Breast Cancer Res Treat (2016) 158:43–50
DOI 10.1007/s10549-016-3864-2

PRECLINICAL STUDY

Aberrant nocturnal cortisol and disease progression in women with breast cancer

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Received: 7 June 2016 / Accepted: 9 June 2016 / Published online: 17 June 2016

Abstract While a relationship between disruption of circadian rhythms and the progression of cancer has been hypothesized in field and epidemiologic studies, it has never been unequivocally demonstrated. We determined the circadian rhythm of cortisol and sleep in women with advanced breast cancer (ABC) under the conditions necessary to allow for the precise measurement of these variables. Women with ABC ($n = 97$) and age-matched controls ($n = 24$) took part in a 24-h intensive physiological monitoring study involving polysomnographic sleep measures and high-density plasma sampling. Sleep was scored using both standard clinical metrics and power spectral analysis. Three-harmonic regression analysis and functional data analysis were used to assess the 24-h and sleep-associated patterns of plasma cortisol, respectively. The circadian pattern of plasma cortisol as described by its timing, timing relative to sleep, or amplitude was indistinguishable between women with ABC and age-matched controls ($p's > 0.11$, t-tests). There was, however, an aberrant spike of cortisol during the sleep of a subset of women, during which there was an eightfold increase in the amount of objectively measured wake time ($p < 0.004$, Wilcoxon Signed-Rank). This cortisol aberration was associated with cancer progression such that the larger the aberration, the shorter the disease-free interval (time from initial diagnosis to metastasis; $r = -0.30$, $p = 0.004$; linear regression). The same aberrant spike was present in a similar percent of women without ABC and associated with concomitant sleep disruption. A greater understanding of this sleep-related cortisol abnormality, possibly a vulnerability trait, is likely important in our understanding of individual variation in the progression of cancer.

Keywords Cortisol · Breast cancer · Survival · Sleep · Circadian

Background

Circadian rhythms are a fundamental aspect of nature, being found in all organisms from single cellular to humans. The human circadian pacemaker, located in the suprachiasmatic nucleus of the hypothalamus, coordinates diverse clocks found in tissues around the body to each other and to the outside world. Disruption of circadian rhythms can have a profound negative influence on many areas of human health and physiology, including the disruption of the normal function of endocrine, immune, neurologic, psychiatric, and cardiovascular systems [1]. It has been surmised, based on examination of the daily rhythm of salivary cortisol concentrations in ambulatory settings, that a disruption of circadian rhythms may underlie some of the observed interindividual variation in the progression of a variety of cancers [2–4]. This theory is reinforced by epidemiologic evidence that associates

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presumptive circadian disruption with an increased risk of development and progression of cancer, such as might occur in individuals working overnight shifts [5] or those with frequent long-distance plane travel [6]. Sufficient evidence has been accumulated to the point that the World Health Organization concluded that 'shift work that involves circadian disruption' is a probable human carcinogen [7, 8].

This evidence, however, is indirect and there have been no previous studies in humans that have examined the normalcy of circadian rhythms in those with cancer, especially in women with breast cancer, who have been studied most extensively in this context. One common manner in which circadian rhythms in humans can be accurately measured is through the observation of plasma cortisol, which rises prior to habitual wake time and falls throughout the day, reaching a nadir in the evening [9]. Under controlled conditions, this pattern of cortisol is very consistent [10] and has a strong genetic component [11]. The timing of the fitted peak of plasma cortisol, which is coincident with the end of the normal sleep period, is a good measure of the timing of the circadian clock (a 'hand of the clock') [12]. This cyclicity of cortisol is thought to have direct influence on sleep itself [13], while sleep has just a small feedback influence onto plasma cortisol concentrations [14]. Many studies have examined the relationship between sleep and cancer incidence and progression [15–17] and found an association between disrupted sleep and a more rapid rate of cancer progression and higher incidence of cancer. Given the hypothesized relationships among circadian rhythms, cortisol, sleep, and cancer mortality, it was the purpose of this study to determine if there are any abnormalities in the circadian variation of cortisol in women with advanced breast cancer, as compared to healthy controls, and to determine if these are related to disruption of sleep or to the progression of the cancer.

Methods

Recruitment

Women with advanced breast cancer ($n = 97$, ABC) and age-matched controls ($n = 24$) were recruited from the Army of Women website, the Stanford Cancer Center, and through distribution of local flyers. Women with ABC had either metastatic (75 %) or locally recurrent (25 %) breast cancer and no other active cancers within the past 10 years. All women were postmenopausal, nonsmoking, had Karnofsky Performance Status of 70 % or higher [18], and were in otherwise relatively stable health. Other exclusion criteria included bilateral lymph node removal, low hematocrit (<30), hospitalization for major psychiatric illness within the prior year, and current substance use disorder. Use of corticosteroids, glucocorticoids, benzodiazepines, or melatonin within the week preceding and during the in-laboratory study was prohibited. Participants were not allowed to have performed shift work within 3 months of the study and could not travel two or more time zones for 2 weeks preceding participation. Participants who did not live in the Pacific time zone and traveled to Stanford Hospital were kept in their home time zone during their study.

Approximately 2 weeks prior to study, participants completed a variety of questionnaires to assess mood, stress, and specific psychiatric disorders: Center for Epidemiologic Studies Depression Scale (CES-D [19]), Positive and Negative Affect Scale (PANAS [20]), Perceived Stress Scale (PSS [21]), Stanford Acute Stress Reaction Questionnaire (SASRQ [22]), State-Trait Anxiety Index (STAI [23]), Post Traumatic Stress Disorder Checklist – Civilian Version (PCL-C [24]), and the Difficulties in Emotion Regulation Scale (DERS [25]). Medical information was also collected from participants and their medical records. Disease-free interval (DFI) was defined as the time between initial cancer diagnosis to the next recurrence or metastasis. The primary source of this information was the participant's medical record. If that was not available, the participant's oncologist was contacted or the information was obtained from the participant herself.

Prelaboratory protocol

Prior to the in-laboratory protocol, ambulatory sleep/wake patterns were recorded for 2 weeks, using a combination of sleep logs and wrist-worn actigraphs (Actiwatch 2, Philips-Respironics, Bend OR). The actigraph movement data were used to determine gross patterns of sleep and wake [26], using commercially available software (Actiware 5, Respironics, Bend OR) in combination with the sleep logs. Habitual bed and wake times were calculated as the average of 14 recorded days excluding divergences greater than 60 min.

In-laboratory protocol

Participants stayed for 28 h in specialized rooms at either the Clinical and Translational Research Unit at Stanford Hospital or the Stanford Sleep Disorders Clinic. Participation started approximately seven hours after habitual wake time and was completed 10 h after habitual wake time the next day. An 8-h period of darkness was scheduled to be centered around the midpoint of habitual bed/wake

times. Lights were dim (<15 lux) during periods of scheduled wake and off (<0.05 lux) during periods of scheduled sleep. To avoid the metabolic consequences of large meals, participants were provided equicaloric hourly snacks, the sum total of which satisfied their nutritional requirements for the duration of the study [27]. Blood samples were collected at 20–60 min intervals via an indwelling venous catheter, kept patent with a 0.9 % sodium chloride/1000 U heparin drip, attached to an infusion pump with 1.5 m (during waking hours) or 3 m (during scheduled sleep) extension tubing to allow for uninterrupted blood collection from an adjacent room during sleep.

Cortisol assessment and analysis

At least 1 cc of the whole blood was collected via the catheter into a tube coated with ethylenediaminetetraacetic acid. Samples were immediately spun for 15 min at 1300 × g in a 4 °C centrifuge; 40 μL of the resultant plasma was decanted and stored at −80 °C until assay for cortisol concentrations using a commercially available solid phase enzyme-linked immunosorbent assay (Immuno-Biological Laboratories, Minneapolis MN). Due to problems with either the collection or assessment of some plasma samples, data from 84 women with ABC (57.8 ± 7.56 years) and all controls (58.3 ± 5.25 years) were included in analyses of diurnal variation, and 68 of the 84 women with ABC (57.6 ± 7.72 years) were included in analyses of cortisol and overnight sleep.

The 24-h rhythm of cortisol was fit with a three-harmonic regression analysis (OriginPro 8.0, Microcal, Northampton MA) to determine the time of the peak of the composite curve and first harmonic (marker of circadian phase), amplitude of the curve (one-half peak-to-trough), and midline estimating statistic of rhythm (MESOR, or the average value around which the curve oscillates). Phase angles (relative time between two points in a cycle) were calculated between habitual wake time and both the peak of the composite curve and the peak of the first harmonic (phase angle of entrainment). The 24-h rhythm and overnight data were also fit with a shape-naïve technique, functional principal component analysis (fPCA) [28] using R (v2.11.1, R Foundation for Statistical Computing, Vienna Austria) [29]. Briefly, a nine-Fourier-based function was fit to each string of cortisol data, either over the entire protocol or just the scheduled sleep time. Fourier equations were subjected to functional data analysis that reduced the complexity of the data by determining the equations that maximally explain the variance found across all equations. The eigenvalues of first four fPCA components were subjected to further analysis as noted below.

Sleep assessment

An hour before bedtime, electrodes were applied to the participant's face (above and below the left and right outer canthi to record the electro-oculogram, below the chin to record the electromyogram) and scalp (electroencephalogram, EEG, using a Quik-Cap, Neuroscan, Charlotte NC) [30]. These data were collected using a Siesta system (Compumedics, El Paso TX) and sleep staged (wake, N1, N2, N3, REM) according to standard criteria by a single expert polysomnographic technician [31]. Each 30 s of artifact-free EEG data (C3–A2) were fast Fourier transformed to obtain relative power in delta (0.75–4.5 Hz), theta (4.5–8.5 Hz), alpha (8.5–12.5 Hz), sigma (12.5–15.5 Hz), and beta (15.5–35.5 Hz) bands (PRANA, PhiTools, Strasbourg France).

Statistics

Summary data and correlation analyses were completed using Excel (v.11.8332.8333, Microsoft, Redmond WA) and nonparametric correlations and multivariate regression using OriginPro (v.8.0.63.988SR6, OriginLab, Northampton MA). Data are presented as mean ± SD.

Ethics, consent, and permissions

All procedures were approved by the Stanford University Institutional Review Board (IRB-7033) and conformed to the principles set forth in the Declaration of Helsinki. All participants signed an Informed Consent prior to initiation of any study procedures.

Results

Normal diurnal cortisol in women with ABC

We examined the diurnal variation in plasma cortisol in both women with advanced breast cancer ($n = 97$, ABC) and age-matched controls ($n = 24$) (Table 1) using a modified constant posture routine coupled with high-frequency blood sampling through an indwelling venous catheter. Various aspects of the diurnal cortisol rhythm were extrapolated from plasma cortisol concentrations using a three-harmonic regression analysis (Fig. 1, Table 2). There were, however, no differences between controls and women with ABC in the quantity (amplitude, mesor), absolute timing (clock time of the peak of the first harmonic and composite fits), or relative timing (phase angle—time between habitual wake time and the peaks of the first harmonic and composite fits) of cortisol (Fig. 1,

Table 1 Demographics of the participants with advanced breast cancer (ABC) and the controls

	ABC ($n = 97$)	Control ($n = 27$)	p value (test)
Age	57.6 ± 7.47 (45–75)	57.1 ± 5.14 years (51–71)	0.71 (t-test)
BMI	27.4 ± 5.60 (18.6–42.6)	25.7 ± 4.24 (19.2–37.3)	0.15 (t-test)
Ethnicity			
Not hispanic	93	25	0.32 (χ^2-test)
Hispanic	3	2	
Race			
White	84	25	0.59 (χ^2-test)
Black/African-American	7	1	
Asian	4	0	
Multiple	1	0	
Education			
Bachelor's or higher	55	15	0.92 (χ^2-test)
Did not complete college	42	12	
Income	$60,000–$79,999	$20,000–$39,999	0.76 (χ^2-test)
Marital status			
Married	56	6	0.04 (χ^2-test)
Divorced	24	14	
Single	9	4	
Widowed	4	1	
Separated	3	1	
Other	1	0	
Number of children	1.67 ± 1.36 (0–5)	1.56 ± 1.27 (0–5)	0.70 (t-test)
Live alone?	Yes, $n = 28$ (29 %)	Yes, $n = 13$ (48 %)	0.07 (χ^2-test)

Table 2). There were also no differences in variability between controls and women with ABC in any of these variables (p's > 0.09, F-tests). Using a shape-naïve approach to quantitate the diurnal pattern of plasma cortisol, we also found no difference between the patterns of diurnal cortisol in women with ABC and controls (eigenvalues comparisons of the first four fPCA components, p's > 0.11, t-tests). Therefore, using both predefined (three-harmonic regression) and naïve (fPCA) shape analyses, we could find no specific aspect of the diurnal rhythm of cortisol that could discriminate the group of women with ABC from controls.

Abnormal overnight cortisol in women with ABC

A disruption in the overnight pattern of plasma cortisol was evident in a subset of participants. This disruption was characterized by a large peak of cortisol occurring approximately midway through the scheduled sleep episode (Fig. 2). This disruption could be clearly quantified by the second component of fPCA (fPCA2) of the overnight cortisol data (Fig. 2) such that larger positive fPCA2 eigenvalues represented larger, abnormal early night peaks in cortisol.

Aberrant cortisol peak temporally coincident with acute sleep disruption

There was a clear evidence of sleep disruption occurring contemporaneous with the early night cortisol spike. Examination of the participants with the aberrant peak highest (top 10 % of fPCA2 values) revealed an increase in PSG-determined wake between the prespike levels (median = 3.75 %) and post-spike levels (median = 24.3 %) ($p = 0.004$, Wilcoxon Signed-Rank test). There were no differences in the amount of N1, N2, N3, REM, or all non-REM together (p's > 0.12, Friedman ANOVAs) that occurred before, during, or after the spike onset. These results indicate an increase in wake following the spike indicating reduction across all stages of sleep.

There was no consistency as to the state of sleep during which the spike began, as the cortisol spike was preceded by light NREM sleep (N1 or N2) in five participants, deep NREM sleep (N3) in three participants, and REM sleep in one participant. We also examined the power spectrum of the EEG occurring 20–40 min prior to the spike ("baseline") with that occurring 0–20 min prior to the spike ("proximal"). There were no significant differences in any of the major frequency bands (paired t-tests, p's > 0.10)

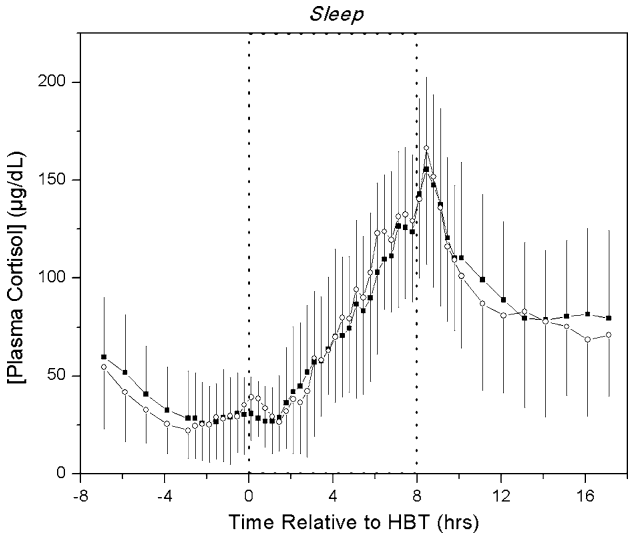

Fig. 1 Comparison of the diurnal profile of plasma cortisol in women with ABC (*shaded square*, $n = 84$) and control women (*circle*, $n = 24$). Data were aligned with habitual bedtime (HBT) and are plotted as average with SD. The approximate time of sleep is indicated with *vertical dotted lines*

between the baseline EEG and that occurring proximal to the early night cortisol spike. Thus, we could detect nothing grossly unusual in the sleep that immediately preceded the early night spike in cortisol.

Aberrant cortisol peak not related to psychological traits

This disruption of nocturnal cortisol was not related to various psychological traits, including measures of depression (CES-D score), affect (PANAS total scores for positive and negative affect), anxiety (STAI trait anxiety score), emotional regulation (DERS), and various measures related to stress (PSS, SASRQ, PCL-C scores) (|*r*|-values < 0.14, p's > 0.18; linear correlations with fPCA2).

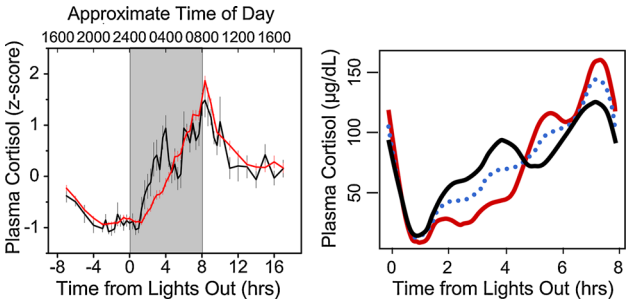

Fig. 2 Average ± SD 24-h (*left*) and overnight (*right*) curves of plasma cortisol of participants with high (*black*, $n = 10$) and low (*red*, $n = 58$) eigenvalues of fPCA2. Data were z-score transformed prior to plotting. Data were aligned based on the midpoint of habitual bed/wake times—the top x-axis shows the approximate time of day for a 'participant' whose mid-sleep point was 04:00. In the right panel, the fPCA2 curves for high (*black*) and low (*red*) eigenvalues of fPCA2 are plotted, along with the average curve (*dotted blue*), over the course of the 8 h of scheduled sleep in darkness. Those with an abnormal nocturnal cortisol peak are represented by high fPCA2 values (note the increase 3–4 h after lights out)

Aberrant cortisol peak related to ER status and site of metastases

To examine whether any aspect of the disease or its treatment might be associated with the occurrence of the early night cortisol peak, we ran a series of Spearman correlations between fPCA2 and the following variables: chemotherapy, hormonal therapy, or monoclonal antibody use within 2 months of cortisol collection; metastases to bone or organ; whether cancer was metastatic or locally recurrent; stage of initial diagnosis; estrogen receptor (ER)-positivity, progesterone receptor (PR)-positivity, human epidermal growth factor receptor 2 (HER2)-positivity, and negativity on these three markers (triple negative); use of antidepressants, steroids, benzodiazepines, medications affecting pain, or medications affecting sleep. Metastases to bone or organs rather than local recurrence ($r = -0.37$,

Table 2 Plasma cortisol measures

	ABC	Control	*p* value
Peak (composite)	07:50 ± 1 h 45 min	07:23 ± 1 h 28 min	0.27
Peak (1st harmonic–circadian phase)	08:59 ± 1 h 27 min	08:38 ± 1 h 20 min	0.32
ψ Habitual Wake Time (HWT) → peak composite	−0.49 ± 1.41 h	0.03 ± 1.28 h	0.11
ψ Habitual Wake Time (HWT) → peak 1st harmonic (relative circadian phase)	−1.64 ± 1.13 h	−1.22 ± 0.99 h	0.11
Amplitude	61.7 ± 18.5 µg/dL	61.3 ± 16.1 µg/dL	0.92
Mesor	69.8 ± 18.0 µg/dL	68.4 ± 20.6 µg/dL	0.74
Adjusted r^2	0.75 ± 11	0.74 ± 0.09	0.64

A comparison of metrics derived from three-harmonic regression analysis of plasma cortisol in women with advanced breast cancer (ABC) and controls is shown. Comparisons were made with two-tailed, unpaired *t*-tests. Phase angle (ψ) represents the time between two events, habitual wake time (HWT) and the peak of either the composite fit or the fit of the first harmonic, with negative values indicating the peak occurred after HWT. The adjusted r^2 is a measure of the goodness of fit of the regression analyses

$p = 0.002$), use of steroids ($r = 0.26$, $p = 0.03$), ER-negative status ($r = -0.25$, $p = 0.04$), and higher stage of initial diagnosis ($r = 0.31$, $p = 0.009$) were all related to higher fPCA2 values (early night cortisol peak), as described by univariate analysis. These four factors were entered into a multiple regression model predicting fPCA2 ($F_{4,64} = 4.99$, $p = 0.001$, adj. $r^2 = 0.19$) with metastases to bones or organs ($t = -2.36$, $p = 0.02$) and ER status ($t = -2.01$, $p = 0.048$) were contributing to the prediction of fPCA2, while the use of steroids ($t = 1.80$, $p = 0.08$) and the initial stage of diagnosis ($t = 1.29$, $p = 0.20$) were no longer contributing to the variance associated with fPCA2. Thus, the magnitude of the early night spike in cortisol in women with ABC was associated with distant metastases and ER negativity.

Aberrant peak associated with DFI

Given the association of cortisol disruption with survival in women with ABC [2–4, 32, 33], we examined a proxy measure of cancer progression, disease-free interval (DFI, i.e., the time from initial diagnosis of breast cancer to recurrence). The shorter the DFI, the more rapid the progression of metastatic disease and the shorter the overall survival [34]. We found no association between DFI and parametric measures of the diurnal rhythm of cortisol ($|r|$-values < 0.18, p's > 0.10, linear regressions). There was, however, a linear relationship between DFI and the aberrant peak in the overnight cortisol data (fPCA2, $r = -0.30$, $p = 0.004$), such that the greater the fPCA2 component (i.e., the larger the early night peak in cortisol, Fig. 2), the shorter the DFI (Fig. 3). There were no identifiable relationships between DFI and the other components of the overnight cortisol (fPCA1, $r = -0.01$, $p = 0.95$; fPCA3, $r = 0.14$, $p = 0.57$; fPCA4, $r = -0.01$, $p = 0.67$). As fPCA2 was related to both ER status and whether the cancer had metastasized, we added these to a multiple regression model of fPCA2 and its prediction of DFI. While the overall model remained significant ($F_{3,65} = 3.78$, $p = 0.01$, adj. $r^2 = 0.12$), neither ER status ($t = 1.74$, $p = 0.09$) nor metastases ($t = 0.51$, $p = 0.61$) contributed to the model, while fPCA2 remained a predictor of the variance associated with DFI ($t = -2.12$, $p = 0.04$). Thus, the magnitude of early night spike in cortisol in women with ABC was associated with DFI independent of other risk factors associated with DFI.

Subset of healthy women without ABC also have aberrant cortisol peak

A subset of women without ABC also exhibited early night cortisol spikes. Using fPCA, we examined the overnight cortisol data in both women with and without ABC, as a single analytic cohort. Again, fPCA2 represented the magnitude of the early night spike in cortisol. There was no difference in fPCA2 values between control women and those with ABC ($p = 0.24$, t test). To examine whether there was the same association between the early night spike and sleep, we examined the sleep in the control women with the highest fPCA2 scores (18 %, $n = 4$). In these relatively few control women with early night spikes, there was evidence of sleep disruption following the spike, with a 12.9 % median increase in wake during the 20 min of the initial rise in cortisol and a 26.4 % median increase in wake during the subsequent 70 min of elevated cortisol. Given the small number of women in this category, however, reliable statistical comparison was not possible but the changes were consistent with that which was observed in the women with ABC.

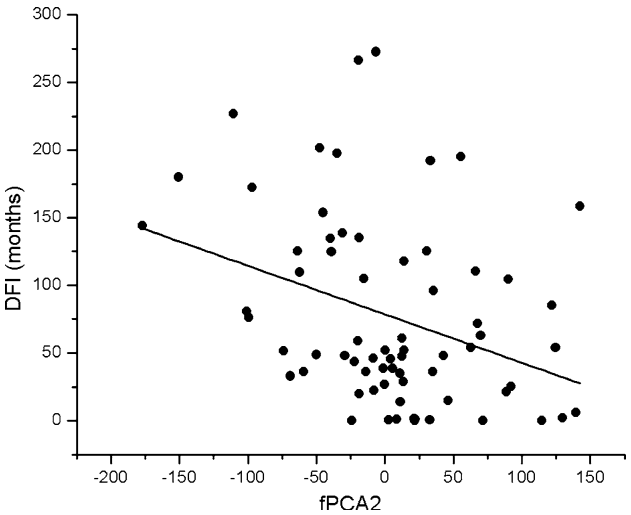

Fig. 3 Correlation of fPCA2 and DFI. Eigenvalues of fPCA2 from analysis of overnight cortisol patterns of women with ABC ($n = 68$, *shaded circle*) are well correlated with disease-free interval (DFI) (adj. $r = -0.30$, $p = 0.004$; linear regression, *solid line*) such that the higher the fPCA2 (i.e., the more apparent an early night peak is in the overnight cortisol), the shorter the DFI

Discussion

The occurrence of an atypical, early night spike in cortisol was associated with a shorter DFI and concomitant disruption of sleep in women with ABC. As early night cortisol peaks occurred in a similar percentage of women without ABC, these peaks likely represent a trait vulnerability that, under pathological conditions such as breast cancer, predispose individuals to worse health outcomes. To our knowledge, these early night peaks have not been previously reported in either healthy women or those with cancer or other pathologies. This is not altogether unsurprising given the difficulty in obtaining high-frequency, overnight plasma cortisol data, and the infrequency with

which middle-aged women are studied in such a setting. Further research is necessary to determine if these early night peaks are specific to postmenopausal women, perhaps caused by changes that occur during menopause (e.g., hot flashes), or are more generalizable to the entire population.

The aberrant early night cortisol peak was not associated with a variety of factors that might theoretically influence cortisol, including depressive symptoms, positive and negative affect, anxiety, emotion regulation, and stress. The early night peak was weakly associated with distant metastases and ER negativity of the tumor. While it is possible that the early night cortisol peak might predispose to ER-negative tumors or metastases, a prospective study of precancerous women would be necessary to properly address this. Conversely, while the presence of ER-negative tumors could induce changes in cortisol rhythms, we found a similar proportion of women with aberrant peaks in our small control sample. It is also important to note that the magnitude of the early night cortisol peak was *still* associated with DFI even after accounting for the influence of ER negativity and metastases.

The early night cortisol peak was temporally linked to sleep disruption such that contemporaneous with this cortisol peak, there was a significant increase in the amount of objectively determined wake. While cortisol-mediated disruption of sleep may lead to shortened DFI [15], there are many other possible connections between the early night cortisol peak and shortened DFI, including mediation through sympathetic activation [35] or direct action of cortisol [36–38]. As our blood sampling occurred in 20-min intervals, we could not determine whether the increase in cortisol caused the awakening or if the awakening caused the increase in cortisol.

Contrary to our a priori hypothesis, none of our measures of the circadian rhythmicity of plasma cortisol exhibited any differences between the women with and without ABC. While the control sample was relatively small, the evidence from this study is inconsistent with the idea that a global disruption of circadian rhythmicity occurs in women with ABC. We and others have previously reported that there is a disruption of the normal diurnal slope of salivary concentrations of cortisol that is associated with survival in a variety of cancers [2, 3, 32]. This flattening of diurnal salivary cortisol, however, does not seem to represent a disruption of circadian rhythms [39]. Caution should be observed in imputing the normalcy of circadian rhythms from the diurnal slope of salivary cortisol.

Conclusions

If indeed this unusual cortisol peak represents an alterable vulnerability to more aggressive forms of breast cancer, it will be important to better understand the role that this aberrant peak has in relation to the development and, perhaps, survival with ABC. Future work will be necessary to determine the physiologic role that this aberrant peak plays in the pathogenesis and progression of breast cancer and whether it represents a general risk factor for other pathologies in women.

Acknowledgments This work was supported by the National Cancer Institute (R01CA118567) and the National Center for Research Resources (UL1RR025744) at the National Institutes of Health. We thank our research participants for their time, wisdom, and willingness to participate, and the Dr. Susan Love Research Foundation's Love/Avon Army of Women Program for their assistance in recruitment. We also wish to thank the nursing staff of the Clinical Translational Research Unit for staffing the studies, Ms. Chung-Ping Liao and Mr. Ryan Fisicaro for conducting the cortisol assays, and Mr. Daniel East for scoring the sleep data. We wish to thank Dr. Youngmee Kim for suggesting valuable edits to the manuscript.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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