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Relationships of salivary cortisol and melatonin rhythms to sleep quality, emotion, and fatigue levels in patients with newly diagnosed lung cancer

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ABSTRACT

Purpose: After being diagnosed with lung cancer, patients often experience sleep disturbance, anxiety, depression, and fatigue. These symptoms may occur because of changes in neurotransmitter secretion caused by tumors. This study investigated the correlation of cortisol and melatonin rhythms with sleep quality, anxiety, depression, and fatigue levels in patients with newly diagnosed lung cancer.
Method: We conducted a case–control study and recruited 40 patients with newly diagnosed lung cancer and 40 healthy adults.
Results: The patient group had a lower salivary melatonin level and flatter slope ($p < 0.001$ and $p < 0.001$), higher salivary cortisol level and steeper slope ($p < 0.001$ and $p < 0.001$), higher sleep disturbance level ($p = 0.004$), and higher depression level ($p < 0.001$). The multivariate linear regression analysis indicated that the cortisol slope ($p = 0.005$) and fatigue score ($p = 0.032$) predicted the sleep quality score ($p = 0.011$).
Conclusion: Overall, the patients with newly diagnosed lung cancer had poorer sleep quality, higher depression levels, lower salivary melatonin levels, higher cortisol levels, and flatter melatonin and cortisol slopes than did the controls. The fatigue level and cortisol slope significantly predicted sleep quality. Therefore, the assessment of cortisol and melatonin rhythms and levels could provide crucial information that may be beneficial for managing symptoms in patients with newly diagnosed lung cancer.

1. Introduction

Lung cancer has a high incidence and mortality rate. In 2013 in the United States, approximately 200,000 patients received a lung cancer diagnosis, and approximately 150,000 people died from lung cancer (Siegel et al., 2013). Lung cancer is also the leading cause of death among all cancers in Europe (Lung Cancer Europe, 2016). Because of substantial improvements in lung cancer treatment in recent years, the survival rate of patients with lung cancer has increased considerably. However, many patients with lung cancer experience several physiological, emotional, and cognitive problems (American Cancer Society, 2012). In particular, compared with patients who are newly diagnosed with other types of cancer, the sleep problems experienced by patients newly diagnosed with lung cancer are more severe (Park et al., 2016); these sleep disturbance may also be related to their prognosis (Velamuri, 2009). In addition to sleep problems, patients who are newly diagnosed with lung cancer often experience anxiety and depression, which can lead to feelings of fatigue (Zarogoulidis et al., 2013).

The secretion of neurotransmitters and immune substances may change because of tumor formation (Besedovsky et al., 2012). In patients with lung cancer, tumors may harm tissues and cause inflammation. Moreover, cytokines regulating innate immune responses can be activated to influence the hypothalamic–pituitary–adrenal (HPA) axis and increase cortisol levels (Schrepf et al., 2013).

Proinflammatory cytokines can be activated through an increase in anti-inflammatory cytokine production (Tian et al., 2014), which

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can reset the suprachiasmatic nucleus, change melatonin levels and rhythms (Wilking et al., 2013), affect the central nervous system, induce pathophysiological and lifestyle changes, and trigger psychological stress. All of these symptoms can result in anxiety, depression, fatigue, and sleep problems (Han et al., 2012). However, few studies have explored the effect of melatonin and cortisol rhythms on these symptoms. These changes may influence the quality of life of patients with lung cancer before they receive treatment and may even influence their cancer treatment and survival period (Reyes-Gibby et al., 2008). In addition, a high body mass index (BMI), sleepiness during the daytime, and fatigue are highly correlated with depression (Pickering et al., 2014), while sex and age have been reported to affect sleep quality, sleep duration, HPA axis regulation, and melatonin and cortisol levels (Cajochen et al., 2013).

In the present study, we examined the cortisol and melatonin rhythms of patients with newly diagnosed lung cancer, as well as the changes in their cancer symptoms. In addition, we investigated the correlation of their cortisol and melatonin rhythms with their sleep quality and anxiety, depression, and fatigue levels.

2. Materials and methods

2.1. Study design and sample

Data for this study were collected between August 1, 2013 and June 31, 2015. A purposive sampling approach was adopted, and the research targets were inpatients with newly diagnosed lung cancer in a local hospital in Northern Taiwan. We included patients whose diagnosis was based on their first tissue biopsy; also included were those who had not received lung-cancer-related treatment and were able to communicate. We excluded patients (1) who were shift workers before hospitalization because shift work can negatively impact the circadian clock, (2) who were too weak to complete a questionnaire interview or submit a salivary sample, or (3) who had a mental disorder.

Using a matched-pair design, we paired 40 healthy adults with no history of cancer (control group) with the patients with lung cancer according to their age, BMI, and sex.

2.2. Measures

We used the Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), Brief Fatigue Inventory (BFI), and a questionnaire on demographics and disease characteristics to collect patient data. In addition, we performed a radioimmunoassay (RIA) to measure salivary cortisol and melatonin levels.

The PSQI was developed by Buysse et al. (1989). It contains 19 self-assessment items for assessing the severity of sleep problems, with seven dimensions for assessing sleep quality (i.e., subjective sleep quality, time required to fall asleep, sleep duration, sleep efficiency, sleep disturbance, usage of sleeping pills, and daytime dysfunction). The total score ranges from 0 to 21 points, with higher scores indicating poorer sleep quality. A total score of >8 points indicates that a person has severe sleep problems (Vargas et al., 2010). The Cronbach's α for the PSQI is 0.83 and for the Taiwanese version of the PSQI is 0.79 (Tzeng et al., 2012).

The HADS was developed by Zigmond and Snaith (1983). It is a 4-point scale consisting of anxiety and depression subscales, both of which have total score ranges from 0 to 21 points, with higher scores indicating higher levels of anxiety or depression. The Cronbach's α for the anxiety and depression subscales of the HADS is 0.93 and 0.90, respectively. Zigmond and Snaith (1983) reported that a total score of <8 points on the anxiety or depression subscale indicates that a person does not have an anxiety or depression problem; 8–10 points indicates a suspected case of anxiety or depression; and ≥11 points indicates a definite case of anxiety or depression. According to another study involving patients with cancer, the Cronbach's α for the anxiety and depression subscales of the Taiwanese version of the HADS is 0.82 and 0.77, respectively (Chen et al., 1999).

The BFI was developed by Mendoza et al. (1999). It comprises a 10-point Likert scale, with scores of 0, 0–3, 4–7, and 7–10 indicating no fatigue, mild fatigue, moderate fatigue, and severe fatigue, respectively. The Cronbach's α for both the original English and Taiwanese versions of the BFI was 0.96 (Lin et al., 2006; Mendoza et al., 1999).

Although cortisol and melatonin levels are conventionally measured in blood samples, blood sampling is invasive; instead, we performed a RIA to measure salivary cortisol and melatonin levels because saliva has been identified as an appropriate substitute for blood for this procedure (Waller et al., 2016). Sample contamination with food residue or fluid was avoided by asking the patients' to rinse their mouths, and then waiting at least 15 min before collecting the samples. Saliva samples were collected from all participants through expectoration into a sterile container over a 10-min period, after which they were immediately stored in a refrigerator at −20 °C. The melatonin and cortisol levels were subsequently measured using commercially available RIA kits (Taiwan Life Support Systems, Inc., Taiwan).

Before the RIA analysis, the samples were centrifuged to remove particulate matter. Then, we established a melatonin and cortisol analysis system, referring to Wilson and Miles (1978). This procedure was repeated five times for each sample to estimate the precision of the system. The intraassay and interassay coefficients of variation (CVs) for melatonin RIAs were 2.0% and 11.8%, respectively, and the detection limit was 1.4 μg/mL. For cortisol, the intraassay and interassay CVs were 5.0% and 14.2%, respectively, and the detection limit was 0.9 μg/mL.

Because changes in cortisol and melatonin levels over the course of a day follow a skewed exponential curve, each sample was log transformed to obtain the daily cortisol and melatonin slopes (Sephton et al., 2013), which were calculated at three consecutive time points using RIA to determine the rate of time change (μg/dL). The unstandardized beta (i.e., the slope of a regression line) represents the corrected rhythms of salivary cortisol and melatonin in a day (Posadas et al., 2012). Notably, a flatter slope indicates a smaller change in cortisol and melatonin levels in a day, compared with steeper slopes (Bower et al., 2005).

2.3. Procedure

This study is part of a large-scale investigation, and the results of that survey have previously been published by Chang and Lin (2017). Approval for this study was obtained by the Institutional Review Board of Taipei Medical University after confirmation that patient care would be unaffected and that the collected data would be kept confidential and used only for academic research (approval number: 201205045). After explaining the research purposes and procedures to the participants and obtaining written consent, we interviewed all of the participants, invited them to complete the questionnaire, and collected their saliva. Saliva samples were collected three times daily (9 a.m., 2 p.m., and 9 p.m.), and at least 3 mL of saliva was collected each time.

2.4. Data analysis

The sample size was calculated using the G-power 3.1 computer program. A sample size of approximately 40 participants per group provided 80% power to detect effect sizes of 0.65, assuming