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Sympathetic and parasympathetic activity in cancer-related fatigue: More evidence for a physiological substrate in cancer survivors

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Summary Fatigue is a notable clinical problem in cancer survivors, and understanding its pathophysiology is important. This study evaluated relationships between fatigue and both sympathetic and parasympathetic nervous system activity in breast cancer survivors. Norepinephrine and heart rate variability (HRV) were evaluated at rest, as well as during and after a standardized laboratory speech and mental arithmetic stressor. The participants, 109 women who had completed treatment for stage 0—IIIA breast cancer within the past two years, were at least two months post surgery, radiation or chemotherapy, whichever occurred last. Women who reported more fatigue had significantly higher norepinephrine and lower HRV before and after the stressor than their less fatigued counterparts. Fatigue was not related to treatment or disease variables including treatment type, cancer stage, time since diagnosis, and time since treatment.

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Importantly, the relationship between HRV and cancer-related fatigue was sizeable. Based on research that has demonstrated characteristic age-related HRV decrements, our findings suggest a 20-year difference between fatigued and non-fatigued cancer survivors, raising the possibility that fatigue may signify accelerated aging. Furthermore, lower HRV and elevated norepinephrine have been associated with a number of adverse health outcomes; accordingly, fatigue may also signal the need for increased vigilance to other health threats.

Fatigue is the most common problem among long-term cancer survivors (Bower et al., 2006a), as well as the symptom that interferes most with their daily life (Cleeland et al., 2003; Ganz et al., 2002). Fatigue adversely affects overall quality of life, as well as many daily activities including mood, the sleep-wake cycle, and personal relationships (Bower et al., 2002; Collado-Hidalgo et al., 2006; Lawrence et al., 2004). Fatigue is a normal and expected response to chemotherapy and radiation (Smets et al., 1993). However, fatigue may persist many years beyond cancer treatment in a substantial number of cancer survivors (Prue et al., 2006). For example, in a longitudinal study of 763 breast cancer survivors, 34% were fatigued 5—10 years after diagnosis, compared to 35% 1—5 years after diagnosis; 21% of the women were fatigued at both assessments, suggesting more severe or persistent fatigue among a significant proportion of cancer survivors (Bower et al., 2006b).

In general, neither disease type nor treatment variables have demonstrated reliable associations with fatigue in cancer survivors. Specifically, type of cancer, disease stage at diagnosis, tumor size, number of nodes involved, presence and site of metastases, time since diagnosis, the type or extent of cancer treatment (including chemotherapy regime, dose, and cycles, and type of radiation), length of treatment, and time since treatment completion do not consistently predict the occurrence or severity of fatigue among survivors (Prue et al., 2006).

Autonomic nervous system functioning may play an important role in cancer-related fatigue. Higher parasympathetic activity facilitates energy conservation, while prolonged heightened sympathetic activity puts undue energy demands on the body (Thayer and Sternberg, 2006). The combination of sympathetic overactivity and parasympathetic underactivity has been linked with a number of adverse health outcomes (Mark, 1996; Thayer and Lane, 2007). In non-cancer populations, sympathetic overactivity and parasympathetic underactivity have been linked to fatigue (Segerstrom and Nes, 2007; Tak et al., 2009). Both higher sympathetic activity and lower parasympathetic activity also facilitate activation of the proinflammatory cytokine network; fatigued breast cancer survivors have higher levels of circulating proinflammatory cytokines compared to their nonfatigued counterparts (Bower et al., 2007). Accordingly, sympathetic overactivity and parasympathetic underactivity may be important biomarkers of cancer-related fatigue and may also have an etiological role.

The variability in heart rate that is attributable to respiration is directly mediated by the vagus nerve and serves as a marker for parasympathetic activity (often referred to as vagal tone) (Berntson et al., 1993). Healthy adults with lower HRV had more fatigue when performing cognitively demanding tasks than those with higher HRV (Segerstrom and Nes, 2007). In addition, lower HRV was associated with driver-related fatigue (Egelund, 1982), as well as greater fatigue after prolonged exercise (Hautala et al., 2001). Low vagal tone is also associated with an exaggerated proinflammatory profile due to the cholinergic anti-inflammatory pathways of the parasympathetic nervous system (Tracey, 2009).

Norepinephrine is the principal sympathetic nervous system neurotransmitter. Adolescents reporting chronic fatigue had higher levels of norepinephrine than controls (Wyller et al., 2008). Similarly, male shift workers who had higher levels of norepinephrine reported more fatigue than those who reported less fatigue (Park et al., 2006). Norepinephrine induces transcription factor nuclear factor κB (NF-κB), an intracellular signaling molecule that regulates proinflammatory cytokine gene expression (Straub and Härle, 2005).

In healthy individuals, increased sympathetic activity and decreased parasympathetic activity represent adaptive fight-or-flight responses to stressors, followed by heightened parasympathetic and lowered sympathetic activity post-stressor (Porges, 1995). It is possible that fatigued individuals do not show these same fluctuations, making it difficult for them to meet and recover from stress-related metabolic demands.

Accordingly, the current study examined relationships between fatigue and autonomic activity at rest, as well as in response to a standardized laboratory stressor in breast cancer survivors. Our central hypothesis was that more fatigued women would have higher norepinephrine and lower HRV than less fatigued women. We also addressed the question of whether changes in HRV and norepinephrine over time differed depending on women's level of fatigue.

1. Method

1.1. Participants

The study data were drawn from the baseline sample of a clinical trial addressing the potential benefits of yoga for breast cancer survivors, and participants were recruited through breast cancer clinics and media announcements. Women could not participate in our study if they were currently practicing yoga, took yoga classes within the last 6 months, or practiced yoga for more than 3 months over their lifetime. Eligible women had completed treatment for stage 0—IIIA breast cancer within the past two years (except for tamoxifen/aromatase inhibitors) and were at least two months post surgery, radiation, or chemotherapy (whichever occurred last). Screening exclusions included a prior history of breast or any other cancer except basal or squamous cell, more than 5 h a week of vigorous physical exercise, a body mass index (BMI) of 40 or greater, diabetes, chronic obstructive