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Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: Prevalence, risk factors, and fall risk

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Abstract

Purpose—CIPN is a common toxicity associated with chemotherapy, but researchers rarely study its risk factors, fall risk, and prevalence in long-term breast cancer survivors. We aimed to determine CIPN prevalence, risk factors, and association with psychological distress and falls among long-term breast cancer survivors.

Methods—We conducted cross-sectional analyses among postmenopausal women with a history of stage I–III breast cancer who received taxane-based chemotherapy. Participants reported neuropathic symptoms of tingling/numbness in hands and/or feet on a 0–10 numerical rating scale. We conducted multivariate logistic regression analyses to evaluate risk factors associated with the presence of CIPN and the relationship between CIPN and anxiety, depression, insomnia, and patient-reported falls.

Results—Among 296 participants, 173 (58.4%) reported CIPN symptoms, 91 (30.7%) rated their symptoms as mild and 82 (27.7%) rated them moderate to severe. Compared with women of normal weight, being obese was associated with increased risk of CIPN, (adjusted OR 1.94, 95% CI: 1.03–3.65). Patients with CIPN reported greater insomnia severity, anxiety, and depression than those without (all $p<0.05$). Severity of CIPN was associated with higher rates of falls, with 23.8%, 31.9%, and 41.5% in the “no CIPN,” “mild,” and “moderate-to-severe” groups, respectively, experiencing falls ($p=0.028$).

Conclusions—The majority of long-term breast cancer survivors who received taxane-based chemotherapy reported CIPN symptoms; obesity was a significant risk factor. Those with CIPN also reported increased psychological distress and falls. Interventions need to target CIPN and comorbid psychological symptoms, and incorporate fall prevention strategies for aging breast cancer survivors.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Experiments comply with the current laws of the United States.

Keywords

chemotherapy; breast cancer; peripheral neuropathy; falls; obesity

BACKGROUND

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, painful, and debilitating side effect of many standard chemotherapy regimens, including platinum agents, taxanes, vinca alkaloids, and proteasome inhibitors such as bortezomib[1]. CIPN develops within weeks or months after the initiation of chemotherapy, and may last from months to years after chemotherapy completion[1]. Patients with CIPN typically experience paresthesia (tingling, numbness), pain, and muscle weakness, and may exhibit significant functional decline and diminished QoL[1, 2].

Taxane-induced peripheral neuropathy (TIPN) is common among breast cancer survivors. During chemotherapy, 70.8% (95% CI=43.5–98.1) of patients report experiencing TIPN[3]. Recent studies suggest that the prevalence of TIPN after completion of chemotherapy ranges from 23% to 80% [4–6]. CIPN prevalence has been shown to decrease over time, with 68.1% (57.7–78.4) reporting CIPN within 1 month after chemotherapy completion, 60.0% (36.4–81.6) at 3 months, and 30.0% (6.4–53.5) 6 months or more after chemotherapy completion[3]. Clinical risk factors such as age, neuropathy at baseline, smoking, and diabetes have been shown to increase CIPN prevalence[6–10].

Even though its prevalence decreases over time, at least 30% of patients still suffer from CIPN 6 months or more after finishing chemotherapy. Long-term follow-up of such patients is limited and very little literature exists on its prevalence more than three years after chemotherapy completion[4]. Understanding long term CIPN rates and their association with psychological comorbidities and sequelae such as falls will lead to improvements in symptom management and interventions. We are attempting to fill this gap in the literature with our manuscript. The primary aim of the study is to describe the prevalence of CIPN and to identify its risk factors among long-term breast cancer survivors who received taxane-based adjuvant/neoadjuvant chemotherapy. The secondary aims are to determine the association between CIPN and psychological symptoms as well as patient-reported falls.

METHODS

Study Design and Patient Population

We drew participants from the follow-up assessment of Wellness after Breast Cancer (WABC), a longitudinal prospective study that focused on identifying biological determinants of symptom distress and disease outcomes in women with hormone receptor-positive breast cancer taking aromatase inhibitors (AIs). Details of the study design have been previously published.[11] We recruited baseline participants from breast cancer clinics in an academic tertiary care teaching hospital and a community hospital between November 2011 and June 2014. We conducted two-year follow-up assessments in the same settings between January 2014 and November 2015. Eligible participants for the longitudinal study

were postmenopausal women with a history of stage I–III hormone receptor-positive breast cancer who were current users of a third-generation AI for at least 6 months or who had discontinued AI use before the full duration of prescribed therapy. Trained research assistants approached potential study subjects in the waiting area of the oncology clinics. After obtaining written informed consent from participants, we gave them a self-report survey. The Institutional Review Board of the University of Pennsylvania approved the study protocol.

Of the original 670 participants in WABC who participated in the follow-up questionnaires, 371 were excluded from analysis because they did not receive taxane-based chemotherapy and 3 were excluded for not completing the questions on CIPN symptoms, resulting in a sample size of 296.

Study Variables

Primary outcome: Neuropathic symptoms of tingling/numbness—Participants used a 0–10 numerical rating scale to report neuropathic symptoms of tingling/burning/numbness in their hands and feet in the seven days prior to completing the questionnaire. A score of 0 meant no symptoms, while 10 indicated symptoms as bad as could be imagined. Consistent with cancer-related symptom rating scales[12, 13], we categorized neuropathy symptoms into four groups: 0 indicated no symptoms, 1–3 indicated mild symptoms, 4–6 indicated moderate symptoms and 7–10 indicated severe symptoms.

Secondary dependent variable: Patient-reported outcomes of anxiety, depression, insomnia, and falls—We measured patient-reported outcomes of anxiety and depression with the standard Hospital Anxiety and Depression Scale, a widely recognized 11-item scale used to assess emotional affect[14].

We measured patient-reported insomnia with the 7-item Insomnia Severity Index, which includes severity of sleep onset, sleep maintenance, early morning awakening problems, dissatisfaction with sleep, interference of sleep difficulties with daytime function, distress caused by sleep difficulties, and noticeability of sleep problems by others[15]. Each item is rated on a 5-point Likert scale, with total scores ranging from 0 to 28. A score of 0–7 indicates no insomnia, 8–14 indicates mild insomnia, 15–21 indicates moderate insomnia, and 22–18 indicates severe insomnia. It has been shown to be a reliable and valid instrument to detect cases of insomnia in the general population and is sensitive to treatment response in clinical patients[15].

In addition, we measured falls based on both the methods of past studies[16] and on recommendations made by international expert consensus[17]. Participants reported whether in the past 12 months they had experienced any fall, including a slip or trip, in which they lost their balance and landed on the floor, ground, or lower level, and if so, how many falls.

Covariates

We acquired demographic factors such as age, race, education level, employment status, and tobacco use through patient self-report. We obtained clinical factors such as diabetes status,

time since last chemotherapy, use of aromatase inhibitors, and breast cancer recurrence through chart abstraction.

Statistical Analysis

Data analysis was performed using STATA 12.0 for Windows (STATA Corporation, College Station, TX). We initially performed descriptive statistics and bivariate analyses. Then we developed multivariate logistic regression to evaluate risk factors associated with the presence of moderate to severe chemotherapy-induced peripheral neuropathy. We included variables with a significance level below 0.20 in the bivariate analyses in the multivariate model. To evaluate how CIPN may impact specific psychological-comorbidities and falls, we performed chi-square analyses to compare individuals with and without CIPN. Statistical tests were 2-sided, and P values of <0.05 indicated significance. Our sample size was determined by the parent study. Assuming that 50% of participants would have CIPN and any risk factors with a distribution of 50%, with 300 participants we were powered at 80% to detect an odds ratio of less than 0.52 or greater than 1.9 at 0.05 significance.

RESULTS

Participant Characteristics

Among the 296 participants with a history of early stage ER-positive breast cancer who received taxane-based chemotherapy, mean age was 62.0 years (SD 9.0; range 28.3–89.0), the majority were white (87.2%), mean time since breast cancer diagnosis was 6.3 years (SD 3.0), and mean time since last chemotherapy was 5.6 years (SD 3.0). Among participants, 108 (36.4%) were overweight (BMI between 25 and 30) and 93 (31.4%) were obese (BMI > 30). At the time of the survey, twenty-five participants (8.4%) had baseline diabetes, 53.7% had chemotherapy within the past 5 years, and 54.3% were still taking an aromatase inhibitor. See Table 1 for a detailed summary of patient characteristics.

Prevalence and Severity of CIPN

At the time of the survey, with a mean time since last chemotherapy of 5.6 years, 58.4% of participants reported neuropathy symptoms. Thirty percent of participants rated their neuropathy symptoms as mild (1–3 out of 10 point scale) and 27.7% rated their neuropathic symptoms of tingling/burning/numbness as moderate to severe (4–10 out of 10 point scale).

Factors Associated with CIPN

The prevalence of CIPN among different subgroups of patients based on their characteristics is summarized in Table 1. Importantly, older age is associated with a higher prevalence of CIPN (67.6% in participants order than 65 years vs. 55.4% in participants younger than 65, p=0.066). Higher BMI is also associated with a higher incidence of CIPN, with a prevalence of 48.4% in participants with normal weight, 60.2% in overweight participants, and 66.7% in obese participants (p=0.036). The prevalence of CIPN decreases with time: 64.8% of participants who finished chemotherapy within 5 years reported CIPN, while only 51.2% of those who finished chemotherapy longer than 5 years ago experienced CIPN (p=0.022). There was no significant association between CIPN prevalence and diabetes status, aromatase inhibitor usage, or recurrence status. There is very little power to evaluate the

correlation between diabetes and CIPN as only 25 patients had a history of diabetes. In multivariate logistic regression analyses, including age, BMI, time since last chemotherapy and diabetes status, being obese was associated with increased risk for experiencing CIPN, with adjusted odds ratios of 1.94 (95% CI: 1.03–3.65) (Table 2).

CIPN Severity and Psychological-comorbidities

We also evaluated the relationship between CIPN prevalence and patient-reported co-morbidities such as anxiety, depression, and insomnia. Figure 1 shows the relationship between CIPN severity and rates of psychological co-morbidities. Higher severity of CIPN is associated with greater rates of insomnia ($p < 0.001$), anxiety ($p = 0.001$), and depression ($p = 0.016$).

CIPN Severity and Falls

Figure 2 shows the correlation between CIPN severity and rate of falls. Severity of CIPN was associated with a higher rate of falls, with incidences at 23.8%, 31.9%, and 41.5% in the no-CIPN, mild, and moderate-to-severe groups, respectively (p=0.028). We conducted bivariate logistic regression analyses to evaluate risk factors – including CIPN severity, age, and BMI – associated with the incidence of falls and found that compared to women with no CIPN, moderate to severe CIPN was associated with a higher incidence of fall, with adjusted odds ratios of 2.27 (95% CI: 1.24–4.16) (Table 3).

DISCUSSION

This is one of the first cross sectional studies on long-term breast cancer survivors to assess the prevalence of CIPN. To date, most studies assessing CIPN prevalence and severity are within 1–3 years of completing adjuvant taxane therapy[3–5]. The rate of CIPN ranges from 23% to 81% among breast cancer survivors who received adjuvant taxane treatment 6 months to 3 years ago [3–6]. Our study assessed CIPN prevalence in a mean follow-up time of 5.6 years and found that 58.4% of patients reported persistent PN. This is consistent with a recent study of 462 women cancer survivors enrolled in an exercise trial in which 208 (45%) had CIPN symptoms an average of 6 years after treatment[18]. The data suggest the CIPN persists rather than resolving as expected for a substantial population of women with breast cancer.

We identified obesity as a significant risk factor for persistent CIPN with an odds ratio of 1.94. Our study is consistent with prior studies that have observed that obesity is a risk factor for CIPN[19–22]. Obesity has been reported to increase diabetic neuropathy[23], insulin resistance, and toxic adiposity, and obesity-related complications, including dyslipidemia, may cause diabetic-induced peripheral neuropathy[24]. In addition, obese patients have higher body surface areas and therefore receive higher doses of chemotherapy than patients at a normal weight, which may cause higher rates of CIPN[25]. Prior studies have suggested that risk factors for CIPN include age [6, 10], being African-American[7], baseline diabetes, baseline neuropathy[8], and a history of smoking[9]. In addition, a number of studies have demonstrated that polymorphism in genes such as FGD4[26], CYP3A4[27], and CYP2C8[28, 29], as well as genes involved in taxane metabolism, distribution, and

elimination, and genes involved in axon outgrowth[30] and congenital neuropathy[31] may increase the risk of CIPN. Further, a recent genome-wide association study of taxane-induced peripheral neuropathy (TIPN) showed that SNP rs3125923 was significantly associated with grade 3–4 TIPN[19]. In order to personalize preventative and therapeutic efforts, more research is needed to identify and validate clinical and genetic risk factors for long-term CIPN among breast cancer survivors.

To the best of our knowledge, this is the first study to report on the association between CIPN and increased anxiety, depression, and insomnia in breast cancer survivors. CIPN has been associated with pro-inflammatory states such as upregulation of pro-inflammatory cytokines [32, 33] and anxiety, depression, and sleep disturbance have all been associated with elevated levels of pro-inflammatory cytokines[34–37]. Obesity has also been associated with elevated pro-inflammatory cytokines[38]. The elevated pro-inflammatory state may serve as a shared mechanism underlying persistent CIPN, obesity, and increased psychological comorbidities.

Our study demonstrates a correlation between CIPN severity and an increased rate of falls among breast cancer survivors. In a recent exercise trial of women cancer survivors (n=462), the 208 (45%) women with CIPN symptoms experienced worse physical functioning, altered walking patterns, and more falls than women without CIPN symptoms[18]. Although these two studies differ in patient populations, with our study focusing on breast cancer survivors who have taken or are taking aromatase inhibitors enrolled in an ambulatory clinical care setting, whereas this study focused on breast cancer survivors participating in an exercise clinical trial with function assessments as its primary aim, the results are similar[18]. Our study found that moderate to severe CIPN not only doubled the fall rate, but could also be detrimental to aging breast cancer survivors' quality of life and functional independence. These findings contribute to a small but growing number of studies indicating that CIPN significantly increases the risk of falls among cancer survivors[39, 40]. These studies provide strong evidence for conducting additional research to evaluate interventions for the treatment of persistent CIPN and the prevention of falls in aging breast cancer survivors, especially those who are taking aromatase inhibitors, which are known to worsen bone health and increase the risk of fractures.

Several limitations need to be acknowledged. We do not have detailed information on the neuropathic symptoms the participants described such as unilateral versus bilateral symptoms, nor do we have information on neuropathic symptoms prior to chemotherapy. Therefore, we do not know for sure that our participants reported CIPN versus peripheral neuropathy symptoms from other etiology. On the other hand, the majority of the participants reported no history of diabetes or other co-morbidities, which makes CIPN most likely. In addition, we used a 0–10 numerical rating scale to measure severity of tingling or numbness. While this scale has been widely used in pain assessment and research, future CIPN research should use validated CIPN measurements such as FACT/GOG-Ntx or the Neuropathy Pain Scale. Our patient population was composed of estrogen receptor-positive post-menopausal women, which is the majority of breast cancer survivors. Therefore, our findings may not apply to estrogen receptor-negative patients or premenopausal women. Lastly, our study's cross-sectional design limits inferences of causality between CIPN and

psychological comorbidity or falls. Future prospective validation should be performed to explore a possible causal relationship.

Despite these limitations, we found that close to one in two women with breast cancer may experience persistent CIPN and that obesity is a risk factor for this condition. Women who experience persistent CIPN also report greater anxiety, depression, and insomnia. Further, persistent CIPN is associated with double the risk of falls in this population. Understanding the mechanism of persistent CIPN is essential for future research. Interventions are needed to decrease CIPN symptoms, improve psychological wellbeing, and prevent falls in women with breast cancer.

Our study demonstrates the need for additional research to improve treatment of persistent CIPN because it negatively impacts multiple aspects of quality of life and has significant long-term sequelae, such as an increased risk of falls. Further studies need to focus on the etiology of long term CIPN and potential identification of a common underlying mechanism that explains the strong association among obesity, CIPN, and psychological distress. Additional research on early interventions needs to target obesity, CIPN, and comorbid psychological symptoms, and to incorporate fall prevention strategies for aging breast cancer survivors.

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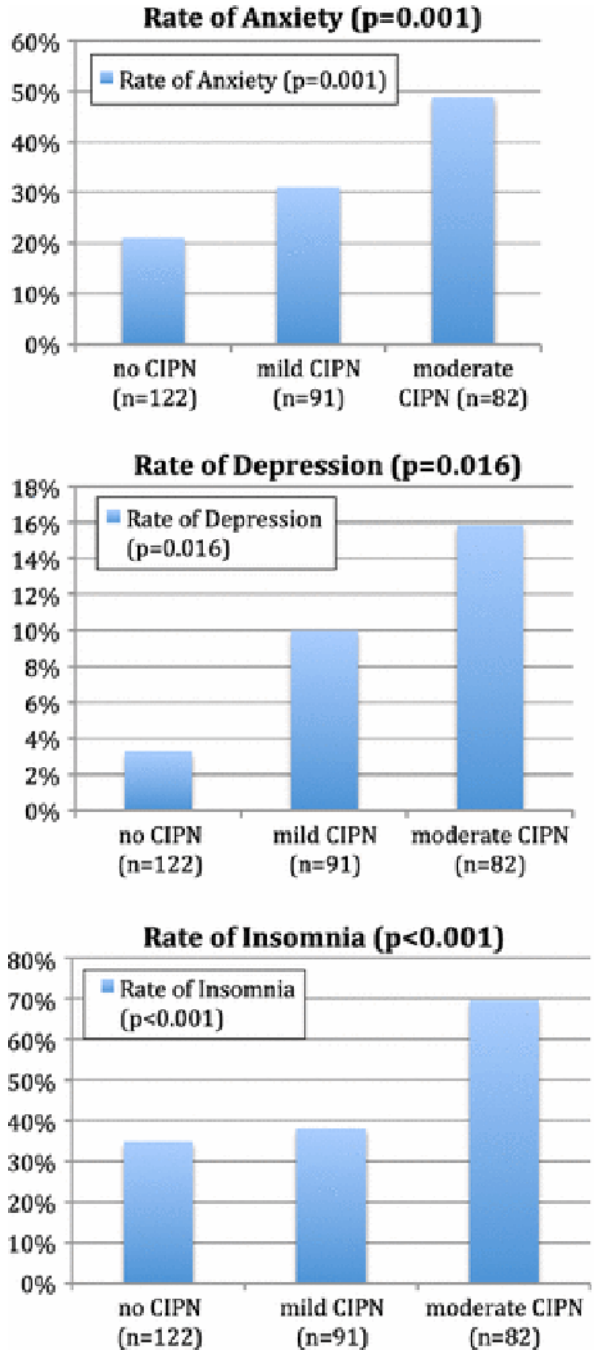

Figures 1.

A–C. CIPN Severity and Psychological Co-morbidities

(A) CIPN Severity and Rate of Anxiety

(B) CIPN Severity and Rate of Depression

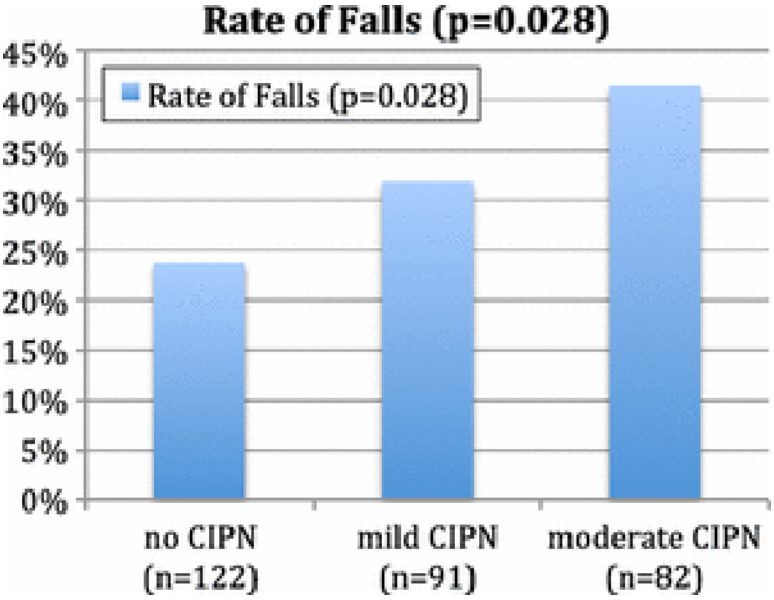

Figure 2.
CIPN Severity and Kate of Falls

Table 1

Demographic Characteristics of Participants at Time of Survey

	Total participants	With * CIPN	P-value
	N	%	
Total	296	58.4	
Age			0.066
<=65	222	55.4	
>65	74	67.6	
Race			0.53
White	258	57.8	
Non-White	38	63.2	
Educational level			0.67
High school or less	45	55.6	
College or above	251	59.0	
Employment			0.91
Employed	177	58.2	
Not employed	119	58.8	
Body mass index, kg/m^2			***0.036***
<25	95	48.4	
25 to 30	108	60.2	
>30	93	66.7	
Tobacco use			0.70
Current smoker	14	57.1	
Previous smoker	124	61.3	
Never smoked	158	56.3	
Diabetes status			0.15
Yes	25	72.0	
No	271	57.2	
Time since chemo (years)			***0.022***
<=5	159	64.8	
>5	123	51.2	
Currently on AI			0.98
Yes	161	58.4	
No	135	58.5	
Recurrence			0.88
Yes	23	56.5	
No	268	58.2	

* CIPN definition: A neuropathic symptoms score other than 0 on a 0–10 score scale (Ottaiano A)

Table 2

Multivariate Logistic Regressioa Model for CIPN

	Bivariate Analysis		Multivariate Analysis	
	OR (95%) CI)	**P-value**	**AOR (95% CI)**	**P-value**
Age				
<=65	1		1	
>65	1.68 (0.96–2.92)	0.066	1.42 (0.78–2.60)	0.25
Body mass index, kg/m^2				
< 25	1		1	
25 to 30	1.61 (0.92–2.81)	0.094	1.42 (0.79–2.55)	0.24
>30	2.13 (1.18–3.84)	*0.012*	1.94 (1.03–3.65)	*0.039*
Time since last chemo (years)				
<=5	1		1	
>5	0.57 (0.35–0.92)	*0.022*	0.63 (0.33–1.03)	0.067
Diabetes status				
No	1		1	
Yes	1.92 (0.78–4.76)	0.15	1.02 (0.33–2.76)	0.96

Table 3

Multivariate Logistic Regression Model for Falls

	Bivariate Analysis	
	OR (95% CI)	**P-value**
CIPN severity		
None	1	
Mild	1.5 (0.82–2.75)	0.19
Moderate to severe	2.27 (1.24–4.16)	*0.008*
Age		
<=65	1	
>65	0.75 (0.42–1.36)	0.35
Body mass index, kg/m^2		
<25	1	
25 to 30	1.19 (0.66–2.14)	0.57
>30	0.93 (0.50–1.74)	0.82