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Title

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Permalink

<https://escholarship.org/uc/item/4bp6c636>

Journal

Behavioral Neuroscience, 130(3)

ISSN

0735-7044

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Publication Date

2016-06-01

DOI

10.1037/bne0000107

Peer reviewed

SPECIAL ISSUE: BEHAVIORAL NEUROSCIENCE OF SLEEP

Sleep Quality and Depressive Symptoms After Prostate Cancer: The Mechanistic Role of Cortisol

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A substantial portion of men treated for prostate cancer report clinically significant sleep problems and disturbance in sleep quality constitutes significant risk for the development of depressive symptoms in survivors. Dysregulation in biological stress processes underlies the impact of poor sleep on the onset and/or progression of depressive symptoms, yet few studies have sought to identify potential neurobiological mechanisms (e.g., HPA axis activation) underlying this association in PC survivors. The present study examines the relationships between sleep disturbance, depressive symptoms, and indices of diurnal cortisol patterns among men treated for prostate cancer. In total, 66 men (84.8% White; mean age = 65.8 years, $SD = 9.04$) treated in the prior 2 years for localized prostate cancer were recruited. They completed questionnaires to measure sleep quality and depressive symptoms at study entry (T1) and 4 months later (T2). They also provided 4 saliva samples per day, over 3 days, at T1. Three cortisol indices were computed: diurnal slope, area under the curve (AUC_g), and cortisol awakening response (CAR). Analyses indicate that, controlling for body mass index and age, worse sleep quality at T1 was significantly associated with higher levels of depressive symptoms at T2. Significant indirect effects were observed for cortisol slope (indirect effect = $-.17$, 95% CI [$-.61$, $-.01$]) and AUC_g (indirect effect = $-.14$, 95% CI [$-.43$, $-.01$]), but not CAR. Results suggest that dysregulation in HPA activity acts as a neurobiological mechanism of the impact of sleep disruption on depressive symptoms in men with prostate cancer.

Keywords: prostate cancer, sleep, cortisol, depressive symptoms, HPA axis

Individuals with cancer are particularly vulnerable to disturbances in sleep. Prevalence rates of significant sleep problems for patients with varying types of cancer are estimated at 30% to 50%

(Savard & Morin, 2001); men treated for prostate cancer have a heightened risk for developing a sleep problem. Symptoms such as urinary and bowel problems, hot flashes, and night sweats are commonly reported after radical prostatectomy, radiation therapy, or hormone treatments, and have potential to disrupt sleep. In fact, insomnia has been reported as a clinically significant symptom occurring in 32% of men treated for prostate cancer by radical prostatectomy (Savard et al., 2005), and men undergoing various treatments for prostate cancer ($n = 861$) named insomnia (32%) as the most frequently reported symptom (Hervouet et al., 2005).

Disturbance in sleep presents specific vulnerability for the development of depressive symptoms in cancer survivors (Irwin, Olmstead, Ganz, & Haque, 2013). Positive relationships between sleep disturbance and depressive symptoms in prostate cancer survivors have been documented (e.g., Dirksen, Epstein, & Hoyt, 2009). In a prospective longitudinal study, Miaskowski et al. (2011) examined trajectories of sleep disturbance following radiation treatment for prostate cancer ($n = 82$) and found that higher levels of depressive symptoms were associated with higher levels of sleep disturbance at baseline, as well as over the entire 6 months of the study. Such findings underlie the notion that dysregulation

This article was published Online First January 28, 2016.

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This research was supported by funds from the UCLA Cousins Center for Psychoneuroimmunology, and the following support from NIH: T32-MH15750; SC1-CA187494. All authors declare there are no conflicts of interest.

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in sleep, or poor sleep quality, presents a specific vulnerability to depression after prostate cancer treatment. It is posited that poor sleep drives dysregulation in biological stress and immune processes, which together contribute to the onset and/or progression of depressive symptoms (see Irwin, 2015). Yet, few studies have sought to identify potential biological mechanisms underlying the association between sleep dysregulation and depressive symptoms in prostate cancer survivors.

Positive associations of depressive symptoms and aberrant cortisol output have been documented (Stetler & Miller, 2011), as initial hypothalamic-pituitary-adrenal (HPA) axis overactivation dampens prefrontal inhibition of a sustained stress response, which in turn leads to adrenal overstimulation in a feedback loop that eventually terminates in anhedonic states (e.g., Gold, 2015). However, the association of depression to HPA hyperactivity varies considerably across patient groups, study methodology, and depressive features with some studies failing to find an effect (see Stetler & Miller, 2011). Such variation in findings necessitates additional research with specific patient populations and contexts. Limited numbers of studies have found evidence for associations of depression and HPA activity in cancer populations (Jehn et al., 2006; Lutgendorf et al., 2008; Sephton et al., 2009). In fact, in studies of women with breast cancer, cortisol, and psychosocial stress are more strongly related to depressive symptoms than treatment factors (see Bower, 2008).

Typically, during sleep, blood levels of cortisol fall (Besedovsky, Lange, & Born, 2012) and chronic sleep disturbance has been associated with activation of the HPA pathway (Besedovsky et al., 2012). However, the impact of sleep problems on cortisol dysregulation in the context of cancer survivorship remains inconclusive. A study of breast cancer patients (Sephton, Sapolsky, Kraemer, & Spiegel, 2000) showed more frequent nighttime awakenings to be linked to higher nocturnal cortisol levels, and an association of poorer sleep quality and shorter sleep duration with flattened diurnal cortisol slopes was documented in a Chinese sample of breast cancer patients (Ho, Fong, Chan, & Chan, 2013). Yet, another study found no association between sleep and the diurnal cortisol rhythm in either breast cancer patients and healthy controls (Carlson, Campbell, Garland, & Grossman, 2007).

The purpose of this study was to examine the relationships of sleep disturbance, depressive symptoms, and diurnal cortisol patterns in men treated for prostate cancer. This investigation was guided by three sets of hypotheses: (a) poorer sleep quality at study entry (T1) will be related to greater depressive symptoms four months later (T2) and to dysregulation in cortisol (i.e., flatter diurnal cortisol slope, smaller cortisol awakening response [CAR], and greater area under the curve [AUC]); (b) indicators of dysregulated cortisol will be related to greater depressive symptoms; and (c) cortisol indices will mediate the relationship between sleep quality and depressive symptoms.

Method

Participants and Procedures

Men who completed radical prostatectomy or radiation therapy for localized prostate cancer within the prior two years were recruited to take part in a larger study on "health-related quality of life after prostate cancer." Sixty-six nonsmoking participants were recruited via

Table 1
Participant Characteristics ($N = 66$)

Characteristic	Full sample
<i>M</i> Age	65.8 ($SD = 9.04$)
Ethnicity (%)	
White (non-Hispanic)	84.8
African American/Black	10.6
Hispanic/Latino	3.1
Native American	1.5
Education (%)	
High school degree	10.7
Some post-high school	21.2
2- or 4-year college degree	34.8
Advanced degree	33.3
Annual household income (%)	
\$15,000 or less	3.1
\$15,001–\$45,000	9.2
\$45,001–\$75,000	26.2
\$75,001–\$100,000	21.5
\$100,001 or more	40.0
Job status (%)	
Full-time	35.4
Part-time	10.8
Retired	47.7
Unemployed/disabled	6.1
Relationship status (%)	
Married/partnered	89.4
Widowed/divorced	7.5
Single, never married	3.1
Treatment (%)	
Prostatectomy/surgery	71.2
Radiation therapy	31.8
<i>M</i> months since diagnosis	28.6 ($SD = 20.45$)
<i>M</i> months since treatment	15.6 ($SD = 7.53$)
<i>M</i> Gleason sum	6.0 ($SD = 1.45$)

Note. Several participants reported receipt of more than one treatment type.

physician/clinic referrals, community outreach, advertisement, and an institutional tumor registry database (see Table 1). Participants were excluded for presence of medical conditions (including active infection) or medications, including steroids, that could confound cortisol evaluation. After informed consent, participants completed questionnaires at study entry (T1) and again 4 months later (T2). They self-reported demographic, disease-related, and psychological/psychosocial (e.g., depression and sleep quality) variables. At T1 participants also provided saliva samples (four times per day over 3 days) for measurement of cortisol output. Men received \$50 for taking part in the study. All procedures were approved by the authors' Institutional Review Boards.

Questionnaire Measures

Depressive symptoms were measured at T1 and T2 with the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a 20-item scale designed to measure depressive symptomatology in the general population. The scale assesses symptoms experienced within the past week on a 4-point scale (0 = rarely or none of the time to 3 = most or all of the time); total scores range from 0 to 60. Standard cut-offs are 16 for mild/moderate symptoms and 23 for more significant levels of depressive symptoms (Radloff, 1977). In the present study, Cronbach's alpha = .89.

Sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Participants responded to questions about their sleep over the last month. The PSQI accounts for several aspects of sleep including overall quality, latency, duration, efficiency, disturbances, use of sleeping medication, and daytime dysfunction. Studies have indicated that the PSQI has high reliability as well as content validity and ecological validity (e.g., Carpenter & Andrykowski, 1998). An overall sleep quality score was computed using standard scoring procedures; higher scores indicate worse sleep quality and scores ≥ 5 are considered clinically meaningful (Buysse et al., 1989).

Measurement of Cortisol in Saliva

Diurnal cortisol was assessed with saliva samples collected at home using Salivette collection tubes (Sarstedt, Inc.). Participants collected saliva upon awakening (morning), 30 min after awakening, 8 hr postawakening, and at bedtime. Significant day-to-day variation in diurnal cortisol is commonly observed (Smyth et al., 1997). To achieve adequate reliability in measurement, it is recommended that salivary cortisol be collected over multiple, consecutive days to capture stable characteristics (Adam & Kumari, 2009). Thus, saliva was collected for three consecutive days.

Participants were instructed not to eat, drink, or brush teeth for at least 20 min before each sampling. Each day, participants self-reported compliance with collection instructions via a sample collection log. Participants were also instructed to call or text a voicemail line after each sample collection to record collection time and further ensure compliance. Average sample collection times were: waking: 6:17 a.m. ($SD = 1:01$); 30 min postwaking: 6:49 a.m. ($SD = 1:02$); 8 hr postwaking: 2:42 p.m. ($SD = 1:40$); bedtime: 11:34 p.m. ($SD = 1:45$). Participants refrigerated samples until return and they were stored in a -20°C freezer until analysis. Concentrations of salivary free cortisol were measured in duplicate using a commercially available chemiluminescence-immunoassay at the TUD Biopsychology Laboratory in Dresden, Germany. Assay sensitivity was measured to be $.015 \mu\text{g/dL}$. The lower detection limit is $.41 \text{ nmol/L}$, and interassay and intraassay coefficients of variance are $<10\%$.

Because raw cortisol values are typically skewed, data were log-transformed and all cortisol values were averaged across collection days. Three cortisol indices were computed: diurnal slope, AUC_g , and CAR. The diurnal slope was calculated as the decrease from highest morning sample to the evening sample. Greater slope values reflect more rapid declines in cortisol levels (lower evening values), whereas smaller values reflect flatter diurnal rhythms (higher evening values). To examine overall cortisol volume, AUC_g across day was computed using the trapezoidal method based on hours after awakening (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The 30-min measure was excluded from this calculation as early morning increase of cortisol is relatively independent from overall cortisol volume (Chida & Steptoe, 2009). Finally, the CAR was assessed by cortisol increase from awakening (averaged across days) to the second cortisol sample (30 min postawakening; averaged across days). These parameters characterize the distinctive circadian pattern of cortisol secretion but likely represent different aspects of HPA axis function and may be independently regulated. For instance, it is sug-

gested that the CAR is mediated by an extrapituitary pathway to the adrenals from the suprachiasmatic nucleus in the hypothalamus (Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010).

Data Analyses

Descriptive statistics and zero-order correlations were computed for key variables. Relevant biobehavioral (e.g., body mass index) and disease-specific variables (e.g., treatment type) were examined to identify possible covariates. Variables with associations with depressive symptoms or cortisol were included in subsequent statistical models. Covariate by predictor interactions were also examined. To determine the relationship of sleep quality and depressive symptoms, and whether cortisol indices mediated this relationship, bootstrapping analyses were conducted using methods described by Preacher and Hayes (2008) for estimating total, direct, and indirect effects. Three models were tested using bootstrapping with 10,000 resamples via PROCESS procedure for SPSS to test effects as determined by bias-corrected 95% confidence intervals (Hayes, 2012).

Results

Descriptives and Preliminary Analyses

On average, participants scored below screening thresholds for depressive symptoms at study entry ($M = 8.9$, $SD = 8.1$; range = 0–36) and at follow-up ($M = 10.87$, $SD = 10.02$; range = 0–37). However, 15 men scored ≥ 16 on the CES-D at T1, indicating the possibility of mild to moderate levels of depressive symptoms; six of these were ≥ 23 , which is indicative of more significant symptoms.

Further, on average, men scored 6.38 ($SD = 3.68$) on the PSQI at T1, with nearly 64% of the sample scoring at or above the clinically meaningful threshold (T2: $M = 5.32$, $SD = 3.24$). This level of sleep disturbance in the present sample is slightly higher than the mean score of 5.25 ($SD = 2.93$) reported by Miaskowski et al. (2011) in a sample of 82 prostate cancer patients prior to treatment initiation. A significant portion of the sample also reported prostate-specific physical symptoms with high potential to interrupt sleep. For instance, nearly 25% of the sample reported moderate to severe problems with urinary function with 63% stating having to use the bathroom in the middle of the night more than 3 times per week. Only body mass index (BMI) and age were related to mediating or outcome variables and so only these variables were entered as covariates in subsequent models. No significant sleep quality by covariate interactions were observed.

Model Testing

Three models were tested to evaluate direct and indirect effects on depressive symptoms with potential mediators (i.e., cortisol indices; see Table 2). In addition, all models included BMI and age (not shown in table). Across models, younger age ($B = -.03$; $p < .01$) and higher BMI ($B = .04$; $p < .05$) were associated with lower depressive symptoms. Younger age was also associated with lower AUC_g ($B = -.02$; $p < .05$).

In each model, worse sleep quality at study entry was significantly associated with higher levels of depressive symptoms four

Table 2
Direct and Indirect Effects for Sleep Quality and Cortisol Indices on Depressive Symptoms

Variable	Effect	SE	p	95% CI	
				Lower	Upper
Model 1: Sleep Quality → Cortisol Slope → Depressive Symptoms					
Effect of sleep quality on slope	-.24	.06	<i>p</i> < .001	-.36	-.11
Direct effect of sleep quality	.28	.10	<i>p</i> < .01	.08	.48
Indirect effect	-.17	.13		-.61	-.01
Model 2: Sleep Quality → AUC → Depressive Symptoms					
Effect of sleep quality on AUC	.22	.06	<i>p</i> < .01	.09	.36
Direct effect of sleep quality	.25	.10	<i>p</i> < .05	.05	.45
Indirect effect	-.14	.10		-.43	-.01
Model 3: Sleep Quality → CAR → Depressive Symptoms					
Effect of sleep quality on CAR	<.01	.04	<i>ns</i>	-.07	.08
Direct effect of sleep quality	.16	.08	<i>p</i> < .05	.01	.32
Indirect effect	<.01	.08	<i>ns</i>	-.05	.03

Note. Confidence intervals (CIs) containing zero are interpreted as not significant. All models include participant age and body mass index as statistical covariates. AUC = area under the curve; CAR = cortisol awakening response.

months later. Significant indirect effects were observed for cortisol slope (indirect effect = $-.17$, 95% CI [$-.61$, $-.01$]) and AUC_g (indirect effect = $-.14$, 95% CI [$-.43$, $-.01$]), but not CAR. Flatter slope and less overall cortisol output was related to higher depressive symptoms. These results suggest the relationship of sleep quality with depressive symptoms can be partially explained by at least two of the three tested indices of cortisol processes. Notably, each model accounted for 45%-47% of variance of depressive symptoms.

Post hoc analyses were conducted to consider the possibility that sleep quality acted as a mediator of cortisol's impact on depressive symptoms (reverse mediation models). These models either resulted in nonsignificant or small indirect effects of sleep quality.

Discussion

These results support the possibility that dysregulation in HPA activity acts as a biological mechanism through which sleep disruption impacts depressive symptoms in men with prostate cancer. Consistent with prior studies in other populations, it may be that interruption in standard sleep cycles contributes to the dysregulation of cortisol activity (e.g., Besedovsky, Lange, & Born, 2012), which may ultimately contribute to the neurobiologically driven emotional dysregulation that underlies depression (e.g., Gold, 2015). Cancer-related physical symptoms and psychological stress likely work to stimulate arousal and suppress sleep further contributing to activation of the biological stress systems.

Interestingly, worse sleep quality exhibited associations with flatter cortisol slope and greater AUC, but not CAR. Likewise, cortisol slope and AUC_g (but not CAR) had significant indirect effects on depressive symptoms. To better understand these findings, it is important to distinguish these indices. The CAR is a measure of the rapid increase in cortisol that occurs 30–45 min after awakening. Golden et al. (2013) examined cortisol in a study of 935 community-dwelling adults (ages 45–84). They found that the CAR was associated with a lower cortisol level upon awakening and during morning hours but not associated with cortisol patterns across the day or AUC_g . Further, they found AUC_g to be most closely associated with bedtime cortisol values. Our results suggest that cortisol indices that reflect overall cortisol volume and

daily rhythm (e.g., diurnal slope, AUC_g) might be more sensitive to perceptions of sleep quality rather than CAR, which might reflect a distinct component of HPA axis activity.

This study illuminates the role of a potential biological pathway between the impact of sleep quality on a largely psychological and behavioral outcome (i.e., depressive symptoms). Future work should consider the extent to which dysregulation of cortisol and other glucocorticoids might inform the impact of sleep on disease risk and progression. Alterations in diurnal cortisol patterns have been linked to a number of health outcomes in cancer patients, including disease progression and early mortality (e.g., Cohen et al., 2012; Sephton et al., 2013; see also Armaiz-Pena, Cole, Lutgendorf, & Sood, 2013). Further, prolonged exposure to cortisol can contribute to glucocorticoid resistance at the cellular level, ultimately dampening the inhibitory effects of cortisol on inflammatory processes (Miller, Cohen, & Ritchey, 2002). Elevations in inflammation are associated with mortality in cancer, including prostate cancer (Ko et al., 2012; Lutgendorf & Sood, 2011).

This study represents only one possible pattern of relationships and remains correlational; causality cannot be determined. Given our relatively small sample size, replication in larger samples is needed. Also, this study relied on self-report measures of sleep quality. Studies that buttress self-report measures with more objective observational methods (e.g., actigraphy) and examinations of specific sleep problems (e.g., sleep duration) will be informative. Specific sleep parameters and patterns might have unique relationships with cortisol. For instance, longer sleep duration has been shown to have a buffering impact on cortisol increases over time in older adults (Rueggeberg, Wrosch, & Miller, 2012).

Although this study points to cortisol as a possible mechanism of the impact of sleep over time, it is important to note that it was measured at T1. Future work that incorporates periodic repeated measurements of HPA axis activity over time will better elucidate its mechanistic role and contribute to the specificity of the cortisol effect observed in the current study. Finally, future research that includes a noncancer comparison group will make a strong contribution and help distinguish to what extent such findings are specific to men with prostate cancer. Investigations in other cancer groups have suggested salivary cortisol is associated with depres-

sion differently in the cancer context. Du et al. (2013) showed that depressed lung cancer patients had lower diurnal variation in salivary cortisol compared with healthy individuals or nondepressed lung cancer patients. Changes in inflammation from cancer and cancer treatments might invoke unique dynamics in cortisol release (see Antoni et al., 2006).

Despite these limitations, this is the first study to our knowledge to show an association between sleep, cortisol, and depressive symptoms in prostate cancer survivors. We recommend that future work characterize related immune processes that may be implicated. For instance, inflammatory processes which are sensitive to sleep (Irwin, 2015) might be further contributing to depression risk. The degree to which sleep and cortisol are associated with disease outcomes in prostate cancer patients also deserves attention. Further, recent work has demonstrated the gender-specificity of the specific action of cortisol and glucocorticoid receptors in vulnerability to depression (Suarez, Sundry, & Erkanli, 2015), which highlights the importance of sex hormones in addition to cortisol, and further supports the role of hormones as target mechanisms for additional study. Finally, this study isolated the 2-year period following treatment. To enhance clinical relevance, understanding the impact of sleep disturbance at more targeted times in the cancer trajectory will be useful.

This study examined the relationship of perceptions of sleep quality, cortisol regulation, and depressive symptoms. More attention is needed in understanding and treating sleep problems, stress, and mood disturbance after prostate cancer. Clinicians should more routinely assess sleep problems among prostate cancer patients and research that identifies the biological and psychological impact of sleep problems is warranted.

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Received June 30, 2015

Revision received August 17, 2015

Accepted September 22, 2015 ■

Correction to Hupbach and Fieman (2012)

In the article “Moderate Stress Enhances Immediate and Delayed Retrieval of Educationally Relevant Material in Healthy Young Men,” by Almut Hupbach and Rachel Fieman (*Behavioral Neuroscience*, 2012, Vol. 126, No. 6, pp. 819–825. <http://dx.doi.org/10.1037/a0030489>), there are computational errors in the last sentence of the **Memory Performance** section. “($M = .30$, $SD = .11$ for CPS, and $M = .13$, $SD = .17$ for the warm water control).” should read instead: “($M = .03$, $SD = .11$ for CPS, and $M = .13$, $SD = .17$ for the warm water control).”

<http://dx.doi.org/10.1037/bne0000152>