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Stress management reduces intraindividual cortisol variability, while not impacting other measures of cortisol rhythm, in a group of women at risk for breast cancer☆,☆☆,★

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ABSTRACT

Objective: The stress hormone cortisol exhibits a diurnal rhythm throughout the day, as well as within person variability. Recent statistical approaches allow for the estimation of intraindividual cortisol variability ("ICV") and a greater ICV has been observed in some mood disorders (major depression, remitted bipolar disorder); however, ICV has not been examined following stress management. In this secondary analyses of an efficacious randomized clinical trial, we examine how ICV may change after cognitive behavioral stress management (CBSM) among healthy stressed women at risk for breast cancer. Second, we concurrently compare other calculations of cortisol that may change following CBSM.

Methods: Multilevel modeling (MLM) was applied to estimate ICV and to test for a group by time interaction from baseline, post-intervention, to 1 month following CBSM. Forty-four women were randomized to the CBSM; 47 to the comparison group; mean age of the entire group was 44.2 ($SD = 10.27$).

Results: After controlling for relevant covariates, a significant time by group interaction emerged (β estimate = -.070; $p < .05$), such that CBSM participants demonstrated a lower ICV following CBSM compared to the comparison group. The interaction for cortisol slope and cortisol output (area under the curve) approached significance (β estimates = -.10 and -.062, respectively; p's < .08), while other cortisol outcomes tested were not significantly changed following CBSM.

Conclusion: ICV may represent a novel index of cortisol dysregulation that is impacted by CBSM and may represent a more malleable within-person calculation than other, widely applied cortisol outcomes. Future research should examine these relationships in larger samples, and examine ICV and health outcomes.

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Introduction

The stress hormone cortisol is a potent endogenous anti-inflammatory glucocorticoid produced by the adrenal cortex. Cortisol exhibits a diurnal rhythm throughout the day, with an initial rise in the morning (referred to as the "cortisol awakening response" or CAR; [39]) and an anticipated decline throughout the day. Given cortisol's role in the immune system [37], in addition to tumor biology [16,36] there is a wealth of interest in the extant literature examining relations among cortisol rhythm in cancer populations (for review see [6,13]). For example, a flatter cortisol slope (corresponding a less pronounced decline in cortisol throughout the day), maintains predictive value of decreased survival in breast cancer [33] and, most recently, in lung cancer [32]. Further, a flatter cortisol slope (thought to represent cortisol dysregulation throughout the day) is related to clinical outcomes such as fatigue in breast cancer patients [9]. However, less is known about cortisol rhythms among healthy populations, who may be at risk for cancer.

Given that cortisol is released during times of stress, there is a robust body of literature examining changes in cortisol rhythm across those experiencing disturbances in mood. For example, higher evening cortisol, resulting in a flatter cortisol slope throughout the day, has been observed in those suffering from chronic stress [1], patients with psychotic major depression [7], and depressed patients with coronary artery disease [8]. Indeed, meta-analysis confirms that depressed individuals demonstrate increased morning and evening cortisol levels

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[20]. In cancer populations, specifically, — a group which may be at risk for developing psychological distress [26] – cortisol rhythm is related to social isolation in breast cancer patients, such that greater cortisol output is related to those experiencing the least amount of social support [35]. In ovarian cancer, a greater difference between morning and evening cortisol values is significantly related to greater functional disability, fatigue and vegetative depression [38]. Conversely, breast cancer patients who meet criteria for PTSD or prior major depressive disorder exhibit decreased plasma cortisol [22]. Collectively, while cortisol rhythm is notably altered within psychiatric disturbances, it remains difficult to compare across studies given the many different calculations applied.

An emerging cortisol calculation that is related to a number of psychiatric conditions, yet has received less attention, is estimating the degree to which an individual's cortisol output may be erratic on a given day. Referred to as intraindividual cortisol variability (ICV, [31]), this variability estimate is similar to what has been termed beep-level variance [27], cortisol pulsatility [41] and approximate entropy in cortisol production [29]. In clinical populations, higher cortisol ICV is seen among those with remitted bipolar disorder [17] and major depressive disorder [27,29] suggesting that a more erratic cortisol rhythm is related to psychiatric disorder. These relationships were recently extended to a group of women undergoing surgery for suspected endometrial cancer, where greater depressive symptoms were related to a more erratic cortisol output [31]. It remains less clear how such relationships extend to healthy, stressed populations or how ICV is impacted by stress management intervention.

If ICV is associated with increased stress and depressive symptoms, then interventions designed to address these symptoms should improve ICV. A number of clinical trials have applied stress management in cancer populations in an effort to potentially attenuate cortisol production. For example, participation in cognitive behavioral stress management in cancer populations resulted in a decrease in afternoon cortisol levels [4,28] as well as total 24 hour urinary cortisol output [3]. These changes also parallel changes in participants' perceived ability to relax [28]. Similarly, in breast cancer patients, supportive expressive therapy and mindfulness based cancer recovery both resulted in a more normalized cortisol slope (e.g., greater decline throughout the day) compared to controls [11]. Similar to the cross-sectional studies of mood disturbances and cortisol rhythm reviewed above, this literature is limited by the number of cortisol calculations applied, leaving unanswered questions such as which calculations are most sensitive to change and which are most relevant to health outcomes? It is therefore germane to examine multiple cortisol calculations including ICV, concurrently following participation in a stress management intervention.

Given these limitations in the current literature, the present study aimed to examine changes in cortisol rhythm among healthy stressed women at risk for breast cancer due to family history. Women were randomized to a cognitive behavioral stress management (CBSM) intervention or to a wait-list control condition. This 10-week intervention was shown to reduce perceived stress and depressive symptoms and, further, those that practiced relaxation more frequently demonstrated the greatest reductions in these parameters [25]. For the current secondary analysis, it was hypothesized that women randomized to the CBSM condition would demonstrate lower ICV immediately after the intervention and during the immediate follow-up period (1 month post-intervention). No specific hypotheses were put forth for other cortisol outcomes, given the heterogeneity of cortisol outcomes across the relevant literature reviewed above.

Methods

Study design

The present study is a secondary data analysis of a larger randomized controlled trial of the effects of CBSM on antibody response to vaccine among stressed women at risk for breast cancer. Eligible participants completed a baseline (T1) questionnaire and then were randomized to either CBSM or a wait-list comparison group. Outcome variables were collected at baseline (T1), immediately post-intervention or 10-week waiting period (T2), and one month (T3). While data was collected at 6 months (T4), and 7 months (T5) post-intervention, the present study examines data from only the T1, T2 and T3 time points consistent with hypotheses regarding potential effects of the intervention. Comparison group women were offered the full CBSM intervention after completing questionnaires at all time points. Participant flow through each stage of the study is illustrated in Fig. 1.

Participants

Participants were recruited from the greater Seattle area and were eligible if they were between the ages of 18–60, reported having any family history of breast cancer, had a healthy immune system, and elevated levels of distress. Participants were screened for psychological distress and women reported distress at a ½ standard deviation above the population mean for at least one of the 4-item instruments given (Perceived Stress Scale and the Breast Cancer Worry Scale). Exclusion criteria included prior diagnosis of cancer or autoimmune disease, current major depressive episode, (or other unmanaged mood disorder), history of psychotic disorder, smoking or substance dependence, consuming more than 10 drinks of alcohol a week, previous Hepatitis A diagnosis or Hepatitis A vaccination. All study procedures were approved by the Fred Hutchinson Center Institutional Review Board. Informed consent was obtained in writing from all participants before study entry.

Intervention

Women randomized to the intervention condition were asked to attend 10, 2-hour, group CBSM sessions (4–10 women) on a weekly basis. The CBSM intervention was based on an existing intervention for women with early stage breast cancer [5]. Elements of the intervention were similar to the existing CBSM intervention and included education on awareness of the effects of stress, cognitive reframing, cognitive coping skills training, assertiveness training, anger management, and various relaxation techniques (e.g., including progressive muscle relaxation, guided imagery, and mindfulness meditation). All CBSM sessions were led by female licensed clinical psychologists, master-level social workers, postdoctoral fellows, or psychology interns. Adherence to the intervention protocol was ensured by the study author (BAM) reviewing recorded audio taped according to a module-specific Intervention Integrity Checklist.

Cortisol

Salivary cortisol was collected across 5 time points throughout the day (at awakening, 30 min following awakening, 11 AM, 5 PM and at bedtime, hereafter referred to as “evening”) for 2 consecutive days prior to the intervention, immediately following the 10 week intervention, and at 1 month follow-up.

Analytic Plan

The primary research question in the present analyses was whether the cognitive behavioral stress management intervention was related to changes in ICV from T1 to T3. However, as a host of calculations exist in the extant literature of cortisol rhythm and overall output [14], we included 5 cortisol output calculations in addition to ICV (described below) which are commonly reported. Specifically, given their previously reported relationship with psychosocial factors in cancer populations, we chose to calculate the following: 1) cortisol slope [33], 2) evening cortisol [23], 3) morning cortisol [22], 4) the cortisol awakening response [24] and 5) total cortisol area under the curve