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Circadian disruption and biomarkers of tumor progression in breast cancer patients awaiting surgery

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ABSTRACT

Psychological distress, which can begin with cancer diagnosis and continue with treatment, is linked with circadian and endocrine disruption. In turn, circadian/endocrine factors are potent modulators of cancer progression. We hypothesized that circadian rest–activity rhythm disruption, distress, and diurnal cortisol rhythms would be associated with biomarkers of tumor progression in the peripheral blood of women awaiting breast cancer surgery. Breast cancer patients ($n = 43$) provided actigraphic data on rest–activity rhythm, cancer-specific distress (IES, POMS), saliva samples for assessment of diurnal cortisol rhythm, cortisol awakening response (CAR), and diurnal mean. Ten potential markers of tumor progression were quantified in serum samples and grouped by exploratory factor analysis. Analyses yielded three factors, which appear to include biomarkers reflecting different aspects of tumor progression. Elevated factor scores indicate both high levels and strong clustering among serum signals. Factor 1 included VEGF, MMP-9, and TGF-β; suggesting tumor invasion/immunosuppression. Factor 2 included IL-1β, TNF-α, IL-6R, MCP-1; suggesting inflammation/chemotaxis. Factor 3 included IL-6, IL-12, IFN-γ; suggesting inflammation/T_H1-type immunity. Hierarchical regressions adjusting age, stage and socioeconomic status examined associations of circadian, distress, and endocrine variables with these three factor scores. Patients with poor circadian coordination as measured by rest–activity rhythms had higher Factor 1 scores ($R^2 = .160$, $p = .038$). Patients with elevated CAR also had higher Factor 1 scores ($R^2 = .293$, $p = .020$). These relationships appeared to be driven largely by VEGF concentrations. Distress was not related to tumor-relevant biomarkers, and no other significant relationships emerged. Women with strong circadian activity rhythms showed less evidence of tumor promotion and/or progression as indicated by peripheral blood biomarkers. The study was not equipped to discern the cause of these associations. Circadian/endocrine aberrations may be a manifestation of systemic effects of aggressive tumors. Alternatively, these results raise the possibility that, among patients with active breast tumors, disruption of circadian activity rhythms and elevated CAR may facilitate tumor promotion and progression.

Abbreviations: CAR, cortisol awakening response; EFA, exploratory factor analysis; ER, estrogen receptor; HER2/neu, human epidermal growth factor 2; HPA, hypothalamic–pituitary–adrenal; IES, Impact of Events Scale; IFN, interferon; IL, interleukin; MCP, monocyte chemotactic protein; MEMS, Medication Event Monitoring System; MMP, matrix metallopeptidase; POMS, Profile of Mood States; PR, progesterone receptor; SCN, suprachiasmatic nucleus; TGF, transforming growth factor; T_H, T-helper; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; WASO, wake after sleep onset.

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1. Introduction

Disruption of circadian rhythms can increase breast cancer risk and hasten disease progression. Compelling new animal, cell, and molecular research is revealing the biology that links circadian disruption with tumor incidence and growth (Escobar et al., 2012, 2010; Fu and Lee, 2003). An accumulation of evidence, including convincing epidemiologic data, led the World Health Organization to conclude in 2007 that shift work is probably carcinogenic (Class 2A; Straif et al., 2007). In turn, animal research has shown conclusively that circadian disruption accelerates tumor progression (Fu and Lee, 2003). Several independent clinical studies have demonstrated that circadian rhythms have prognostic value with regard to mortality rates among patients with breast cancer (Sephton et al., 2000), colorectal cancer (Mormont et al., 2000; Innominato et al., 2009; Lévi et al., 2014), renal cell carcinoma (Cohen et al., 2012), and lung cancer (Sephton et al., 2013). Circadian disruption in cancer patients may have multiple etiologies: a portion of the increased variance in rhythms may be attributed to physiological effects of the tumor (Mormont and Levi, 1997). However, psychological distress – a symptom commonly experienced by cancer patients – can also markedly disrupt sleep and circadian rhythms (Sephton and Spiegel, 2003; Van Reeth et al., 2000). Studies suggest that distress and poor sleep may have serious repercussions for breast cancer patients (Eismann et al., 2010; Palesh et al., 2007). Psychological distress appears to increase breast cancer risk and shorten survival time (Chida et al., 2008; Spiegel and Giese-Davis, 2003), and poor sleep efficiency is prognostic for early breast cancer mortality (Palesh et al., 2014). The effects of stress and circadian disruption on cancer progression may be interconnected, and may be mediated by endocrine and immune factors (Antoni et al., 2006; Eismann et al., 2010).

The central circadian clock in the hypothalamic suprachiasmatic nucleus (SCN) generates behavioral rhythms and coordinates circadian fluctuations in peripheral cell growth, protein synthetic machinery, activation/secretion, and apoptosis (Mohawk et al., 2012; Lowrey and Takahashi, 2011). Because each of these activities is relevant to tumor growth, factors that entrain or disrupt SCN rhythms have potential to affect cancer progression (Filipski et al., 2002). The means by which the SCN coordinates peripheral cell rhythms is under investigation, but a strong candidate mechanism is via fluctuation in hypothalamic–pituitary–adrenal (HPA) axis activity. Other signal cascades may arise from circadian rhythms in sympathetic nervous activity and melatonin release.

Circadian disruption may amplify the detrimental, cancer-promoting aspects of certain psychoneuroendocrine and immune pathways. Poorly coordinated behavioral and endocrine circadian rhythms increase daily tumor growth rates (Savvidis and Koutsilieris, 2012) and impact anti-tumor immunity (Cermakian et al., 2013; Eismann et al., 2010; Hanahan and Weinberg, 2011). Our group has developed a theoretical model for use in the cancer context, positing pathways by which circadian, psychological distress, and endocrine factors influence one another and may in turn affect tumor progression (Sephton and Spiegel, 2003; Eismann et al., 2010). This theory is based upon data from a wide range of research areas, and suggests three pathways by which cancer-relevant immunity may be affected via circadian rest–activity rhythms, psychosocial factors, and endocrine activation. Each of these pathways has documented influence on aspects of immunity relevant to tumor defense (Fig. 1; Eismann et al., 2010).

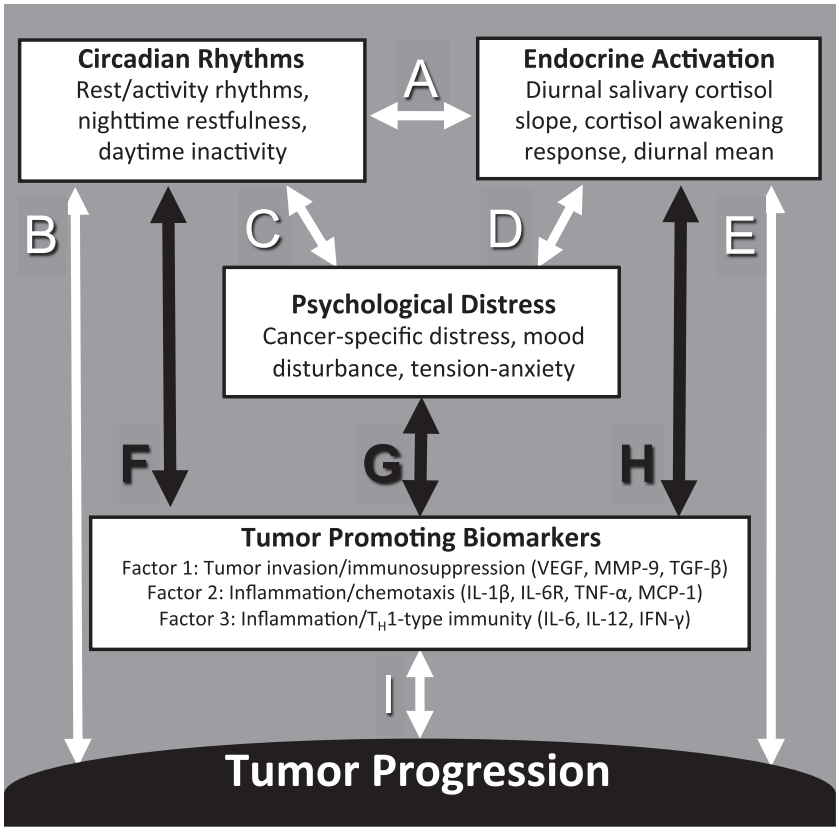

Fig. 1. Hypotheses were based on a model that posits associations of circadian rhythms (Arrow F), distress (Arrow G) and endocrine (Arrow H) function with tumor promoting serum biomarkers (black arrows; modified from Eismann et al., 2010). Tests of Arrows A, C, and D were already conducted within the current sample and reported in Dedert et al., 2012.

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