

Association of the Physiological Stress Response With Depressive Symptoms in Patients With Breast Cancer

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Objective: The literature on the relationship of depressive symptoms and stress hormones after cancer diagnosis has been mixed, with some studies showing a relationship and other studies showing none. Time since diagnosis may explain these contradictory findings. This study examined the relationship of depressive symptoms to stress hormones in patients with breast cancer using 12-month longitudinal data. **Methods:** Patients with Stage II or III breast cancer ($n = 227$) were assessed every 4 months from diagnosis/surgery to 12 months. They completed the Centers for Epidemiological Studies Depression Scale (CES-D) Iowa Short Form and the Perceived Stress Scale and blood samples were obtained to measure stress hormones (i.e., cortisol, adrenocorticotropin hormone, norepinephrine, and epinephrine). **Results:** Depressive symptoms were negatively related to cortisol levels ($\beta = -0.023, p = .002$) but were positively related to rate of change in cortisol ($\beta = 0.003, p = .003$). Adrenocorticotropin hormone, epinephrine, and norepinephrine did not covary with depressive symptoms (all p values $> .05$). When the CES-D and Perceived Stress Scale were both used to predict cortisol, only the CES-D was significantly related ($\beta = -0.025, p = .017$). **Conclusions:** Depressive symptoms were negatively related to cortisol, but this relationship changed from the time of diagnosis/surgery through 12 months. Cortisol may initially provide a buffering effect against depression during the stress of initial diagnosis and treatment, but this relationship seems to change over time. **Key words:** cancer, depression, stress, cortisol.

ACTH = adrenocorticotropin hormone; CES-D = Centers for Epidemiological Studies Depression Scale.

INTRODUCTION

Among women with breast cancer, 20% to 30% experience significant depressive symptoms (1). Depressive symptoms are associated with poorer survival (2). Alterations in the physiological stress response (such as differences in cortisol and the catecholamines) may be a pathway through which depressive symptoms affect disease course (3). Changes in the stress response have been documented in people with depression, such as increases in cortisol from the hypothalamic-pituitary-adrenal axis and changes in the catecholamines, epinephrine, and norepinephrine. Most studies have shown no association between depressive symptoms and adrenocorticotropin hormone (ACTH), however (4–6).

Research from noncancer populations may not apply to patients with cancer because of stress response abnormalities associated with cancer diagnosis (7). Some cancer studies have shown positive relationships of morning cortisol and depressive symptoms (8,9), but others have shown no relationship (10,11). Depressive symptoms were more consistently related to evening cortisol (8,11). Cortisol output has been found to be unrelated to depressive symptoms, whereas cortisol slope was related to depressive symptoms (9–11). However, these data come from cross-sectional designs, and studying patients with cancer across time could illuminate the source of the inconsistencies. The only longitudinal studies have been trials of psychological treatments in patients with cancer, with some providing indirect evidence of the relationship of stress hormones and depression (12–14), although others show no relationship (15–17).

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This study investigates the longitudinal association of depressive symptoms with stress hormones in a sample of patients with breast cancer. Previous research with this sample had shown that change over time in subjective stress was related to natural killer cell lysis (18). This suggests that the relationship of depressive symptoms and stress hormones may also change across time. In addition to investigating the relationship of depression and stress hormones, the potential role of subjective stress was examined. Because depression and stress are related, these secondary analyses tested whether perceived stress was related to stress hormones and if perceived stress could account for the relationship of depression and stress hormones.

METHODS

Participants and Procedures

The study was conducted after approval by the institutional review board. A convenience sample of patients ($n = 227$) accrued between surgery and the start of adjuvant treatment and consented for participation in a randomized controlled trial of a biobehavioral intervention (see previous report for a description of accrual procedures (19)) were used. Inclusion criteria included a recent diagnosis of stage II or III breast cancer. Exclusion criteria were refusal of cancer treatment, a diagnosis of mental retardation, untreated psychopathology (self-reported), or neurologic/immunological disorders. Participants were accrued between May 1994 and May 2000.

The mean of initial assessment was approximately 37 days (range, 14–101) after surgery. Blood was drawn between 8:00 and 11:00 AM at each assessment to reduce diurnal variation. Patients were regularly instructed by the staff as well as study personnel to not eat after midnight, though, to have fluid intake. Participants sat for 10 minutes before blood collection. Catecholamines and ACTH were collected on 158 of the 227 participants as the collection of catecholamines and ACTH began after the first 69 participants were accrued. Participants with catecholamine/ACTH data were more likely to be stage II than stage III ($p = .026$) and to have lumpectomy than mastectomy ($p = .043$). Blood was transported by courier and treated with heparin to prevent clotting. After transport, blood was centrifuged and serum was frozen (-80°C without preservatives and in 12×75 polypropylene tubes). Patients were then randomized to Intervention and Assessment or Assessment Only arms and the Intervention cohorts began treatment (20), which concluded at 12 months. Subsequent assessments occurred at 4, 8, and 12 months. As most women were undergoing active treatment and often visiting the medical centers, all assessments occurred during clinic visits and questionnaire and blood data were often collected during the same medical appointments (approximately 90% on the same day and another 4% within a week). Participants were recruited in 13 cohorts (waves), and endocrine analyses were run for each cohort within 2 weeks of the cohort completing the 12-month blood draw. All four samples for each cohort (baseline and

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4-, 8-, and 12-month) were run together. The intervention did not significantly affect depression in the entire sample but reduced depressive symptoms for those with high initial depressive symptoms (21).

Measures

Depressive Symptoms

Depressive symptoms were measured using the Iowa short form (22) of the Center for Epidemiological Studies Depression Scale (CES-D (23)). The Iowa short form consists of 11 items from the full-length (20-item) CES-D. Each item is rated on a 3-point scale from 0 (*hardly ever or never*) to 2 (*much or most of the time*) over the previous week. Total scores range from 0 to 22, and higher scores reflect greater depressive symptoms. Internal consistency was 0.74. Unlike other measures of depressive symptoms, the CES-D is relatively unaffected by physical symptoms and is, therefore, commonly used in research with medical patients (24). This short form of the CES-D was also preferable to other measures because it includes only two physical symptoms, appetite and sleep changes.

Subjective Stress

The Perceived Stress Scale (PSS) was used to measure subjective stress (25). The 10-item version was used and consists of 10 items measuring perceptions of one's stress and ability to cope with stress (example item "How often have you felt nervous or stressed?"). Items are rated on a 0 (never) to 4 (very often scale) and, after reverse scoring for four items, are summed to create a total score in which total scores indicate greater perceptions of stress. The 10-item PSS has been shown to have adequate reliability and validity (26).

Cortisol

Cortisol levels in plasma were measured. All determinations were made using the Cortisol Coat-A-Count RIA (Diagnostic Products Corporation, Los Angeles, CA). Per the manufacturer, intra-assay variation is 4.3% and interassay variation is 5.2%. Sensitivity is 0.2 µg/dl. Normal levels for serum morning cortisol are between 5 and 23 µg/dl.

Adrenocorticotropin Hormone

ACTH was measured using the Immulite 1000, with reagents manufactured specifically for this instrument (Diagnostic Products Corporation). Per the manufacturer, intra-assay coefficient of variation is 5.6% and inter-assay coefficient of variation is 7.8%. Sensitivity is 9 pg/ml. This assay was read and calculated with the System Luminometer 400 (Nichols Institute, San Clemente, CA).

Catecholamines

Norepinephrine and epinephrine determinations were made by high-performance liquid chromatography with ElectroChemical Detection using Standards and Chemistry (Alumina extraction) purchased from ChromSystems, Munich,

Germany (US affiliate Thermo-Alko, Beverly, MA). C-18 Columns were purchased from the Waters Corporation (Milford, MA). Per manufacturer, intra-assay variation, interassay variation, and sensitivity for norepinephrine were 3%, 6%, and 15 pg/ml, respectively. For epinephrine, values were 6%, 13%, and 6 pg/ml.

Analytic Strategy

Hierarchical linear modeling was used to test the association of depressive symptoms with stress hormones, and all analyses were conducted using SPSS. One model was constructed for each of the four, natural log-transformed outcomes (cortisol, ACTH, norepinephrine, epinephrine). Outcome variables were log transformed consistent with recommendations that advise transformation due to skew in endocrine data (27). Depressive symptoms were time varying and continuous in all models. The following variables were entered as controls: chemotherapy and radiation therapy (time varying), estrogen and progesterone receptor status, time from surgery to baseline, age, income, and study arm. Unconditional growth models were constructed using linear and quadratic trajectories as the only predictors for each outcome. Quadratic effects were not included in subsequent models if the effects were not significant in the unconditional growth models. The quadratic effect was only significant for ACTH and was not included in the models for cortisol, epinephrine, and norepinephrine. These models also included a random intercept coefficient and tested whether a random slope coefficient significantly improved model fit; however the random slope coefficient was not significant in any model. The random intercept was significant and was retained in all models. Then, a series of models were run using all control variables, depressive symptoms, and interaction terms with linear and, when indicated, quadratic trends. For significant effects, the antilog was used to transform coefficients back to regular unit values, and the antilog was reported in text. We chose to use the continuous CES-D score; a dichotomous variable created by a cut point would result in loss of power (28).

For significant main effects of depressive symptoms, secondary analyses examined the role of subjective stress. We first tested if perceived stress was related to stress hormones using the same hierarchical linear modeling outlined above; the same control variables were used. Second, both perceived stress and depressive symptoms were entered into a model to determine which variable significantly predicted the stress hormone outcome.

RESULTS

The average participant was middle aged (mean age = 50.58), white (90%), and in a relationship (73%) and had middle to high socioeconomic status (14.34 years of education, mean = family income of US\$65,000/y). A slight majority had received radiation therapy (52%) and the majority received chemotherapy (87%). Table 1 lists the descriptive statistics for the

TABLE 1. Means and Standard Deviations for Measures of Depressive Symptoms, Perceived Stress and Stress Hormones Across Assessments

	Baseline, M (SD)	4 mo, M (SD)	8 mo, M (SD)	12 mo, M (SD)
CES-D	6.08 (3.69)	4.90 (4.02)	4.32 (3.77)	4.12 (3.79)
Percent above clinical cutoff	19.8	13.7	11.4	10.9
PSS	18.44 (6.99)	15.69 (7.29)	15.08 (6.80)	14.92 (6.91)
Cortisol, µg/dl	11.02 (4.77)	11.99 (5.44)	13.18 (5.02)	12.84 (5.18)
Median	10.10	10.80	13.07	12.25
ACTH, pg/ml	21.56 (11.72)	18.71 (10.75)	17.45 (9.27)	18.62 (11.13)
Median	19.75	14.95	14.30	15.95
Epinephrine, pg/ml	29.31 (19.17)	26.91 (15.70)	26.32 (14.93)	26.30 (15.37)
Median	23.00	24.06	22.17	23.58
Norepinephrine, pg/ml	330.79 (153.38)	339.72 (169.44)	372.44 (178.25)	359.40 (177.33)
Median	294.94	308.76	349.54	308.11

CES-D = Center for Epidemiological Studies Depression scale; PSS = 10-item Perceived Stress Scale. ACTH = adrenocorticotropin hormone; M = mean; SD = standard deviation.

Clinically significant distress cutoff for CES-D was a score of 10.

TABLE 2. Nonparametric Correlations of the Natural Log-Transformed Stress Hormones With the CES-D at Each of the Four Assessments

CES-D	Cortisol	ACTH	Epinephrine	Norepinephrine
Baseline	-0.082	-0.098	-0.042	-0.039
4-mo	-0.109	0.030	0.001	-0.153
8-mo	-0.060	0.068	-0.207 ^a	-0.055
12-mo	0.002	-0.051	-0.248 ^a	-0.138

CES-D = Center for Epidemiological Studies Depression Scale; ACTH = adrenocorticotropin hormone.

^a $p < .05$.

endocrine and psychological measures (CES-D and PSS). Table 2 lists the correlations of the CES-D with the log-transformed stress hormones at each assessment. Nonparametric (Spearman ρ) correlations of change in the CES-D from baseline to 12 months to change in the stress hormones from baseline to 12 months were as follows: cortisol, -0.026 ($p = .74$); ACTH, 0.117 ($p = .27$); epinephrine, 0.252 ($p = .014$); and norepinephrine, -0.085 ($p = .41$).

Primary Analyses

Table 3 summarizes the fixed effects from the final model for each outcome. For significant effects of depressive symptoms, the antilog was used to return the coefficients from Table 3 to the original units and is reported here in the text. Depressive symptoms and cortisol covaried, with higher depressive symptoms associated with lower cortisol levels ($p = .002$; antilog of coefficient from Table 3: -0.208 , 95% confidence interval [CI] = -0.252 to -0.098). Also, depressive symptoms were positively associated with a linear rate of change in cortisol ($p = .002$; antilog of coefficient from Table 3: 0.004 , 95% CI = 0.001 – 0.005), indicating that higher depressive symptoms were associated with a more positive slope in cortisol over time. Figure 1 shows how the relationship of depressive symptoms and cortisol changed over time. For graphical displays, a cutpoint of 10 and above was used to indicate significant depressive symptoms (29), although the continuous measure of depressive symptoms was used in all statistical analyses. Time-varying CES-D scores were used to create the groups in Figure 1. Although only linear change was included in the analyses, the lines in the graphs are not straight because of the changing effect of depressive symptoms over time and smoothing of the interpolation line. We also ran additional multiple regressions at each time point (baseline, 4, 8, 12), predicting both the natural log of cortisol (lnCort) and the level of cortisol predicted by the mixed-effects model (pred) from CES-D (with covariates listed above) to demonstrate that the CES-D and cortisol were more strongly related at baseline than at later time points. Results indicated that the CES-D and cortisol were most strongly related at baseline (lnCort: -0.018 , $p = .065$, CI = -0.037 to 0.001 ; pred: -0.020 , $p < .001$, CI = -0.026 to -0.013) and 4 months (lnCort: -0.020 , $p = .092$, CI = -0.043 to 0.003 ; pred: -0.015 , $p < .001$, CI = -0.022 to -0.008) than 8 months (lnCort: 0.001 , $p = .90$, CI = -0.015

to 0.017 ; pred: -0.001 , $p = .71$, CI = -0.008 , to 0.006) or 12 months (lnCort: 0.005 , $p = .50$, CI = -0.010 to $.021$; pred: 0.006 , $p = .10$, CI = -0.001 to 0.013).

Depressive symptoms were not associated with ACTH levels ($p = .31$), linear rate of change in ACTH ($p = .24$), or quadratic rate of change in ACTH ($p = .40$), indicating that depressive symptoms were unrelated to the level of ACTH or slope of ACTH across time. Depressive symptoms were not associated with norepinephrine levels ($p = .47$) or associated with differences in slope or linear rate of change in norepinephrine during this period ($p = .78$).

Depressive symptoms were not associated with epinephrine levels ($p = .56$). Higher depressive symptoms showed a trend of being negatively associated with linear rate of change (slope) in epinephrine, indicating that a more negative slope in epinephrine over time was associated with higher depressive symptoms ($p = .065$; antilog of coefficient from Table 3: -0.002 , 95% CI = -0.005 to 0.0001). However, this effect did not reach significance.

TABLE 3. Summary of Fixed Effects for Final Models of Stress Hormone Trajectories

Effect	Estimate	p	95% Confidence Interval
Cortisol			
Intercept	2.211	<.001	1.911 to 2.510
Linear	0.031	.243	-0.021 to 0.084
CES-D	-0.023	.002	-0.038 to -0.008
CES-D \times Linear	0.003	.002	0.001 to 0.005
ACTH			
Intercept	3.010	<.001	2.465 to 3.554
Linear	-0.078	.407	-0.262 to 0.107
Quadratic	0.004	.633	-0.013 to 0.021
CES-D	-0.011	.361	-0.034 to 0.012
CES-D \times Linear	0.005	.211	-0.003 to 0.012
CES-D \times Quadratic	-0.0003	.341	-0.001 to 0.0003
Epinephrine			
Intercept	3.389	<.001	2.984 to 3.795
Linear	-0.047	.198	-0.118 to 0.024
CES-D	0.003	.778	-0.018 to 0.024
CES-D \times Linear	-0.002	.065	-0.005 to 0.0001
Norepinephrine			
Intercept	5.486	<.001	5.186 to 5.787
Linear	0.071	.007	0.019 to 0.122
CES-D	-0.004	.569	-0.020 to 0.011
CES-D \times Linear	-0.0002	.797	-0.002 to 0.002

CES-D = Center for Epidemiological Studies Depression Scale; ACTH = adrenocorticotropin hormone.

The parameter estimates were calculated using hierarchical linear modeling and maximum likelihood estimation. Outcomes are the natural log of the stress hormone, and values reported in the table are for the original models of the transformed outcomes. Significant effects of depressive symptoms were back-transformed into the original units and are reported in the text. Controls are not shown for clarity. The linear term refers to monthly changes since the baseline assessment.

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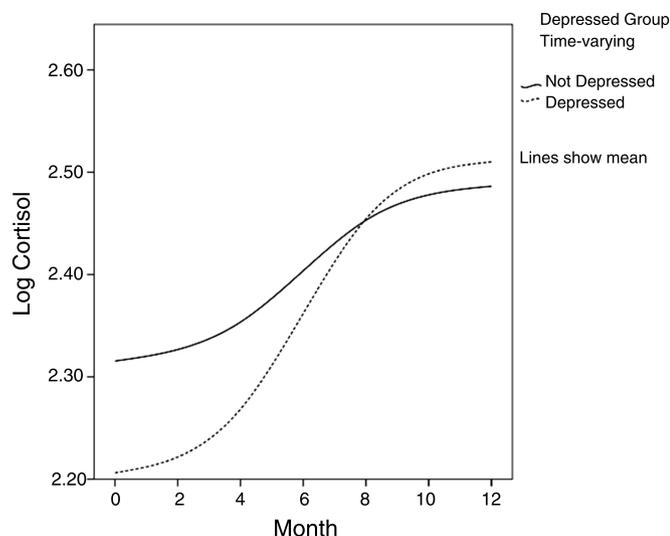


Figure 1. Log-transformed cortisol trajectories. The y-axis refers to predicted cortisol level. Low and high depressive symptom groups were created using a cutpoint of 10 on the time-varying CES-D (CES-D at each assessment was used to create groups for that assessment) and are presented for graphical purposes only. The following variables were controls in all analyses: chemotherapy and radiation therapy, estrogen and progesterone receptor status, time from surgery to baseline, age, income, and study arm (intervention versus assessment only). Sample sizes for the groups at each time point were as follows: baseline not depressed: $n = 182$, baseline depressed: $n = 45$; 4 months not depressed: $n = 170$, 4 months depressed: $n = 27$; 8 months not depressed: $n = 171$, 8 months depressed: $n = 22$; 12 months not depressed: $n = 164$, 12 months depressed: $n = 20$. CES-D = Center for Epidemiological Studies Depression Scale.

Secondary Analyses

Because depressive symptoms were significantly associated with cortisol, secondary analyses first considered the relationship of subjective stress to cortisol. Subjective stress showed a trend toward significance when predicting cortisol ($\beta = -0.007$, $t = -1.760$, $p = .079$) and change in cortisol over time ($\beta = 0.001$, $t = 1.870$, $p = .062$). Second, when both depression and subjective stress were variables in the model, depressive symptoms were significantly related to overall level of cortisol ($\beta = -0.025$, $t = -2.390$, $p = .017$) and were significantly related to linear change (slope) of cortisol ($\beta = 0.003$, $t = 2.233$, $p = .026$). However, subjective stress was not related to overall level of cortisol ($\beta = 0.003$, $t = 0.455$, $p = .65$) or linear change of cortisol over time ($\beta = -0.0003$, $t = -0.346$, $p = .73$).

DISCUSSION

The present study investigated the covariation of stress hormones with depressive symptoms in a sample of patients with breast cancer in the year after diagnosis and surgery. We confirmed our hypothesis that the relationship of depressive symptoms and stress hormones changed over time. Depressive symptoms were related to rate of change in cortisol and epinephrine but were unrelated to ACTH, epinephrine, and norepinephrine. Secondary analyses suggested that the relationship of depressive symptoms to cortisol was not accounted for by any relationship to subjective stress.

Results suggest that depressive symptoms are initially related to lower cortisol and that the first year postdiagnosis is a

period of change in the relationship of depressive symptoms and the levels of morning cortisol. Some research has suggested that heightened cortisol during stress can buffer against negative affect (30). Because stress was highest near diagnosis in this sample (18), morning cortisol seemed to provide a buffering effect against depressive symptoms during this high-stress time, but the buffering effect faded over the first year as stress decreased. Depressive symptoms were also associated with greater increases in cortisol. As indicated in Figure 1 and the significant change in slope associated with depressive symptoms, the relationship of depressive symptoms to cortisol became weaker over time, consistent with cortisol providing a buffering effect only during initial stress. These results suggest that the relationship of depressive symptoms to stress hormones is in flux in the year after diagnosis.

Results showed that ACTH, epinephrine, and norepinephrine were unrelated to depressive symptoms, unlike cortisol. Past research on depressive symptoms and ACTH has shown disparate results (4). Even chronic stress (e.g., traumatic events and caregiving) does not have a consistent relationship to ACTH (31). For epinephrine and norepinephrine, some evidence suggests that peripheral catecholamines may be elevated in people with depressive symptoms (6), but the effect of an additional stressor (breast cancer treatment) may have hidden any association with norepinephrine or epinephrine.

The data are considered within the limitations of the study. The study was conducted within high-volume, stressful oncology clinics. Most of the sample was receiving chemotherapy, so blood collection for count monitoring was routine. We were able to achieve appointments for the study patients in the morning hours, albeit not a specific time, and time of awakening on the day of the blood draws was not available. We anticipate compliance with instructions to not eat before the blood draw but do not know so for a fact. Our single-assessment results for morning cortisol may differ when diurnal cortisol slope and afternoon and evening measures are used. We used serum collection for the catecholamines. A more general catecholamine measure could be achieved with 24-hour urine collection (32). Although the latter is feasible in some settings, it was not in this clinical context. It is difficult to know how robust the effects reported are. The design used a depressive symptom measure, and the large and homogeneous sample increased power. Other designs, such as contrasting smaller groups composed of patients with or without a diagnosis of major depression (4) or more heterogeneous groups, would be a useful compliment to these findings.

In summary, the results suggest that changes in the stress response may be one mechanism through which depressive symptoms affect health and outcomes in breast cancer survivors (33). The physiological stress response can influence cancer outcome through immune function (3) as well as more directly (34). The study showed a negative relationship between stress hormones and depressive symptoms that differ from previous research (8–11) in cancer samples. However, previous cancer studies were conducted at a variety of points after diagnosis whereas this study spanned the first year. Essentially, the

changes in cortisol related to depressive symptoms were decreased amounts of cortisol during a stressful period and not elevation of morning cortisol. Overall, the relationships between psychological variables such as depressive symptoms and stress hormones are neither obvious nor simple, although they are important for understanding stress and coping in both the healthy and those with disease.

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