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# Morning Chronotype Decreases the Risk of Chemotherapy-Induced Peripheral Neuropathy in Women With Breast Cancer

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## ABSTRACT

**Background:** 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.

**Methods:** We recruited women with breast cancer awaiting adjuvant chemotherapy, including four cycles of docetaxel. Participants reported peripheral neuropathy symptoms of numbness/tingling at the baseline, and at 4 weeks after completion of chemotherapy. Candidate psychiatric factors associated with CIPN were assessed at the baseline, 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.

**Results:** Among 48 participants, 29 participants developed CIPN. The morning chronotype was inversely associated with CIPN (odds ratio, 0.06; confidence interval, 0.01–0.74;  $P=0.028$ ) after adjusting for age, BMI, education, type of operation, alcohol use, smoking, sleep quality, depression, and anxiety.

**Conclusion:** 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.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT01887925

**Keywords:** Breast Cancer; Adjuvant Chemotherapy; Chemotherapy-Induced Peripheral Neuropathy; Chronotype

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#### Disclosure

The authors have no potential conflicts of interest to disclose.

#### Author Contributions

Conceptualization: Son KL. Data curation: Kim TY, Im SA, Lee KH. Formal analysis: Son KL. Funding acquisition: Hahm BJ. Methodology: Jung DY. Writing - original draft: Son KL. Writing - review & editing: Jung DY, Lee KM, Yeom CW, Oh GH, Spiegel D.

## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>2</sup> Thus, in breast cancer patients, complications induced by cancer treatments affect QoL over a long period of time.

Peripheral neuropathy is one of the most frequent adverse event induced by chemotherapy, especially taxanes.<sup>3</sup> Peripheral neuropathy occurs in 11–64% of patients receiving chemotherapy, is usually chronic, and recovery from symptoms is often incomplete.<sup>4,5</sup> 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.<sup>6</sup> However, the role of psychiatric factors associated with CIPN is unknown, except one report that suggested an association between anxiety and persistent CIPN.<sup>7</sup> Psychiatric symptoms are known to affect not only QoL but are also related to developing treatment complications.<sup>8</sup> Therefore, investigating the prognostic role of psychiatric symptoms is important to prevent complications and alleviate mental distress.

Circadian rhythm disruption is associated with complications of chemotherapy.<sup>7-9</sup> 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.<sup>10</sup> In previous studies, we showed that such misalignment between preferred and actual sleep time was associated with shorter disease-free interval in breast cancer,<sup>11</sup> and that late chronotypes were associated with greater likelihood of chemotherapy-induced nausea and vomiting in this population.<sup>9</sup> However, to our knowledge, there has been no study investigating the relationship between chronotype and CIPN. 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 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. 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.

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. 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. Patients who had worked on shifts in the preceding 6 months were also ineligible, as shift work could disrupt the circadian rhythm.

The current study proposed to identify the effect of chronotype on CIPN in patients with breast cancer. To investigate peripheral neuropathy induced by chemotherapy, subjects with moderate or higher numbness/tingling symptoms at the 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**).

We included only one chemotherapy regimen including docetaxel 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,  $n = 88$ ). Of them, we selected 50 participants who were without moderate or higher numbness/tingling symptoms before adjuvant chemotherapy. Two of them refused follow-up. In total, 48 participants were included in the analyses (**Fig. 1**).

### Measures

#### *CIPN*

Participants reported numbness and tingling on a numerical rating scale of 0–10 based on symptoms during the previous 24 hours. In previous studies using the same scale, it was reported that a grade of 3 or higher corresponded to moderate or severe peripheral neuropathy.<sup>12</sup> In this study, the same criterion was used to define peripheral neuropathy.

#### *Chronotype*

The chronotype was assessed with the Composite Scale of Morningness (CSM).<sup>13</sup> CSM is a 13-item scale, consisting of 9 items derived from Morningness-eveningness questionnaire

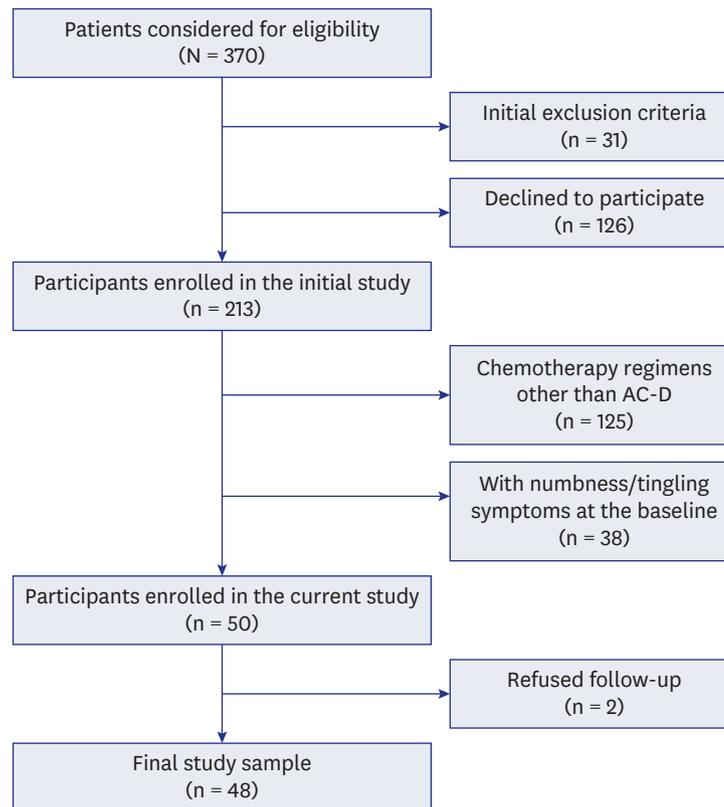


Fig.1. Flow chart summarizing enrollment of participants.

(MEQ) and 4 items from the Diurnal Type Scale. Smith et al.<sup>13</sup> 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.<sup>14,15</sup>

#### *Sleep quality*

Sleep quality and disturbance were assessed using the Pittsburgh Sleep Quality Index (PSQI).<sup>16</sup> 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.<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup>

### Statistical analyses

Socio-demographic and clinical characteristics of participants with and without CIPN were compared using Student's *t*-test, Wilcoxon rank-sum test, and  $\chi^2$  test. Univariate logistic regression analyses were conducted to examine the variables associated with CIPN. A multivariate 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.

### Ethics statement

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1105-092-363), and the clinical trial registration number was NCT01887925 ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)). Written informed consent was obtained from all participants.

## 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, 21%, 54% and 25% of the subjects were classified as morning, intermediate, and evening chronotypes, respectively.

The characteristics of the groups with and without CIPN are also presented in **Table 1**. There was 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 ( $P = 0.013$ ). Sleep quality at the baseline was also poorer in participants with CIPN than in those without CIPN ( $P = 0.048$ ).

### Predictive factors for CIPN

Univariate analyses showed that CIPN was significantly less in the morning chronotype (odds ratio [OR], 0.08; confidence interval [CI], 0.01–0.63;  $P = 0.016$ ) than in other chronotypes, and higher education (OR, 4.58; CI, 1.29–16.27;  $P = 0.019$ ) was significantly associated with CIPN (**Table 2**).

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 (type of operation, alcohol use, and smoking) 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, 0.12; CI, 0.02–0.85;  $P = 0.034$ /model 2: OR, 0.09; CI, 0.01–0.74;  $P = 0.025$ /model 3: OR, 0.06; CI, 0.01–0.74;  $P = 0.028$ ) (**Table 3**).

**Table 1.** Characteristics of participants according to CIPN

Characteristics	Total (n = 48)	No CIPN (n = 19)	CIPN (n = 29)	P value
Age	45.5 [39.5–51.0]	47.0 [42.5–51.0]	44.0 [38.0–53.0]	0.513
Age > 50 yr	15 (31.2)	7 (36.8)	8 (27.6)	0.720
BMI, kg/m <sup>2</sup>	22.2 [20.7–23.8]	22.3 [20.3–23.8]	22.0 [21.0–24.0]	0.937
BMI > 23 kg/m <sup>2</sup>	17 (37.0)	6 (33.3)	11 (39.3)	0.924
Married	44 (91.7)	17 (89.5)	27 (93.1)	1.000
College graduates or higher	23 (47.9)	5 (26.3)	18 (62.1)	0.033*
Employment				1.000
Homemaker	25 (52.1)	10 (52.6)	15 (51.7)	
Work place	23 (47.9)	9 (47.4)	14 (48.3)	
≥ One alcoholic drinks per week	6 (12.5)	3 (15.8)	3 (10.3)	0.911
Current smoker	5 (10.4)	2 (10.5)	3 (10.3)	1.000
Disease stage				0.135
I	5 (10.4)	0 (0.0)	5 (17.2)	
II	37 (77.1)	17 (89.5)	20 (69.0)	
III	6 (12.5)	2 (10.5)	4 (13.8)	
Operation				1.000
BCS	32 (66.7)	13 (68.4)	19 (65.5)	
TM	16 (33.3)	6 (31.6)	10 (34.5)	
Radiation therapy	38 (79.2)	15 (78.9)	23 (79.3)	1.000
Chronotype				0.013*
Morning	10 (20.8)	8 (42.1)	2 (6.9)	
Intermediate	26 (54.2)	8 (42.1)	18 (62.1)	
Evening	12 (25.0)	3 (15.8)	9 (31.0)	
PSQI	5.0 [3.0–7.0]	3.0 [2.0–7.0]	5.0 [4.0–8.0]	0.048*
Good sleep	42 (87.5)	18 (94.7)	24 (82.8)	0.435
Poor sleep	6 (12.5)	1 (5.3)	5 (17.2)	
HADS-D	5.0 [4.0–10.0]	6.0 [4.0–10.0]	5.0 [4.0–9.0]	0.710
Not depressed	30 (62.5)	11 (57.9)	19 (65.5)	0.819
Depressed	18 (37.5)	8 (42.1)	10 (34.5)	
HADS-A	6.0 [3.0–8.5]	6.0 [3.5–7.0]	6.0 [3.0–9.0]	0.458
Not anxious	35 (72.9)	15 (78.9)	20 (69.0)	0.668
Anxious	13 (27.1)	4 (21.1)	9 (31.0)	

Values are presented as mean ± standard deviation or median [interquartile range] or number (%). CIPN = chemotherapy-induced peripheral neuropathy, BMI = body mass index, BCS = breast-conserving surgery, TM = total mastectomy, PSQI = Pittsburgh Sleep Quality Index, HADS = Hospital Anxiety and Depression Scale (HADS-D and HADS-A: subscales for depression and anxiety, respectively).

## DISCUSSION

This study investigated the association between chronotype and occurrence of CIPN in breast cancer patients receiving adjuvant chemotherapy using docetaxel. Morning chronotype was a protective factor against CIPN. 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.<sup>20</sup> Taxane-induced peripheral neuropathy (TIPN) is known to be associated with increased risk of falls and sleep disorders as well as decreased subjective QoL.<sup>21</sup> 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 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.<sup>22</sup> From an evolutionary point of view, DNA replication occurs at night, to avoid DNA damage by sunlight, and mitosis occurs

**Table 2.** Univariate analyses of predictors for CIPN

Factors	Univariate analyses	
	OR (95% CI)	P value
Age at baseline		
< 50 yr	1.00 (reference)	
≥ 50 yr	0.65 (0.19–2.25)	0.500
BMI, kg/m <sup>2</sup>		
< 23 kg/m <sup>2</sup>	1.00 (reference)	
≥ 23 kg/m <sup>2</sup>	1.29 (0.37–4.47)	0.683
Marital status		
Unmarried	1.00 (reference)	
Married	1.59 (0.20–12.36)	0.659
Education		
High school graduate or lower	1.00 (reference)	
College graduates or higher	4.58 (1.29–16.27)	0.019*
Employment		
Homemaker	1.00 (reference)	
Work place	1.04 (0.33–3.30)	0.951
History of alcohol		
< 1 alcoholic drinks per week	1.00 (reference)	
≥ 1 alcoholic drinks per week	0.62 (0.11–3.43)	0.580
History of smoking		
No current smoker	1.00 (reference)	
Current smoker	0.98 (0.15–6.50)	0.984
Disease stage		
I or II	1.00 (reference)	
III	1.36 (0.22–8.27)	0.739
Operation		
BCS	1.00 (reference)	
TM	1.14 (0.33–3.92)	0.835
Radiation therapy		
No	1.00 (reference)	
Yes	1.02 (0.25–4.24)	0.976
Chronotype		
Intermediate	1.00 (reference)	
Morning	0.08 (0.01–0.63)	0.016*
Evening	0.75 (0.16–3.53)	0.716
Sleep quality		
Good	1.00 (reference)	
Poor	3.75 (0.40–34.96)	0.246
Depression		
Not depressed	1.00 (reference)	
Depressed	0.72 (0.22–2.38)	0.594
Anxiety		
Not anxious	1.00 (reference)	
Anxious	1.69 (0.44–6.54)	0.449

CIPN = chemotherapy-induced peripheral neuropathy, OR = odds ratio, CI = confidence interval, BMI = body mass index, BCS = breast-conserving surgery, TM = total mastectomy.

throughout the day.<sup>23</sup> 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.<sup>24</sup> 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. The occurrence of CIPN also could depend 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.<sup>20</sup> Several studies show that the immune system is regulated by circadian

**Table 3.** Multivariate analyses of predictors for CIPN

Factors	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Chronotype						
Intermediate	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Morning	0.12 (0.02–0.85)	0.034*	0.09 (0.01–0.74)	0.025*	0.06 (0.01–0.74)	0.028*
Evening	1.28 (0.23–7.13)	0.777	1.43 (0.24–8.46)	0.696	0.98 (0.11–8.59)	0.985
Age, ≥ 50 yr	1.71 (0.30–9.59)	0.543	2.37 (0.37–15.33)	0.363	1.99 (0.27–14.63)	0.500
BMI, ≥ 23 kg/m <sup>2</sup>	1.28 (0.31–5.37)	0.735	1.43 (0.33–6.19)	0.633	1.80 (0.36–8.97)	0.476
College graduates or higher	3.79 (0.88–16.37)	0.075	4.54 (0.95–21.65)	0.058	5.19 (0.99–27.23)	0.051
Operation (TM)	-	-	2.43 (0.40–14.81)	0.335	2.65 (0.34–20.42)	0.351
≥ 1 alcoholic drinks per week	-	-	1.13 (0.13–9.79)	0.909	1.82 (0.16–21.35)	0.632
Current smoker	-	-	1.38 (0.10–19.04)	0.812	1.99 (0.09–43.45)	0.661
Poor sleep quality	-	-	-	-	1.37 (0.07–26.62)	0.837
Depression	-	-	-	-	0.41 (0.08–2.22)	0.304
Anxiety	-	-	-	-	4.18 (0.48–36.42)	0.195

CIPN = chemotherapy-induced peripheral neuropathy, OR = odds ratio, CI = confidence interval, BMI = body mass index, TM = total mastectomy.

rhythm, disruption of which induces inflammation. Adams et al.<sup>25</sup> 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.<sup>26</sup> Adams et al.<sup>25</sup> 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.

This study has several strengths. First, this study was the first to investigate the association between psychiatric factors and the occurrence of CIPN. Lee et al.<sup>7</sup> reported that pretreatment anxiety was associated with persistence of CIPN, but did not reveal the relationship between anxiety and incidence of CIPN. 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 a self-reported scale. 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. Third, several previous studies have reported circadian rhythmicity in the symptoms of peripheral neuropathy,<sup>27,28</sup> which may have contributed to the association of chronotype with CIPN. In our study, the analysis related above could not be performed because the information on severity of CIPN by time of day was not collected. Fourth, it is possible that chemotherapy, including docetaxel, changed the participants' chronotype by inducing sleep phase advance or delay. In this study, the chronotype was measured only before chemotherapy, so we could not determine the change in chronotype. Fifth, this study analyzed the relationship between docetaxel-induced peripheral neuropathy and chronotype. However, chemotherapeutic agents that can induce CIPN primarily include platinum-based drugs, taxanes, ixabepilone and thalidomide.<sup>29</sup> Therefore, the generalizability of our findings may be limited.

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.

## REFERENCES

- Phillips JL, Currow DC. Cancer as a chronic disease. *Collegian* 2010;17(2):47-50.  
[PUBMED](#) | [CROSSREF](#)
- Jung KW, Won YJ, Kong HJ, Lee ES. Community of Population-Based Regional Cancer Registries. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2015. *Cancer Res Treat* 2018;50(2):303-16.  
[PUBMED](#) | [CROSSREF](#)
- Kerckhove N, Collin A, Condé S, Chaleteix C, Pezet D, Balaýssac D. Long-term effects, pathophysiological mechanisms, and risk factors of chemotherapy-induced peripheral neuropathies: a comprehensive literature review. *Front Pharmacol* 2017;8:86.  
[PUBMED](#) | [CROSSREF](#)
- Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. *J Neurol* 2002;249(1):9-17.  
[PUBMED](#) | [CROSSREF](#)
- Stubblefield MD, Burstein HJ, Burton AW, Custodio CM, Deng GE, Ho M, et al. NCCN Task Force Report: Management of Neuropathy in Cancer. *J Natl Compr Canc Netw* 2009;7 Suppl 5:S1-26.  
[PUBMED](#) | [CROSSREF](#)
- Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer* 2008;44(11):1507-15.  
[PUBMED](#) | [CROSSREF](#)
- Lee KM, Jung D, Hwang H, Son KL, Kim TY, Im SA, 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* 2018;108:14-9.  
[PUBMED](#) | [CROSSREF](#)
- Jung D, Lee KM, Kim WH, Lee JY, Kim TY, Im SA, et al. Longitudinal association of poor sleep quality with chemotherapy-induced nausea and vomiting in patients with breast cancer. *Psychosom Med* 2016;78(8):959-65.  
[PUBMED](#) | [CROSSREF](#)
- Lee KM, Jung DY, Hwang H, Kim WH, Lee JY, Kim TY, et al. Late chronotypes are associated with neoadjuvant chemotherapy-induced nausea and vomiting in women with breast cancer. *Chronobiol Int* 2017;34(4):480-91.  
[PUBMED](#) | [CROSSREF](#)
- Wittmann M, Dinich J, Mellow M, Roenneberg T. Social jetlag: misalignment of biological and social time. *Chronobiol Int* 2006;23(1-2):497-509.  
[PUBMED](#) | [CROSSREF](#)
- Hahn BJ, Jo B, Dhabhar FS, Paresh O, Aldridge-Gerry A, Bajestan SN, et al. Bedtime misalignment and progression of breast cancer. *Chronobiol Int* 2014;31(2):214-21.  
[PUBMED](#) | [CROSSREF](#)
- Kober KM, Mazor M, Abrams G, Olshen A, Conley YP, Hammer M, et al. Phenotypic characterization of paclitaxel-induced peripheral neuropathy in cancer survivors. *J Pain Symptom Manage* 2018;56(6):908-919.e3.  
[PUBMED](#) | [CROSSREF](#)
- Smith CS, Reilly C, Midkiff K. Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *J Appl Psychol* 1989;74(5):728-38.  
[PUBMED](#) | [CROSSREF](#)
- Bohle P, Tilley AJ, Brown S. Psychometric evaluation of the early/late preferences scale. *Ergonomics* 2001;44(10):887-900.  
[PUBMED](#) | [CROSSREF](#)
- Di Milia L, Wikman R, Smith P. Additional psychometric evidence and construct validity for a revised preferences scale of morningness. *Chronobiol Int* 2008;25(5):776-87.  
[PUBMED](#) | [CROSSREF](#)

16. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193-213.  
[PUBMED](#) | [CROSSREF](#)
17. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh sleep quality index. *J Psychosom Res* 1998;45(1):5-13.  
[PUBMED](#) | [CROSSREF](#)
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70.  
[PUBMED](#) | [CROSSREF](#)
19. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res* 2002;52(2):69-77.  
[PUBMED](#) | [CROSSREF](#)
20. Kerckhove N, Collin A, Condé S, Chaletex C, Pezet D, Balaýssac D. Long-term effects, pathophysiological mechanisms, and risk factors of chemotherapy-induced peripheral neuropathies: a comprehensive literature review. *Front Pharmacol* 2017;8:86.  
[PUBMED](#) | [CROSSREF](#)
21. Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast Cancer Res Treat* 2016;159(2):327-33.  
[PUBMED](#) | [CROSSREF](#)
22. Johnson CH. Circadian clocks and cell division: what's the pacemaker? *Cell Cycle* 2010;9(19):3864-73.  
[PUBMED](#) | [CROSSREF](#)
23. Nikaido SS, Johnson CH. Daily and circadian variation in survival from ultraviolet radiation in *Chlamydomonas reinhardtii*. *Photochem Photobiol* 2000;71(6):758-65.  
[PUBMED](#) | [CROSSREF](#)
24. Norma VG, Badrán AF, Barbeito CG. Daily variations in colchicine-induced apoptosis in duodenal crypts. *Chronobiol Int* 2005;22(1):79-88.  
[PUBMED](#) | [CROSSREF](#)
25. Adams KL, Castanon-Cervantes O, Evans JA, Davidson AJ. Environmental circadian disruption elevates the IL-6 response to lipopolysaccharide in blood. *J Biol Rhythms* 2013;28(4):272-7.  
[PUBMED](#) | [CROSSREF](#)
26. Perry MG, Kirwan JR, Jessop DS, Hunt LP. Overnight variations in cortisol, interleukin 6, tumour necrosis factor alpha and other cytokines in people with rheumatoid arthritis. *Ann Rheum Dis* 2009;68(1):63-8.  
[PUBMED](#) | [CROSSREF](#)
27. Kim HK, Lee SY, Koike N, Kim E, Wirianto M, Burish MJ, et al. Circadian regulation of chemotherapy-induced peripheral neuropathic pain and the underlying transcriptomic landscape. *Sci Rep* 2020;10(1):13844.  
[PUBMED](#) | [CROSSREF](#)
28. Burish MJ, Chen Z, Yoo SH. Emerging relevance of circadian rhythms in headaches and neuropathic pain. *Acta Physiol (Oxf)* 2019;225(1):e13161.  
[PUBMED](#) | [CROSSREF](#)
29. Banach M, Juranek JK, Zygulska AL. Chemotherapy-induced neuropathies-a growing problem for patients and health care providers. *Brain Behav* 2016;7(1):e00558.  
[PUBMED](#) | [CROSSREF](#)