Chemotherapy induced peripheral neuropathy onset increases the early risk for depression and anxiety in breast cancer survivors

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Abstract

Purpose

Chemotherapy induced peripheral neuropathy (CIPN) occurs commonly in breast cancer (BrCa) patients and contributes to falls. Depression and anxiety in cancer survivors leads to reduced quality of life, increased mortality and also increases fall risk. Therefore, we investigated the association between CIPN with depression and anxiety in BrCa survivors.

Methods

Data were extracted from Optum's De-identified Clinformatics® Data Mart Database years 2012–2015. Among women, three groups were derived based on BrCa and CIPN status: BrCa+/CIPN+, BrCa+/CIPN-, and BrCa-/CIPN-. Risk ratios (RR) determined the change in risk of depression and anxiety from the 12-month pre-index period to post-index period I (0–6 months) and II (7–12 months) for each group separately. The ratio of the RR (RRR) determined if the change in risk of outcomes was different for BrCa+/CIPN + compared to BrCa+/CIPN- and BrCa-/CIPN-.

Results

The RR was significantly elevated for all groups ($p < 0.05$) in the post-index periods I (depression, RR = 1.22–1.65; anxiety, RR = 1.26–1.73) and II (depression, RR = 1.41–2.16; anxiety, RR = 1.46–2.05), with BrCa+/CIPN + exhibiting the largest RR. The RRR for depression was significantly elevated for BrCa+/CIPN + compared to BrCa+/CIPN- and BrCa-/CIPN- for post-index periods I (RRR = 1.35 and 1.33, respectively) and II (RRR = 1.53 and 1.50, respectively). The RRR for anxiety was significantly elevated for BrCa+/CIPN + compared to BrCa+/CIPN- and BrCa-/CIPN- for post-index periods I (RRR = 1.37 and 1.31, respectively) and II (RRR = 1.41 and 1.28, respectively).

Conclusion

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.

Introduction

Peripheral neuropathy is a longstanding and well-recognized risk factor for increased falls and disability in the general population [1-2]. 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) [3].

Predictably, CIPN in BrCa survivors is strongly associated with decreased mobility, increased falls, and increased disability [4-5].

Dysfunction in attention, executive functioning, and memory are also observed with chemotherapy [6]. However, it is unclear whether chemotherapy exposure is associated with depression and/or anxiety [7]. Cancer survivors diagnosed with depression and anxiety (Dep/Anx) have a reduced quality of life, increased utilization of healthcare resources, and increased mortality [7-8]. Moreover, Dep/Anx have been demonstrated to be independent fall risk factors in older populations as well as in cancer patients specifically [9-11]. 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 [10-11]. Therefore, confirmation of the association of CIPN to 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. demonstrated that BrCa survivors with CIPN symptoms five years after the completion of chemotherapy have an increased prevalence of Dep/Anx as compared with BrCa survivors without these symptoms [12]. 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. has shown that CIPN can be identified in insurance claims data [13], 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 hypothesized 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-).

Methods

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 [14]. 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 January 1, 2012 to December 31, 2014 (three full calendar years) were used for this analysis. Data are de-identified and the University of Michigan's Institutional Review Board approved this study as non-regulated.

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 non-oral administered chemotherapy agents.

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 malignant (174.x) and non-malignant (233.0) BrCa and CIPN (357.6). See **Supplementary Table 1** 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 July 1, 2013 to June 30, 2014 (one-year period) among women with BrCa that had at least 18-months of health plan enrollment 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 July 1, 2013 to June 30, 2014 in order to isolate incident cases. Since the majority of CIPN cases are diagnosed by the 6-month time point after starting chemotherapy [15], 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 to better capture how CIPN may be temporally involved in the early development of Dep/Anx, leaving a 12-month pre-index period to ascertain baseline data, which is common for claims-based research [16].

In order to determine if the association of CIPN with Dep/Anx is beyond the effect of BrCa, two comparison groups were used: women with BrCa+/CIPN- and BrCa-/CIPN -. For the BrCa+/CIPN- group, two steps were taken to account for similarity with the BrCa+/CIPN+ group. First, incident BrCa cases were included to account for the effect of a newly diagnosed condition on mental health disorders. Second, the methods were designed so the index date for the BrCa+/CIPN- group was similar to the BrCa+/CIPN+ group. Specifically, the first claim for BrCa, without a BrCa claim in the 12-months preceding, was identified from January 1, 2013 to September 31, 2013. Since chemotherapy typically starts approximately three months after the initial diagnosis of BrCa [17], the index date for the BrCa+/CIPN- group was three 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 author DGW), as previously described [18]. Since BrCa is more common among older ages, the BrCa-/CIPN- group was much younger on average than the BrCa+ groups. While age adjustment was performed, the BrCa-/CIPN- group was modified (in a random fashion) to represent an age distribution that better reflected the BrCa groups (more closely aligned to the BrCa+/CIPN+ group) to enhance interpretation of unadjusted comparisons.

Following group allocation, individuals were included if they were: (1) ≥18 years of age; (2) had ≥12-months of continuous health plan enrollment in the pre-index period to ascertain baseline data [14]; and

(3) had ≥12-months of continuous health plan enrollment in the post-index period for the outcome measures.

Depression and anxiety

Dep/Anx were identified using at least one ICD-9-CM code (see **Supplementary Table 1**), in the 12-month pre-index period and in the post-index period by two subsequent 6-month periods (i.e., 0-6 and 7-12 months). Dep/Anx were examined as cumulative throughout the study period. For example, if an individual had depression in the pre-index period, they were considered to have depression in the two 6-month post-index 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.

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 from the index date, and whether the BrCa was malignant or non-malignant were included. Chemotherapy exposure was determined as ≥1 outpatient pharmacy claim for any relevant chemotherapy agents or ≥1 medical claim for any relevant HCPCS codes for non-oral administered chemotherapy. Chemotherapy included neurotoxic and non-neurotoxic agents and are included **Supplementary Table 1** [19]. Baseline comorbidities were identified in the 12-month pre-index period by at least one claim with an ICD-9-CM code for substance abuse problems (i.e., alcohol and drug dependence, nondependent abuse of drugs, and personal history of tobacco use), type 2 diabetes, sleep disorders (i.e. insomnias, circadian rhythm disorders, somnolence disorders, parasomnia disorders, and other sleep disorders), and kidney problems (i.e., acute kidney failure, renal sclerosis, and chronic kidney disease stages 1-5, dialysis, and/or kidney transplant), as previously described [20-23].

Statistical analysis

Pre-index descriptive characteristics were summarized 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 pre- and post-index Dep/Anx were calculated as the sample proportion ± the margin of error with a z-value of 1.96 [13]. Logistic regression models were developed to compare the odds ratio (OR with 95% CI) of Dep/Anx for each period (i.e., pre-index and two 6-month post-index periods) before and after adjusting for pre-index covariates that were significantly different between groups.

Risk ratios (RR with 95% CI) were estimated to quantify the change in risk of Dep/Anx from the pre- to post-index periods for each group. A difference-in-difference analysis was conducted to determine if the change in risk of Dep/Anx from pre- to post-index periods was different for the BrCa+/CIPN+ group as compared to the BrCa+/CIPN- and BrCa-/CIPN- groups. In particular, a generalized linear model with

repeated measures, a binomial distribution, and a log link function was used before and after adjusting for pre-index covariates that were significantly different 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 RR (RRR; 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.

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 pre- to post-index 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 unknown cases. We therefore performed two related analyses to examine for the possibility of confounding and selection bias by race, as described previously [14]. 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 unadjusted results from the restricted sample with complete data on race. Possible selection bias by race was assessed by comparing the unadjusted 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.

Results

Pre-index descriptive characteristics of women with BrCa+/CIPN+ (n=244), BrCa+/CIPN- (n=8,870), 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 malignant 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 unadjusted prevalence of pre- and post-index Dep/Anx is quantitatively presented in **Table 2** and visually presented in **Figure 1**. The unadjusted and adjusted OR of pre- and post-index Dep/Anx is presented in **Table 3**. In the pre-index 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-. For depression in the post-index periods, BrCa+/CIPN+ had a higher prevalence compared to BrCa-/CIPN- 0-6 months post-index and a higher prevalence compared to both groups 7-12 months post-index. For anxiety in the post-index periods, BrCa+/CIPN+ had a higher prevalence compared to both groups for 0-6- and 7-12-months post-index. The findings were

unchanged after adjusting for pre-index covariates that were significantly different between groups (**Table 3**) and after adjusting for all covariates (data not shown).

The unadjusted RR for the change in pre to post-index risk of Dep/Anx are presented in **Table 2** and visually presented in **Figure 1**. All groups exhibited a significant increase in the risk of Dep/Anx in the 0-6 months post-index period (RR=1.22 to 1.65 for depression, RR=1.26 to 1.73 for anxiety, all $p<0.05$) and 7-12 months post-index period (RR=1.41 to 2.16 for depression, RR=1.46 to 2.05 for anxiety, all $p<0.05$) compared to the pre-index period, with the BrCa+/CIPN+ group exhibiting the largest increase. When the RR was estimated for 7-12 months post-index as compared to 0-6 months post-index, all groups exhibited an elevated RR for depression with the BrCa+/CIPN+ group having the highest RR; although, the elevated RR was marginally statistically insignificant for the BrCa+/CIPN+ group ($p=0.060$). The increased risk was similar across groups for anxiety for 7-12 months post-index period as compared to 0-6 months post-index period, but was not statistically significant for the BrCa+/CIPN+ group (RR=1.19; 95% CI=0.91-1.55).

The results of the difference-in-difference analysis is presented in **Table 4**. The unadjusted RRR for depression was significantly elevated for BrCa+/CIPN+ compared to both groups for both 6-month post-index periods compared to the pre-index period, and even for the 7-12 months compared to the 0-6 months post-index period. The unadjusted RRR for anxiety was significantly elevated for BrCa+/CIPN+ compared to both groups for both 6-month post-index periods compared to the pre-index period, but not for the 7-12 months compared to the 0-6 months post-index period. The findings were similar for Dep/Anx after adjustment for pre-index covariates that were significantly different between groups.

Sensitivity analysis

Due to only 43.9% of the BrCa+/CIPN+ cohort receiving definite chemotherapy, a sensitivity analysis was performed to determine if there were differences of Dep/Anx prevalence within the BrCa+/CIPN+ stratified by definite chemotherapy exposure. The prevalence and change in pre- and post-index 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, RR, OR, and RRR is presented in **Supplementary Tables 2-4**. 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 RRs. 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.

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 pre-index prevalence of these mental health disorders. Further, the increased risk of depression associated with the onset of CIPN continued in the second 6-month post-index period following estimated chemotherapy initiation. 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. has demonstrated that BrCa survivors' CIPN symptoms were associated with increased depression, anxiety, and sleep disorders at five years post-chemotherapy treatment [12]. 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. demonstrated that BrCa survivors with CIPN symptoms at one year often persist five years later [24]. 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 five years post-chemotherapy treatment [24]. 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 [25]. In addition, our results show that BrCa survivors have a relatively increased Dep/Anx prevalence compared to their peers without a BrCa diagnosis, evidence that is also well established in the literature [25-27].

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 diagnosisOur temporal association demonstrates that CIPN is associated with increased odds of Dep/Anx at 0-6 months and this continues at 7-12 months after a CIPN diagnosis among BrCa survivors. This is a novel finding as CIPN symptoms can abate before one-year post-chemotherapy, but it is possible that patients' risk for developing Dep/Anx may continue beyond one-year post CIPN diagnosis.

Our findings may have clinical relevance. Supportive care providers may consider screening BrCa survivors for Dep/Anx and/or revaluating fall risk after a diagnosis of CIPN. Functionally, CIPN has been independently associated with a reduced quality of life, as well as falls [4-5]. 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 [10-11]. Further, Huang et al has demonstrated that depression is a significant risk factor for falls in cancer survivors independent of CIPN [9]. 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. has described that despite the American Society of Clinic 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 [13]. Therefore, supportive care providers may consider duloxetine as opposed to gabapentinoids, per the recent ASCO guidelines [28], 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 [29].

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 pro-inflammatory cytokines

including interleukin-1, interleukin-6, and c-reactive protein [30]. Elevations in plasma levels of these cytokines have been associated with Dep/Anx [31]. 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 [32-33]. 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, psychologic factors related to the burden of walking instability and difficulty performing everyday activities may also be responsible for CIPN associated Dep/Anx [34].

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, chemotherapeutic use, and neuropsychiatric diagnoses are likely underrepresented approximations. Due to a likely underrepresented chemotherapeutic use and use of an ICD-9 code, we are unable to definitively determine whether peripheral neuropathy is truly due to chemotherapy. While claims data are not particularly sensitive in identifying CIPN, it has been found to be specific [13]. In our study, we did not record group differences in antidepressant use or cancer severity and so these are possible unaccounted for confounders. First, CIPN's association with the development of Dep/Anx in the post-index time periods is unlikely to be explained by differences in antidepressant medications given the similar pre-index levels of Dep/Anx in each of the three groups suggesting that the groups likely had comparable proportions of antidepressant use. Second, 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 didn't have access to group differences in cancer severity we did record group differences in malignant and non-malignant cancer which demonstrated less malignant cancer in BrCa+/CIPN+ vs. BrCa+/CIPN-. Lastly, we did not record history of prior psychiatric disease aside from Dep/Anx or the socioeconomic status of the survivors, which are known risk factors for the development of Dep/Anx in this patient population [6].

In summary, this study suggests that the onset of CIPN in BrCa survivors is associated with an early increased risk of developing Dep/Anx. Clinically, recognition of CIPN is important for its impact on neuromuscular function, mobility, and fall risk. Our work also suggests that CIPN may serve as a previously unrecognized risk factor predisposing BrCa survivors to Dep/Anx, which is known to diminish quality life, increase mortality, and compound fall risk.

Declarations

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

Ethics Approval:

This article does not contain any studies with human participants performed by any of the authors. Data are de-identified and the University IRB approved this study as non-regulated.

Consent to participate: Data are de-identified and from insurance claims and therefore this section doesn't apply.

Consent to publication: Data are de-identified and from insurance claims and therefore this section doesn't apply.

Availability of data: The data that support the findings of this study are available from Optum's De-identified Clinformatics® Data Mart Database but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Optum's De-identified Clinformatics® Data Mart Database.

Availability of code: Code is available from the authors upon reasonable request.

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Brendan L. McNeish and Daniel G. Whitney. The first draft of the manuscript was written by Brendan L. McNeish and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1

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

	BrCa+/CIPN+ (n = 244)	BrCa+/CIPN- (n = 8,870)	BrCa-/CIPN- (n = 1,125,711)
	% (n)	% (n)	% (n)
Age, mean (SD)	61.7 (11.9)[1]	66.5 (13.6)[2]	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 (3,347)	50.0 (562,856)
≥65 years	41.8 (102)	58.7 (5,209)	46.0 (517,827)
Race		[2]	
White	66.4 (162)	67.4 (5,982)	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 (1,243)	13.9 (156,424)
U.S. region of residence		[2]	
West	32.8 (80)	30.7 (2,720)	27.7 (311,432)
Midwest	23.0 (56)	21.0 (1,862)	22.5 (253,488)
South	34.4 (84)	33.9 (3,006)	36.3 (408,762)
Northeast	9.8 (24)	14.5 (1,282)	13.5 (152,029)
Malignant BrCa	71.3 (174)[1]	95.5 (8,469)	0 (0)
Chemotherapy			
Any chemotherapy	43.9 (107)[1,2]	10.2 (903)[2]	0.5 (5,774)
Neurotoxic chemotherapy agents	40.6 (99)[1,2]	9.4 (832)[2]	0.4 (3,961)
Comorbidities			
Substance abuse	15.2 (37)[2]	13.1 (1,161)[2]	6.9 (78,112)
Type 2 diabetes	18.0 (44)	20.1 (1,786)[2]	16.6 (186,933)
Any sleep disorder	11.9 (29)	10.5 (932)[2]	8.6 (96,456)
Insomnias	7.8 (19)	6.1 (537)[2]	5.0 (56,474)

	BrCa+/ClPN+ (n = 244)	BrCa+/ClPN- (n = 8,870)	BrCa-/ClPN- (n = 1,125,711)
Circadian rhythm disorders	*	*	0.1 (563)
Somnolence disorders	4.5 (11)	5.0 (447)[2]	4.0 (44,509)
Parasomnia disorders	*	*	0.1 (508)
Other sleep disorders	*	0.3 (23)	0.3 (2,799)
Renal Disease	4.9 (12)[1]	9.6 (848)[2]	6.7 (75,418)
Acute kidney failure	*	2.1 (185)[2]	1.3 (14,864)
Renal sclerosis	*	0.2 (19)[2]	0.1 (1,165)
CKD stages 1–3	4.5 (11)	7.5 (664)[2]	5.4 (60,661)
CKD stages 4+	*	2.1 (182)[2]	1.3 (14,449)

CKD, chronic kidney disease.

*n≤10 events and not reported to maintain patient de-identification and group comparisons not performed.

[1]$p<0.05$ compared to BrCa+/CIPN-.

[2]$p<0.05$ compared to BrCa-/CIPN-.

Table 2

Unadjusted prevalence and risk ratio (RR) of pre- and post-index depression and anxiety among women with (+) or without (-) breast cancer (BrCa) and chemotherapy-induced peripheral neuropathy (CIPN).

	BrCa+/CIPN+ (n = 244)	BrCa+/CIPN- (n = 8,870)	BrCa-/CIPN- (n = 1,125,711)
Depression			
Prevalence, % (95% CI)			
Pre-index	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)
RR (95% CI)			
0–6 months vs. pre-index	1.65 (1.14, 2.38)	1.22 (1.15, 1.29)	1.23 (1.22, 1.24)
7–12 months vs. pre-index	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)			
Pre-index	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)
RR (95% CI)			
0–6 months vs. pre-index	1.73 (1.22, 2.44)	1.26 (1.18, 1.36)	1.31 (1.29, 1.31)
7–12 months vs. pre-index	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)

CI, confidence interval.

Table 3

Odds ratio (OR) of pre- and post-index depression and anxiety among women with (+) or without (-) breast cancer (BrCa) and chemotherapy-induced peripheral neuropathy (CIPN).

	Depression		Anxiety	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pre-index				
BrCa+/CIPN + vs. BrCa+/CIPN-	0.85 (0.59, 1.20)	0.92 (0.64, 1.32)	1.24 (0.88, 1.75)	1.10 (0.77, 1.58)
BrCa+/CIPN + vs. BrCa-/CIPN-	1.11 (0.79, 1.58)	0.96 (0.68, 1.38)	1.85 (1.32, 2.59)	1.56 (1.10, 2.20)
Post-index 0–6 months				
BrCa+/CIPN + vs. BrCa+/CIPN-	1.23 (0.92, 1.66)	1.29 (0.95, 1.75)	1.88 (1.42, 2.50)	1.60 (1.19, 2.16)
BrCa+/CIPN + vs. BrCa-/CIPN-	1.62 (1.22, 2.17)	1.37 (1.02, 1.85)	2.74 (2.07, 3.62)	2.27 (1.71, 3.03)
Post-index 7–12 months				
BrCa+/CIPN + vs. BrCa+/CIPN-	1.50 (1.14, 1.97)	1.53 (1.16, 2.03)	2.02 (1.54, 2.65)	1.74 (1.31, 2.31)
BrCa+/CIPN + vs. BrCa-/CIPN-	1.98 (1.52, 2.59)	1.64 (1.25, 2.15)	2.82 (2.17, 3.68)	2.26 (1.72, 2.97)

CI, confidence interval. *Compared to BrCa+/CIPN-, models adjusted for age (as continuous), malignant BrCa, chemotherapy exposure, and any renal disease; compared to BrCa-/CIPN-, models adjusted for chemotherapy exposure and substance abuse problems.

Table 4

The ratio of the risk ratio (RRR) of pre- to post-index depression and anxiety among women with (+) or without (-) breast cancer (BrCa) and chemotherapy-induced peripheral neuropathy (CIPN).

	Depression		Anxiety	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
0–6 months vs. pre-index				
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. pre-index				
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)

CI, confidence interval. *Compared to BrCa+/CIPN-, models adjusted for age (as continuous), malignant BrCa, chemotherapy exposure, and any renal disease; compared to BrCa-/CIPN-, models adjusted for chemotherapy exposure and substance abuse problems.

Figures

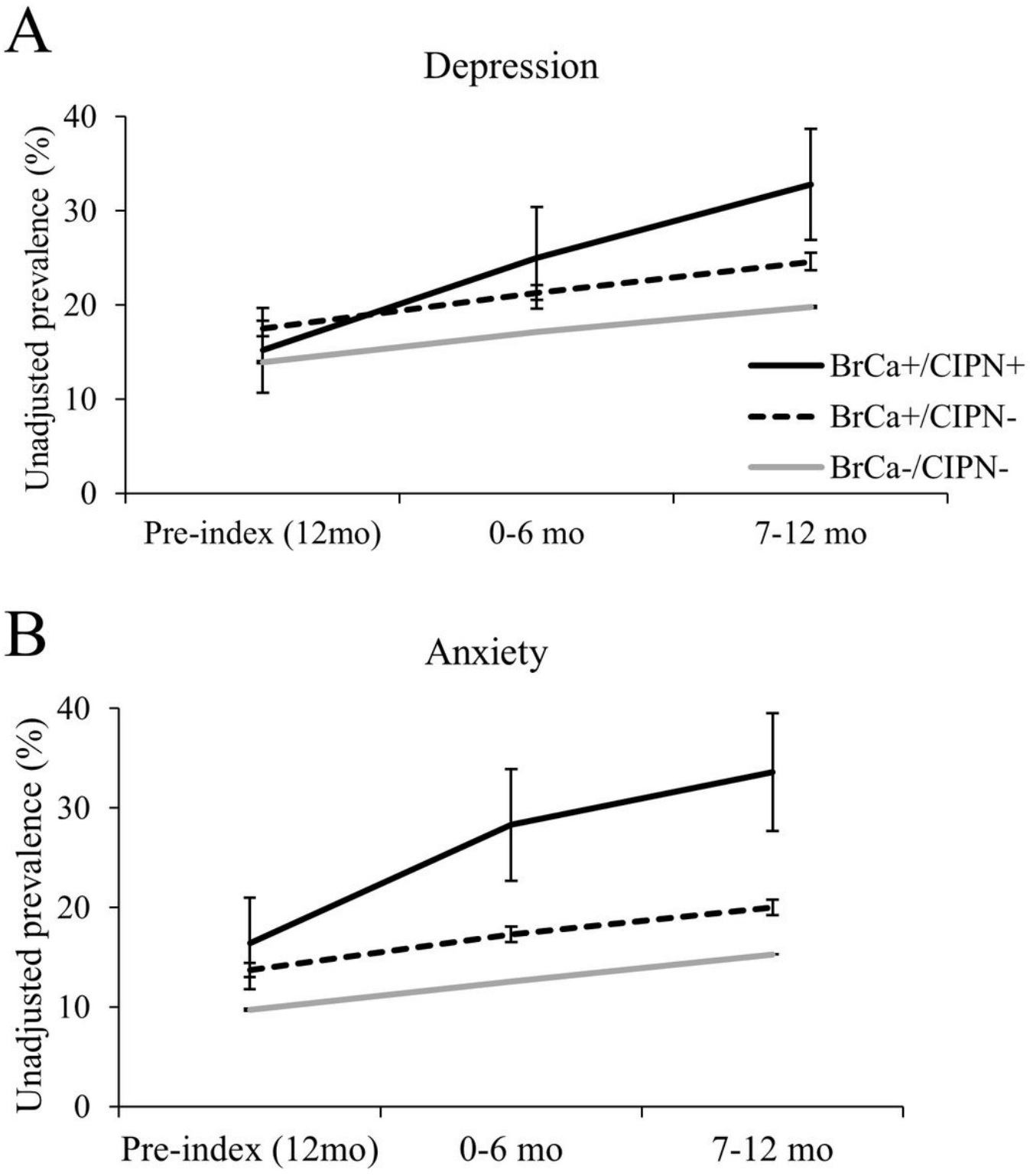

Figure 1

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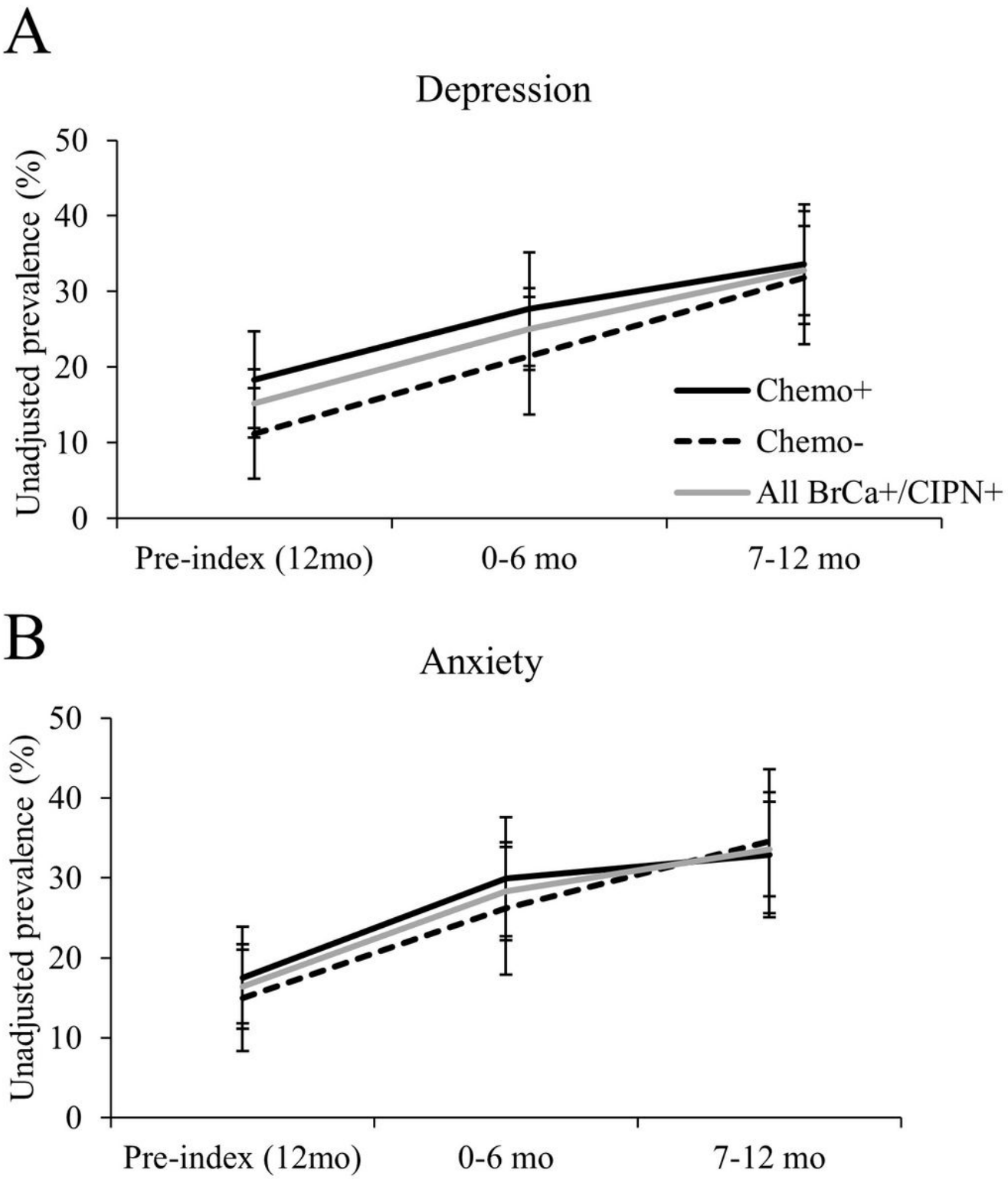

Figure 2

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