Title

Cortisol Awakening Response as a Prospective Risk Factor for Depressive Symptoms in Women After Treatment for Breast Cancer

Journal

Psychosomatic Medicine, 79(7)

ISSN

0033-3174

Authors

Kuhlman, Kate Ryan
Irwin, Michael R
Ganz, Patricia A
et al.

Publication Date

2017-09-01

DOI

10.1097/psy.0000000000000499

Peer reviewed

HHS Public Access

Author manuscript

Psychosom Med. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Psychosom Med. 2017 September ; 79(7): 763–769. doi:10.1097/PSY.0000000000000499.

Cortisol awakening response as a prospective risk factor for depressive symptoms in women after treatment for breast cancer

Kate Ryan Kuhlman, Ph.D.[1,2], **Michael R. Irwin, M.D.**[2,5], **Patricia A. Ganz, M.D.**[3,5], **Catherine M. Crespi, Ph.D.**[3,4], **Laura Petersen, M.S.**[3], **Arash Asher, M.D.**[6], and **Julienne E. Bower, Ph.D.**[1,2,3]

[1]Department of Psychology, University of California Los Angeles, Los Angeles, California

[2]Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, California

[3]Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, California

[4]Department of Biostatistics, Fielding School of Public Health, University of California Los Angeles, Los Angeles, California

[5]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California

[6]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California

Abstract

Objective—To investigate hypothalamic-pituitary-adrenal axis (HPA-axis) functioning as a neurobiological risk factor for depressive symptoms in an ongoing longitudinal, observational study of women undergoing treatment and recovery from breast cancer. Many women with breast cancer experience depressive symptoms that interfere with their treatment, recovery, and quality of life. Psychosocial risk factors for depression among cancer patients and survivors have been identified, yet neurobiological risk factors in this population remain largely unexamined.

Methods—Women recently diagnosed with early-stage breast cancer (n = 135) were enrolled before starting neoadjuvant/adjuvant treatment (radiation, chemotherapy, endocrine therapy). At baseline, participants collected saliva samples to measure diurnal HPA-axis functioning for 3 days: at waking, 30 minutes post-waking, 8 hours post-waking, and bedtime. Participants also completed a standardized measure of depressive symptoms (Center for Epidemiological Studies-Depression Scale; CES-D) at baseline and 6 months after completion of primary treatment. Multivariate regression was used to predict continuous depressive symptoms at 6-months post-treatment from continuous depressive symptoms at baseline, cortisol awakening response (CAR), and other measures of diurnal HPA-axis functioning.

Corresponding author: Kate Ryan Kuhlman, Ph.D., Postdoctoral Fellow, Franz Hall-Department of Psychology, University of California, Los Angeles, 502 Portola Plaza, Los Angeles, CA 90095, krkuhlman@ucla.edu.

Conflicts of interest: none.

Results—The magnitude of CAR predicted changes in depressive symptoms over time, such that women with a higher CAR showed a greater increase from baseline to 6 months post-treatment, $b = 5.67$, $p = .023$. Diurnal slope and total cortisol output were not associated with concurrent depressive symptoms or their change over time.

Conclusions—Elevated CAR may be a neurobiological risk factor for increases in depressive symptoms in the months after breast cancer treatment and warrants further investigation.

Keywords

HPA-axis; depression; breast cancer; cortisol awakening response; risk factor; CAR; longitudinal

Introduction

Diagnosis with breast cancer is a major life event that elicits increases in depressive symptoms within 12 months for up to 50% of women (1,2), and 38% of women with breast cancer demonstrate persistently elevated depressive symptoms for up to 16 months following diagnosis (3). The reentry transition, or the period of time after treatment completion, is a time of particular risk for the development and persistence of depressive symptoms (4). This is important because depression interferes with beneficial health behaviors such as exercise and healthy eating (5) as well as reengagement with pre-diagnosis activities (6). Studies to date have predominantly focused on psychosocial predictors of depression in cancer survivors, and therefore our understanding of neurobiological risk factors for depression in this population is lacking. Atypical functioning of the hypothalamic-pituitary-adrenal axis (HPA-axis), a component of the body's physiological stress response system, is associated with depression (See 7,8). In fact, elevated salivary cortisol, a systemic indicator of HPA-axis functioning, prospectively predicts the onset of depression in otherwise healthy adolescent and adult samples (9–13); however, studies examining functioning of the HPA-axis prior to cancer treatment as a predictor of depressive symptoms during recovery remain rare.

Salivary cortisol displays a diurnal pattern in healthy individuals, with high concentrations immediately after waking, an immediate increase within 30–40 minutes after waking, and steady declines throughout the day (14,15). The increase in cortisol that occurs between waking and 30 minutes post-waking is known as the cortisol awakening response (CAR) (16). The CAR is thought to indicate the body's effort to mobilize resources to meet the demands of the coming day (17,18) but also may be a measure of adrenal sensitivity to adrenocorticotropic hormone (ACTH)(19), the precursor to cortisol release from the adrenal gland. Diurnal regulation of cortisol is often reflected by a slope from waking to bedtime, and is reflective of circadian regulation (20). Finally, total cortisol across the day (area under the curve with respect to ground or AUCg) can be used as an indication of both circadian regulation and activation to stressors throughout the day (21,22).

Anomalies in the functioning of the HPA-axis are consistently shown in depressed individuals compared to controls; these include elevated cortisol during recovery from stress, atypical responses to pharmacological challenge (e.g., dexamethasone suppression test), and elevated basal concentrations of cortisol (23,24). In cancer patients and survivors, depressive

symptoms have been associated with elevated diurnal cortisol in the morning (25) and evening (26,27). A flat diurnal cortisol profile has also been linked to persistent fatigue in breast cancer patients (28), as well as earlier mortality in patients with ovarian, epithelial, and lung cancer (29–31). Taken together, these studies have contributed to growing interest in HPA-axis functioning as an indicator of both psychological distress and circadian rhythm disruption which have repeatedly been linked with morbidity and mortality in cancer (32–35).

Indices of HPA-axis function have also been examined as prospective predictors of depressive symptoms and episodes. In studies conducted with adolescents, elevated cortisol at 8 am predicts major depressive disorder (MDD) one year later (36) and increases in depressive symptoms 3 years later (11). CAR prospectively predicted the onset of depressive episodes during late adolescence one year (9) and 2.5 years later (13). Similar findings have been observed in adult women, with cortisol at 8 am predicting MDD 13 months later (12). To our knowledge, only one study by Hsiao et al. has examined whether HPA-axis functioning prospectively predicted depressive symptoms in the context of breast cancer, and found that elevated cortisol in the evening was associated with depressive symptoms among breast cancer survivors over 14 months (37). Assessment of the HPA-axis in Hsiao and colleagues (2013) occurred nearly 5 years after treatment completion. Thus, whether HPA-axis functioning after diagnosis and before adjuvant treatment (e.g., radiation, chemotherapy) prospectively predicts depressive symptoms in the early survivorship period remains largely unknown. This is an important gap in our understanding because there may be psychological and biological indicators of risk for depressive illness that emerge in the immediate aftermath of major life events, such as cancer diagnosis and surgery.

The goal of this study was to examine whether HPA axis functioning, as measured by CAR, diurnal slope, and AUCg, was cross-sectionally associated with depressive symptoms after breast cancer diagnosis and before the onset of adjuvant treatment, and longitudinally with depressive symptoms 6 months after adjuvant treatment completion. We hypothesized that a flat diurnal profile and larger AUCg would be associated with greater depressive symptoms at baseline (prior to neoadjuvant/adjuvant therapy) and a larger CAR would be associated with greater increases in depressive symptoms 6 months post-treatment.

Methods

Participants

Subjects in this study represent a subgroup participating in a prospective, longitudinal study of women with breast cancer designed to identify predictors of cancer-related fatigue. Women were eligible for participation in the main study if they met the following criteria: 1) newly diagnosed with early-stage, resectable breast cancer (Stage 0, I, II, IIIA); 2) had not started adjuvant or neoadjuvant therapy with chemotherapy, radiation, trastuzumab, and/or endocrine therapy; 3) able to speak, read, and understand English. Additional criteria for inclusion in the present study included contributing at least two complete saliva sampling days, and completion of the 6 month follow-up assessment. The UCLA Institutional Review Board approved the study procedures, and written informed consent was obtained from all participants.

The present study included data from 135 of the total 271 women enrolled in the larger, ongoing, longitudinal study. Of the 271 women in the larger study, 157 opted to participate in the salivary cortisol assessment. There were no significant differences at baseline in age, ethnicity, education, income, marital status, depressive symptoms, history of depression, surgery type, or cancer stage between women with cortisol data and those without, all ps > .16. Of these 157 women with cortisol data, 14 participants did not have at least 2 complete days of data for computation of CAR, AUCg, and diurnal slope. Of the 143 women with complete baseline data, 135 women (95.1%) completed the 6-month post-treatment follow-up assessment. The mean time between the baseline and 6 month post-treatment assessment was 270 (SD = 91) days, or approximately 9 months. All data collection for the present analyses occurred between February 2013 and June 2016.

Procedures

Participants were recruited from oncology clinics in the Los Angeles metropolitan area. Upon informed consent and study enrollment, participants received a link via email to demographic, medical, and psychosocial questionnaires on www.Qualtrics.com. The majority completed the baseline assessment after definitive surgical resection of their breast tumor, but before adjuvant therapy (chemotherapy, radiation, endocrine therapy, trastuzumab). For those who received neoadjuvant chemotherapy prior to surgery, the baseline assessment was conducted prior to onset of neoadjuvant chemotherapy. At the baseline visit, participants were also provided with instructions for completing the saliva samples before the start of any adjuvant therapy.

Participants were followed over time and completed assessments at a 6 month post-treatment follow-up, which was targeted to occur 6 months after the completion of surgery, radiation, and/or chemotherapy, whichever occurred last as part of primary treatment. At this assessment, participants were again sent a link to online questionnaires. Our research team also conducted a review of participant medical records to confirm patient treatment information.

Measures

Depression—Depressive symptoms in the past week were assessed via the Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977) at the baseline assessment and 6 month post-treatment follow-up. The CES-D has been identified as useful in measuring psychosocial functioning in cancer patients (38), has demonstrated good sensitivity and specificity for major depressive episodes determined via semi-structured clinical interview (39,40), and is recommended as a valid assessment of emotional distress in cancer patients (41), specifically breast cancer (42). The CES-D is a 20-question, self-report instrument with excellent reliability and validity. Scores on the CES-D can range from 0–60, and a score of 16 or higher indicates clinically significant depressive symptoms (43), and is commonly used to indicate psychological distress within samples of women with breast cancer (44–46). This measure also demonstrated good internal consistency in the current sample (α = .87). Trained research staff also administered structured clinical interviews using the Structured Clinical Interview for DSM for assessment of current and past depressive episodes at the baseline assessment (47).

HPA-axis functioning—At the baseline assessment, participants were instructed to take 4 saliva samples at designated times each day for 3 days to assess diurnal regulation of the HPA-axis: immediately upon waking, 30 minutes post-waking, 8 hours post-waking, and at bedtime. Research staff color coded salivettes to indicate each respective time point. Women were given detailed instructions about collection, including taking the first sample "when eyes were open but hadn't yet gotten out of bed," not to eat or drink during the 20 minutes before each sample, and to store the salivettes in the refrigerator until their next research appointment. Importantly, women were instructed not to take samples on a day when they did not follow these procedures. Participants recorded the time and date of each saliva sample on a form provided by the research team, which is a valid and reliable method of assessing sample times among adults (48).

Saliva samples were shipped on dry ice to the TUD Biopsychology Laboratory in Dresden, Germany directed by Dr. Clemens Kirschbaum. Saliva samples were stored at −20 degrees C until analysis. After thawing, salivettes were centrifuged at 3,000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary concentrations were measured using commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The lower limit of detection for this assay is 0.011 µg/dL. Sample and reagent handling was semi-automated using a liquid handling robot (Genesis, Tecan, Switzerland) and quality control samples of low, medium, and high cortisol concentrations were run on each microtiter plate assayed. The intra and interassay coefficients for cortisol were both below 8%.

Cortisol samples were considered invalid if collected more than 15 minutes before or after the designated sample time. Participants who did not have 2 complete days of valid cortisol were excluded from analyses. The CAR and diurnal slope were computed consistent with past studies examining HPA-axis functioning as a prospective predictor of depression (9). Specifically, CAR was computed as the average difference between cortisol 30 minutes post-waking and cortisol at waking. Negative CAR values were recoded as 0 to reduce overlap between CAR and diurnal slope indices and consistent with past studies (49,50). Diurnal slope was computed by subtracting the mean cortisol immediately upon waking from mean cortisol at bedtime and then dividing by mean number of hours awake. Total cortisol output was computed using trapezoidal aggregation with all 4 saliva samples (51). Specifically, we summed the area of the trapezoid between waking and +30 post-waking, +30 minutes post-waking and +8 hours post-waking, and +8 hours post-waking and bedtime, using hours between sample times as the base of each trapezoid.

Data Analysis

Continuous variables were tested for normality. For all multivariate analyses, diurnal slope and AUCg were transformed using the natural log transformation to reduce skew and kurtosis. To test our hypothesis that HPA-axis functioning would be concurrently associated with greater depressive symptoms and prospectively predict increases in depressive symptoms in women with breast cancer, we conducted multiple linear regression analyses using SPSS v23. The assumptions of linearity and normality were met for all analyses. We first fit an unadjusted model examining the association between each HPA index (CAR,

AUCg, and diurnal slope) and baseline depressive symptoms. We then fit an adjusted model with our a priori covariates: waking time, age, cancer stage, surgery type, and history of depression. We then fit unadjusted models examining the association between each HPA-axis index and 6 month post-treatment symptoms while controlling for baseline depressive symptoms. We then adjusted these models for our a priori covariates. Age and history of depression were included as covariates because they have been previously identified as potential risk factors for depression in women with breast cancer (3). Waking time was included as a covariate because waking times can be highly heterogeneous across individuals and also influence the magnitude of CAR (52,53). Indeed, waking times in our sample ranged from 3:30 am to 9:05 am, $\bar{x}$ = 6:37 (SD = 1:08), and CAR and waking time were significantly correlated, r = −.198, p = .021. Time between the baseline and 6 month post-treatment assessment, surgery type, adjuvant treatment type were included as covariates because participants varied in each of these domains and treatment characteristics such as these may influence the risk of psychological distress in women with breast cancer or operate as proxies for disease characteristics that influence physiological processes, such as functioning of the HPA-axis. Complete information related to key clinical characteristics was not available for some women including disease stage (n = 8), surgery type (n = 4), chemotherapy (n = 1), radiation (n = 1), and endocrine therapy (n = 8). Due to this missing data, the adjusted model includes complete data for 117 women. We also used multiple imputation in SPSS to estimate data for these missing clinical variables to test the fully adjusted model.

Results

Women in this sample were predominantly white, married, and had a bachelor's degree or higher. All participants had surgery as part of their treatment. The majority had surgery (lumpectomy or mastectomy) as their initial treatment, followed by radiation and/or chemotherapy, and endocrine therapy. Ten women received neoadjuvant chemotherapy before surgery. On average, participants displayed the expected pattern of cortisol throughout the day, with an increase immediately upon waking followed by a decline throughout the day. Depressive symptoms were prevalent in this sample, such that 33.3% (n = 45) reported clinically significant (CES-D ≥16) depressive symptoms at baseline, 25.9% (n = 35) reported clinically significant depressive symptoms at the 6 month post-treatment assessment, and 43.0% showed an increase in depressive symptoms from baseline to the 6 month follow-up. See Table 1 for detailed demographic and clinical characteristics of the sample.

We conducted separate, unadjusted multiple regression analyses to determine whether indices of HPA-axis functioning were associated with depressive symptoms at the baseline assessment. None of the indices were associated with depressive symptoms at baseline: CAR, B = −2.19, SE = 2.77, t = −0.79, p = .43, diurnal slope, B = −27.78, SE = 25.00, t = −1.00, p = .27, and total cortisol output (AUCg), B = −0.26, SE = 1.86, t = −0.14, p = .89. These results were unchanged when adjusted for covariates, all ps > .13.

We then conducted separate, unadjusted multiple regression analyses examining each index of HPA-axis functioning as a predictor of depressive symptoms at 6 month post-treatment

while controlling for depressive symptoms at baseline. CAR was a significant predictor of depressive symptoms at 6 months post-treatment controlling for depressive symptoms at baseline, $R^2 = .42$, $F = 44.08$, $p < .001$, such that having a larger CAR at baseline predicted increases in depressive symptoms over time, B = 5.67, $SE = 2.46$, $t = 2.30$, $p = .023$. See Figure 1 for depressive symptoms at 6 months post-treatment by CAR magnitude. The association between CAR and change in depressive symptoms remained significant, B = 5.47, $SE = 2.64$, $t = 2.07$, $p = .040$, after adjusting for average time at waking on CAR sampling days, age, cancer stage, adjuvant treatment type, surgery type, and time between assessments. This adjusted model reflects complete data for 117 women. However, the pattern of results did not differ when using multiple imputations to estimate for these missing data. See Table 2 for adjusted model of CAR predicting depressive symptoms at 6 months post-treatment. When history of major depression was included as a covariate, the association between CAR and increases in depressive symptoms trended in the same direction but became non-significant, B = 4.10, $SE = 2.12$, $t = 1.93$, $p = .055$.

Notably, participants with a history of depression had significantly higher depressive symptoms at baseline, $\bar{x} = 18.37$ ($SD = 12.21$) vs. 11.33 ($SD = 9.73$), $t(133) = -3.19$, $p = .002$, but did not differ in HPA-axis functioning, all ps > .22. Given this finding, we conducted a post hoc analysis examining whether history of depression moderated the association between baseline CAR and increases in depressive symptoms from pre- to 6 months post-treatment. However the inclusion of the interaction between history of depression and CAR did not improve model fit, $\Delta F = 0.06$, $p = .82$, and the interaction was non-significant, B = −1.10, $SE = 4.68$, $t = -0.24$, $p = .82$. We then stratified our sample based upon depressive symptoms at baseline using the clinical threshold (CES-D ≥ 16). Among participants whose depressive symptoms were below the clinical threshold at baseline (n =89), a larger CAR was a robust predictor of increases in depressive symptoms, B = 5.54, $SE = 2.10$, $t = 2.64$, $p = .010$. Among participants whose depressive symptoms were high at baseline (n = 46), CAR was not a significant predictor of increases in depressive symptoms, B = 2.31, $SE = 5.77$, $t = 0.40$, $p = .69$.

We observed a non-significant trend suggesting that diurnal slope was associated with change in depressive symptoms from baseline to 6 months post-treatment. There was a trend suggesting that a flatter diurnal slope at baseline predicted increases in depressive symptoms over time, in an unadjusted model: B = 52.08, SE = 27.86, t = 1.86, p = .064 (overall model fit $R^2 = .41$, $F = 40.94$, $p < .001$). However, the association between diurnal slope and change in depressive symptoms was not significant when accounting for average time at waking on saliva sampling days, age, cancer stage, adjuvant treatment type, surgery type, time between assessments, and history of depression, B = 36.41, $SE = 27.24$, $t = 1.34$, $p = .18$. Total cortisol output was not associated with changes in depression from baseline to 6 months post-treatment, B = 0.40, $SE = 1.61$, $t = 0.25$, $p = .80$, and these results were unchanged in models adjusted for covariates, p = .73.

Discussion

Depression is prevalent in women with breast cancer during and after treatment (4). Prevalence of elevated depressive symptoms in our sample were comparable to past studies

of cancer survivors in the immediate aftermath of diagnosis (3,54), and symptoms remained elevated at the 6 month follow-up. We observed no associations between HPA-axis functioning and depressive symptoms at baseline. However, having a larger CAR at baseline prospectively predicted elevated depressive symptoms at 6 months post-treatment, independent of depressive symptoms at baseline. CAR, measured prior to any neoadjuvant or adjuvant treatment, may be a neurobiological risk factor for increasing depressive symptoms during recovery from breast cancer.

Our results are consistent with past studies showing that a larger CAR prospectively predicted depressive episodes and increases in symptoms in both adolescents and adults for up to 3 years (9,13). It is possible that in this study, a larger CAR may be an indicator of greater psychophysiological stress in the setting of a major life stressor, such as a diagnosis of breast cancer, and therefore greater risk for increasing depressive symptoms. CAR may also be an indicator of adrenal sensitivity to ACTH (19). During sleep, ACTH receptors on the adrenal cortex are inhibited; upon waking, these receptors are disinhibited, triggering the release of glucocorticoids, or cortisol (19). Thus, psychological and environmental stressors may contribute to hypersecretion of corticotrophin releasing hormone (CRH) or enhanced adrenal sensitivity to ACTH, which is released in response to CRH. Past studies have identified sleep quantity (55), early life adversity (56), and recent daily life stress as meaningful predictors of CAR (17,57). However, CAR is also more than 40% heritable (18,58), suggesting that CAR may be both a genetically and environmentally sensitive neurobiological risk factor for depressive illness. To this end, more studies are needed to characterize environmental, psychological, and biological predictors of CAR.

It is important to note that the prospective association between CAR and elevated depressive symptoms was reduced to non-significance when accounting for history of MDD. Previous studies have shown a prospective association between CAR and depression even when accounting for history of depression (9,13). Women in our sample with a history of depression showed no differences in HPA-axis functioning when compared to women without a history of depression, and collinearity statistics were not indicative of multicollinearity between CAR and history of depression (VIF = 1.09). However, women with a history of depression in our sample had significantly higher depressive symptoms at baseline that exhibited very little change over time. Thus, it is possible that our results differed from previous work because CAR is primarily a predictor of depression risk in those with low concurrent depressive symptoms. Indeed, post hoc analyses showed that CAR was a predictor of elevated depressive symptoms at 6 months post-treatment for women with low depressive symptoms at the baseline assessment, but not for women with high symptoms at baseline. This would be consistent with the observation that individuals with remitted depression demonstrated a larger cortisol awakening response than non-depressed controls (59), and asymptomatic young adults at familial risk for depression exhibit larger CAR than those without family history of depression (60). This is also consistent with a long-standing conceptualization that hypersecretion of CRH, the initial hormone in the HPA cascade, represents an endophenotype for internalizing psychopathology risk, whereas persistence and severity of different types of psychopathology (e.g., depression and PTSD) are associated with diverging patterns of HPA-axis dysregulation (61).

We did not observe a significant association between a flat diurnal slope and concurrent or future depressive symptoms, although we observed a trend that was consistent with a previous study of breast cancer survivors. Hsiao et al. (2013) found that elevated cortisol in the late evening was associated with increases in depressive symptoms over 14 months while CAR was not (37). There are several methodological reasons that could explain any inconsistencies between our findings. Most notably, HPA-axis measurements in Hsiao and colleagues (2013) were collected an average of 5 years post-treatment. Exposure to neoadjuvant and adjuvant treatments may have implications for functioning of the immune system and the HPA-axis. Our study collected cortisol before the onset of any adjuvant or neoadjuvant treatment. In addition, the Hsiao and colleagues (2013) cortisol assessment included data collected on several days over 14 months, with no sampling days occurring consecutively. In our study, cortisol assessments occurred across three days during the time between diagnosis and treatment initiation. Approximately 50% of HPA-axis functioning is attributable to day-to-day variation (62), therefore our study likely differed substantially from that of Hsiao and colleagues (2013) in what each HPA-axis index reflected. Future longitudinal investigations are needed to inform whether the prospective association between CAR and depressive symptoms observed here are independent or interdependent from the associations between a flattened diurnal slope and behavioral correlates observed in other studies.

This study extends the observation that CAR is a prospective predictor of depression by showing that pre-treatment CAR prospectively predicts increases in depressive symptoms in women following treatment for breast cancer. This study reflects depressive symptoms reported on a self-report questionnaire, the CES-D, and therefore does not reflect prediction of diagnosed depressive episodes. Given our sample size, we did not examine the association between CAR and a dichotomous indicator of clinically significant depressive symptoms. However, the research showing associations between depressive symptoms and negative outcomes in breast cancer survivors have focused predominantly on continuous measures of depressive symptoms, suggesting a graded relationship. Indeed, a recent examination of depressive symptoms and episodes assessed repeatedly over the 16 months following breast cancer diagnosis found that 38% of women with breast cancer report consistently elevated depressive symptoms, while only one third of those women met criteria for depressive episodes (3). Given this information, continuous self-report measures of symptoms may cast a wider net for survivors experiencing psychological distress than a clinical diagnosis of MDD would. Continuously measured symptoms are useful specifically in this population given that CES-D measured depressive symptoms predict mortality risk in cancer survivors (38). Further, intervention studies with this population have predominantly focused on alleviating depressive symptoms and there remains a paucity of research on interventions for MDD in breast cancer survivors (63).

These findings should be considered in the context of this study’s limitations. First, this study is specific to females with early stage breast cancer. The sample was primarily white and well-educated, reflecting the geographic area from which women were recruited, and replication is warranted. However, it is encouraging that our findings converge with previous studies in both adults and adolescents without cancer (9,12,13). Finally, an expert consensus report was recently published recommending best practices in the measurement of CAR

(52). Data collection for this study began well before these guidelines were available and our sample collection protocol deviated slightly from the recommendations. In particular, CAR was estimated from 2 samples (waking and 30 minutes post-waking) instead of the recommended 3 or more samples (waking, 30 mins, and 45 minutes post-waking), and sample times were recorded by participant self-report and not corroborated by an objective measure such as EMS or a time-stamped photograph. These deviations impeded our ability to make inferences about the temporal dynamics of CAR activation and regulation, which was not one of our research aims. Our sampling protocol and instructions otherwise adhered to the published guidelines.

Integration of our results with previous studies suggests that CAR may be a genetically and environmentally influenced neurobiological marker that identifies women at risk for increasing depressive symptoms following breast cancer diagnosis (9,60). Of particular clinical relevance, elevated depressive symptoms at diagnosis are known to portend poor outcomes in cancer populations (1,34,38), and there are freely available opportunities to screen for this (e.g., use of PHQ-9). However, CAR may help to identify women who do not report elevated symptoms but are still at risk. Future studies are needed to further establish CAR as a clinically useful risk factor for predicting depressive illness and potentially, response to treatment. The benefits of psychosocial interventions for adult cancer patients on emotional adjustment and functional outcomes have been documented for more than two decades (64–66). Evaluating CAR is a potentially effective approach to identifying women with breast cancer who would benefit from psychosocial interventions targeted at improving quality of life, health, and well-being during cancer treatment and recovery.

Acknowledgments

This work was supported by the National Cancer Institute (R01 CA160427) awarded to Julienne E. Bower. Preparation of this manuscript was made possible by the National Institute of Mental Health (T32MH015750) awarded to Dr. Kate Ryan Kuhlman. We would also like to thank our participants for their willingness to participate in this study during such a challenging time in their lives.

Abbreviations

HPA-axis	hypothalamic pituitary adrenal axis
CAR	cortisol awakening response
MDD	Major Depressive Disorder
AUCg	area under the curve with respect to ground or AUCg
ACTH	adrenocorticotropic hormone
CES-D	Center for Epidemiological Studies – Depression Scale

References

1. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ. 2005; 330(7493):702. [PubMed: 15695497]

2. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, Meader N. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011; 12(2):160–174. [PubMed: 21251875]

3. Stanton AL, Wiley JF, Krull JL, Crespi C, Hammen C, Allen J, Barrón M, Jorge A, Weihs K. Depressive episodes, symptoms, and trajectories in women recently diagnosed with breast cancer. Breast Cancer Res Treat. 2015; 154(1):105–115. [PubMed: 26420401]

4. Stanton AL, Ganz PA, Rowland JH, Meyerowitz B, Krupnik J, Sears S. Promoting adjustment after treatment for cancer. Cancer. 2005; 104(S11):2608–2613. [PubMed: 16247779]

5. Ventura EE, Ganz PA, Bower JE, Abascal L, Petersen L, Stanton A, Crespi C. Barriers to physical activity and healthy eating in young breast cancer survivors: modifiable risk factors and associations with body mass index. Breast Cancer Res Treat. 2013; 142(2):423–433. [PubMed: 24177756]

6. Steiner JF, Cavender TA, Nowels CT, Beaty B, Bradley C, Fairclough D, Main D. The impact of physical and psychosocial factors on work characteristics after cancer. Psychooncology. 2008; 17(2):138–147. [PubMed: 17429833]

7. Bhagwagar Z, Cowen PJ. “It”s not over when it’s over’: persistent neurobiological abnormalities in recovered depressed patients. Psychol Med. 2008; 38(3):307–313. [PubMed: 18444278]

8. Pariante CM, Lightman SL. The HPA axis in major depression: Classical theories and new developments. Trends Neurosci. 2008; 31(9):464–468. [PubMed: 18675469]

9. Adam EK, Doane LD, Zinbarg RE, Mineka S, Craske M, Griffith. Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. Psychoneuroendocrinology. 2010; 35(6):921–931. [PubMed: 20079576]

10. Goodyer IM, Park RJ, Netherton CM, Herbert J. Possible role of cortisol and dehydroepiandrosterone in human development and psychopathology. Br J Psychiatry. 2001; 179(3):243–249. [PubMed: 11532802]

11. Halligan SL, Herbert J, Goodyer I, Murray L. Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. Biol Psychiatry. 2007; 62(1):40–46. [PubMed: 17188253]

12. Harris TO, Borsanyi S, Messari S, Stanford K, Cleary SE, Shiers HM, Brown GW, Herbert J. Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. Br J Psychiatry. 2000; 177(6):505–510. [PubMed: 11102324]

13. Vrshek-Schallhorn S, Doane LD, Mineka S, Zinbarg RE, Craske MG, Adam EK. The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. Psychol Med. 2013; 43(3):483–493. [PubMed: 22652338]

14. Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology. 2009; 34(10):1423–1436. [PubMed: 19647372]

15. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychobiological research: A overview. Neuropsychobiology. 1989; 22(3):150–169. [PubMed: 2485862]

16. Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, Von Auer K, Jobst S, Kaspers F, Kirschbaum. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. Life Sci. 1997; 61(26):2539–2549. [PubMed: 9416776]

17. Adam EK, Hawkley LC, Kudielka BM, Cacioppo JT. Day-to-day dynamics of experience–cortisol associations in a population-based sample of older adults. Proc Natl Acad Sci. 2006; 103(45): 17058–17063. [PubMed: 17075058]

18. Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): facts and future directions. Int J Psychophysiol. 2009; 72(1):67–73. [PubMed: 18854200]

19. Clow A, Hucklebridge F, Stalder T, Evans P, Thorn L. The cortisol awakening response: More than a measure of HPA axis function. Neurosci Biobehav Rev. 2010; 35(1):97–103. [PubMed: 20026350]

20. Kalsbeek A, van der Spek R, Lei J, Endert E, Buijs RM, Fliers E. Circadian rhythms in the hypothalamo–pituitary–adrenal (HPA) axis. Mol Cell Endocrinol. 2012; 349(1):20–29. [PubMed: 21782883]

21. Kidd T, Carvalho LA, Steptoe A. The relationship between cortisol responses to laboratory stress and cortisol profiles in daily life. Biol Psychol. 2014; 99:34–40. [PubMed: 24582772]

22. Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol Bull. 2007; 133(1):25. [PubMed: 17201569]
23. Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology. 2005; 30(9):846–856. [PubMed: 15961250]
24. Lopez-Duran NL, Kovacs M, George CJ. Hypothalamic-pituitary-adrenal axis dysregulation in depressed children and adolescents: A meta-analysis. Psychoneuroendocrinology. 2009; 34(9): 1272–1283. [PubMed: 19406581]
25. Sephton SE, Dhabhar FS, Keuroghlian AS, Giese-Davis J, McEwen BS, Ionan AC, Spiegel D. Depression, cortisol, and suppressed cell-mediated immunity in metastatic breast cancer. Brain Behav Immun. 2009; 23(8):1148–1155. [PubMed: 19643176]
26. Lutgendorf SK, Weinrib AZ, Penedo F, Russell D, DeGeest K, Costanzo ES, Henderson PJ, Sephton SE, Lucci JA III, Cole S, Sood AK, Lubaroff DM. Interleukin-6, Cortisol, and Depressive Symptoms in Ovarian Cancer Patients. J Clin Oncol. 2008; 26(29):4820. [PubMed: 18779606]
27. Weinrib AZ, Sephton SE, Degeest K, Penedo F, Bender D, Zimmerman B, Kirschbaum C, Sood AK, Lubaroff DM, Lutgendorf SK. Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. Cancer. 2010; 116(18):4410–4419. [PubMed: 20564155]
28. Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology. 2005; 30(1):92–100. [PubMed: 15358446]
29. Schrepf A, Thaker PH, Goodheart MJ, Bender D, Slavich GM, Dahmoush L, Penedo F, DeGeest K, Mendez L, Lubaraoff DM, Cole SW, Sood AK, Lutgendorf SK. Diurnal cortisol and survival in epithelial ovarian cancer. Psychoneuroendocrinology. 2015; 53:256–267. [PubMed: 25647344]
30. Sephton SE, Lush E, Dedert EA, Floyd AR, Rebholz WN, Dhabhar FS, Spiegel D, Salmon P. Diurnal cortisol rhythm as a predictor of lung cancer survival. Brain Behav Immun. 2013; 30:S163–S170. [PubMed: 22884416]
31. Sephton SE, Sapolsky RM, Kraemer HC, Spiegel D. Diurnal cortisol rhythm as a predictor of breast cancer survival. J Natl Cancer Inst. 2000; 92(12):994–1000. [PubMed: 10861311]
32. Hamer M, Chida Y, Molloy GJ. Psychological distress and cancer mortality. J Psychosom Res. 2009; 66(3):255–258. [PubMed: 19232239]
33. Mormont, Mc, Lévi, F. Circadian-system alterations during cancer processes: A review. Int J Cancer. 1997; 70(2):241–247. [PubMed: 9009166]
34. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol Psychiatry. 2003; 54(3):269–282. [PubMed: 12893103]
35. Stevens RG. Circadian disruption and breast cancer: From melatonin to clock genes. Epidemiol Camb Mass. 2005; 16(2):254.
36. Goodyer IM, Herbert J, Tamplin A, Altham PME. Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. Br J Psychiatry. 2000; 177:499–504. [PubMed: 11102323]
37. Hsiao F-H, Chang K-J, Kuo W-H, Huang C-S, Liu Y-F, Lai Y-M, Jow G-M, Ho RTH, Ng S-M, Chan CLW. A longitudinal study of cortisol responses, sleep problems, and psychological well-being as the predictors of changes in depressive symptoms among breast cancer survivors. Psychoneuroendocrinology. 2013; 38(3):356–366. [PubMed: 22818228]
38. Pinquart M, Duberstein PR. Depression and cancer mortality: A meta-analysis. Psychol Med. 2010; 40(11):1797–1810. [PubMed: 20085667]
39. Lyness JM, Noel T, Cox C, King DA, Conwell Y, Caine ED. Screening for depression in elderly primary care patients: A comparison of the center for epidemiologic studies—depression scale and the geriatric depression scale. Arch Intern Med. 1997; 157(4):449–454. [PubMed: 9046897]
40. Mulrow CD, Williams JW, Gerety MB, Ramirez G, Montiel OM, Kerber C. Case-finding instruments for depression in primary care settings. Ann Intern Med. 1995; 122(12):913–921. [PubMed: 7755226]

41. Vodermaier A, Linden W, Siu C. Screening for Emotional Distress in Cancer Patients: A Systematic Review of Assessment Instruments. J Natl Cancer Inst. 2009; 101(21):1464–1488. [PubMed: 19826136]
42. Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: Evaluation of the center for epidemiological studies depression scale (Ces-d). J Psychosom Res. 1999; 46(5):437–443. [PubMed: 10404478]
43. Radloff LS. The CES-D scale a self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1(3):385–401.
44. Weitzner MA, Moncello J, Jacobsen PB, Minton S. A pilot trial of paroxetine for the treatment of hot flashes and associated symptoms in women with breast cancer. J Pain Symptom Manage. 2002; 23(4):337–345. [PubMed: 11997203]
45. Liu L, Fiorentino L, Natarajan L, Mills PJ, Sadler GR, Dimsdale JE, Rissling M, He F, Ancoli-Israel S. Pre-treatment symptom cluster in breast cancer patients is associated with worse sleep, fatigue and depression during chemotherapy. Psychooncology. 2009; 18(2):187–194. [PubMed: 18677716]
46. Rottmann N, Hansen DG, Hagedoorn M, Larsen PV, Nicolaisen A, Bidstrup PE, Würtzen H, Flyger H, Kroman N, Johansen C. Depressive symptom trajectories in women affected by breast cancer and their male partners: a nationwide prospective cohort study. J Cancer Surviv. 2016; 10(5):915–926. [PubMed: 27084710]
47. First, MB., Gibbon, M. [Accessed January 5, 2015] The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). 2004. (http://psycnet.apa.org/psycinfo/2004-12821-011)
48. Kraemer HC, Giese-Davis J, Yutsis M, O'Hara R, Neri E, Gahhagher-Thompson D, Taylor CB, Spiegel D. Design decisions to optimize reliability of daytime cortisol slopes in an older population. Am J Geriatr Psychiatry. 2006; 14(4):325–333. [PubMed: 16582041]
49. Kuhlman KR, Repetti RL, Reynolds BM, Robles TF. Change in parent-child conflict and the HPA-axis: Where should we be looking and for how long? Psychoneuroendocrinology. 2016; 68:74–81. [PubMed: 26963373]
50. Kuhlman KR, Geiss EG, Vargas I, Lopez-Duran NL. Differential associations between childhood trauma subtypes and adolescent HPA-axis functioning. Psychoneuroendocrinology. 2015; 54:103–114. [PubMed: 25704913]
51. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology. 2003; 28(7):916–931. [PubMed: 12892658]
52. Stalder T, Kirschbaum C, Kudielka BM, Adam EK, Pruessner JC, Wüst S, Dockray S, Smyth N, Evans P, Hellhammer DH, Miller R, Wetherell MA, Lupien SJ, Clow A. Assessment of the cortisol awakening response: Expert consensus guidelines. Psychoneuroendocrinology. 2016; 63:414–432. [PubMed: 26563991]
53. Edwards S, Evans P, Hucklebridge F, Clow A. Association between time of awakening and diurnal cortisol secretory activity. Psychoneuroendocrinology. 2001; 26(6):613–622. [PubMed: 11403981]
54. Krebber AMH, Buffart LM, Kleijn G, Riepma IC, de Bree R, Leemans CR, Becker A, Brug J, van Straten A, Cuijpers P, Verdonck-de Leeeuw IM. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology. 2014; 23(2): 121–130. [PubMed: 24105788]
55. Vargas I, Lopez-Duran N. Dissecting the impact of sleep and stress on the cortisol awakening response in young adults. Psychoneuroendocrinology. 2014; 40:10–16. [PubMed: 24485471]
56. Quevedo K, Johnson AE, Loman ML, LaFavor TL, Gunnar M. The confluence of adverse early experience and puberty on the cortisol awakening response. Int J Behav Dev. 2012; 36(1):19–28. [PubMed: 22383860]
57. Chida Y, Steptoe A. Cortisol awakening response and psychosocial factors: A systematic review and meta-analysis. Biol Psychol. 2009; 80(3):265–278. [PubMed: 19022335]
58. Wüst S, Federenko I, Hellhammer DH, Kirschbaum C. Genetic factors, perceived chronic stress, and the free cortisol response to awakening. Psychoneuroendocrinology. 2000; 25(7):707. [PubMed: 10938450]

59. Vreeburg SA, Hoogendijk WG, van Pelt J, DeRijk RH, Verhagen JCM, van Dyck R, Smit JH, Zitman FG, Penninx BWJH. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: Results from a large cohort study. Arch Gen Psychiatry. 2009; 66(6):617–626. [PubMed: 19487626]

60. Mannie ZN, Harmer CJ, Cowen PJ. Increased waking salivary cortisol levels in young people at familial risk of depression. Am J Psychiatry. 2007; 164(4):617–621. [PubMed: 17403975]

61. Ehlert U, Gaab J, Heinrichs M. Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus–pituitary–adrenal axis. Biol Psychol. 2001; 57(1–3):141–152. [PubMed: 11454437]

62. Ross KM, Murphy ML, Adam EK, Chen E, Miller GE. How stable are diurnal cortisol activity indices in healthy individuals? Evidence from three multi-wave studies. Psychoneuroendocrinology. 2014; 39:184–193. [PubMed: 24119668]

63. Carvalho AF, Hyphantis T, Sales PMG, Soeiro-de-Souza MG, Macêdo DS, Cha DS, McIntyre RS, Pavlidis N. Major depressive disorder in breast cancer: A critical systematic review of pharmacological and psychotherapeutic clinical trials. Cancer Treat Rev. 2014; 40(3):349–355. [PubMed: 24084477]

64. Antoni MH, Lehman JM, Kilbourn KM, Boyers AE, Culver JL, Alferi SM, Yount SE, McGregor BA, Arena PL, Harris SD, Price AA, Carver CS. Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. Health Psychol. 2001; 20(1):20. [PubMed: 11199062]

65. Jacobsen PB, Jim HS. Psychosocial interventions for anxiety and depression in adult cancer patients: Achievements and challenges. CA Cancer J Clin. 2008; 58(4):214–230. [PubMed: 18558664]

66. Meyer TJ, Mark MM. Effects of psychosocial interventions with adult cancer patients: A meta-analysis of randomized experiments. Health Psychol. 1995; 14(2):101–108. [PubMed: 7789344]

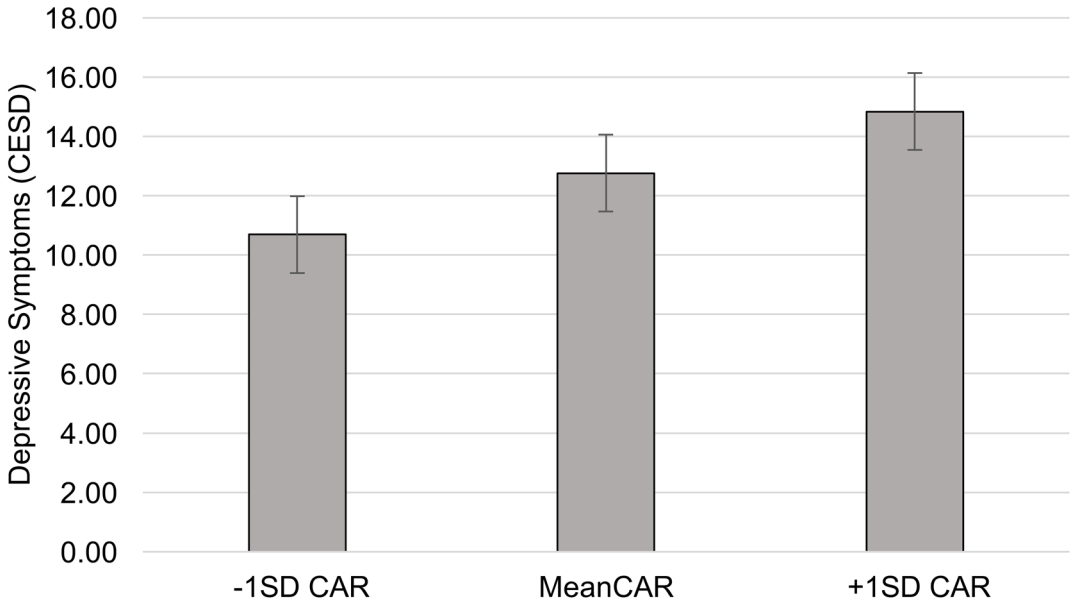

Figure 1.

Estimated depressive symptoms (±SE) at 6 months post-treatment for breast cancer by low (−1SD), average, and high (+1SD) pre-treatment cortisol awakening response (CAR) when adjusting for baseline depressive symptoms.

Table 1

Descriptive characteristics of study sample at baseline assessment (n = 135)

Characteristic	M (SD)	% (n)
Age	56.34 (11.01)	
Married		68.1 (92)
Education		
High School Diploma		3.7 (5)
Some college		23.0 (31)
BA/BS degree		39.3 (53)
Graduate degree		34.0 (46)
Race/Ethnicity *		
Hispanic		8.9 (12)
White		74.1 (100)
Black		5.2 (7)
Asian		11.1 (15)
Other		9.6 (13)
Income		
< $60,000		19.7 (26)
$60,000–100,000		18.9 (25)
> $100,000		61.4 (81)
Cancer Stage		
0		17.3 (22)
1		50.4 (64)
2		26.8 (34)
3		5.5 (7)
Surgery type		
Lumpectomy		61.8 (81)
Mastectomy		38.2 (50)
Treatment *		
Chemotherapy		30.4 (41)
Radiation therapy		66.7 (90)
Endocrine therapy		66.2 (88)
Depressive symptoms		
Pre-treatment CES-D	12.74 (10.61)	
6 month post-treatment CES-D	11.41 (11.29)	
History of MDD		20.0 (27)
HPA-axis function (μg/dl)		
CAR	0.23 (0.33)	
Diurnal Slope	−0.04 (0.03)	
AUCg	8.01 (3.28)	

* Indicates that groups are not mutually exclusive

Table 2

Unstandardized regression coefficients predicting symptoms of depression (CES-D) in women with breast cancer at the 6 month post-treatment follow-up assessment from baseline depressive symptoms, CAR, clinical characteristics.

	R^2	B (SE)	*t*
	.45**		
Baseline CES-D		0.67 (0.08)	8.12**
CAR		5.47 (2.64)	2.07*
Age		0.07 (0.08)	0.82
Time between assessments		−0.01 (0.02)	−0.48
Waking time on sampling days		.00 (.00)	−0.83
Cancer Stage		−1.21 (1.40)	−0.86
Surgery type		1.87 (2.50)	0.75
Chemotherapy		0.36 (3.17)	0.12
Radiation		2.50 (2.92)	0.85
Endocrine therapy		−1.34 (1.92)	−0.70

** $p < .01$,

* $p < .05$