Presence and Distress of Chemotherapy-Induced Peripheral Neuropathy Symptoms in Upper Extremities of Younger and Older Breast Cancer Survivors

Susan Storey, PhD, RN,[1] Andrea Cohee, PhD, RN,[1] Diane Von Ah, PhD, RN,[1] Eric Vachon, PhD, RN,[1] Noah R. Zanville, PhD, RN,[2] Patrick O. Monahan, PhD,[3,4] Timothy E. Stump, MA,[3] and Victoria L. Champion, PhD, RN[1]

1 Indiana University School of Nursing, Indianapolis, IN

2 Miami Cancer Institute, Baptist Health South Florida, Miami, FL

3 Indiana University School of Medicine, Indianapolis, IN

4 Richard M. Fairbanks School of Public Health, Indianapolis, IN

Abstract

Purpose

The purpose of this study was to determine whether the presence of upper extremity chemotherapy-induced peripheral neuropathy (CIPN) symptoms (burning, pins/needles, numbness, pain and skin crawls) varied according to age (< 45 years) or (55-70 years); and to examine age group differences in upper extremity CIPN symptom distress.

Methods

A secondary analysis of younger (n=505) and older (n=622) breast cancer survivors. Inclusion criteria were age < 45 years of age or 55-70 years of age; 3-8 years post-diagnosis; having received the chemotherapy regimen of Taxol®, Adriamycin®, and Cytoxan®; and without recurrence. The Symptom Survivor Checklist was used to assess presence and distress of upper extremity CIPN symptoms. Analyses explored whether age group predicted CIPN symptom presence and distress, while controlling for sociodemographic and medical variables.

Results

Older BCS reported fewer pins/needles, numbness and pain symptoms (OR .623-.751). Heart disease (OR 1.6-1.7) and progesterone-negative breast cancer (OR .663) also were significantly associated with CIPN symptoms. Symptom distress ratings did not differ by age groups; both age

This is the author's manuscript of the article published in final edited form as:

Storey, S., Cohee, A., Von Ah, D., Vachon, E., Zanville, N., Monahan, P. O., Stump, T. E., & Champion, V. (2020). Presence and Distress of Chemotherapy-Induced Peripheral Neuropathy Symptoms in Upper Extremities of Younger and Older Breast Cancer Survivors. Journal of Patient-Centered Research and Reviews.7(4), 295-303. https://dx.doi.org/10.17294/2330-0698.1757

groups indicated distress from CIPN symptoms, with 25% or more reporting as “moderately” or as “quite a bit” of distress.

Conclusion

Younger BCS reported more upper extremity CIPN symptoms. BCS in both groups continued to report bothersome CIPN symptoms years post-treatment. Findings from this study will assist clinicians in identifying BCS at higher risk for upper-extremity CIPN and inform the development of appropriate tailored interventions to mitigate these symptoms and facilitate restoration to age-related baseline functional status thereby improving quality of life for BCS.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most prevalent, persistent, and disruptive symptoms associated with common antineoplastic treatments (e.g., taxanes) for breast cancer.[1-5] Approximately two-thirds of breast cancer survivors (BCS) report symptoms of CIPN during cancer treatment, [6] with as many as 42% reporting lingering symptoms for up to 3 years post treatment.[2, 7-10] Symptoms of CIPN include sensations of burning, pins/needles, numbness,[1, 5, 9] pain[1, 5] and/or skin crawls affecting the hands and/or feet.[1, 4, 5, 11-13] Although treatments have improved, the continued reliance on taxanes (e.g., Paclitaxel) and other neurotoxic agents to treat breast cancer has contributed to serious, and at times, permanent changes that significantly interfere with survivors' daily functioning.[5, 7, 9, 11, 12]

The onset of CIPN in BCS has been associated with sociodemographic (age [7, 11, 14, 15] race, [2, 9, 15] income,[16] education,[16] and alcohol consumption)[16] and medical characteristics (comorbidities,[5, 11, 16] hormone status,[2] tumor size,[10] body mass index,[2, 9, 15] number of positive nodes,[10] and years from diagnosis.[17, 18] Age in particular may be an important risk factor in both CIPN symptom presence and distress.[7, 11, 14, 15] While several studies have found a higher prevalence and longer duration of CIPN symptoms in older BCS (60 years of age and older),[2, 7, 11, 14-16] others have found a higher prevalence of CIPN symptoms in younger BCS. [2, 19] Yet still,

some studies found no association between age and the presence of CIPN symptoms. [20, 21] Most of these studies have concentrated exclusively on the lower extremities, with little focus on upper extremity CIPN symptoms. Determining the impact of upper extremity CIPN symptoms is important to study as fine motor movements can be impaired, [22] potentially interfering with the ability of BCS to perform daily activities. Understanding age-related differences in the presence and impact of upper extremity (shoulder, arms, hands and fingers) CIPN symptoms is important, given that symptoms may differentially affect independence and quality of life. [5, 17, 19] While lower extremity CIPN may be more distressing for older BCS (e.g., concerns about increased falls), upper extremity CIPN may be more distressing for younger BCS (e.g., concerns about managing work and family responsibilities).

The purpose of this study was to examine upper extremity CIPN symptoms among BCS according to age group (younger versus older BCS). The aims of this study were twofold. Aim 1 sought to determine whether the presence of upper extremity CIPN symptoms (burning, pins/needles, numbness, pain and skin crawls) varied according to age group. Aim 2 sought to examine age group differences in upper extremity CIPN symptom distress. This information will be particularly useful for clinicians and researchers challenged in the care of long-term and troubling symptoms of CIPN. Findings from this study will assist with identifying BCS at higher risk for CIPN and inform the development of tailored interventions to mitigate these symptoms.

Methods

Study Design and Sample

This study is a secondary analysis of 1,127 BCS (younger and older) using data from a cross-sectional quality of life study that included several self-reported measures for common symptoms experienced by BCS. Details of the parent study have been described previously.[23]

Briefly, BCS were eligible for the if they were 1) 45 years old or younger (younger BCS) or 55-70 years old (older BCS) at diagnosis; 2) 3-8 years post-diagnosis without recurrence; and 3) received a chemotherapy regimen that included Paclitaxel, Doxorubicin, and Cyclophosphamide as part of their initial breast cancer treatment. BCS 46-54 years of age were excluded to avoid the potential confounding peri-menopausal timeframe. The study was approved by the coordinating university's institutional review board.

Measures

Sociodemographic variables (independent variables). Sociodemographic variables, including age, race, income, education, and alcohol consumption were self-reported. Age was coded as a dichotomous variable of younger (45 years or younger) and older (55-70 years) which was consistent with the targeted enrollment groups, as it is less common for BCS over 70 years of age to receive this treatment regimen. Race was coded as a categorical variable (white or non-white), income was coded as a dichotomous variable (< $75,000 or ≥ 75, 000) and education was coded as a continuous variable for years of education. Alcohol consumption was queried by asking, "On those days that you drink alcoholic beverages, about how many do you usually have?" Response options were > 5 drinks, 3-5 drinks, 1-2 drinks, and I do not drink (none). For this study, the alcohol consumption variable was recoded into categories of ≥ 3 drinks per day, 1-2 drinks per day, or none.

Medical variables (independent variables). Medical information was collected via self-report from BCS and included comorbidities (heart disease, hypertension and diabetes), hormone status, tumor size, body mass index (BMI; calculated from height and weight), number of positive nodes, and years from diagnosis. Researchers reviewed medical records to verify patient-reported information.

Chemotherapy-induced peripheral neuropathy symptoms (dependent variables). The Symptom Survivor Checklist was developed for this study based on review of CIPN literature. [1, 4, 5, 11-13] The Symptom Survivor Checklist is a 12-item scale that assesses five common upper extremity CIPN symptoms on the affected side, including burning, pins/needles, numbness, pain and skin crawls. BCS were asked if the symptoms were present (yes/no). If present, then BCS rated the extent to which they were bothered or distressed by symptoms on a 5-point ordinal scale (0 = not at all; 1= slightly; 2 = moderately; 3 = quite a bit; 4 = extremely). Higher scores were indicative of greater symptom distress. Cronbach's alpha for this scale in our study was 0.78.

Data analysis. Data analysis was conducted using SPSS version 25.0 (IBM Corp., Armonk, NY) and significance was set at $p = .05$. Two-tailed tests were used for all comparisons. Prior to the analysis, Shapiro-Wilks tests were used to test for normality of the data. Descriptive statistics were used to summarize the distributions of sociodemographic and medical variables. To examine age group differences in sociodemographic and medical characteristics, we used Pearson chi-square tests for categorical variables (race, income, marital status, comorbidities, hormone status, alcohol consumption) and independent t-tests for continuous variables (years of education, BMI, years from diagnosis, number of positive nodes, tumor size).

For aim 1, we first conducted five separate Pearson chi-square tests to determine if there was a significant association between age group and the presence of each of the five upper-extremity CIPN symptoms (burning, pins/needles, numbness, pain and skin crawls). Three significant symptoms were analyzed in a series of separate binary logistic regression analyses to determine whether age group was associated with the presence of the symptoms, while controlling for sociodemographic (age, race, income, education, and alcohol consumption) and

medical (heart disease, hypertension and diabetes, hormone status, tumor size, BMI, number of positive nodes, and years from diagnosis) variables that theoretically could influence CIPN. In the regression model, each symptom was entered as a dependent variable; age was an independent variable along with other sociodemographic and medical covariates. Using a backward deletion approach, statistically non-significant sociodemographic and medical characteristics were removed until the final model was achieved.

For aim 2, Mann Whitney U tests were conducted to examine age group differences in symptom distress. Participants who did not report any CIPN symptoms were removed from the Mann Whitney U analysis. If significant, backward deletion ordinal logistic regression analyses would have been conducted to determine if age group predicted symptom distress, while controlling for sociodemographic and medical characteristics.

Results

Sample Characteristics

Sociodemographic and medical characteristics of younger (n = 505) and older (n = 622) BCS are shown in Table 1. On average, BCS were 6 years post treatment. Compared to older BCS, younger BCS had significantly higher incomes, were more likely to be married, had fewer comorbidities, consumed more alcohol, and had more years of education.

Aim 1. Presence of CIPN Symptoms

Table 2 shows the Chi Square results for the presence of upper extremity CIPN symptoms for the total sample and by age group. Age group (younger age) was significantly associated with three CIPN symptoms, pins/needles ($p = .021$), numbness ($p < .001$), and pain ($< .001$).

Results of logistic regression analyses are summarized in Table 3. Age significantly predicted the presence of pins/needles, numbness and pain symptoms. Older BCS had lower odds of reporting upper extremity pins/needles, numbness and pain symptoms compared to younger BCS (OR .623-.751). Comorbid heart disease also was a significant predictor of these three upper-extremity CIPN symptoms. BCS with heart disease were 1.6-1.7 times more likely to report pins/needles, numbness and pain symptoms. Additionally, hormone status predicted the presence of the pins/needles symptom. Those with positive progesterone receptor status (PR+) had lower odds (OR .663) of experiencing the pins/needles symptom. While statistically significant, the variation (R^2) in the dependent variable based on our models ranged from 2.3-2.9%, demonstrating a small but reliable relationship between age and upper extremity CIPN symptoms (pins/needles, numbness, pain).

Aim 2. Symptom Distress

Table 4 shows the level of distress associated with CIPN symptoms by age group. Distress scores ranged from 1 (slightly) to 3 (quite a bit), with the typical score (i.e., median) indicating BCS were slightly or moderately distressed. It should be noted that 2 or 3, depending on the symptom, was not only the maximum score, but also the 75th percentile, indicating that 25% of BCS perceived "moderately" or "quite a bit" of distress for each symptom. Mann Whitney U tests showed no significant age group differences in upper extremity CIPN symptom distress. Given that there were no statistically significant age group differences in symptom distress scores, ordinal logistic regression was not conducted.

Discussion

The purpose of this study was to describe the presence and distress level of upper extremity CIPN symptoms in BCS three or more years post-treatment. The findings of this study

offer several key insights. First, our findings add to the literature showing that younger BCS report the presence of upper extremity CIPN symptoms more often than older BCS. Second, comorbid heart disease and hormone status were risk factors for upper extremity CIPN symptoms. Third, both younger and older BCS continued to report upper extremity CIPN symptoms as distressing several years post-treatment.

Aim 1. Presence of CIPN Symptoms

While factors such as treatment duration and the intensity of taxane exposure BCS receive during treatment are known factors for developing chronic CIPN,[10-12] the role of age on these symptoms is less clear. In our study, we found younger BCS were more likely to report upper extremity CIPN symptoms of pins/needles, numbness and pain compared to their older counterparts. This finding is consistent with other studies that have shown younger BCS may be at higher risk of developing CIPN symptoms.[2, 19] Ali and colleagues found younger BCS had a higher lower risk of CIPN than younger BCS. However, the researchers did not discuss how CIPN was defined by location, limiting the ability to generalize the finding to other BCS populations.[2] Although underlying mechanisms contributing to age-related differences in CIPN symptoms are not clear, one possible explanation is that unlike younger BCS, older BCS may have pre-existing neuropathy and/or other neurodegenerative loss from comorbid conditions that lessen their perception of these symptoms.

In contrast to our findings, other studies have shown that older BCS are at increased risk for CIPN symptoms. Hershman and colleagues linked clinical trial data with Medicare claims and found older age to be the only demographic factor associated with the presence of upper and lower extremity CIPN symptoms.[13] However, the mean age of the sample was older (73 years of age), which may have influenced the study findings, additionally the lack of access to baseline

neurologic status, to determine if symptoms of neuropathy were pre-existing or new onset; may have resulted in higher reporting of symptom presence impacting the results of the study.

Similarly, Lichtman and colleagues examined neurotoxicity (neurosensory, neuromotor, neurocortical or neurocerebellar) symptoms among BCS (N =1048) in three age categories (< 55 years, 55-64 years and ≥65 years).[24] Compared to those in the younger age categories, women ≥ 65 years of age (n=272) reported earlier onset and the presence of neurotoxicity with first and second-line chemotherapy treatments.[24] However, the focus of the study was specific to neurotoxicity; which may influence neuropathy but cannot be directly extrapolated to CIPN symptoms.

Other researchers have found no association between age and CIPN symptoms. Schneider and colleagues studied BCS (n = 4,554) in three age categories (≤45, 46-65, and > 65 years) all receiving adjuvant taxane therapy.[25]Although they found CIPN symptoms in upper and lower extremities were common complications of treatment, age was not an associated factor. [25] However, the researchers indicated that a lack of uniform and validated CIPN assessments may have decreased the reliability of the study findings. More research is needed to assess if upper extremity CIPN symptoms differ by age among BCS.

Although diabetes has been noted as a risk factor for CIPN in BCS,[13] we did not find diabetes to be associated with upper extremity CIPN in our study. This finding may be related to the typical presentation of CIPN symptoms in the lower extremities in people with diabetes [26] whereas our study focused on upper extremity symptoms. Additionally, the number of BCS with comorbid diabetes (n = 121) in this study was low. An important finding from our study was that BCS with comorbid heart disease were more likely to report the presence of pins/needles, numbness and pain symptoms in the years following treatment. Heart disease, hypertension, and

diabetes, the most frequently documented comorbidities [27, 28-33] in BCS, are all associated with an increased risk of CIPN.[6, 30, 31] The BCS in our study received the same therapeutic regimen that included two of the most common cardiotoxic chemotherapies (Doxorubicin, and Paclitaxel). Because we examined heart disease broadly, we were not able to identify specific cardiac pathologies, nor determine if they occurred prior to or after cancer diagnosis and treatment, limiting our ability to determine if cardiovascular disease is a direct risk factor for CIPN, especially in the upper extremities. The influence of comorbid heart disease on CIPN symptoms among BCS has not been well studied. As BCS are living longer, the role of comorbid conditions on CIPN symptoms is important to understand and warrants further research. Clinicians should assess for the presence of CIPN symptoms in BCS with a history of heart disease.

Finally, although estrogen status did not predict upper extremity CIPN symptoms, progesterone status did. Specifically, BCS who were PR+ were less likely to report sensations of pins/needles in the years following treatment than BCS who were PR-. Our findings are consistent with other researchers who found that PR- status was associated with an increased risk of developing CIPN.[9] Studies have suggested that progesterone may have neuroprotective effects on the central and peripheral nervous systems by promoting repair of myelin.[33, 34]Although, the degree to which this may reduce the severity of taxane-induced CIPN is unclear. More research is needed to understand the role of hormone status on the symptoms of CIPN.

Aim 2. Symptom Distress

Results of our study found that even an average of six years post-treatment, BCS reported being distressed by their CIPN symptoms. However, although younger BCS were more likely

than older BCS to report upper extremity CIPN symptoms; we found no difference in distress levels with both younger and older BCS.

Studies examining differences by BCS age on symptom distress from upper extremity CIPN, are lacking. We found two studies that assessed CIPN symptom distress by age. Tanabe and colleagues found CIPN symptoms were more severe and persistent among older (≥ 60 years old) BCS.[14] However, the authors assessed CIPN symptoms in combination of upper and lower extremities, and did not differentiate symptom distress by location of upper or lower extremity. Wong and colleagues assessed age-related differences in a both upper and lower extremity CIPN symptoms of cancer survivors (n = 425), and found younger cancer survivors reported more severe pain and more interference in activity from CIPN symptoms when compared to older cancer survivors.[19] However, the study included heterogenous cancer diagnoses as well as survivors with metastatic disease which may have influenced the findings. Other studies have shown younger survivors with CIPN report more difficulty with general activities, work, and other components of quality of life,[19, 35, 36] an important finding given that they have not experienced nor adapted to the age-related losses that commonly occur with aging.[19]

The lack of association between age and CIPN distress we observed in the present study may have been a result of our choice of measure, which only assessed upper extremity CIPN symptoms. Future research should assess the symptom experience of upper and lower CIPN symptoms individually as well as collectively. Assessing upper and lower extremity function separately in BCS may provide helpful information as it relates to the differential impact of CIPN on function, and daily activities.

It is important to note, although we did not observe an age specific difference in the level of distress from upper extremity CIPN symptoms, both younger and older BCS still indicated

distress from these symptoms even years post treatment; with 25% or more reporting "moderately" or as "quite a bit" of distress, depending on the particular symptom. This finding supports other research that illustrates the lingering long-term impact of CIPN symptoms experienced by BCS. Future research should consider examining upper extremity CIPN symptoms in younger and older BCS longitudinally across the trajectory of cancer treatment into survivorship.

This study had several strengths. This study contributes to a growing body of literature by identifying age-related differences in three upper extremity CIPN symptoms. To our knowledge, this is one of the first studies to evaluate the impact of age and medical variables on specific upper extremity CIPN symptoms in BCS, and one of the first to evaluate this in a cohort > 3 years post treatment. Results from our analysis were drawn from a large, nationally representative sample of BCS that received one of the most common taxane-based regimens (a primary driver of CIPN in BCS), increasing the generalizability of the findings. The study included a 10-year separation between younger and older BCS, reducing variation in the sample. Given our findings that younger BCS are at risk, future research should explore the development and testing of age appropriate interventions to restore function, reduce distress, and improve quality of life.

Findings from this study also need to be considered in the context of several limitations. First, because of the cross-sectional study design, neurological diagnostic testing was not available, which limited the ability to identify baseline CIPN symptoms or determine if the symptoms evolved over time. Second, the upper age limit of older BCS in our study was 70 years of age, whereas other studies included much older subjects 65 or more years of age which may have influenced these findings. Third, we did not have access to information on cumulative

exposure to taxanes for participants, which could have an impact on CIPN symptoms. Fourth, because African American women, who have a 2- to 3-fold higher risk of taxane-induced CIPN than Caucasian women,[11, 13] were not well represented in this study, this limits generalizability to other race/ethnicities. Finally, although the Survivor Symptom Checklist demonstrated an acceptable Chronbach alpha, additional validation of the tool is warranted. Despite these limitations, the findings from this study add to the body of knowledge as it relates to the presence and distress of upper extremity CIPN symptoms from the younger and older BCS's perspective, which is an understudied area.

Implications for Practice

The information from this study will be particularly useful for clinicians and researchers challenged in the care of long-term and troubling CIPN symptoms. We found upper extremity CIPN symptoms can be distressing for BCS years post-treatment. CIPN symptoms are typically assessed in combination with lower extremity symptoms at the onset and intermittently during active treatment for cancer. Our findings elucidate the need for ongoing assessment and monitoring of upper extremity CIPN symptoms in BCS throughout the cancer trajectory well into survivorship. These assessments can facilitate referrals to rehabilitative programs to implement age-specific rehabilitative interventions geared towards maximizing safety and physical function improving overall quality of life for BCS.

Our findings have integral implications for occupational and rehabilitative staff when developing treatment plans aimed towards improving safety and functional performance for long-term BCS in survivorship programs. Of particular importance is our finding that younger BCS — for whom work is likely to be a critical issue — are more likely than older BCS to report pain, tingling, and numbness in their upper extremities. Although research specific to upper

extremity CIPN symptoms in BCS is nominal, several studies have implicated CIPN (upper/lower combined) symptoms (including the presence, number, type and duration of symptoms) with difficulty performing work-related tasks.[36-38] Successful rehabilitation efforts can facilitate strategies to increase participation in work, earlier return to work and improve activities of daily living, and overall quality of life.

Future research should consider examining upper extremity CIPN symptoms longitudinally in a more diverse sample of BCS across the trajectory of cancer treatment into survivorship. Additionally, research testing age-appropriate tailored interventions towards mitigating these symptoms, can thereby facilitate restoration to age-related baseline functional status and improve quality of life for BCS.

References

1. Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: A comprehensive survey. *Cancer Treat Rev*. 2014;40(7):872-882.
2. Ali MM, Moeller M, Rybicki L, Moore HC. Long-term peripheral neuropathy symptoms in breast cancer survivors. *Breast Cancer Res Treat*. 2017;166(2):519-526.
3. Majithia N, Temkin SM, Ruddy KJ, et al. National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: Outcomes and lessons. *Support Care Cancer*. 2016;24(3):1439-1447.
4. Jang CE, Jung MS, Sohn EH, et al. The evaluation of changes in peripheral neuropathy and quality-of-life using low-frequency electrostimulation in patients treated with chemotherapy for breast cancer: A study protocol. *Trials*. 2018;19:526. https://biomedcentral.com/articles/10.1186/s13063-018-2874-2. Accessed January 14, 2020.
5. Kırca K, Kutlutürkan S. Symptoms experience and quality of life in the patients with breast cancer receiving the taxane class of drugs. *Eur J Breast Health*. 2018;14(3):148-155.
6. Coffeen U, Sotomayor-Sobrino MA, Jiménez-González A, et al. Chemotherapy-induced neuropathic pain characteristics in Mexico's National Cancer Center pain clinic. *J Pain Res*. 2019;12:1331-1339.
7. Eckhoff L, Knoop A, Jensen M, Ewertz M. Persistence of docetaxel-induced neuropathy and impact on quality of life among breast cancer survivors. *Eur J Cancer*. 2015;51(3):292-300.

8. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*. 2014;155(12):2461-2470.

9. Bao T, Basal C, Seluzicki C, et al. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: Prevalence, risk factors, and fall risk. *Breast Cancer Res Treat*. 2016;159(2):327-333.

10. Bandos H, Melnikow J, Rivera DR, et al. Long-term peripheral neuropathy in breast cancer patients treated with adjuvant chemotherapy: NRG Oncology/NSABP B-30. *J Natl Cancer Inst*. 2017;110(2):149-156.

11. Bhatnagar B, Gilmore S, Goloubeva O, et al. Chemotherapy dose reduction due to chemotherapy induced peripheral neuropathy in breast cancer patients receiving chemotherapy in the neoadjuvant or adjuvant settings: A single-center experience. *SpringerPlus*. 2014;3(1):366. https://springerplus.springeropen.com/articles/10.1186/2193-1801-3-366. Accessed January 14, 2020.

12. Ewertz M, Qvortrup C, Eckhoff L. Chemotherapy-induced peripheral neuropathy in patients treated with taxanes and platinum derivatives. *Acta Oncol*. 2015;54(5):587-591.

13. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014;32(18):1941-1967.

14. Tanabe Y, Hashimoto K, Shimizu C, et al. Paclitaxel-induced peripheral neuropathy in patients receiving adjuvant chemotherapy for breast cancer. *Int J Clin Oncol*. 2013;18(1):132-138.

15. Greenlee H, Hershman DL, Shi Z, et al. BMI, lifestyle factors and taxane-induced neuropathy in breast cancer patients: The pathways study. *J Natl Cancer Inst*. 2017;109(2):1-8.

16. Hershman DL, Till C, Wright JD, et al. Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 years or older in southwest oncology group clinical trials. *J Clin Oncol*. 2016;34(25):3014-3022.

17. Molassiotis A, Cheng HL, Lopez V, et al. Are we mis-estimating chemotherapy-induced peripheral neuropathy? Analysis of assessment methodologies from a prospective, multinational, longitudinal cohort study of patients receiving neurotoxic chemotherapy. *BMC Cancer*. 2019;19(1):132. https://biomedcentral.com/10.1186/s12885-019-5302-4. Accessed January 14, 2020.

18. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. *Ann Neurol*. 2017;81(6):772-781.

19. Wong ML, Cooper BA, Paul SM, et al. Age-related differences in patient-reported and objective measures of chemotherapy-induced peripheral neuropathy among cancer survivors. *Support Care Cancer*. 2019;27(10):3905–3912.

20. Nurgalieva Z, Xia R, Liu CC, et al. Risk of chemotherapy-induced peripheral neuropathy in large population-based cohorts of elderly patients with breast, ovarian, and lung cancer. *Am J Ther*. 2010;17(2):148-158.

21. Wolf SL, Barton DL, Qin R, et al. The relationship between numbness, tingling, and shooting/burning pain in patients with chemotherapy-induced peripheral neuropathy (CIPN) as measured by the EORTC QLQ-CIPN20 instrument, N06CA. *Support Care Cancer*. 2012;20(3):625-632.

22. Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy. *Frontiers in Molecular Neuroscience*. 2017;10(174):1-24. https://doi.org/10.3389/fnmol.2017.00174

23. Champion VL, Wagner LI, Monahan PO, et al. Comparison of younger and older breast cancer survivors and age-matched controls on specific and overall quality of life domains. *Cancer*. 2014;120(15):2237-2246.

24. Lichtman S, Hurria A, Cirrincione C, et al. Paclitaxel efficacy and toxicity in older women with metastatic breast cancer: Combined analysis of CALGB 9342 and 9840. *Ann Oncol*. 2011;23(3):632-638.

25. Schneider BP, Zhao F, Wang M, et al. Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer. *J Clin Oncol*. 2012;30(25):3051-3057.

26. Hicks, C. W., & Selvin, e. (2019). Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. Current diabetes Reports. 19(10), 86 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6755905/

27. Sharma N, Narayan S, Sharma R, et al. Association of comorbidities with breast cancer: An observational study. *Trop J Med Res*. 2016;19(2):168-171.

28. Edwards BK, Noone AM, Mariotto AB, et al. Annual report to the nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer*. 2014;120(9):1290-1314.

29. Ewertz M, Land LH, Dalton SO, Cronin-Fenton D, Jensen MB. Influence of specific comorbidities on survival after early-stage breast cancer. *Acta Oncol*. 2018;57(1):129-134.

30. Fu M, Axelrod D, Guth A, et al. Comorbidities and quality of life among breast cancer survivors: A prospective study. *J Pers Med*. 2015;5(3):229-242.

31. Kus T, Aktas G, Kalender ME, et al. Taxane-induced peripheral sensorial neuropathy in cancer patients is associated with duration of diabetes mellitus: A single-center retrospective study. *Support Care Cancer*. 2016;24(3):1175-1179.

32. Roy S, Vallepu S, Barrios C, Hunter K. Comparison of comorbid conditions between cancer survivors and age-matched patients without cancer. *J Clin Med Res*. 2018;10(12):911-919.

33. Schumacher M, Guennoun R, Stein DG, De Nicola AF. Progesterone: therapeutic opportunities for neuroprotection and myelin repair. *Pharmacol Ther*. 2007;116(1):77-106.

34. Roglio I, Bianchi R, Camozzi F, et al. Docetaxel-induced peripheral neuropathy: Protective effects of dihydroprogesterone and progesterone in an experimental model. *J Peripher Nerv Syst*. 2009;14(1):36-44.

35. Beijers A, Mols F, Dercksen W, Driessen C, Vreugdenhil G. Chemotherapy-induced peripheral neuropathy and impact on quality of life 6 months after treatment with chemotherapy. *J Community Support Oncol*. 2016;12(11):401-406.

36. Zanville NR, Nudelman KN, Smith DJ, et al. Evaluating the impact of chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) on perceived ability to work in breast cancer survivors during the first year post-treatment. *Support Care Cancer*. 2016;24(11):4779-4789.

37. Tofthagen C, Visovsky C, Rodriguez R. Chemotherapy-induced peripheral neuropathy: An algorithm to guide nursing management. *Clin J Oncol Nurs*. 2013;17(2):138-144.

38. Miaskowski C, Mastick J, Paul SM, et al. Chemotherapy-induced neuropathy in cancer survivors. *J Pain Symptom Manage*. 2017;54(2):204-218.

Table 1. Comparison of Sociodemographic and Medical Characteristics of Younger and Older Breast Cancer Survivors

Variables	**Younger Survivors < 45 years (N = 505)**	**Older Survivors ≥ 55 years (N = 622)**	***p*-value**
	N (%)		
Race			
White	459 (91)	582 (94)	.114
Non-White	46 (9)	30 (6)	
Income			
< 75, 000	224 (44)	427 (72)	<.001
≥ 75, 000	271 (55)	167 (28)	
Marital status			
Married	417(83)	419 (69)	<.001
Non-Married	85 (17)	188 (31)	
Missing	3 (.6)	15 (2.4)	
Comorbidities			
Heart disease: Yes	36 (7)	83 (13)	<.001
Hypertension: Yes	74 (15)	328 (53)	<.001
Diabetes: Yes	28 (6)	93 (15)	<.001
Positive Hormone Status	334 (67)	452 (75)	.011

Estrogen: Yes Progesterone: Yes Her 2 Neu: Yes	298 (62) 111 (27)	383 (65) 129 (25)	.408 .548
Alcohol consumption 0 drinks 1-2 drinks 3 or more	 144 (29) 294 (58) 67 (13)	 251 (40) 347 (56) 24 (3.6)	 <.001
Mean (standard deviation)			
Years of education	14.8 (2.6)	14.1 (2.7)	<.001
Body mass index	27.8 (6.1)	28.4 (5.9)	.102
Years from diagnosis	5.9 (1.5)	6 (1.5)	.336
Number of positive nodes	1.5 (2.6)	1.7 (3.2)	.272
Tumor size (cm)	2 (1.4)	1.9 (1.3)	.394

Table 2. Presence of Peripheral Neuropathy Symptoms by Total Sample and between Younger and Older Breast Cancer Survivors (Chi Square).

Symptom	All N = 1127	Younger N = 505	Older N = 622	*p*-value
	N (%)	N (%)	N (%)	
Burning	119 (9)	60 (12)	59 (10)	.284
Pins/needles	368 (33)	185 (37)	183 (30)	.021
Numbness	442 (39)	232 (46)	210 (34)	<.001
Skin crawls	109 (10)	58 (11)	51 (8)	.085
Pain	347 (31)	189 (37)	158 (25)	<.001

Table 3. Predictors of Symptom Presence (yes/no) among Breast Cancer Survivors (Logistic Regression)

Pins/needles, *N*= 368, X^2 = 4.92, DF (4), R^2 = .029, p <.001					
Variable	Standard Beta	SE Beta	*p*-value	Odds Ratio	95% CI
Older vs younger BCS	-.286	.144	.048	.751	.566 .997
Heart disease (present vs not present)	.457	.224	.041	1.6	1.019 2.451
PR hormone status (positive vs negative)	-.412	.163	.005	.663	.495 .886
Numbness, *N* = 442, X^2 = 5.056, DF (4), R^2 = .023, p = .001					
Variable	Standard Beta	SE Beta	*p*-value	Odds Ratio	Confidence interval
Older vs younger BCS	-.449	.137	.001	.638	.488 .835
Heart disease (present vs not present)	.466	.218	.032	1.59	1.04, 2.44
Pain, *N* = 347, X^2 = 3.17, DF (3), R^2 = .025, p <.001					

Variable	Standard Beta	SE Beta	*p*-value	Odds Ratio	Confidence interval
Older vs younger BCS	-.474	.145	.001	.623	.469 .827
Heart disease (present vs not present)	.551	.223	.013	1.7	1.12, 2.68

Table 4. Comparison of Symptom Distress by Age Groups (Mann Whitney U)

Symptom	**Score Range**	**Younger**	**Older**	
	Potential Range[a] (Actual Range)	***Median (P25, P75)***	***Median (P25, P75)***	***p*-value**
Burning **N = 290**	0-4 (1-3)	N = 120 2.0 (1, 2)	N = 170 2.0 (1, 3)	.521
Pins/needles **N = 347**	0-4 (1-2)	N = 173 1.0 (1, 2)	N = 174 1.0 (1, 2)	.992
Numbness **N = 376**	0-4 (1-3)	N = 193 2.0 (1, 3)	N = 183 2.0 (1, 2)	.117
Pain **N = 332**	0-4 (1-2)	N = 181 1.0 (1, 2)	N = 151 1.0 (1, 2)	.330
Skin Crawls **N = 107**	0-4 (1-3)	N = 56 2.0 (1, 2)	N = 51 2.0 (1, 3)	.885