuries to their hands (57.9%, $p = .048$) and arms (47.6%, $p = .038$). Carpal tunnel syndrome was the most common condition reported by the survivors with only hand CIN. While no information is available on the onset of carpal tunnel syndrome in relationship to the initiation of CTX, this finding warrants further investigation given that 3.8% of the general population carpal tunnel syndrome.⁶⁴

Pain characteristics of patients with CIN

In terms of the pain characteristics listed in Table 2, it is difficult to compare our findings with previous reports because the majority of the studies of CIN in cancer survivors focused on the determination of occurrence rates using the National Cancer Institute Common Toxicity Criteria⁶⁵ or the occurrence rates for common symptoms on the CIPN20 scale.^{11,16,19,66} In the one study that reported severity scores,¹⁷ survivors were asked to rate the severity of numbness and tingling as a single item. In terms of pain severity, while no studies have established cutpoints for CIN, in our study, survivors' worst pain scores were in the moderate to severe range for both the upper and lower extremities.⁶⁷ In terms of the interference items that were adapted from the Brief Pain Inventory,^{68,69} our scores were in the mild to moderate range. When compared with other studies, our survivors' interference

scores were similar to scores reported by oncology patients experiencing taxane-induced arthralgias and myalgias,⁷⁰ but lower than scores reported by oncology patients with bone metastasis⁶⁷ or oncology patients with a variety of neuropathic pain conditions.⁷¹ In order to better assess interference with function in the upper extremities, additional items need to be developed for the BPI.

While the PQAS was developed for and used in studies of neuropathic pain,^{41,42,72–75} our study is the first to use it to evaluate the qualities associated with CIN. Consistent with previous descriptions of CIN (for reviews see^{6,62,76}), numb, followed by unpleasant and tingling, were the three qualities with the highest severity ratings in both the upper and lower extremities. The scores for numb and tingling in the survivors with CIN were higher than those reported by patients with low back pain and osteoarthritis, but lower than scores reported by patients with carpal tunnel syndrome.⁷⁴ Differences in these pain quality scores may reflect different underlying mechanisms for these chronic pain conditions.

Differences in demographic and clinical characteristics

Little information is available on the demographic and clinical characteristics that increase an individual's risk for the development of CIN. Data from two recent reviews^{62,77} and a study from the Southwest Oncology Group⁷⁸ found that older age, African race, prior treatment with a neurotoxic agent, a history of smoking, diabetes mellitus, autoimmune disease, folate/vitamin B12 deficiency, decreased creatinine clearance, neuropathy prior to the initiation of CTX, and sensory changes during CTX were associated with the development of CIN. However, in the registry studies of CIN in cancer survivors,^{11,12,16} risk factors for CIN were not evaluated.

While no between group differences were found in the years since cancer diagnosis and the presence or extent of metastatic disease, a number of demographic and clinical characteristics provide new insights into potential risk factors for CIN. In terms of demographic characteristics, consistent with the risk factors for CIN noted above, as well as risk factors associated with painful diabetic neuropathy,^{79–82} survivors with CIN were older and had a lower annual household income.

An extremely important finding from our study, that is consistent with recent reports in diabetic neuropathy,^{79,80} is the association between comorbidity and CIN. The SCQ score assesses not only the number but the impact of comorbidities on an individual. It should be noted that the difference in SCQ scores between the survivors with and without CIN represents not only a statistically significant but a clinically meaningful difference (Cohen's $d = .40$).⁸³ In terms of specific co-morbidities, a higher percentage of survivors with CIN reported the occurrence of osteoarthritis and back pain. Both of these conditions are reported to have a neuropathic component which may suggest a predisposition for neuropathic pain.^{84–88}

A novel finding in our study is that a higher percentage of survivors with CIN were born prematurely. This finding may be partially explained by the growing body of preclinical and clinical evidence that suggests that the extensive exposure to painful stimuli and stress that premature infants experience results in prolonged and irreversible changes to the peripheral

and central nervous systems (for reviews see^{89–91}). These changes may place an individual who was born prematurely at higher risk for CIN. Given the small number of survivors who were born prematurely, this finding warrants confirmation in future studies. However, if replicated it may be an important screening question prior to the initiation of CTX given that 18% of infants worldwide and 11.4% of infants in the United States are born prematurely.⁹²

In terms of previous injuries or surgeries to the upper and lower extremities, the only significant finding was that a higher percentage of patients with CIN reported an injury to their hands. This finding is consistent with our previous work that demonstrated that a higher percentage of women who reported pain in their breast prior to surgery experienced persistent pain following the procedure.^{93,94} Of note, a higher number of breast biopsies was associated with the occurrence of preoperative breast pain in these patients.^{38,95} Taken together, these findings suggest that previous injury can influence the development of CIN.

Consistent with previous reports in patients with colon cancer who received oxaliplatin⁹⁶ and patients with breast cancer who received docetaxel,⁹⁷ as well as patients with fibromyalgia⁹⁸ and diabetes mellitus,⁹⁹ patients with CIN had a higher BMI. As expected, and consistent with recent studies,^{78,100} patients with CIN were more likely to have received a combination of a platinum and a taxane compound and had received higher cumulative doses of CTX. This finding may be related to the receipt of two different classes of CTX drugs that have both overlapping (e.g., mitochondrial dysfunction) and differential (e.g. formation of platinum-DNA adducts, taxanes' interference with the stabilization of microtubules (for reviews see^{63,101}) mechanisms for CIN. However, patients with CIN reported a slightly lower number of previous cancer treatments. This finding may relate to the diverse types of cancers included in this study because some cancers may have been detected at an earlier stage and/or different cancers require fewer types of treatments.

Differences in sensations

In terms of differences in the effect of neurotoxic CTX on sensory modalities (i.e., light touch (Figures 1 to 3 and Supplemental Table 1), pain (Table 4), temperature (Table 5), vibration (Table 6)), the overall findings are in the expected direction including more severe changes in patients with CIN and more severe changes associated with distal as compared to proximal sites. However, this study is the first to provide a detailed characterization of changes in sensation at multiple sites in both the upper and lower extremities. In terms of an evaluation of light touch sensation, while no recommendation exists for the size of the monofilament to use to test the upper extremities, most clinicians use a 5.07 monofilament to evaluate for diabetic neuropathy. Our findings suggest that a finer monofilament should be used to assess survivors for changes in light touch sensation.

Vibration thresholds are known to vary by age. In one study that evaluated non-diabetic patients (n=662, mean age 66.1, range 55 to 85 years),¹⁰² the mean vibration thresholds in the upper extremities ranged from 7.9 volts (± 2.0 for patients ≤ 70 years of age) to 9.4 volts (± 3.7 for patients >70 years of age). For the lower extremities, the range was 15.3 volts (± 7.1 for patients ≤ 70 years of age) to 20.5 volts (± 9.8 for patients >70 years of age). Given that, in our study, the mean age of the survivors with CIN was 60.9, the increases in vibration thresholds in their lower extremity sites represent clinically meaningful changes.

Of note, in a study of patients with diabetes,¹⁰³ a vibration threshold of >25 volts was associated with an 8-fold increase in the likelihood of developing a diabetic foot ulcer.

Differences in function and postural control

Grip strength and the Pegboard test were used to evaluate for differences in upper extremity strength and dexterity (Table 6). In the only study identified that compared patients who were CTX naïve (n=20), to patients who received CTX (n=9),¹⁰⁴ the mean grip strengths were 33.5 kg (± 8.5) and 30.1 kg (± 11.4), respectively. For both groups of patients in our study, the mean grip strengths were lower which may be related to differences in the mean age of the patients and the fact that survivors without CIN did receive CTX.

In the manual provided by the manufacturer of the Purdue Pegboard test, healthy individuals were able to insert 17.95 pins in 30 seconds using their dominant hand with clinically meaningful decrements of -1 (15.91) to -2 (13.88) standard deviations.¹⁰⁵ While no studies were identified that used this test of upper extremity function in survivors with CIN, our findings suggest that both groups have some clinically meaningful decrements which may not be related to CIN. A potential factor that could influence performance on the Pegboard test is age.^{54,106} Given that the survivors with CIN were older than the survivors without CIN and they had slightly worse performance on the Pegboard test, the influence of age and other demographic (e.g., gender, handedness) and clinical characteristics on tests of hand function warrant consideration in future studies.

A growing body of evidence suggests that patients with CIN are at increased risk for falling.^{18,20,107-109} In terms of the effects of CIN on lower extremity function, in the one study that compared 20 breast cancer patients who had taxane-induced CIN to 20 healthy controls, TUG scores in the breast cancer patients (6.69 ± 0.99) were worse than in the healthy controls (5.85 ± 0.86).¹⁰⁸ While the survivors with CIN in the current study had worse TUG scores than survivors without CIN, both groups of survivors in the current study had worse TUG scores than the patients with breast cancer who had taxane-induced CIN.¹⁰⁸ However, the TUG scores of the cancer survivors in the current study are lower than 13.5 which is associated with a higher risk for falls.¹¹⁰

Similarly, the FAB scores of our cancer survivors are almost identical to those reported by Wampler and colleagues for the patients with breast cancer who completed taxane treatment.¹⁰⁸ In addition, the mean FAB scores in our study were above the clinically meaningful cutoff score of 25 that is associated with a higher risk of falls.⁵⁹ The findings for muscle testing confirm previous reports that CIN is primarily a sensory neuropathy.

Limitations

A number of limitations warrant consideration. Given the cross-sectional nature of our study, the associations identified between demographic and clinical characteristics warrant confirmation as predictors of CIN in a prospective, longitudinal study. Second, survivors were not evaluated using quantitative sensory testing. Rather, subjective and objective measures were used that could be easily implemented in clinical practice. While only survivors who received a platinum and/or a taxane compound were included in our study,

other CTX agents induce CIN (for reviews see^{63,101}). Therefore, our findings may not generalize to survivors who received other types of neurotoxic CTX.

Conclusions

Despite these limitations, our study is the largest study of CIN in cancer survivors. The detailed characterization of changes in sensation, function, and postural control serves as benchmark data for future studies of neurotoxic CTX in cancer survivors and for clinical trials of pharmacologic and nonpharmacologic interventions. In addition, many of the differences in demographic and clinical characteristics, as well as in the objective measures, between survivors with and without CIN, are similar to those found in other forms of peripheral neuropathy (e.g., diabetic neuropathy, anti-retroviral therapy).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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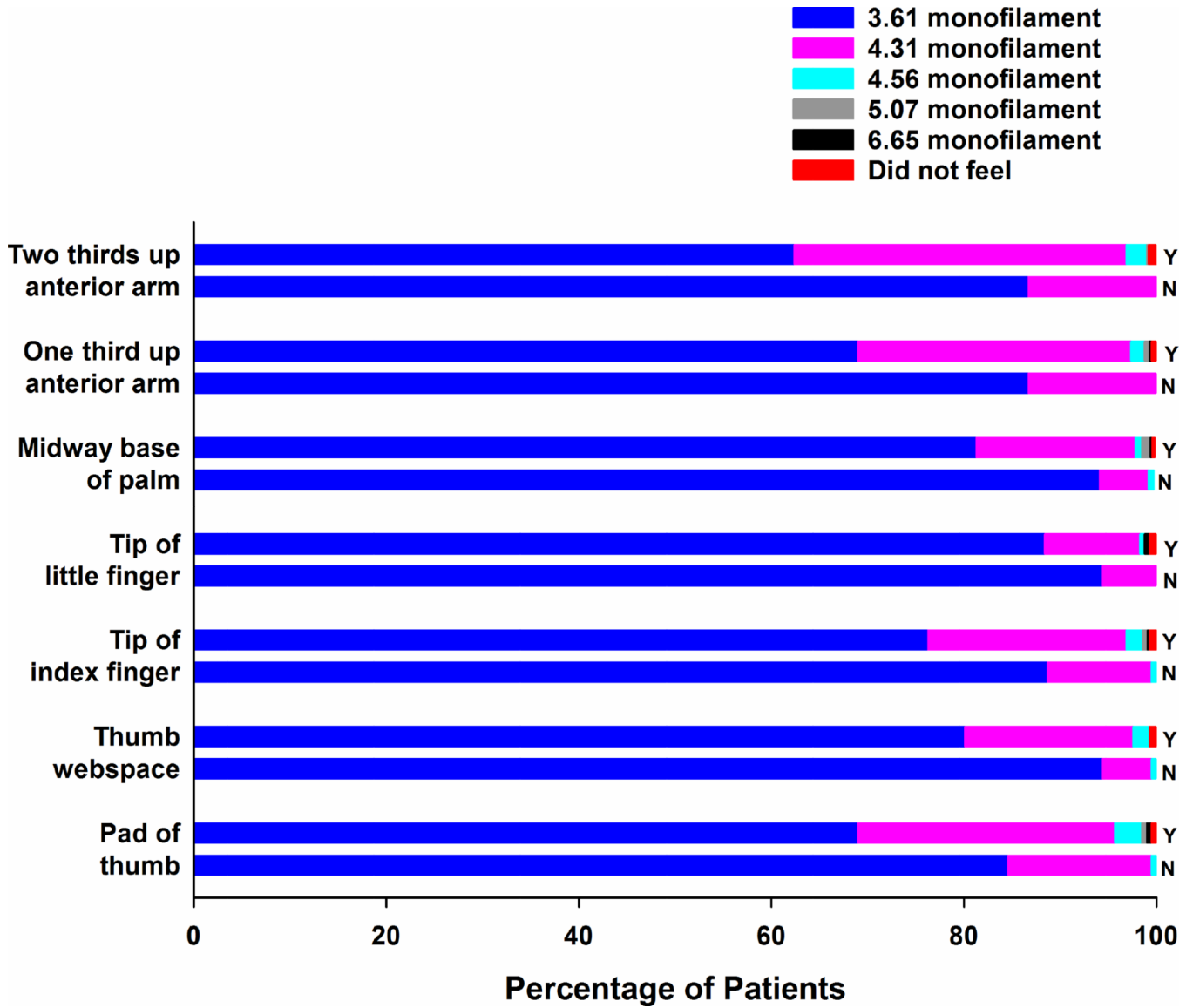


Figure 1. Percentages of patients with (Y) and without (N) chemotherapy-induced neuropathy who felt each of the Semmes Weinstein monofilaments at each of the sites tested in the upper extremities.

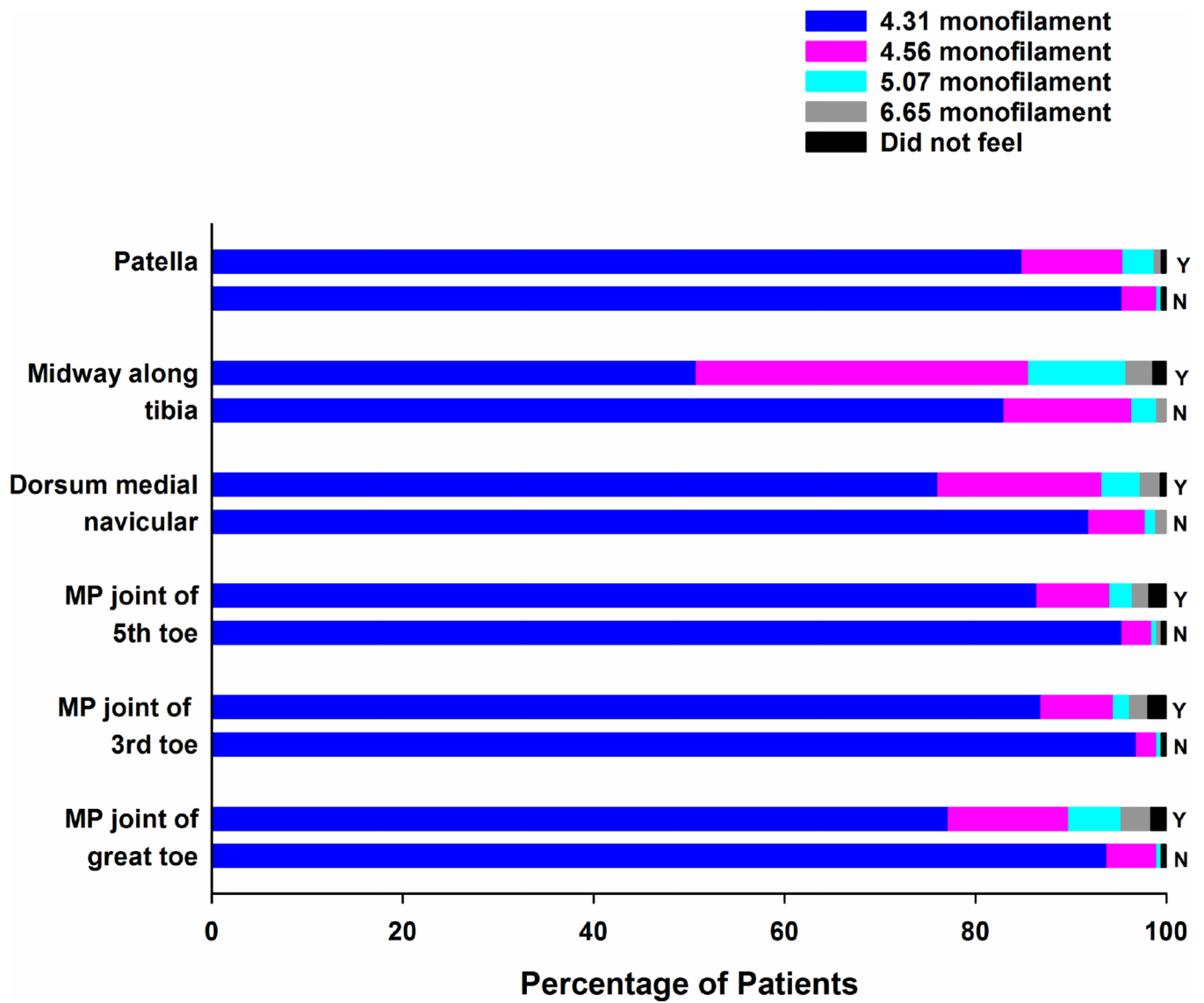


Figure 2. Percentages of patients with (Y) and without (N) chemotherapy-induced neuropathy who felt each of the Semmes Weinstein monofilaments at each of the sites tested on the dorsal surface of the lower extremities.

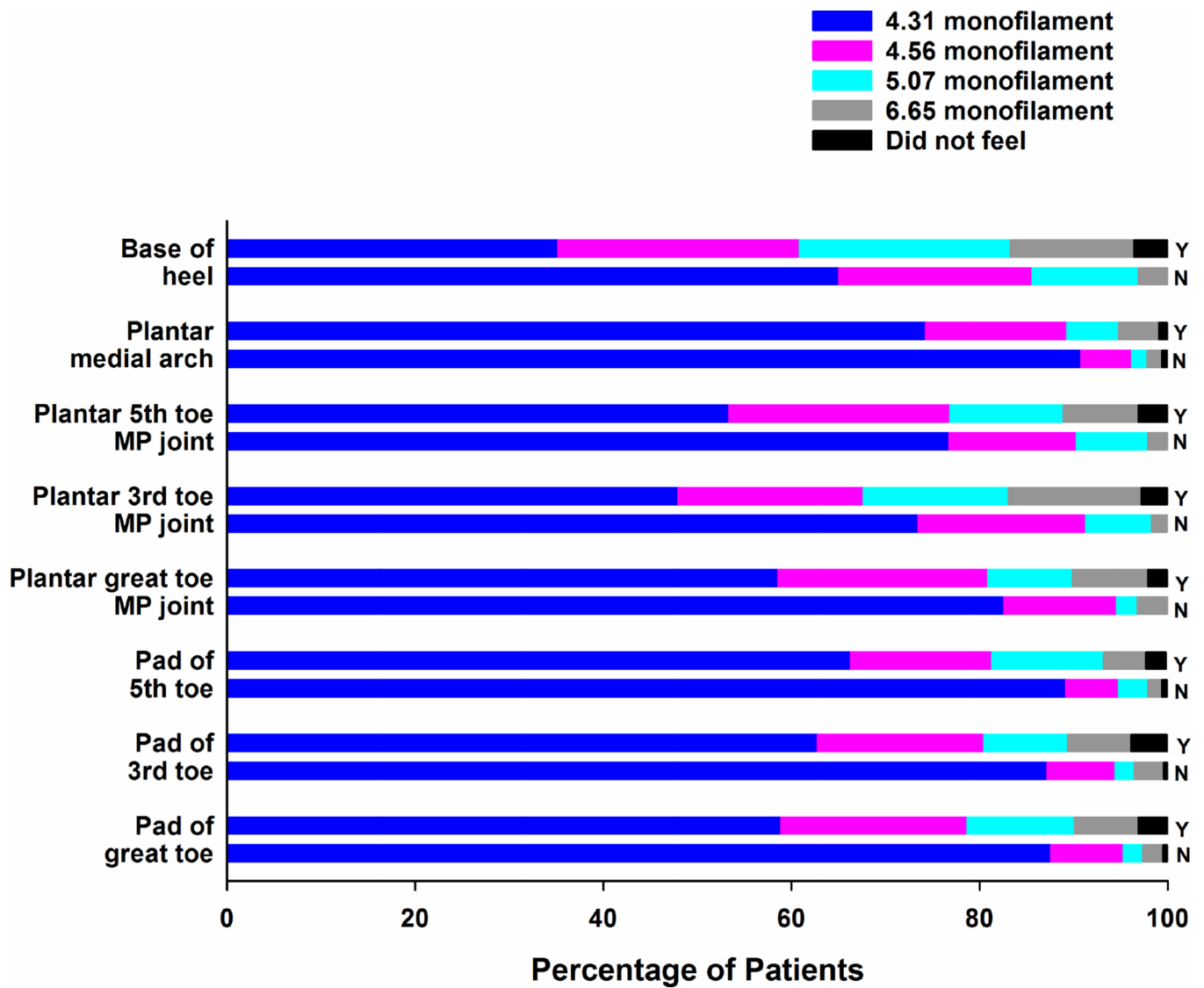


Figure 3. Percentages of patients with (Y) and without (N) chemotherapy-induced neuropathy who felt each of the Semmes Weinstein monofilaments at each of the sites tested on the plantar surface of the lower extremities.

Table 1

Differences in Demographic Characteristics Between Cancer Survivors With (n=426) and Without (n=197) Chemotherapy Induced Neuropathy (CIN)

Characteristic	No CIN 31.6% (n=197)	CIN 68.4% (n=426)	Test, p-value
	Mean (SD)	Mean (SD)	
Age (years)	58.38 (12.27)	60.90 (10.52)	t=-2.48, .013
Education (years)	16.42 (2.61)	16.37 (2.76)	t=0.20, .839
	% (n)	% (n)	
Female	80.7 (159)	86.6 (368)	FE, .072
Married/partnered	63.2 (122)	60.9 (252)	FE, .592
Lives alone	27.7 (54)	29.2 (122)	FE, .774
Employed	49.2 (97)	42.1 (179)	FE, .100
Ethnicity			
White	82.2 (162)	77.2 (329)	X ² = 2.17, .539
Asian/Pacific Islander	6.1 (12)	7.0 (30)	
Black	4.1 (8)	5.2 (22)	
Hispanic/Mixed/Other	7.6 (15)	10.6 (45)	
Annual household income			
<\$30,000	14.8 (27)	23.3 (92)	U, .031
\$30,000 – \$69,999	19.1 (35)	21.0 (83)	
\$70,000 – \$99,999	21.3 (39)	16.2 (64)	
>\$100,000	44.8 (82)	39.5 (156)	
Child care responsibilities	19.2 (37)	13.3 (56)	FE, .069
Adult care responsibilities	3.8 (7)	3.8 (15)	FE, 1.000

Abbreviations: FE = Fisher's Exact test, U = Mann Whitney U test, SD = standard deviation

Table 2

Differences in Clinical Characteristics Between Cancer Survivors With (n=426) and Without (n=197) Chemotherapy-Induced Neuropathy (CIN)

Characteristic	No CIN (1) 31.6% (n=197)	CIN (2) 68.4% (n=426)	Test, p-value
	Mean (SD)	Mean (SD)	
Karnofsky Performance Status score	91.20 (9.33)	83.22 (10.21)	t=9.51, <.001
Body mass index (kg/m ²)	24.85 (5.03)	26.56 (5.55)	t=-3.63, <.001
Number of comorbidities	1.47 (1.35)	2.02 (1.48)	t=-4.46, <.001
Self-Administered Comorbidity Questionnaire score	2.87 (2.96)	4.20 (3.39)	t=-4.99, <.001
Alcohol Use Disorders Identification Test score	2.85 (2.50)	2.24 (2.20)	t=3.05, .002
Years since cancer diagnosis	4.40 (4.82)	4.82 (4.84)	t=-1.01, .311
Number of prior cancer treatments	3.32 (0.98)	3.12 (0.97)	t=2.37, .018
Number of current cancer treatments	0.46 (0.60)	0.41 (0.59)	t=0.86, .392
Number of metastatic sites (out of 7)	0.70 (0.75)	0.75 (0.78)	t=-0.67, .503
Number of metastatic sites without lymph node involvement	0.16 (0.52)	0.22 (0.57)	t=-1.29, .198
	% (n)	% (n)	
Smoker (ever)	33.0 (64)	37.8 (160)	FE, .279
Exercise on a regular basis (% yes)	87.2 (170)	85.9 (365)	FE, .707
Born prematurely (% yes)	1.1 (2)	6.6 (26)	FE, .002
Surgery on arms (% yes)	17.9 (35)	21.5 (91)	FE, .335
Surgery on hands (% yes)	8.2 (16)	10.6 (45)	FE, .387
Surgery on legs (% yes)	21.8 (42)	24.7 (103)	FE, .475
Surgery on feet (% yes)	15.0 (29)	17.0 (71)	FE, .638
Injury to arms (% yes)	25.8 (50)	26.3 (110)	FE, .992
Injury to hands (% yes)	23.7 (45)	34.7 (143)	FE, .008
Injury to legs (% yes)	18.8 (36)	22.4 (93)	FE, .338
Injury to feet (% yes)	26.7 (51)	27.9 (115)	FE, .770
Comorbid conditions (% yes)			

Characteristic	No CIN (1) 31.6% (n=197)	CIN (2) 68.4% (n=426)	Test, p-value
	Mean (SD)	Mean (SD)	
Osteoarthritis	16.8 (33)	30.3 (129)	FE, <.001
Back pain	23.9 (47)	34.7 (148)	FE, .007
Depression	17.3 (34)	23.9 (102)	FE, .061
High blood pressure	19.8 (39)	26.5 (113)	FE, .072
Heart disease	4.1 (8)	7.5 (32)	FE, .115
Diabetes	4.6 (9)	5.6 (24)	FE, .702
Lung disease	6.6 (13)	4.7 (20)	FE, .339
Anemia or blood disease	4.6 (9)	5.9 (25)	FE, .574
Ulcer or stomach disease	3.0 (6)	3.8 (16)	FE, .817
Kidney disease	0.0 (0)	2.3 (10)	FE, .035
Liver disease	0.0 (0)	3.3 (14)	FE, .007
Rheumatoid arthritis	2.0 (4)	2.8 (12)	FE, .786
Pain not related to cancer	51.8 (101)	58.0 (246)	FE, .163
Type of cancer			X ² = 17.41, .002
Breast	57.4 (113)	54.9 (234)	
Colon	4.6 (9)	9.6 (41)	1<2
Lung	5.6 (11)	1.9 (8)	1>2
Ovarian	4.6 (9)	10.6 (45)	1<2
Other	27.9 (55)	23.0 (98)	
Any metastatic disease	58.2 (114)	60.2 (253)	FE, .660
Chemotherapy regimen			X ² = 7.86, .020
Only a platinum compound	28.6 (56)	22.3 (95)	
Only a taxane compound	51.0 (100)	46.9 (200)	1<2
Both a platinum and a taxane compound	20.4 (40)	30.8 (131)	
Dose of platinum compound for patients who received only a platinum (mg)	778.94 (563.32)	1323.95 (923.29)	U, <.001
Dose of taxane compound for patients who received only a taxane (mg)	1113.11 (517.80)	1365.27 (1172.54)	U, .010
Dose of drugs for patients who received both a platinum and a taxane compound			
Platinum dose (mg)	2845.75 (1341.27)	3224.51 (1469.18)	U, .072
Taxane dose (mg)	1223.01 (564.85)	1625.18 (883.10)	U, .008
Patients who had a dose reduction or delay due to neuropathy (% (n))	1.6 (3)	13.8 (56)	FE, <.001

Abbreviations: FE = Fisher's Exact test, kg = kilograms, m² = meters squared, mg = milligrams, U = Mann Whitney U test, SD = standard deviation

Table 3

Pain Characteristics of the Cancer Survivors With Chemotherapy-Induced Neuropathy (CIN)

Characteristic	Lower Extremity (n=405)	Upper Extremity (n=311)
	Mean (SD)	Mean (SD)
Pain Characteristics		
Duration of CIN (years)	3.94 (4.24)	3.62 (4.08)
Pain now	3.60 (2.27)	2.77 (2.06)
Average pain	3.99 (2.11)	3.11 (2.14)
Worst pain	6.04 (2.54)	4.65 (2.66)
Days per week in pain	3.63 (3.03)	3.60 (3.01)
Hours per day in pain	14.94 (9.46)	12.94 (9.84)
Pain Interference Scale		
Balance Routine activities ⁺	3.58 (3.04)	2.54 (2.71)
Walking ability	3.36 (3.02)	0.45 (1.44)
Enjoyment of life	2.86 (2.80)	2.13 (2.68)
Normal work	2.69 (2.82)	2.74 (2.73)
Sleep	2.74 (2.87)	1.56 (2.40)
General activity	2.65 (2.68)	2.48 (2.68)
Mood	2.38 (2.51)	1.90 (2.32)
Relations with other people	1.53 (2.28)	0.78 (1.65)
Sexual activity	0.95 (2.14)	0.70 (1.96)
Mean interference score	2.55 (2.21)	1.72 (1.88)
Pain Qualities Assessment Scale Scores		
Numb	5.41 (3.04)	3.86 (2.86)
Unpleasant	4.49 (2.47)	3.62 (2.50)
Tingling	4.32 (3.02)	3.18 (2.83)
Intense	3.24 (2.49)	2.61 (2.32)
Dull	3.11 (2.75)	2.37 (2.47)
Cramping	2.86 (3.20)	1.78 (2.63)
Electrical	2.53 (3.06)	1.82 (2.65)
Shooting	2.47 (2.92)	1.59 (2.48)
Sharp	2.33 (2.87)	1.38 (2.30)
Aching	2.20 (2.72)	1.81 (2.52)
Heavy	2.08 (2.73)	1.29 (2.29)
Cold	2.06 (2.83)	1.44 (2.36)
Radiating	2.06 (2.74)	1.27 (2.23)
Hot	1.98 (2.69)	1.01 (1.97)
Tender	1.93 (2.50)	1.58 (2.29)

Characteristic	Lower Extremity (n=405)	Upper Extremity (n=311)
	Mean (SD)	Mean (SD)
Sensitive skin	1.80 (2.32)	1.34 (2.13)
Throbbing	1.73 (2.59)	1.30 (2.25)
Itchy	1.04 (2.06)	0.82 (1.91)
Intense – surface pain	3.27 (2.71)	2.92 (2.55)
Intense – deep pain	3.29 (2.82)	2.41 (2.65)

[†]Dressing, toileting, typing

Abbreviations: SD = standard deviation

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Table 4

Differences in the Percentage of Sites in the Dominant Lower and Upper Extremities That Did Not Feel Pain Between Cancer Survivors With (n=426) and Without (n=197) Chemotherapy Induced Neuropathy (CIN)

Site	No CIN 31.6% (n=197)	CIN 68.4% (n=426)	p-value*
	% (n)	% (n)	
Lower Extremity Sites			
Pad of great toe	32.3 (63)	59.0 (248)	<.001
Pad of 3 rd toe	32.3 (63)	58.7 (247)	<.001
Pad of 5 th toe	22.1 (43)	50.8 (214)	<.001
Plantar great toe MP joint [†]	40.5 (75)	69.1 (226)	<.001
Plantar 3 rd toe MP joint [†]	51.4 (95)	82.9 (271)	<.001
Plantar 5 th toe MP joint [†]	45.9 (85)	79.5 (260)	<.001
Plantar medial arch [†]	18.4 (34)	43.7 (143)	<.001
Base of heel	50.3 (98)	79.7 (333)	<.001
MP joint of great toe	8.7 (17)	20.4 (86)	<.001
MP joint of 3 rd toe	4.6 (9)	16.0 (67)	<.001
MP joint of 5 th toe	5.1 (10)	19.0 (80)	<.001
Dorsum medial navicular [†]	5.9 (11)	9.8 (32)	.140
Midway along tibia	11.3 (22)	23.4 (98)	<.001
Patella	6.2 (12)	14.8 (62)	.002
Upper Extremity Sites			
Pad of thumb	22.6 (44)	38.5 (162)	<.001
Thumb webspace	12.3 (24)	19.2 (81)	.038
Tip of index finger	6.7 (13)	24.0 (101)	<.001
Tip of little finger	4.1 (8)	9.5 (40)	.023
Midway base of palm	4.1 (8)	6.9 (29)	.205
One third up anterior arm	5.6 (11)	6.4 (27)	.857
Two thirds up anterior arm	6.7 (13)	10.7 (45)	.138

* Fisher's Exact test

[†] Completed on 512 of 623 cancer survivors

Abbreviation: MP = metocarpophalangeal

Table 5

Differences in the Percentage of Sites in the Dominant Lower and Upper Extremities That Did Not Feel Cold Between Cancer Survivors With (n=426) and Without (n=197) Chemotherapy Induced Neuropathy (CIN)

Site	No CIN 31.6% (n=197)	CIN 68.4% (n=426)	p-value *
	% (n)	% (n)	
Lower Extremity Sites			
Top of great toe at 1 st MP joint	47.7 (93)	62.6 (265)	.001
Pad of great toe	64.6 (126)	80.9 (342)	<.001
Dorsum of foot midpoint	24.6 (48)	36.4 (154)	.004
Medial malleolus	33.8 (66)	45.6 (193)	.007
Upper Extremity Sites			
Pad of index finger	15.9 (31)	29.6 (125)	<.001
Pad of little finger	28.7 (56)	37.4 (158)	.037
Dorsal metacarpal area of the hand	7.7 (15)	9.7 (41)	.455
Wrist	3.1 (6)	5.7 (24)	.226

* Fisher's Exact test

Abbreviations: MP = metocarpophalangeal

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Table 6 Differences in the Vibration Thresholds, Grip Strength, Pegboard Test, Heel Lift, Balance, and Reflexes in the Dominant Extremities Between Cancer Survivors With (n=426) and Without (n=197) Chemotherapy Induced Neuropathy (CIN)

Site	No CIN 31.6% (n=197)	CIN 68.4% (n=426)	t-test,* p-value	A %	B %
	Mean (SD)	Mean (SD)			
Vibration Thresholds (volts)					
Dorsal IP joint of great toe	17.01 (10.64)	25.14 (14.66)	-8.06, <.001	1.5	8.0
Medial malleolus	20.98 (11.23)	28.10 (13.53)	-6.85, <.001	2.1	9.0
Patella	22.12 (10.80)	27.26 (11.90)	-5.31, <.001	1.5	3.3
Dorsal IP joint of thumb	5.19 (2.26)	6.92 (4.56)	-6.31, <.001	0.0	0.0
Dorsal IP joint of index finger	5.77 (3.10)	7.44 (4.56)	-5.32, <.001	0.0	0.0
Ulnar prominence of the wrist	6.99 (2.81)	9.18 (5.51)	-6.52, <.001	0.0	0.0
Lateral epicondyle	10.33 (4.31)	12.71 (6.23)	-5.49, <.001	0.0	0.0
Additional Tests					
Grip strength (kilograms)	27.70 (8.01)	25.39 (8.28)	3.25, .001	n/a	n/a
Number of pins in 30 seconds	14.63 (2.48)	14.04 (2.26)	2.92, .004	n/a	n/a
Heel lift (seconds)	14.16 (2.98)	12.63 (4.56)	4.97, <.001	n/a	n/a
Timed get up and go test (seconds)	6.57 (1.51)	7.75 (2.49)	-7.27, <.001	n/a	n/a
Fullerton Advanced Balance test	36.17 (4.77)	33.25 (6.69)	6.18, <.001	n/a	n/a
Achilles reflex (% (n) absent)	54.2 (104)	78.2 (326)	FE, <.001	n/a	n/a

* Independent sample t-test

Abbreviations: A = Percentage of cancer survivors without CIN who did not feel the maximum vibration threshold, B = Percentage of cancer survivors with CIN who did not feel the maximum vibration threshold, IP = interphalangeal, n/a = not applicable, SD = standard deviation

Table 7

Differences in Muscle Strength Testing in the Dominant Lower and Upper Extremities Between Cancer Survivors With (n=426) and Without (n=197) Chemotherapy Induced Neuropathy (CIN)

Location	Extremity	0 ⁺		1 ⁺		2 ⁺		3 ⁺		4 ⁺		5 ⁺		p-value*
		% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	
Extension of great toe	No CIN	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	5.1 (10)	94.9 (185)	<.001		
	CIN	0.7 (3)	0.9 (4)	1.4 (6)	2.8 (12)	16.8 (71)	77.3 (327)							
Dorsiflexion of ankle	No CIN	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	1.0 (2)	98.5 (192)	.004						
	CIN	0.5 (2)	0.0 (0)	0.2 (1)	1.2 (5)	5.2 (22)	92.9 (393)							
Plantar flexion of ankle	No CIN	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	2.6 (5)	96.9 (188)	.010						
	CIN	0.5 (2)	0.0 (0)	0.2 (1)	1.4 (6)	6.6 (28)	91.2 (385)							
Abduction of the little finger	No CIN	0.0 (0)	0.0 (0)	0.5 (1)	0.5 (1)	13.3 (26)	85.6 (167)	<.001						
	CIN	0.0 (0)	0.0 (0)	1.7 (7)	5.9 (25)	23.6 (100)	68.8 (291)							
Opposition of thumb and little finger	No CIN	0.0 (0)	0.0 (0)	0.5 (1)	1.0 (2)	3.6 (7)	94.9 (185)	<.001						
	CIN	0.2 (1)	0.0 (0)	1.2 (5)	4.5 (19)	15.1 (64)	79.0 (334)							
Wrist extension	No CIN	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	2.1 (4)	97.9 (191)	.001						
	CIN	0.0 (0)	0.2 (1)	0.7 (3)	1.4 (6)	7.3 (31)	90.3 (381)							

* Mann Whitney U test

† Medical Research Council Scale: 0=no flicker of movement, 1=visible contraction without movement of the site, 2=movement of the site but not against gravity, 3=movement over the full range against gravity, 4=movement against gravity and resistance, 5=normal