# A Psychological Intervention Reduces Inflammatory Markers by Alleviating Depressive Symptoms: Secondary Analysis of a Randomized Controlled Trial

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**Objectives:** To test experimentally whether a psychological intervention reduces depression-related symptoms and markers of inflammation among cancer patients and to test one mechanism for the intervention effects. Depression and inflammation are common among cancer patients. Data suggest that inflammation can contribute to depressive symptoms, although the converse remains untested. **Methods:** As part of a randomized clinical trial, newly diagnosed breast cancer patients ($n = 45$) with clinically significant depressive symptoms were evaluated and randomized to psychological intervention with assessment or assessment only study arms. The intervention spanned 12 months, with assessments at baseline, 4, 8, and 12 months. Mixed-effects modeling tested the hypothesis that the intervention reduced self-reported depressive symptoms (Center for Epidemiological Studies Depression scale, Profile of Mood States Depression and Fatigue subscales, and Medical Outcomes Study-Short Form 36 Bodily Pain subscale) and immune cell numbers that are elevated in the presence of inflammation (white blood cell count, neutrophil count, and helper/suppressor ratio). Mediation analyses tested whether change in depressive symptoms, pain, or fatigue predicted change in white blood cell count, neutrophil count, or the helper/suppressor ratio. **Results:** The intervention reduced significantly depressive symptoms, pain, fatigue, and inflammation markers. Moreover, the intervention effect on inflammation was mediated by its effect on depressive symptoms. **Conclusions:** This is the first experiment to test whether psychological treatment effective in reducing depressive symptoms would also reduce indicators of inflammation. Data show that the intervention reduced directly depressive symptoms and reduced indirectly inflammation. Psychological treatment may treat effectively depressive symptoms, pain, and fatigue among cancer patients. **Key words:** psychological intervention, cancer, depression, white blood cell count, inflammation, pain, fatigue.

**CES-D** = Center for Epidemiological Studies-Depression scale, Iowa short form; **SF-36** = Medical Outcomes Study-Short Form 36; **KPS** = Karnofsky Performance Status.

## INTRODUCTION

Depression and inflammation are common among cancer patients, and both may damage quality of life and health. Estimated rates of depression range from 8% to 40% (1). For those who are depressed, disruptions in quality of life, anxiety, fatigue, pain, and symptom distress are likely (2). Inflammation, too, is common among cancer patients. Systemic inflammation may result directly from the tumor, which can release proinflammatory cytokines, or it may arise as cancer cells are identified as foreign by the immune system (3,4). Even after the cancer is removed, inflammation can be triggered by surgical, radiation, or chemotherapy treatments. Inflammation is considered to be a cancer-promoting factor (3,4), and both depression and inflammation predict increased risk of cancer death (5,6).

Many studies have shown that indicators of depression and inflammation covary, but the direction of the effect is unknown. Meta-analyses show depression to be reliably associated with elevated inflammatory markers (C-reactive protein, interleukin-6, and interleukin-1) (7) and changes in immune cell numbers, which are indicative of an inflammatory reaction (e.g., elevated white blood cell [WBC] and neutrophil counts, and a high T helper/T suppressor cell ratio) (8). Among cancer patients, depressive symptoms are associated with elevated plasma interleukin-6, an important marker of inflammation (9). In addition, uncontrolled studies have suggested that inflammation and depression both change concurrent with antidepressant treatment (10–14).

Despite the numbers of studies showing covariation, the direction of the effect is still unknown. Unidirectional, causal relationships between depression and inflammation are plausible, as is a bidirectional one. Of the three possibilities, the strongest empirical support is available for the effects of inflammation on depressive symptoms (15,16). Animal studies have shown that the pharmacologic induction of inflammation can cause mice to exhibit "sickness behaviors" (17): lowered food intake and a reduction in pleasurable behaviors. In humans, observational studies found that cancer patients receiving inflammation-inducing interferon-$\alpha$ therapy reported depression-like symptoms: fatigue, difficulty sleeping, irritability, loss of appetite, weight loss, and low mood (16). No studies have tested whether depression can cause inflammation, although it is plausible (15).

The aim of the present study is to investigate the effect of depressive symptoms on markers of inflammation, and we do so with an experiment. Specifically, we study cancer patients with significant depressive symptoms who were randomized to either psychological treatment or assessment only, reasoning that such an experiment would manipulate depression. For convenience, data from a randomized clinical trial of a psychological intervention for cancer patients (n = 227) were used. As conceptualized, the multicomponent intervention was designed to reduce stress, lower emotional distress, enhance social adjustment, improve compliance with cancer

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treatment, and enhance health behaviors (e.g., diet, physical activity). Depressive symptoms were not an intervention target; however, psychological interventions for cancer patients, in general, affect depressed mood (18). As previously reported, the intervention achieved robust gains across psychological, behavioral, health, and immunity outcomes (19,20). Knowing this, we thought it is possible to explore other biobehavioral processes—in this case, depressive symptoms and inflammation markers—in the subset of patients who entered the trial with significant depressive symptoms ($n = 45$).

We test hypotheses in two contexts: Part 1 tests if patients receiving the intervention showed improvements in depressive symptoms and further, a reduction of inflammatory responses. Two secondary symptoms, fatigue and pain, were also examined, as both correlate with inflammation (21) and are relevant for cancer patients (22). To assess inflammation, we examined changes in immune cell numbers that are seen in the presence of inflammation or infection. WBC count, a nonspecific biomarker of inflammation, was used. The proliferation of WBCs and their secretion of cytokines are instrumental in the inflammatory pathway (3,4). WBC is usually elevated during acute or chronic infections (23) and many chronic illnesses (e.g., cardiovascular disease, hypertension, diabetes) (24–26). Secondary measures of inflammation were neutrophil count and the ratio of CD 4 + T helper cells to CD8 + T suppressor/cytotoxic cells. Neutrophils contribute directly to autoimmunity and chronic inflammation (27), and an elevated T helper/suppressor cell ratio is characteristic of the immune response to bacterial infections (23,28) and correlates with other indications of inflammation (e.g., tumor necrosis factor-$\alpha$) (29). Although "gold standard" measures—Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnoses for depression or C-reactive protein for inflammation—were not available, the measures used are valid and reliable correlates of depressive disorder and inflammation and have been used as such by others (5,23,25,27,28,30,31). Provided Part 1 data show that the intervention did, in fact, achieve both outcomes, Part 2 mediation analyses provide a test of directionality. That is, we test the reduction in depressive symptoms as a mechanism (i.e., mediator) for a reduction in inflammation. In combination, these analyses test whether experimental manipulation of depressive symptoms can effect change in inflammatory markers.

## METHODS

### Overview of the Randomized Controlled Trial Procedures and Findings

Detailed eligibility and accrual information have been published (19,20). Newly diagnosed regional breast cancer (Stage II/III) patients, surgically treated, and awaiting the start of adjuvant therapies, were eligible. As previously reported, participants did not differ from eligible nonparticipants on sociodemographic, disease, and prognostic characteristics, or recommended treatment (20). Patients ($n = 227$) were randomized to intervention and assessment arm ($n = 114$) vs. assessment only arm ($n = 113$), as described, and there were no demographic or disease/treatment differences between the two arms.

After accrual, an assessment consisting of an in-person structured interview, questionnaire completion, chart review, and a 60-mL blood draw was completed. For those randomized to the intervention arm, the intervention was conducted in small groups of eight to 12 patients and led by two psychologists. The format was 4 months of weekly 1½-hour sessions (intensive phase) followed by eight monthly sessions (maintenance phase). In combination, a total of 26 sessions (39 therapy hours) over 12 months were delivered. As previously described, patient attendance for the intervention sessions was high (85%) (20). Follow-up assessments occurred at 4 (postintensive phase), 8, and 12 months (postmaintenance phase). This protocol was approved by local Institutional Review Boards and conducted in accordance with an assurance approved by and filed with the U.S. Department of Health and Human Services.

By the 4-month follow-up, the intervention had reduced anxiety, increased perceived social support, improved dietary habits, improved T-cell function (blastogenesis), reduced rates of smoking, and resulted in less variability in chemotherapy-relative dose intensity for the intervention participants (20). There were no significant intervention effects on absolute numbers of lymphocyte subsets (CD3, CD4, CD8, or CD56 counts) or natural killer cell cytotoxicity. As previously reported, at 12 months, intervention-related gains in distress and T-cell blastogenesis were maintained, and the former mediated a significant improvement in physical health (fewer symptoms/signs and higher functional status) (19).

### Substudy Participants and Procedures

We used data from patients ($n = 45$) who, on accrual, reported clinically significant depressive symptoms based on the Center for Epidemiological Studies-Depression scale, Iowa short form ≥10 (CES-D) (31). Figure 1 depicts study flow. After the initial assessment, 23 patients had been randomized to the intervention arm and 22 were randomized to the assessment only arm. Study arms were equivalent on demographic, prognostic, and cancer treatments. However, patients in the intervention arm had poorer functional status (Karnofsky Performance Status (KPS) at baseline (32). Table 1 provides descriptive data.

At the baseline assessment, patients were a median of 34 days (range = 17–81 days) post surgery. Thereafter, patients began adjuvant treatment, if recommended. At 4 months, the majority (84%; $n = 38$) were in treatment. However, by 8 months, only 10% ($n = 4$) remained in treatment and by 12 months, all (100%) had completed treatment. Retention at 12 months was high. Of the 45 patients, 37 (82%) patients remained, with the loss of four patients to recurrence and four to study withdrawal. Overall, 150 assessments (83%) were completed. Retention rates compared favorably with both psychotherapy trials with depressed outpatients and intervention trials with cancer patients (e.g., 71%) (33).

### Measures

#### *Depressive Symptoms*

The CES-D Iowa short form (31) was the primary measure for depressive symptoms. Eleven items (e.g., "I felt everything I did was an effort," "I felt sad") were rated on a 3-point Likert scale based on patients' feelings during the previous week. Scores can range from 0 to 22, and scores of ≥10 indicate clinically significant depressive symptoms. Coefficient $\alpha$ reliability was 0.77.

#### *Depressed Mood and Fatigue*

From the Profile of Mood States (34), the 15-item depressed mood subscale (e.g., "Unhappy," "Sorry for things done," "Sad") and the 7-item fatigue subscale (e.g., "Worn out," "Listless," "Exhausted") were used. Patients rated mood in the past week on a 5-point Likert scale ranging from "Not at all" to "Extremely." Coefficient $\alpha$ reliabilities were 0.93 and 0.91, respectively.

#### *Quality of Life Related to Pain*

The Bodily Pain subscale from the Medical Outcomes Study-Short form (SF-36) (35) was used. The two-item scale asks patient to rate pain over the past month in terms of severity (a 6-point Likert-type scale ranging from "None" to "Very Severe") and interference with normal activity (a 5-point Likert-type scale ranging from "Not at all" to "Extremely"). Scores range

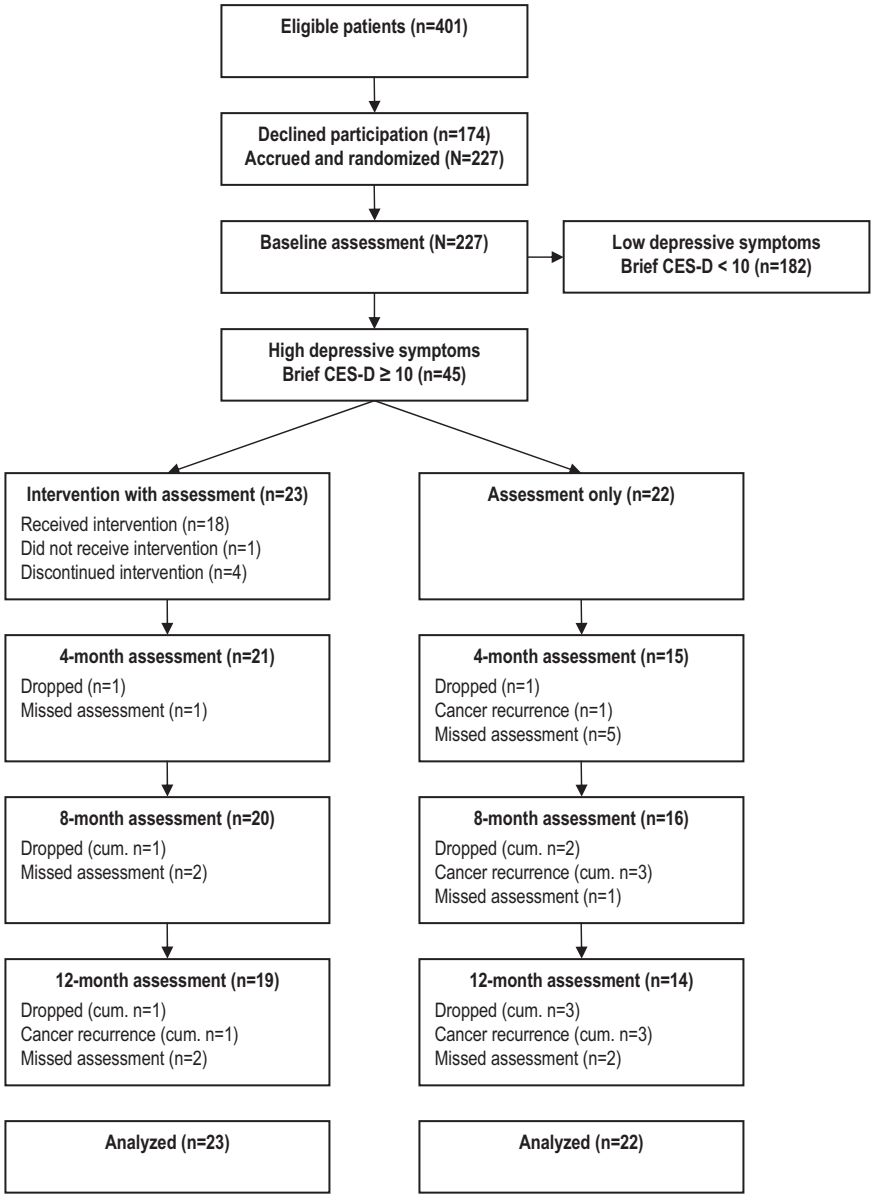


Figure 1. Flow of participants. CES-D = Center for Epidemiological Studies-Depression scale, Iowa short form; cum. = cumulative.

from 0 to 100 with higher scores reflecting better quality of life (i.e., less pain). The interitem correlation was 0.72.

### *Health Status*

A research nurse, blind to study arm assignment, completed two measures after a structured interview with the patient, chart/record review, and, if necessary, consultation with the patient's physician. 1) "The KPS (32) measure provided a global indicator of functional status. The scale ranges from 100 ("Normal; no complaints; no evidence of disease") to 0 ("Dead") with 10-point intervals, each with explicit descriptors indicating symptoms and physical restrictions (e.g., 70 = "Cares for self; unable to carry on normal activity or do active work"). Interrater reliability ranges from 0.70 to 0.97 (36)." 2) Infectious Symptoms: A rating scale (1994 version) used by the Southwest Oncology Group (19,37) documented the type and severity of treatment toxicities. The measure includes an Infection subscale, which consists of five items: wound; respiratory; urinary tract; abscess; and other infection. Response options reflect toxicity grade (0 = "None" to 4 = "Life threatening").

### *Health Behaviors*

Three measures were used: 1) The Food Habits Questionnaire (38) assesses dietary choices and eating patterns in five domains: avoiding fat; food substitution; modification of food preparation; replacing high-fat with low-fat foods; and fruit and vegetable intake. The $\alpha$ reliability is 0.79, and test-retest reliability is 0.77. 2) A 7-day report of physical activity, based on the Seven-Day Exercise Recall of the Stanford Heart Disease Prevention Program (39), provided a summary index of energy expenditure. 3) Patients were queried as to their smoking status, and if smoking, they were asked their daily intake (participants used cigarettes only; one cigarette = 1 tobacco unit).

### *Inflammation*

Complete blood cell counts and differentials were obtained. Identification of lymphocyte subsets utilized peripheral blood leukocytes labeled with fluorescent-conjugated monoclonal antibodies (20). CD3 + (total T), CD4 + (helper T), CD8 + (cytotoxic/suppressor T), and CD56 + (natural killer) cells were measured. Serum albumin was monitored as an indicator of nutritional

**TABLE 1. Equivalence of Assessment Only and Intervention Study Arms on Demographic, Prognostic, and Treatment Variables**

| Variables | Assessment Only, $n$ = 22 Mean (SD) or $n$ (%) | Intervention, $n$ = 23 Mean (SD) or $n$ (%) | $p$ |
|---|---|---|---|
| Demographic | | | |
| Age (years) | 50 (11.6) | 50 (8.6) | .93 |
| Race ($n$, % minority) | 4 (18%) | 5 (22%) | .77 |
| Partner status ($n$, % partnered) | 14 (64%) | 17 (69%) | .46 |
| Education (years) | 13.9 (2.5) | 15.3 (3.3) | .11 |
| Family income ($K/year) | 81.8 (158) | 73.6 (76.5) | .83 |
| Prognostic | | | |
| Tumor size (cm) | 2.9 (1.2) | 3.5 (1.8) | .22 |
| Stage ($n$, % Stage II) | 19 (86%) | 21 (91%) | .60 |
| Nodes ($n$, % positive) | 15 (68%) | 14 (61%) | .61 |
| ER/PR ($n$, % positive) | 13 (59%) | 16 (70%) | .46 |
| Menopausal status ($n$, % post) | 12 (55%) | 11 (48%) | .65 |
| Baseline Karnofsky Performance Status | 85.5 (7.4) | 77.8 (10.4) | .007 |
| Treatment | | | |
| Surgery ($n$, % modified radical mastectomy) | 11 (50%) | 16 (70%) | .18 |
| Chemotherapy ($n$, % yes) | 19 (86%) | 19 (83%) | .73 |
| Radiation therapy ($n$, % yes) | 11 (50%) | 11 (48%) | .88 |
| Hormonal therapy ($n$, % yes) | 17 (77%) | 16 (70%) | .56 |

ER/PR = estrogen/progesterone receptor status; $p$ indicates the outcome of analysis of variance or $\chi^2$ test.

status. Neutrophil count (% neutrophil × total WBC count) and the helper/suppressor ratio (CD4 + T cell count / CD8 + T cell count) were calculated.

## RESULTS

### Part 1: Experimental Test of the Intervention on Depressive Symptoms and Inflammatory Signs

Mixed-effects modeling was used to test the effects of study arm (intervention vs. assessment only), Time (linear change in months), Time$^2$ (quadratic change in months), and the Study Arm × Time and Study Arm × Time$^2$ interactions. The effects of interest were the interactions. Inclusion of a quadratic term was determined through examination of the Bayseian Information Criterion and the Akaike Information Criterion. Analyses considered the potential role of cancer treatments and patient health status on the outcomes of interest. As all patients underwent surgery, it was not included, and it is also the case that surgery type determines adjuvant therapy (e.g., patients receiving lumpectomy also receive radiation therapy). Thus, chemotherapy and radiotherapy were entered as categorical variables (chemotherapy and radiation [$n$ = 20] vs. chemotherapy only [$n$ = 18] vs. radiation alone or no adjuvant treatment [$n$ = 7]). In addition, KPS and infectious symptoms were recorded at each assessment and these variables were included as time-varying covariates. Continuous covariates were transformed into $z$ scores to aid interpretation. Analyses were intent-to-treat with all available data analyzed. We used the Statistical Package for the Social Sciences v16.0 (40).

Table 2 shows the results of the mixed-effects models for the behavioral outcomes. Figure 2A shows the trajectories of CES-D over the follow-up. The study arms were not significantly different at baseline ($p$ = .26), but they did differ in their recovery rates, as hypothesized. A significant Study Arm × Time effect indicated that depressive symptoms declined significantly faster for intervention participants ($p$ = .04). For Profile of Mood States depressed mood, study arms were not significantly different at baseline ($p$ = .20). Thereafter, the intervention arm reported more rapid improvement over time (Study Arm × Time, $p$ = .02). A significant Study Arm × Time$^2$ effect indicated that, for the intervention group, improvement was rapid in the early months and then stabilized ($p$ = .02). Trajectories for Profile of Mood States fatigue are shown in Figure 2B. The study arms were equivalent at baseline ($p$ = .61), and a significant Study Arm × Time effect showed greater reductions in fatigue for the intervention arm ($p$ = .048). Trajectories for SF-36 Pain are shown in Figure 2C. The study arms did not differ at baseline ($p$ = .22). Thereafter, improvements in reports of pain were significantly faster for patients in the intervention arm ($p$ = .04).

Table 3 shows the results of the mixed-effects model analyses for the immune outcomes. All three of the mixed models were linear, as quadratic terms did not improve model fit. The trajectories for WBC count are shown in Figure 3A. There was no baseline group difference ($p$ = .37), and there was a significant Study Arm × Time effect, with the intervention arm showing reductions in WBCs over time ($p$ = .005). Results were similar for neutrophil counts. The study arms did not differ at baseline ($p$ = .67). Thereafter, the groups diverged, and the group difference was significant ($p$ = .006). Trajectories for the T helper/suppressor ratio are shown in Figure 3B. The study arms did not differ significantly at baseline ($p$ = .09), and there was a significant group difference in rate of change ($p$ = .02).

To summarize, for patients with significant depressive symptomatology at study entry, the intervention reduced depressive symptoms as well as related measures of depressed mood, fatigue, and impairments due to pain. Moreover, the intervention was associated with reductions in inflammation, as operationalized here.

### Part 2: Mediation Analyses Testing Depressive Symptom Reduction as a Mechanism for Intervention-Related Immune Change

To test the causal pathway, data from three assessments were needed. Baseline data provided values for control, the 8-month assessment provided depressive symptoms mediators, and the 12-month assessment was used for the inflammatory markers. The rationale for choosing the 8-month data (rather than the 4-month data) to assess depressive symptoms is as follows. As previously detailed (41), the intensive phase of the intervention had ended at 4

**TABLE 2. Mixed Models Comparing Assessment Only and Intervention Arm Trajectories in Psychological Outcomes ($n$ = 45)**

| | CES-D Depressive Symptoms | | | POMS Depressed Mood | | | POMS Fatigue | | | SF-36 Bodily Pain | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Estimate | (SE) | $p$ | Estimate | (SE) | $p$ | Estimate | (SE) | $p$ | Estimate | (SE) | $p$ |
| Predictors | | | | | | | | | | | | |
| Intercept | 11.32 | (0.48) | <.001 | 10.53 | (2.03) | <.001 | 10.57 | (1.47) | <.001 | 47.71 | (6.06) | <.001 |
| Linear change (time) | −0.70 | (0.27) | .01 | −0.06 | (0.51) | .91 | −0.10 | (0.09) | .28 | 3.89 | (1.48) | .01 |
| Quadratic change (time$^2$) | 0.03 | (0.02) | .14 | −0.005 | (0.03) | .88 | | — | | −0.18 | (0.10) | .06 |
| Effects of psychological intervention | | | | | | | | | | | | |
| Intervention[a] | 0.63 | (0.55) | .26 | 2.92 | (2.30) | .21 | 0.85 | (1.65) | .61 | −8.42 | (6.86) | .22 |
| Intervention × Time | −0.62 | (0.30) | .04 | −1.52 | (0.58) | .01 | −0.21 | (0.11) | .048 | 3.46 | (1.68) | .04 |
| Intervention × Time$^2$ | 0.03 | (0.02) | .20 | 0.10 | (0.04) | .02 | | — | | −0.19 | (0.11) | .10 |
| Control variables | | | | | | | | | | | | |
| Performance Status (KPS)[b] | −0.17 | (0.23) | .47 | −1.47 | (0.65) | .03 | −0.78 | (0.38) | .04 | 5.54 | (1.91) | .004 |
| Infectious symptoms[b] | 0.34 | (0.19) | .08 | 0.32 | (0.60) | .59 | 0.03 | (0.35) | .93 | −4.43 | (1.72) | .01 |
| Treatment | | | | | | | | | | | | |
| Chemo + Radiation[c] | | 0 | | | 0 | | | 0 | | | 0 | |
| Chemotherapy only | 0.23 | (0.33) | .47 | 1.24 | (2.43) | .61 | 0.68 | (1.77) | .70 | −8.12 | (7.28) | .27 |
| No chemotherapy | 1.10 | (0.41) | .009 | −0.62 | (3.29) | .85 | 0.04 | (2.39) | .99 | 2.48 | (9.87) | .80 |
| Treatment × Time | | | | | | | | | | | | |
| Chemo + Radiation[c] | | 0 | | | 0 | | | 0 | | | 0 | |
| Chemotherapy only | 0.25 | (0.34) | .46 | −0.17 | (0.62) | .78 | 0.08 | (0.11) | .50 | −2.46 | (1.80) | .18 |
| No chemotherapy | 1.06 | (0.43) | .02 | 0.26 | (0.81) | .75 | 0.19 | (0.15) | .21 | −3.61 | (2.34) | .13 |
| Treatment × Time$^2$ | | | | | | | | | | | | |
| Chemo + Radiation[c] | | 0 | | | 0 | | | — | | | 0 | |
| Chemotherapy only | −0.01 | (0.02) | .78 | 0.003 | (0.04) | .95 | | — | | 0.16 | (0.12) | .19 |
| No chemotherapy | −0.05 | (0.03) | .09 | 0.01 | (0.05) | .88 | | — | | 0.13 | (0.16) | .42 |

[a] Assessment only = 0; Intervention = 1.
[b] Time-variant covariate, standardized.
[c] Reference category.
KPS = Karnofsky Performance Status; CES-D = Center for Epidemiological Studies-Depression scale, Iowa Short Form; POMS = Profile of Mood States; SF-36 = Medical Outcomes Study Short Form-36;–indicates the parameter was not estimated.

months; however, the patients continued to demonstrate gains at the 8-month assessment, which was midway in the maintenance phase. The present data show that the largest reductions in depressive symptoms had been reached by the 8-month assessment (Fig. 2). Also relevant is that adjuvant treatment may affect inflammation, and by the 8-month assessment, 90% of patients had completed cancer treatments. For the test, the criteria recommended by MacKinnon et al. (42) were used (Fig. 4). For Criterion 1, the indirect effect of the independent variable (study arm) on the dependent variable via the mediator (a product of paths A and B) must be significantly different from zero. For Criterion 2, both paths A and B must be significant. Procedurally, baseline levels of the mediator (depressive symptoms) and dependent variables (immunity) are entered for control. Additional control variables (KPS, infectious symptoms, or adjuvant treatment) were used when their inclusion improved the models ($p < .20$) based on $\chi^2$ difference test. (The $p < .20$ rule was used to maintain an adequate ratio of parameters to subjects.) As recommended (43), bootstrap analyses were employed. Direct and indirect effects were estimated, using Analysis of Moment Structures v16.0 software (44).

Table 4 shows the results of the mediation analyses. Depicted in Figure 4 are the analyses testing whether the primary measure of depressive symptoms (CES-D) mediated the intervention effect on the primary measure of inflammation (WBC). The requirements for mediation were met. There was a significant indirect effect of study arm on WBC via depressive symptoms (Criterion 1, $p = .006$). In addition, the effect of study arm on 8-month depressive symptoms (Path A, $p = .003$) and the effect of 8-month depressive symptoms on 12-month WBC (Path B, $p < .001$) were significant (Criterion 2). Also, as shown in Table 4, the CES-D effect was reliable, as it was replicated across the secondary immune measures. The mediation findings were also robust across psychological symptoms. Repeating the analyses using depressed mood or pain as mediators produced identical results. Fatigue mediated the intervention effect also, but only for the helper/suppressor ratio. These analyses show, reliably, that the intervention directly reduced depressive symptoms and indirectly reduced markers of inflammation.

Post hoc analyses were conducted to rule out a plausible alternative hypothesis for the findings. The intervention included multiple components, such as a component on health behavior change. Because health behavior change might influence inflammation, we tested whether intervention-related changes in health behaviors (i.e., exercise, diet, or cigarette use) significantly mediated intervention effects on WBC, neutrophil count, or the helper/suppressor ratio.

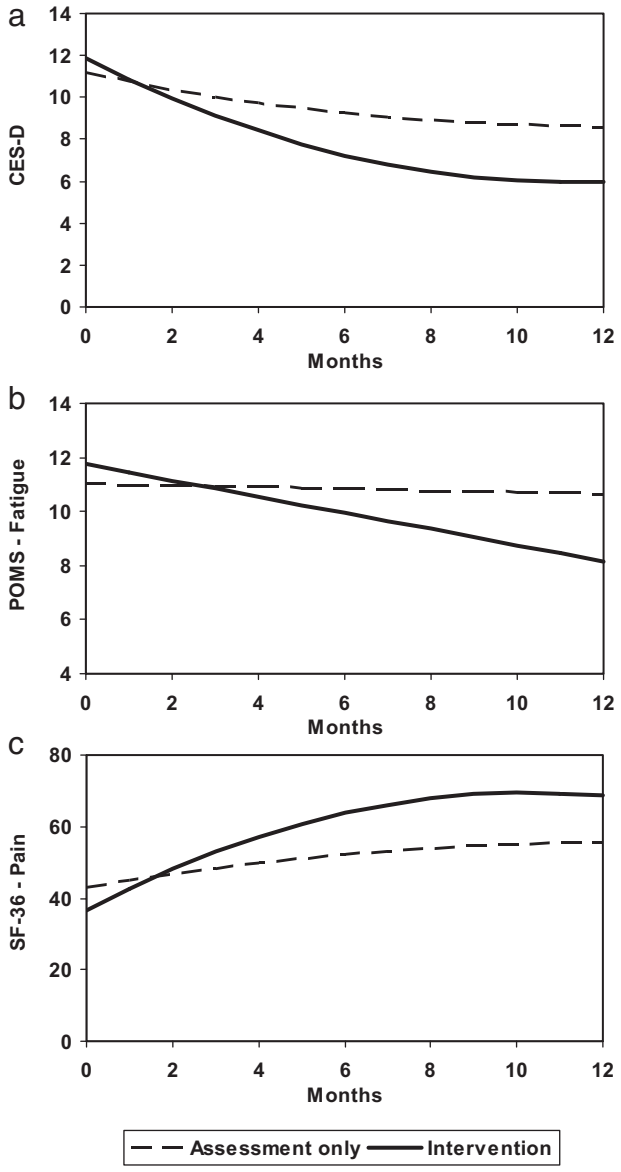


Figure 2. Among patients with significant depressive symptoms, those randomized to the intervention arm showed significant improvement in depressive symptoms, fatigue, and pain compared with patients randomized to the assessment only arm. For Center for Epidemiological Studies-Depression scale, Iowa short form (CES-D) and Profile of Mood States (POMS), higher scores indicate greater distress; for SF-36 Pain, higher scores indicate less pain.

As in the main analyses, each behavioral variable was paired with each immune outcome. Mediation was nonsignificant in all cases (all $p$ values $>.18$). As a final check, a multiple mediation model was specified which tested whether the cumulative effect of the three behavioral variables might mediate significantly the intervention effect on immunity, and it did not. Mediation was nonsignificant for all markers of inflammation ($p > .37$). In combination with the primary analyses above, the data show changes in psychological/affective processes, per se, yielded the change in inflammatory processes independent of any health behavior change.

## DISCUSSION

These data show that a psychological intervention, which alleviated depressive symptoms for newly diagnosed cancer patients, subsequently lowered cell numbers that are indicative of inflammation. This is the first randomized trial to test this complex hypothesis. Prior data have shown that inflammation and depression are correlated and that inflammation can cause depression-like symptoms, but the present data are novel in providing experimental support for the reciprocal direction.

Part 1 data have important clinical implications. Depression is a common problem among cancer patients (1). Unfortunately, depression in the cancer patient is usually undiagnosed and therefore untreated. For example, in one screening study, 112 patients with major depressive disorder were identified, but only 19 (17%) of them were being treated for this disorder (45). Excepting the most obvious symptoms, such as suicidal ideation, psychopathology symptoms may be trivialized as a "normal" reaction to the diagnosis, and/or symptoms may be recognized but attributed to impaired physical status only (46).

There has been no intervention trial focused on the cancer patient with major depressive disorder despite the lengthy distress and disability that accompanies major depressive disorder (2). As assessment arm data demonstrate, depressive symptoms remained elevated for up to a year as patients received standard medical care. As a group, there was no improvement in depressed mood, and half remained above the CES-D clinical cutoff at 12-month follow-up. Despite the fact that the biobehavioral intervention was not designed to treat significant depressive symptomatology per se, it was apparently effective in doing so. Pain and fatigue, two of the most common and distressing symptoms of cancer and its treatment (22), also improved. Thus, psychological treatments could provide multiple benefits to the cancer patient burdened with major depressive disorder and be an effective alternative to other treatments, such as pharmacotherapy.

Part 2 data suggest a directional effect wherein changing depressive symptoms elicited a reduction in inflammation. Mechanisms for the effect are unknown, but other physiological changes have been observed post psychological treatment of depression. For example, there is a nascent literature showing psychotherapy to elicit changes in brain metabolism which, in some studies, mirrored those changes effected by pharmacotherapy (see 47). Although the extent of the physiological changes are unknown, if the alterations extend to neurotransmitter availability (as do those of pharmacotherapy), downstream normalization of the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes, and consequently, immune activation, is possible (15). There may also be treatment-related changes in exposure and reactivity to stress. Miller and colleagues (48) showed depressed patients to have altered physiological reactivity to a laboratory-induced stressor, including relative glucocorticoid insensitivity and consequent elevations in proinflammatory cytokines. The authors speculated that

**TABLE 3. Mixed Models Comparing Assessment Only and Intervention Arm Trajectories in Inflammation Outcomes ($n$ = 45)**

| | White Blood Cells | | | Neutrophil Count | | | Helper/Suppressor Ratio | | |
|---|---|---|---|---|---|---|---|---|---|
| | Estimate | (SE) | *p* | Estimate | (SE) | *p* | Estimate | (SE) | *p* |
| Predictors | | | | | | | | | |
| Predictors | | | | | | | | | |
| Intercept | 4.86 | (0.45) | <.001 | 2.67 | (0.34) | <.001 | 1.82 | (0.31) | <.001 |
| Linear change (time) | −0.02 | (0.03) | .52 | 0.04 | (0.02) | .09 | −0.01 | (0.02) | .59 |
| Effects of psychological intervention | | | | | | | | | |
| Intervention[a] | 0.45 | (0.49) | .37 | 0.16 | (0.37) | .67 | 0.59 | (0.34) | .09 |
| Intervention × Time | −0.11 | (0.04) | .005 | −0.07 | (0.03) | .006 | −0.04 | (0.02) | .02 |
| Control variables | | | | | | | | | |
| Performance Status (KPS)[b] | 0.01 | (0.14) | .92 | −0.03 | (0.07) | .71 | 0.01 | (0.06) | .92 |
| Infectious symptoms[b] | 0.09 | (0.12) | .43 | 0.03 | (0.06) | .58 | 0.05 | (0.04) | .28 |
| Treatment | | | | | | | | | |
| Chemo + Radiation[c] | | 0 | | | 0 | | | 0 | |
| Chemotherapy only | 1.60 | (0.52) | .003 | 1.29 | (0.40) | .002 | 0.64 | (0.37) | .09 |
| No chemotherapy | 0.68 | (0.69) | .33 | 0.59 | (0.53) | .27 | 0.56 | (0.50) | .27 |
| Treatment × Time: | | | | | | | | | |
| Chemo + Radiation[c] | | 0 | | | 0 | | | 0 | |
| Chemotherapy only | −0.05 | (0.04) | .19 | −0.06 | (0.03) | .04 | −0.03 | (0.02) | .10 |
| No chemotherapy | 0.10 | (0.05) | .06 | −0.01 | (0.04) | .89 | 0.07 | (0.03) | .01 |

[a] Assessment only = 0; Intervention = 1.
[b] Time-variant covariate, standardized.
[c] Reference category.
KPS = Karnofsky Performance Status.

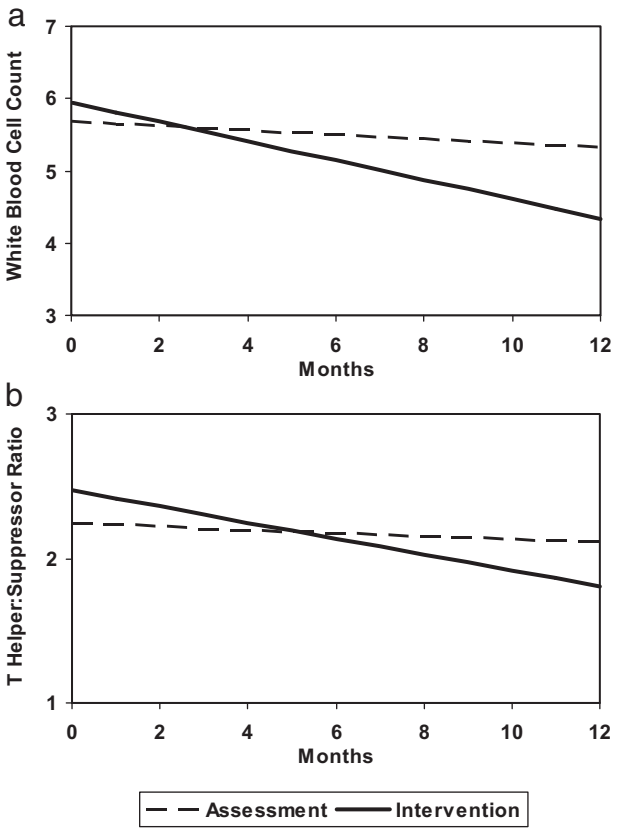


Figure 3. Among patients with significant depressive symptoms, those randomized to the intervention arm showed significant reduction in inflammatory indicators compared with no change among those randomized to the assessment only arm.

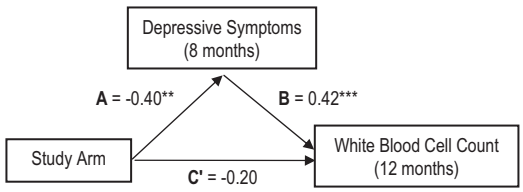


Figure 4. Analyses showed that change in depressive symptoms (Center for Epidemiological Studies-Depression) mediated the intervention effect on inflammation (white blood cell count). *$p < .05$; **$p < .01$; ***$p < .001$.

such a pattern might "facilitate the sustained expression of inflammatory mediators" (48).

In addition, self-report of pain mediated the intervention effect on inflammatory markers, and fatigue mediated the effect on the T helper/suppressor ratio. Pain, depression, and fatigue often occur concurrently, and are regarded as a symptom cluster (22). Their covariation is thought to be caused, at least in part, by inflammation (21). It has been suggested that inhibiting the inflammation response could ameliorate depressive symptoms and the pain/depression/fatigue cluster (16,21). The present data suggest that causality may be bidirectional. Although the exact mechanisms are unknown, the present data suggest that pain and, to a lesser extent, fatigue may contribute to the prolongation of inflammation seen in depression.

Although this study is an experiment and the results show depressive symptoms to be a mediator of the intervention effect on inflammation, we cannot confirm that depressive symptoms are the mechanism for the interven-

**TABLE 4. Mediation Analyses Testing Depressive Symptoms, Fatigue, and Pain as Mediators of the Intervention Effects on Inflammation Correlates ($n$ = 45)**

| Mediator | Outcome | Path A | | Path B | | Indirect Effect (A × B) | |
|---|---|---|---|---|---|---|---|
| | | Estimate[a] | $p$ | Estimate | $p$ | Estimate | $p$ |
| Brief CES-D | WBC | −0.40 | .003 | 0.42 | <.001 | −0.15 | .006 |
| | Neutrophil count | −0.40 | .003 | 0.35 | .003 | −0.11 | .02 |
| | Helper/suppressor ratio | −0.40 | .003 | 0.57 | <.001 | −0.22 | .002 |
| POMS depressed mood | WBC | −0.31 | .03 | 0.37 | .004 | −0.09 | .04 |
| | Neutrophil count | −0.31 | .03 | 0.29 | .02 | −0.08 | .06 |
| | Helper/suppressor ratio | −0.31 | .03 | 0.47 | <.001 | −0.13 | .04 |
| POMS fatigue | WBC | −0.36 | .002 | 0.24 | .07 | −0.04 | .38 |
| | Neutrophil count | −0.36 | .002 | 0.10 | .42 | −0.01 | .91 |
| | Helper/suppressor ratio | −0.36 | .002 | 0.39 | .002 | −0.12 | .008 |
| SF-36 bodily pain | WBC | 0.35 | .002 | −0.27 | .04 | −0.08 | .03 |
| | Neutrophil count | 0.35 | .002 | −0.34 | .002 | −0.11 | .02 |
| | Helper/suppressor ratio | 0.35 | .002 | −0.41 | <.001 | −0.14 | .009 |

[a] Estimates are standardized.

CES-D = Center for Epidemiological Studies-Depression scale, Iowa Short Form; POMS = Profile of Mood States; SF-36 = Medical Outcomes Study Short Form-36; WBC = white blood cell count; Path A indicates the directional path from study arm to the mediator; Path B indicates the directional path from the mediator to the immune outcome.

tion effects. A second study, wherein patients are randomized to conditions which manipulate the intervention's effects on depressive symptoms (e.g., a trial comparing two treatments, only one of which would alleviate depression) would be needed to establish causality (42,43). Further, although the data are compelling in showing a directional effect from depressive symptoms to inflammatory markers, they do not provide evidence against the alternate direction. It is plausible that altering inflammation may have a salutary effect on depressive symptoms; however, the design of the present study precludes testing this hypothesis. Because this psychological intervention could not directly affect inflammation, as pharmacotherapy could, our data would not be useful for a test of inflammation's effects on depressive symptoms. Instead, the analyses demonstrate one mechanism by which this intervention affected inflammation—through reduced depressive symptoms. For these data, we were able to rule out one plausible alternative explanation for the effects—health behavior change. Further, objective health data (nurse-rated infectious symptoms and performance status) were available and included as controls in all analyses.

These data need be considered in context. This is a secondary analysis, and the study was not designed to treat depression or study inflammation as a mechanism. Although not ideal, the measures used are valid and reliable correlates of depression and inflammation and have been used by others (5,23,25,30,31,49) for this purpose. That the intervention did alleviate depressive symptoms is in line with findings from the trial showing anxiety reduction, as anxiety and depression are comorbid for roughly half of patients found with either diagnosis (1,2), and changing one can often improve the other. Many components of our intervention were similar to common cognitive behavioral treatments for anxiety or depressive disorders (e.g., problem solving, assertive communication, relaxation training), although others were not (e.g., medical information).

Accepting these limitations, this trial also offered advantages to studying these issues. By design, the sample was homogeneous and randomization was done within strata. This method was likely key to finding that, even with a smaller sample size, equivalence between study arms on distress, sociodemographic factors, and all prognostic and cancer treatment variables was possible. The randomization identifies the biobehavioral intervention, per se, as the factor which altered inflammation. Studies thus far in the literature, using nonexperimental designs (10–14,49), have reported effects vulnerable to other hypotheses (e.g., maturation). Having multiple assessments across 12 months permitted identification of the temporal order of depression symptom and inflammation effects. Finally, the robust intervention effects (19,20) increased the likelihood of finding effects with a smaller sample size.

The data contribute to a growing literature documenting the benefits of psychological interventions for medically ill populations, which range from emotional distress and quality of life improvement (18) to parameters traditionally falling within the physical realm, such as immune function. The immune outcomes tested here may be particularly relevant for cancer. Using WBC count as a proxy for inflammation, Shankar et al. (5) demonstrated that inflammation prospectively predicted cancer mortality in 3189 initially cancer-free persons. Data from our trial show that elevations in WBC and neutrophil counts—along with behavioral variables, such as fatigue, poorer physical functioning, and lower ratings of general health—preceded the clinical detection of recurrence by at least 17 months (50).

The present randomized clinical trial was designed to test the hypothesis that a psychological intervention would

reduce risk of recurrence and improve survival for patients with cancer, and the intervention was successful in doing so (51). Based on the present data, it is plausible that inflammation mediated such effects, and this hypothesis will be tested in a future analysis. Apart from any potential disease outcome benefits, the present data underscore the importance of behavioral interventions as a component of comprehensive care of the cancer patient. If, as has been hypothesized, depressive symptoms and inflammation reciprocally influence one another, prolonging symptomatology for the cancer survivor, a psychological intervention which interrupts this process would have long-term health and quality of life benefits in addition to providing needed relief from depressive symptoms.

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