

Finding Positive Meaning and Its Association With Natural Killer Cell Cytotoxicity Among Participants in a Bereavement-Related Disclosure Intervention

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ABSTRACT

This study tested the hypothesis that cognitive processing about a past bereavement would produce increases in goals and priorities indicative of finding positive meaning from the loss. It was further hypothesized that increases in meaning-related goals would be associated with changes in immune function, specifically increased natural killer cell cytotoxicity (NKCC). Cognitive processing was manipulated using written emotional disclosure. Forty-three women who had lost a close relative to breast cancer wrote about the death (cognitive processing/disclosure group) or about nonemotional topics weekly for 4 weeks. Contrary to predictions, written disclosure did not induce changes in meaning-related goals or NK cell parameters. However, women in both experimental groups who reported positive changes in meaning-related goals over the study period also showed increases in NKCC. Results suggest that prioritizing goals emphasizing relationships, personal growth, and striving for meaning in life may have positive biological correlates but that solitary written disclosure may not be sufficient to induce changes in these goals in response to a past bereavement.

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INTRODUCTION

The association between exposure to stressful events and changes in the human immune system is now well documented. A variety of stressful life experiences, ranging from acute experimental stressors (e.g., mental arithmetic) to more chronic naturalistic stressors (e.g., divorce, bereavement) have been associated with changes in both enumerative and functional immune parameters (1). However, little is currently known about how psychological responses to these stressors may influence immunological outcomes. In particular, positive psychological responses to stress, and positive psychological outcomes that may occur following stressful life events, have rarely been examined in psychoneuroimmunological investigations.

The possibility that traumatic events may provoke positive psychological changes has been a theme of literature, poetry, and philosophy for centuries and has recently gained recognition in the research literature on recovery from trauma (2–5). In particular, many individuals report finding positive meaning in their lives following a major stressor. The term *finding meaning* is used here to describe an enhanced sense of the value and importance of one's life, coupled with (and potentially inspired by) a more acute awareness of life's fragility and preciousness. One of the key elements of finding meaning is a clarification of the values and goals that imbue one's life with a sense of meaning and purpose and a new or renewed commitment to those goal pursuits. Of note, this conceptualization of finding meaning, which focuses on the significance of the stressful event for the individual's life, goals, and future, can be contrasted with efforts to understand or make sense of the traumatic experience (6).

A growing number of studies have found that some individuals are able to find positive meaning from even the most stressful of life events, including bereavement (6,7); diagnosis with life-threatening conditions, such as HIV/AIDS (8,9) and cancer (10,11); coping with impaired fertility (12); or suffering a heart attack (13) or stroke (14). These individuals typically report positive shifts in their view of themselves, their relationships

with others, and their priorities and goals in the aftermath of the stressor. In particular, priorities and goals related to personal growth and the importance of interpersonal relationships have been noted to increase. Overall, studies suggest that individuals who are able to derive positive meaning following a stressful life event also show better psychological adjustment (6,9,10,12).

To date, there has been only minimal examination of the effects of finding meaning on physical health outcomes or specific physiological systems, including the immune system. Affleck et al. (13) found that heart attack patients who perceived benefits from their attack, including changes in philosophy of life and values, were less likely to have another attack and had lower levels of morbidity at an 8-year follow-up. Cruess et al. (15) found that women diagnosed with early-stage breast cancer who reported finding more benefits from the cancer experience following a structured psychological intervention also showed decreases in serum cortisol. We examined the association among finding meaning, changes in the immune system, and mortality in a group of HIV-seropositive gay men who had recently lost a close friend or partner to AIDS (7). *Finding meaning* was defined in this study as a major shift in values, priorities, or perspectives in response to the bereavement. The discovery of meaning was associated with positive changes in a key immunological marker of HIV progression and a lower rate of AIDS-related mortality over a 4- to 9-year follow-up period, controlling for potential biobehavioral and psychosocial confounds. These data provide preliminary evidence that finding meaning may be an important outcome of stressful life experiences for physical as well as psychological well-being.

At this point, it is unclear *how* people are able to construe positive meaning from trauma, and specifically whether psychological responses to the event play a role. We have proposed that cognitive processing in response to a stressful event may promote the discovery of positive meaning from the experience (7). *Cognitive processing* can be defined as actively thinking about a stressful situation, the thoughts and feelings it evokes, and its implications for one's life and future (16). Cognitive processing is hypothesized to promote the revision of pre-existing beliefs and assumptions about the self and the world to be consistent with the reality of the traumatic experience (17). We hypothesize that cognitive processing may also promote a reconsideration of the direction of one's life and one's priorities and goals, thereby facilitating the discovery of positive meaning from the event. In support of this hypothesis, we have shown that men who engaged in cognitive processing in response to the loss of a friend or lover to AIDS were more likely to find meaning from the death (7). Similar results were reported by Calhoun et al. (18), who found that stressor-related cognitive processing was significantly correlated with posttraumatic growth in a study of college undergraduates. However, because cognitive processing and meaning-related changes were assessed cross-sectionally in both of these reports, the causal link between these constructs could not be determined.

This study was designed to experimentally test our theoretical model linking cognitive processing, finding positive meaning, and changes in specific immune parameters. Despite increased interest in finding meaning, no previous studies have specifically tried to induce meaning shifts using an experimental intervention.

We manipulated cognitive processing using a version of the emotional disclosure paradigm developed by Pennebaker (19). We selected this paradigm because it is specifically designed to elicit active contemplation of a stressful experience, including one's "deepest thoughts and feelings" about the experience. In the standard disclosure paradigm, individuals are assigned to write either about the most stressful or traumatic event they have ever experienced or about a variety of trivial topics for brief periods of time over several days. Disclosure has been associated with positive changes in immune parameters (20–22), and fewer health center visits (23) among college undergraduates, and with improvements in disease status among patients with immunologically related medical conditions (24,25). Evidence suggests that cognitive changes in disclosure essays (including increased use of words related to cognitive processing) are associated with more positive health outcomes (20,26), supporting the idea that cognitive processing may be an important part of the disclosure process.

Study participants were women who had lost a close relative to breast cancer and perceived themselves to be at increased risk for developing this disease. We were interested in this group because they, like the bereaved HIV-positive men in our earlier study, faced both the loss of a significant other to a particular disease and the threat of developing that disease themselves. We hypothesized that this dual stressor may heighten the threat of mortality associated with bereavement, leading to more in-depth reflection on one's own life and goals and potentially provoking more profound shifts in meaning. Previous research has shown that women who have lost a parent to cancer report elevated levels of cancer-related distress even 14 years after the death (27), suggesting that this group may be an important target for psychological interventions (28).

Immune analyses for this study focused on the natural killer (NK) cell subset of the immune system, because of both its importance for general immune regulation and its potential role in controlling the development and metastatic spread of tumor cells. NK cells are part of the nonspecific immune response and have the ability to kill both virally infected cells and certain types of tumor cells. Some investigators have theorized that the NK cell system may play an important role in immunosurveillance against tumor cells (29), based in part on studies showing lower levels of NK activity in healthy individuals with a high familial incidence of cancer (30), although this is a controversial area. The NK system was also of interest because it has been shown to respond to psychological states similar to those considered in this study, including emotional manipulations (31) and psychological interventions (32,33).

The central hypotheses of this study were as follows: (a) Bereavement-related disclosure will lead to increases in goals and priorities related to finding meaning, and (b) increases in importance of meaning-related goals and priorities will lead to increases in NK cell cytotoxicity (NKCC). We focused here on changes in the importance of meaning-related priorities and goals, such as cultivating relationships and seeking personal growth, because increases in these goals are one of the central components of finding meaning. In addition, there is evidence that goal engagement is important for overall psychological well-being (34) and may have physiological relevance, includ-

ing links to the immune system (35). Although the primary analyses focused on changes that occurred after disclosure, we also examined the association between meaning-related goals and NK cell parameters at baseline. We hypothesized that women who rated meaning-related goals as more important at study entry would also show higher levels of NKCC.

METHOD

Participants

Forty-three women who had lost a close relative to breast cancer and perceived themselves to be at higher than average risk for developing breast cancer participated in this study between February 1997 and May 1998. Participants were recruited from cancer-related organizations (i.e., Revlon–University of California, Los Angeles (UCLA) Breast Center, UCLA Tumor Registry, Wellness Community), bereavement-related organizations (i.e., bereavement support groups, hospice-related bereavement services, Motherless Daughters), advertisements in local newspapers, public service radio announcements, and informational flyers. Recruitment materials indicated that the purpose of the study was to assess the psychological and immunological effects of writing about “personal life events.” To avoid priming participants for writing about a traumatic topic and specifically about the death of their relative (36), women who phoned about the study were informed only that the writing sessions might involve writing about life events “of an emotional nature.” In addition, they were informed that study participation involved completing questionnaires and an interview focusing specifically on their relative’s death.

Of the 167 women who responded to our recruitment materials, 156 agreed to complete a telephone screening interview to assess their eligibility for the study. Women were eligible for study participation if they had lost a mother, sister, grandmother, and/or aunt to breast cancer; if their relative had died after they were 10 years old; and if they perceived themselves to be at higher than average risk for developing breast cancer. Exclusion criteria included (a) age under 20 or over 60 years old; (b) blood/needle phobic; (c) history of immunologically related disease or condition that might affect the immune system; (d) regular use of immunosuppressive medication; (e) history of psychiatric hospitalization, severe psychological distress in last 6 months, or current use of psychotropic medication; (f) consumption of more than 15 alcoholic beverages per week; and (g) use of illicit drugs. Women who had lost their aunts or grandmothers to breast cancer were asked additional screening questions to determine the impact of the loss. Only those women who indicated that they were close to their aunt/grandmother, that their aunt/grandmother had played an important role in their lives, and that they remembered the death of their aunt/grandmother were eligible for study participation.

Eighty-four (54%) of the 156 women screened were excluded for reasons related to age, medical status, medication use, and failure to meet bereavement- and risk-related criteria (e.g., relative diagnosed with breast cancer but still alive, did not perceive self to be at increased risk for breast cancer). Of the 72 women who were eligible, 10 elected not to participate because

of scheduling problems or distance from UCLA (or both), 18 scheduled initial appointments but were unable or elected not to participate and were never seen, and 1 did not complete the follow-up assessment.

Participants averaged 42.14 years of age ($SD = 8.32$, range = 24–60). The majority were White ($n = 35$), with a smaller number of Asian American/Pacific Islander ($n = 4$), African American ($n = 3$), and Latina ($n = 1$) participants. The sample was quite well educated; all participants had completed some college, 17 were college graduates, and 18 had postgraduate training. Most of the participants were employed either full time ($n = 23$) or part time ($n = 11$) at study entry, and just over one half of the women were either married ($n = 15$) or involved in an intimate relationship ($n = 8$). Twenty-two had children.

The majority of study participants had lost their mother to breast cancer ($n = 34$), with a smaller number having lost their sister ($n = 1$), their aunt ($n = 4$), or their mother and their sister ($n = 4$). The deaths occurred an average of 12 years prior to study entry (range = 0–34 years). The average age of the participants at the time of their relative’s death was 30 years (range = 14–58 years). Many participants had other relatives who had been diagnosed with breast cancer ($n = 24$), and a substantial minority had lost more than one relative to this disease ($n = 13$). There was no difference between the women who participated in the study and those who were eligible but did not participate in terms of current age or age at relative’s death. A higher percentage of women who did not participate had lost a sister to breast cancer, whereas a higher percentage of women who did participate had lost both a mother and a sister.

Procedure

Participants were screened over the phone to determine their eligibility for the study then scheduled for a baseline (Time 1) assessment. All assessments were scheduled within the same 2-hr time period in the morning (8:00 a.m.–10:00 a.m.) to control for diurnal variations in immune parameters. The timing of the assessments was also scheduled to coincide with the follicular phase of each participant’s menstrual cycle (i.e., Days 1–7) to control for possible effects of menstrual phase on immune outcomes. Participants were asked to refrain from consuming food, drinking alcohol or caffeine, using tobacco, taking nonprescription medication, and engaging in strenuous exercise during the 12-hr period prior to their appointment. Participants were mailed a consent form and questionnaire packet to complete before their first appointment.

At the initial assessment, a baseline blood sample was drawn after a 15- to 20-min rest period. A semistructured interview was then conducted by Julie E. Bower, focusing on the circumstances of the relative’s illness and death. In addition to objective information (e.g., date of death), the interview assessed the circumstances of the death and the participant’s psychological response to the loss. After the interview, participants were randomly assigned to either the emotional disclosure ($n = 20$) or control condition ($n = 23$) by a trained research assistant. Bower was blind to the random assignment. Participants were blocked on menopausal status to ensure equal proportions of pre- and

postmenopausal women in each condition. Participants in each group were assigned to write about a particular topic at home once a week for 4 weeks; this weekly schedule was used to maximize the effectiveness of the intervention (37). The instructions for each condition followed those used in previous disclosure studies, with one notable exception: Rather than having participants in the emotional disclosure condition write about any stressful or traumatic experience, they were specifically instructed to write about the death of their relative to cancer, including their emotional reactions to her death and the implications of her death for their own lives. Participants in the control condition were asked to write about a variety of non-emotional topics, such as plans for the day and a description of their homes.

All participants were asked to schedule one 20-min block of time per week during which they could sit down and write undisturbed about their assigned topic. Four mailing envelopes were provided, along with a booklet in which to write the essays. The day before each scheduled writing session, a research assistant contacted participants to remind them of the writing assignment. Participants were asked to mail back the assignments each week and were contacted by phone if the assignments were not received.

Four weeks after the initial assessment (and within 1 week of the final writing session), participants returned to UCLA for a follow-up (Time 2) appointment. Participants again completed questionnaires the evening before their scheduled appointments for collection that morning. After a 15- to 20-min rest period, blood samples were drawn, and a second interview was conducted focusing on changes the participants may have experienced following their relative's death. After the interview, participants were thoroughly debriefed and thanked. They were paid \$50 for their participation.

Measures of psychological variables. The Life Goals Inventory (38) was used to assess the importance of values and goals related to finding meaning. This inventory includes 16 life goals that individuals frequently endorse as important in their lives. Participants were asked to indicate the importance of each goal on a 7-point scale that ranged from 1 (*not at all important*) to 7 (*extremely important*). Previous factor analysis of this scale in a sample of HIV positive gay men revealed two factors, labeled Intrinsic Life Goals and Extrinsic Life Goals by Kemeny et al. (39). This factor structure was recently corroborated and replicated in two additional populations using structural equation modeling (40). Intrinsic and Extrinsic Life Goals emerged as distinct latent factors, and the individual paths from the indicators to the latent constructs were each significant. The strength of associations between the latent factors and the item indicators was the same across the three samples (HIV-positive gay men, HIV-negative gay men, and college undergraduates).

This study focused on the Intrinsic Goals subscale of the Life Goals Inventory, which includes nine goals that are closely related to finding meaning, including personal development ("develop myself as a person," "explore new possibilities or be adventurous"), interpersonal relationships ("cultivate close friendships," "give and receive love"), and "strive for meaning in my life." The Intrinsic Goals subscale has demonstrated discriminant validity in samples of healthy college students and

in both HIV-positive and HIV-negative gay men (40). Specifically, the scale does not correlate with measures of depressed mood, self-esteem, social desirability, and negative affectivity in these samples. Internal reliability of the Intrinsic Goals subscale in this sample was .85. The Intrinsic Goals subscale was administered at Time 1 and Time 2.

Depression was assessed with the Center for Epidemiological Studies–Depression scale (CES–D), a 20-item scale designed by Radloff (41) to assess depressive symptomatology in the general population. Respondents indicated how often they had experienced a variety of affective and vegetative symptoms in the past week on a 4-point scale that ranged from 0 (*rarely or none of the time*) to 3 (*most or all of the time*). The CES–D has good reliability and validity in both clinical and community samples (41). Internal reliability of the CES–D in this sample was .94. Higher scores on this measure indicate a higher level of depressive symptomatology, with scores greater than 16 suggesting the presence of clinically significant symptoms of depression. The CES–D was administered at Time 1 and Time 2.

A subscale of the Texas Revised Inventory of Grief (42) (TIG) was used to assess current feelings of grief about the target relative's death. This 13-item scale taps common symptoms of grief, including "I very much miss her," "I can't help thinking about her," and "I still get upset when I think about her." Respondents rated the truthfulness of each item on a 5-point scale that ranged from 1 (*completely false*) to 5 (*completely true*). This measure has acceptable reliability and validity, with a coefficient alpha of .86 and evidence showing that the intensity of feelings varies as expected over time (42). Cronbach's alpha for the TIG in the current sample was .85. The TIG was administered at Time 1 and Time 2.

An essay evaluation scale modeled after that of Pennebaker and Beall (23) was administered as a manipulation check at Time 2. This scale asks respondents to report about the extent to which their essays were personal and revealing of their emotions; how much they had told others about the essay topics, had wanted to talk about them, and had actively held back from telling others about them; and how difficult and frustrating the writing had been. As an additional measure of cognitive processing, participants were asked at the Time 2 interview to rate the extent to which they had reflected on their relative's death since the study began on a 10-point scale that ranged from 1 (*not at all*) to 10 (*a great deal*).

Measures of potential confounding variables. Health behaviors that may influence immune status were assessed with a self-report questionnaire, including use of caffeine, alcohol, recreational drugs, vitamin supplements, and medications (prescription and nonprescription) in the last 7 days. Nutrition, exercise, and sleep (average number of hours of sleep nightly and number of nights on which less sleep was obtained than needed) in the last 7 days were also assessed.

Immunologic measures. NK cells were defined as CD3–/CD56+/CD16+ and enumerated using flow cytometry with three-color immunofluorescence. NKCC was measured in a standard 3-hr ⁵¹Cr release assay with K562 cells as target cells (see 31

for a detailed description of NK cytotoxicity procedures used in our immunology laboratory). NKCC values are expressed as percentage specific lysis at a 50:1 target:effector cell ratio.

RESULTS

Sample Characteristics

An examination of baseline psychological characteristics revealed significant differences between the control and experimental groups on the CES-D and TIG, with the control group reporting higher levels of depressive symptomatology and grief than the experimental group at baseline (for CES-D, $M = 17.0$, $SD = 13.5$ for controls, and $M = 9.6$, $SD = 8.0$ for experimental participants; for TIG, $M = 3.8$, $SD = 0.6$ for controls, and $M = 3.3$, $SD = 0.9$ for experimental participants). These differences appeared to be attributable to the random assignment of all 4 women who had lost both their mother and their sister to the control condition; these women had higher levels of both depression and grief at baseline compared with the others, and when they were excluded from the analysis differences on these measures were no longer significant. No group differences were observed on other bereavement-related characteristics, importance of meaning-related goals, NK cell parameters, or demographic characteristics (i.e., ethnicity, employment status, partner status, educational level, number of children).

Mean TIG scores for both groups fell between the scale midpoint of 3 (*partly true and partly false*) and 4 (*mostly true*), suggesting a moderate level of current grief. The scale items that were most strongly endorsed included "No one will ever take her place in my life" ($M = 4.7$, $Mdn = 5$), "I very much miss her" ($M = 4.5$, $Mdn = 5.0$), and "I feel it's unfair that she died" ($M = 3.8$, $Mdn = 5$).

Essay Characteristics and Reflection Ratings

The mean number of essays received from women in the experimental group was 3.45 (range = 0–4) and from women in the control group was 3.65 (range = 1–4). There were 5 women (3 in the experimental group and 2 in the control group) from whom none or only one of the required essays was received, although all reported that they had completed each of the four writing assignments. When data for these women were deleted from the main analyses, the effects were essentially identical; thus, we decided to retain these participants for analyses examining effects of disclosure.

Women in the experimental group rated their essays as more personal and more emotionally revealing than women in the control group and reported that they had wanted to talk to someone about the essay topics more and had actively held back from telling others about the topics more than women in the control group ($ps < .01$). Participants in each group rated the essays as equally frustrating. Essay ratings for the experimental group were comparable to those seen in other disclosure studies (21). Overall, these results support the validity of the disclosure paradigm in that the disclosure condition appeared to elicit more emotional writing about personally meaningful topics than did the trivial topics condition.

During the Time 2 interview, all but 2 participants indicated that they had reflected on their relative's death since the study began (both of these were in the control condition). There was no difference between disclosure and control group participants in how much they had reflected on the death during the 4-week study period (disclosure group mean reflection rating = 6.9, $SD = 2.2$; control group mean reflection rating = 6.2, $SD = 2.8$).

Potential Biobehavioral Confounds

Before conducting our primary analyses, we assessed a number of potential confounding variables that might account for the variance observed in the immunological outcome measures (43). Results showed that use of caffeine, alcohol, and vitamins were correlated with NKCC at Time 1, Time 2, or both; hours of sleep and use of vitamins were correlated with NK cell percentage at Time 1, Time 2, or both (all $ps < .10$). These variables were thus used as controls in analyses involving these immunologic outcomes. Neither age nor menopausal status was associated with NK cell parameters.

Many of the study participants ($n = 29$) reported using prescription or nonprescription medications (or both) in the week prior to study entry. Most of the medications used could be grouped into two general categories: (a) hormonal preparations (e.g., oral contraceptives) and (b) non-narcotic analgesics/anti-inflammatories (e.g., ibuprofen). We conducted independent-samples t tests to determine whether use of either type of medication was associated with the primary immune parameters. Neither use of hormonal preparations nor use of analgesics/anti-inflammatories was associated with NKCC or NK cell percentage at Time 1 or Time 2 (all $ps > .10$). Of note, although participants were screened for use of immunosuppressive medications, a small number did report using nasal inhalers containing steroids ($n = 2$) and narcotic analgesic combinations ($n = 2$). Use of each of these medications was treated as a covariate in analyses involving immune parameters.

Baseline Correlations

We first examined the association between importance of meaning-related values and NK cell parameters at Time 1. As predicted, importance of meaning-related goals was positively correlated with NKCC at Time 1 ($r = .33$, $p < .05$); women who placed more importance on meaning-related goals had higher levels of NKCC. This correlation remained significant in analyses controlling for potential behavioral confounds (i.e., use of caffeine, alcohol, and medication use) as well as analyses controlling for depression. Of note, depressive symptomatology was negatively correlated with importance of meaning-related goals at Time 1 ($r = -.44$, $p < .01$) but was not significantly correlated with NK cell parameters.

Effects of Essay Writing

We hypothesized that bereavement-related written disclosure would induce increases in importance of meaning-related goals. However, a 2×2 Group (disclosure vs. control) \times Time (Time 1 vs. Time 2) mixed-model repeated measures analysis of variance (ANOVA) revealed no significant main effects of

group or time and, more important, no Group \times Time interaction on importance of meaning-related goals (all F s < 1; see Table 1 for mean scores on meaning-related goals at Time 1 and Time 2). Thus, contrary to predictions, written disclosure did not cause changes in the importance of goals related to finding meaning over the course of this 1-month study.

We also examined the effect of written disclosure on changes in NK cell parameters, as writing may have had immune effects that were independent of goal shifts. A 2×2 Group (disclosure vs. control) \times Time (Time 1 vs. Time 2) mixed-model repeated measures ANOVAs on both NK cell percentage and NKCC revealed no significant main effects of group and no significant Group \times Time interaction for either measure (all F s < 1; see Table 1 for mean NKCC and NK cell percentage scores at Time 1 and Time 2). There was a marginally significant effect of time on NK cell percentage, $F(1, 38) = 3.12, p < .09$; in both experimental groups, NK cell percentage decreased slightly from Time 1 to Time 2. Thus, in contrast to results obtained in previous studies with other immune subsystems (i.e., proliferative response to Phytohemagglutinin, antibody titers to Epstein-Barr virus, antibody response to hepatitis vaccination), written disclosure was not associated with changes in the percentage or cytotoxicity of circulating NK cells.

Additional analyses were conducted excluding the 4 participants with elevated CES-D scores at baseline; these yielded the same pattern of results for both meaning-related goals and NK cell parameters. We also examined a number of bereavement-related factors that may have influenced study results, including number of years since relative's death (death less than 10 years ago vs. over 10 years ago based on median split), type of relative lost (first vs. second degree), and other family history of breast cancer diagnosis or death. There was no evidence that these variables moderated the effect of disclosure on meaning-related goals, NK cell percentage, or NKCC. Finally, we conducted analyses to determine whether women who were more distressed or reported more grief at study entry were more likely to show changes in goals or NKCC. We found no evidence that scores on the CES-D or the TIG moderated the experimental effects.

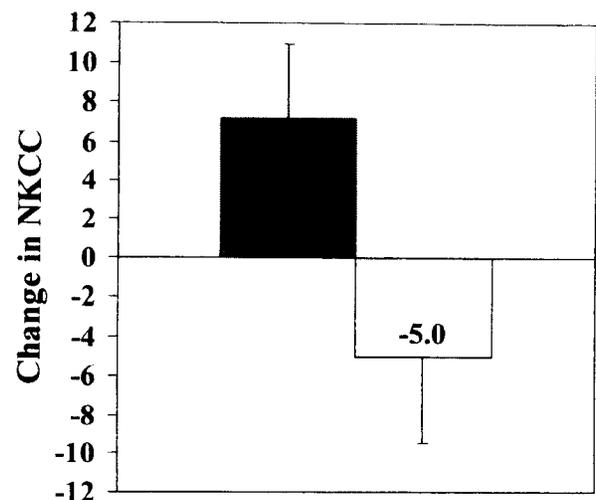
TABLE 1
Descriptive Statistics for Meaning-Related Goals and Natural Killer (NK) Cell Parameters at Time 1 (Preintervention) and Time 2 (Postintervention)

Parameter	Time 1		Time 2	
	M	SD	M	SD
Importance of meaning-related goals				
Disclosure group	53.8	8.1	54.4	6.1
Control group	53.9	8.0	54.0	8.6
NK cell cytotoxicity				
Disclosure group	44.3	18.2	47.2	17.5
Control group	48.2	19.5	49.2	18.8
NK cell percentage				
Disclosure group	9.4	3.8	8.7	3.4
Control group	10.0	5.0	9.6	4.3

Individual Differences in Goal Changes and NKCC

Our second major hypothesis was that changes in meaning-related goals from pre- to postintervention would be associated with changes in NKCC. We were unable to test this hypothesis by comparing experimental groups because the disclosure intervention did not lead to changes in meaning-related goals. Instead, we examined individual differences in goal shifts among participants in both experimental conditions. Changes in goal importance were observed among both disclosure and control group participants (mean change = .33, range = -6-10). Participants were classified into groups on the basis of changes in their scores on the Life Goals Inventory from Time 1 to Time 2. Participants whose scores either changed in a positive direction (i.e., rated meaning-related goals as more important; $n = 14$) or stayed at the same high level ($n = 3$) were classified as "improved/high meaning," whereas participants whose scores changed in a negative direction (i.e., rated meaning-related goals as less important; $n = 19$) or stayed at the same low level ($n = 1$) were classified as "declined/low meaning." Of note, there was no association between experimental group assignment and improvement group classification.

A 2×2 Group (improved/high vs. declined/low) \times Time (Time 1 vs. Time 2) mixed-model repeated measures ANOVA computed on NK cell parameters revealed a significant Group \times Time interaction for NKCC. As shown in Figure 1, NKCC increased from Time 1 to Time 2 among participants classified as improved/high on meaning-related goals, whereas NKCC de-



■ Improved/High on Meaning-Related Goals
□ Declined/Low on Meaning-Related Goals

FIGURE 1 Change in natural killer cell cytotoxicity (NKCC) associated with change in importance of meaning-related goals from pre- to postintervention. Individuals who rated meaning-related goals as more important or whose goal ratings remained high over the course of the study ("improved/high" group; $n = 17$) showed an increase in NKCC, whereas those who rated these goals as less important or whose ratings stayed low ("declined/low" group; $n = 20$) showed a decrease in NKCC.

creased among those classified as declined/low, $F(1, 35) = 4.29$, $p < .05$. This effect remained significant in analyses controlling for baseline depression scores, changes in depression scores from pre- to postintervention, and potential behavioral confounds. In addition, the Group \times Time interaction for NKCC remained significant after excluding the 4 women whose scores on the life goals measure did not change from Time 1 to Time 2. Thus, shifts in meaning-related goals were correlated with changes in NKCC from pre- to postexperiment. Change in percentage of NK cells was not observed, suggesting that the functional capacity of these cells rather than their number or distribution was associated with goal shifts.

DISCUSSION

The theoretical model guiding this investigation proposed that actively thinking about a past stressor, or cognitive processing, would lead to positive shifts in goals and priorities related to finding positive meaning from the experience. Furthermore, this model predicted that increases in meaning-related goals would be associated with changes in immunological parameters, and specifically in increases in NKCC. Results offered only partial support for these hypotheses. We found no evidence that cognitive processing, in the form of writing about the loss of a relative to breast cancer, was associated with changes in meaning-related goals or NK cell parameters; however, we did find a positive association between importance of meaning-related goals and NKCC, both at baseline and over the course of study participation. These results are discussed later.

Effects of Written Disclosure

Contrary to predictions, writing about the death of one's relative did not elicit positive changes in importance of meaning-related goals, and disclosure did not lead to changes in NK cell percentage or NKCC. Prior research conducted with college undergraduates has shown positive effects of disclosure on psychological and immune variables (37), although the specific outcomes of interest here have not been assessed previously. Why were effects not seen in this study?

It is possible that differences in our experimental paradigm, such as having participants write at home rather than in a supervised laboratory setting, may have affected results. Conducting the follow-up assessment within 1 week of the final writing assignment may not have allowed sufficient time for disclosure effects to emerge, although immune effects were observed 1 week after disclosure in an earlier study (20). In addition, the heterogeneity of our sample may have influenced study results. There was considerable variability in the participants' age at their relative's death, the number of years since the loss, and the extent to which they had already thought and talked about the experience; although we found no evidence that these or other bereavement-related factors influenced responses to disclosure, our sample may not have been sufficiently large to capture these effects.

The intervention might have been more effective if participants had been allowed to select their own disclosure topic, as has been done in most previous disclosure studies. Disclosure

interventions have been successful when participants are instructed to write about a specific topic; for example, Stanton et al. (44) found that breast cancer patients who were asked to write about their thoughts and feelings about their cancer experience showed improvements in psychological and physical well-being compared with women who wrote only about the factual aspects of the experience. However, several studies have *not* shown effects of writing about bereavement on mental or physical health outcomes, even among recently bereaved individuals (45,46). Positive effects of bereavement-related disclosure may be particularly difficult to detect when the study occurs several years after the bereavement experience, as was the case for many participants in our study. Although women who have lost relatives to breast cancer do report elevated levels of cancer-related distress up to 14 years after the relative's death (27), it is unclear whether these women also experience prolonged or complicated grief reactions that might be amenable to psychological intervention. Of note, we found no evidence that women who reported higher levels of grief or depressive symptomatology at study entry were more likely to benefit from the disclosure intervention.

Finally, it is possible that the standard disclosure paradigm may not be effective in eliciting changes in meaning-related priorities and goals. To date, research on finding meaning has been primarily descriptive in nature; relatively little is known about how individuals are able to find meaning for themselves, and even less is known about the role of external interventions in promoting meaning changes. We used disclosure as a means of eliciting cognitive processing, which has been linked to finding meaning in observational studies (7,18). However, a few sessions of solitary, written disclosure may not be sufficient to induce the level of cognitive processing necessary for provoking changes in intrinsic values and goals in a systematic way; indeed, our results suggest that this type of writing did not lead to an overall increase in reflection on the relative's death, outside of the 20-min writing session. Instead, a more intensive intervention may be required, involving more time and possibly an interpersonal context providing guidance and support. One example of this type of intervention is supportive-expressive therapy, which focuses specifically on existential themes related to finding meaning and is conducted in groups over an extended time frame (47). There is also evidence that a more didactic, structured group intervention emphasizing reappraisals of the event and positive coping strategies may be effective in helping individuals find benefits from certain types of stressors (48); whether this approach specifically affects life goals has not been determined. Given the potential importance of meaning-related goals for psychological and physical health, future research should more carefully explore the ways in which individuals are able to derive meaning from traumatic life events, particularly whether meaning changes can be prompted by disclosure or other psychological interventions.

We have discussed why the writing intervention used in this study may not have prompted changes in meaning-related goals. What, then, might have caused the goal changes that did occur? Recall that shifts in goal importance were observed among individuals in both the disclosure and control conditions over the

course of the study. These changes may have resulted from natural fluctuations in goal importance or from external events or triggers in participants' lives. It is also possible that some women may have reordered their goals as a result of study participation. Simply being part of a study focusing on breast cancer and, in particular, having the opportunity to discuss their relative's death during the initial interview may have prompted a reconsideration of goals and priorities for some participants. This finding is consistent with the idea that in the absence of a powerful intervention the discovery of meaning seems to be an idiosyncratic process, dependent on aspects of an individual's personality, life circumstances, and response to the triggering event. The identification of these individual difference factors is another critical step in understanding positive adaptation to stressful events and determining who may benefit most from psychological interventions.

Finding Meaning and NKCC

The second major goal of this study was to test the hypothesis that increases in the importance of meaning-related goals would be associated with increases in NK cell function. To evaluate the association between goal changes and NKCC in the absence of a disclosure effect, we collapsed data across experimental groups. The results showed that at baseline, women who placed greater importance on goals such as cultivating relationships, personal development, and striving for meaning in life had higher levels of NKCC. Furthermore, women who rated these goals as more important after study participation also showed increases in NKCC from pre- to postintervention. The relation between meaning-related goals and NKCC remained significant in analyses controlling for a number of potential psychosocial and biobehavioral confounds, including depressed mood, reducing the plausibility that other factors may have mediated this effect.

Because the changes in meaning-related goals were not caused by the experimental manipulation, we cannot conclude that shifts in goals provoked changes in NK cell activity. However, both the cross-sectional and longitudinal data do support an association between importance of meaning-related goals and NK cell function. To our knowledge, this is the first study to show an association between prioritization of goals related to finding meaning and an immunological outcome. These findings are consistent with results from an earlier study, in which we found that shifts in goals and priorities indicative of finding meaning were associated with both positive immunological changes and a lower rate of mortality among bereaved HIV-positive men (7). Statements reflective of finding meaning in that study (coded from transcripts of bereavement interviews) included greater appreciation for loved ones, emphasis on relationships, new personal growth goals, and a commitment to enjoying and appreciating life more fully; these statements are very similar to items on the Life Goals Inventory used in this investigation. Together, results from these studies provide preliminary evidence that individuals who place greater importance on intrinsic goals, such as personal growth, relationships with oth-

ers, and finding meaning in life, may show positive changes in certain components of the immune system.

Physiological mediators of the association between meaning-related goals and NK cell parameters have not been determined. The sympathetic nervous system and hypothalamic-pituitary-adrenal axis are responsive to psychological triggers such as stress and depression and have demonstrated effects on NK cells in vivo and in vitro (49,50). However, little is known about the relation between "positive" psychological states and these physiological systems. It is possible that prioritizing meaning-related goals may promote more adaptive autonomic or neuroendocrine responses to stress, such as more rapid cortisol adaptation to repeated stressors (51), or may have direct beneficial effects on neural and hormonal factors, such as decreases in baseline cortisol (15). The physiological mechanisms through which finding meaning gets "under the skin" and influences the immune system is a current focus of our research.

Goal Engagement and Immunity

This study adds to a growing body of literature on positive psychological states (52) and the potential for positive change and growth following exposure to trauma (2-5). We focused here on one dimension of positive change: increased or renewed importance of goals linked to intrinsic values such as relationships, personal growth, and finding meaning in life (53). Increased goal importance may indicate a greater striving toward or engagement with particular life goals. This type of goal engagement may represent an important motivational domain that has linkages to neurophysiological systems relevant to the immune system. Older theories have posited that a generalized goal disengagement (e.g., giving up) may have health implications (54), and current animal research on defeat suggests neurophysiological and immunological changes coincident with a disengaged or defeated state (55,56). This study supports the possibility that a generalized form of goal engagement—one relevant to more intrinsic goals, such as finding meaning—may have positive immunological correlates. Our results also suggest that this type of goal engagement may be difficult to promote and that a relatively brief, solitary intervention such as written disclosure may be insufficient to affect changes in this domain.

REFERENCES

- (1) Herbert TB, Cohen S: Stress and immunity in humans: A meta-analytic review. *Psychosomatic Medicine*. 1993, 55:364-379.
- (2) Janoff-Bulman R, Frantz CM: The impact of trauma on meaning: From meaningless world to meaningful life. In Power M, Brewin C (eds). *The Transformation of Meaning in Psychological Therapies*. London: Wiley, 1997.
- (3) Taylor SE: Adjustment to threatening events: A theory of cognitive adaptation. *American Psychologist*. 1983, 41:1161-1173.
- (4) Tedeschi RG, Calhoun LG: *Trauma and Transformation: Growing in the Aftermath of Suffering*. Thousand Oaks, CA: Sage, 1995.
- (5) Park CL, Folkman S: Meaning in the context of stress and coping. *Review of General Psychology*. 1997, 1:115-144.

- (6) Davis CG, Nolen-Hoeksema S, Larson J: Making sense of loss and benefiting from the experience: Two construals of meaning. *Journal of Personality and Social Psychology*. 1998, 75:561–574.
- (7) Bower JE, Kemeny ME, Taylor SE, Fahey JL: Cognitive processing, discovery of meaning, CD4 decline, and AIDS-related mortality among bereaved HIV seropositive gay men. *Journal of Consulting and Clinical Psychology*. 1998, 66:979–986.
- (8) Schwartzberg SS: Struggling for meaning: How HIV-positive gay men make sense of AIDS. *Professional Psychology: Research and Practice*. 1993, 24:483–490.
- (9) Updegraff JA, Taylor SE, Kemeny ME, Wyatt GE: Positive and negative effects of HIV-infection in women with low socioeconomic resources. *Personality and Social Psychology Bulletin*. 2002, 28:382–394.
- (10) Taylor SE, Lichtman RR, Wood JV: Attributions, beliefs about control, and adjustment to breast cancer. *Journal of Personality and Social Psychology*. 1984, 46:489–502.
- (11) Andrykowski MA, Brady MJ, Hunt JW: Positive psychological adjustment in potential bone marrow transplant recipients: Cancer as a psychosocial transition. *Psycho-Oncology*. 1993, 2:261–276.
- (12) Tennen H, Affleck G, Mendola R: Causal explanations for infertility: Their relationship to control appraisals and psychological adjustment. In Stanton A, Dunkel-Schetter C (eds), *Infertility: Perspectives From Stress and Coping Research*. New York: Plenum, 1991, 109–132.
- (13) Affleck G, Tennen H, Croog S, Levine S: Causal attributions, perceived benefits, and morbidity after a heart attack: An 8-year study. *Journal of Consulting and Clinical Psychology*. 1987, 55:29–35.
- (14) Thompson SC: The search for meaning following a stroke. *Basic and Applied Social Psychology*. 1991, 12:81–96.
- (15) Cruess DG, Antoni MH, McGregor BA, et al.: Cognitive-behavioral stress management reduces serum cortisol by enhancing benefit finding among women being treated for early stage breast cancer. *Psychosomatic Medicine*. 2000, 62:304–308.
- (16) Greenberg MA: Cognitive processing of trauma: The role of intrusive thoughts and reappraisals. *Journal of Applied Social Psychology*. 1995, 25:1262–1296.
- (17) Horowitz MJ: *Stress Response Syndromes* (2nd ed.). New York: Aronson, 1986.
- (18) Calhoun LG, Cann A, Tedeschi RG, McMillan J: A correlational test of the relation between posttraumatic growth, religion, and cognitive processing. *Journal of Traumatic Stress*. 1999, 13:521–527.
- (19) Pennebaker JW: Writing about emotional experience as a therapeutic process. *Psychological Science*. 1997, 8:162–166.
- (20) Esterling BA, Antoni MH, Fletcher MA, Margulies S, Schneiderman N: Emotional disclosure through writing or speaking modulates latent Epstein-Barr virus antibody titers. *Journal of Consulting and Clinical Psychology*. 1994, 62:130–140.
- (21) Pennebaker JW, Kiecolt-Glaser JK, Glaser R: Disclosure of traumas and immune function: Health implications for psychotherapy. *Journal of Consulting and Clinical Psychology*. 1988, 56:239–245.
- (22) Petrie KJ, Booth RJ, Pennebaker JW, Davison KP, Thomas MG: Disclosure of trauma and immune response to a hepatitis B vaccination program. *Journal of Consulting and Clinical Psychology*. 1995, 63:787–792.
- (23) Pennebaker JW, Beall SK: Confronting a traumatic event: Toward an understanding of inhibition and disease. *Journal of Abnormal Psychology*. 1986, 95:274–281.
- (24) Kelley JE, Lumley MQ, Leisen JCC: Health effects of emotional disclosure in rheumatoid arthritis patients. *Health Psychology*. 1997, 16:331–340.
- (25) Smyth JM, Stone AA, Hurewitz A, Kaell A: Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis. *Journal of the American Medical Association*. 1999, 281:1304–1309.
- (26) Pennebaker JW, Mayne TJ, Francis ME: Linguistic predictors of adaptive bereavement. *Journal of Personality and Social Psychology*. 1997, 72:863–871.
- (27) Zakowski SG, Valdimarsdottir HB, Bovbjerg DH, et al.: Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer. *Annals of Behavioral Medicine*. 1997, 19:362–369.
- (28) Bovbjerg DH, Valdimarsdottir HB: Interventions for healthy individuals at familial risk for cancer: Biobehavioral mechanisms for health benefits. In Baum A, Anderson B (eds), *Psychosocial Interventions for Cancer*. Washington, DC: American Psychological Association, 2001.
- (29) Whiteside TL, Herberman RB: The role of natural killer cells in human disease. *Clinical Immunology and Immunopathology*. 1989, 53:1–23.
- (30) Strayer DR, Carter WA, Brodsky I: Familial occurrence of breast cancer is associated with reduced natural killer cytotoxicity. *Breast Cancer Research and Treatment*. 1986, 7:187–192.
- (31) Futterman AD, Kemeny ME, Shapiro D, Fahey JL: Immunological and physiological changes associated with induced positive and negative mood. *Psychosomatic Medicine*. 1994, 56:499–511.
- (32) Fawzy FI, Kemeny ME, Fawzy NW, et al.: A structured psychiatric intervention for cancer patients: Changes over time in immunological measures. *Archives of General Psychiatry*. 1990, 47:729–735.
- (33) Kiecolt-Glaser JK, Glaser R, Williger D, et al.: Psychosocial enhancement of immunocompetence in a geriatric population. *Health Psychology*. 1985, 4:25–41.
- (34) Carver CS, Scheier MF: *On the Self-Regulation of Behavior*. New York: Cambridge University Press, 1998.
- (35) Kemeny ME, Gruenewald T: Affect, cognition, the immune system and health. In Mayer EA, Saper C (eds), *The Biological Basis for Mind Body Interactions: Progress in Brain Research Series*. Amsterdam: Elsevier Science B.V., 2000, 291–308.
- (36) Cole SW: Negative physical health effects of psychological inhibition in disclosure study control groups. Manuscript submitted for publication.
- (37) Smyth JM: Written emotional expression: Effect sizes, outcome types, and moderating variables. *Journal of Consulting and Clinical Psychology*. 1998, 66:174–184.
- (38) Kemeny ME: The Life Goals Inventory. Unpublished manuscript.
- (39) Kemeny ME, Reed G, Taylor SE, Visscher B, Fahey JL: Negative HIV-specific expectancies predict immunological evidence of HIV progression. Unpublished manuscript.
- (40) Kemeny ME, Dickerson S, Gruenewald T, Bower J, Lu Q: Validation of a measure of life goals and priorities. Unpublished manuscript.
- (41) Radloff LS: The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977, 1:386–401.

- (42) Faschingbauer TR, Zisook S, DeVaul R: The Texas Revised Inventory of Grief. In Zisook S (ed), *Biopsychosocial Aspects of Bereavement*. Washington, DC: American Psychiatric Press, 1987, 109–128.
- (43) Kiecolt-Glaser JK, Glaser R: Methodological issues in behavioral immunology research with humans. *Brain, Behavior, and Immunity*. 1988, 2:67–78.
- (44) Stanton AL, Danoff-Burg S, Sworowski LA, et al.: Randomized, controlled trial of written emotional expression and benefit finding in breast cancer patients. *Journal of Clinical Oncology*. 2002, 20:4160–4168.
- (45) Range LM, Kovac SH, Marion MS: Does writing about bereavement lessen grief following sudden, unintentional death? *Death Studies*. 2000, 24:115–134.
- (46) Stroebe M, Stroebe W, Schut H, Zech E, van den Bout J: Does disclosure of emotions facilitate recovery from bereavement? Evidence from two prospective studies. *Journal of Consulting and Clinical Psychology*. 2002, 70:169–178.
- (47) Spiegel D, Classen C: *Group Therapy for Cancer Patients: A Research-Based Handbook of Psychosocial Care*. New York: Basic Books, 2000.
- (48) Antoni MH, Lehman JM, Kilbourn KM, et al.: Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early stage breast cancer. *Health Psychology*. 2001, 20:20–32.
- (49) Friedman EM, Irwin MR: Modulation of immune cell function by the autonomic nervous system. *Pharmacology and Therapeutics*. 1997, 74:27–38.
- (50) McEwen BS, Biron CA, Brunson KW, et al.: The role of adrenocorticoids as modulators of immune function in health and disease: Neural, endocrine, and immune interactions. *Brain Research Reviews*. 1997, 23:79–133.
- (51) Epel ES, McEwen BS, Ickovics JR: Embodying psychological thriving: Physical thriving in response to stress. *Journal of Social Issues*. 1998, 54:301–322.
- (52) Seligman MEP, Csikszentmihalyi M: Positive psychology [Special issue]. *American Psychologist*. 2000, 55(1).
- (53) Ryan RM, Sheldon KM, Kasser T, Deci EL: All goals are not created equal: An organismic perspective on the nature of goals and their regulation. In Gollwitzer PM, Bargh JA (eds), *The Psychology of Action: Linking Cognition and Motivation to Behavior*. New York: Guilford, 1996, 7–26.
- (54) Schmale AH: Giving up as a final common pathway to changes in health. *Advances in Psychosomatic Medicine*. 1972, 8:20–40.
- (55) Fleshner M, Laudenslager ML, Simons L, Maier SL: Reduced serum antibodies associated with social defeat in rats. *Physiology and Behavior*. 1989, 45:1183–1187.
- (56) Stefanski V, Ben-Eliyahu S: Social confrontation and tumor metastasis in rats: Defeat and beta-adrenergic mechanisms. *Physiology and Behavior*. 1996, 60:277–282.