

## Subclinical Peripheral Neuropathy Is a Common Finding in Colorectal Cancer Patients Prior to Chemotherapy

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### Abstract

**Purpose:** Of the numerous complications associated with cancer and cancer treatment, peripheral neuropathy is a deleterious and persistent patient complaint commonly attributed to chemotherapy. The present study investigated the occurrence of subclinical peripheral neuropathy in patients with colorectal cancer before the initiation of chemotherapy.

**Experimental Design:** Fifty-two patients underwent extensive quantitative sensory testing (QST) before receiving chemotherapy. Changes in multiple functions of primary afferent fibers were assessed and compared with a group of healthy control subjects. Skin temperature, sensorimotor function, sharpness detection, and thermal detection were measured, as was touch detection, using both conventional (von Frey monofilaments) and novel (Bumps detection test) methodology.

**Results:** Patients had subclinical deficits, especially in sensorimotor function, detection of thermal stimuli, and touch detection that were present before the initiation of chemotherapy. The measured impairment in touch sensation was especially pronounced when using the Bumps detection test.

**Conclusions:** The patients with colorectal cancer in this study exhibited deficits in sensory function before undergoing chemotherapy treatment, implicating the disease itself as a contributing factor in chemotherapy-induced peripheral neuropathy. The widespread nature of the observed deficits further indicated that cancer is affecting multiple primary afferent subtypes. Specific to the finding of impaired touch sensation, results from this study highlight the use of newly used methodology, the Bumps detection test, as a sensitive and useful tool in the early detection of peripheral neuropathy. *Clin Cancer Res*; 18(11); 3180–7. ©2012 AACR.

### Introduction

Dysfunction in peripheral nerve function commonly referred to as peripheral neuropathy is found among patients with cancer at various time points in the disease due to numerous causes. Metastasis, infiltration, or physical impingement of tumors into or onto peripheral nerves or nerve roots results in neurologic symptoms that may lead to initial diagnosis (1–3). Alternatively, tumor-derived factors or sensitized immunologic responses may result in paraneoplastic neurologic symptoms that range in severity from mild muscle weakness, gait disturbance, and minor sensory

loss to profound generalized demyelination and severe pain (4–7). Finally, cancer treatments including surgery, radiation, and chemotherapy can also produce a host of neurologic symptoms due to peripheral nerve damage (1, 8, 9).

Our group has placed an emphasis on better defining the mechanisms of chemotherapy-induced peripheral neuropathies (CIPN; refs. 10–14). Quantitative sensory tests (QST) are used to assess performance of the different classes of primary afferent fibers (15). Touch detection measured with von Frey filaments is used to assess function of large myelinated A $\beta$  fibers (10, 12–14). Detection of sharp pain assesses function of A $\delta$  fibers. Finally, function of C-fibers is evaluated by using thermal detection.

The distribution of sensory symptoms in patients with CIPN appears in an identical stocking and glove distribution whether induced by vincristine, taxol, bortezomib (12–14), oxaliplatin, or thalidomide (not yet published) and includes gait disturbances and loss of manual dexterity, numbness, and pain. Three distinct symptomatic areas are reported by patients with chronic painful CIPN. First, there is an area of ongoing pain that is invariably located on the glabrous surfaces of the tips of the fingers and toes and only sometimes includes the dorsal surfaces. Proximal to the painful area is an area of numbness but not necessarily pain

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### Translational Relevance

This study provides evidence that subclinical peripheral neuropathy is widespread among patients with colorectal cancer before the initiation of chemotherapy, implicating cancer as a major contributing factor to the later development of treatment-related peripheral neuropathy. The widespread deficits observed in these patients further implicate robust changes in multiple primary afferent fiber subtypes. Together these findings highlight the importance of early detection and modification of neuropathy symptoms.

in the palms and soles of the feet, termed the "border zone." Skin above the wrists and ankles is usually free of symptoms. Follow-up of patients with chronic neuropathy following bortezomib (10), taxol, and vincristine (Boyette-Davis, manuscript submitted) shows similar levels of pain at 1 to 3 years when reexamined.

The pronounced deficits and persistence in sensory dysfunction observed in CIPN underscore the need to better determine the factors that predispose patients to this complication. This led to the question of whether subsets of patients already exhibit some degree of sensory abnormalities before beginning chemotherapy. To address this question, QST was conducted on groups of patients with colorectal before initiation of their chemotherapy treatments.

### Materials and Methods

#### Subjects

Subjects consisted of 52 patients (33 males, 19 females) with colorectal cancer about to begin chemotherapy at the MD Anderson Cancer Center (Houston, TX) and 31 healthy volunteers (15 males, 16 females) who were either faculty or staff. Of the 52 patients who participated the distribution of disease stage [American Joint Committee on Cancer (AJCC), v.6] was IIA:3, IIB:1, IIC:3, IIIA:4, IIIB:13, IIIC:6, IVA:16, and IVB:6. There was no significant difference in age between patients and control subjects. The average age of patients was 53.4 ( $\pm 1.4$ ), whereas controls subjects were 51.5 ( $\pm 2.6$ ) years old. Participants in both the patient and control groups were excluded if there was evidence of ongoing neuropathy or of a preexisting condition other than colorectal cancer which might increase the risk for neuropathy, including diabetes and previous chemotherapy treatment. All study participants signed an informed consent that had been previously approved by the Institutional Review Board. The testing of patients occurred just before the first treatment with chemotherapy.

#### QST procedures

Three sites, the tip of the index finger, the thenar eminence, and the volar surface of the forearm, were chosen for QST testing to coincide with the distribution of CIPN symptoms as described above.

#### Skin temperature

To assess skin temperature as a general metric of autonomic tone in the extremities, a radiometer was placed gently against the skin at each site for approximately 2 seconds.

#### Touch detection thresholds

Touch detection was measured using 2 methods to assess function in large myelinated fibers. First, the well-known up-down method using von Frey monofilaments (Semmes-Weinstein) was applied (10). Testing began by applying a monofilament with a bending force of 0.02 g to the skin for approximately 1 second. If this stimulus went undetected, the next higher force monofilament was applied to the same location. If application of the monofilament was detected, the next lower filament was administered. This continued until the same filament was detected for 3 applications and assigned as the touch detection threshold.

We also used a new method to assess touch detection in which subjects use a fingertip to detect small particles (bumps) of varying height (bumps detection) on a smooth surface (16). The Bumps device consists of 3 etched glass plates (11.5 cm  $\times$  15 cm), each of which contains twelve 1.5  $\times$  1.5 inch squares. Within each square, there are 5 flat circles, each of a different color. Located over one of the circles within each square is a bump that is 550  $\mu$ m in diameter. Bumps on plate 1 of the 3 plate series vary from 2.5 to 8.0  $\mu$ m in height, bumps on plate 2 vary from 8.5 to 14.0  $\mu$ m in height, whereas bumps on plate 3 range from 14.5 to 26  $\mu$ m in height. Participants began each session using bumps that ranged from 8.5 to 14  $\mu$ m. Subjects were instructed to use the index finger of the dominant hand to explore the 5 circles within each square, beginning with the upper left square and moving from left to right and top to bottom. Patients were unable to see the location of the bump and must report to the examiner that in which colored circle they perceived the bump.

The examiner recorded correct responses of participants during testing. If participants could correctly identify the location of bumps on plate 2, they progressed to plate 1 (2.5–8  $\mu$ m). Patients unable to detect the location of bumps on plate 2 were presented with plate 3 (14.5–26  $\mu$ m). The Bumps detection threshold was determined to be the smallest bump correctly identified in sequence to the next 2 higher bumps (16).

#### Grooved pegboard test

Sensorimotor function and manual dexterity were assessed with the grooved pegboard test (10, 17). Patients were instructed to fill a 5-by-5 slotted pegboard in an ordered fashion, either across the rows or down the columns. The time subjects took to complete the board for both the dominant and the nondominant hand was measured.

#### Sharpness detection threshold

Sharpness detection reflecting function in A $\delta$  fibers was determined using a weighted 30-gauge metal cylinder

(10, 18). A series of weights (8, 10, 16, 20, 32, 64, and 128 g) were applied in an ascending order to the skin for approximately 1 second. Following each application, subjects were instructed to report whether each stimulus produced the sensation of touch, pressure, sharp, or pain. The sharpness detection threshold was defined as the mean weight of the stimuli deemed "sharp" or "painful" from 3 trials that were separated by an average interval of 30 to 90 seconds.

**Thermal detection thresholds**

Warmth and heat pain thresholds were used as a measure of C-fiber function as previously described (10). Heat ramps were delivered using a 3.2 × 3.2 cm<sup>2</sup> Peltier probe applied to the skin (Medoc, Inc). The baseline temperature of the probe was set at 32°C and the temperature increased at a rate of 0.30°C/s. Subjects signaled when the probe was first perceived as warm (*warmth threshold*) and then painful (*heat threshold*). Upon determination of the heat threshold, the trial was immediately terminated and the probe returned to baseline temperature. The final threshold for each site was defined as the mean of 3 trials, which were separated by an average of 30 to 90 seconds. If a subject failed to perceive warm or heat pain, the cutoff temperature of 52°C was recorded as the default. The threshold to detection of cooling (*cool threshold*) and then cold pain (*cold pain threshold*) was similarly determined, except that the temperature was decreased at a rate of 0.50°C/s. If a subject failed to perceive cool or cold pain, the cutoff of 3°C was recorded as the default value.

**Results**

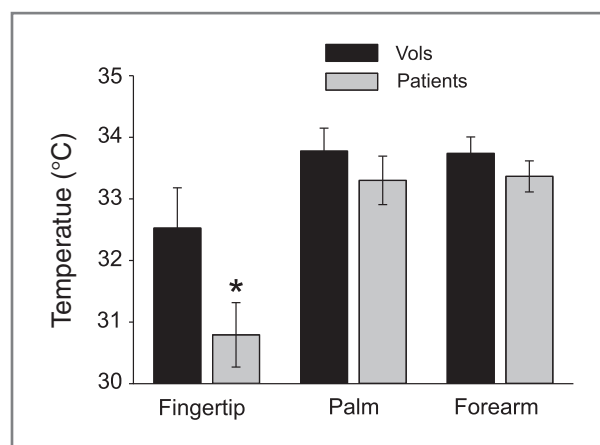
At the time of baseline testing, none of the patients or subjects complained of pain, numbness, tingling, or any other symptoms of neuropathy. There was no skin or nail abnormalities, overt gait disturbance, or difficulty with the tasks of daily living.

**Skin temperature**

The results for comparison of skin temperature are shown in Fig. 1. As shown in the pair of bars at left, skin temperature was significantly lower in the fingertips of patients with colorectal cancer than in control subjects, running on average 2.3°C cooler ( $P < 0.05$ ). This trend was also observed in the thenar eminence (center pair) and volar forearm as well (right hand pair of bars), but these were not significant.

**Touch detection thresholds**

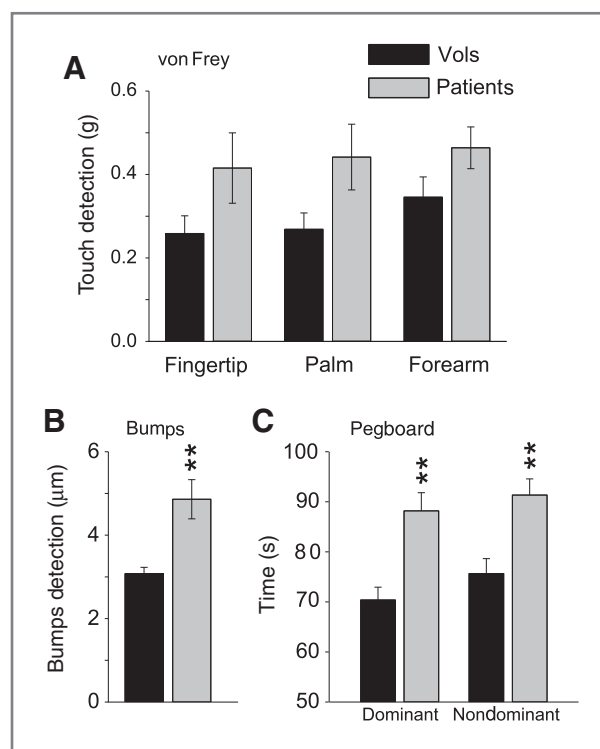
Touch detection threshold assessed using von Frey filaments at all 3 test sites did not differ between the groups, although there was a trend for the patients to have elevated thresholds (Fig. 2A). The healthy volunteer's mean von Frey detection thresholds were 0.26 ± 0.04 g at the fingertip, 0.27 ± 0.04 g at the thenar eminence, and 0.34 ± 0.04 g on the volar forearm, whereas these values for the patients were 0.42 ± 0.08 g ( $P = 0.34$ ), 0.44 ± 0.08 g ( $P = 0.08$ ), and 0.46 ± 0.05 g ( $P = 0.16$ ), respectively. Within the patient group,



**Figure 1.** The bar graph shows the mean (and SE) skin temperature (°C) in the volunteer (Vols; black bars) and the patient with colorectal cancer (gray bars) groups. The site measured is noted at the bottom of the graph. \*,  $P < 0.05$ .

males had significantly elevated thresholds in the fingertip ( $0.55 \pm 0.12$  g;  $P = 0.03$ ) when compared with female patients ( $0.23 \pm 0.04$  g).

The Bumps test clearly revealed deficits in touch sensation as indicated by significant differences in bump detection



**Figure 2.** The bar graphs show the mean (and SE) for the QST measures of large myelinated fiber functions in the volunteer (Vols; black bar) and patient with colorectal cancer (gray bars) groups. The results for the von Frey touch detection threshold (g) for each test site are labeled at the bottom of A. The results for the bumps detection threshold (µm) conducted using the index finger of the dominant hand are shown in B. Finally, the slotted pegboard times (s) for the dominant and nondominant hands are shown in C. \*\*,  $P < 0.01$ .

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thresholds between the groups (Fig. 2B). Bump detection threshold in patients threshold of ( $4.86 \pm 0.47 \mu\text{m}$ ) was 158% that of the volunteers ( $3.07 \pm 0.15 \mu\text{m}$ ,  $P < 0.001$ ). Similar to the findings for von Frey thresholds, male patients had higher thresholds for Bumps detection ( $5.78 \pm 0.82 \mu\text{m}$ ;  $P = 0.03$ ) than female patients ( $3.23 \pm 0.26 \mu\text{m}$ ).

### Grooved pegboard test

The grooved peg board is a sensorimotor task that like the von Frey and bumps detection tests is dependent on large afferent fiber inputs (and outputs). As shown in Fig. 2C, there was a significant impairment in the time it took patients to complete the grooved pegboard test, both for the dominant ( $P < 0.01$ ) and the nondominant hands ( $P < 0.01$ ). Overall, the deficit was about the same between hands with the patients requiring 17.8 seconds longer to complete the task using their dominant hand and 15.7 seconds using their nondominant hand. Male patients took longer to complete the pegboard test than females for both the dominant ( $96.34 \pm 4.96$  vs.  $73.61 \pm 2.71$ ;  $P > 0.01$ ) and the nondominant hands ( $98.72 \pm 4.23$  vs.  $78.22 \pm 3.27$ ;  $P > 0.01$ ).

### Sharpness detection threshold

Although sharpness detection thresholds for patients tended to be lower at all 3 test sites, this finding was not significant at any test site (Fig. 3). Specifically, sharpness detection thresholds for the volunteers were  $32.5 \pm 0.66$  g in the fingertip,  $33.8 \pm 0.37$  g in the thenar eminence, and  $33.7 \pm 0.26$  g at the volar forearm, whereas these values in the patient group were  $33.7 \pm 2.2$  g ( $P = 0.64$ ),  $25.7 \pm 2.3$  g ( $P = 0.59$ ), and  $17.1 \pm 1.8$  g ( $P = 0.90$ ), respectively.

### Thermal detection thresholds

Patients showed numerous deficits in the ability to detect warmth and heat pain and showed increased sensitivity to

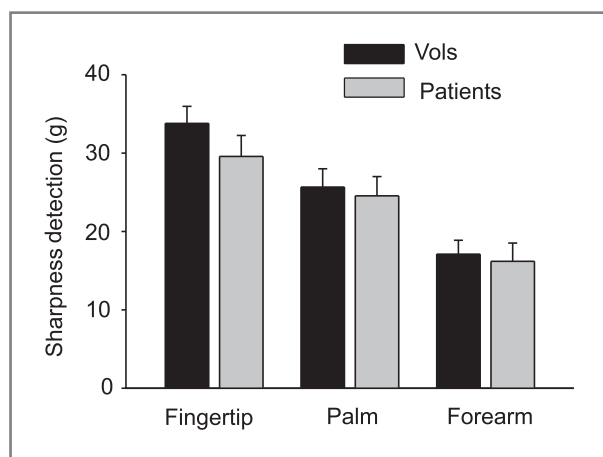


Figure 3. The bar graph shows the mean (and SE) for the sharpness detection thresholds (g) for the volunteer (Vols; black bars) and the patient with colorectal cancer (gray bars) groups. The data for each site are indicated by the labels at the bottom of the figure.

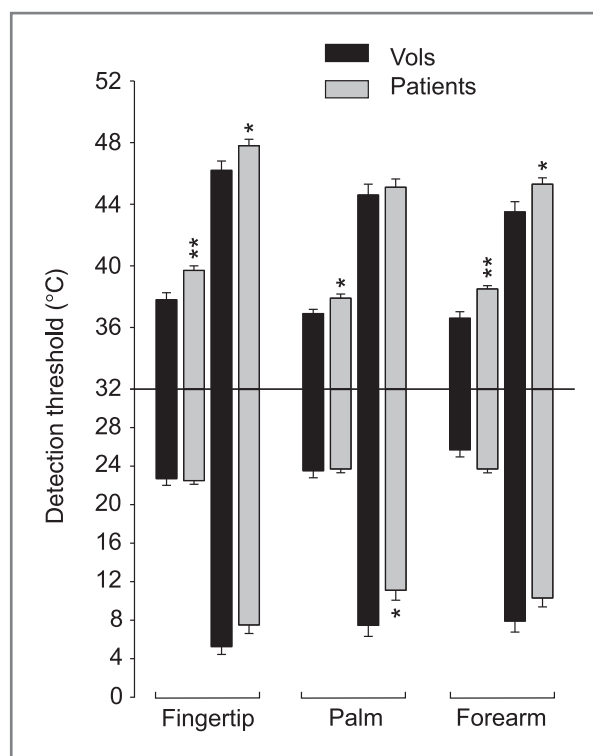


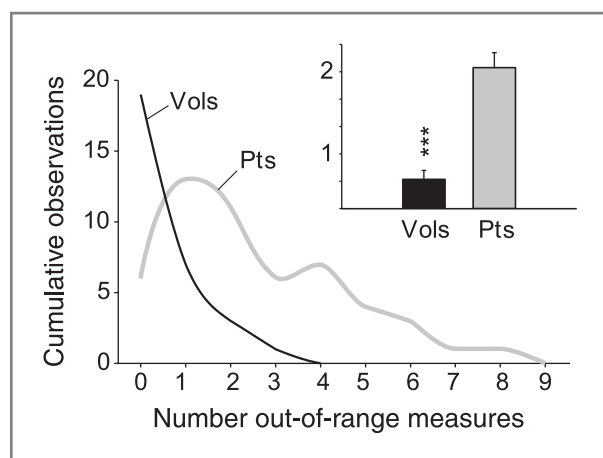
Figure 4. The upward going bar graphs show the mean (and SE) temperatures ( $^{\circ}\text{C}$ ) for the detection of Peltier probe warming from baseline at  $32^{\circ}\text{C}$  (first 2 pairs of upward going bars in each set of 4) and then the heat pain threshold (second pair of upward going sets of 4 bars) for the volunteer (Vols; black bars) and patient with colorectal cancer (gray bars) groups. The downward going bar graphs show the mean (and standard error) temperatures ( $^{\circ}\text{C}$ ) for the detection of Peltier probe cooling from a baseline at  $32^{\circ}\text{C}$  (first 2 pairs of downward going bars in each set of 4) and then the cold pain threshold (second pair of upward going sets of 4 bars) for the volunteer (black bars) and patient with colorectal cancer (gray bars) groups. The test sites are indicated at the bottom of the graph. \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ .

cold pain (Fig. 4). The ability to detect skin warming was impaired at all test sites ( $P < 0.05$ – $0.01$ ), whereas heat pain threshold was found elevated at the fingertip and the volar surface of the forearm ( $P < 0.05$ ). Although the ability to detect skin cooling did not appear to be affected, hyperalgesia to skin cooling was clearly observed with all test sites achieving significance at the palm (thenar eminence,  $P = 0.03$ ). Cold pain was described uniformly as burning. Gender differences were seen for skin warming and heat pain threshold, but not for skin cooling or cold pain threshold within the patient group. In all areas tested, males had elevated thresholds for warmth detection (fingertip and thenar eminence:  $P > 0.001$ ; volar surface of the forearm:  $P = 0.03$ ) and heat pain (fingertip and thenar eminence:  $P > 0.01$ ; volar surface of the forearm:  $P = 0.01$ ) when compared with female patients.

### General neuropathy score

An overall neuropathy score was generated for each subject by summing the number of observations where any





**Figure 5.** The line plot shows the cumulative observations of QST measures more than 2SD from the volunteer mean for each of the volunteers (Vols; black line) and the patients (Pts) with colorectal cancer (gray line). The bar graphs show the mean out-of-range QST observations per volunteer (black bar) and patients with colorectal cancer (gray bar). \*\*\*,  $P < 0.001$ .

of the measures listed above were greater than 2 SDs from the mean of the volunteer data set. The results of this analysis are shown in Fig. 5. In total, 46 of 52 patients had at least one out-of-range measure, with the mean being  $2.6 \pm 0.27$  observations. In contrast, only 6 of 31 volunteers exhibited out-of-range measures, with the mean being  $0.53 \pm 0.16$  observations ( $P < 0.001$ ). The cumulative observation plot highlights the basic premise that although this apparent disease-related subclinical neuropathy is subtle, it is also nevertheless widespread. Comparison of neuropathy score to tumor stage did not reveal a relationship between these parameters, although all patients in this study had received surgical resection of their primary tumor. There was also no correlation between neuropathy score to prior patient-reported history of alcohol or tobacco use (data not shown).

## Discussion

As reviewed above, it is widely recognized that neuropathy and neuropathic pain are often major complications in patients with cancer and may arise from a number of sources, including tumor invasion of peripheral nerves, surgical injury, treatment with radiation, or many types of chemotherapy. The main finding in this study is that subclinical deficits in sensory detection in the extremities (hands) are a surprisingly common observation in patients with colorectal cancer before undergoing chemotherapy. These deficits are most pronounced in the detection of low-threshold mechanical stimuli, sensorimotor performance, and the detection of thermal stimuli. The spatial pattern of deficits, wherein the largest deficits appear distally and are less pronounced proximally, parallels that in patients with chronic CIPN (10) found in 20% to 60% of patients following many types of cancer treatment (12, 19–21). Further in this regard, skin temperature at the fingertips

was cooler in patients than at other skin sites, which also parallels observations from patients with chronic CIPN (10). Given that patients with colorectal cancer often develop a decreased threshold to cold pain during treatment (22), it might be expected that this increased sensitivity would be detected along with other subclinical findings; however, the present data found only minor changes to cold pain detection. This may then indicate that increased sensitivity to cold pain for patients with colorectal is an occurrence that is more specific to treatment. Indeed, cold hyperalgesia is most often seen with one form of colorectal cancer treatment, oxaliplatin, than with other treatments such as cisplatin (22).

The development of a subclinical neuropathy in patients with colorectal cancer potentially has interesting implications for treatments. The most commonly used agent for early-stage colorectal cancer is oxaliplatin. As cited above, this agent is unfortunately associated with peripheral neuropathy and especially an increased sensitivity to cold. Irinotecan is another chemotherapeutic agent without neuropathic toxicities (23), but it is only used for more advanced stages of colorectal cancer and has no beneficial role in the adjuvant setting. Hence, the data presented here represent an important first step in the development of studies aimed at identifying patients at-risk so that alternative treatment paradigms with the limited agents available could be explored. Possibilities include alterations in dosing schedule and/or route of administration.

The findings from this study suggest that chemotherapeutics alone may not be the only cause of neuropathy in patients receiving chemotherapy but that the cancer disease process is also a contributing factor. Longer term studies focused on clinical outcomes in patients with normal or near-normal baseline QST function versus those with more significant sensory impairment are needed to examine the possibility that patients with preexisting neuropathy may develop more severe sensory impairment during active chemotherapy resulting in a more severe CIPN.

There are factors that can predispose a person to develop symptoms of neuropathy, including chronic alcohol use and prior cancer treatment, as well as diseases such as diabetes (24, 25). Patients with these known predisposing factors were excluded in the present study. In addition, patients were compared with an age-matched control group in an attempt to minimize other unknown co-morbid conditions. Unexpectedly, male patients had greater impairments in touch detection, grooved pegboard completion, and thermal detection than female patients. This may present an interesting avenue for future research. While it is possible that there are other unidentified factors that influenced the development of this subclinical neuropathy, these factors are not likely to have made a major contribution to the results. Overwhelmingly, the common factor that differentiated patients from control subjects here was the presence of cancer.

The mechanism by which cancer might contribute to distal neuropathy is intriguing. Our findings suggest the presence of a paraneoplastic syndrome with a neurologic

component, such that the severity had not progressed to the level that would elicit symptoms but with manifestations that caused the functional changes detected by QST. Because none of our patients were screened for neural-reactive antibodies, the possibility that a paraneoplastic syndrome may exist on a more widespread subclinical level than previously appreciated cannot be excluded. Each of the patients in this study was post-resection of their primary tumor, although many had at least some residual tumor. Thus, tumor-derived factors may contribute. Yet, there was not a correlation between cancer stage and the magnitude of sensory deficits, suggesting that initial tumor burden- and tumor-derived factors do not make a major contribution to the subclinical deficits. While it is possible that the analysis merely lacked power to detect this relationship, it is also feasible that a significant correlation was not detected because *any* level of tumor burden potentially contributes to the detected neuropathy. Regardless of cancer stage, the presence of the tumor could lead to the release of tumor-derived factors which could influence nerve functioning. For example, it is known that peripheral innervation density decreases in CIPN and distal innervation density shows marked variability between individuals (26). This potential difference did not emerge in QST variability in healthy controls but may identify patients at particular risk from disease-related neurotoxicity.

Therefore, a potential common disease-related mechanism contributing to subclinical neuropathy could be the underlying inflammatory response to the disease. The expression of several proinflammatory cytokines is increased in patients with cancer, although there is also a good deal of individual variability (27). Proinflammatory cytokines are found in cells that reside in dorsal root ganglia and in skin, such as tissue macrophages, Langerhans cells, and most especially keratinocytes. All have various degrees of proximity to the myelinated nerves that innervate touch receptors in the superficial dermis, the unmyelinated nerves to the epidermis and nerves to hair follicles. Following nerve injury, there is an increase in proinflammatory cytokines in and around peripheral nerves and in the dorsal root ganglia (28–30). Blockade of these cytokines prevents the development of both inflammatory and nerve injury–induced pain (31–37). The effects of cytokines on peripheral nerves could contribute to the clinical presentation of chemoneuropathy and account for the known risk and protective factors. Myelinating and non-myelinating Schwann cells express receptors for TNF, IFN, interleukin (IL)-1, and IL-6 and activation of these receptors leads to activation of NF- $\kappa$ B and c-jun pathways that in turn result in downregulation of myelin synthesis, increased expression of the p75 nerve growth factor receptor, dedifferentiation, and proliferation (38–41). Exposure of peripheral nerves to inflammatory cytokines thus results in extirpation of myelin and perineural swelling as observed in the early stages of Wallerian degeneration. While more work is needed to determine the differing impact that these inflammatory mediators have on myelinating versus nonmyelinating Schwann cells in regard to neuropathy presentation, the phenotypic changes out-

lined here would be expected to have more pronounced impact on A $\beta$  and A $\delta$  fiber function that is dependent on myelination, but less so on C-fibers. This would thereby lead to findings similar to those observed in patients here and those with CIPN. Although the authors are not aware of any published work investigating peripheral innervation in subclinical neuropathy, we have documented loss of both epidermal nerve fibers and Meissner corpuscle innervation in patients with CIPN (10, 42). Therefore, while our patients with subclinical neuropathy presented with similar deficits to those with CIPN, the contributions of demyelination remain to be determined.

A second finding in this study is that a newly used QST, the *Bumps* detection test, was proven to be a keenly sensitive tool for detecting subtle deficits in touch sensation. Performance of the healthy volunteers on the bumps tests was nearly identical to that reported in a previous study (16). The degree of deficit observed in the patient population in the present study was intermediate to the previously studied patients with confirmed diagnoses of clinical neuropathy (16). In the present study, the Bumps test was more sensitive than the more traditionally used von Frey monofilament test. While patients showed significantly impaired Bumps thresholds when compared with control subjects, they did not have significant impairments in von Frey detection. Taken together, these results indicate that the Bumps test provides a new, and perhaps superior, avenue for QST methodology. The Bumps test is completed by the patient, with minimal participation by the test administrator. In contrast, von Frey monofilaments require more consistent influence from a test administrator, especially in terms of application of the monofilament. These and other subtle differences in the use of these methods may influence the improved sensitivity of the Bumps test. Furthermore, previous work showed that bumps detection threshold at the fingertip was strongly correlated to the density of Meissner corpuscles (16). This suggests that the deficits in QST performance in the patients with colorectal cancer may be associated with loss of peripheral innervation density. Importantly, pronounced loss of innervation density has been found both in patients with chronic CIPN (10, 42) and in experimental animals treated with chemotherapeutics (43–45). Loss of epidermal nerve fiber density as well as the development of the behavioral phenotype of CIPN in experimental animals is prevented with the proinflammatory cytokine suppressant minocycline, again suggesting that this may be an important component contributing to the subclinical neuropathy observed here as well as the potential later development of CIPN.

In conclusion, almost all patients with colorectal cancer exhibited subclinical sensory dysfunction suggestive of mild peripheral neuropathy before starting chemotherapy, although quantitative morphologic studies are needed to confirm this possibility. Importantly, the Bumps test was more sensitive than von Frey monofilaments in detecting impaired touch sensation and may be a useful tool for diagnosing early-stage neuropathy. Additional studies are needed to determine whether patients with mild,

subclinical sensory dysfunction are at a greater risk for developing clinically evident neuropathy during chemotherapy and persistent neuropathic sensory loss and pain following chemotherapy.

### Disclosure of Potential Conflicts of Interest

C.S. Cleeland has a commercial research grant from AstraZeneca and is a consultant for Bristol Myers Squibb. W.R. Kennedy's son holds a financial and business interest in Neuro Devices, Inc., which holds the patent to the "Bumps" device used in this study. This relationship has been reviewed and managed by the University of Minnesota in accordance with its conflict of interest policies. The other authors disclosed no potential conflicts of interest.

### Authors' Contributions

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