The associations between diurnal cortisol patterns, self-perceived social support, and sleep behavior in Chinese breast cancer patients

Authors: Rainbow T. H. Ho[ab]*, Ted C. T. Fong[a], Caitlin K. P. Chan[b], Cecilia L. W. Chan[b]

Affiliations: [a] Centre on Behavioral Health, 2/F, The Hong Kong Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road, Pokfulam, Hong Kong.

[b] Department of Social Work & Social Administration, 5/F, Building C (Social Sciences), Jockey Club Tower, The Centennial Campus, The University of Hong Kong, Pokfulam, Hong Kong.

Corresponding author:

Rainbow Tin-hung Ho, Centre on Behavioral Health, 2/F, The Hong Kong Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road, Pokfulam, HKSAR

Phone number: 852-2831-5169; E-mail: tinho@hku.hk; Fax no: 852-2816-6710

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Summary

Objective: This study examined the relationships between diurnal cortisol patterns and sleep behavior, social support, psychological factors, and perceived health status in breast cancer patients.

Methods: One hundred and eighty-one breast cancer patients completed a self-report questionnaire that combined the Hospital Anxiety and Depression Scale, the Yale Social Support Scale, and self-perceived measures of physical health, stress, sleep quality, total sleep hours, and time of awakening. Salivary cortisol was collected upon waking, at 1200 h, 1700 h, and 2100 h on two consecutive days. Multiple regression analysis was performed on the diurnal cortisol slope that was derived from slope analysis of the log-transformed cortisol data.

Results: Controlling for the initial cortisol level, a flatter diurnal cortisol slope was significantly associated with a later time of awakening, higher negative social support, poorer perceived health, poorer sleep quality, and shorter total sleep hours. Anxiety and depression were not significantly correlated with the slope.

Conclusions: The results indicate a subtle dysregulation in hypothalamic-pituitary-adrenal axis functioning in patients with highly negative social support, poor perceived health, poor sleep quality, a later time of awakening, and insufficient sleep hours.

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1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in stress regulation; cortisol is its hormonal end product (Gunnar & Quevedo, 2007). Cortisol secretion typically exhibits a circadian rhythm with a early-morning peak followed by a gradual decline and a late-evening trough (Stone et al., 2001). In patients with breast cancer, aberrant diurnal cortisol patterns have been found in the form of a lower early-morning peak and a slower decline (Touitou et al., 1996). The altered rhythm, as a manifestation of anomalous activity of the HPA axis, is linked to outcomes such as fatigue, depression and early mortality (Sephton et al., 2000; Bower et al., 2005; McGregor & Antoni, 2009). As Abercrombie et al. (2004) noted, the prognostic value of the diurnal rhythm suggests that investigation into the associated physiological and psychological factors is warranted.

Disturbances in sleep behavior such as poor sleep quality, insomnia, and early awakening are important concerns among breast cancer patients (Davidson et al., 2002; Lee et al., 2004). Whereas one previous study of breast cancer patients (Sephton et al., 2000) showed more frequent nocturnal awakenings to be linked to higher nocturnal cortisol levels, another study (Carlson et al., 2007) found no association between sleep quality or sleep duration and the diurnal cortisol slope. For psychological factors, social support has been shown to be a protective factor against mortality risks in breast cancer patients (Trunzo & Pinto, 2003; Friedman et al., 2006; Kroenke et al., 2006). Despite the demonstrated reciprocal relationship between psychological and physiological functioning in general (Bauer, 1994), two previous studies of metastatic breast cancer patients (Turner-Cobb et al., 2000; Abercrombie et al., 2004) found no significant associations between social support and HPA axis functioning.

In general, the small sample sizes in previous studies of the relationships between diurnal cortisol patterns and sleep behavior or social support have led to a lack of statistical power, thus rendering the results inconclusive. To address this issue, we conducted a cross-sectional study with a sample of 181 breast cancer patients to explore the relationships between diurnal cortisol patterns, social support, and sleep behavior. Specifically, we hypothesized that 1) breast cancer patients with a higher level of negative social support or a lower level of positive social support would show a flattened diurnal cortisol slope and 2) patients who reported better sleep behavior, in terms of better sleep quality, earlier time of awakening, and longer total sleep hours would show a steeper diurnal cortisol slope.

2. Methods

2.1. Subjects and procedures

This study recruited 181 breast cancer patients from four cancer resource centers in Hong Kong using letters and phone calls. During the screening interview, the study's purposes, risks, and benefits were explained to the participants, who then provided written informed consents. They were instructed to complete the self-report questionnaire and to collect salivary cortisol measurements at home. Ethical approval was obtained from a local institutional review board. The exclusion criteria were metastases and recurrence of breast cancer, a history of major psychiatric illness, pregnancy, and inability to read Chinese.

2.2 Measures

2.2.1 Anxiety and depression

The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983; Leung et al., 1999) is a 14-item 4-point Likert scale that assesses anxiety (7 items) and depression (7 items). The subscale score is classified into four categories: normal = 0-7, mild = 8-10, moderate = 11-14, and severe = 15-21. In this study, the scale had good Cronbach's alpha scores of 0.86 and 0.75 for the anxiety and depression subscales, respectively.

2.2.2 Social support

The Yale Social Support Index (Seeman & Berkman, 1988) assesses the perceived quantity and quality of positive social support (3 items) and negative social support (3 items) for cancer patients, with higher scores indicating greater degrees of both. In this study, the scale had Cronbach's alpha scores of 0.58 and 0.62 for positive and negative social support, respectively.

2.2.3 Salivary cortisol

Participants used Salivette tubes to collect saliva samples at four time-points on two consecutive days: wake-up, 1200 h, 1700 h, and 2100 h . The mean (SD) collection time was 0719 h (70 min), 1225 h (42 min), 1729 h (39 min), and 2136 h (40 min). Four data points were excluded upon screening for outliers in collection times (>4 SD deviation from mean). The participants were reminded not to brush their teeth or eat prior to sample collection to avoid contamination and were advised to follow their normal daily routines otherwise. Collected tubes were kept frozen until they underwent laboratory analysis of the salivary cortisol using an enzyme-linked immunoassay kit (Salimetrics, PA, USA). The intra-assay and inter-assay coefficients of variation were 3% and 10%.

2.2.4 Sleep behavior and other measures

The participants also used a 10-point scale (a score of five indicating level or condition same as usual, with a score above five indicating higher than usual) to evaluate self-perceived levels of health, stress, and sleep quality. Information on time of awakening and total sleep hours was also reported.

2.3 Statistical analysis

The slope analysis was carried out on the four cortisol measurements (Abercrombie et al., 2004; Vedhara et al., 2006). The raw cortisol data displayed considerable skewness (0.76 - 2.00) and kurtosis (0.28 - 6.16). Preliminary analyses showed no significant differences in the cortisol measurements across days (t = 0.11 - 1.67, $p >$ 0.05). Thus, the data were log-transformed and aggregated across days in the slope analysis, which regressed the log-transformed data on the four measurement occasions to produce the diurnal cortisol slope. A steeper (more negative) diurnal slope indicated a faster decline in cortisol, whereas a flatter (more positive) slope indicated a slower decline. Correlational and regression analyses were carried out between the diurnal cortisol slope and the study variables, namely, perceived health, perceived stress, sleep behavior, anxiety, depression, and social support. Statistical significance was set at the 0.05 level.

3. Results

3.1 Descriptive profiles of participants

Table 1 displays the characteristics of the study participants. The 181 female participants were middle-aged (M = 48.3 years, SD = 7.5) and had an average cancer duration of 22.4 months (SD = 13.3). Most of the participants were married (72.4%) and had completed secondary education (69.6%). Around 40% and 18% of them showed at least mild symptoms of anxiety and depression, respectively. The median scores (interquartile ranges) of the raw cortisol levels (in nmol/L) at the four time points were 7.24 (4.79 – 9.79), 3.45 (2.35 – 4.55), 1.96 (1.35 – 3.03), and 1.24 (0.69 – 1.79). Based on the log-transformed cortisol data, an expected pattern of diurnal cortisol decline (in log nmol/L per hour) was obtained (M = -0.08, SD = 0.04).

[Insert Table 1 about here]

3.2 Correlational analyses

Table 2 lists the bivariate correlations between the diurnal cortisol patterns and the study variables. Although the initial cortisol level was significantly and negatively correlated with age, it was not significantly associated with any of the other study variables. The diurnal cortisol slope was found to be significantly and positively associated with perceived stress and negative social support but negatively associated with perceived health and total sleep hours. As expected, the initial cortisol level was significantly and negatively correlated with the diurnal cortisol slope (r = -0.71, p < 0.01), suggesting a steeper diurnal decline for participants with a higher cortisol level at awakening.

[Insert Table 2 about here]

3.3 Regression analyses

To understand the associations between the study variables and the diurnal cortisol slope, a two-step regression analysis was conducted. The Step 1 model, which included age and initial cortisol level, explained 52.0% of the variance in the diurnal slope, with the initial cortisol level being a significant predictor (β = -0.73, t = -12.8, p < 0.01). The Step 2 model, which incorporated the independent variables, significantly explained an additional 6.7% of the variance. These results indicated that, after taking into account the effects of the age and initial cortisol level, the diurnal cortisol slope was significantly and positively associated with time of awakening (β = 0.22, t = 3.57, p < 0.01) and negative social support (β = 0.12, t = 2.04, p < 0.05) and negatively associated with perceived health (β = 0.19, t = 3.33, p < 0.01), sleep quality (β = -0.13, t = -2.17, p < 0.05), and total sleep hours (β = -0.21, t = -3.32, p < 0.01).

[Insert Table 3 about here]

4 Discussion

Contrary to previous findings (Turner-Cobb et al., 2000; Abercrombie et al., 2004), this study showed that patients' perception of a higher level of negative social support was associated with a flatter diurnal cortisol pattern, lending partial support to hypothesis 1. The results suggest that patients with a lower level of negative social support may cope with stressful situations more effectively, leading to a steeper diurnal cortisol pattern. As Porter (2012) recently proposed, psychosocial interventions could adopt social support strategies that focus on the role of the cancer patients' family members and friends in promoting healthy daily routines; thus could improve patients' circadian cortisol rhythms. In contrast the diurnal cortisol pattern was not linked to positive social support. This lack of association echoes the findings of previous studies of social interaction and endocrine outcomes (Seeman, 1996; Seeman & McEwen, 1996; Seeman, 2000). In one study, the negative relationship between positive social support and endocrine activity was only found in men (Seeman et al., 2002). Seeman and colleagues found that women tended to be less reactive to positive emotions and more susceptible to negative social interactions, resulting in a higher risk for emotional distress. Other research studies (Schuster et al., 1990; Ito et al., 1998) have suggested that negative rather than supportive interactions are more predictive of depressed moods. These findings may be related to the well-developed physiological arousal and flight-or-fight responses, and could plausibly be attributed to the instinct to avoid dangerous situations. More studies are needed to corroborate these findings and to elucidate the role of gender in the underlying mechanisms of the body's physiological response, and the neuroscience of both the positive and negative social interactions.

This study's findings on the negative relationships that diurnal cortisol slope has with sleep quality and total sleep hours and its positive relationship with time of awakening provide supporting evidence for hypothesis 2. The results suggest that adequate sleep hours and good sleep quality may influence positive adjustment to stress and thus produce steeper diurnal cortisol patterns. However, a later time of awakening was linked to flatter diurnal cortisol patterns. Taking into account the early-morning peak feature of cortisol secretion in a typical circadian rhythm, the initial cortisol level displayed by the participants who woke up later likely reflects a level below the expected peak phase of secretion, thus contributing to the flatter diurnal cortisol slope. This implies that waking up earlier while maintaining adequate sleep hours by going to bed earlier may facilitate steeper diurnal cortisol patterns. Cognitive behavioral interventions and training in relaxation techniques may facilitate such a stable sleep pattern and thus a better HPA axis functioning (Savard et al., 2005; Porter, 2012).

In addition, participants with a better level of perceived health exhibited a steeper diurnal cortisol slope. This result appears to suggest a possible link between subjective perception of individual health and objective immune functioning. At the same time, consistent with the findings of Vedhara and colleagues (2006), neither anxiety nor depression were significantly associated with the diurnal cortisol patterns. This could be attributed to the use of a state measure rather than a trait measure of mood, as the latter, but not the former, has been found to affect cortisol rhythm (Polk et al., 2005). The result may also be a reflection of the relatively healthy mental profile of the present sample, in which the anxiety and depression levels were below the clinical diagnosis cut-off for the majority of the participants. In previous studies, the established relationship between a flattened cortisol pattern and psychological distress was observed only in clinically depressed groups, but not in non-depressed healthy groups (Burke et al., 2005; Hsiao et al., 2010). These results possibly reflect dysregulation of the HPA axis in response to severe and long-term exposure to psychological distress. Further studies are needed to compare the cortisol responses to psychological distress across clinical and healthy populations.

This study has a number of limitations. First, the causal direction of the associations between the diurnal cortisol patterns and the study variables remains unclear. It is plausible that bidirectional relationships exist among the variables. For instance, a flatter diurnal cortisol pattern could lead to higher negative social support and interfere with the sleep behavior of the patients, leading to shorter total sleep hours or a later time of awakening. Previous studies have examined the predictive effect of diurnal cortisol patterns on seven-year survival rates and shown that flatter diurnal cortisol patterns significantly predicted earlier mortality (Sephton et al., 2000). Future longitudinal studies could elucidate the nature of this relationship. Second, participants were requested to record the specific times at which they collected their saliva samples to monitor sampling compliance. As previous research indicates (Kudielka et al., 2003), inaccurate recording or noncompliance with the sample collection time may occur and affect the validity of the results. The self-reporting nature of the time of awakening and total sleep hours may have recall and subjective biases. Electronic devices such as electronic MEMS caps and actigraphy can provide more objective and unbiased estimates of these variables (Porter, 2012), but at a much greater cost. Third, the results could be confounded by unmeasured variables such as fatigue and emotional expression (Bower et al., 2005; Giese-Davis et al., 2006) or poorly measured variables. The internal consistency of the Yale Social Support Index, in particular the positive social support ($\alpha < 0.60$), was rather low even as a three-item scale in this study. More reliable measurement scales of social support in cancer patients would be helpful for further studies. Additionally, the self-perceived measures of perceived health, perceived stress, and sleep behavior were each based on a single item response. The absence of validated assessment scales for these variables might weaken the credibility of the results.

5 Conclusions

The current study demonstrates that earlier time of awakening, longer total sleep hours, better sleep quality, a better level of perceived health, and a lower level of negative social support are related to a favorable stress endocrine response in terms of steeper diurnal cortisol patterns in breast cancer patients. Diurnal cortisol patterns are not associated with either anxiety or depression levels. Our results indicate that collecting diurnal salivary cortisol measures facilitates a better understanding of potential correlates of the immune stress response of diurnal cortisol patterns.

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Table(s)

Table 1 Demographic characteristics and descriptive statistics of the sample.

Variables (n = 181)	Mean ± SD
Age (years)	48.3 ± 7.5
Cancer duration (months)	22.4 ± 13.3
Education level	
Secondary / Tertiary or above (%)	69.6 / 30.4
Marital status	
Single / Married / Divorced (%)	19.3 / 72.4 / 8.3
Perceived health	4.81 ± 1.16
Perceived stress	4.75 ± 1.78
Sleep quality	5.21 ± 1.38
Total sleep hours, hours	7.20 ± 1.40
Time of awakening, hours	7.25 ± 1.25
Anxiety	6.42 ± 3.64
Normal / Mild / Moderate / Severe (%)	60.7 / 26.4 / 11.2 / 1.7
Depression	4.61 ± 3.64
Normal / Mild / Moderate / Severe (%)	82.1 / 12.3 / 5.6 / 0
Positive social support	11.08 ± 1.49
Negative social support	6.94 ± 1.76
Initial cortisol level (log nmol/L)	2.05 ± 0.45
Diurnal cortisol slope (log nmol/L per hour)	-0.08 ± 0.04

Table 2 Correlations between diurnal cortisol patterns and the study variables (n = 181).

Variables	Initial level	Diurnal slope
Age	-0.19*	0.10
Cancer duration	-0.04	0.01
Perceived health	-0.02	-0.17*
Perceived stress	-0.10	0.16*
Sleep quality	-0.01	0.02
Total sleep hours	0.11	-0.16*
Time of awakening	-0.09	0.15
Anxiety	0.07	0.01
Depression	0.01	0.02
Positive social support	-0.05	-0.06
Negative social support	-0.10	0.26**

* $p < 0.05$; ** $p < 0.01$.

Table 3 The hierarchical regression analysis predicting diurnal cortisol slope (n = 181).

	$\triangle R^2$	$\triangle F$	β
Step 1	52.0%	82.9**	
Age			-0.04
Initial cortisol level			-0.73**
Step 2	6.7%	3.69**	
Perceived health			-0.19**
Perceived stress			-0.01
Sleep quality			-0.13*
Total sleep hours			-0.21**
Time of awakening			0.22**
Anxiety			-0.07
Depression			-0.04
Positive social support			-0.05
Negative social support			0.12*
Total	58.7%	20.6**	

* $p < 0.05$; ** $p < 0.01$; $\triangle R^2$: change in adjusted *R* square; $\triangle F$: change in *F* value; β: standardized regression coefficients.

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Conflict of Interest

The authors declared that there is no conflict of interest related to this study.

Contributors

Contributions of authors:

Author Rainbow T.H. Ho designed and guided the whole study.

Author Ted C.T. Fong was responsible for the data analysis and preparation of the first draft.

Author Caitlin K.P. Chan helped the literature search and wrote up the introduction.

Author Cecilia L.W. Chan helped manage the implementation of the study and data collection

All authors contributed to this study and approved the submitted manuscript.

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