Psychological Distress and Cancer Survival: A Follow-Up 10 Years After Diagnosis

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Objective: This study tested the predictive role of psychological distress in cancer survival, while attempting to overcome several important methodological and statistical limitations that have clouded the issue. **Methods:** Measures collected on a range of emotional and cognitive factors in the early postdiagnostic period and at 4-month intervals up to 15 months after diagnosis were used to predict survival time up to 10 years among 205 cancer patients heterogeneous in disease site, status, and progression. **Results:** With the use of both baseline and repeated measures, depressive symptomology was the most consistent psychological predictor of shortened survival time, after controlling for several known demographic and medical risk factors. **Conclusions:** Given the importance of depressive symptoms to cancer survival, discussion focuses on the possible mechanisms mediating this relationship, the importance of psychological screening of cancer patients, and need for further research. **Key words:** depressive symptoms, survival, time dependence.

CES-D = Center for Epidemiological Studies Depression scale; **CI** = confidence interval; **HR** = hazard ratio; **MI** = multiple imputation

INTRODUCTION

Cancer patients who outlive their prognoses often believe there is a direct relationship between their psychological states and their long-term survival (1). In the research community, considerable controversy surrounds the issue of whether cognitive and emotional states can influence long-term survival after cancer diagnosis. To date, research has explored the predictive role of both general psychological states and specific features. Measures of general emotional and/or cognitive condition have typically been shown to have little or no value in predicting length of disease-free and/or overall survival (2, 3). Several specific psychological features have been shown to influence cancer course, including depression (4) and "fighting spirit" (or helplessness/hopelessness) (5). Lack of social support has also been shown to play a predictive role (6). Several well-controlled studies have demonstrated that psychosocial intervention can lengthen survival in both early and advanced stage cancer patients (7, however see 8).

The role of the psyche in cancer course is lent support by such findings, but it is not difficult to find studies that contradict them, by showing null effects for the role of such specific factors as depression (9), hopelessness (10), and anxiety (11). Research has shown self-reported physical health to be a more important predictor of survival than psychological distress (12). Some have argued that current evidence for the role of psychological influences is inconclusive at best (13). Whether psychological factors affect cancer course has important implications, both for the role of psychological screening and treatment of cancer patients, and for our understanding of the role of the mind in the disease process.

Several methodological problems have contributed to the uncertainty surrounding the mind-cancer issue. Failure to control for important medical and demographic risk factors can inflate the importance of psychological factors in cancer survival. On the other hand, even when such control is in place, small sample sizes have limited the power of analyses to detect the effects of psychological factors, which may be small in comparison to powerful medical and demographic effects like cancer stage and gender. Furthermore, when samples are restricted to advanced stage patients, the role of psychological factors may be extremely difficult to detect, because the forward momentum of cancer-related biological processes is very strong.

As noted, measures of general psychological state have usually not predicted cancer course. But the use of a single measure of cognitive and/or emotional distress may mix specific features that have effects on cancer course with those that do not, thereby weakening or nullifying psychological influences. Measurement timing may also be important. Measures collected once, early in the postdiagnostic period, have been commonly used to predict survival years later (2, 11). High levels of distress are common in the postdiagnosis and cancer treatment periods (14). If measures of such distress largely reflect a patient's short-term reaction to the stresses of diagnosis and medical treatment, they may be unlikely to have long-term prognostic value, given evidence that chronic psychological conditions are more likely to lead to physiological disruption and serious health problems than short-lived states (15). Longitudinal designs that track individual psychological change over time can assess the role of psychological states measured both in the short-term aftermath of diagnosis and later in time, once some degree of cognitive and emotional adaptation to the disease has been made (16). Longitudinal designs can also track the progression of a cancer (from lower to higher stages, for example) and its treatment so as to examine the relative predictive weight of medical and psychosocial factors as they change over time.

The present research attempted to overcome the methodological limitations of past research described here to obtain a more definitive picture of the role of psychological state in long-term cancer survival. A large sample of cancer patients,

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heterogeneous in both cancer stage and site, but homogeneous in time since diagnosis, were enrolled in a longitudinal study that assessed several demographic, medical, and psychological variables over a year-long interval after cancer diagnosis. Survival status was assessed 10 years after diagnosis. Given that, among the various psychological features studied, affective states have been most strongly implicated in cancer survival (4), this research included several indicators of emotional state and coping, including positive and negative mood, anxiety, and depressive symptoms. Other factors shown to relate to adjustment were also measured, including sense of control (17) and perceived stress (18). Given the demonstrated role of patient-reported physical health status as a predictor of survival (12), the predictive value of such a measure was also tested.

METHODS

Participants

Patients were eligible for study participation if they met the following criteria: 1) 18 years of age or older; 2) contact permission had been granted by the primary physician; 3) able to speak and read English or French; 4) medical treatment accepted at the Jewish General Hospital; and 5) cancer diagnosis within the past 4 months. All patients were newly diagnosed. No inclusion conditions were placed on either site of cancer or stage at diagnosis. During the 2-year accrual period of the study, a total of 524 eligible patients were invited to participate, and 205 patients (39%) were enrolled. The study required regular participation over a 1-year period (see below), which may have influenced the enrollment rate. Participants were slightly younger than decliners (56.3 years vs. 60.8 years) and were more likely to be women (75% vs. 64%).

Each participant completed scaled questionnaires with one of two trained interviewers blind to the research purposes. A baseline interview occurred as soon as possible after diagnosis (M = 11 weeks), and follow-up interviews took place at 4, 8, and 12 months after baseline (M = 7, 11, and 15 months after diagnosis). Seventy-two individuals did not complete the entire year-long study, due to death (N = 38), deteriorating health, or other reasons. Because the time-dependent regression analyses used here accommodate such "missing data" (see *Data Analysis*), data from all 205 patients were used. Analyses comparing the 72 noncompleters with the rest of the sample on all baseline demographic, medical, and psychological variables found only one difference: Patients with data at all four time points were more likely to be diagnosed with breast cancer than with other cancers, $\chi^2(1) = 9.32, p < .002$.

Measures

At study entry, the following information was collected: age, gender, marital status, cancer site, cancer stage, histopathological grade, number of positive lymph nodes, and cancer treatment protocol.[1] Clinical information on tumor grade and nodal status was abstracted from hospital charts using a standardized protocol. A clinician naïve to the study purpose reviewed operative and pathology reports for cancer stage and tumor characteristics (size and histological grade when available), nodal status, and metastatic spread. Given the variety of cancer types in the sample, a local, regional, and metastatic system was used. Trained interviewers collected current treatment information and all psychological measures during each of the four interviews.

The following psychological measures assessed affective state and mood, impact of events, and sense of control. First, the 20-item *CES-D* (20) assessed depressive symptoms. This scale has been validated in both cancer and non-cancer populations (21). In this sample, coefficient α = .78. Second, the *Impact of Events–Intrusion Subscale* (22) was used. The Impact of Events scale assesses subjectively experienced stress related to an adverse life event. The 7-item intrusion subscale measures the degree to which intrusive or distracting thoughts increase distress, and has been more strongly linked with psychological distress than the avoidance subscale (18). In this sample, coefficient α for this subscale = .86. Third, the 9-item *Lewis, Firich, and Parsell Anxiety Scale* (23) was used, and has also been normed among cancer patients (sample α = .87). The 130-item *Mood Adjective Check List* (24) measures both pleasant and unpleasant mood. In the present research, the 12 major mood factors were used as items. Factor analysis of these items (25; cf., 26) showed that 6 items comprised a pleasant mood subscale, α = .75; four items formed an unpleasant mood subscale, α = .66. Two factor items, "serious" and "boastful," were dropped due to poor loadings. Fifth, the single-item *Cantril's Ladder* (27) assessed sense of control over current life events on a 0 (no control) to 10 (most control possible) scale. Finally, a single-item self-report of *physical health status* [very poor = 1 to excellent = 5] was completed (28). Similar to the commonly used ECOG performance status measure (29), past research has found this report to correlate highly with physician's assessments (30) and to predict mortality (28).

Outcome

For all patients, survival status, and, if deceased, the date and cause of death were sought from one of three sources: the hospital chart, hospital oncology clinic records, or provincial government health and social service agency records. Complete follow-up data were obtained for all but five patients, who were censored in survival analyses and the last hospital contact was recorded as the follow-up time (31).

Data Analyses

Multivariate Cox proportional hazards regression models were conducted using the SAS PHREG procedure (32). In these survival analyses, our interest was in the effect of the predictor variables on the time to death from cancer. As such, four individuals who died from a noncancer cause (three cardiac arrest victims and one acquired immune deficiency syndrome victim) were censored at the time of death.

The variables considered important to survival and used to form the core model were the following: age, gender, cancer site, cancer stage, treatment status, histopathological grade, and number of positive lymph nodes. The cancer site variable was dichotomized into breast vs. other diagnosis, given the predominance of breast patients and the heterogeneity of the other diagnoses. Given the small number of metastatic patients (N = 14), stage was coded as advanced (regional and metastatic) vs. localized to enhance analytic reliability (31). This basic "late" vs. "early" staging division is a regular predictor of survival (33). Treatment was coded as systemic (chemotherapy, radiation, the combination of the two, or either in combination with surgery) vs. local (surgery only or no treatment; only two patients were untreated).

Some patients had unknown values for histopathological status and lymph node status. To include all patients in the analyses, these values were replaced by MI with the use of NORM software (34). MI is considered a superior technique to deal with missing data than other, more commonly known and used methods (35), and is robust except when there is a very large proportion of missingness in the data set (36). In the present study, 14% of patients were missing only nuclear grade data, 12% were missing only lymph node data, and 20% were missing data on both variables. Preliminary analyses showed that the present data met the assumptions of MI (37). All independent and dependent variables used in the baseline models were used in imputation. Two other variables, the number of weeks since diagnosis and marital status, were also included.[2,3]

The distribution of imputed values for each missing datum was averaged

[1] For lymphoma, a histopathological grade was based on the Working Formulation (19). The number of positive lymph nodes was grouped into categories; the Ann Arbor classification (19) was used to facilitate scoring for several cases.

[2] Preliminary analyses showed that both variables were nonsignificant predictors of survival. But variables not used in analyses can be used in MI to provide possible additional evidence for missing values on other variables (37).

[3] When missing data on lymph node invasion were present for brain tumor patients, a value of zero was set, given that most brain cancers do not spread to regional lymph nodes (38).

before analysis, given both the large number of analyses performed and to obtain Cox regression model fit indices.

The data were shown to conform to the proportional hazards assumption of Cox regression analysis using the SAS LIFETEST procedure (32). The core baseline Cox model was fit, after which each psychological variable was entered separately. This tested whether each psychological variable contributed to survival over and above the contribution of all demographic and medical covariates. The fitting of separate models was done to preserve an acceptable events (deaths): predictors ratio, and to avoid problems caused by collinearity among the psychological variables (39). Psychological predictors found significant in these separate models were entered into a single, stepwise model.

Two sets of Cox models were constructed, each using the core and core + psychological variable fitting strategy: the first one used only baseline data, and the second, a time-dependent covariates analysis, assessed whether the most recent information available for each patient predicted survival. Because many patients show changes in medical and psychological status over time, time-dependent analyses can provide an improved estimation of prognosis over that provided by the use of baseline measures alone (40). Because the information that is "most recent" varies across patients, the predictive effects of a variable are not bound to a specific time point. This has both theoretical and clinical usefulness because it means that measurement of a variable has prognostic value when taken at various points in the prediction interval–up to 15 months postdiagnosis in the present case.

RESULTS

Patient Characteristics

Table 1 displays the demographic and medical characteristics of the sample, measured at baseline, arranged according to patient mortality status 10 years later. Of the 205 patients, 125 were alive at this time whereas 80 had died. The median survival time was 110 months (range = 3 to 131). Approximately 48% of the sample had breast cancer; the remainder had one of 14 other diagnoses, including lung, colon, head and neck, prostate, uterine, ovarian, and colon and rectal cancers. Compared with new cases in the North American population at the time of study accrual (mid-1980s) (41), this sample included a higher proportion of new breast cancer patients; the remaining diagnoses were sampled at a rate closely reflecting the proportion of new cancer cases.

Table 1 indicates a moderate degree of psychological distress in this sample (14, 42, 43), but patients reported fair to good physical health. Comparisons on the psychological variables at baseline between those alive vs. deceased generally

TABLE 1. Demographic, Medical, and Psychological Characteristics at Baseline, According to Vital Status at End of Follow-Up (n = 205)

Variable	Alive (n = 125)		Deceased (n = 80)	
	N	%	*N*	%
Demographic/Medical Risk Factors				
Gender				
Male	25	20.0	27	33.8
Female	100	80.0	53	66.3
Age	55.8 ± 12.5		57.1 ± 13.6	
Cancer Site				
Breast	71	56.8	27	33.8
Other	54	43.2	53	66.3
Histopathological grade*				
I–well differentiated	22	17.6	11	13.8
II–moderately differentiated	76	60.8	41	51.3
III–poorly differentiated	27	21.6	28	35.0
Number of lymph nodes positive*				
0	88	70.4	29	36.3
1–3	32	25.6	28	35.0
4–9	4	3.2	16	20.0
≥10	1	.8	7	8.8
Cancer stage				
Local	80	64.0	22	27.5
Regional	42	33.6	47	58.8
Metastatic	3	2.4	11	13.8
Treatment				
Surgery only	54	43.2	28	35.0
Chemotherapy, radiation	71	56.8	52	65.0
	Means ± SD		Means ± SD	
Psychological Factors				
Subjective physical health	3.8	0.9	3.7	1.2
Sense of control	6.8	2.2	6.3	2.6
Pleasant mood	15.0	4.1	14.8	4.6
Unpleasant mood	13.1	3.0	12.7	2.9
Anxiety	16.2	5.9	17.4	6.7
Impact of events	12.1	4.9	13.4	5.7
Depressive symptoms	19.9	8.3	21.7	9.4

Age is measured in means ± SD.

* Includes values derived from imputation.

Note: The column labeled "Alive" includes four patients censored as noncancer deaths.

TABLE 2. HRs, CIs, and Significance of Variables from Cox Regression Models on Baseline and Time-Dependent Data

Variable	Baseline			Time Dependent		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Demographic/medical risk factors						
Gender (male)	1.05	.60–1.85	.85	1.21	.69–2.12	.51
Age	1.02	1.00–1.03	.12	1.01	.99–1.03	.23
Cancer site (nonbreast)	2.66	1.43–4.95	.002	2.29	1.26–4.17	.007
Histopathological grade	1.69	1.16–2.45	.006	1.70	1.18–2.46	.005
Positive lymph nodes	1.57	1.19–2.07	.001	1.30	.99–1.70	.06
Cancer stage (advanced)	2.02	1.11–3.69	.02	4.50	2.29–8.87	.0001
Treatment (systemic)	1.42	.83–2.42	.20	2.29	1.43–3.65	.0005
Psychological factors						
Subjective physical health	.99	.80–1.21	.89	.79	.64–0.98	.03
Sense of control	.91	.82–1.00	.05	.86	.78–0.94	.002
Pleasant affect	1.01	.96–1.07	.75	.99	.94–1.04	.57
Unpleasant affect	.94	.87–1.01	.09	.93	.86–1.01	.08
Anxiety	1.03	0.99–1.07	.13	1.03	.99–1.07	.15
Impact of events	1.05	1.00–1.09	.04	1.07	1.02–1.12	.006
Depressive symptoms*	1.03	1.00–1.06	.03	1.06	1.03–1.08	.0001

Psychological variables entered univariately after entry of all demographic/medical risk factors.

* Also significant in stepwise models, including demographic/medical risk factors and other univariately significant psychological variables.

Notes. Coding of dichotomous variables was as follows: Gender 1 = male; 0 = female; marital status 1 = single, divorced, widowed; 0 = married; cancer site 1 = lung, colon, etc.; 0 = breast; cancer stage 1 = regional and metastatic; 0 = local; treatment 1 = chemotherapy, radiation, both, either in combination with surgery; 0 = surgery only. In the time-dependent models, treatment and all psychological variables were time dependent.

show small differences in the expected direction. All psychological variables were significantly intercorrelated ($p < .0001$), ranging from 0.65 (depression and anxiety) to −0.21 (impact of events and perceived control).

Baseline Prediction of Survival

The left side of Table 2 presents HR and 95% CI from baseline data analyses. The core model using the 7 medical and demographic risk factors was highly significant, χ^2 (7) = 58.72, $p < .0001$. When adjusted for other medical and demographic variables, cancer site (nonbreast), higher histopathological grade and nodal status, and higher cancer stage were significant predictors of survival time. Three baseline psychological variables were univariately significant predictors of survival after adjustment for the baseline covariates in the model–CES-D depressive symptoms, impact of events, and sense of control (see Table 2). With the use of a stepwise regression model that included all seven core risk factors before these three psychological variables were evaluated for entry, only depressive symptoms was a unique psychological predictor, HR = 1.03, CI = 1.00 to 1.06, $p < .05$ (model χ^2 [8] = 62.22, $p < .0001$). In a stepwise model using median splits on the three psychological variables, only depressive symptoms significantly predicted survival time, HR = 1.62, CI = 1.02 to 2.56, $p < .05$.[4]

Figure 1 presents the survival curves for high and low CES-D score groups, based on a median split of the data, and after adjustment (45) for the most powerful medical risk factors from the baseline models: cancer site, histopathological grade, and nodal status. Patients with higher CES-D scores showed slightly lower survival rates from 5 months postdiagnosis. However, beginning at 15 to 25 months postdiagnosis, the survival rates of the two patient groups diverge substantially, suggesting a "time-delayed" effect of depressive symptoms on survival (46).

Time-Dependent Prediction of Survival

The Cox regression model, including the risk factors measured both at baseline and over time (treatment status) was significant, χ^2 (7) = 77.41, $p < .0001$. Cancer site and histopathological grade predicted survival, as did treatment status (see right side of Table 2). The significance of treatment in this analysis may reflect the fact that patients receiving systemic treatment up to 15 months after diagnosis were battling serious disease conditions.

Entry of each time-dependent psychological variable into separate models found four of prognostic significance: higher CES-D depressive symptoms, sense of control, impact of events, and subjective physical health (Table 2). In a stepwise regression model, only depressive symptoms emerged as a unique predictor, HR = 1.06, CI = 1.03 to 1.08, $p < .0001$ (model χ^2 [8] = 81.03, $p < .0001$). With the use of median splits of the data in a stepwise model, depressive symptoms was the sole unique predictor of survival, median HR = 2.04, CI = 1.29 to 3.24, $p < .005$.

The prognostic importance of CES-D depressive symptoms in these time-dependent analyses suggests that this variable may reflect chronic levels of symptomology over time. This variable showed high stability over the four measurement

[4] In analyses using a median split at a score of 16 on the CES-D, this variable did not predict survival time. Although it is often used to demarcate clinical depression, a CES-D score of 16 may be an unreliable cut point (44). In the present sample, 66.8% (N = 137) had scores of 16 or above at baseline (M = 20.65; median = 19).

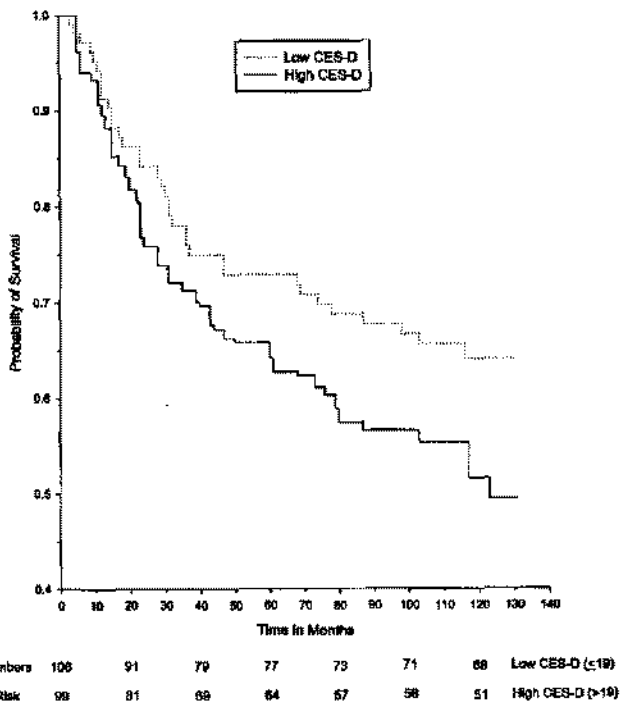

Figure 1. Overall survival according to level of depressive symptomology measured at baseline (3 months postdiagnosis). Curves have been adjusted for diagnostic category, histological grade, and nodal status.

points, $\alpha = 0.79$. CES-D means across the four time points were 20.65 ($SD = 8.95$), 18.54 ($SD = 8.12$), 17.70 ($SD = 6.83$), and 17.94 ($SD = 6.98$), respectively. Repeated-measures ANOVAs on available patient data showed that depressive symptoms changed (dropped) significantly only between the first two measurement points [$F(1,652) = 6.39$, $p < .01$] and not thereafter (p values $> .05$).

It is possible that patients reporting more depressive symptomology had cancers with poorer prognoses or had more advanced disease. The t tests compared the level of depressive symptoms across levels of cancer site, stage, and treatment status at each measurement point. At baseline, breast cancer patients were more likely than nonbreast patients to have higher levels of depressive symptoms, $p < .005$. Yet breast patients showed better survival rates. No other differences were found (all p values $> .05$).

Supplementary Cox regression analyses confirmed that the effect of depressive symptoms on survival was not dependent on diagnostic category (through the use of an interaction term) in baseline and time-dependent models, both p values $>.05$. Neither were CES-D scores at each time point higher among patients receiving more toxic medical treatment (chemotherapy), all p values $> .05$.

Spearman correlations between depressive symptoms and both histological grade and nodal status showed no relations at any time point (all p values $> .05$). The possibility that the distress-survival relation was a "side effect" of advanced disease condition was not supported by survival analyses which excluded metastatic patients ($N = 191$), which again found a predictive role for depressive symptoms. Finally, the CES-D has seven somatic items (47), which, in medical populations, may tap symptoms of disease rather than depression (48). But survival analyses using nonsomatic CES-D scores (13 items) again found a significant predictive role for depressive symptoms in both univariate and multivariate models: in the baseline multivariate model, using continuous variables, HR = 1.06, CI = 1.01 to 1.10, $p < .05$; in the time-dependent multivariate model, HR = 1.05, CI = 1.01 to 1.10, $p < .05$. The full CES-D and nonsomatic CES-D scores were highly correlated at each time point ($r_{range} = .87$ to .91), indicating that full CES-D scores were not heavily influenced by responses to somatic items.

DISCUSSION

Past research into the role of psychological factors in long-term cancer prognosis has shown mixed results (13). Research in the area presents considerable challenges and the present study was designed to overcome a number of methodological and analytic problems that may have clouded results in this area. Using both early post-diagnostic and repeated measurements over a 15-month period, depressive symptomology was a consistent psychological predictor of shortened survival time in this heterogeneous sample of cancer patients. This was found after controlling for demographic and clinical risk factors.

Other research has linked depressive symptomology with reduced cancer survival (46, 49, 50). Watson et al. (50) found, as in the present research, both early postdiagnostic and time-dependent depressive symptom scores to predict survival time. Recent work has also linked this variable with shortened survival among heart disease patients (51) and with the incidence of stroke (52). The average CES-D score in this sample at baseline was higher than the oft-used clinical cut point, and the ability to detect a role for depressive symptoms in this sample may have been linked to these higher scores. This study tested the prognostic value of seven specific psychological factors, most of which have not often been measured in cancer survival research. Because depressive symptomology alone was generally shown to be of prognostic importance, past research, which found null results by using measures that combine specific states, may have underestimated the impact of such specific conditions as depression.

It must be noted that the psychological measures in this study were to some degree intercorrelated. Research has shown that depression may be a psychological concomitant of subjective stress (49), which the impact of events scale is designed to measure. Depressive symptoms and sense of control may also have a theoretical link. Taylor et al. (53) suggest that the effect of beliefs, including those of personal control, have their effect on health through emotional states such as depression. Thus, future attempts to converge on key psychological predictors of survival would still benefit by examining a number of potentially important psychological variables. Self-reported physical health status did not predict survival in this study. However, this relation has been found among the

elderly (28) and those with advanced cancers, among whom physical concerns are more predominant (12).

Why is Depressive Symptomology Linked to Reduced Survival Time?

One explanation for the link between depressive symptoms and reduced survival is that distressed individuals believe that their lives are coming to an end, given either the generally poor prognosis for their particular cancer, the advanced stage of their disease, or both. If this explanation were true, distress would be a result of poor prognosis or shortened survival, not a predictor of it. Both of the Cox models showing depressive symptoms to have predictive value after adjustment for medical variables, and several supplementary analyses pointed to the independent importance of distress to survival.

Several mechanisms have been proposed to mediate or explain the distress-survival relation, including endocrinological and immunological pathways (49, 54, 55) and reduced medical compliance (54, however see 56, 57). If cancer precipitates distress (58) and distress affects cancer course, as the present results indicate, a positive feedback loop may be operating to further the disease. Specifically, cancer diagnosis and the physical effects of the disease may predispose to distress, which, if maintained over time, then enhances disease progression. Longitudinal research exploring the ongoing transaction between psychological and biological factors may enhance our understanding of such a process.

The present study had several limitations. In this sample, 75% were women, and they are known to evidence more depressive symptoms than men (59), a finding indirectly supported by the present results showing higher depressive symptoms among breast patients. Gender did not predict survival time, and breast cancer patients showed better survival rates, whereas patients with higher depressive symptomology had poorer survival rates. Although these findings indicate that the predictive effects of depressive symptoms were not "carried" by women and the breast cancer diagnosis, research in this area should use more balanced samples of men and women.

The nonbreast cancer group in the study sample included cancers with very different prognoses, and potentially different psychological consequences. Also, two clinical risk factors used as predictors here–nuclear grade and nodal status–may have different prognostic value for different cancer diagnoses. Clinical risk factors not included here, such as comorbidity (60), socioeconomic status (61), and smoking status (62) could potentially reduce the relation between psychological state and survival. Also, whereas the need to preserve a sizable and balanced grouping required the division of cancer treatment into systemic vs. local treatment, this may have masked mortality-relevant differences between, for example, those receiving chemotherapy and those receiving radiation. Relatedly, whereas treatment is administered according to the disease circumstances of each patient, future research should examine the effect of distress on medical treatment decision making.

Finally, patients in the study were self selected, and only 39% of available patients were enrolled. Study enrollment tends to be lower in more serious disease populations, and the average accrual into cancer clinical trials is <3% of the cancer patient population (63). However, self selection of a minority of a population raises the issue of generalizability. This issue has been considered most problematic in psycho-oncology research when the resulting sample is unrepresentative of the psychological state of the population in question. The present sample showed a broad spectrum of scores on all psychological variables and the levels of distress were comparable with those found in other samples of heterogeneous cancer patients. Aside from attending physician refusal, highly distressed patients may have been less likely than others to volunteer for this research (64). If so, the present results may represent a *conservative* estimate of the impact of depressive symptoms on survival. That said, these results cannot be generalized beyond the kind of patient who volunteers for psycho-oncology research.

To conclude, the present study found that both baseline and time-dependent measures had value in predicting long-term survival. Replication of these results is in order, and future research of this kind will be benefited by ever-tighter control over demographic, clinical risk, and endocrine and immune system factors, homogeneous diagnostic and treatment groups, and large patient samples with many events to allow for the testing of many predictors. However, this research suggests that screening for depressive and other distress symptoms could fruitfully be done at any point in the approximately year-long interval after cancer diagnosis. Levels of distress remained quite stable over this interval in this sample (65). Such screening could serve as a basis of referral for therapeutic intervention, given that psychotherapy has been found to reduce depressive symptoms (54). Such screening could not only assess current symptom levels, but also probe for prediagnostic history of distress (66). Research probing prediagnostic psychological history may be particularly important to understanding why depressive symptoms measured in the early postdiagnostic period can predict long-term survival, given the relative importance of enduring rather than short-lived psychological conditions in physical health (15).

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