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ORIGINAL REPORT

Decrease in Depression Symptoms Is Associated With Longer Survival in Patients With Metastatic Breast Cancer: A Secondary Analysis

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ABSTRACT

Purpose
Numerous studies have examined the comorbidity of depression with cancer, and some have indicated that depression may be associated with cancer progression or survival. However, few studies have assessed whether changes in depression symptoms are associated with survival.

Methods
In a secondary analysis of a randomized trial of supportive-expressive group therapy, 125 women with metastatic breast cancer (MBC) completed a depression symptom measure (Center for Epidemiologic Studies–Depression Scale [CES-D]) at baseline and were randomly assigned to a treatment group or to a control group that received educational materials. At baseline and three follow-up points, 101 of 125 women completed a depression symptom measure. We used these data in a Cox proportional hazards analysis to examine whether decreasing depression symptoms over the first year of the study (the length of the intervention) would be associated with longer survival.

Results
Median survival time was 53.6 months for women with decreasing CES-D scores over 1 year and 25.1 months for women with increasing CES-D scores. There was a significant effect of change in CES-D over the first year on survival out to 14 years ($P = .007$) but no significant interaction between treatment condition and CES-D change on survival. Neither demographic nor medical variables explained this association.

Conclusion
Decreasing depression symptoms over the first year were associated with longer subsequent survival for women with MBC in this sample. Further research is necessary to confirm this hypothesis in other samples, and causation cannot be assumed based on this analysis.

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INTRODUCTION

Can psychosocial factors such as depression influence cancer survival? Researchers have examined this intriguing question in studies testing associations between depression and cancer survival[1] and in studies testing whether psychosocial interventions that reduce depression can prolong survival,[2-6] although none of these studies was designed a priori to test these associations. Although differences across studies in cancer type, depression definitions, and measures limit definitive conclusions,[7] an answer is emerging to the question of whether depression is associated with shorter survival. The answer seems to be yes.[1]

A recent meta-analysis of 31 prospective studies found a 25% higher mortality rate for patients with cancer with depressive symptoms and a 39% higher mortality rate for those with major depression, after adjusting for prognostic factors.[1] This analysis clarifies earlier reviews of the role of depression in cancer progression.[7-12] Results from intervention studies are less conclusive. The results of new intervention studies examining survival and efforts to replicate studies showing that psychosocial interventions prolonged cancer survival[2,13] are mixed; one study has shown such an effect,[4,6] but some studies show no difference in survival outcomes despite improvements in distress.[3,5,14,15] The important question of whether treating depression can prolong survival in patients with cancer remains unanswered.

Strong research and clinical evidence suggests that depression and cancer co-occur, with bidirectional relationships potentially linking depression with cancer progression.[16-21] Researchers have

found prevalence rates of up to 38% for major depression and 58% for depression-spectrum syndromes, depending on the cancer site[22] and stage.[23] Cancer's multiple traumatic losses can lead to or restimulate depression.[24-26] To examine whether treating depression can affect survival, researchers must test whether changes are associated with survival. If depression improves, will survival lengthen?

Studies investigating depression and survival from breast cancer yield divided results[27-37] and highlight the impact of multiple measures on outcome. In a study of 24,696 older patients with breast cancer at any stage in the United States, patients diagnosed with depression within 2 years before cancer died sooner than patients without depression.[31] In a population-based study of 20,593 patients with early- or late-stage breast cancer in Denmark, patients hospitalized for depression died sooner.[35] Conversely, researchers found no association between depression and survival in a study of 49 patients with metastatic breast cancer (MBC),[37] or in a study of 297 patients with primary breast cancer.[28] In studies in which researchers demonstrated significant associations between depression and survival, participants more often reported depression multiple times, through multiple diagnoses,[31] diagnoses of persistent depression,[35] or multiple measurements during the study.[34]

Few survival studies assess changes in depression.[2,7,20] Single measurements of depression may obscure results because chronic or major depression is associated more strongly with cancer survival.[11,38,39] Depression that is present at a single time point and resolves in a timely manner might be an appropriate and adaptive response to diagnosis and not a risk factor for shorter cancer survival,[7,40] a point reinforced by findings that repression of distress predicts poor cancer outcomes.[41-43]

Specific physiologic mechanisms and treatment nonadherence may link depression and cancer progression. Depression may promote cancer through dysregulation of respiratory sinus arrhythmia,[19,44] effects on the hypothalamic-pituitary-adrenal (HPA) axis,[45,46] immune suppression,[9] or increases in inflammation.[20,47] Depression reduces adherence to treatment recommendations, which can impact physiologic outcomes.[4,48-50] Because people can improve deficits in respiratory sinus arrhythmia,[51] inflammation,[20] HPA axis function,[52] adherence to treatment,[53] and other features of depression through intervention, examining whether changes in depression improve survival is timely and essential.

In the current secondary analysis, we hypothesized that decreases in depressive symptoms in patients with MBC over the first year of a randomized clinical trial (RCT) would be associated significantly with subsequent survival. Because of possible bidirectional associations, tests were two-tailed.

METHODS

Sample

Between 1991 and 1996, we screened 155 women for eligibility for this RCT of supportive-expressive group therapy (SET) and excluded 30 women before random assignment (12 were excluded as a result of disease progression, seven were ineligible after medical record review, and 11 did not want to continue; Fig 1). Thus, 125 women provided written informed consent, approved by the Stanford Institutional Review Board. We included women with documented metastatic or recurrent (n = 3) breast cancer (recurrence in the same breast after lumpectomy and judged by our medical oncologist to have equivalent prognoses). We excluded women

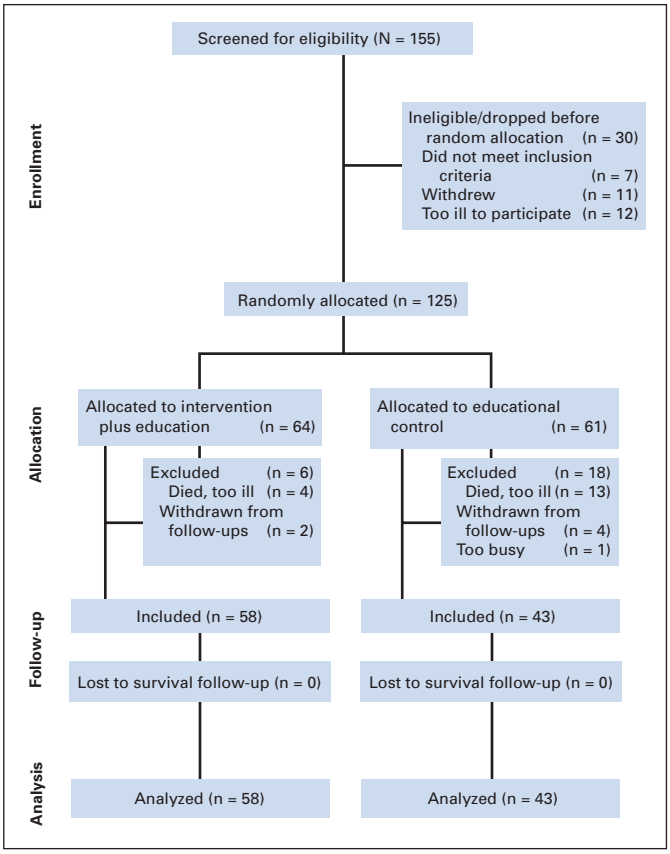

Fig 1. CONSORT diagram.

with a Karnofsky performance score of less than 70, so that all participants were engaging in normal activity. All participants lived in the Greater San Francisco Bay Area, spoke English, and could complete questionnaires. We excluded women who did not have metastasis beyond positive supraclavicular lymph nodes, had active cancers within 10 years (other than breast cancer, basal cell or squamous cell carcinomas of the skin, in situ cancer of the cervix, or melanoma with a Breslow depth < 0.76 mm), or had medical conditions that could affect short-term survival.

All participants (N = 125) received educational materials and completed the Center for Epidemiologic Studies–Depression Scale (CES-D), among other measures, at baseline (before random assignment) and at 4, 8, and 12 months (for more complete information on this study, see Spiegel et al[3] or Giese-Davis et al[54]). The treatment group received 1 year of SET (n = 64), which was not offered to the control group (n = 61).

In the primary analysis to test our hypothesis, we included all 101 of 125 women who provided at least one CES-D follow-up questionnaire so that the linear slope of change in depression symptoms over 1 year could be estimated. Change in depression score is estimated from the data and, therefore, has a certain error variance that is not considered in the analysis.

Of the 24 excluded women, 17 women had died or were too ill to complete the questionnaires, five women withdrew, and two women were too busy or no longer interested. Table 1 lists the demographic and medical information for both included and excluded women. Women providing follow-up data were significantly less depressed at baseline, less likely to be estrogen receptor negative, and had less often received chemotherapy and more often received hormone therapy, which are all indicators of a less advanced disease state.

Depression Symptoms

The CES-D[55] is a self-report Likert-type scale rated for the past week from 0 (rarely) to 3 (most or all of the time) and includes 20 common affective

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Table 1. Demographic, Medical, and Independent Variables Measured at Baseline for Patients With Metastatic Breast Cancer Included and Excluded From Primary Analyses (N = 125)

Variable	Included Patients (n = 101)		Excluded Patients (n = 24)		Effect Size, SRD
	No.	%	No.	%	
CES-D baseline*					−0.25
Mean	11.06		15.42		
SD	9.11		10.48		
CES-D slope					
Mean	0.05		—		
SD	0.92				
Age, years					0.04
Mean	53.53		51.79		
SD	10.61		10.87		
Age at initial diagnosis, years					0.01
Mean	47.37		46.50		
SD	10.11		10.80		
Age at metastatic diagnosis, years					0.02
Mean	51.24		50.54		
SD	10.30		10.38		
Disease-free interval, months					−0.04
Mean	45.77		47.66		
SD	35.94		34.24		
Time from metastatic diagnosis to study entry, months					0.16
Mean	27.37		17.04		
SD	40.59		29.34		
No. of years of education					0.08
Mean	16.09		16.21		
SD	2.58		2.41		
Ethnicity					
Asian	8	7.9	0	0.0	0.08
Black	1	1.0	0	0.0	0.01
Hispanic	1	1.0	2	8.3	−0.07
Native American	2	2.0	0	0.0	0.02
White	87	86.1	22	91.7	−0.06
Other	2	2.0	0	0.0	0.02
Marital status					
Married	59	58.4	12	50.0	0.08
Never married	10	9.9	1	4.2	−0.06
Separated	2	2.0	1	4.2	−0.02
Divorced	23	22.8	9	37.5	−0.15
Widowed	6	5.9	1	4.2	−0.02
Other	1	1.0	0	0.0	−0.01
Household income					−0.27
< $20,000	14	13.9	3	12.5	
$20,000-$39,999	11	10.9	7	29.2	
$40,000-$59,999	25	24.8	7	29.2	
$60,000-$79,999	12	11.9	2	8.3	
$80,000-$99,999	13	12.9	2	8.3	
≥ $100,000	25	24.8	3	12.5	
Estrogen receptor status					
Negative†	15	14.9	10	41.7	−0.27
Positive	80	79.2	13	54.2	
Treatment					
Chemotherapy*	43	42.6	17	70.8	−0.28
Hormone therapy†	84	83.2	13	54.2	0.29
Site of metastasis					−0.01
Chest wall	29	28.7	9	37.5	
Bone	44	43.6	6	25.0	
Viscera	28	27.7	9	37.5	

NOTE. Included sample includes every woman who had completed at least one follow-up CES-D questionnaire and for whom a slope of CES-D over 1 year could be created. Excluded sample includes every woman for whom no follow-up CES-D questionnaires were completed and for whom no slope could be created. Significance tests were two-tailed.

Abbreviations: SRD, success rate difference; CES-D, Center for Epidemiologic Studies–Depression Scale; SD, standard deviation.

*$P < .05$.

†$P < .01$.

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symptoms (13 items) and somatic symptoms (seven items) of depression.[56] Researchers designed this scale as an epidemiologic instrument for community samples. It does not provide a diagnostic criterion for depression, although a score of 16 or higher indicates clinically significant depression. Previous test-retest reliability coefficients for patients with breast cancer and healthy controls were adequate at 0.57 ($P = .001$) and 0.51 ($P = .001$), respectively, over 2.5 weeks.[57] Cronbach's α was 0.89 at baseline.

Survival

Research staff obtained follow-up survival data from the participants, their families, and/or physicians or by consulting the Social Security Death Index. A death certificate confirmed all reported deaths. Breast cancer was the cause of death for 94.4% of the sample. Three patients died of cardiopulmonary causes, two died of neurologic disease, and one died of colon cancer. Cause of death was determined either by death certificate (82%) or medical records (18%).

Intervention: SET

Researchers designed this RCT to replicate a previous finding that women with MBC randomly assigned to SET lived significantly longer than women assigned to a control group.[13] In the current trial, women randomly assigned to SET received weekly 1.5-hour group sessions led by cotherapy teams. Researchers encouraged women to attend SET sessions for at least a year, and many attended until just before death. Women randomly assigned to SET in this trial improved significantly with regard to trauma symptoms, mood disturbance,[58] pain,[59] and emotion regulation.[54] However, we could not demonstrate an overall increase in survival time for the intervention group, although in a significant moderator analysis, estrogen receptor–negative women lived longer in the treatment group.[3]

Educational Control Group

We randomly assigned half of the women to a control group that received educational materials only. Thirty-two women (53%) in the control group and 35 women (55%) in the treatment group used these resources.

Analysis

In the primary a priori analysis, we used Cox proportional hazards to test for the effects of linear slope of change[60] in CES-D depression symptoms over 1 year (as a continuous variable) on survival up to 14 years. The equation also included treatment condition (intervention or control), geographic site (San Francisco, San Jose, or Stanford), and all interactions (with all variables centered).[61] For descriptive purposes only, we used Kaplan-Meier analysis with a split at zero CES-D change over 1 year ($<$ zero = decreasing; $\geq$ zero = increasing) as the independent variable to illustrate the effect sizes and as a basis for reporting the median survival statistics.

In sensitivity analyses, the analysis structure was the same; however in the first analysis, we excluded all women who died in the first year, excluding nine additional women who had died (n = 92). In the second analysis, for all 101 women, we excluded all last CES-D follow-ups just before death (and recalculated the slope of change in CES-D), resulting in a sample of 93 women, because prior evidence suggests that a common spike (increase) in CES-D symptoms occurs at this last follow-up point.[62] In the third analysis, we split the CES-D into Affective and Vegetative subscales based on prior work[56,63] and reran the original analysis.

We also examined whether baseline demographic or medical variables were significantly associated with CES-D slope of change over 1 year to test whether CES-D slope was a proxy for another underlying prognostic variable. To test this association, we conducted a one-way analysis of variance with CES-D slope of change over 1 year as the dependent variable and the demographic or clinical variable (with all levels if categorical or median split if continuous), geographic site, treatment condition, and all interactions as independent variables.

RESULTS

Primary Analysis

For women with decreasing CES-D scores over 1 year, overall median survival time was 53.6 months (n = 48), compared with 25.1 months for women with increasing scores (n = 53). A decrease in CES-D score over 1 year was significantly associated with longer survival over 14 years (n = 101; hazard ratio [HR], 1.68; 95% CI, 1.16 to 2.45; $P = .007$; Table 2, Fig 2), but we could not demonstrate any significant interaction effect of treatment condition by CES-D decrease on survival (HR, 1.48; 95% CI, 0.70 to 3.13; $P = .30$; Table 2).

Sensitivity Analyses

We challenged our results to investigate alternative explanations that would eliminate the finding. First, we removed all women from the sample who had died in the first year of the study, and we continued to find that a decrease in CES-D over 1 year was significantly associated with longer survival (n = 92; HR, 1.53; 95% CI, 1.04 to 2.26; $P = .03$).

Second, when we removed the last CES-D follow-up before death, we continued to find that a decrease in CES-D over 1 year was significantly associated with longer survival (n = 93; HR, 1.54; 95% CI, 1.05 to 2.26; $P = .03$). Thus, the result we found does not seem to be a result of early death or the biasing effects of the preterminal depression.

Table 2. Cox Regression Analysis on Survival for Change in Depression Symptoms (Slope) Over 1 Year by Treatment Group Versus Control Group by Site for Women With Metastatic Breast Cancer (n = 101)

Factor	B	SE	Wald	*df*	*P*	Hazard Ratio	95% CI
CES-D slope	0.52	0.19	7.37	1	.007	1.68	1.16 to 2.45
Condition	0.13	0.25	0.26	1	.613	1.13	0.70 to 1.85
Site, San Francisco	−0.10	0.34	0.09	1	.770	0.91	0.47 to 1.75
Site, Stanford	0.00	0.30	0.00	1	1.000	1.00	0.55 to 1.81
Condition × CES-D slope	0.39	0.38	1.07	1	.302	1.48	0.70 to 3.13
Condition × San Francisco	−2.21	0.68	10.57	1	.001	0.11	0.03 to 0.42
Condition × Stanford	−0.79	0.61	1.69	1	.194	0.45	0.14 to 1.49
CES-D slope × San Francisco	−0.75	0.51	2.17	1	.141	0.47	0.18 to 1.28
CES-D slope × Stanford	−0.78	0.52	2.24	1	.134	0.46	0.17 to 1.27
Condition × CES-D slope × San Francisco	0.23	1.01	0.05	1	.820	1.26	0.18 to 9.01
Condition × CES-D slope × Stanford	0.57	1.04	0.30	1	.582	1.77	0.23 to 13.43

NOTE. Cox regression analysis included condition, dummy variables for sites (San Francisco and Stanford), and the interaction between condition and sites. All variables were centered.

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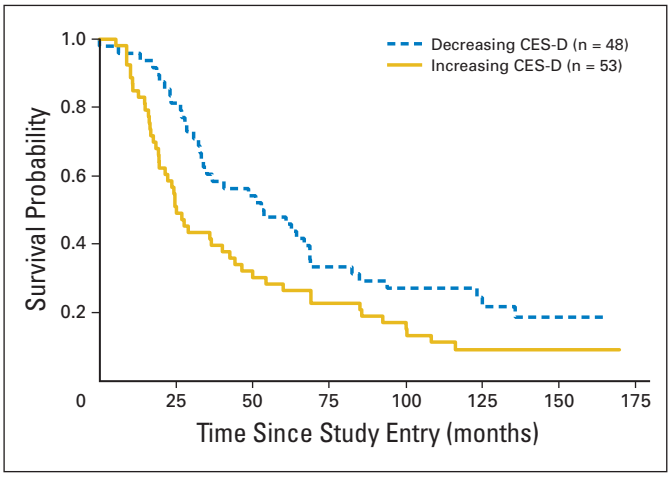

Fig 2. Kaplan-Meier survival curve for increasing (solid gold line) versus decreasing (dashed blue line) Center for Epidemiologic Studies–Depression Scale (CES-D) symptoms during the initial intervention year in a randomized trial of supportive-expressive group therapy. Breast cancer was the cause of death for 94.4% of the patients.

Third, when we split the CES-D into two subscales,[56,63] we continued to find that a decrease in either subscale over 1 year was associated significantly with longer survival (Affective scale: n = 101; HR, 2.72; 95% CI, 1.36 to 5.47; $P = .005$; Vegetative scale: n = 101; HR, 2.65; 95% CI, 1.32 to 5.32; $P = .006$).

Effect of Baseline Demographic and Prognostic Variables on Change in CES-D

We could not demonstrate that age at random assignment, age at initial diagnosis (> and < 50 years), age at metastatic diagnosis, disease-free interval, time from metastasis to study entry, years of education, ethnicity, household income, estrogen receptor status, chemotherapy, hormone therapy, site of metastasis, Karnofsky performance score, dexamethasone use, and antidepressant use were related significantly to slope of change in CES-D over 1 year. However, a significant treatment condition by marital status interaction effect on CES-D change over 1 year (n = 101; $F_{1,89} = 4.85$; $P = .03$) indicated that married women in the control group became more depressed over time, whereas women who were not married became less depressed. The opposite was true for the treatment group. Having found this significant result, we added marital status to the main equation (and its interactions) to examine whether it was a proxy for change in CES-D and might eliminate the significant survival effect. We found that CES-D decrease over 1 year still significantly predicted longer survival with marital status in the equation (n = 101; HR, 1.80; 95% CI, 1.17 to 2.75; $P = .007$).

Impact of Baseline CES-D on Survival

Although our primary hypothesis was that a decrease in CES-D over 1 year would predict significantly longer survival, we examined the impact of baseline CES-D scores as a post hoc analysis. There was no significant effect of baseline CES-D on survival over 14 years (n = 125; HR, 0.98; 95% CI, 0.95 to 1.01; $P = .11$).

DISCUSSION

As hypothesized in this secondary analysis, we found that decreases in depression symptoms over the first year of an RCT predicted longer survival times over the ensuing 14 years for a sample of 101 women with metastatic or recurrent breast cancer. Women with improving depressive symptoms had longer median survival times (53.6 months) compared with women with worsening symptoms (25.1 months). The magnitude of this effect, the roughly doubling of survival time, is comparable to that observed in studies of depression and mortality from heart disease.[64] We could not demonstrate that SET enhanced this effect significantly. Instead, for all women in the study, the more they decreased depression symptoms, the longer their survival, suggesting that any effective intervention may enhance this result. We did not find that antidepressant use was significantly associated with change in depression. Sensitivity analyses and examination of the Kaplan-Meier curve (Fig 1) indicate that the survival disadvantage is not a result of an increase in depression in the preterminal phase or primarily a result of vegetative symptoms, but rather reflects an effect of affective and somatic depression change over 1 year on mortality 2 to 14 years later.

The novelty of our study is that we found that a decrease in depression over the initial intervention year of this randomized intervention trial predicted survival many years later. This result extends past research demonstrating that multiple measurements of depression more often significantly predict survival.[31,34,35,38] Multiple measurements make it possible to test whether an individual's depression symptoms have changed (eg, the measure reflects a state) or their response reflects a chronic style or trait.[7] It is unfortunate that in prior studies with multiple measures of depression, researchers have not often used these additional data. Because of this limitation, our study is one of only a few studies to test the process of change in depression as it relates to cancer survival.[2,20]

Similar to cardiovascular disease,[64,65] cancer researchers increasingly find significant associations between depression and endocrine dysregulation,[45] heart rate variability,[19] inflammatory markers,[17,20,66] and mortality end points.[1] Some hypothesize that these relationships represent a common mechanism of disease.[44,66-71]

We have previously reported greater cortisol dysregulation among patients with MBC than among controls[72] and that dysregulation of diurnal cortisol predicts shorter survival for patients with breast cancer.[73] Strong evidence exists that cortisol dysregulation is common in depression.[19,74] Abnormal glucocorticoid levels may represent a failed response to the chronic inflammatory aspects of cancer, which depression may exacerbate.[20] Tumor cells can co-opt certain mediators of inflammation such as nuclear factor-κB and growth-promoting cytokines and angiogenic factors to promote tumor progression and metastasis. Such chronic inflammation with relatively constant cytokine release into the circulation may trigger a glucocorticoid response that disrupts circadian variation in cortisol levels. This may induce a cycle of glucocorticoid resistance that disrupts negative feedback and glucocorticoid control,[66] as we found in patients with MBC.[75] Thus, there may be an inflammatory cytokine-mediated influence on diurnal cortisol that is associated with breast cancer and its progression. This effect would be worsened by the HPA axis dysregulation associated with depression, which is also connected to cytokines that trigger sickness behavior[76-79] and is coupled with HPA axis hyperactivity.[80,81] Dexamethasone, which is commonly given during chemotherapy,[82] can also impact these physiologic systems. Dysregulation is also associated with sleep and other circadian system disruptions.[73,83] Alleviating depression may reduce this inflammatory cycle,[20] in addition to reducing sickness signs and symptoms.[84]

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Correlation does not equate with causation even though the change in depression in our sample preceded the survival outcomes.[64] A third proxy variable, that current research has not identified, could drive both outcomes. Caution interpreting these results is warranted because tumors themselves can induce depression-like behavior in rats[21] and it is possible that the developing cancer has broad physiologic and psychological impact that is reported at the symptom level as depression.[85]

We did not measure treatment adherence. However, decreasing depression may accompany an improvement in both health behaviors and adherence[53] and may mediate physiologic and survival outcomes.[4,48]

A possible clinical implication of our study is that although becoming depressed shortly after diagnosis may be a normal, necessary, and healthy experience of grieving and adjustment, if depression lingers, it may have toxic survival consequences.[7,11] Future research needs to examine these processes of change in depression symptoms and their physiologic and survival correlates.

The details of these associations must await future research; however, here we have evidence that the course of depression over 1 year predicts subsequent survival time and that adjustment for prognostic variables does not alter significance. Treatment of depression, both psychotherapeutic and pharmacologic, is feasible and effective even in advanced cancer.[86-89] Although we were unable to show that an intervention likely to decrease depression was associated with increased survival, we did demonstrate that decreasing depression, with or without formal intervention, may improve not only the quality but also the quantity of life for women with advanced breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Janine Giese-Davis, Helena C. Kraemer, David Spiegel
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