JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

# Vagal Regulation, Cortisol, and Sleep Disruption in Women with Metastatic Breast Cancer

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**Study Objectives:** To determine the relationship between hypothalamic pituitary axis (HPA) dysregulation, vagal functioning, and sleep problems in women with metastatic breast cancer.

**Design:** Sleep was assessed by means of questionnaires and wrist actigraphy for 3 consecutive nights. The ambulatory, diurnal variation in salivary cortisol levels was measured at 5 time points over 2 days. Vagal regulation was assessed via respiratory sinus arrhythmia ($RSA_{TF}$) during the Trier Social Stress Task.

**Participants:** Ninety-nine women (54.6 ± 9.62 years) with metastatic breast cancer.

**Results:** Longer nocturnal wake episodes (r = 0.21, p = 0.04, *N* = 91) were associated with a flatter diurnal cortisol slope. Sleep disruption was also associated with diminished $RSA_{TF}$. Higher RSA baseline scores were significantly correlated with higher sleep efficiency (r = 0.39, p = 0.001, N = 68) and correspondingly lower levels of interrupted sleep (waking after sleep onset, WASO; r = −0.38, p = 0.002, N = 68), lower average length of nocturnal wake episodes (r = −0.43, p < 0.001, N = 68), and a lower self-reported number of hours of sleep during a typical night (r = −0.27, p = 0.02, N = 72). Higher RSA AUC was significantly related to higher sleep efficiency (r = 0.45, p < 0.001, N = 64), and a correspondingly lower number of wake episodes (r = −0.27, p = 0.04, N = 64), lower WASO (r = −0.40, p = 0.001, N = 64), and with lower average length of nocturnal wake episodes (r = −0.41, p = 0.001, N = 64). While demographics, disease severity, and psychological variables all explained some portion of the development of sleep disruption, 4 of the 6 sleep parameters examined (sleep efficiency, WASO, mean number of waking episodes, average length of waking episode) were best explained by RSA.

**Conclusions:** These data provide preliminary evidence for an association between disrupted nocturnal sleep and reduced RSA the subsequent day, confirming an association between disrupted nocturnal sleep and flattened diurnal cortisol rhythm in women with metastatic breast cancer. They suggest that the stress-buffering effects of sleep may be associated with improved parasympathetic tone and normalized cortisol patterns during the day.

**Keywords:** Sleep disruption, RSA, breast cancer, cortisol

**Citation:** Palesh O; Zeitzer JM; Conrad A; Giese-Davis J; Mustian KM; Popek V; Nga K; Spiegel D. Vagal regulation, cortisol, and sleep disruption in women with metastatic breast cancer. *J Clin Sleep Med 2008*;4(5):441-449.

Sleep disruption is 2 to 3 times more common in cancer patients than in the general population.[1,2] In our previous studies of 97 women with metastatic breast cancer,[3,4] nearly two-thirds (63%) reported symptoms of disrupted nocturnal sleep. Other studies have found a similar prevalence of disrupted sleep and insomnia in cancer patients[5-11] and among breast cancer patients in particular.[5,6]

Disrupted sleep and insomnia in particular are associated with several negative physical and psychiatric consequences in the general population, including fatigue, psychiatric illness (major depression in particular), physical complaints, substance abuse, reduced quality of life, and cognitive imparment.[12-19,20] Some data also suggest that sleep loss and/or chronic insomnia may negatively influence cardiac function,[21,22] immune function,[23] and glucose regulation,[24-26] thereby increasing early mortality.[27-29] Little is known about insomnia and its consequences in cancer patients, but it would be reasonable to expect that the consequences of insomnia in this population would be similar to or worse than those in the general population. In cancer patients, sleep disturbance may exacerbate concurrent cancer and/or treatment-related symptoms such as fatigue, mood disturbance, and gastrointestinal distress and may lead to reduced quality of life (QOL) and to the development of psychiatric illness and reduced overall health.[3,30-33]

The pathophysiology of sleep disruption is not well understood,[34] and the precise physiological pathway for the development of sleep disruption and its relationship with cancer are largely unknown. In the non-cancer population, evidence shows that people with insomnia have an elevated response to stress in general,[35,36] and psychiatric disorders linked to sleep disruption and/or hyperarousal, such as major depression, post-traumatic stress disorder, and generalized anxiety disorder, are

**Submitted for publication October, 2007**
**Accepted for publication June, 2008**
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all known to be associated with hypothalamic-pituitary-adrenal axis (HPA) dysregulation.[20,37] Past research has linked insomnia to activation of the stress-response system (notably the HPA axis with its activation measured by an increased production of cortisol[38]), but whether HPA activation causes insomnia or whether insomnia produces HPA activation is unknown.[39]

Besides HPA dysregulation, sleep disruption has been linked to other physiologic markers including changes in metabolism, muscle tone, and heart rate. Changes in heart rate, specifically respiratory sinus arrhythmia (RSA), can be used as a proxy measurement of general parasympathetic tone.[40] Respiratory sinus arrhythmia (RSA) is an indicator of the delicate balance between the normal slowing of heart rate during expiration and the speeding up of heart rate during inspiration. Heart rate and consequently RSA is signaled by centers in the medulla oblongata, specifically the nucleus ambiguus, which directly affects the parasympathetic responses of the nervous system on the heart through the vagus nerve. The vagus nerve slows heart rate during expiration by decreasing the rate of sinoatrial node firing and activating the nucleus ambiguus; however, during inspiration the nucleus accumbens is inhibited and the vagus nerve is not stimulated, allowing heart rate to rise. Given this, RSA is an important marker of parasympathetic tone, and impaired or dysregulated RSA has been implicated in stress-related disorders.

RSA is a measurement of the covariation of heart rate with respiration. Heart rate increases during inspiration, when intrathoracic pressure and blood flow to the heart decrease, and decreases during expiration, when pressure and blood flow increase. Diminished RSA has been associated with both worse medical (i.e., cardiac)[41] and psychiatric (i.e., depression)[42] health. Some preliminary studies suggest that RSA is at least associated and might even be predictive of insomnia in healthy subjects. Irwin and colleagues[43] found that RSA correlates with electroencephalographic delta sleep and morning reports of sleep quality, sleepiness, and fatigue in subjects with alcohol dependence. This association between RSA and sleep disruption is illustrated by the findings of El-Sheikh and Buckhalt,[44] who reported that children with less vagal regulation during a reaction-time task had poorer self-reported and actigraphy-measured sleep.

Evidence suggests that lower RSA and higher cortisol levels are associated with sleep disruption. Examination of endocrine and autonomic activity in cancer patients with insomnia has the potential to shed light not only on cancer-specific insomnia but also on the additive or multiplicative interaction of cancer physiology and insomnia. Thus, measurement of cortisol levels, along with assessment of vagal tone, might help explain the causes of existing sleep disturbances in women with metastatic breast cancer and suggest possible targets for therapeutic intervention.

## METHODS

### Participants

The inclusion criteria for the study required the presence of metastatic breast cancer or recurrent breast cancer, age $\geq$ 45 years, score < 70% on the Karnofsky rating, residency in the Greater San Francisco Bay area, and a proficiency in English.

A total of 111 participants were eligible and consented to participate in the study out of a pool of 221 women screened. Women were recruited through oncologists at Stanford University Medical Center and in the Bay Area by means of newspaper advertisements and word-of-mouth from subjects and patients. Twenty-five women were not eligible. Eighty-three women were eligible but declined participation; another 2 died before the study began. Of the remaining 111 participants, 5 were too busy to participate, one declined participation, one felt too ill, one had an accident, and 4 were excluded after reporting steroid medications in their baseline medication logs, leaving 99 participants who completed demographic and self-report measures. Out of these patients, 2 provided inadequate biological or saliva samples. Seven participants did not complete actigraphy data, and 31 participants did not participate in the Trier Social Stress Test (TSST) testing or did not provide analyzable data for calculation of the RSA.

Participants were excluded from the study if they had active cancers within the past 10 years other than breast cancer, basal cell or squamous cell carcinomas of the skin, or in situ cancer of the cervix. They were also excluded if they had positive supraclavicular lymph nodes as the only metastatic lesion at the time of initial diagnosis. We also excluded patients who had a concurrent medical condition likely to influence short term survival, or who used a corticosteroid within the preceding month Those with a history of major psychiatric disorder for which patient was hospitalized or medicated were also excluded, although patients with mild depression or anxiety not requiring hospitalization or pharmacotherapy were allowed to enter the study.

### Demographic Data

Demographic information and medical history obtained from a brief self-report measure are provided in Table 1. Thirty-nine patients (39.4%) took antidepressant medications in this study. The breakdown of types of antidepressant usage is reported by Spiegel et al.[45] and is as follows: 18.2% on SSRIs, 11.1% on SNRIs, 2.0% on tricyclic antidepressants, 1.0% on bupropion, 1.0% on an SNRI/tricyclic combination, 2.0% on an SNRI and bupropion, 1.0% on an SSRI and tricyclic, 2.0% on an SSRI/bupropion combination, and 1.0% on hypericum. Nineteen patients (19.2%) took medication specifically prescribed for treating disrupted sleep during study baseline, and 14 patients were taking medication for sleep during test measurements. Of 19 patients taking medications at baseline, 6 patients were taking benzodiazepines, 6 were taking over-the-counter sleep aids or supplements, 5 were taking hypnotic sleep medications, and the remainder of patients were using antidepressant and prescription antihistamine medications for sleep.

### Procedures

Women in the study collected saliva for cortisol measurement for 2 days, completed questionnaires, wore actigraphs[46] to monitor their sleep-wake cycles for 3 days, and participated in the TSST approximately 1-2 weeks after the cortisol baseline collections. The TSST, a standardized social and cognitive stress test, consisted of telling the participants that they would have 5 min to prepare a speech for a job interview and another 5 min to do mental math.[47] Baseline measurements of resting

**Table 1**—Descriptive Statistics for Demographic and Medical Variables in Metastatic Breast Cancer Participants (N = 99)

| Demographic Variable | Statistics |
|---|---|
| Age, mean ± SD (range) | 54.65 ± 9.62 (36-80) |
| Education, No. (%) | |
| Trade or High School | 3 (3%) |
| Some College | 33 (33.3%) |
| Bachelor's Degree | 20 (20.2%) |
| Some Graduate School | 9 (9.1%) |
| Advanced Degree | 34 (34.3%) |
| Race, No. (%) | |
| Asian | 10 (10.1%) |
| Black | 2 (2.0%) |
| American Indian | 2 (2.0%) |
| White | 84 (84.8%) |
| Other/Unknown | 1 (1.0%) |
| Ethnicity, No (%) | |
| Hispanic | 8 (8.1%) |
| Marital Status, No (%) | |
| Married | 67 (67.7%) |
| Never married | 7 (7.1%) |
| Divorced/Separated | 19 (19.2%) |
| Widowed | 6 (6.1%) |
| Household Income, No (%), $ | |
| < 20,000 | 5 (5.1%) |
| 20,000-39,999 | 18 (18.2%) |
| 40,000-59,999 | 11 (11.1%) |
| 60,000-79,999 | 16 (16.2%) |
| 80,000-99,999 | 12 (12.1%) |
| ≥ 100,000 | 27 (27.3%) |
| Don't know/not reported | 10 (10.1%) |

RSA were taken prior to beginning of the stress task (See Giese-Davis[63] for details of our TSST procedures).

The initial autonomic data assessment at the baseline point started at a median time of 6.3 min (from instructions) to a median stop time of 15.5 min (from instructions). The median length of the TSSTs from instructions to 60 min post-assessment was 107 minutes. But RSA during the task (area under the curve or AUC) was only recorded from baseline to 10-min post-assessment. Thus the length of time that the RSA was recorded is 107-6.3-50 = 50.7 minutes.

## Measures

### Demographic and Medical Variables

Women completed a brief, self-report measure assessing demographic characteristics, including age, marital status, family size, living circumstances, ethnicity, education, employment, and family income. They also answered questions about history of diagnosis of cancer. Disease and treatment information was extracted from medical records.

### Perceived Stress Scale (PSS)

PSS[48] is a measure evaluating perception of stress in the past month. For this project we implemented a version that included 10 items, e.g., "In the last month how often have you…felt difficulties were piling up so high that you could not overcome them?" The measure utilizes a 5-point Likert-type scale: 0 = "Never" to 4 = "Very Often." A total score is computed by summing ten items.

### Beck Depression Inventory (BDI)

The BDI[49] is well-known and widely used measure of depression. BDI-II consists of 21 questions and a response scale ranging from 0 to 3. The BDI has established validity and reliability across multiple studies.

### The Pain-Rating Scale

The Pain-rating scale[50,51] is a 9-item measure used in our earlier studies of metastatic breast cancer patients. For the purposes of this study we used a question that inquired about ratings of current pain and suffering.

### The Structured Clinical Interview for DSM-IV (SCID)

SCID[52] is designed to establish a reliable and valid DSM-IV Axis I diagnosis. The SCID was used to assess whether patients met clinical criteria for a depression diagnosis. For the purposes of this study we created a variable that included those women who were diagnosed via SCID as having depression and those who were also taking antidepressant medications.

### Cortisol

For 2 consecutive days, saliva was collected at waking, 30 min after waking, and at 12:00, 17:00, and 21:00 hours. Patients were given wrist timers to remind them to collect saliva at the required times, and saliva swabs (Sarstedt, Inc., Newton, NC) were collected in electronic bottles (provided by AARDEX Ltd Zug, Switzerland) that marked the times when the bottles were opened. Saliva samples were refrigerated after collection and stored at −70°C within 2 days of collection. Samples were assayed using a luminescence immunoassay (Immuno-Biological Laboratories Inc, Hamburg, Germany). Assay sensitivity was 0.015 μg/dL, and intra-assay variations on low, medium, and high controls were 2.78%, 10.45%, and 4.79% respectively. Inter-assay coefficients of variation for low, medium, and high controls were 10.9%, 10.5%, and 5.5%. Participants were instructed not to eat, drink, smoke, brush their teeth, or use mouthwash 30 min before the saliva collection and to postpone collection if they had mouth wounds. Alcohol consumption was discouraged on the days when saliva samples were collected.

### Collection and Computation of $RSA_{TF}$

Placement of electrodes and sensors, data recording, and data reduction followed conventions and published guidelines.[53] Briefly, cardiopulmonary channels were sampled at 400 Hz using a standard lead II ECG and thoracic and abdominal bellows (Lafayette Instrument, Lafayette, IN) connected to pneumographic transducers (James Long Company, Inc, Caroga Lake, NY). Data were analyzed with MATLAB (Mathworks, Inc., Natick, MA). High frequency (RSA fluctuation, lnHF), low frequency (lnLF), and very low frequency (lnVLF) power of heart

period variability was computed as the natural logarithm of the summed power spectral density of RR interval between 0.15-0.5 Hz, 0.07-0.15 Hz, and 0.0033-0.07 Hz respectively. A respiration-controlled transfer function, adjusting the lnHF estimate of RSA for respiratory rate and depth alteration confounds ($RSA_{TF}$), was quantified by fast Fourier transform (FFT) and the averaged periodogram method relating RR interval to lung volume oscillations at the peak respiratory frequency.[54] RR interval and tidal volume time series were resampled at 4 Hz and partitioned into 60-s segments, overlapping by 30 sec. Each segment was then linearly detrended and Hanning windowed to remove any transition effects. Zero padding enlarged the segments to 64 sec. FFT was applied to each segment for frequency decomposition. The resulting power spectral density functions for RR intervals and tidal volume were adjusted to account for attenuation produced by the Hanning window. For each segment, the cross-spectral density was calculated by multiplying the square roots of the power spectral densities of both variables at each sample point. The average of the cross-spectral densities was computed for each segment. The ratio of the averaged cross-spectral density and the power spectral density of the tidal volume signal represents the transfer function magnitude. The measure of TF-RSA magnitude was the value of this function at the peak respiratory frequency, which was automatically detected as the greatest local maximum in the 0.13-0.5 Hz tidal volume power spectral density function. Spectral coherence for $RSA_{TF}$ was required to be at least 0.5 for the TF-RSA estimate to be valid. The physiological data were reviewed by a senior psychophysiologist blind to patient information. Improbable or inconsistent values prompted reanalysis.

In the current study, baseline RSA provides a snapshot of the parasympathetic tone among women with metastatic breast cancer—a chronic stress condition, whereas the RSA in response to the TSST provides a direct assessment of acute stress reactivity--the ability of these women to mount appropriate PNS responses to acute stressors while simultaneously having a chronic stress-inducing illness. The inclusion of both measures is common in studies.

### Actigraphy Measures of Sleep Disruption

A wrist actigraph (Micro Mini-Motionlogger, Ambulatory Monitoring, Systems, Ardsley, NY) was worn during baseline cortisol collection. An actigraph is capable of detecting arm movement through the use of an accelerometer and represents a useful proxy for detecting sleep and wake cycles.[55] Data were stored as 60-s epochs. Data were analyzed using Action 4 (v1.13) and ACT Millenium (beta v3.8.8.9) software (Ambulatory Monitoring, NY). Measures derived from this analysis included duration of time in bed (TIB), latency to sleep onset (SL) from entry into bed, sleep efficiency (SE) calculated as the ratio of time asleep to TIB, number and average length of nocturnal wake episodes (WE), and total duration of wake after sleep onset (WASO).

### Self-Report Measures of Sleep

On the day of their TSST test, patients were asked to complete a brief questionnaire that asked them to report their average number of hours of sleep per night.

### Data Analyses

Cortisol data were log transformed to stabilize variance. Baseline cortisol slope was calculated by regressing cortisol values on time from waking on all points for the 2 days. The waking cortisol was the average of waking levels for 2 days, and the waking rise was the 2-day average of the difference between the cortisol levels at waking and 30 min post-waking. Steeper diurnal cortisol slopes represent cortisol levels that are declining throughout the day as they normally do. Steeper slopes are represented by lower or more negative slope values. Flatter slopes represent cortisol values that are more abnormal, and include cortisol levels that decline slowly, have abnormal peaks in the afternoon or evening, or levels that actually increase throughout the day. These fluctuations are represented by less negative or even positive slope values.[56] We report means and standard deviations for actigraphy data. Instead of means and standard deviations for cortisol data, we report cortisol scores at the median (50th percentile) and the interquartile ranges (25th and 75th percentiles) because of non-normal distribution and outliers.

Area under the curve (AUC) is a summary measure that is routinely used in research when there are multiple repeated measurements over time. Since we assessed RSA multiple times during the TSST, we decided to use AUC to preserve power and avoid increasing Type I error associated with multiple testing. In our study, a graph of the AUC consists of the area under the RSA values measured over time. To calculate the AUC we used the formula proposed by Pruessner et al.[57] We calculated the AUC from 6 summary time points (baseline, anticipation, speech, math, 5-min post-assessment, 10-min post-assessment). There were 3 other time points (paced breathing at 9.0, 11.0 and 15.0 cpm) that were excluded from the AUC calculation. The initial autonomic data assessment at the baseline point started a median time of 6.3 min (from instructions) to a median stop time of 15.5 min (from instructions).The median length of the TSSTs from instructions to 60 min post-assessment was 107 minutes. But RSA was only recorded from baseline to 10-min post- assessment.

RSA outliers >2 SD from the group mean that appeared improbable for that individual or measure were eliminated. Less than 1% of data were excluded. RSA data are presented as medians (50th percentile) and interquartile ranges (25th and 75th percentiles). Spearman rank correlations were used to evaluate the associations among sleep variables, cortisol levels, and RSA.

Several of our sleep variables were not normally distributed. Specifically, sleep latency, WASO, and average wake episode were positively skewed while sleep efficiency was negatively skewed. We attempted to log-transform our variables, both latency and average wake episodes became more normally distributed while WASO and sleep efficiency remained skewed. We attempted to transform sleep efficiency and WASO using other types of transformations but were unsuccessful. As a result of that we dichotomized those two variables using median split and conducted logistic regressions. Multiple linear regressions were conducted with the other 4 sleep variables.

Four linear and 2 logistic regression models were conducted using sleep variables as dependent variables and demographic,

**Table 2**—Descriptive Statistics for Medical Variables in Metastatic Breast Cancer Participants

| Variable | N | Percentile | | |
|---|---|---|---|---|
| | | 25th | Median (50th) or % | 75th |
| Log cortisol slope (2-day mean) | 96 | −0.21 | −0.16 | −0.11 |
| Waking cortisol (2-day mean) | 97 | 0.42 | 0.53 | 0.71 |
| 30 min waking rise in cortisol (2-day mean) | 97 | −0.04 | 0.21 | 0.47 |
| RSA baseline | 72 | 0.03 | 0.05 | 0.08 |
| RSA AUC | 68 | 0.13 | 0.22 | 0.35 |
| Disease free interval, months | 93 | 13.5 | 37.0 | 85.0 |
| Estrogen receptor negative, No. (%) | 27 | | 29.3% | |
| Dominant site of metastasis at study entry, No. (%) | 93 | | | |
| Bone | | | 21 (22.6%) | |
| Chest | | | 33 (35.5%) | |
| Viscera | | | 39 (41.9%) | |
| Chemotherapy, No. (%) | 93 | | 80 (86%) | |
| Radiation, No. (%) | 92 | | 75 (81.5%) | |
| Hormonal therapy, No. (%) | 93 | | 61 (65.6%) | |

disease severity, psychological and physiological variables as independent variables. Since we had an unacceptable ratio of variables to participants we reduced our independent variables. We entered the resulting variables in blocks of 3: demographics, disease severity and physiological and psychological variables. The first block included age, the second block included treatment (radiation, chemotherapy or hormone) and dominant site of metastasis, and the third block included perceived measures of perceived stress, depression, sleep medication, pain baseline cortisol log and RSA AUC. We used the backward method to find the solution with the best predictors.

## RESULTS

Estimates from 2 nights of actigraphy indicate that participants spent 478.5 ± 77.15 minutes (7.98 hours ± 1.29 hours), median = 492 minutes (8.2 hours) (range, 228.7-636.0) in bed, taking an average of 11.50 ± 10.24 minutes to fall asleep, median = 8.67 minutes (range, 0-51.67), and had a wakefulness after sleep onset (WASO) of 71.44 ± 50.34 minutes, median = 55.67 (range, 5.67-225.3), giving a sleep efficiency of 84.5 ± 10.6%, median = 88 (range, 55.3-98.9). Participants had 15 ± 6.6 wake episodes each night, median = 14.5 (range, 2.7-31), each with a duration of 4.81 ± 2.62 minutes, median = 4.16 (range, 1.48-16.6). Self-report indicated a habitual 7.6 ± 1.33 hours of sleep per night, median = 8 (range, 4-12).

As seen in Table 3, there were several associations between self-reported number of hours of typical sleep and the actigraphic measure of total number of hours in bed (TIB) during the 2 recording nights. In addition, the self-reported typical sleep length correlated significantly and positively with the number of wake episodes and wake after sleep onset (WASO).

### Sleep Disruption, Demographics, Disease Severity and Psychological Variables

The correlations are presented in Table 4. TIB correlated negatively with age ($r = -0.24$, $p = 0.02$), chemotherapy ($r = -0.29$, $p = 0.006$), pain intensity ($r = -0.23$, $p = 0.03$) and depression measured by SCID ($r = 0.21$, $p = 0.05$). Mean sleep latency was associated with radiation ($r = 0.21$, $p = 0.05$), perceived stress scale ($r = -0.22$, $p = 0.04$). Mean sleep efficiency was positively associated with dominant site of metastases being chest only vs. bone or viscera ($r = 0.27$, $p = 0.01$). WASO was negatively related to metastases site being chest only ($r = -0.31$, $p = 0.003$) and positively to hormone therapy ($r = 0.24$, $p = 0.03$). Mean number of wake episodes was negatively associated with age ($r = -0.23$, $p = 0.03$), metastases site being chest only ($r = -0.23$, $p = 0.03$) and positively with medication for sleep ($r = 0.26$, $p = 0.012$) and receiving hormone therapy ($r = 0.23$, $p = 0.03$). Average wake episode period was only related to dominant site of metastasis and was negatively associated with it ($r = -0.28$, $p = 0.006$).

### Cortisol Descriptives and Sleep Disruption

Cortisol was measured in micrograms per deciliter (μg/dL). On Day 1, wake cortisol was 0.58 ± 0.30; wake+30 min cortisol was 0.83 ± 0.43; noon cortisol was 0.37 ± 0.78; 5 pm cortisol was 0.17 ± 0.20; and 9 pm cortisol was 0.16 ± 0.40. On Day 2, wake cortisol was 0.56 ± 0.33; wake+30 min cortisol was 0.79 ± 0.48; noon cortisol 0.33 ± 0.76; 5 pm cortisol was 0.17 ± 0.25; and 9 pm cortisol was 0.09 ± 0.22. The medians for cortisol values are presented in Table 2. There was a significant Spearman correlation between a flatter cortisol slope and the average length of wake episodes at night ($r = 0.21$, $p = 0.04$, $N = 91$). There were no significant relationships between the 2-day mean of waking cortisol or cortisol rise and other measures of sleep.

### RSA Descriptives

The medians for RSA descriptives are presented in Table 2. Higher RSA baseline levels were significantly correlated with higher sleep efficiency ($r = 0.39$, $p = 0.001$, $N = 68$) and a correspondingly lower WASO ($r = -0.38$, $p = 0.002$, $N = 68$), lower average length of nocturnal wake episodes ($r = -0.43$, $p < 0.001$, $N = 68$), and a lower self-reported number of hours of sleep during a typical night ($r = -0.27$, $p = 0.02$, $N = 72$). Higher RSA AUC was significantly related to higher sleep efficiency ($r = 0.45$, $p < 0.001$, $N = 64$), and a correspondingly lower number of wake episodes ($r = -0.27$, $p = 0.04$, $N = 64$), lower WASO ($r = -0.40$, $p = 0.001$, $N = 64$), and with lower average length of nocturnal wake episodes ($r = -0.41$, $p = 0.001$, $N = 64$).

**Table 3**—Spearman rho Intercorrelations Among Sleep Measures in Women with Metastatic Breast Cancer

| | Mean Total Time in Bed (min) | Mean Latency (min) | Mean Sleep Efficiency | Mean Number of Wake Episodes | Mean Wake after Sleep Onset (min) | Average Wake Episode period (min) |
|---|---|---|---|---|---|---|
| Objective (Actiwatch) | | | | | | |
| Mean total time in bed (min) | — | — | — | — | — | — |
| Mean latency (min) | 0.27** | — | — | — | — | — |
| Mean sleep efficiency | −0.05 | −0.35** | — | — | — | — |
| Mean number of wake episodes | 0.38** | 0.32** | −0.69** | — | — | — |
| Mean wake after sleep onset (min) | 0.28** | 0.39** | −0.96** | 0.75** | — | — |
| Average wake episode period (min) | 0.02 | 0.25* | –0.75** | 0.17 | 0.74** | — |
| Self-Report | | | | | | |
| How many hours do you typically sleep in a night? | 0.63** | 0.11 | −0.09 | 0.27* | 0.24* | 0.08 |

*p < 0.05. **p < 0.01.

### Predictors of Sleep

*Predicting Sleep Efficiency.* Sleep efficiency was positively predicted by a dominant site of metastasis being chest and higher RSA AUC. The hierarchical regressions were conducted in 3 steps. After backward selection a test of the full model with three predictors (hormone use, radiation treatment and RSA AUC) were statistically significant, $\chi^2$ (3, $N$ = 63) = 12.96, p = 0.005, indicating that predictors as a set distinguished between high and low sleep efficiency.

Prediction success for high efficiency was 57%, with 84.8% for low efficiency for an overall success rate of 71%. According to the Wald criterion, only RSA AUC was significant in predicting sleep efficiency ($z$: 3.89, p = 0.049). Sleep efficiency was best predicted by RSA AUC even after the addition of demographic, disease severity and psychological variables.

*Predicting WASO*. The hierarchical regressions were conducted in 3 steps. After backward selection a test of the full model with two predictors (hormone use and RSA AUC) were statistically significant, $\chi^2$ (2, N = 63) = 12.33, p = 0.002, indicating that these predictors as a set distinguished between frequent and less frequent WASO.

Prediction success for frequent WASO was 87.9%, with 53.5% for less frequent WASO for an overall success rate of 71.4%. According to the Wald criterion, only RSA AUC was significant in predicting WASO ($z$: 4.62, p = 0.03). WASO was best predicted by RSA AUC even after the addition of demographic, disease severity and psychosocial variables.

*Predicting Total Time in Bed.* Time in bed was significantly predicted by whether or not patients were receiving chemotherapy, pain and depression. This model accounted for a large amount of the variance in changes in TIB [$F_{3,59}$ = 6.23, p = 0.001], $R^2$ = *0.24;* adjusted $R^2$ = 0.20]. The only significant predictor of less time in bed was whether or not patients received chemotherapy ($\beta$ = −0.38, p = 0.001).

*Predicting Sleep Latency.* Sleep latency was significantly predicted by chemotherapy and radiation treatments and perceived stress. This model accounted for large amount of the variance in sleep latency [$F_{3,59}$ = 3.7, p = 0.02], $R^2$ = *0.16;* adjusted $R^2$ = 0.12]. Two significant predictors were chemotherapy ($\beta$ = −0.30, p = 0.02) and stress score ($\beta$ = −0.25, p = 0.04). Women who received chemotherapy and had higher stress levels had shorter sleep latency.

*Predicting Mean Number of Wake Episodes.* Greater number of Wake Episodes was significantly predicted by taking sleep medications and lower RSA AUC. This model accounted for a large amount of variance in predicting mean number of wake episodes. [$F_{2,60}$ = 5.16, p = 0.009], $R^2$ = *0.15;* adjusted $R^2$ =0.12]. The best predictors for Mean Number of Wake Episodes were taking sleep medications ($\beta$ = 0.25, p = 0.04) and RSA AUC ($\beta$ = −0.28, p = 0.02).

*Predicting Average Wake Episode.* Longer wake episodes were significantly predicted by increased depression and by lower RSA. This model accounted for a moderate amount of the variance in changes in hours of sleep [$F_{2,60}$ = 60.07, p = 0.004], $R^2$ = *0.17;* adjusted $R^2$ = 0.14]. The best predictors for Average Wake Episode were depression ($\beta$ = −0.26, p = 0.03) and RSA AUC ($\beta$ = −0.36, p = 0.004).

## DISCUSSION

We confirmed previous findings of a relationship between a flatter diurnal cortisol slope and a longer average length of wake episodes during the sleep episode, an objective marker of insomnia.[49,51] We also found that low $RSA_{TF}$ during the TSST was associated with various objective measures of sleep disruption, including lower sleep efficiency and an increased fragmentation of sleep. With the addition of demographics, disease severity, and psychological variables, our findings suggest that RSA is the most consistent and significant predictor of sleep continuity disturbance. While demographics, disease severity and psychological variables all explained some portion of the development of sleep disruption, 4 of the 6 sleep parameters we examined (Sleep efficiency, WASO, Mean Number of Waking Episodes, Average Length of Waking Episode) were best explained by $RSA_{TF}$.

Previous research in general population found robust replicable association between depression and sleep, with many studies finding that sleep disruption predicts depression in many patients. Surprisingly there were no associations between BDI scores, actigraphy variables and our measures of RSA. However, we found a small correlation between a measure of depression that was created to include patients who either had a diagnosis of depression on SCID and/or were taking antidepressant medication for depression symptoms. We found that our depression measure correlated at 0.21 with total time in bed

**Table 4**—Spearman rho correlations among sleep measures, demographics, disease severity and psychological and physiological markers in women with metastatic breast cancer

| | Total Time in Bed | Latency | Sleep Efficiency | WASO | Mean Number of Wake Episodes | Average Wake Episode period | Hours of Sleep Last Night |
|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | |
| Age | −0.24* | −0.08 | 0.03 | −0.07 | −0.23* | 0.06 | 0.10 |
| Race | 0.05 | 0.08 | −0.09 | 0.14 | 0.10 | 0.11 | 0.12 |
| Marital status | −0.07 | 0.09 | −0.13 | 0.11 | 0.09 | 0.04 | −0.06 |
| Medication for sleep | 0.10 | 0.02 | −0.12 | 0.14 | 0.26* | −0.02 | −0.02 |
| Disease Severity | | | | | | | |
| Dominant Site | | | | | | | |
| Chest | −0.14 | −0.17 | 0.27** | −0.31** | −0.23* | −0.28** | −0.04 |
| Bone | −0.03 | 0.20 | −0.13 | 0.14 | 0.10 | 0.08 | −0.20 |
| Viscera | 0.16 | 0.02 | −0.16 | 0.19 | 0.18 | 0.19 | 0.21 |
| Disease-free interval | −0.13 | −0.04 | 0.15 | −0.18 | −0.20 | −0.06 | −0.06 |
| Chemotherapy | −0.29** | −0.14 | −0.12 | 0.04 | 0 | 0.09 | −0.14 |
| Radiation | −0.08 | 0.21* | −0.14 | 0.10 | 0.13 | 0.09 | −0.08 |
| Hormone | 0.16 | 0.20 | −0.19 | 0.24* | 0.23* | 0.12 | −0.08 |
| Estrogen receptor status | 0.10 | 0.18 | −0.05 | 0.07 | 0.03 | 0.05 | −0.13 |
| Psychological Variables | | | | | | | |
| Pain intensity | −0.23* | −0.02 | 0.02 | −0.08 | −0.10 | −0.05 | −0.04 |
| SCID/Antidepressant | 0.21* | 0.05 | −0.02 | 0.07 | 0.13 | −0.04 | 0.05 |
| PSS | −0.02 | −0.22* | 0.06 | −0.07 | −0.12 | −0.04 | −0.13 |
| BDI | 0.02 | −0.07 | −0.05 | 0.05 | −0.06 | 0.11 | −0.07 |
| Physiological Variables | | | | | | | |
| 2-day baseline log cortisol slope | −0.05 | 0.05 | −0.12 | −0.12 | 0.09 | 0.01 | 0.21* |
| 2-day cortisol rise 30 min post-waking | −0.10 | −0.10 | −0.12 | −0.19 | 0.15 | 0.04 | 0.20 |
| 2-day waking cortisol | −0.20 | −0.03 | −0.08 | 0.08 | −0.12 | −0.08 | −0.07 |
| RSA baseline | −0.08 | −0.21 | 0.17 | 0.39** | −0.38** | −0.22 | −0.43** |
| RSA AUC | 0.07 | −0.12 | 0.31* | 0.45** | −0.40** | −0.26* | −0.41** |

*p < 0.05; **p < 0.01

(p = 0.045) and $RSA_{TF}$ baseline at (r = −0.29, p = 0.01). There were no other associations found between depression, RSA and sleep disruption. The magnitude of these associations is small, suggesting that the robust association between depression and sleep disruption found in the general population might not be generalizable to the sleep disruption that we see in cancer patients.

A previous paper by our group[63] discussed the relationship between depression and RSA in this sample, showing that depressed women had lower RSA (lnHF) than nondepressed women. In exploratory analyses, low frequency RSA (lnLF) and very low frequency RSA (lnVLF) were also significantly lower in depressed patients. There were no differences in basal $RSA_{TF}$, a measure adjusting RSA for respiratory confounds. However, analyses revealed no differences in respiratory rate or tidal volume between depressed and non-depressed patients that would account for the observed group differences in RSA. Based on these data, Giese-Davis and colleagues suggested that there may be a broader dysregulation of autonomic function among these women with metastatic breast cancer, specifically autonomic oscillatory activity that accounts for the observed differences in RSA among depressed and non-depressed patients. In the current analyses we are using $RSA_{TF}$, which would not be expected to be associated with depression; our data supports this, as BDI scores were not correlated with $RSA_{TF.}$

While these findings are preliminary and correlational, to our knowledge they represent the first analysis of both hormonal and autonomic responses in individuals with insomnia and metastatic breast cancer. Disruption of both hormonal and sleep/activity circadian cycles is more common among cancer patients than among healthy individuals.[58] This disruption predicts poor prognosis[49,51] and may be caused by stress and its management as well as other factors possibly including tumor biology. The primary aim of this study was to explore associations among HPA dysregulation, vagal functioning, and sleep problems in women with metastatic breast cancer.

In healthy people, cortisol levels peak early in the morning and reach a nadir at the end of the waking day. However, in one-third to two-thirds of women with metastatic breast cancer, circadian rhythms are disrupted and diurnal cortisol slopes are either flattened, have multiple peaks, or are elevated at the end of the day.[42] Prior studies have found that alterations in circadian rhythms are associated with both higher risk of developing cancer[59] and a poorer cancer prognosis[60] for those previously diagnosed. A previous study by Sephton and colleagues[42] found that a flattened diurnal cortisol pattern in metastatic breast cancer patients predicted a shorter survival. In addition, these authors reported a relationship between frequent awakenings and abnormal cortisol rhythms in metastatic breast cancer, which we confirmed in our study. Although we conducted multiple correlations on cortisol and sleep variables, we hypothesized that, in line with our previously published research,[49] we would find a specific association between flatter cortisol slope and number of awakenings during the night. Thus, a disrupted cortisol

rhythm may have serious medical implications in women with breast cancer. Longitudinal studies would allow us to determine whether insomnia symptoms serve as moderators or mediators of circadian disruption in women with breast cancer.

Insomnia symptoms (measured by lower sleep efficiency, higher length of wake after sleep onset, and average sleep episodes) were associated with a lower baseline RSA and RSA AUC. Sleep involves a neurophysiological switch from predominantly sympathetic to parasympathetic tone.[61] Lower RSA is associated with decreased parasympathetic functioning in insomniacs,[62] and attenuated parasympathetic functioning is associated with increased stress and poorer emotional regulation.[34] In a previous study on this same sample, depression was significantly associated with baseline high, low, and very low frequency heart-rate variability during stress task (TSST) (all uncorrected for respiration),[63] providing evidence for the link between lower parasympathetic functioning and increased depression. Although our study is cross-sectional and no inferences of causation can be made, the relationship between RSA and insomnia also suggest that adverse health consequences of disrupted sleep at night may be related to reduced parasympathetic tone during the day. In future studies, it would be informative to examine longitudinally the relationships between insomnia, depression, and RSA. This research will provide new avenues (both pharmaceutical and psychological) for treatment of psychiatric disorders and might have implications for cancer treatments and survival.

It is possible that tumor biology or other biological factors associated with cancer (and its progression or treatment) causes lower RSA, which in turn disrupts sleep; however, this seems unlikely because of the clear association between heart rate variability and depression in other populations. Alternatively, disruption of sleep itself might cause lower RSA. The same issue of directionality applies to the flattened cortisol slope. Caution must also be taken in interpreting the cortisol data, because collection occurred only during the daytime. It is possible that the rhythm of cortisol, which typically peaks around waking and reaches a nadir around bedtime, is shifted relative to the sleep cycle, which would give the appearance of a flattened daytime slope. This question can only be answered by assessing cortisol levels over a 24-h period. Further studies need to be conducted to replicate the accuracy and validity of our findings

Despite the high prevalence of sleep disruption in this population, there has been relatively little study of insomnia, autonomic functioning, and hormonal patterns in women with breast cancer and metastatic breast cancer in particular. This study offers a preliminary look at sleep disruption and associated changes in hormonal and autonomic nervous system markers, providing further clues to why poor sleep is bad for health. Interventions aimed at correcting autonomic functioning and hormone disruptions might prove valuable in treating insomnia in women with cancer.

## ACKNOWLEDGMENTS

This research was supported by NIA/NCI Program Project AG18784, CA118567 (DS) and 1 R01 CA118567-01A1 (DS). It was also supported in part by grant 5 M01 RR000070 from the National Center for Research Resources, National Institutes of Health.

We would like to thank Eric Neri for his support with data cleaning and analyses.

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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