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Chemotherapy-induced peripheral neuropathy onset is associated with early risk of depression and anxiety in breast cancer survivors

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Abstract

Objective: The objective was to assess for an association between chemotherapy-induced peripheral neuropathy (CIPN) onset and development of depression and anxiety in breast cancer (BrCa) survivors.

Methods: A retrospective observational cohort was used and identified from Optum's De-identified Clinformatics® Data Mart Database years 2012–2015. Three groups of women were derived based on BrCa and CIPN status: BrCa+/CIPN+ ($n = 244$), BrCa+/CIPN− ($n = 8870$), and BrCa−/CIPN− ($n = 1{,}125{,}711$). The ratio of the prevalence ratios (RPR) determined if the change in risk of depression and anxiety from the 12-month preindex period to postindex period I (0–6 months) and II (7–12 months) was different for BrCa+/CIPN+ compared to BrCa+/CIPN− and BrCa−/CIPN−.

Results: The adjusted RPR for depression was significantly elevated for BrCa+/CIPN+ compared to BrCa+/CIPN− and BrCa−/CIPN− for postindex periods I (RPR = 1.35 [1.10,1.65] and 1.33 [1.08,1.63], respectively) and II (RPR = 1.53 [1.21,1.94] and 1.50 [1.17,1.93], respectively). The RPR for anxiety was significantly elevated for BrCa+/CIPN+ compared to BrCa+/CIPN− and BrCa−/CIPN− for postindex periods I (RPR = 1.37 [1.12,1.67] and 1.31 [1.06,1.61], respectively) and II (RPR = 1.41 [1.13,1.76] and 1.28 [1.02,1.62], respectively).

Conclusions: Among BrCa survivors, CIPN onset is associated with a subsequent increased 12-month risk of depression and anxiety. Depression and anxiety screening should be considered in BrCa+/CIPN+ survivors, particularly given their known impact on fall risk. The observed association between CIPN and an increased risk of depression and anxiety should be further studied in prospective studies.

KEYWORDS
breast cancer, chemotherapy, psychological, quality of life, supportive care

1 | BACKGROUND

Peripheral neuropathy is a longstanding and well-recognised risk factor for increased falls and disability in the general population (Karvonen-Gutierrez & Ylitalo, 2013; Richardson & Hurvitz, 1995). Breast cancer (BrCa) survivors frequently receive systemic chemotherapy, often including neurotoxic agents such as taxanes, which are known to disrupt the function of the peripheral nervous system

thereby causing chemotherapy-induced peripheral neuropathy (CIPN) (Seretny et al., 2014). Predictably, CIPN in BrCa survivors is strongly associated with decreased mobility, increased falls, and increased disability (Kolb et al., 2016; Winters-Stone et al., 2017).

Dysfunction in attention, executive functioning, and memory are also observed with chemotherapy (Runowicz et al., 2016). However, it is unclear whether chemotherapy exposure is associated with depression and/or anxiety (Hamer et al., 2009). Cancer survivors diagnosed with depression and anxiety (Dep/Anx) have a reduced quality of life, increased utilisation of health care resources, and increased mortality (Hamer et al., 2009; Klaassen et al., 2019). Moreover, Dep/Anx have been demonstrated to be independent fall risk factors in older populations as well as in cancer patients specifically (Huang et al., 2018; Kvelde et al., 2015; Sturnieks et al., 2016). Importantly, if Dep/Anx development were associated with the onset of CIPN in BrCa patients, these survivors would be at particularly increased risk for falls and their sequelae (Kvelde et al., 2015; Sturnieks et al., 2016). Therefore, confirmation of the association of CIPN with Dep/Anx development could help supportive care providers target mental health screening as well as fall prevention strategies in this high fall risk population.

Currently, it is not clear whether BrCa survivors who develop CIPN are at increased risk for developing depression and/or anxiety. Bao et al. (2016) demonstrated that BrCa survivors with CIPN symptoms 5 years after the completion of chemotherapy have an increased prevalence of Dep/Anx as compared with BrCa survivors without these symptoms. However, the initial prevalence of Dep/Anx was not reported and, therefore, it remains unknown whether Dep/Anx develops before, during, or after the onset of CIPN.

Gewandter et al. (2020) have shown that CIPN can be identified in insurance claims data, which offers the possibility of efficiently creating a cohort of cancer survivors with which to study CIPN and its association with development of Dep/Anx. The purpose of this observational cohort study was to leverage insurance claims data to determine whether the development of CIPN is associated with an increased risk for Dep/Anx among women with BrCa. We hypothesised that women with BrCa who develop CIPN (BrCa+/CIPN+) would have a larger increase in 12-month risk of Dep/Anx as compared to women with BrCa who do not develop CIPN (BrCa+/CIPN−) and women without BrCa or CIPN (BrCa−/CIPN−).

2 | METHODS

2.1 | Data source

The Optum's De-identified Clinformatics® Data Mart Database was leveraged for this study. This national single private payer administrative claims database stores medical and outpatient pharmacy data from individuals covered by commercial or Medicare Advantage insurance plans in the United States (Whitney et al., 2019). To be enrolled in a private payer insurance plan, the beneficiary either pays for insurance coverage or is covered by their employer or a spouse who has employer-based coverage that extends to family members. Therefore, this sample may represent a slightly more affluent sector of the population and study findings should be interpreted within the scope of this privately insured sample. Medical, procedure, and outpatient pharmacy claims from 1 January 2012 to 31 December 2014 (three full calendar years) were used for this analysis. Data are deidentified and the Institutional Review Board identified this study as nonregulated.

Medical conditions were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Chemotherapy agents were identified using the generic names of relevant medications and relevant Healthcare Common Procedure Coding System (HCPCS) codes for nonoral administered chemotherapy agents.

2.2 | Sample selection

The primary group of interest was women with BrCa that developed CIPN. BrCa and CIPN were identified by ≥1 claim from any source (e.g., inpatient, outpatient) that contained the ICD-9-CM codes for invasive (174.x) and non-invasive (233.0) BrCa and CIPN (357.6) as McNeish et al. (2021) described. See Table S1 for the full list of ICD-9-CM codes. To identify incidence of CIPN in women with BrCa, the first claim of CIPN was identified from 1 July 2013 to 30 June 2014 (1-year period) among women with BrCa that had at least 18-months of health plan enrolment prior to this CIPN claim date. Individuals were excluded if they had a claim for CIPN in the 18-months prior to the first CIPN claim from 1 July 2013 to 30 June 2014 in order to isolate incident cases. Since the majority of CIPN cases are diagnosed by the 6-month time point after starting chemotherapy (Pereira et al., 2015), the index date (i.e., start date of follow-up) for the BrCa+/CIPN+ group was 6-months prior to their first CIPN claim date. This allowed for 12 months of the post index data collection to better capture how CIPN may be temporally involved in the early development of Dep/Anx and left a 12-month preindex period to ascertain baseline data, which is common for claims-based research (Chang et al., 2012).

In order to determine the effect of CIPN's association with Dep/Anx in BrCa survivors, we created three groups: BrCa+/CIPN+, BrCa+/CIPN+, and BrCa+/CIPN−. These three groups allowed us to determine if the association of CIPN with Dep/Anx was beyond an association with just BrCa alone. We took two steps to match the index time period between the BrCa+/CIPN+ and BrCa+/CIPN− groups to allow for better comparison. First, incident BrCa cases were included to account for the effect of a newly diagnosed cancer on mental health disorders. Specifically, the first claim for BrCa, without a BrCa claim in the 12 months preceding, was identified from 1 January 2013 to 31 September 2013. Second, since chemotherapy typically starts approximately 3 months after the initial diagnosis of BrCa (Kupstas et al., 2019), the index date for the

BrCa+/CIPN− group was 3 months after the first BrCa claim. Therefore, the index date for both the BrCa+/CIPN+ and BrCa+/CIPN− groups is approximately similar to the time course of BrCa diagnosis and treatment.

The second comparison group included women that had no claims for BrCa or CIPN, and their index date was randomly assigned in the calendar year 2013 using a uniform distribution (visually inspected by the author), as described by Whitney, Bell, et al. (2020). Since BrCa is more common among older ages, the "background" population, that is, the group without BrCa and CIPN, was much younger on average compared to the BrCa groups. Our goal for this background group was simply to provide slightly more interpretable estimates for the crude prevalence of Dep/Anx in Table 2. We did this by balancing the age distributions such that differences in age across groups was minimal. While this does not fully remove confounding by age, it does mitigate the effects by different age distributions and allows for improved interpretations of crude estimates as it relates to confounding by age. This process involved identifying the highest sample size possible in a random fashion from the BrCa−/CIPN− group, to limit selection bias, which reflected a similar age distribution as the BrCa+ groups. We were able to maximally identify 45,028 young women (4%), 562,856 middle-aged women (50%), and 517,827 elderly women (46%) without BrCa and CIPN.

Following group allocation, individuals were included if they were as follows: (1) ≥ 18 years of age; (2) had ≥12 months of continuous health plan enrolment in the preindex period to ascertain baseline data (Whitney et al., 2019); and (3) had ≥12 months of continuous health plan enrolment in the postindex period for the outcome measures.

2.3 | Depression and anxiety

The prevalence of Dep/Anx were identified using at least one ICD-9-CM code (see Table S1), in either the 12-month preindex period, the postindex period I (0–6 months) or in the post index period II (7–12 months). Dep/Anx were examined as cumulative throughout the study period. For example, if an individual had depression in the preindex period, they were considered to have depression in the two 6-month postindex periods. This was done to identify the overall group burden of Dep/Anx and because it is not possible to determine with high accuracy if depression or anxiety is in remission, cured, or active using claims data over single 6- to 12-month periods.

2.4 | Covariates

Covariates were selected based on their relevance to CIPN, BrCa, depression, anxiety, and availability and reliability in administrative claims databases. Age, race, and region of residence in the United States at the time of the index date, and whether the BrCa was invasive or noninvasive were included in the data collection. Chemotherapy exposure was determined as ≥1 outpatient pharmacy claim for any relevant chemotherapy agents or ≥1 medical claim for any relevant HCPCS codes for nonoral administered chemotherapy. Chemotherapy included neurotoxic and non-neurotoxic agents and are included Table S1 (Cavaletti & Marmiroli, 2010). Baseline comorbidities were identified in the 12-month preindex period by at least one claim with an ICD-9-CM code for substance abuse problems, type 2 diabetes, sleep disorders, and kidney problems, as Whitney, Warschausky, et al. (2020) described.

2.5 | Statistical methods

Preindex descriptive characteristics were summarised for each group and compared using the chi-squared test for categorical variables or the independent *t*-test for continuous variables; 95% binomial confidence intervals (CI) for the prevalence estimates of preindex and postindex Dep/Anx were calculated as the sample proportion ± the margin of error with a *z*-value of 1.96.

Prevalence ratios (PR with 95% CI) were estimated to quantify the change in risk of Dep/Anx from the preindex to postindex periods for each group. A difference-in-difference analysis was conducted to determine if the change in risk of Dep/Anx from preindex to postindex periods was different for the BrCa+/CIPN+ group as compared to the BrCa+/CIPN− and BrCa−/CIPN− groups. In particular, a generalised linear model with repeated measures, a binomial distribution, and a log link function was used before and after adjusting for preindexindex covariates that were significantly different and clinically meaningful between groups. The interpretation of the difference-in-difference analysis was focused on the relative change for BrCa+/CIPN+ as compared to the BrCa+/CIPN− and BrCa−/CIPN− groups, which is assessed by the ratio of the PR (RPR; a numerical approximation of the time by exposure interaction) from the groups being compared. This analytic strategy is a strength as it uses a within-person design thus limiting bias from confounding as each group serves as their own internal control.

2.6 | Sensitivity analysis

We performed two sets of sensitivity analyses. First, we are unable to determine if polyneuropathy after a BrCa diagnosis is truly due to chemotherapy. We therefore examined the trends in preindex to postindex Dep/Anx among the BrCa+/CIPN+ group stratified by those with or without chemotherapy exposure. Second, we did not adjust for race due to the extent of missing or of unknown race. We therefore performed two related analyses to examine for the possibility of confounding and selection bias by race (Whitney et al., 2019). Briefly, analyses that did and did not adjust for race were conducted on the restricted study sample that had complete data on race. Possible confounding by race was assessed by comparing the race adjusted and crude results from the restricted sample with complete data on

race. Possible selection bias by race was assessed by comparing the crude results from the restricted sample with complete data on race with the main analysis (i.e., full sample not adjusting for race).

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

3 | RESULTS

Preindex descriptive characteristics of women with BrCa+/CIPN+ ($n = 244$), BrCa+/CIPN− ($n = 8870$), and BrCa−/CIPN− ($n = 1{,}125{,}711$) are presented in Table 1. Compared to BrCa+/CIPN−, BrCa+/CIPN+ patients were 4.8 years younger, had a lower proportion with invasive BrCa, had a higher proportion of chemotherapy exposure, and had a lower prevalence of renal disease (all $p < 0.05$). Compared to BrCa−/CIPN−, BrCa+/CIPN+ had a higher proportion of chemotherapy exposure and a higher prevalence of substance abuse disorders ($p < 0.05$).

The crude prevalence of preindex and postindex Dep/Anx are quantitatively presented in Table 2 and visually presented in Figure 1. When comparing the confidence intervals in the preindex period, BrCa+/CIPN+ had a similar prevalence of depression compared to both groups, a similar prevalence of anxiety compared to BrCa+/CIPN−, and a higher prevalence of anxiety compared to BrCa−/CIPN−. When comparing confidence intervals for depression in the postindex periods, BrCa+/CIPN+ had a similar prevalence compared to BrCa−/CIPN− 0-6 months postindex and a higher prevalence compared to both groups 7–12 months postindex. Finally, when comparing the respective confidence intervals for anxiety in the postindex periods, BrCa+/CIPN+ had a higher prevalence compared to both groups for 0- to 6- and 7- to 12-month postindex, Table 2.

The crude PR for the change in pre to postindex risk of Dep/Anx are presented in Table 2 and visually presented in Figure 1. All groups exhibited a significant increase in the PR points estimates of Dep/Anx in the 0–6 months postindex period (PR = 1.22 to 1.65 for depression, PR = 1.26 to 1.73 for anxiety, all $p < 0.05$) and 7–12 months

TABLE 1 Descriptive characteristics of women with (+) or without (−) breast cancer (BrCa) and chemotherapy-induced peripheral neuropathy (CIPN)

	BrCa+/CIPN+($n = 244$) % (n)	BrCa+/CIPN−($n = 8870$) % (n)	BrCa−/CIPN−($n = 1{,}125{,}711$) % (n)
Age, mean (SD)	61.7 (11.9)[a]	66.5 (13.6)[b]	61.8 (14.7)
18–40 years	4.1 (10)	3.5 (314)	4.0 (45,028)
41–64 years	54.1 (132)	37.7 (3347)	50.0 (562,856)
≥65 years	41.8 (102)	58.7 (5209)	46.0 (517,827)
Race		2	
White	66.4 (162)	67.4 (5982)	65.3 (734,942)
Black	6.2 (15)	7.2 (636)	7.5 (84,161)
Hispanic	9.8 (24)	8.4 (749)	9.5 (107,028)
Asian	4.1 (10)	2.9 (260)	3.8 (43,156)
Other/unknown	13.5 (33)	14.0 (1243)	13.9 (156,424)
U.S. region of residence		2	
West	32.8 (80)	30.7 (2720)	27.7 (311,432)
Midwest	23.0 (56)	21.0 (1862)	22.5 (253,488)
South	34.4 (84)	33.9 (3006)	36.3 (408,762)
Northeast	9.8 (24)	14.5 (1282)	13.5 (152,029)
Invasive BrCa	71.3 (174)[a]	95.5 (8469)	0 (0)
Chemotherapy[c]			
Any chemotherapy	43.9 (107)[a,b]	10.2 (903)[b]	0.5 (5774)
Neurotoxic chemotherapy agents	40.6 (99)[a,b]	9.4 (832)[b]	0.4 (3961)
Comorbidities			
Substance abuse	15.2 (37)[b]	13.1 (1161)[a]	6.9 (78,112)
Type 2 diabetes	18.0 (44)	20.1 (1786)[a]	16.6 (186,933)
Any sleep disorder	11.9 (29)	10.5 (932)[a]	8.6 (96,456)
Renal disease	4.9 (12)[a]	9.6 (848)[a]	6.7 (75,418)

[a]$p < 0.05$ compared to BrCa+/CIPN−.
[b]$p < 0.05$ compared to BrCa−/CIPN−.
[c]Chemotherapy exposure was between the index date and post index date II.

TABLE 2 Crude prevalence and prevalence ratio (PR) of preindex and postindex depression and anxiety among women with (+) or without (−) breast cancer (BrCa) and chemotherapy-induced peripheral neuropathy (CIPN)

	BrCa+/CIPN+(*n* = 244)	BrCa+/CIPN−(*n* = 8870)	BrCa−/CIPN−(*n* = 1,125,711)
Depression			
Prevalence, % (95% CI)			
Preindex	15.2 (10.7, 19.7)	17.5 (16.7, 18.3)	13.9 (13.9, 14.0)
0–6 months	25.0 (19.6, 30.4)	21.3 (20.4, 22.1)	17.1 (17.1, 17.2)
7–12 months	32.8 (26.9, 38.7)	24.6 (23.7, 25.5)	19.8 (19.8, 19.9)
PR (95% CI)			
0–6 months vs. preindex	1.65 (1.14, 2.38)	1.22 (1.15, 1.29)	1.23 (1.22, 1.24)
7–12 months vs. preindex	2.16 (1.53, 3.06)	1.41 (1.33, 1.49)	1.42 (1.42, 1.43)
7–12 months vs. 0–6 months	1.32 (0.99, 1.74)	1.16 (1.10, 1.22)	1.16 (1.15, 1.17)
Anxiety			
Prevalence, % (95% CI)			
Preindex	16.4 (11.7, 21.0)	13.7 (13.0, 14.4)	9.7 (9.7, 9.8)
0–6 months	28.3 (22.6, 33.9)	17.3 (16.5, 18.1)	12.6 (12.6, 12.7)
7–12 months	33.6 (27.7, 39.5)	20.0 (19.2, 20.8)	15.3 (15.2, 15.3)
PR (95% CI)			
0–6 months vs. preindex	1.73 (1.22, 2.44)	1.26 (1.18, 1.36)	1.31 (1.29, 1.31)
7–12 months vs. preindex	2.05 (1.47, 2.86)	1.46 (1.37, 1.56)	1.57 (1.56, 1.58)
7–12 months vs. 0–6 months	1.19 (0.91, 1.55)	1.16 (1.09, 1.23)	1.21 (1.20, 1.22)

Abbreviation: CI, confidence interval.

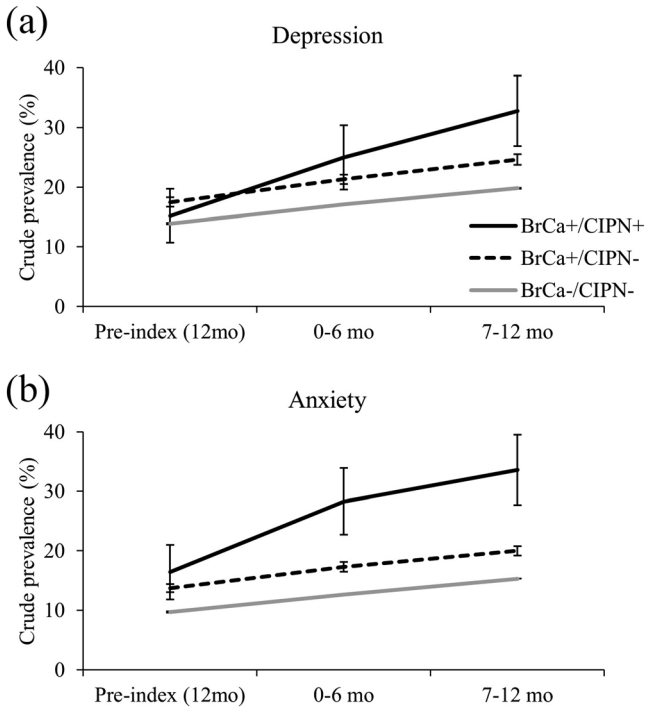

FIGURE 1 (a) Crude prevalence of depression at preindex, 0–6 months, and 7–12 months between BrCa+/CIPN+, BrCa+/CIPN−, and BrCa−/CIPN− groups. (b) Crude prevalence of anxiety at preindex, 0–6 months, and 7–12 months between BrCa+/CIPN+, BrCa+/CIPN−, and BrCa−/CIPN− groups. (BrCa: breast cancer; CIPN: chemotherapy induced peripheral neuropathy; +: presence; −: absence)

postindex period (PR = 1.41 to 2.16 for depression, PR = 1.46 to 2.05 for anxiety, all $p < 0.05$) compared to the preindex period. When the PR was estimated for 7–12 months postindex as compared to 0–6 months postindex, all groups exhibited an elevated PR for depression with the BrCa+/CIPN+ group having the highest PR; although, the elevated PR was not statistically significant for the BrCa+/CIPN+ group ($p = 0.060$). The increased risk was similar across groups for anxiety for 7–12 months postindex period as compared to 0–6 months postindex period, but was not statistically significant for the BrCa+/CIPN+ group (PR = 1.19; 95% CI = 0.91–1.55).

The results of the crude and adjusted difference-in-difference analysis are presented in Table 3. Adjustments were made for preindex covariates that were both significantly different and clinically meaningful between groups. The adjusted RPR for depression was significantly elevated for BrCa+/CIPN+ compared to BrCa+/CIPN− and BrCa−/CIPN− for postindex periods I (RPR = 1.35 [1.10,1.65] and 1.33 [1.08,1.63], respectively) and II (RPR = 1.53 [1.21,1.94] and 1.50 [1.17,1.93], respectively). The RPR for anxiety was significantly elevated for BrCa+/CIPN+ compared to BrCa+/CIPN− and BrCa−/CIPN− for postindex periods I (RPR = 1.37 [1.12,1.67] and 1.31 [1.06,1.61], respectively) and II (RPR = 1.41 [1.13,1.76] and 1.28 [1.02,1.62], respectively).

3.1 | Sensitivity analysis

Due to only 43.9% of the BrCa+/CIPN+ cohort receiving definite chemotherapy, a sensitivity analysis was performed to determine if

TABLE 3 The ratio of the prevalence ratio (RPR) of preindex to postindex depression and anxiety among women with (+) or without (−) breast cancer (BrCa) and chemotherapy-induced peripheral neuropathy (CIPN)

	Depression		Anxiety	
	Crude RPR (95% CI)	Adjusted[a] RPR (95% CI)	Crude RPR (95% CI)	Adjusted[a] RPR (95% CI)
0–6 months vs. preindex				
BrCa+/CIPN+ vs. BrCa+/CIPN−	1.35 (1.11,1.66)	1.35 (1.10,1.65)	1.36 (1.11,1.67)	1.37 (1.12,1.67)
BrCa+/CIPN+ vs. BrCa−/CIPN−	1.34 (1.10,1.64)	1.33 (1.08,1.63)	1.33 (1.08,1.62)	1.31 (1.06,1.61)
7–12 months vs. preindex				
BrCa+/CIPN+ vs. BrCa+/CIPN−	1.54 (1.21,1.95)	1.53 (1.21,1.94)	1.40 (1.12,1.75)	1.41 (1.13,1.76)
BrCa+/CIPN+ vs. BrCa−/CIPN−	1.52 (1.20,1.92)	1.50 (1.17,1.93)	1.31 (1.05,1.63)	1.28 (1.02,1.62)
7–12 months vs. 0–6 months				
BrCa+/CIPN+ vs. BrCa+/CIPN−	1.13 (1.00,1.28)	1.13 (1.00,1.28)	1.03 (0.94,1.13)	1.03 (0.94,1.13)
BrCa+/CIPN+ vs. BrCa−/CIPN−	1.13 (1.00,1.28)	1.12 (0.99,1.26)	0.99 (0.90,1.08)	0.97 (0.89,1.07)

Abbreviation: CI, confidence interval.

[a]Compared to BrCa+/CIPN−, models adjusted for age (as continuous), invasive BrCa, chemotherapy exposure, and any renal disease; compared to BrCa−/CIPN−, models adjusted for chemotherapy exposure and substance abuse problems.

there were differences of Dep/Anx prevalence within the BrCa+/CIPN+ group stratified by definite chemotherapy exposure. The prevalence and change in preindex and postindex Dep/Anx were similar for the BrCa+/CIPN+ group when stratified by chemotherapy exposure (Figure 2). For those with complete data on race, the prevalence, PR, and RPR is presented in Tables S2 and S3. There was no evidence of confounding or selection bias by race for any group when depression was examined. However, for anxiety, there was a slightly lower prevalence among the BrCa+/CIPN+ group compared to the primary analysis, but no difference in the PRs. Further, there was no evidence of selection bias by race when anxiety was examined, but there was slight evidence of confounding by race for the BrCa+/CIPN+ group. However, this was modest and the conclusions remain similar as the primary analysis.

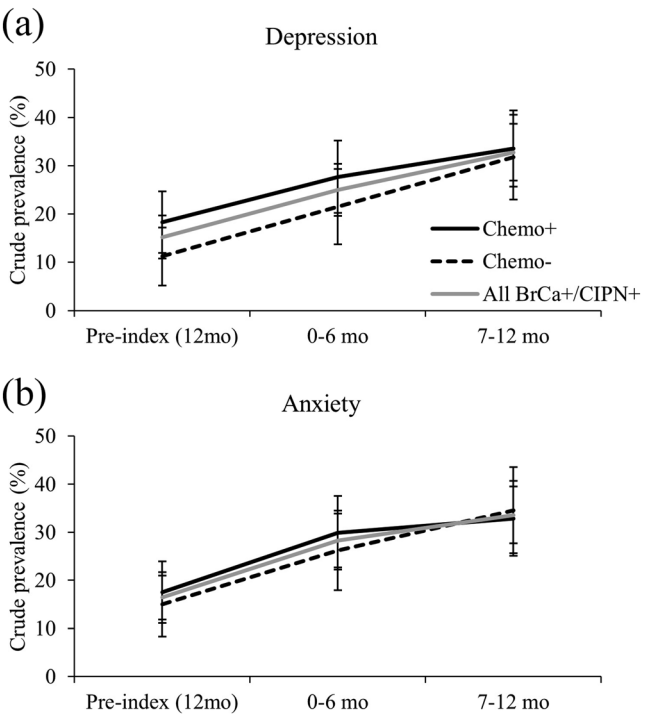

FIGURE 2 (a) Crude prevalence of depression at preindex, 0–6 months, and 7–12 months within BrCa+/CIPN+ including Chemo+, Chemo−, and all BrCa+/CIPN+. (b) Crude prevalence of anxiety at preindex, 0–6 months, and 7–12 months within BrCa+/CIPN+ including Chemo+, Chemo−, and all BrCa+/CIPN+. (BrCa: breast cancer; CIPN: chemotherapy induced peripheral neuropathy; Chemo: chemotherapy exposure; +: presence; −: absence)

4 | DISCUSSION

The findings from this study suggest that among women with BrCa, CIPN is associated with an increased risk of Dep/Anx in the 12-month interval following chemotherapy initiation. Specifically, women with BrCa and CIPN exhibit a higher 12-month risk of developing Dep/Anx compared to women with BrCa without CIPN and women without BrCa or CIPN. These findings are significant despite the patient groups having a similar preindex prevalence of these mental health disorders. This study provides evidence that women with BrCa who develop CIPN have a disproportionately elevated 12-month risk of Dep/Anx.

Previously, Bao et al. (2016) have demonstrated that BrCa survivors' CIPN symptoms were associated with increased depression, anxiety, and sleep disorders at 5 years postchemotherapy treatment. Of note, their study did not investigate temporal changes of Dep/Anx with a CIPN diagnosis or specifically establish CIPN's association with Dep/Anx in the early time frame after CIPN onset. Recently, Bennedsgaard et al. (2020) demonstrated that the CIPN symptoms that BrCa survivors have at 1 year often persist 5 years later. Moreover, these survivors demonstrated a trend towards increased

Dep/Anx and a significantly lower quality of life when compared to BrCa survivors without CIPN at 5 years postchemotherapy treatment (Bennedsgaard et al., 2020). Our findings are also consistent with prior studies demonstrating that the prevalence of Dep/Anx in BrCa survivors is approximately 10–22% and 10%, respectively (Zainal et al., 2013). Consistent with the literature, our results show that BrCa survivors have a relatively increased Dep/Anx prevalence compared to their peers without a BrCa diagnosis and their prevalence are estimated at 5–15% and 5–20%, respectively (Carreira et al., 2018; Mitchell et al., 2011; Zainal et al., 2013).

An important aspect of our study is the establishment of the association between onset of CIPN and risk of Dep/Anx in a relatively short period after a CIPN diagnosis.

We demonstrate that at both 0–6 months and 7–12 months after the CIPN index event, there is increased risk for developing Dep/Anx in BrCa survivors. This is a novel finding as CIPN symptoms can abate before 1-year postchemotherapy, but patients' risk for developing Dep/Anx may continue.

Our findings may have clinical relevance. Supportive care providers may consider screening BrCa survivors for Dep/Anx and/or re-evaluating fall risk after a diagnosis of CIPN. Functionally, CIPN has been independently associated with a reduced quality of life, as well as falls (Kolb et al., 2016; Winters-Stone et al., 2017). Additionally, prior work indicates that Dep/Anx contribute significantly to reduced mobility, quality of life, and an increased risk for falls in patients without the complication of cancer (Kvelde et al., 2015; Sturnieks et al., 2016). Further, Huang et al. (2018) have demonstrated that depression is a significant risk factor for falls in cancer survivors independent of CIPN. Therefore, prompt screening, treatment, and referral to a rehabilitative provider may mitigate further decrements in mobility and quality of life in survivors with CIPN. Finally, Gewandter et al. (2020) have described that despite the American Society of Clinical Oncology's (ASCO) recommendation for duloxetine to be prescribed as first line treatment for CIPN in BrCa survivors, gabapentin remains the leading medication prescribed for the treatment of CIPN. Therefore, supportive care providers may consider duloxetine as opposed to gabapentinoids, per the recent ASCO guidelines (Loprinzi et al., 2020), in the treatment of CIPN symptoms with the added benefit that duloxetine may also help to prevent or treat depression or anxiety in these patients (Torta et al., 2011).

CIPN's association with development of Dep/Anx may be explained by alterations in neurobiology secondary to chemotherapy administration. One possible mechanism is a chemotherapy induced proinflammatory cellular microenvironment with upregulated levels of proinflammatory cytokines including interleukin-1, interleukin-6, and c-reactive protein (Howren et al., 2009). Elevations in plasma levels of these cytokines have been associated with Dep/Anx (Haapakoski et al., 2015; Howren et al., 2009). Another mechanism could be the alteration of neurotrophic factors by chemotherapy administration that are important in the maintenance and repair of the central and peripheral nervous system. Brain-derived neurotrophic growth factor levels have been implicated in both Dep/Anx in individuals with CIPN where lower levels are correlated with increased depression, anxiety, and CIPN in lymphoma and multiple myeloma patients (Azoulay et al., 2019; Szudy-Szczyrek et al., 2020). It is biologically plausible that chemotherapy could alter levels of circulating brain-derived neurotrophic growth factor and may contribute to both CIPN as well as depression and/or anxiety in BrCa survivors. Finally, psychological factors related to the burden of walking instability and difficulty performing everyday activities may also be responsible for CIPN associated Dep/Anx (Dziemidok et al., 2015).

4.1 | Study limitations

Our study is not without limitations, and many stem from the use of claims data, which is dependent on patient report and provider input. Therefore, the prevalence of CIPN, chemotherapy use, and Dep/Anx are likely underrepresented approximations. Moreover, less than half of the BrCa+/CIPN+ cohort had an identifiable billing reimbursement claim for chemotherapy exposure. The reason for this may be due to poor sensitivity of detecting chemotherapy exposure using claims data, or that the chemotherapy exposure that led to peripheral neuropathy (i.e., CIPN) occurred prior to the study period. To capture relevant time periods, we made an assumption of the time between the CIPN index event and the CIPN diagnosis, which was based on clinical experience and the literature (Seretny et al., 2014). It is possible this lag time varied among individuals and was not detected using claims data. This may explain why individuals had a physician diagnosis of CIPN, but no identifiable chemotherapy. Therefore, due to a likely underrepresented chemotherapy use and use of an ICD-9 code for CIPN, we are unable to definitively determine whether peripheral neuropathy is truly due to chemotherapy. However, Gewandter et al. (2020) have demonstrated the specificity of the ICD-9 code, "Polyneuropathy due to Drugs," for CIPN in a cancer population, and therefore, it is unlikely another drug other than neurotoxic chemotherapy could have caused the neuropathy. Additionally, we cannot conclude with certainty that clinicians properly coded Dep and Anx, separately, given the clinical overlap. In our study, we did not record group differences in antidepressant use or cancer severity and so these are possible unaccounted for confounders. It is possible that more severe cancer was treated with greater amounts of chemotherapy such that disease severity rather than the development of CIPN resulted in BrCa+/CIPN+ survivors developing increased Dep/Anx. While we did not have access to group differences in cancer severity, we did record group differences in invasive and noninvasive cancer, which demonstrated less invasive cancer in BrCa+/CIPN+ versus BrCa+/CIPN−. The relatively small sample size of the BrCa+/CIPN+ cohort and unmeasured confounding may have introduced bias. For example, while we examined for relevant comorbidities, there may be other indicators of medical complexity confounding the primary analyses. Further, the sample may not be representative of the greater BrCa+/CIPN+ population, and the findings should be interpreted within the context of this privately insured cohort. Lastly, we did not record history of prior psychiatric disease aside from Dep/Anx or the socio-economic status of the survivors, which are known risk factors

for the development of Dep/Anx in this patient population (Runowicz et al., 2016).

In summary, this study suggests that the onset of CIPN in BrCa survivors is associated with an increased and early risk for developing Dep/Anx compared to BrCa survivors without CIPN and their peers without BrCa. Moving forward, research should focus on validating the relationship and mechanism between CIPN and Dep/Anx as it may help to inform future clinical decision making concerning screening for and treatment of Dep/Anx in BrCa survivors. Collectively, BrCa survivors with CIPN may benefit from early screening after CIPN onset to facilitate treatment to reduce mortality and to optimise quality of life in the setting of Dep/Anx. Future prospective studies are necessary to determine if Dep/Anx development is associated with CIPN onset and if Dep/Anx adds to the known fall risk of BrCa survivors with CIPN.

CONFLICTS OF INTEREST

All authors deny having conflicts of interest for the submitted work.

PREVIOUS PRESENTATION OF RESEARCH

All authors deny that the work has been previously presented or published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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