Sleep Medicine 55 (2019) 14–21

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Disruption of sleep, sleep-wake activity rhythm, and nocturnal melatonin production in breast cancer patients undergoing adjuvant chemotherapy: prospective cohort study

Wentao Li [a, e], Carol Chi-Hei Kwok [b], Dominic Chun-Wan Chan [b], Amy Wing-Yin Ho [c], Chung-Shun Ho [c], Jihui Zhang [d], Yun Kwok Wing [d], Feng Wang [a], Lap Ah Tse [a, *]

[a] Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China
[b] Department of Oncology, Princess Margaret Hospital, Hong Kong SAR, China
[c] Department of Chemical Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China
[d] Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong SAR, China
[e] Department of Obstetrics and Gynecology, Monash University, Australia

ARTICLE INFO

Article history:
Received 29 August 2018
Received in revised form
10 November 2018
Accepted 28 November 2018
Available online 14 December 2018

Keywords:
Circadian rhythm
Melatonin
Sleep
Sleep-wake activity rhythm
Breast cancer
Anti-cancer treatment

ABSTRACT

Objective: This prospective cohort study captured the patterns of sleep, sleep-wake activity rhythm, and first-morning urinary melatonin in breast cancer patients undergoing adjuvant chemotherapy.
Methods: Breast cancer patients undergoing adjuvant chemotherapy wore wrist actigraph for 168 h and collected first-morning void urine samples before treatment, during the first, and at the last cycle of chemotherapy. We converted actigraphy data into sleep duration, sleep efficiency, nighttime total wake time, percent rhythm, F-statistic, amplitude, mesor, and acrophase. We then assessed urinary 6-sulfatoxymelatonin (aMT6s) levels.
Results: This cohort contained 180 participants. Compared with the baseline, sleep efficiency during the first and last cycle decreased by 10.16% [95% confidence interval (95% CI): 5.85%, 14.47%] and 5.01% (95% CI: 0.50%, 9.53%), respectively. Similarly, percent rhythm decreased by 27.20% (95% CI: 19.95%, 34.45%) during the first cycle and 21.20% (95% CI: 13.52, 28.89) during the last cycle. Taking the baseline as the reference, aMT6s levels during the first and last cycle decreased by 11.27% (95% CI: 0.37%, 22.16%) and 14.74% (95% CI: 2.34, 27.11), respectively.
Conclusion: The first administration of adjuvant chemotherapy is associated with sleep disturbance and sleep-wake activity rhythm disruption among breast cancer patients, while the disturbance and disruption during the last cycle are less severe; nevertheless, repeated administration of chemotherapy results in progressive impairment of nocturnal melatonin production.

1. Introduction

Sleep disturbance and weak sleep-wake activity rhythm are prevalent among breast cancer patients undergoing anti-cancer treatment [1]. Studies have reported that 65.8–66.0% of breast cancer patients had poor sleep quality before receiving adjuvant chemotherapy [1,2]. The adverse impact of sleep disturbance and weak sleep-wake activity rhythm is a clinical concern. Sleep disturbance is associated with poor quality of life, fatigue, and depression in breast cancer patients [1,3]. Weak sleep-wake activity rhythm is evident to be a prognostic risk factor associated with poor survival of cancer patients and the side effects of anti-cancer treatment [4–6]. Furthermore, disruptions in sleep and sleep-wake activity rhythm may disrupt the production of nocturnal melatonin, which is an endogenous hormone playing a pivotal role in alleviating oxidative stress and regulating the immune and hematological system [7,8]. Objective monitoring of sleep and sleep-wake activity rhythm is a prerequisite for taking the precautions to counteract potential hazards of sleep-related disruptions in breast cancer patients undergoing anti-cancer treatment.

Longitudinal studies assessing subjective sleep quality before and during breast cancer adjuvant chemotherapy could not reach a

* Corresponding author. JC School of Public Health and Primary Care, The Chinese University of Hong Kong, 4/F School of Public Health and Primary Care, Prince of Wales Hospital, Sha Tin, N.T., Hong Kong SAR, China.
E-mail address: shelly@cuhk.edu.hk (L.A. Tse).

https://doi.org/10.1016/j.sleep.2018.11.022
1389-9457/

consensus regarding the change of sleep quality over time. While one study suggested a worsening of sleep quality after the beginning of chemotherapy [1]. In addition, other studies found that the sleep quality score did not change significantly over time [2,9]. This discrepancy echoes further evidence using objective actigraph to measure sleep patterns in breast cancer patients who receive adjuvant chemotherapy. As to the measurement of sleep-wake activity rhythm, most studies that repeatedly used actigraph in the trajectory of adjuvant chemotherapy among breast cancer patients were cross-sectional studies [10–14]. Only one longitudinal study conducted among 95 patients repeatedly used wrist actigraph for 72-h before and during adjuvant chemotherapy, and observed a progressive deterioration of sleep-wake activity rhythm over the course of chemotherapy [15]. Sleep-wake activity rhythm presents different patterns on weekdays and weekends [16]. However, existing studies conducted wrist actigraph measurements for a maximum of three random days in a week [11,12,15], which may not be able to represent an entire picture of the rhythm and thus are vulnerable to information bias. The comparability between actigraphy-derived parameters of sleep-wake activity rhythm is also unknown. First-morning void urinary 6-sulfatoxymelatonin (aMT6s), the major metabolite of melatonin, is used as a surrogate of nocturnal melatonin secretion because it closely correlates with nocturnal melatonin output and the peak level of melatonin in plasma [17]. To the best of our knowledge, no study has ever described the pattern of nocturnal melatonin production in breast cancer patients undergoing adjuvant chemotherapy.

This prospective study aims to longitudinally capture the patterns of sleep, sleep-wake activity rhythm, and nocturnal melatonin production using 168-h actigraphy and first morning urinary aMT6s prior to and during adjuvant chemotherapy in breast cancer patients. We hypothesize that sleep, sleep-wake activity rhythm, and melatonin secretion are significantly disrupted during chemotherapy.

2. Materials and methods

2.1. Study design

We consecutively invited all pathologically diagnosed stage I–III postoperative female primary breast cancer patients who needed chemotherapy at local cancer centers to participate in this study between May 2015 and December 2016. According to their disease condition and personal will, patients received one of the three adjuvant chemotherapy regimens: six cycles of FEC-T (5-fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel), four cycles of AC (doxorubicin and cyclophosphamide), and four cycles of TC (docetaxel and cyclophosphamide). Chemotherapy cycles normally last for 21 days, and chemotherapy agents are administered on day one, which means the recipients could rest for 20 days before the start of the next cycle. We followed up all cohort members until the completion of planned chemotherapy or the end of the last cycle if they did not complete planned cycles. This study was performed according to the principles outlined by the Helsinki Declaration and obtained approval from the local Ethics Committee. Written informed consents were obtained from all participants.

2.2. Data collection

Trained interviewers conducted a face-to-face interview with each participant on the same day of recruitment. The interviewers used a questionnaire to obtain information on socio-demographics and lifestyle factors including age, education level, family income, marital status, and drinking history. Of note, this questionnaire has been used in our previous cancer studies [18,19]. Regarding alcohol consumption, those who drank beer, wine, and liquor for at least once per month and lasted for over six months were defined as drinkers. We also used the Pittsburgh Sleep Quality Index (PSQI) to evaluate the subjective sleep quality of participants in the past month at baseline. Global PSQI scores ≧5 represent a significant degree of sleep disturbance [20]. We reviewed medical records to access information on clinical conditions including surgery type, cancer stage, chemotherapy regimen, concurrent medication use (corticosteroids, 5-HT3 receptor antagonist, and hypnotics), performance status (Eastern Cooperative Oncology Group score), and comorbidities (renal, hepatic, cardiovascular, pulmonary, musculoskeletal, and endocrine diseases). Each participant was asked to wear a piece of GENEActiv Original (Activinsights Company, UK) device, a validated actigraph [21], on her non-dominant wrist for three times prior to and during chemotherapy. First, participants wore the device for a week before chemotherapy (baseline). Second, participants wore the device during the first week of the first cycle (beginning of chemotherapy). Finally, those who received AC or TC regimen wore the device during the first week of the fourth cycle (end of chemotherapy), and those who had FEC-T wore the device during the first week of the third cycle (end of FEC). Measurements uniformly started from 6 pm of the interview day or the day of chemotherapy infusion and lasted for 168 h. Thus, measurements during chemotherapy accounted for one-third of the duration of the chemotherapy cycle. Participants were expected to collect three first-morning void urine samples. They were instructed to collect a baseline urine sample in the morning of hospital visit before receiving chemotherapy. Chemotherapy recipients routinely visited the hospital 10–14 days after receiving chemotherapy infusion in each cycle for safety surveillance. Urine samples regarding the beginning and end of chemotherapy were collected in the mornings of these hospital visits (between day 10 and 14 of cycles) in the first and last cycle (fourth cycle for AC and TC, third cycle for FEC). We trained participants to collect at least 10 ml first-morning void urine in a standard container on the scheduled day and store the urine sample in a refrigerator at home before bringing it to the hospital. We further stored the sample at −80 °C in our lab. The longest interval between sample collection and analysis was 34 months.

2.3. Assessment of actigraphy data

The actigraph records movements in three mutually vertical axes (x, y, and z). The measurement frequency was 100 Hz. We used GENEActiv Sleep Macro (v4), a macro developed by the actigraph manufacture, to compute nighttime sleep duration, sleep efficiency, and nighttime total wake time at each measurement. A manufacture defined software automatically calculated a gravity-subtracted sum of vector magnitudes (SVM) with data of the three axes (x, y, and z): SVMg s = [(x 2 + y 2 + z 2) ½ − 1 g] [22]. Data of SVM were converted into five parameters namely percent rhythm, F-statistic, amplitude, mesor, and acrophase [23]. Both percent rhythm and F-statistic are indices describing the comparability between observation and a rhythm model. Percent rhythm is a percentage of variation that can be explained by the fitted rhythm model. F-statistic is a test value for using a rhythm model to summarize data, which represents “goodness of fit”. Low levels of these two parameters suggest dampened rhythms. Amplitude stands for the height of the rhythm, which equals the distance between the maximum and minimum activity. Thus, low amplitude symbols a suppression of the robustness of sleep-wake activity rhythm. Mesor is a midline estimating statistic of the rhythm, and it represents mean activity level of the wearer. Low mesor indicates reduced activity. Acrophase means the time of day of peak activity, which can be used to describe the phase shift of sleep-wake activity rhythm. A later time

suggests more phase delay. There are no standard cut-offs for the five parameters in cancer patients because their values are determined by disease condition, treatment type, make and model of actigraph, and length of measurement, which vary substantially in current research. Data of non-wearing duration were not used to calculate the parameters. If the sum length of a wearing was less than 120 h (5/7 of 168 h), the wearing was considered incomplete and its data were not analyzed further.

2.4. Assessment of aMT6s

Urine aMT6s was assayed by an ultra-performance liquid chromatography-negative electrospray ionization tandem mass spectrometry (UPLC-MS/MS) method (Waters Acquity Xevo TQD system, Waters Corporation, Milford, MA, USA). Urine samples were diluted with a phosphate buffer solution containing deuterium-labeled aMT6s internal standard, centrifuged and injected into the UPLC-MS/MS system for chromatographic separation from matrix interference and tandem mass spectrometric quantitation. This method had a lower limit of quantitation at 0.5 nmol/L, with a linear analytical range up to 2500 nmol/L. Four in-house quality control samples, mean values of 5 nmol/L, 30 nmol/L, 300 nmol/L, and 750 nmol/L, were included in each batch of sample analysis. The intra-assay coefficients of variation (CV) were 4.9%, 4.1%, 2.8%, and 2.4%, respectively. The inter-assay CV were 7.9%, 4.6%, 4.1%, and 1.7%, respectively. The recoveries at these concentrations were between 101 and 102%. There was no significant matrix interference, and the relative carryover for consecutive samples was <0.02%. All aMT6s levels were creatinine-adjusted. Urine creatinine was measured by the kinetic Jaffé method, with a Cobas 8000 Modular Analyzer and manufacturer's optimized reagents (F. Hoffmann-La Roche Ltd, Basel, Switzerland). Both the intra- and inter-assay CV for creatinine were <3%.

2.5. Study endpoints

The primary endpoints of this study are sleep efficiency, percent rhythm, and first morning urinary aMT6s. Secondary endpoints include sleep duration, nighttime total wake time, F-statistic, amplitude, mesor, and acrophase.

2.6. Statistical analysis

We used linear mixed-effects models with restricted maximum likelihood methods to describe the changes in actigraphy-derived parameters and first morning urinary aMT6s before and during chemotherapy. We performed both univariable and multivariable models for all actigraphy-derived parameters and urinary aMT6s. For all models, values at the beginning and end of chemotherapy were compared with the baseline data. The multivariable linear mixed-effects models adjusted for age (continuous); educational level (below high school/high school or above); marital status (married/single or divorced or widowed); alcohol drinking (yes/no); family income level (≤14,999/≥15,000 HKD/month); body mass index (≤22.9/23.0–24.9/≥25.0); menopausal status (premenopausal/postmenopausal); performance status (0/≥1); surgery type (mastectomy/lumpectomy or breast-conserving therapy); comorbidity (yes/no); cancer stage (I/II/III); chemotherapy regimen (AC/FEC-T/TC); hypnotics (yes/no); and use of corticosteroids (5-HT3 receptor antagonist). Since there were missing values for marital status (3.89%) and family income (12.78%), we employed multiple imputations with five iterations to increase the power and validity of multivariable analyses. Time of measurement (baseline, the beginning of chemotherapy, and the end of chemotherapy) was treated as a fixed effect variable in all models. Covariates served as fixed effect variables in multivariable models. All models also included a random effect at the individual level with random intercept and subject identity.

We employed the analysis of intraclass correlation to test the comparability among percent rhythm, F-statistic, and amplitude since they all represent the robustness of sleep-wake activity rhythm (resemble each other) and were measured at the same timings of measurements. The intraclass correlation coefficient (ICC) is an inferential statistic that can describe how strong different indices in the same group resemble each other [24]. Since these indices have different units and scales, we used z-score standardization to capacitate comparisons. We used two-way mixed average measures of the intraclass correlation to test the consistency of pairwise z-score standardized indices [25].

We also compared the parameters of sleep-wake activity rhythm between weekdays and weekend days at baseline using paired Student's t test or Wilcoxon signed-rank test. Sleep conditions at weekend nights (Friday and Saturday) were compared with those at weekday nights (Sunday to Thursday). The comparison of overall fit statistics including percent rhythm and F-statistic were not feasible because two days on the weekend were too short to generate a robust estimation of overall fitness.

We used IBM SPSS Statistics Version 22 for the statistical analysis.

3. Results

We successfully recruited 193 participants into the cohort. A total of 190 participants provided complete data for the first (baseline) actigraph measurement. After that, 13 participants were decided that they do not need adjuvant chemotherapy by oncologists. Among the remaining 180 participants, 175 and 136 of them provided complete data for the second (beginning of chemotherapy) and third (end of chemotherapy) measurements. The numbers of participants who provided first-morning void urine samples at baseline, the beginning, and the end of chemotherapy were 166, 132, and 104, respectively. Fig. 1 shows the flowchart.

3.1. Characteristics of the cohort

Table 1 shows the socio-demographic and clinical characteristics of the cohort members. The median age of participants was 53 years old. Most participants had a high school or above education (68.89%) and were married (72.25%). The proportion of participants who reported sleep disturbance (PSQI≧5) at baseline was 76.33%. In total, 85.00% of participants had good performance status. Mastectomy (71.67%) was the dominant surgery type. The proportions of participants who received FEC-T, AC, and TC were 44.44%, 28.89%, and 26.67%, respectively.

3.2. Patterns of actigraphy-derived parameters and first morning urinary aMT6s

Table 2 and Fig. 2 show the values of actigraphy-derived parameters and creatinine-adjusted first morning urinary aMT6s at three measurements around chemotherapy. The fixed effects of time (measurement sequence) on all parameters and urinary aMT6s were statistically significant in both univariable and multivariable linear mixed-effects models, suggesting that the administration of adjuvant chemotherapy significantly altered sleep, sleep-wake activity rhythm, and nocturnal melatonin production among breast cancer patients. Taking baseline data as the reference, sleep duration and nighttime wake time at the beginning of chemotherapy increased by 12.62% [95% confidence interval (95% CI): 1.40%, 23.87%] and 56.54% (95% CI: 34.65%, 78.43%), while sleep

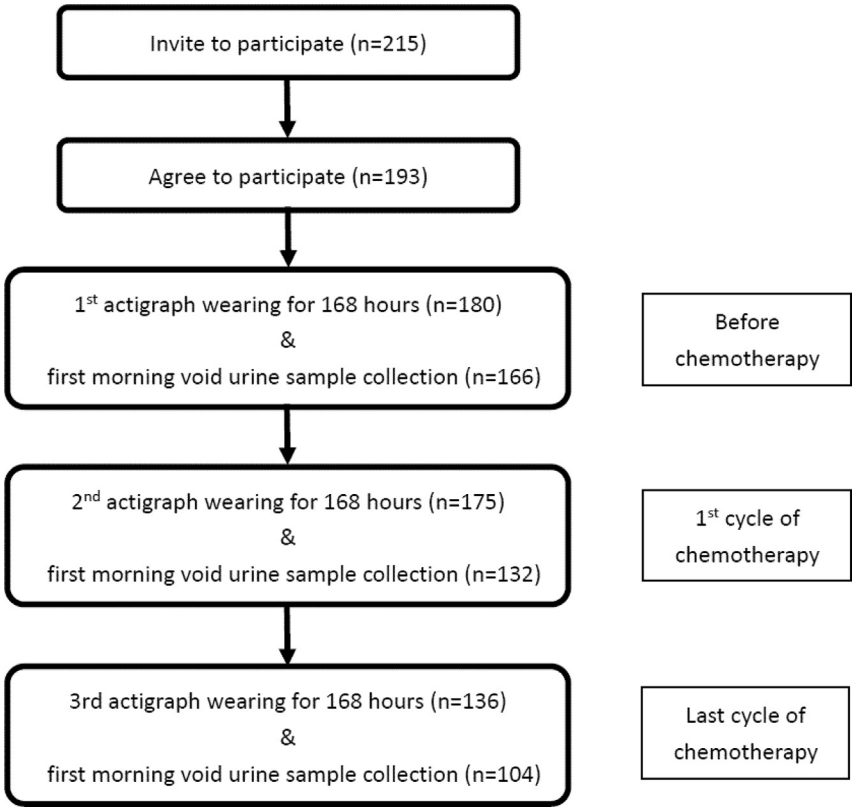

Fig. 1. Flowchart of the study.

efficiency decreased by 10.16% (95% CI: 5.85%, 14.47%). Percent rhythm, F-statistic, amplitude, and mesor at the beginning of chemotherapy decreased by 27.20% (95% CI: 19.95%, 34.45%), 32.04% (95% CI: 22.81%, 41.26%), 20.88% (95% CI: 15.91%, 25.85%), and 34.98% (95% CI: 28.76%, 41.19%), respectively. Sleep duration and nighttime wake time at the end of chemotherapy were shorter than those at the beginning of treatment, but they were still significantly longer than baseline values. Although values of sleep efficiency, percent rhythm, F-statistic, and mesor at the end of chemotherapy were still significantly lower than baseline values, they were higher than those at the beginning of chemotherapy. Regarding acrophase, the difference between baseline and the beginning of chemotherapy was not statistically significant; but acrophase at the end of chemotherapy was 29-min (95% CI: 8-min, 50-min) earlier than that at baseline. The deterioration in first-morning urinary aMT6s level over the course of chemotherapy was accumulative; values at the beginning and end of chemotherapy decreased by 11.27% (95% CI: 0.37%, 22.16%) and 14.74% (95% CI: 2.34, 27.11) than that at baseline.

3.3. Comparability of parameters of sleep-wake activity rhythm

The agreement between percent rhythm and F-statistic was excellent (ICC: 0.972, $p = 0.001$). Amplitude also had high consistency with percent rhythm (ICC: 0.758, $p = 0.001$) and F-statistic (ICC: 0.723, $p = 0.001$).

3.4. Comparison of sleep-wake activity rhythm between weekdays and weekends

The differences in sleep duration, sleep efficiency, nighttime total wake time, and amplitude between weekdays and weekend days were not statistically significant. However, participants had a higher level of mesor and a later phase of acrophase on weekends (Table 3).

4. Discussion

This longitudinal study suggests that sleep, sleep-wake activity rhythm, and nocturnal melatonin production are rapidly disrupted after the administration of the first cycle of adjuvant chemotherapy in breast cancer patients. There is an “adaption” at the end of chemotherapy, manifested by the partial recovery of sleep duration, sleep efficiency, nighttime wake time, percent rhythm, F-statistic, and mesor. Acrophase at the end of chemotherapy is significantly earlier than that at baseline. Repeated administration of chemotherapy is associated with progressive impairment of nocturnal melatonin production.

While the hazards of sleep disturbance in breast cancer patients are concerning, understanding of the pattern of sleep prior to and during chemotherapy is insufficient. Studies assessing subjective sleep quality could not reach an agreement regarding the change over time [1,2,9]. A previous longitudinal study used actigraph among 97 breast cancer patients found that sleep duration increased significantly from the baseline to the first and last cycles, but the study did not find a significant overall time effect for nighttime total wake time [9]. Our study demonstrated a substantial sleep disturbance during chemotherapy, which was manifested by the prolongation of sleep duration and nighttime wake time as well as a decrease in sleep efficiency. There was a phenomenon of “adaption” to sleep disturbance during the last cycle. As to sleep-wake activity rhythm, this study is in line with previous findings that sleep-wake activity rhythm is weakened during chemotherapy [10,11,15]. However, there are two distinguishing

Table 1
Selected characteristics of study participants who received chemotherapy (n = 180).

Variable	Median (range)
Age	53 (22, 74)
	n (%)
Educational level	
Below high school	56 (31.11)
High school or above	124 (68.89)
Marital status	
Single/divorced/widowed	48 (27.75)
Married	125 (72.25)
Family income (HKD/month)	
≤14,999	78 (49.68)
≥15,000	79 (50.32)
Menopausal status	
Premenopausal	86 (47.78)
Postmenopausal	94 (52.22)
Body mass index	
≤22.9	77 (42.78)
23.0–24.9	33 (18.33)
≥25.0	70 (38.89)
PSQI	
≤4	40 (23.67)
≥5	129 (76.33)
Performance status (ECOG)	
0	153 (85.00)
≥1	27 (15.00)
Comorbidity[a]	
No	93 (51.67)
Yes	87 (48.33)
Cancer stage[b]	
I	24 (13.33)
II	105 (58.33)
III	51 (28.33)
Surgery type	
Lumpectomy/BCT	51 (28.33)
Mastectomy	129 (71.67)
Chemotherapy regimen	
FEC-T	80 (44.44)
AC	52 (28.89)
TC	48 (26.67)

Abbreviations: BCT, breast conserving therapy; ECOG, Eastern Cooperative Oncology Group; HKD, Hong Kong dollar; AC, doxorubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide-docetaxel; TC, docetaxel, cyclophosphamide; PSQI, Pittsburgh Sleep Quality Index.

[a] Including renal, hepatic, cardiovascular, pulmonary, musculoskeletal, and endocrine diseases.

[b] AJCC breast cancer staging system, seventh edition.

results which were not discovered in the previous cohort study [15]. (i) We found that acrophase at the end of chemotherapy was significantly earlier (29 min) than that at baseline; (ii) we observed an "adaption" to sleep-wake activity rhythm disruption rather than a progressive deterioration of the rhythm. The large sample size and long actigraph measurement of our study might partly explain the differentiated results from the previous cohort studies. The sufficient sample size (n = 180) in our study provides extra credit for detecting specific changes in the pattern. The use of 168-h wrist actigraph measurement in our study has substantial advantages over shorter measurements in previous studies (typically 48 or 72 h) concerning data validity and reliability. Random measurements shorter than 168-h assume that sleep-wake activity rhythms on different days are similar. This assumption contradicts the fact that the rhythm on weekdays and weekends could be substantially different [16]. In our study, the observed significant differences in mesor and acrophase on weekdays and weekend days further support the necessity of using 168-h actigraphy to describe sleep-wake activity rhythm among cancer patients. In addition, reduced dose intensity at the end of chemotherapy may also contribute to the "adaption" since 65.0% (117/180) of participants had treatment defer and/or dose reduction in the trajectory of chemotherapy, which presents the real-world nature of this longitudinal cohort study.

This study provides the first epidemiological evidence that nocturnal melatonin secretion is progressively impaired over the course of chemotherapy in breast cancer patients receiving chemotherapy. The absence of "adaption" at the end of chemotherapy for aMT6s suggests that the effect on nocturnal melatonin production from sleep disturbance is lasting. It is also possible that other neuroendocrine changes induced by chemotherapy contribute to the progressive suppression of melatonin production, which warrants further research. In addition, we asked participants to collect first morning urine during the second week of cycles rather than the first week due to feasibility consideration, the difference in collection time may partly explain the discrepancy between patterns of sleep-wake activity rhythm and nocturnal melatonin production. Further studies may try to obtain a series of first morning urine samples to further elaborate the pattern of melatonin production, but of course, this attempt would be more participant demanding. In consideration of the critical functions of melatonin in alleviating oxidative stress [7] and interacting with the immune and hematological system [8], this finding suggests that nocturnal melatonin secretion disruption may play roles in the development of fatigue, body weight loss, and hematological toxicity among cancer patients who receive chemotherapy [4,5]. Melatonin secretion presents marked circadian rhythmicity, with levels high between 2 and 4 a.m. and very low at daytime [26]. A single assessment of aMT6s in first-morning void urine sample enables estimation of the nocturnal peak level of melatonin [17], and this method has been widely used in epidemiological studies [26,27]. Findings of this study outlined the potential value of monitoring aMT6s in first-morning void urine among breast cancer patients undergoing chemotherapy to predict the occurrence of side effects including fatigue, weight loss, and hematological toxicity.

Interventions on sleep disturbance and weak sleep-wake activity rhythm in breast cancer patients may have huge potentials on improving quality of life and preventing side effects of anti-cancer treatment. Pharmaceutical agents including hypnotics and melatonin have direct therapeutic value. Furthermore, physical activity, which is one of the strongest synchronizers of sleep-wake activity rhythm [28], can improve sleep behavior and simultaneously benefit physical strength, body composition, and hormone secretion in breast cancer patients [29,30]. Based on findings in this study, we suggest that interventions should be given to breast cancer patients who need adjuvant chemotherapy from the beginning of treatment. For pharmaceutical intervention, it is necessary to monitor sleep conditions and adjust the dosage of medication due to the natural "adaption" in the trajectory of chemotherapy.

Concern over the disruption of sleep and sleep-wake activity rhythm has extended beyond breast cancer. Disrupted sleep-wake activity rhythm is associated with a shorter survival in colorectal cancer patients as well [31,32]. In addition, a longitudinal study using wrist actigraphy also indicated a deteriorated rhythm in patients with colorectal cancer who underwent chemotherapy [4]. However, the changing pattern of the rhythm during a whole course of chemotherapy for the colorectal cancer is unknown as there was only one actigraph measurement (for one to five days) in the whole trajectory of chemotherapy. More importantly, chronochemotherapy, a programmed administration of chemotherapy agents to coincide with relevant circadian rhythm, has demonstrated that it is less toxic and more effective than constant-rate infusion in colorectal cancer [33]. These findings, together with discoveries in breast cancer, outline the importance of sleep-rest activity rhythm in multiple types of cancers and call for more research efforts.

Table 2
Actigraphy derived parameters and first-morning urinary melatonin at three repeated measurements, analyzed with linear mixed-effects modeling.

Parameter/Item	Measurement[a]	Mean (SE)	Percentage of change (95% CI)	p-value of fixed effect of time	
				Univariable	Multivariable[b]
Actigraphy-derived parameters					
Sleep duration (min)	Baseline	341.57 (12.78)	Reference	0.001	0.001
	Beginning	384.72 (14.56)	12.62 (1.40, 23.87)		
	End	374.88 (14.22)	9.75 (4.18, 15.32)		
Sleep efficiency (%)	Baseline	67.07 (1.05)	Reference	0.001	0.001
	Beginning	60.26 (1.19)	−10.16 (−14.47, −5.85)		
	End	63.71 (1.38)	−5.01 (−9.53, −0.50)		
Nighttime total wake time (min)	Baseline	171.25 (10.46)	Reference	0.001	0.001
	Beginning	268.07 (11.90)	56.54 (34.65, 78.43)		
	End	222.11 (13.40)	29.70 (9.98, 49.41)		
Percent rhythm	Baseline	19.21 (0.47)	Reference	0.001	0.001
	Beginning	13.98 (0.53)	−27.20 (−34.45, −19.95)		
	End	15.14 (0.54)	−21.20 (−28.89, −13.52)		
F-statistic	Baseline	211.24 (6.69)	Reference	0.001	0.001
	Beginning	143.57 (6.80)	−32.04 (−41.26, −22.81)		
	End	156.51 (6.57)	−25.91 (−35.41, −16.40)		
Amplitude	Baseline	292.08 (5.33)	Reference	0.001	0.001
	Beginning	231.10 (5.94)	−20.88 (−25.85, −15.91)		
	End	234.71 (5.70)	−19.64 (−24.65, −14.63)		
Mesor	Baseline	150.97 (3.85)	Reference	0.001	0.001
	Beginning	98.16 (3.68)	−34.98 (−41.19, −28.76)		
	End	110.18 (4.59)	−27.02 (−35.27, −18.77)		
Acrophase (decimal time)	Baseline	14.97 (0.14)	Reference	0.003	0.003–0.005
	Beginning	14.85 (0.14)	−0.78 (−2.83, 1.28)		
	End	14.48 (0.15)	−3.25 (−5.58, −0.92)		
First morning urinary marker					
aMT6s/Cr (μmol/mol Creatine)	Baseline	9.13 (0.50)	Reference	0.008	0.009–0.017
	Beginning	8.11 (0.54)	−11.27 (−22.16, −0.37)		
	End	7.79 (0.56)	−14.74 (−27.11, −2.34)		

Abbreviation: SE, standard error; aMT6s, 6-Sulfatoxymelatonin; CI, confidence interval.
[a] Baseline, before chemotherapy; beginning, the first week of the first cycle; end, the first week of the last cycle.
[b] Results of multiple imputation data; adjusted for age, educational level, marital status, alcohol drinking, family income level, body mass index, menopausal status, performance status, surgery type, comorbidity, cancer stage, chemotherapy regimen, use of corticosteroids, 5-HT3 receptor antagonist, and hypnotics.

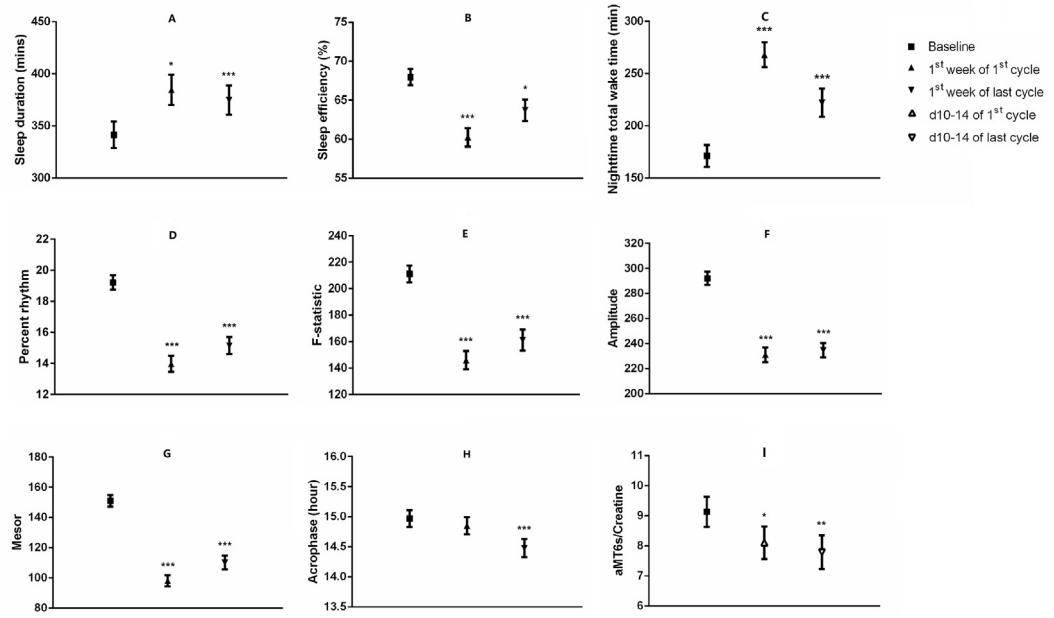

Fig. 2. Changes in sleep, sleep-wake activity rhythm, and first morning urinary aMT6s over the course of adjuvant chemotherapy among breast cancer patients. (A) Night sleep duration; (B) Sleep efficiency; (C) Nighttime total wake time; (D) percent rhythm; (E) F-statistic; (F) Amplitude; (G) Mesor; (H) Acrophase; (I) aMT6s/Creatinine. *p-value < 0.05; ** p-value < 0.01; ***p-value ≦ 0.001 for comparisons between each time point and baseline.

Table 3
Sleep and sleep-wake activity rhythm on weekdays and weekends at baseline.

Variable	Mean ± sd/median (IQR)		p-value
	Weekday	Weekend	
Sleep duration (min)	341.32 ± 77.09	351.15 ± 89.59	0.096[a]
Sleep efficiency (%)	67.68 ± 13.50	65.39 ± 15.44	0.179[a]
Nighttime total wake time (min)	175.86 (115.55, 240.76)	179.01 (118.02, 264.15)	0.137[b]
Amplitude	292.56 ± 71.85	290.82 ± 83.10	0.61[a]
Mesor	149.22 ± 51.75	162.42 ± 70.55	0.001[a]
Acrophase	14.96 (13.90, 16.04)	15.32 (13.80, 16.41)	0.002[b]

Abbreviation: IQR, interquartile range.
[a] Paired t test.
[b] Wilcoxon signed-rank test.

This study is characterized by several strengths including the prospective cohort design, 168-h actigraph measurement, objective measurement of actigraphy and aMT6s, and utilization of multivariable mixed-effects models. However, there are several limitations. First, 24.4% of participants could not provide credible actigraphy data at the end of chemotherapy as most of them prematurely terminated chemotherapy or changed treatment. It is possible that drop-out participants at the last measurement had worse sleep quality and sleep-wake activity rhythm than those who provided complete data, resulting in an effect of "survival of the fit". However, given the comparable drop-out rate (18.6%) at the end of chemotherapy in the previous longitudinal study [15], we believe that "survival of the fit" could not overwhelmingly explain the "adaption" to sleep disturbance and sleep-wake activity rhythm disruption in our participants. Second, the number of urine samples was smaller than that of individuals with actigraphy data, demonstrating the lower acceptability of donating urine samples among our participants since urine is generally considered "insanitary" in the local culture. Third, a mid-chemotherapy measurement may provide extra information on the trend of circadian rhythm in the trajectory of chemotherapy. Nevertheless, we did not involve a midcourse measurement because the combination of long device wearing and excessive device measurements results in a low response and poor compliance. We decided to opt for the advantage of 168-h measurement to overcome the major limitation in previous studies concerning insufficient measurement duration instead. Finally, there is evidence that certain beta-blockers may disrupt nocturnal melatonin release, which potentially impact on the finding regarding first morning urinary aMT6s [34]. We were unable to obtain information on the use of beta-blockers in medical records of the oncology department.

In conclusion, the first administration of adjuvant chemotherapy is associated with sleep disturbance and sleep-wake activity rhythm disruption among breast cancer patients, while the disturbance and disruption at the last administration are less severe. Repeated administration of chemotherapy results in progressive impairment of nocturnal melatonin production.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors thank Ms. Xiaona Lin, Ms. Tess Tsoi, and Ms. Bonnie Kwok for their contribution to this study. This study did not receive any funding. The authors declare that they have no conflict of interest.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.11.022.

References

[1] Liu L, Fiorentino L, Natarajan L, et al. Pre-treatment symptom cluster in breast cancer patients is associated with worse sleep, fatigue and depression during chemotherapy. Psycho Oncol J Psychol Soc Behav Dimens Cancer 2009;18(2):187–94.
[2] Sanford SD, Wagner LI, Beaumont JL, et al. Longitudinal prospective assessment of sleep quality: before, during, and after adjuvant chemotherapy for breast cancer. Support Care Cancer 2013;21(4):959–67.
[3] Fortner BV, Stepanski EJ, Wang SC, et al. Sleep and quality of life in breast cancer patients. J Pain Symptom Manag 2002;24(5):471–80.
[4] Ortiz-Tudela E, Lurisci I, Beau J, et al. The circadian rest-activity rhythm, a potential safety pharmacology endpoint of cancer chemotherapy. Int J Cancer 2014;134(11):2717–25.
[5] Li W, Kwok CC, Chan DC, et al. Weak circadian rhythm increases neutropenia risk among breast cancer patients undergoing adjuvant chemotherapy. Breast Cancer Res Treat; 2017.
[6] Palesh O, Aldridge-Gerry A, Zeitzer JM, et al. Actigraphy-measured sleep disruption as a predictor of survival among women with advanced breast cancer. Sleep 2014;37(5):837–42.
[7] Tan D-X. Melatonin: a potent, endogenous hydroxyl radical scavenger. Endocr J 1993;1:57–60.
[8] Carrillo-Vico A, Guerrero JM, Lardone PJ, et al. A review of the multiple actions of melatonin on the immune system. Endocrine 2005;27(2):189–200.
[9] Liu L, Rissling M, Natarajan L, et al. The longitudinal relationship between fatigue and sleep in breast cancer patients undergoing chemotherapy. Sleep 2012;35(2):237–45.
[10] Berger AM, Wielgus K, Hertzog M, et al. Patterns of circadian activity rhythms and their relationships with fatigue and anxiety/depression in women treated with breast cancer adjuvant chemotherapy. Support Care Cancer 2010;18(1):105–14.
[11] Wielgus KK, Berger AM, Hertzog M. Predictors of fatigue 30 days after completing anthracycline plus taxane adjuvant chemotherapy for breast cancer. Oncol Nurs Forum 2009;36(1):38–48.
[12] Ancoli-Israel S, Liu L, Rissling M, et al. Sleep, fatigue, depression, and circadian activity rhythms in women with breast cancer before and after treatment: a 1-year longitudinal study. Support Care Cancer 2014;22(9):2535–45.
[13] Sultan A, Choudhary V, Parganiha A. Worsening of rest-activity circadian rhythm and quality of life in female breast cancer patients along progression of chemotherapy cycles. Chronobiol Int 2017;34(5):609–23.
[14] Liu L, Rissling M, Neikrug A, et al. Fatigue and circadian activity rhythms in breast cancer patients before and after chemotherapy: a controlled study. Fatigue 2013;1(1–2):12–26.
[15] Savard J, Liu L, Natarajan L, et al. Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. Sleep 2009;32(9):1155–60.
[16] Vitale JA, Roveda E, Montaruli A, et al. Chronotype influences activity circadian rhythm and sleep: differences in sleep quality between weekdays and weekend. Chronobiol Int 2015;32(3):405–15.
[17] Graham C, Cook MR, Kavet R, et al. Prediction of nocturnal plasma melatonin from morning urinary measures. J Pineal Res 1998;24(4):230–8.
[18] Li M, Tse LA, Chan WC, et al. Nighttime eating and breast cancer among Chinese women in Hong Kong. Breast Cancer Res 2017;19(1):31.
[19] Tse LA, Yu IT, Qiu H, et al. A case-referent study of lung cancer and incense smoke, smoking, and residential radon in Chinese men. Environ Health Perspect 2011;119(11):1641–6.

[20] Buysse DJ, Reynolds 3rd CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28(2):193–213.
[21] Esliger DW, Rowlands AV, Hurst TL, et al. Validation of the GENEA accelerometer. 2011. Med Sci Sports Exerc 2011;43(6):1085–93.
[22] GENEActiv Instruction Manual v 1.2. [cited 2017 4/20]; Available from: https://www.activinsights.com/wp-content/uploads/2014/03/geneactiv_instruction_manual_v1.2.pdf.
[23] Zuther P, G.S., Lemmer B. Chronos-Fit, revised Version 1.06. 2009. Available from: http://www.ma.uni-heidelberg.de/inst/phar/lehre/chrono.html.
[24] Koch GG. Intraclass correlation coefficient. Encyclop Stat Sci 1982.
[25] De Vet HC, Terwee CB, Mokkink LB, et al. Measurement in medicine: a practical guide. Cambridge University Press; 2011.
[26] Schernhammer ES, Hankinson SE. Urinary melatonin levels and postmenopausal breast cancer risk in the Nurses' Health Study cohort. Cancer Epidemiol Biomark Prev 2009;18(1):74–9.
[27] Sigurdardottir LG, Markt SC, Rider JR, et al. Urinary melatonin levels, sleep disruption, and risk of prostate cancer in elderly men. Eur Urol 2015;67(2):191–4.
[28] Vitale JA, Lombardi G, Weydahl A, et al. Biological rhythms, chronodisruption and chrono-enhancement: the role of physical activity as synchronizer in correcting steroids circadian rhythm in metabolic dysfunctions and cancer. Chronobiol Int 2018:1–13.
[29] Bruno E, Roveda E, Vitale J, et al. Effect of aerobic exercise intervention on markers of insulin resistance in breast cancer women. Eur J Cancer Care (Engl) 2018;27(2), e12617.
[30] Roveda E, Vitale JA, Bruno E, et al. Protective effect of aerobic physical activity on sleep behavior in breast cancer survivors. Integr Cancer Ther 2017;16(1):21–31.
[31] Innominato PF, Focan C, Gorlia T, et al. Circadian rhythm in rest and activity: a biological correlate of quality of life and a predictor of survival in patients with metastatic colorectal cancer. Cancer Res 2009;69(11):4700–7.
[32] Innominato PF, Giacchetti S, Bjarnason GA, et al. Prediction of overall survival through circadian rest-activity monitoring during chemotherapy for metastatic colorectal cancer. Int J Cancer 2012;131(11):2684–92.
[33] Levi F, Zidani R, Misset J-L. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. Lancet 1997;350(9079):681–6.
[34] Stoschitzky K, Sakotnik A, Lercher P, et al. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol 1999;55(2):111–5.