McNeish Brendan L. (Orcid ID: 0000-0002-8285-168X)

Main Text:

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

Running Title: Risk of depression/anxiety is associated with CIPN

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=8,870), 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 pre-index period to post-index 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 post-index 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

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BrCa-/CIPN- for post-index 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: Quality of life; Supportive Care; Psychological; Breast Cancer; Chemotherapy

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

Background

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.[9,10] 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. 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. 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.[13] 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 Institutional Review Board identified 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 invasive (174.x) and non-invasive (233.0) BrCa and CIPN (357.6) as McNeish et al. described.[15] 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,[16] 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 pre-index period to ascertain baseline data, which is common for claims-based research.[17]

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 January 1, 2013 to September 31, 2013. Second, since chemotherapy typically starts approximately three months after the initial diagnosis of BrCa,[18] 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 the author), as described by Whitney et al.[19] Since BrCa is more common among older ages, the "background" population, i.e., 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: (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

The prevalence of Dep/Anx were identified using at least one ICD-9-CM code (see **Supplementary Table 1**), in either the 12-month pre-index period, the post-index 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 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 at the time of the index date, and whether the BrCa was invasive or non-invasive 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 non-oral administered chemotherapy. Chemotherapy included neurotoxic and non-neurotoxic agents and are included **Supplementary Table 1**.[20] 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, type 2 diabetes, sleep disorders, and kidney problems, as Whitney et al described.[21]

Statistical Methods

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.

Prevalence ratios (PR 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 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.

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 of unknown race. We therefore performed two related analyses to examine for the possibility of confounding and selection bias by race.[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 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.

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 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 pre- and post-index Dep/Anx are quantitatively presented in **Table 2** and visually presented in **Figure 1**. When comparing the confidence intervals 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-. When comparing confidence intervals for depression in the post-index periods, BrCa+/CIPN+ had a similar prevalence compared to BrCa-/CIPN- 0-6 months post-index and a higher prevalence compared to both groups 7-12 months post-index. Finally, when comparing the respective confidence intervals 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, **Table 2**.

The crude PR 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 PR points estimates of Dep/Anx in the 0-6 months post-index 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 post-index period (PR=1.41 to 2.16 for depression, PR=1.46 to 2.05 for anxiety, all $p<0.05$) compared to the pre-index period. When the PR was estimated for 7-12 months post-index as compared to 0-6 months post-index, 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 post-index period as compared to 0-6 months post-index 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 pre-index 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 post-index 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 post-index 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).

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+ group 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, PR, and RPR is presented in **Supplementary Tables 2-3**. 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.

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. 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 the CIPN symptoms that BrCa survivors have at one year often persist five years later.[22] 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.[22] 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.[23] 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.[23–25]

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 one-year post-chemotherapy, 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 reevaluating 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.[9,10] Further, Huang et al has demonstrated that depression is a significant risk factor for falls in cancer survivors independent of CIPN.[11] 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 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.[13] Therefore, supportive care providers may consider duloxetine as

opposed to gabapentinoids, per the recent ASCO guidelines,[26] 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.[27]

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.[28] Elevations in plasma levels of these cytokines have been associated with Dep/Anx.[28,29] 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.[30,31] 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.[32]

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.[3] 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 and colleagues 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.[13] 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 didn't have access to group differences in cancer

severity we did record group differences in invasive and non-invasive cancer which demonstrated less invasive cancer in BrCa+/CIPN+ vs. 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 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 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 optimize 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.

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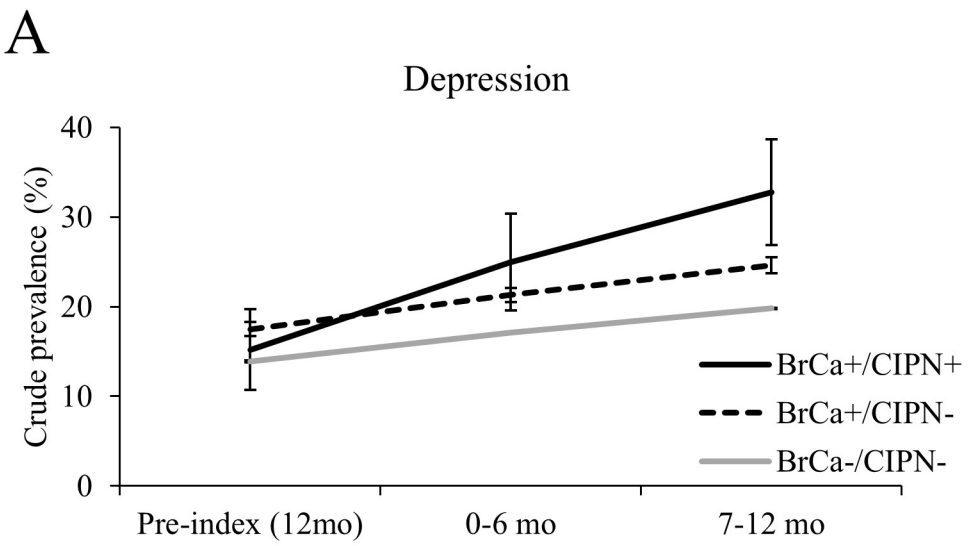
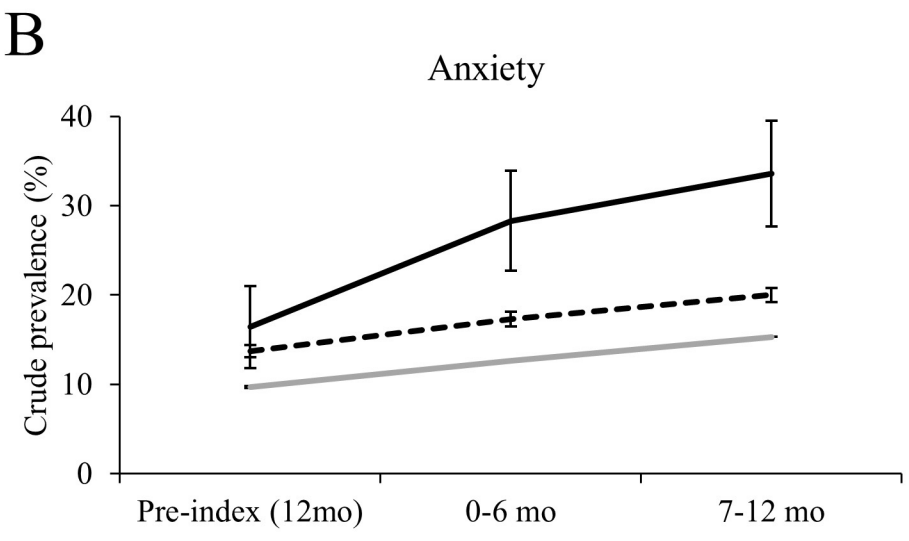
Figure Legends

Figure 1: A, Crude Prevalence of Depression at Pre-index, 0-6 months, and 7-12 months between BrCa+/CIPN+, BrCa+/CIPN-, and BrCa-/CIPN- groups. **B**, Crude Prevalence of Anxiety at Pre-index, 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).

Figure 2: A, Crude Prevalence of Depression at Pre-index, 0-6 months, and 7-12 months within BrCa+/CIPN+ including Chemo+, Chemo-, and all BrCa+/CIPN+. **B**, Crude Prevalence of Anxiety at Pre-index, 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).





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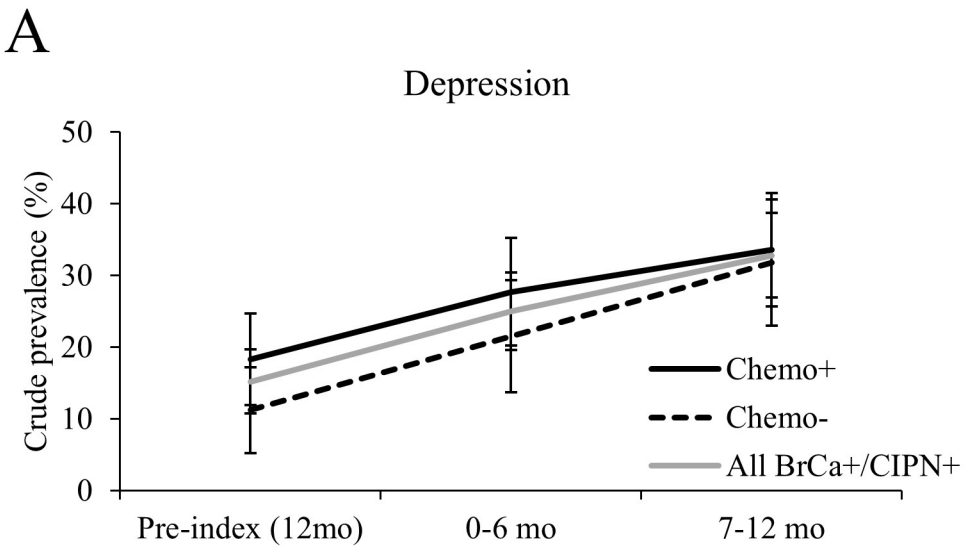

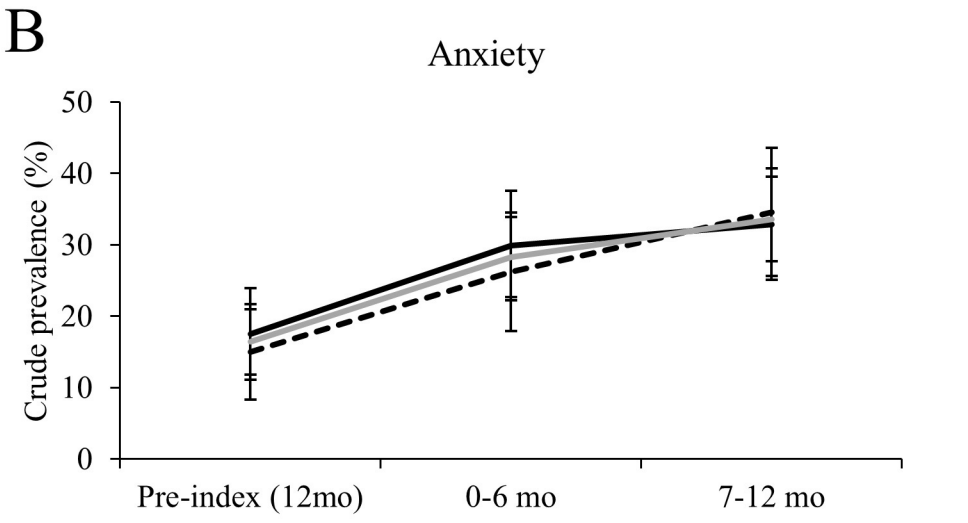

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