Morning chronotype decreases the risk of chemotherapy-induced peripheral neuropathy in women with breast cancer

Kyung-Lak Son  
Dongguk University Ilsan Hospital

Dooyoung Jung  
Ulsan National Institute of Science and Technology

Kwang-Min Lee  
Mind Lab Place Psychiatry Clinic

Chan-Woo Yeom  
National Rehabilitation Center

Kyu-Han Oh  
Seoul National University Hospital

Tae-Yong Kim  
Seoul National University Hospital

Seock-Ah Im  
Seoul National University Hospital

Kyung-Hun Lee  
Seoul National University Hospital

David Spiegel  
Stanford University

Bong-Jin Hahm  (hahmbj@gmail.com)  
Seoul National University

Research Article

Keywords: Breast cancer, adjuvant chemotherapy, chemotherapy-induced peripheral neuropathy, chronotype

DOI: https://doi.org/10.21203/rs.3.rs-120820/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

The purpose of this longitudinal prospective cohort study was to investigate the role of chronotype in the incidence of chemotherapy-induced peripheral neuropathy (CIPN) among women with breast cancer. A total of 128 subjects with breast cancer awaiting adjuvant chemotherapy without peripheral neuropathy participated in this study. The presence of CIPN was defined as a response of 3 or higher on a peripheral neuropathy subscale in the MD Anderson Symptom Inventory. Candidate psychiatric factors associated with CIPN were assessed, using the Composite Scale of Morningness, the Pittsburgh Sleep Quality Index, and the Hospital Anxiety and Depression Scale. To examine the association between chronotype and CIPN, we built logistic regression models, adjusting for demographic, clinical, and other psychiatric variables. Forty-nine participants received a chemotherapy regimen containing docetaxel, of which 29 (59%) developed CIPN. We performed subgroup analyses of docetaxel-treated participants. The morning chronotype was inversely associated with CIPN (odds ratio, 0.07; confidence interval, 0.01–0.48; \( p = 0.016 \)) after adjusting for age, BMI, education, alcohol use, smoking, disease stage, sleep quality, depression, and anxiety. Our results suggest that the morning chronotype is a protective factor against the development of CIPN in patients with breast cancer who were treated with docetaxel.

Introduction

Cancer survival rate has increased sharply over the past two decades due to early diagnosis and improved treatment strategies. Cancer is more appropriately considered a chronic rather than a terminal illness\(^1\). As the number of cancer survivors and their survival time increases, their quality of life (QoL) after cancer treatment has become a more important issue, as has the management and treatment of complications that have a significant effect on QoL.

Breast cancer is the most common cancer among women in the Republic of Korea, excluding thyroid cancer\(^2\). According to the 2015 nationwide cancer statistics in Korea, breast cancer occurred at a relatively young age compared to other cancers, and the 5-year survival rate was 92%, an increase of 14% from 20 years ago\(^2\). Thus, in breast cancer patients, complications induced by cancer treatments affect QoL over a long period of time.

Peripheral neuropathy occurs in 30–40% of patients treated with adjuvant chemotherapy for breast cancer, is usually chronic, and recovery from symptoms is often incomplete\(^3,4\). Therefore, identification of risk factors, early detection and treatment of chemotherapy-induced peripheral neuropathy (CIPN) is essential for long-term management of breast cancer patients.

Among the risk factors for CIPN, clinical factors including chemotherapeutic regimen, cumulative dose and pre-existing neuropathy are known, and demographic factors include age and obesity\(^3\). However, the role of psychiatric factors associated with CIPN is unknown, except one report that suggested an association between anxiety and persistent CIPN\(^5\). Psychiatric symptoms are known to affect not only
QoL but are also related to developing treatment complications\textsuperscript{6}. Therefore, investigating the prognostic role of psychiatric symptoms is important in order to prevent complications and alleviate mental distress.

Circadian rhythm disruption is associated with complications of chemotherapy\textsuperscript{5–7}. Chronotype is a behavioral manifestation influenced by individual differences in the timing of the endogenous circadian system. It is divided into morning, intermediate, and evening types. The discrepancy between personal chronotype and the socially preferred one, which may disrupt the circadian rhythm inducing poor general health, is called social jetlag, and evening chronotypes are known to be vulnerable to it\textsuperscript{8}. In previous studies, we showed that such misalignment between preferred and actual sleep time was associated with shorter disease-free interval in breast cancer\textsuperscript{9}, and that late chronotypes were associated with greater likelihood of chemotherapy-induced nausea and vomiting in this population\textsuperscript{7}. Given these findings, we hypothesized that since chronotype and chemotherapy complications are related to each other, the incidence of CIPN may be higher in the evening chronotype than the other chronotypes due to the vulnerability to social jetlag, and the morning chronotype protects against CIPN.

**Methods**

**Study Design**

The present study was conducted as one component of a primary cohort study named "The effects of circadian genes on sleep and associated symptoms in breast cancer patients under chemotherapy", which was designed to evaluate the effects of sleep-related factors and genes on complications of breast cancer chemotherapy. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. The study protocol approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1105-092-363), and the clinical trial registration number was NCT 01887925 (www.ClinicalTrials.gov).

The participants of the primary study were recruited from Seoul National University Hospital, which is a tertiary general hospital in Seoul, Republic of Korea, and were consecutively enrolled between February 2012 and May 2014\textsuperscript{6}. Clinical staff approached potential participants diagnosed with breast cancer who visited an oncologist's outpatient clinic for adjuvant chemotherapy and provided detailed information about the study\textsuperscript{6}. Written informed consent was obtained from all participants.

The inclusion criteria of the primary study were women aged 18 to 70 years with early-stage breast cancer, while waiting for adjuvant chemotherapy after completion of surgery, medically stable, and without a history of another cancer or significant medical conditions that could affect mood and sleep\textsuperscript{6}. Individuals with a history of psychiatric treatment for more than 1 month were excluded due to the possible effects of psychiatric symptoms and psychotropic medications\textsuperscript{6}. Patients who had worked on shifts in the preceding 6 months were also ineligible, as shift work could disrupt the circadian rhythm\textsuperscript{6}. 
The current study proposed to identify the effect of chronotype on CIPN in patients with breast cancer. In order to investigate peripheral neuropathy newly induced by chemotherapy, subjects with significant peripheral neuropathy at baseline were excluded. CIPN was defined as peripheral neuropathy symptoms of more than moderate severity 4 weeks after completion of chemotherapy.

**Participants**

For the primary study, we approached 370 patients, of which 31 patients were ineligible. Among 339 eligible patients, 126 patients declined to participate. A total of 213 female patients from the oncology clinic were enrolled at baseline in the primary study (Fig. 1).

In the current study, we selected participants from the primary study, who were without significant peripheral neuropathy before adjuvant chemotherapy. Of the 213 participants, 77 patients were excluded. Thus, a total of 136 participants were recruited at the baseline of the current study (Fig. 1).

We included only two chemotherapy regimens in the current study to ensure homogeneity: AC-D (adriamycin and cyclophosphamide given once every two weeks for 4 cycles, followed by docetaxel administered once every two weeks for 4 cycles) and FAC (5-fluorouracil, adriamycin, cyclophosphamide given once every two weeks for 6 cycles). Five participants who were treated with chemotherapies other than the above two regimens were excluded. Three other participants refused follow-up. In total, 128 participants were included in the analyses (Fig. 1).

**Measures**

**CIPN**

The 13th item "numbness" scale of the M.D. Anderson Symptom Inventory (MDASI), which was designed to measure cancer-induced symptoms, was used to measure peripheral neuropathy. Participants reported numbness and tingling on a numerical rating scale of 0–10 based on symptoms during the previous 24 h. In previous studies using the same scale, it was reported that a grade of 3 or higher corresponded to moderate or severe peripheral neuropathy\(^{10,11}\). In this study, the same criterion was used to define peripheral neuropathy.

**Chronotype**

The chronotype was assessed with the Composite Scale of Morningness (CSM)\(^{12}\). CSM is a 13-item scale, consisting of 9 items derived from Morningness-eveningness questionnaire (MEQ) and 4 items from the Diurnal Type Scale. Smith et al.\(^{12}\) reported that the CSM provided a better psychometric evaluation than MEQ. The total CSM score ranges from 13 to 55: the higher score represents the morning chronotype, and the lower score denotes the evening chronotype. Therefore, we categorized chronotypes into three groups: "morning chronotype", "intermediate chronotype", and "evening chronotype" based on the quartiles of CSM score, with the highest quartile representing the morning chronotype, the middle two quartiles the intermediate chronotype, and the lowest quartile the evening chronotype\(^{13,14}\).
Sleep Quality

Sleep quality and disturbance were assessed using the Pittsburgh Sleep Quality Index (PSQI)\textsuperscript{15}. The PSQI scores range from 0 to 21. A higher score indicates poorer sleep quality, and a score higher than 8 was used to indicate poor sleepers in a previous validation study for the cancer patients\textsuperscript{16}. Therefore, a cutoff value of 8 was used to define significantly poor sleep quality in the current study.

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) can be used to measure psychological adjustment\textsuperscript{17}. It comprises two sub-scales of anxiety and depression, consisting of seven questions each. We defined significant anxiety and depression as a score of 8 or higher on the respective subscales based on previous studies\textsuperscript{18}.

Statistical Analyses

Socio-demographic and clinical characteristics of participants with and without CIPN were compared using Student's t-test and Chi-square test. Univariate logistic regression analyses were conducted to examine the variables associated with CIPN. A multivariable logistic regression model was built to identify the independent factors predicting CIPN. Variables that showed $p < 0.1$ in the univariate analyses were retained as covariates in the multivariate analysis, and we also included theoretical predictors as covariates. Statistical analyses were performed using R version 3.4.4 (https://www.r-project.org), and $p$-values $< 0.05$ were considered statistically significant.

Results

Demographic and Clinical Characteristics

The participants’ baseline demographic and clinical characteristics are shown in Table 1. In terms of the chronotype based on the quartiles of the CSM score, 25%, 50% and 25% of the subjects were classified as morning, intermediate, and evening chronotypes, respectively.

The characteristics of the groups with and without CIPN are presented in Table 2. Since the incidence of CIPN differs significantly according to the chemotherapeutic agent, we conducted an interaction analysis of chronotype-chemotherapy regimen. The interaction between chronotype and chemotherapy regimen was significant ($p = 0.041$) in multivariate logistic regression analysis of age, BMI, education, chronotype, chemotherapy regimen, and chronotype-chemotherapy regimen interaction. Therefore, we analyzed the two subgroups separately according to the chemotherapy regimen, namely the AC-D and the FAC subgroup. Table 2 presents a comparison of the characteristics between the groups who experienced CIPN and those who did not, according to the chemotherapy regimen.

The incidence of CIPN in the AC-D and the FAC subgroups was 59.2% and 30.4%, respectively. The comparison of the AC-D subgroup showed a significant difference between the chronotypes of
participants with and without CIPN, and the morning chronotype ratio was lower and the other chronotype ratios were higher in the group manifesting CIPN \( (p = 0.007) \). Sleep quality was also poorer in participants with CIPN than in those without CIPN in the AC-D subgroup \( (p = 0.031) \). In the FAC subgroup, no factors with significant differences in CIPN occurrence were found.

### Predictive Factors for CIPN

In the AC-D subgroup, univariate analyses showed that CIPN was significantly less in the morning chronotype (odds ratio [OR], 0.09; confidence interval [CI], 0.01–0.46; \( p = 0.008 \)) than in other chronotypes, and higher education (OR, 3.82; CI, 1.17–13.66; \( p = 0.031 \)) was significantly associated with CIPN. In the FAC subgroup, univariate analyses did not show any factors which were significantly associated with CIPN (Table 3).

Multivariate analyses were performed only on the AC-D subgroup. Three models were built for the multivariate logistic regression analyses. Model 1 included demographic factors (age, BMI, and education) as covariates of chronotype. Model 2 was analyzed with additional clinical variables (alcohol use, smoking, and disease stage) along with those analyzed in model 1. Model 3 included psychiatric variables (sleep quality, depression, and anxiety) in addition to those analyzed in model 2. In all the models chronotype was significantly correlated with CIPN occurrence, and morning chronotype was a significant protective factor against the development of CIPN (model 1: OR, 0.09; CI, 0.01–0.53; \( p = 0.015 \) / model 2: OR, 0.09; CI, 0.01–0.53; \( p = 0.016 \) / model 3: OR, 0.07; CI, 0.01–0.48; \( p = 0.016 \)) (Table 4). Education was not significantly associated with CIPN in all models.

### Discussion

The study investigated the association between chronotype and occurrence of CIPN in women with breast cancer. Although there was no association between chronotype and CIPN in the FAC subgroup, morning chronotype was a protective factor against CIPN in the AC-D subgroup, which was treated with docetaxel-containing chemotherapy regimen. To our knowledge, this longitudinal observational study is the first to examine the association between chronotype and CIPN.

Docetaxel belongs to the taxane family of drugs and is known as a potent inducer of CIPN\(^{19}\). The results of this study also showed that the incidence of CIPN was twice as high (59.2% vs. 30.4%) in the AC-D subgroup than the other. Taxane-induced peripheral neuropathy (TIPN) is known to be associated with increased risk of falls and sleep disorders as well as decreased subjective QoL\(^{20}\). Several studies identified predictive factors for TIPN. Obesity and age have been suggested as risk factors; however, it is difficult to predict patients who develop TIPN. This study has implications for identifying the morning chronotype as a strong protective factor for TIPN.

The study findings are based on the relationship between pharmacology of docetaxel and chronobiology. Docetaxel inhibits the division of rapidly growing cells via microtubule stabilization. Cell cycle and circadian rhythm are linked\(^{21}\). From an evolutionary point of view, DNA replication occurs at night, to
avoid DNA damage by sunlight, and mitosis occurs throughout the day. We have described the individual differences in endogenous circadian rhythm as a chronotype. Thus, we can infer that the occurrence of TIPN is associated with chronotype. Norma et al. analyzed the degree of apoptosis in duodenal cells after administering colchicine, a microtubule stabilizing agent, to several groups of mice at different times. They reported a nearly two-fold higher degree of apoptosis in the group that received colchicine at 8AM compared with the other groups. Therefore, the occurrence of CIPN also depends on the administration time and chronotype, due to the similar mechanism with colchicine.

Another mechanism of TIPN involves increased neuroinflammation in the spinal cord and dorsal root ganglia. Several studies show that the immune system is regulated by circadian rhythm, disruption of which induces inflammation. Adams et al. reported that circadian rhythm disruption increases the secretion of IL-6, a proinflammatory cytokine, and activates inflammation. The secretion of IL-6 has been reported to exhibit circadian rhythm in patients with rheumatoid arthritis, with elevated levels in the morning. Adams et al. suggested that circadian rhythm disruption interferes with rhythmicity of IL-6 secretion, which elevates IL-6 level and exacerbates inflammation. As the evening and intermediate chronotypes are vulnerable to circadian rhythm disruption compared to the morning chronotype, we can appreciate this study showing that morning chronotype is protective against CIPN.

Many chemotherapy agents are associated with cell division cycles, and chronomodulated chemotherapy is associated with chemotherapy-induced adverse effects. However, according to a recent meta-analysis, the incidence of complications in chronomodulated chemotherapy was reported to be inconsistent in each study. This finding suggests variation in the association between chronobiology and chemotherapy complications according to the conditions of the study participants and chemotherapy regimen. In the present study, no association was observed between chronotype and CIPN in the FAC subgroup. It has been known that 5-fluorouracil, adriamycin, and cyclophosphamide are less likely to cause peripheral neuropathy. Peripheral neuropathy in the FAC-administered subgroup might be mediated via mechanisms other than direct neurotoxicity of the chemotherapeutic agents, therefore the association with the chronotype would not have been significant.

This study has several strengths. First, this study was the first to investigate the association between psychiatric factors and CIPN. Lee et al. reported that pretreatment anxiety was associated with persistence of CIPN. However, we excluded patients with peripheral neuropathy prior to chemotherapy from the study population, and therefore analyzed factors associated with newly developed peripheral neuropathy after chemotherapy. Second, we designed the present study as a prospective longitudinal study, to avoid recall bias, which generally occurs when analyzing psychiatric factors.

This study has several limitations. First, we did not use a physiological tool to measure peripheral neuropathy, which is the main outcome of the current study, and based on one item in MDASI. Of course, MDASI is a recognized tool used to investigate the complications of cancer therapies. However, the reliability of the study may have increased if we used a scale that included specific questions to measure peripheral neuropathy. Second, the follow-up period was 4 weeks after the completion of chemotherapy,
which is relatively short. CIPN is a clinically significant issue because it often does not improve and becomes chronic even after many years. Follow-up data for several years after completion of chemotherapy can be used to analyze the factors associated with chronic CIPN.

CIPN is a major complication that chronically reduces QoL after chemotherapy in breast cancer patients. We recommend a further long-term follow-up study to investigate the predictive factors for chronic CIPN. We also suggest measurement of biomarkers, such as cytokines, in addition to self-reported scales, to identify the mechanisms of the risk factors associated with CIPN. Further studies are needed to corroborate these findings to enhance the possibility of personalized medicine using chemotherapy based on chronotype to improve the risk/benefit ratio of treatment.

**Declarations**

**Acknowledgement**

This work was supported by the National Research Foundation of Korea (NRF; grant number NRF-2013R1A1A2013480).

**Author contributions**

KL.S. data analysis, manuscript writing; D.J. protocol development; TY.K., SA.I., KH.L. data collection. All authors contributed to the discussion of the results and reviewed the manuscript.

**Conflict of interest**

The authors declare that they have no conflicts of interest

**References**

1. Phillips, J. L. & Currow, D. C. Cancer as a chronic disease. Collegian 17, 47–50 (2010).
2. Jung, K.-W., Won, Y.-J., Kong, H.-J. & Lee, E. S. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2015. Cancer Res. Treat. Off. J. Korean Cancer Assoc. 50, 303–316 (2018).
3. Wolf, S., Barton, D., Kottschade, L., Grothey, A. & Loprinzi, C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. Eur J Cancer 44, 1507–15 (2008).
4. Quasthoff, S. & Hartung, H. P. Chemotherapy-induced peripheral neuropathy. J. Neurol. 249, 9–17 (2002).
5. Lee, K.-M. et al. Pre-treatment anxiety is associated with persistent chemotherapy-induced peripheral neuropathy in women treated with neoadjuvant chemotherapy for breast cancer. J. Psychosom. Res. 108, 14–19 (2018).
6. Jung, D. et al. Longitudinal Association of Poor Sleep Quality With Chemotherapy-Induced Nausea and Vomiting in Patients With Breast Cancer. Psychosom Med 78, 959–965 (2016).
7. Lee, K. M. et al. Late chronotypes are associated with neoadjuvant chemotherapy-induced nausea and vomiting in women with breast cancer. Chronobiol Int 34, 480–491 (2017).
8. Wittmann, M., Dinich, J., Merrow, M. & Roenneberg, T. Social jetlag: misalignment of biological and social time. Chronobiol. Int. 23, 497–509 (2006).
9. Hahm, B. J. et al. Bedtime misalignment and progression of breast cancer. Chronobiol Int 31, 214–21 (2014).
10. Kautio, A.-L., Haanpää, M., Saarto, T. & Kalso, E. Amitriptyline in the Treatment of Chemotherapy-Induced Neuropathic Symptoms. J. Pain Symptom Manage. 35, 31–39 (2008).
11. Theobald, D. E., Kirsh, K. L., Holtsclaw, E., Donaghy, K. & Passik, S. D. An Open-Label, Crossover Trial of Mirtazapine (15 and 30 mg) in Cancer Patients with Pain and Other Distressing Symptoms. J. Pain Symptom Manage. 23, 442–447 (2002).
12. Smith, C. S., Reilly, C. & Midkiff, K. Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. J Appl Psychol 74, 728–38 (1989).
13. Bohle, P., Tilley, A. J. & Brown, S. Psychometric evaluation of the early/late preferences scale. Ergonomics 44, 887–900 (2001).
14. Di Milia, L., Wikman, R. & Smith, P. Additional psychometric evidence and construct validity for a revised preferences scale of morningness. Chronobiol Int 25, 776–787 (2008).
15. Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28, 193–213 (1989).
16. Carpenter, J. S. & Andrykowski, M. A. Psychometric evaluation of the Pittsburgh sleep quality index. J. Psychosom. Res. 45, 5–13 (1998).
17. Zigmond, A. S. & Snaith, R. P. The Hospital Anxiety and Depression Scale. Acta Psychiatr. Scand. 67, 361–370 (1983).
18. Bjelland, I., Dahl, A. A., Haug, T. T. & Neckelmann, D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. J. Psychosom. Res. 52, 69–77 (2002).
19. Kerckhove, N. et al. Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review. Front Pharmacol 8, 86 (2017).
20. Bao, T. et al. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. Breast Cancer Res Treat 159, 327–33 (2016).
21. Johnson, C. H. Circadian clocks and cell division. Cell Cycle 9, 3864–3873 (2010).
22. Nikaido, S. S. & Johnson, C. H. Daily and Circadian Variation in Survival From Ultraviolet Radiation in Chlamydomonas reinhardtii. Photochem. Photobiol. 71, 758–765 (2000).
23. Norma, V. G., Badrán, A. F. & Barbeito, C. G. Daily variations in colchicine-induced apoptosis in duodenal crypts. Chronobiol. Int. 22, 79–88 (2005).
24. Adams, K. L., Castanon-Cervantes, O., Evans, J. A. & Davidson, A. J. Environmental Circadian Disruption Elevates the IL-6 Response to Lipopolysaccharide in Blood. J. Biol. Rhythms 28, 272–277
25. Perry, M. G., Kirwan, J. R., Jessop, D. S. & Hunt, L. P. Overnight variations in cortisol, interleukin 6, tumour necrosis factor and other cytokines in people with rheumatoid arthritis. Ann. Rheum. Dis. 68, 63–68 (2008).

26. Kobayashi, M., To, H., Tokue, A., Fujimura, A. & Kobayashi, E. Cisplatin-induced vomiting depends on circadian timing. Chronobiol. Int. 18, 851–863 (2001).

27. Lévi, F. et al. Chemotherapy of advanced ovarian cancer with 4‘-O-tetrahydropyranyl doxorubicin and cisplatin: a randomized phase II trial with an evaluation of circadian timing and dose-intensity. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 8, 705–714 (1990).

28. Efficacy and safety of chronomodulated chemotherapy for patients with metastatic colorectal cancer: a systematic review and meta-analysis. Asia Pac J Clin Oncol. 3(2), 171–178 (2017)

Tables
Table 1. Demographic and baseline clinical characteristics of participants

| Characteristics                                      | Normal (N=128) |
|------------------------------------------------------|----------------|
|                                                      | Mean ± SD or N (%) |
| Age                                                  | 46.9 ± 7.6 |
| Age ≥ 50 years                                       | 51 (39.8%) |
| BMI, kg/m²                                           | 22.8 ± 2.6 |
| BMI ≥23 kg/m²                                        | 54 (44.3%) |
| Married                                              | 113 (88.3%) |
| College graduates or higher                          | 64 (50.0%) |
| Employment                                           |               |
| Homemaker                                            | 59 (46.1%) |
| Work place                                           | 69 (53.9%) |
| ≥ One alcoholic drinks per week                      | 23 (18.0%) |
| Current smoker                                       | 10 (7.8%) |
| Disease stage                                        |               |
| I                                                    | 51 (39.8%) |
| II                                                   | 71 (55.5%) |
| III                                                  | 6 (4.7%) |
| Operation                                            |               |
| BCS                                                  | 95 (74.2%) |
| TM                                                   | 33 (25.8%) |
| Chronotype                                           |               |
| Morning                                              | 32 (25.0%) |
| Intermediate                                         | 64 (50.0%) |
| Evening                                              | 32 (25.0%) |
| PSQI                                                 | 5.2 ± 3.1 |
| Good sleep                                           | 107 (86.3%) |
| Poor sleep                                           | 17 (13.7%) |
| HADS-D                                               | 5.9 ± 3.3 |
| Not depressed                                        | 89 (69.5%) |
| Depressed                                            | 39 (30.5%) |
| HADS-A                                               | 5.5 ± 3.3 |
| Not anxious                                          | 99 (77.3%) |
| Anxious                                              | 29 (22.7%) |

Abbreviations: BCS, breast-conserving surgery; BMI, body mass index; HADS, Hospital Anxiety and Depression Scale (HADS-D and HADS-A: subscales for depression and anxiety, respectively); PSQI, Pittsburgh Sleep Quality Index; TM, total mastectomy
| Characteristics                        | Whole Chemotherapy Regimens | AC-D Chemotherapy Regimen | FAC Chemotherapy Regimen |
|---------------------------------------|-----------------------------|---------------------------|--------------------------|
| **No CIPN** (n=75)                    | No CIPN (n=20)              | No CIPN (n=55)            |                           |
| Mean ± SD or N (%)                    | Mean ± SD or N (%)          | Mean ± SD or N (%)        |                           |
| **Age**                               | 47.8 ± 7.4 (50.0%)         | 46.3 ± 7.9 (50.0%)        | 48.3 ± 7.1 (50.0%)       |
| **Age ≥ 50 years**                    | 34 (45.3%)                 | 7 (35.0%)                 | 27 (49.1%)               |
| **BMI, kg/m2**                        | 23.0 ± 2.6 (24.2%)         | 22.4 ± 2.7 (24.2%)        | 23.2 ± 2.5 (24.2%)       |
| **BMI ≥25 kg/m2**                     | 34 (47.2%)                 | 6 (31.6%)                 | 28 (52.8%)               |
| **Married**                           | 63 (84.0%)                 | 18 (90.0%)                | 45 (81.8%)               |
| **College graduates or higher**       | 31 (41.3%)                 | 6 (30.0%)                 | 25 (45.5%)               |
| **Employment**                        |                            |                           |                          |
| **Homemaker**                         | 33 (44.0%)                 | 10 (50.0%)                | 23 (41.8%)               |
| **Work place**                        | 42 (56.0%)                 | 10 (50.0%)                | 32 (58.2%)               |
| **One alcoholic drinks per week**     | 15 (20.0%)                 | 3 (15.0%)                 | 12 (21.8%)               |
| **Current smoker**                    | 5 (6.7%)                   | 2 (10.0%)                 | 3 (5.5%)                 |
| **Disease stage**                     |                            |                           |                          |
| I                                     | 30 (40.0%)                 | 1 (5.0%)                  | 29 (52.7%)               |
| II                                    | 43 (57.3%)                 | 17 (85.0%)                | 26 (47.3%)               |
| III                                   | 2 (2.7%)                   | 2 (10.0%)                 | 8 (33.3%)                |
| **Operation**                         |                            |                           |                          |
| **BCS**                               | 58 (77.3%)                 | 13 (65.0%)                | 45 (81.8%)               |
| **TM**                                | 17 (22.7%)                 | 7 (35.0%)                 | 10 (18.2%)               |
| **Radiation therapy**                 | 58 (77.3%)                 | 15 (75.0%)                | 43 (78.2%)               |
| **Chemotherapy**                      |                            |                           |                          |
| AC-D                                  | 20 (26.7%)                 | 14 (70.0%)                | 36 (65.5%)               |
| FAC                                   | 55 (73.3%)                 | 25 (86.2%)                | 19 (79.2%)               |
| **Hormone therapy**                   |                            |                           |                          |
| Good sleep                            | 26 (47.3%)                 |                           |                          |
| Poor sleep                            | 11 (21.6%)                 |                           |                          |
| HADS-D                                | 5.6 ± 3.2 (34.2%)          |                           |                          |
| Not depressed                         | 55 (73.3%)                 | 12 (60.0%)                | 5 (9.4%)                 |
| Depressed                             | 20 (26.7%)                 | 8 (40.0%)                 | 16 (29.1%)               |
| Not anxious                           | 62 (82.7%)                 | 16 (80.0%)                | 46 (83.6%)               |
| Anxious                               | 13 (17.3%)                 | 4 (20.0%)                 | 9 (16.4%)                |

**Abbreviations:** AC-D, Adriamycin/cyclophosphamide and docetaxel; BCS, breast-conserving surgery; BMI, body mass index; FAC, fluorouracil/adriamycin/cyclophosphamide; HADS, Hospital Anxiety and Depression Scale (HADS-D and HADS-A: subscales for depression and anxiety, respectively); PSQI, Pittsburgh Sleep Quality Index; TM, total mastectomy.
## Table 3. Univariate analyses of predictors for CIPN in the AC-D subgroup

| Factors                      | Univariate analyses |          |          |
|------------------------------|---------------------|----------|----------|
|                              | OR (95% CI)         | p-value  |          |
| **Age at baseline**          |                     |          |          |
| < 50 years                   | 1.00 (reference)    |          |          |
| ≥ 50 years                   | 0.71 (0.20-2.46)    | 0.581    | 0.581    |
| **BMI, kg/m2**               |                     |          |          |
| < 23 kg/m2                   | 1.00 (reference)    |          |          |
| ≥ 23 kg/m2                   | 1.40 (0.42-5.01)    | 0.590    | 0.590    |
| **Marital status**           |                     |          |          |
| Unmarried                    | 1.00 (reference)    |          |          |
| Married                      | 1.5 (0.17-13.45)    | 0.698    | 0.698    |
| **Education**                |                     |          |          |
| High school graduate or lower| 1.00 (reference)    |          |          |
| College graduates or higher  | 3.82 (1.17-13.66)   | 0.031    |          |
| **Employment**               |                     |          |          |
| Homemaker                    | 1.00 (reference)    |          |          |
| Work place                   | 0.93 (0.30-2.94)    | 0.906    |          |
| **History of alcohol**       |                     |          |          |
| <1 alcoholic drinks per week | 1.00 (reference)    |          |          |
| ≥1 alcoholic drinks per week | 0.65 (0.11-3.89)    | 0.627    |          |
| **History of smoking**       |                     |          |          |
| No current smoker            | 1.00 (reference)    |          |          |
| Current smoker               | 1.04 (0.16-8.49)    | 0.969    |          |
| **Disease stage**            |                     |          |          |
| I or II                      | 1.00 (reference)    |          |          |
| III                          | 1.44 (0.25-11.20)   | 0.692    |          |
| **Operation**                |                     |          |          |
| BCS                          | 1.00 (reference)    |          |          |
| TM                           | 0.98 (0.30-3.32)    | 0.970    |          |
| **Radiation therapy**        |                     |          |          |
| No                           | 1.00 (reference)    |          |          |
| Yes                          | 1.28 (0.32-5.00)    | 0.723    |          |
| **Hormone Therapy**          |                     |          |          |
| No                           | 1.00 (reference)    |          |          |
| Yes                          | 2.68 (0.66-12.06)   | 0.175    |          |
| **Chronotype**               |                     |          |          |
| Intermediate                 | 1.00 (reference)    |          |          |
| Morning                      | 0.09 (0.01-0.46)    | 0.008    |          |
| Evening                      | 1.12 (0.25-6.13)    | 0.885    |          |
| **Sleep quality**            |                     |          |          |
| Good                         | 1.00 (reference)    |          |          |
| Poor                         | 3.96 (0.57-79.27)   | 0.227    |          |
| **Depression**               |                     |          |          |
| Not depressed                | 1.00 (reference)    |          |          |
| Depressed                    | 0.79 (0.24-2.60)    | 0.694    |          |
| **Anxiety**                  |                     |          |          |
| Not anxious                  | 1.00 (reference)    |          |          |
| Anxious                      | 1.80 (0.49-7.65)    | 0.393    |          |

Abbreviations: BCS, breast-conserving surgery; BMI, body mass index; HADS, Hospital Anxiety and Depression Scale (HADS-D and HADS-A: subscales for depression and anxiety, respectively); PSQI, Pittsburgh Sleep Quality Index; TM, total mastectomy
Table 4. Multivariate analyses of predictors for CIPN in the AC-D subgroup

| Factors                              | Model 1                  | p value | Model 2                  | p value | Model 3                  | p value |
|--------------------------------------|--------------------------|---------|--------------------------|---------|--------------------------|---------|
|                                      | OR (95% CI)              |         | OR (95% CI)              |         | OR (95% CI)              |         |
| Chronotype                           |                          |         |                          |         |                          |         |
| Intermediate                         | 1.00 (reference)         |         | 1.00 (reference)         |         | 1.00 (reference)         |         |
| Morning                              | 0.09 (0.01-0.53)         | 0.015   | 0.09 (0.01-0.53)         | 0.016   | 0.07 (0.01-0.48)         | 0.016   |
| Evening                              | 1.14 (0.21-7.20)         | 0.879   | 1.37 (0.22-10.52)        | 0.748   | 0.95 (0.09-10.83)        | 0.963   |
| Age, ≥ 50 years                      | 1.82 (0.35-12.03)        | 0.496   | 2.25 (0.37-18.20)        | 0.404   | 1.87 (0.26-17.95)        | 0.555   |
| BMI, ≥ 23 kg/m2                      | 1.30 (0.31-5.78)         | 0.718   | 1.41 (0.33-6.43)         | 0.642   | 1.63 (0.34-8.70)         | 0.545   |
| College graduates or higher          | 3.61 (0.85-16.84)        | 0.086   | 3.87 (0.87-19.84)        | 0.082   | 4.45 (0.91-27.08)        | 0.076   |
| ≥1 alcoholic drinks per week         |                          |         |                          |         |                          |         |
| Current smoker                       | 1.66 (0.09-41.20)        | 0.738   | 2.78 (0.11-115.33)       | 0.551   |                          |         |
| Disease stage III                    | 1.91 (0.15-31.53)        | 0.624   | 1.27 (0.08-24.90)        | 0.863   |                          |         |
| Poor sleep quality                   |                          |         |                          |         |                          |         |
| Depression                           |                          |         |                          |         |                          |         |
| Anxiety                              |                          |         |                          |         |                          |         |

Abbreviations: BMI, body mass index