Chemotherapy-Induced Peripheral Neurotoxicity in Cancer Survivors: Predictors of Long-Term Patient Outcomes

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ABSTRACT

Background: Chemotherapy-induced peripheral neurotoxicity (CIPN) is a major adverse effect of cancer treatment. However, its impact remains poorly understood. This study aimed to investigate the impact associated with CIPN on the lives of cancer survivors. **Patients and Methods:** A volunteer sample of 986 individuals who had received neurotoxic chemotherapy completed an anonymous, cross-sectional survey. Outcomes assessed included CIPN symptoms, pain, neuropathic pain, quality of life (QoL), physical activity, and comorbid health conditions via the Self-Administered Comorbidity Questionnaire. **Results:** Respondents had a mean age of 58 years (SD, 10.7), and 83.2% were female. Most were treated for breast (58.9%) or colorectal cancer (13.5%); had received docetaxel (32.7%), paclitaxel (31.6%), or oxaliplatin (12.5%); and had completed treatment 3.6 ± 3.5 years previously. We found that 76.5% of respondents reported current CIPN. Respondents reporting severe CIPN had poorer QoL, more comorbidities, and higher body mass index, and more often received multiple neurotoxic chemotherapies than those with mild CIPN. Respondents who completed the survey ≤1 year after completing chemotherapy did not differ in reported CIPN or pain compared with respondents who completed chemotherapy ≥6 years earlier. However, respondents who completed chemotherapy ≥6 years earlier reported better QoL. Multivariable linear regression analyses revealed predictors of CIPN severity as follows: $F(7, 874) = 64.67$; $P<.001$; $R^2 = 0.34$, including pain ($\beta = -0.36$; $P<.001$), burning pain ($\beta = 0.25$; $P<.001$), sex (male sex associated with greater CIPN: $\beta = 0.14$; $P<.001$), years since completing chemotherapy (shorter time associated with greater CIPN; $\beta = -0.10$; $P<.001$), age ($\beta = 0.80$; $P=.006$), number of comorbid conditions ($\beta = 0.07$; $P=.02$), and body mass index ($\beta = 0.07$; $P=.02$). **Conclusions:** Respondents with a high CIPN symptom burden experienced poorer general health and QoL. Improvements in CIPN may be more likely soon after treatment. However, improvements in QoL may occur over time in those with chronic symptoms. CIPN seems to have lasting impacts on cancer survivors, and understanding risk factors is important to enable the design of further preventive and therapeutic management strategies.

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Background

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a major adverse effect (AE) of cancer treatment that can lead to early treatment cessation, lasting symptoms, and functional difficulties. Commonly used chemotherapies, including taxanes, platinum compounds, vinca alkaloids, bortezomib, and thalidomide, produce CIPN in a significant proportion of patients. With advances in diagnosis and treatment, increasing numbers of patients experience long-term survival.[1] These improvements accompany an increased need to understand the impact of neurotoxic chemotherapies on cancer survivors' lives.

CIPN is characterized by tingling, numbness, and pain in the extremities of the limbs, leading to problems with walking, balance, and fine motor function.[2] It is a major complaint across a range of cancers and neurotoxic agents,[3–6] with a significant impact on quality of life (QoL).[3,7,8] Although studies have investigated the development of chronic CIPN symptoms and their impact over time,[9–12] there is a lack of complete understanding regarding the trajectory of CIPN over the long term and the lasting impact this has on cancer survivors.

This large-scale survey focused on CIPN as a key AE of neurotoxic chemotherapy, using validated measures to assess CIPN, QoL, and physical activity. We aimed to investigate the impacts associated with CIPN symptom burden on the lives of cancer survivors across a range of domains, examining symptoms over time and interactions with other treatment AEs, lifestyle factors, and long-term QoL.

Patients and Methods

We conducted a cross-sectional anonymous online survey of Australian cancer survivors who had received neurotoxic chemotherapy as treatment for cancer. There was no exclusion regarding when participants completed treatment, and patients currently receiving chemotherapy were eligible to participate. Participants were


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recruited between May 2016 and March 2019 via cancer research registers, social media, oncology waiting areas, and websites and newsletters of Australian cancer support and health advocacy organizations. Human research ethics approval was granted by the University of New South Wales Human Research Advisory Panel and the South Eastern Sydney Local Health District Human Research Ethics Committee.

The survey was developed using KeySurvey (WorldAPP; http://www.keysurvey.com). Participants were asked (1) whether they received chemotherapy that a health professional had indicated could cause tingling, numbness, or pins and needles in hands and feet, and (2) to select the chemotherapy they received from a list of neurotoxic agents. Participants were excluded if they answered "no" to the first question *and* stated that they had not received any chemotherapies listed; this combination indicated that they had not received neurotoxic chemotherapy treatment. Responses of excluded participants were not recorded by the survey platform.

Survey Content

The survey took approximately 35 minutes to complete, including demographics, cancer details, other cancer-related AEs, and validated measures outlined as follows.

CIPN symptoms over the past week were assessed using the validated 11-item Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity questionnaire [FACT/GOG-NTX],[13] with scores ranging from 0 to 44 and higher scores indicating higher levels of symptoms. Neuropathic pain was assessed with the Douleur Neuropathique en 4 (DN4) questionnaire,[14] with scores ranging from 0 to 7 and higher scores indicating worsening symptoms. An 11-point numeric pain rating scale (NPRS)[15] assessed the most intense pain over the last 24 hours (0 = no pain; 10 = worst possible pain).

QoL was assessed using the validated RAND 36-Item Short Form Survey (SF-36)[16] across 8 dimensions: physical functioning, bodily pain, role limitations due to physical health problems, personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health. Subscale scores range from 0 to 100, and total scores for the measure range from 0 to 800, with higher scores indicating more optimal functioning.[17]

Comorbid health conditions were assessed using a list of conditions from the Self-Administered Comorbidity Questionnaire,[18] including heart disease, high blood pressure, lung disease, diabetes, ulcer/stomach disease, kidney disease, liver disease, anemia/other blood disease, depression, osteoarthritis, rheumatoid arthritis, or back pain. A free-text field allowed the reporting of additional conditions.

The validated International Physical Activity Questionnaire–Short Form[19] was used to assess physical activity during the past week in metabolic equivalent (MET) minutes, via time spent performing low-, moderate-, and vigorous-intensity activity. Respondents who reported meeting Australian government guidelines for physical activity (600 MET-minutes/week, equivalent to 150 minutes of moderate intensity or 75 minutes of vigorous activity)[20] were compared with those whose activity failed to meet the guidelines.

Respondents ranked the impact of treatment AEs on their lives, including fatigue, pain, neuropathy, nausea/vomiting, anxiety, depression, insomnia, diarrhea, constipation, anemia, changes in sexual function, and infertility. A free-text field allowed the reporting of additional AEs. Respondents ranked as many AEs as were relevant, with 1 indicating the greatest impact.

Statistical Analyses

Statistical analyses were completed using SPSS Statistics version 23.0 (IBM Corp). Descriptive statistics were calculated for demographic and clinical characteristics. For the comparison of respondents reporting current CIPN symptoms to those without symptoms, *t* tests were used for continuous variables and chi-square tests were used for categorical variables. Free-text responses were coded numerically such that they could be included in the analyses. Available case analyses were used, with pairwise deletion used to deal with missing data.

Analyses were conducted comparing respondents reporting high levels of CIPN symptoms (upper-tertile FACT/GOG-NTX; scoring $\geq$17) and low levels of CIPN symptoms (lowest-tertile FACT/GOG-NTX; scoring $\leq$8). Analyses also compared respondents who completed the survey within a year of finishing chemotherapy treatment with those who completed chemotherapy $\geq$6 years earlier.

Multivariable linear regression analyses were performed to investigate associations between CIPN symptoms, clinical characteristics (years since completing chemotherapy, number of comorbid conditions, body mass index [BMI], general pain, burning pain), and sociodemographic characteristics (age, sex). Additional multivariable analyses were performed examining the relationships between QoL, CIPN, and physical activity, corrected for background variables including age, sex, years since completing chemotherapy, number of comorbid conditions, and BMI.

Results

Cancer Survivor Demographic and Clinical Characteristics

Responses were received from 986 eligible respondents, with demographic and clinical characteristics presented in Table 1 and supplemental eTable 1 (available with this article at JNCCN.org). Results are presented as mean ± standard deviation unless otherwise specified.

Respondents had a mean age of 58 ± 10.7 years, and most were female (n=820; 83.2%).

Breast cancer (n=581; 58.9%), colorectal cancer (n=133; 13.5%), and multiple myeloma (n=108; 11.0%) were the most commonly reported cancer types. Reported chemotherapies corresponded to treatments for these cancers: taxanes (docetaxel: n=322 [32.7%]; paclitaxel: n=312 [31.6%]), platinum-based chemotherapies (oxaliplatin: n=123 [12.5%]; cisplatin: n=53 [5.4%]), thalidomide (n=87; 8.8%), and bortezomib (n=82; 8.3%).

One-quarter of respondents (n=247; 25.1%) reported no comorbid health conditions, 30.1% (n=297) reported 1, 20.5% (n=202) reported 2, and 24.3% (n=240) reported ≥3. Comorbid conditions (supplemental eTable 1) included osteoarthritis (n=264; 26.8%), back pain (n=262; 26.6%), high blood pressure (n=226; 22.9%), depression (n=172; 17.4%), and diabetes (n=68; 6.9%).

Burden of Neurotoxicity in Cancer Survivors

Most respondents reported experiencing CIPN during (n=768; 77.9%) and after (n=785; 79.6%) chemotherapy. Most respondents (n=754; 76.5%) reported current CIPN, and 24.1% (n=238) reporting current symptoms indicated that these had not improved since chemotherapy completion. Participants reported experiencing CIPN symptoms for a duration of 3.6 ± 3.5 years.

More respondents with current CIPN reported symptoms affecting their lower limbs (feet: n=689 [91.3%]; hands: n=566 [75.1%]). Accordingly, 28.7% (n=214) of respondents with current CIPN reported moderate-severe difficulties with walking, and 22.7% (n=170) reported moderate-severe difficulties with hand function.

The validated FACT/GOG-NTX questionnaire captured differences in CIPN between respondents with and without current symptoms. Respondents reporting current CIPN had a mean score of 15.8 ± 8.3, whereas respondents without current CIPN had a mean score of 6.0 ± 5.4 ($P<.001$). Similarly, respondents with current CIPN had a mean DN4 score of 2.8 ± 2.2, and those without CIPN had a mean score of 0.8 ± 1.3 ($P<.001$). Respondents with current CIPN reported a mean NPRS score of 4.45 ± 2.57, and those without CIPN reported a mean score of 3.36 ± 2.28 ($P<.001$). Each comparison indicated higher symptom levels in the current CIPN group.

Comparing female and male respondents, men were older (mean age, 63.0 ± 12.6 years vs 57.9 ± 10.1 years for women; $P<.001$) and reported a higher CIPN burden (FACT/GOG-NTX scores: 16.7 ± 8.8 vs 12.9 ± 8.6 for women; $P<.001$). No difference was observed in time since completing chemotherapy, number of comorbid conditions, burning pain, QoL, or BMI.

Participants ranked the impact of cancer treatment AEs on their lives. The largest number of respondents rated fatigue as the AE with the greatest impact (n=423; 42.9% rating it highest). CIPN was most commonly rated as having the second-greatest impact (n=270; 27.4%), followed by pain (n=122; 12.4%), insomnia (n=96; 9.7%), and changes in sexual function (n=95; 9.6%).

Table 1. Demographic and Clinical Characteristics

Characteristic	n (%)
Age, mean (SD), y	58 (10.7)
20–39	41 (4.2)
40–59	447 (45.3)
60–79	479 (48.6)
≥80	13 (1.3)
Not reported	6 (0.6)
Sex	
Female	820 (83.2)
Male	163 (16.5)
Cancer type	
Breast	581 (58.9)
Colorectal	133 (13.5)
Multiple myeloma	108 (11.0)
Ovarian	41 (4.2)
Lymphoma	35 (3.5)
Other	282 (28.6)
Years since completing treatment (SD)	3.6 (3.9)
Currently on chemotherapy	128 (13.0)
Completed chemotherapy ≤1 y ago	262 (26.9)
Completed chemotherapy 2–5 y ago	358 (36.3)
Completed chemotherapy ≥6 y ago	233 (23.7)
Stage at diagnosis	
I	160 (16.2)
II	271 (27.5)
III	341 (31.8)
IV	85 (8.6)
Unknown	153 (15.5)
Neurotoxic chemotherapy type	
Docetaxel	322 (32.7)
Paclitaxel	312 (31.6)
Oxaliplatin	123 (12.5)
Thalidomide	87 (8.8)
Bortezomib	82 (8.3)
Cisplatin	53 (5.4)
Other	113 (11.5)
Unknown	102 (10.3)
Other cancer treatments received	
Radiotherapy	591 (59.9)
Surgery	832 (83.5)

A minority of respondents had tried these treatment for CIPN (n=168; 16.9%). Treatments included pregabalin (n=83; 8.4%), prescription/nonprescription analgesic medication (n=65; 6.6%), exercise (n=51; 5.2%), and acupuncture (n=47; 4.7%). Low rates of treatment reflect the current lack of recommended treatments. Use of duloxetine, the only treatment with a moderate recommendation in the ASCO guidelines,[21,22] was reported by 1.5% (n=15) of respondents.

Long-Term Outcomes in Survivors With Severe Neurotoxicity

Comparing respondents reporting high (upper-tertile FACT/GOG-NTX) versus low (lowest-tertile FACT/GOG-NTX) levels of CIPN symptoms, respondents who reported severe CIPN had poorer QoL scores on all SF-36 subscales ($P<.001$; Table 2, Figure 1A, supplemental eTable 2). Higher general and neuropathic pain were reported by respondents with high CIPN ($P<.001$; Figure 1B, C). Respondents reporting severe CIPN were older ($P<.001$), had a higher BMI ($P<.001$; Figure 1D), and had more comorbid conditions than those in the mild CIPN group ($P<.001$; Table 2). Respondents reporting severe CIPN completed chemotherapy more recently than those with mild CIPN ($P=.024$). Respondents with severe CIPN more often reported receiving multiple neurotoxic chemotherapies (χ^2 [1, n=672] = 5.5; $P=.019$) and were less likely to meet physical activity targets (χ^2 [2, n=672] = 24.1; $P<.001$).

Trajectory of Neurotoxicity

Respondents who completed the survey ≤1 year after completing chemotherapy (n=265; 26.9%) were younger and reported fewer comorbid conditions than those who completed the survey ≥6 years after treatment completion (n=233 [23.7%]; $P<.001$) (Table 3, Figure 2A, supplemental eTable 3). These groups did not differ in CIPN symptoms via FACT/GOG-NTX scores or pain levels via NPRS (Figure 2B, C). Of the respondents who completed chemotherapy within a year of taking the survey, 25.3% (n=65) reported no improvement in CIPN symptoms since finishing treatment, whereas 30.1% (n=66) who completed treatment ≥6 years earlier reported no improvement.

Compared with those who completed treatment recently, respondents who completed chemotherapy ≥6 years earlier had better total QoL (Table 3, Figure 2D) and subscale scores assessing physical, emotional, and social functioning and energy (supplemental eTable 4).

Physical Activity

Most respondents self-reported meeting physical activity guidelines (n=787; 78.9%). These respondents showed better QoL across their total score ($P<.001$; Table 3) and all subscales (supplemental eTable 5). Those meeting the guidelines reported a lower CIPN via FACT/GOG-NTX ($P<.001$), lower BMI ($P<.001$), longer duration of CIPN ($P=.009$), and longer time since chemotherapy completion than those who did not meet the exercise guidelines ($P=.004$). There was no difference between groups in age or number of comorbidities.

Predictors of Long-Term Patient Outcomes

Multivariable linear regression analyses were undertaken to identify predictors of severity of CIPN via FACT/GOG-NTX [$F(7, 874) = 64.67$; $P<.001$; $R^2 = 0.34$]. Variables adding significantly to the predictors included pain (NPRS; $\beta = -0.36$; $P<.001$), burning pain ($\beta = 0.25$; $P<.001$), sex (male sex associated with greater CIPN: $\beta = 0.14$; $P<.001$), years since completing chemotherapy (shorter time associated with greater CIPN: $\beta = -0.10$; $P<.001$), age ($\beta = 0.80$; $P=.006$), number of comorbid conditions ($\beta = 0.07$; $P=.02$), and BMI ($\beta = 0.07$; $P=.02$).

In multivariable linear regression analyses on QoL scores [$F(7, 903) = 103.7$; $P<.001$; $R^2 = 0.45$], significant predictor variables included comorbid conditions

Table 2. Outcomes and Characteristics in Respondents Reporting High Versus Low CIPN

	High CIPN		Low CIPN		
Measure	n	Mean (SD)	n	Mean (SD)	*P* Value
Age	333	59.6 (10.8)	335	56.4 (10.3)	<.001
Number of comorbid health conditions	337	2.0 (1.6)	335	1.2 (1.2)	<.001
Years since completing chemotherapy	326	3.2 (3.1)	325	3.8 (4.0)	.024
General pain (NPRS; score range, 0–10)	336	5.7 (2.5)	334	2.9 (2.0)	<.001
Burning pain (DN4 item 1)	313	0.6 (0.5)	312	0.2 (0.4)	<.001
QoL (SF-36: total score; range, 0–800)	337	402.1 (151.2)	335	595.6 (126.1)	<.001
BMI	326	29.1 (6.9)	327	26.9 (5.3)	<.001

Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neurotoxicity; DN4, Douleur Neuropathique en 4; NPRS, numeric pain rating scale; QoL, quality of life; SF-36, RAND 36-Item Short-Form Survey.

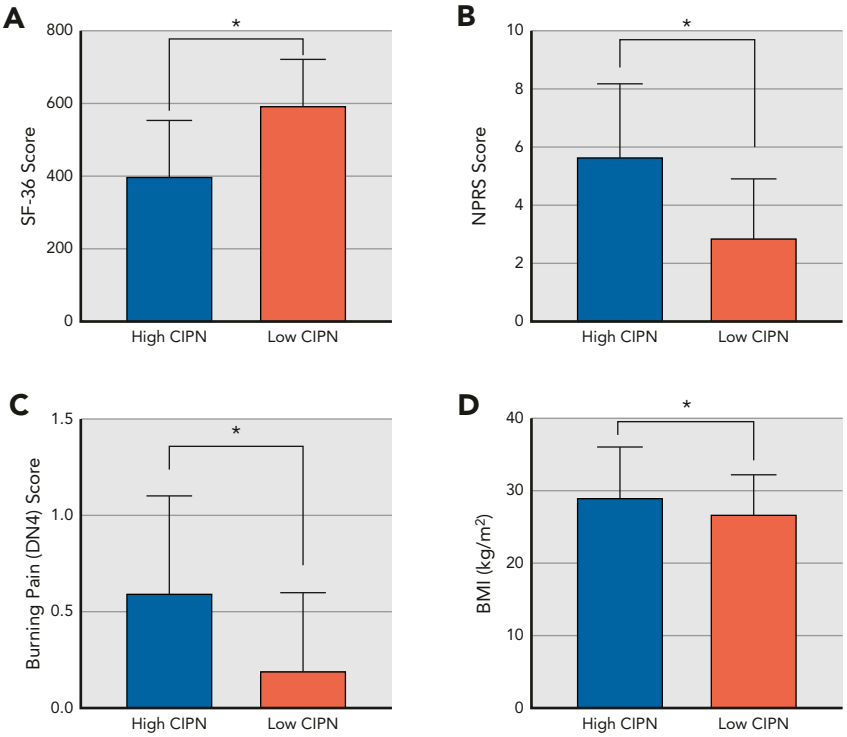

Figure 1. Effect of CIPN severity: (A) QoL score via SF-36, (B) pain level via NPRS, (C) burning pain level via DN4, and (D) BMI. Mean scores for each measure are presented with error bars representing standard deviations.
Abbreviations: CIPN, chemotherapy-induced peripheral neurotoxicity; DN4, Douleur Neuropathique en 4; NPRS, numeric pain rating scale; QoL, quality of life; SF-36, RAND 36-Item Short Form Survey.
*Significant difference, $P<.001$.

($\beta = -33.19$; $P<.001$), CIPN symptoms (FACT/GOG-NTX; $\beta = -8.76$; $P<.001$), years since completing chemotherapy ($\beta = 5.75$; $P<.001$), age ($\beta = 3.13$; $P<.001$), and physical activity ($\beta = 0.01$; $P<.001$).

Discussion

As one of the largest surveys focusing on the self-reported impact of CIPN in cancer survivors, our results reinforce the association of CIPN with lasting impacts across a range of domains. CIPN was reported by the majority of respondents and was associated with functional difficulties and reduced QoL. Multivariable analyses found associations between CIPN severity, pain, and comorbid health conditions. Although CIPN and pain severity persisted over time, respondents who completed chemotherapy a longer time beforehand reported better QoL.

Respondents experiencing high levels of CIPN symptoms more often reported receiving multiple neurotoxic chemotherapies, experiencing more comorbidities, and having a higher BMI than those with low CIPN. Although it is unclear whether higher BMI preceded the development of CIPN, CIPN was associated with multiple negative health impacts, potentially suggesting that respondents with severe CIPN experience poorer health

Table 3. Outcomes and Characteristics Based on Adherence to Physical Activity Guidelines

	Respondents Meeting Guidelines		Respondents Not Meeting Guidelines		
Measure	n	Mean (SD)	n	Mean (SD)	*P* Value
CIPN burden (FACT/GOG-NTX total score; range, 0–44)	782	12.7 (8.3)	153	16.4 (9.4)	<.001
Years since completing chemotherapy	764	3.7 (4.0)	143	2.7 (3.5)	.004
Duration of CIPN symptoms (y)	655	3.7 (3.6)	129	3.0 (2.9)	.009
QoL (SF-36: total score; range, 0–800)	787	524.9 (152.6)	153	407.4 (163.3)	<.001
BMI	762	27.1 (5.9)	150	29.8 (6.2)	<.001

Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neurotoxicity; FACT/GOG-NTX, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity; QoL, quality of life; SF-36, RAND 36-Item Short-Form Survey.

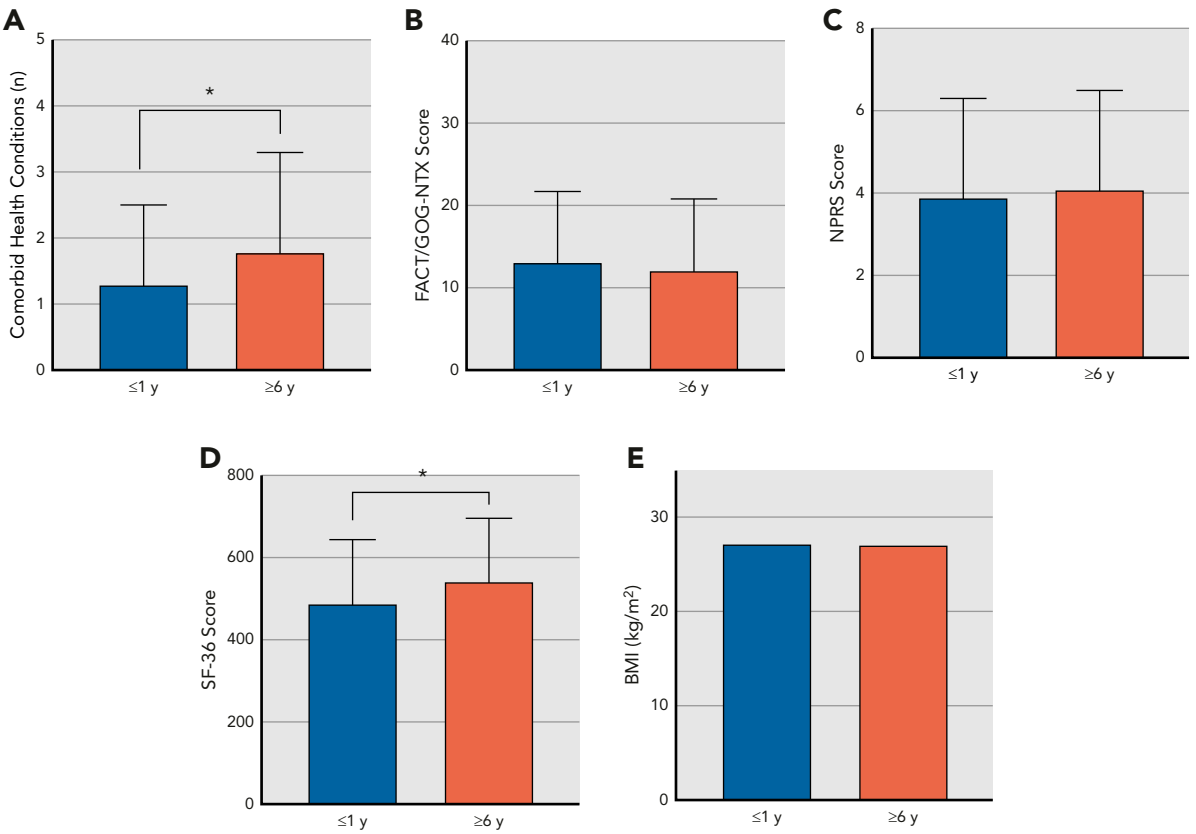

Figure 2. Symptom trajectory in respondents reporting CIPN: (A) number of comorbid health conditions, (B) FACT/GOG-NTX score, (C) pain level via NPRS, (D) QoL score via SF-36, and (E) BMI. Mean scores for each measure are presented with error bars representing standard deviations.
Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neurotoxicity; FACT/GOG-NTX, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity; NPRS, numeric pain rating scale; QoL, quality of life; SF-36, RAND 36-Item Short Form Survey.
*Significant difference, $P<.001$.

more generally. This suggestion is supported by previous research indicating poorer health in patients with CIPN, via greater symptom burden, comorbidities, and disability.[3,9] Higher overall pain reported by respondents with severe CIPN highlights the need to better understand the relationship between pain and neuropathy.

CIPN and pain severity did not differ between respondents who completed chemotherapy recently and those who completed chemotherapy ≥6 years earlier. Despite this finding, better QoL was reported by those who completed chemotherapy ≥6 years earlier. CIPN symptom improvements may be more likely to occur soon after treatment, with symptom levels remaining stable for a proportion of patients with chronic symptoms. However, improvements in QoL with time suggest that a contributing factor may be adaptation to symptoms, with increasing resilience enabling improved QoL despite ongoing symptoms. Although adaptation to CIPN symptoms is challenging to empirically examine, qualitative interview studies have revealed potential coping and adaptive strategies that may be used by patients over time.[23,24]

Further evidence of the relationship between general health, CIPN, and QoL was seen via multiple regression analyses, where predictors of CIPN severity included pain and the number of comorbid conditions. Similarly, the greatest predictors of QoL were the number of comorbid conditions and CIPN symptoms. Both factors predicted decreased QoL, further indicating the role of physical health in maintaining QoL in cancer survivors.

These results are in line with previous survey-based research finding CIPN to be a major complaint in cancer survivors. In a survey of 609 patients who received neurotoxic chemotherapy, 68.8% reported experiencing CIPN.[3] An online survey found CIPN in one-third of 1,506 patients with breast cancer who received chemotherapy[5] and in 78% of 1,360 women with ovarian cancer 2.3 years since completing chemotherapy.[6] Similarly, 52% of 1,182 patients with acute myeloid leukemia reported CIPN 7.3 years postdiagnosis.[4]

Furthermore, our results support previous studies suggesting that CIPN has significant impacts on QoL. Surveys of survivors of colorectal cancer found decreased QoL in respondents with CIPN,[7,8] and respondents with severe CIPN have been found to be more likely to experience anxiety and depression.[25] In patients with ovarian cancer, those with CIPN have reported lower functioning and greater health-related worry.[26] In a survey of patients

with breast cancer, CIPN symptoms were considered a severe burden by two-thirds of the affected patients.[5] In addition, a survey covering various cancer types found patients reporting neurotoxicity reported higher symptom burden and stress, and poorer QoL.[3]

Our study also suggests the positive effects of physical activity on CIPN, with respondents who met the physical activity guidelines reporting lower levels of CIPN. Respondents who reported meeting the guidelines also reported a longer time since completing chemotherapy. However, it is unclear whether this reduced CIPN resulted from exercise reducing their symptoms or from respondents with higher symptom levels being less able to exercise. Previous studies have found higher CIPN in respondents who do not meet recommended physical activity levels,[8] and moderate-vigorous physical activity has been associated with lower CIPN in patients treated using taxanes.[27] A number of studies have suggested a promising role for exercise in CIPN,[28–30] and further research involving exercise programs for cancer survivors is required to clarify the relationship between physical activity and CIPN. Regardless, higher QoL and lower BMI of respondents meeting the activity guidelines indicate the positive effects of physical activity on well-being in cancer survivors.

A strength of our study is its size and the comprehensive nature of the measures used. Although patient-reported outcomes are increasingly used to inform practice,[31] this survey was self-reported and clinical details were not confirmed via medical records. Some respondents were not aware of the details of their diagnosis or treatment (eg, 10.3% did not know the name of their chemotherapy and 15.5% did not know their cancer stage). Cancer survivors may have gaps in knowledge or recall about treatment details and may provide incorrect information.[32] This information gap could have contributed to selection bias because patients who were aware of treatment details or who remembered being informed of potential treatment AEs may have been less likely to have been screened out of the survey. Respondents who had accurate recall may have differed systematically from those who did not have accurate recall (previous research has found that accuracy of recall may decrease with age and vary across cancer types[32]), leading to potential differences in rates of survey completion between these 2 groups. Self-reported physical activity can also provide differing estimates to objective recording,[33] tending to overestimate activity.[34] Research using objective measures of activity is needed to confirm these results.

Participants were recruited primarily via cancer support organizations and may have differed systematically from less-engaged cancer survivors. In addition, individuals with current CIPN may have been more likely to respond than those without symptoms, potentially leading to selection bias. Accordingly, results must be interpreted with a high degree of caution regarding the representativeness of the sample, and inferences cannot be made regarding the overall population incidence or severity of CIPN. The largest respondent group was women with breast cancer, which was expected because breast cancer is one of the most commonly diagnosed cancers in Australia, with one of the highest survival rates[35] among cancers treated using neurotoxic chemotherapy. However, this finding limited our ability to investigate the relative impact of different neurotoxic chemotherapies.

Conclusions

Results of our study indicate that CIPN symptoms are associated with impacts on QoL in the increasing population of cancer survivors. Respondents with severe CIPN were older and had a higher BMI and more comorbidities, suggesting reduced general health in this cohort. The association between physical activity and reduced CIPN symptoms warrants prospective examination to determine the role of exercise in symptom management. Although chronic CIPN may not reduce in severity over time, patients may adapt to chronic neuropathic symptoms and experience improved QoL. Understanding the risk factors related to persistent CIPN is important to enable the design of preventive strategies. There is a current lack of effective preventive measures for CIPN. Dose modification is the only preventive strategy recommended by ASCO guidelines,[22] after the assessment of the risks and benefits of neurotoxic treatment (including consideration of conditions that may predispose a patient toward developing CIPN, such as diabetes or a family history of neuropathy). In addition, duloxetine is currently the only treatment for CIPN with a moderate recommendation. Other therapeutic management strategies have been trialed, including exercise, acupuncture, scrambler therapy, gabapentin or pregabalin, and topical gel treatments, but there is currently a lack of confirmatory evidence for their efficacy.[22] Effective assessment, prevention, and treatment strategies are needed to improve QoL and decrease the considerable impact that CIPN has on the lives of cancer survivors.

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Supplemental online content for:

Chemotherapy-Induced Peripheral Neurotoxicity in Cancer Survivors: Predictors of Long-Term Patient Outcomes

Eva Battaglini, PhD; David Goldstein, MBBS; Peter Grimison, PhD, MBBS; Susan McCullough; Phil Mendoza-Jones; and Susanna B. Park, PhD

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eTable 1. Demographic Characteristics

Characteristic	n (%)
Education level	
No school certificate	13 (1.3)
Secondary school	179 (18.2)
Trade/Apprenticeship	49 (5)
Vocational college	235 (23.8)
Bachelor's degree	293 (29.7)
Postgraduate degree	215 (21.8)
Marital status	
Never married	86 (8.7)
Married/de Facto	733 (74.3)
Divorced/Separated	122 (12.4)
Widowed	40 (4.1)
Current employment status	
Full time	193 (19.6)
Part time	231 (23.4)
Studying	9 (0.9)
Sick leave	37 (3.8)
Retired	364 (36.9)
Not working due to disability	69 (7)
Not employed, looking for work	22 (2.2)
Not employed, not looking for work	43 (4.4)
Language spoken at home	
English only	912 (92.5)
Other	62 (6.3)
Comorbid health conditions	
Osteoarthritis	264 (26.8)
Back pain	262 (26.6)
High blood pressure	226 (22.9)
Depression	172 (17.4)
Diabetes	68 (6.9)
Anemia	65 (6.6)
Heart disease	60 (6.1)
Rheumatoid arthritis	36 (3.7)
Thyroid disorder	35 (3.5)
Liver disease	26 (2.6)
Lung disease	26 (2.6)
High cholesterol	25 (2.5)
Kidney disease	23 (2.3)
Ulcer or stomach disease	21 (2.1)

eTable 2. Outcomes and Characteristics in Respondents Reporting High Versus Low CIPN

	Respondents Reporting High CIPN		Respondents Reporting Low CIPN		
SF-36 Measure	n	Mean (SD)	n	Mean (SD)	*P* Value
Physical functioning	337	54.6 (24.7)	335	82.3 (18.2)	<.001
Role limitations due to physical health	334	29.3 (36.2)	334	73.1 (37.6)	<.001
Role limitations due to emotional problems	336	55.4 (42.4)	335	81.0 (31.5)	<.001
Energy/Fatigue	337	34.5 (20.4)	334	55.1 (19.2)	<.001
Emotional well-being	337	66.3 (19.2)	334	76.7 (16.0)	<.001
Social functioning	337	65.4 (24.3)	335	84.5 (18.4)	<.001
Pain	337	51.2 (25.2)	335	77.1 (19.6)	<.001
General health	337	45.1 (22.3)	335	65.9 (19.8)	<.001

Abbreviations: CIPN, chemotherapy-induced peripheral neurotoxicity; SF-36, RAND 36-Item Short-Form Survey (subscale score range, 0–100).

eTable 3. Outcomes and Characteristics in Respondents ≤1 and ≥6 Years Posttreatment

	≤1 Year Posttreatment		≥6 Years Posttreatment		
Measure	n	Mean (SD)	n	Mean (SD)	*P* Value
CIPN burden (FACT/GOG-NTX total score; range, 0–44)	263	13.2 (8.5)	233	12.2 (8.6)	.19
Age	264	55.9 (11.4)	231	61.0 (10.1)	<.001
Number of comorbid health conditions	265	1.3 (1.2)	233	1.8 (1.5)	<.001
General pain (NPRS; score range, 0–10)	265	3.9 (2.4)	231	4.1 (2.4)	.36
Burning pain (DN4 item 1)	245	0.3 (0.5)	221	0.4 (0.5)	.04
QoL (SF-36: total score; range, 0–800)	265	490.6 (154.1)	233	544.0 (153.1)	<.001
BMI	254	27.2 (5.5)	227	27.1 (5.2)	.77

Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neurotoxicity; DN4, Douleur Neuropathique en 4; FACT/GOG-NTX, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity; NPRS, numeric pain rating scale; QoL, quality of life; SF-36, RAND 36-Item Short-Form Survey.

eTable 4. Outcomes and Characteristics in Respondents ≤1 and ≥6 Years Posttreatment via SF-36

	≤1 Year Posttreatment		≥6 Years Posttreatment		
SF-36 Measure	n	Mean (SD)	n	Mean (SD)	*P* Value
Physical functioning	265	68.0 (25.2)	233	73.0 (23.2)	.02
Role limitations due to physical health	265	46.5 (43.5)	231	64.5 (40.2)	<.001
Role limitations due to emotional problems	264	64.6 (40.2)	233	76.0 (36.3)	.001
Energy/Fatigue	264	43.3 (21.4)	233	49.5 (21.4)	.001
Emotional well-being	264	69.5 (18.5)	232	74.8 (17.2)	.001
Social functioning	265	73.5 (21.8)	233	81.8 (22.4)	<.001
Pain	265	67.7 (23.9)	233	66.2 (23.5)	.49
General health	265	57.1 (22.1)	233	58.6 (22.7)	.47

Abbreviation: SF-36, RAND 36-Item Short-Form Survey (subscale score range, 0–100).

eTable 5. Outcomes and Characteristics in Respondents Based on Adherence to Physical Activity Guidelines

	Respondents Meeting Guidelines		Respondents Not Meeting Guidelines		
SF-36 Measure	n	Mean (SD)	n	Mean (SD)	*P* Value
Physical functioning	787	72.9 (22.2)	153	48.7 (28.6)	<.001
Role limitations due to physical health	784	56.5 (42.0)	152	30.3 (40.2)	<.001
Role limitations due to emotional problems	785	71.5 (38.0)	153	59.3 (42.6)	.001
Energy/Fatigue	787	47.8 (21.3)	151	33.2 (20.5)	<.001
Emotional well-being	786	72.8 (17.6)	151	68.2 (18.2)	.005
Social functioning	787	78.6 (21.5)	153	65.7 (25.6)	<.001
Pain	787	67.4 (23.6)	153	57.2 (27.6)	<.001
General health	787	57.6 (22.4)	153	43.8 (23.2)	<.001

Abbreviation: SF-36, RAND 36-Item Short-Form Survey (subscale score range, 0–100).