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Diurnal cortisol rhythm as a predictor of lung cancer survival

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ABSTRACT

Background: Poorly coordinated diurnal cortisol and circadian rest-activity rhythms predict earlier mortality in metastatic breast and colorectal cancer, respectively. We examined the prognostic value of the diurnal cortisol rhythm in lung cancer.
Methods: Lung cancer patients (n = 62, 34 female) were within 5 years of diagnosis and had primarily non small-cell lung cancer, with disease stage ranging from early to advanced. Saliva collected over two days allowed calculation of the diurnal cortisol slope and the cortisol awakening response (CAR). Lymphocyte numbers and subsets were measured by flow cytometry. Survival data were obtained for 57 patients. Cox Proportional Hazards analyses were used to test the prognostic value of the diurnal cortisol rhythm on survival calculated both from study entry and from initial diagnosis.
Results: The diurnal cortisol slope predicted subsequent survival over three years. Early mortality occurred among patients with relatively "flat" rhythms indicating lack of normal diurnal variation (Cox Proportional Hazards p = .009). Cortisol slope also predicted survival time from initial diagnosis (p = .012). Flattened profiles were linked with male gender (t = 2.04, df = 59, p = .046) and low total and cytotoxic T cell lymphocyte counts (r = −.39 and −.30, p = .004 and .035, respectively). After adjustment for possible confounding factors, diurnal slope remained a significant, independent predictor of survival.
Conclusions: Flattening of the diurnal cortisol rhythm predicts early lung cancer death. Data contribute to growing evidence that circadian disruption accelerates tumor progression.

1. Introduction

Among patients with advancing cancer, dysregulation of circadian physiology is often conspicuous and extensive. Disrupted circadian cycles are evident in endocrine, immune, metabolic, and cellular systems (Mazzoccoli et al., 2010; Hrushesky, 1985; Mormont et al., 2000). Dysregulation of circadian hypothalamic–pituitary-adrenal (HPA) rhythms has been linked specifically with advancing cancer and accelerated tumor growth rates (Mormont and Lévi, 1997; Touitou et al., 1995; Hrushesky et al., 1998; Sephton and Spiegel 2003; Eismann et al., 2010).

Human cortisol peaks 30–45 min after first awakening and drops to a nadir during sleep (Clow et al., 2010). From 30% to 70% of patients with advanced cancer display idiosyncratic rhythm abnormalities including unsynchronized peaks and troughs, consistently high or low levels and erratic circadian fluctuations. Viewed in aggregate, the diurnal cortisol profiles of advanced cancer patients often appear "flattened" (Mormont and Lévi, 1997; Sephton et al., 2000). The diurnal cortisol slope captures multiple types of rhythm deviation and is measurable in saliva (Turner-Cobb et al., 2000; Kraemer et al., 2006; Hellhammer et al., 2009). Elevated diurnal cortisol slope predicts early metastatic breast cancer mortality, independent of other prognostic factors (Sephton et al., 2000). Flattened slopes were associated with low natural killer cell counts and cytotoxicity, sleep disruption, and marital dissolution; none of which explained the cortisol-survival relationship (Sephton et al., 2000). Circadian rest/activity rhythms are also irregular in patients with advancing cancer (Mormont and Lévi,

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1997), and are measurable by wrist-worn actigraphy (Ancoli-Israel et al., 2003). Poor circadian coordination of rest/activity rhythm predicts early mortality over four years in metastatic colorectal cancer patients (Mormont et al., 2000), a finding recently replicated in large multi-site study (Innominato et al., 2009). Among cancer patients, circadian disruption may be a preexisting cause, a correlate of distress and physiological burden, a direct effect of cancer on the brain, and/or a mediator of psychosocial effects on tumor progression (Sephton and Spiegel 2003; Eismann et al., 2010; Chida et al., 2008). A few clinical prospective studies have provided a fascinating demonstration of prognostic value for circadian rhythms in human cancers. These require replication and testing in other cancer types.

As compared with the comorbidities of other cancers, lung cancer-related distress, depression, fatigue, and sleep disruption are extreme (Parker et al., 2008). All these symptoms have been linked with circadian disruption in lung cancer, suggesting that this disease may convey uniquely high circadian disruption-mediated risk (Hrushesky et al., 2009). Lung cancer patients demonstrate markedly poor integration of circadian neuroendocrine-immune function evidenced by high evening cortisol, suppressed melatonin, and changes in the circadian patterns of distribution of peripheral lymphocytes (Mazzoccoli et al., 2003, 2005). Non-small cell lung cancer generally has a better prognosis than small-cell disease; however, five-year survival rates for both are poor (49–75% for early stage, and < 1% for advanced disease).

We examined the prognostic value of the diurnal salivary cortisol rhythm in lung cancer. Secondary analyses explored associations with potential explanatory and/or confounding factors including traditional prognostic indicators, depression, fatigue, and sleep quality. Additional biological factors were chosen based on their relevance in cancer studies of the effects of the stress, sleep, and circadian rhythms (Cole and Sood, 2012; Antoni et al., 2006; Eismann et al., 2010; Mazzoccoli et al., 2003, 2005). These included serum cortisol, sympathetic activation measured by overnight urinary catecholamines, lymphocyte counts and lymphocyte subsets.

2. Methods

2.1. Subjects and procedure

Eligible patients were at least 18 years old and had been diagnosed with Stage I-IV non-small cell lung cancer or with limited to extensive small cell lung cancer during the last five years. Exclusions were made for history of psychiatric hospitalization, alcohol abuse or dependence within the past two months, use of prednisone or concurrent medical conditions likely to influence short-term (six month) survival. A total of 223 patients were referred or approached for this study, 145 (65%) were eligible and of those eligible, 62 (42.7%) patients were enrolled after informed consent. Physician's diagnosis of lung cancer was confirmed. Reasons reported for refusal included feeling too ill, being too busy, or lack of interest.

Participants were scheduled for a one hour interview with a research assistant during which they provided informed consent, demographic, and medical information including smoking history and performance status. A blood sample was drawn and they were given instructions and materials for home-based saliva collection as well as self-report questionnaires. Home-based questionnaires assessed depressive symptoms, fatigue, and sleep difficulties. Eight saliva samples were collected over two consecutive days for measurement of diurnal salivary cortisol profiles. Fifteen-hour overnight urine collection provided estimates of catecholamine hormone release. Blood samples were drawn for flow cytometry. Participants were provided with $100 compensation when home-based data collection materials were returned. Medical data, including cancer stage at diagnosis, was collected both from medical chart review and from the Kentucky Cancer Registry.

2.1.1. Sample characteristics

Study participants ranged in age from 41 to 84 years with a mean age of 64 years (SD = 9.12). Thirty-four (55%) of those enrolled were female and 58 (94%) had non-small cell lung cancer. Eighty-five percent of the sample was Caucasian and 55% had twelve years of education or less. Forty-six percent of the sample was married and 25% were employed. Participants were a mean age of 62 years at the time of lung cancer diagnoses (SD = 8.9). The median time since lung cancer diagnosis was 21 months, with a range of 1 month to 5 years. Six participants (10.7%) scored $\geqslant$ 19 on the BDI, which is consistent with clinically significant depressive symptoms. Table 1 displays the frequency and percentage of participants according to disease status. The sample included similar proportions of early (stage 1, n = 29) and more advanced (stage 2–4, n = 33) disease. Table 2 presents descriptive information for psychological and physiological variables.

Approximately two years after enrollment closed, data tracking for the study was closed and the investigators contacted the Kentucky Cancer Registry and consulted medical records for survival data. Registry and record review yielded documentation of death for 23 patients. Among patients who had died, median time from study entry to death was 317 days (range: 34 days to 2.7 years). Median time from diagnosis to death was 2.7 years (range: 7 months to 6 years). Causes of death included malignant neoplasms of the bronchus or lung (n = 11, 47.8%), chronic obstructive pulmonary disease (n = 1, 4.3%), and acute myocardial infarction (n = 1, 4.3%). Information on cause of death was unavailable for nine of those who died (39.1%). Among the entire sample, median follow up time from study entry was 2.2 years (range 34 days to 3.4 years). Median follow up from the date of lung cancer diagnosis was 4 years (range 7 months to 8.9 years).

2.2. Physiological measures

2.2.1. Diurnal salivary cortisol

At the initial interview subjects received a saliva collection kit and were given instructions for collection. Kits included 8 pre-labeled collection tubes, or "salivette" devices (Walter Sarstedt Inc., Newton, North Carolina) with instructions on how and when to collect saliva samples and a questionnaire covering factors likely to introduce variation in cortisol levels (e.g., stressors, exercise). Subjects were instructed to sample saliva on two consecutive days. Saliva was collected at waking, 45 min after waking (45+), 1600, and 2100 h on each day. This enabled measurement of the diurnal cortisol slope, diurnal mean levels, the cortisol response to awakening (CAR), diurnal mean, area under the curve (AUC), and waking and evening levels. Subjects stored cortisol kits in their refrigerator until they were returned. Samples were centrifuged, aliquoted, and

Table 1
Numbers of participants with each cancer type and stage.

	Frequency	Percent (%)
Non-small cell lung cancer	58	94
Stage I	27	44
II	7	11
III	17	27
IV	7	11
Small cell lung cancer[a]	4	6

[a] Among the four patients with small-cell lung cancer, two had limited, and two had extensive stage cancer.