Positive Affect and Inflammatory Activity in Breast Cancer Survivors: Examining the Role of Affective Arousal

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ABSTRACT

Objective: Given the importance of positive affect and inflammation for well-being in cancer survivors, the current study examined the relationship between high- and low-arousal positive affect and inflammation in 186 women who completed treatment of early-stage breast cancer.

Methods: Measures of high- and low-arousal positive affect were completed within 3 months after treatment completion (baseline). Plasma markers of inflammation, including soluble tumor necrosis factor receptor type II (sTNF-RII), C-reactive protein (CRP), and interleukin-1 receptor antagonist, were assessed at baseline and 6- and 12-month follow-up assessments.

Results: Multilevel modeling analyses showed that high-arousal positive affect was associated with lower levels of sTNF-RII, a marker of TNF activity, at treatment completion and prospectively predicted maintenance of these differences through the 6- and 12-month follow-ups adjusting for biobehavioral confounds ($b = -0.055$, $t(156) = -2.40$, $p = .018$). However, this association was no longer significant when adjusting for fatigue. Exploratory analyses showed that low-arousal positive affect was associated with lower levels of CRP at treatment completion and through the 6- and 12-month follow-ups; this association remained significant after adjusting for fatigue and other confounds ($b = -0.217$, $t(152) = -2.04$, $p = .043$).

Conclusions: The relationship of high-arousal positive affect (e.g., "active") with sTNF-RII seems to be driven by the overlap of high-arousal positive affect with fatigue, whereas the relationship of low-arousal positive affect (e.g., "calm") with CRP was independent of fatigue. Future research should consider affective arousal when examining the association of positive affect with inflammation as this facet of positive affect may have important implications for interpretation of results.

Key words: positive affect, breast cancer, inflammation, arousal.

INTRODUCTION

Although research has traditionally focused on the deleterious effects of chronic stress and its correlates (1), more recent investigations have produced evidence for the influence of positive psychological processes on health. In particular, positive affect, defined as the presence of emotional states that are positive in valence, has been linked to lower overall morbidity and mortality (2,3). However, despite the association of positive affect with improved health outcomes, the physiological mechanisms that underlie this association have not been determined. In addition, there has been minimal examination of positive affect and physiological processes in clinical populations, despite relevance for health and well-being. Thus, the aim of the current study was to examine the prospective association of high- and low-arousal positive affect with markers of inflammation in a sample of women with early-stage breast cancer who recently completed primary cancer treatment.

Positive affect has been prospectively associated with improved outcomes for a wide variety of diseases (e.g., Refs. (3–7)). In the cancer context, preliminary studies have found that positive affect is associated with lower cancer-related mortality among breast cancer patients with recurrent disease (8) and patients with metastatic renal cell

CRP = C-reactive protein, **IL-1ra** = interleukin-1 receptor antagonist, **sTNF-RII** = soluble tumor necrosis factor receptor type II, **TNF** = tumor necrosis factor

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carcinoma (9). Women with early-stage, nonrecurrent breast cancer have high survival rates but are at risk for other health comorbidities that have been inversely linked with positive affect, including cardiovascular disease (10). Furthermore, positive affect is associated with improved psychological adjustment in cancer survivors, including lower anxiety, depressive symptoms, pain, and fatigue, as well as greater quality of life (11–13). Evidence suggests that levels of positive affect reported by cancer survivors are generally high and comparable to healthy adult samples (13,14).

Despite the association between positive affect and improved health outcomes, there has been limited research examining the intermediate mechanisms that may account for the salutary effects of positive affect. One plausible mechanism may be inflammation given its association with all-cause mortality (15) and the onset and progression of a variety of diseases (including many that have been linked to positive affect; e.g., Refs. (16,17)). Research by Steptoe and colleagues (18) aggregating daily assessments of positive affect in healthy middle-aged adults found an inverse relationship between positive affect and circulating levels of interleukin-6 (IL-6) and C-reactive protein (CRP) in women. In addition, these investigators found that positive affect predicted lower reactivity and more efficient recovery of fibrinogen in response to a mental stress task in both men and women (19). Nevertheless, other studies examining positive affect and inflammatory markers have produced mixed results (20–22).

Given our interest in the association of positive affect and physiology, an important defining dimension of positive affect to consider is its level of arousal. The Circumplex Model of Affect (23) characterizes affect on two dimensions: valence and arousal. Valence ranges from positive to negative, whereas arousal ranges from high to low activation. Differentiating between high-arousal positive affect (e.g., excitement) and low-arousal positive affect (e.g., contentment) may be of particular importance as affective arousal has consequences for physiological arousal (24,25). Specifically, autonomic activation is particularly sensitive to high- versus low-arousal positive affect in mood induction studies, with evidence suggesting that high-arousal positive affect is associated with greater autonomic activation than low-arousal positive affect (for review, see Ref. (25)). This may, in turn, have implications for inflammatory processes, given autonomic regulation of the immune system (26). Nevertheless, research investigating differences in the association of high- versus low-arousal positive affect with inflammatory processes is lacking.

Studies have investigated the effects of high- versus low-arousal positive affect on other immune and physiological processes. high-arousal positive affect (but not low-arousal positive affect) has been shown to predict the development of fewer colds after exposure to a rhinovirus or influenza A virus (4,27), steeper cortisol slopes from waking to bedtime and lower evening cortisol (28), and increased longevity (29). However, other observational studies have not found differential effects of high- versus low-arousal positive affect on immune processes, including antibody responses to the hepatitis B vaccine (30) or immune responses (e.g., natural killer cell percentage and activity and percentage of suppressor/cytotoxic T cells) to an experimental mood induction (31). Of note, self-report measures of high- and low-arousal positive affect vary across studies. Although most studies use some combination of the descriptors "calm," "relaxed," and "at ease" for the assessment of low-arousal positive affect (4,27–30), the measurement of high-arousal positive affect is more variable. Previous studies have included all or select items (e.g., "active" and "alert") from the commonly used Positive and Negative Affect Scale (PANAS) (32) positive affect subscale (28,29), whereas others have used other descriptors (e.g., "lively," "full-of-pep," and "energetic"; (4,27,30)). The current study builds on this emerging literature and uses previous research to inform its assessment of high- and low-arousal positive affect.

Examining predictors of inflammation in breast cancer survivors is of particular interest given that inflammation has been associated with recurrence and survival among women treated for early-stage breast cancer (33,34). In addition, inflammation has been associated with behavioral symptoms that plague many breast cancer survivors, including fatigue and depression (e.g., Refs. (35–37)) and is also associated with other health comorbidities that are elevated in this population (38). To advance our understanding of positive affect and inflammation in the cancer context, the aim of the present study was to longitudinally examine the prospective relationship of high- and low-arousal positive affect with circulating markers of inflammation among women with early-stage breast cancer who were followed up for a year after treatment with surgery, radiation, and/or chemotherapy. Given evidence supporting the association of positive affect and improved health and well-being, we hypothesized that both high- and low-arousal positive affect would predict lower levels of inflammatory markers at posttreatment and at 6- and 12-month follow-up assessments controlling for potential biobehavioral confounds. In particular, we were interested in examining the unique association of positive affect and inflammation controlling for negative affect and fatigue given the previous research supporting the association of these factors with inflammation in the cancer context.

METHODS

Participants

Study participants were recruited to participate in a prospective observational cohort study of cognitive functioning after treatment of breast cancer conducted at the University of California, Los Angeles (UCLA).

A detailed description of recruitment and assessment procedures for the primary study can be found elsewhere (39). To be eligible, women were required to be between 21 and 65 years of age with a diagnosis of stage 0 to IIIA breast cancer, before beginning endocrine therapy and within 3 months of completing primary cancer treatment (i.e., surgery, radiation therapy, and/or chemotherapy). Of the 191 women originally enrolled to participate, questionnaire data were unavailable for 5 participants; thus, our primary analyses focus on women who completed the baseline psychological measures of interest (n = 186).

Procedures

Study participants were identified primarily through tumor registry rapid case ascertainment from hospitals where collaborating physicians practiced as well as through direct referral from surgical and medical oncology practices. Recruitment began in May 2007 and ended in February 2011. Women received a brochure describing the study and were asked to contact the research office if they were interested in participating. A telephone screen was conducted to determine eligibility, and women who were eligible were subsequently scheduled for an in-person appointment at UCLA during which they provided blood samples via venipuncture and completed self-report questionnaires and neuropsychological assessments. Weight and height measurements were also obtained to determine body mass index (BMI). In addition, women completed comprehensive neuropsychological assessments as part of the parent study.

Participants returned to the laboratory 6 and 12 months after the baseline to complete follow-up assessments during which they provided blood samples and completed questionnaires and neuropsychological assessments. All assessments were conducted in the morning before 11:00 AM. These assessments were structured to examine the impact of adjuvant endocrine therapies on cognitive functioning following primary treatment of breast cancer (39–41); however, they presented us with the unique opportunity to examine the relationship of positive affect with inflammation in the year after breast cancer treatment. This research was approved the UCLA institutional review board. Informed consent was obtained from all participants.

Measures

Demographic information, including age, ethnicity, relationship status, and socioeconomic status, was collected at baseline by self-report questionnaire. Cancer and treatment-related information (i.e., stage, time since treatment completion and treatment with chemotherapy, radiation therapy, and/or endocrine therapy) was determined from medical chart reviews. Menopausal status was self-reported at baseline.

Questionnaires

High-arousal positive affect at baseline was assessed using the four high-arousal items from the positive affect subscale of the PANAS (32): "excited," "active," "alert," and "enthusiastic." This is consistent with previous research that has used all or select items of this subscale to assess high-arousal positive affect (28,29). This measure assesses the extent to which a participant has experienced each high-arousal positive affect item during the past month on a scale of 1 = "very slightly or not at all" to 5 = "extremely." Items are averaged. Internal consistency was adequate in this sample (α = .854).

Low-arousal positive affect at baseline was assessed using two low-arousal positive affect items from the serenity subscale of the PANAS-X (an expansion of the original PANAS questionnaire; (42)): "calm" and "relaxed." The third item ("at ease") was not included in our questionnaire. This is consistent with previous research that has used these two items to asses low-arousal positive affect (4,27–30). This measure assesses the extent to which a participant has experienced each low-arousal positive affect item during the past week on a scale of 1 = "very slightly or not at all" to 5 = "extremely." Items are averaged. The interitem correlation for this measure was high (r = 0.78, p < .001).

To determine whether any associations between high- and low-arousal positive affect and inflammatory markers are driven by negative affect (or lack thereof), we assessed negative affect at baseline using the negative affect subscale of the PANAS (32)). This measure assesses the extent to which a participant has experienced negative affect during the past month on the same 1–5 scale. Items of the negative affect scale are as follows: "afraid," "scared," "nervous," "jittery," "irritable," "hostile," "guilty," "ashamed," "upset," and "distressed." Furthermore, given the potential overlap of positive affect, particularly high-arousal positive affect, and fatigue, and evidence that fatigue is linked to inflammation in breast cancer survivors (including a subset of patients in this sample (35)), fatigue was also examined as a potential confounder in analyses. Fatigue severity was assessed at baseline using Fatigue Symptom Inventory (43), which includes items assessing "most," "least," and "average" fatigue in the past week on a 0–10 scale.

Inflammatory Markers

Blood samples at baseline as well as at 6- and 12-month follow-up assessments were collected by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at −80°C for subsequent batch testing. We focused on downstream markers of proinflammatory cytokine activity, which are typically produced in larger quantities than the cytokines that induce their production and may provide a more reliable and stable index of cytokine activity (44,45). These included the interleukin-1 receptor antagonist (IL-1ra), a marker of IL-1β activity; the soluble tumor necrosis factor (TNF) receptor type II (sTNF-RII), a marker of TNF-α activity; and CRP, a correlate of IL-6 activity. Plasma levels of IL-1ra and sTNF-RII were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) according to the manufacturer's protocols with a lower limit of detection of 31 and 234 pg/ml for IL-1ra and sTNF-RII, respectively. CRP levels were determined by a high-sensitivity enzyme-linked immunosorbent assay (Immundiagnostik; ALPCO Immunoassays, Salem, NH) according to the manufacturer's protocol but with an extended standard curve to a lower limit of detection of 0.2 mg/l. All samples were run in duplicate, and assays were repeated on two separate assay days for sTNF-RII and IL-1ra; intra-assay and interassay mean levels were used in all analyses. The intra-assay and interassay precisions of all tests were less than or equal to 10%. Immune data for women with a diagnosis of neurologic or immune-related medical conditions (e.g., autoimmune diseases) or an acute infection were excluded (n = 4).

Statistical Analyses

Descriptive analyses were conducted with SPSS version 18.0. To examine the relationship of positive affect with inflammation over time, a two-level multilevel model with time points nested within individuals was run to test the associations of high- and low-arousal positive affect at baseline with markers of inflammation over the 1-year assessment period using SAS version 9.3. Although assessed at all three time points, we focus our analyses on the baseline assessment of high- and low-arousal positive affect given our interest in prospectively predicting inflammation by levels of positive affect and the fact that repeated-measures analyses of variance revealed no change over time for both positive affect measures (p values > .05). Multilevel models are well suited for longitudinal data because they account for the nonindependence of repeated observations. We focus our interpretation on the fixed effects of the model.

Analyses controlled for key covariates that are known to influence inflammation, including age, BMI, and menopausal status (46). We also controlled for cancer-specific covariates, including stage of disease, cancer treatment (radiation, chemotherapy, endocrine therapy), and time since last treatment. Note that all women had completed radiation and/or chemotherapy before their baseline assessment, whereas endocrine therapy could be ongoing throughout the follow-up. Thus, main effects for radiation and

TABLE 1. Demographic and Medical Characteristics of Sample (n = 186)

Sample Characteristics	n (%) or M (SD)
Age, y	51.68 (8.29)
Body mass index, kg/m^2	25.66 (5.35)
Months since last primary treatment	1.18 (1.04)
Race	
White	154 (83.7%)
Other	30 (15.3%)
Don't know/refuse	2 (1.0%)
Hispanic ethnicity	
Yes	20 (10.9%)
No	164 (89.1%)
Marital status	
Married/Partnered	143 (76.9%)
Not married/partnered	43 (23.1%)
Education	
Graduate degree or training	97 (52.2%)
College degree	55 (29.6%)
Some college/associate degree	30 (16.1%)
High school/vocational training	4 (2.1%)
Employment	
Full or part time	121 (65.1%)
Not employed	65 (34.9%)
Annual household income	
≤$60,000	23 (12.0%)
$60,001–100,000	51 (27.9%)
>$100,000	110 (60.1%)
Menopausal status	
Postmenopausal before cancer	97 (52.2%)
Premenopausal	49 (26.3%)
Treatment-induced menopause	40 (21.5%)
Stage	
0	24 (12.9%)
I	85 (45.7%)
II	59 (31.7%)
III	18 (9.7%)
Type of surgery	
Mastectomy	64 (34.4%)
Lumpectomy	122 (65.6%)
Received chemotherapy	
Yes	97 (52.2%)
No	89 (47.8%)
Received radiation	
Yes	138 (74.2%)
No	48 (25.8%)
Received endocrine therapy	
Baseline	0 (0%)
6-mo follow-up	127 (68.3%)
12-mo follow-up	125 (67.2%)

M = mean; SD = standard deviation.

chemotherapy were included at the baseline assessment, whereas endocrine therapy was included as a time-varying covariate. Preliminary analyses indicated that chemotherapy also influenced the changes in inflammatory markers over the follow-up; to account for this effect, a time by chemotherapy interaction was included in the final model. The following covariates were grand-mean centered to aid interpretation: age, months since last treatment, and BMI. Preliminary analyses were also conducted to evaluate whether positive affect influenced the changes in inflammatory markers over time; however these were nonsignificant. Therefore, no positive affect by time interaction was included in the model for either high- or low-arousal positive affect.

Final models included both a random intercept and slope for time at Level 1. The markers of inflammation (i.e., sTNF-RII, IL-1ra, and CRP) were treated as Level 1 outcomes, with baseline positive affect as the Level 2 predictor of interest. Age, negative affect, BMI, menopausal status, treatment with chemotherapy and/or radiation therapy, time since treatment completion, cancer stage, and fatigue were all measured at baseline and included as Level 2 covariates. Treatment with endocrine therapy was assessed at each time point and entered as a Level 1 covariate. All values for markers of inflammation were log transformed to correct for nonnormality. To report the effect sizes of high- and low-arousal positive affect, we used the approach proposed by Raudenbush and Byrk (47), which estimates the residual variance at each level of the multilevel model in both a restricted model without the effect of interest and in a complete model with the effect of interest included. This allows for comparison of the two variance components to determine how much variance is accounted for by the predictor of interest over and above covariates.

RESULTS

Sample demographics are reported in Table 1. On average (standard deviation [SD]), participants were 52 (8.29) years of age, white (84%), partnered (77%) women with college or graduate educations (82%) and annual household incomes greater than $100,000 (60%). Women tended to have earlier-stage cancers (13% stage 0, 46% stage I, 32% stage II, and 10% stage III). More women underwent lumpectomies than mastectomies (66% versus 34%), 74% received radiation therapy, 52% received chemotherapy, and 68% of women received endocrine therapy at one or both of the follow-up assessments.

On average, women reported "moderate" high-arousal positive affect (mean [SD] = 3.06 [0.87]) and "a little" to "moderate" low-arousal positive affect (mean [SD] = 2.16 [0.96]). High-arousal positive affect was negatively correlated with negative affect (r = −0.42, p < .001), BMI (r = −0.17, p = .021), and fatigue (r = −0.49, p < .001) as well as positively correlated with low-arousal positive

TABLE 2. Descriptive Statistics for Markers of Inflammation at Baseline and 6- and 12-Month Follow-Up Assessments

	Baseline (n = 171)		6-mo Follow-Up (n = 157)		12-mo Follow-Up (n = 154)	
Inflammatory Markers	Mean	SD	Mean	SD	Mean	SD
sTNF-RII, pg/ml	2329.45	675.02	2050.85	520.54	2028.41	537.96
IL-1ra, pg/ml	289.92	294.35	252.70	196.44	253.60	161.03
CRP, mg/l	2.96	5.71	1.89	3.56	2.37	5.20

SD = standard deviation; sTNF-RII = soluble tumor necrosis factor receptor type II; IL-1ra = interleukin-1 receptor antagonist; CRP = C-reactive protein.

affect ($r = 0.58$, $p < .001$). Similarly, low-arousal positive affect was negatively correlated with negative affect ($r = -0.55$, $p < .001$) and fatigue ($r = -0.34$, $p < .001$) and positively correlated with age ($r = 0.19$, $p = .009$). Neither high- nor low-arousal positive affect was associated with cancer stage, time since primary treatment, or treatment with chemotherapy, radiation therapy, and endocrine therapy. Descriptive statistics for markers of inflammation at baseline and 6- and 12-month follow-up assessments are reported in Table 2.

Prospective Association of High-Arousal Positive Affect With Inflammation

The primary goal of this study was to examine the association between high- and low-arousal positive affect and levels of inflammatory markers over time. Consistent with hypotheses, results indicate that high-arousal positive affect was associated with significantly lower levels of sTNF-RII at the baseline assessment as well as the 6- and 12-month follow-up assessments ($b = -0.055$, $t(156) = -2.40$, $p = .018$), controlling for age, BMI, menopausal status, cancer stage, time since last treatment, radiation, endocrine therapy, chemotherapy, the interaction between chemotherapy and the linear trend for time, and negative affect . Thus, individuals with higher levels of high-arousal positive affect demonstrated lower levels of sTNF-RII across the three time points, independent of negative affect. This effect accounted for approximately 12% of the residual intercept variance not accounted for by other covariates in the model. However, when fatigue was included in the model, the association of high-arousal positive affect was attenuated and became nonsignificant (Table 3; $b = -0.030$, $t(153) = -1.24$, $p = .218$). High-arousal positive affect at baseline was not associated with CRP or IL-1ra at baseline or prospectively at 6- and 12-month follow-up assessments in models with or without fatigue (p values > .05). To facilitate comparison with studies using the full positive affect subscale of the PANAS (32), we also used the 10-item positive affect subscale, which oversamples high-arousal positive affect and excludes low-arousal positive affect items (25,29). Results were consistent with those reported earlier; specifically, the 10-item positive affect subscale was associated with lower levels of sTNF-RII in analyses that did not include fatigue, and this association became nonsignificant when controlling for fatigue.

Prospective Association of Low-Arousal Positive Affect With Inflammation

Low-arousal positive affect was associated with significantly lower levels of CRP at the baseline assessment as well as the 6- and 12-month follow-up assessments ($b = -0.221$,

TABLE 3. High-Arousal Positive Affect and Related Covariates as Predictors of sTNF-RII in a Two-Level Multilevel Model Using REML Estimation (n = 186)

	sTNF-RII		
Predictors	*B*	SE	*p*
Intercept	7.760	0.133	<.001
Time	−0.006	0.013	.634
High-arousal positive affect	−0.030	0.025	.218
Negative affect	−0.007	0.003	.022
Age	0.008	0.003	.014
Body mass index	0.006	0.003	.081
Fatigue severity	0.025	0.010	.012
Cancer stage (0 is reference group)			
I	0.034	0.061	.574
II	0.057	0.072	.432
III	0.094	0.089	.292
Menopausal status (postmenopausal before cancer is reference group)			
Premenopausal	−0.039	0.057	.497
Treatment-induced menopause	0.006	0.061	.921
Months since last treatment	−0.032	0.020	.119
Radiation therapy	−0.019	0.046	.674
Endocrine therapy	−0.054	0.018	.003
Chemotherapy	0.090	0.056	.108
Time by chemotherapy	−0.075	0.015	<.001

sTNF-RII = soluble tumor necrosis factor receptor type II; REML = restricted maximum likelihood; SE = standard error.

TABLE 4. Low-Arousal Positive Affect and Related Covariates as Predictors of CRP in a Two-Level Multilevel Model Using REML Estimation (n = 186)

	CRP		
Predictors	*B*	SE	*p*
Intercept	0.793	0.572	.167
Time	0.088	0.074	.235
Low-arousal positive affect	−0.217	0.106	.043
Negative affect	−0.017	0.017	.326
Age	−0.013	0.016	.424
Body mass index	0.114	0.016	<.001
Fatigue severity	0.010	0.043	.811
Cancer stage (0 is reference group)			
I	0.404	0.290	.166
II	0.538	0.343	.120
III	1.134	0.425	.009
Menopausal status (postmenopausal before cancer is reference group)			
Premenopausal	−0.598	0.273	.030
Treatment-induced menopause	−0.427	0.289	.141
Months since last treatment	−0.078	0.095	.413
Radiation therapy	−0.081	0.217	.709
Endocrine therapy	−0.317	0.109	.004
Chemotherapy	−0.235	0.263	.374
Time by chemotherapy	−0.212	0.088	.017

CRP = C-reactive protein; REML = restricted maximum likelihood; SE = standard error.

$t(153) = -2.13$, $p = .035$), controlling for age, BMI, menopausal status, cancer stage, time since last treatment, radiation, endocrine therapy, chemotherapy, the interaction between chemotherapy and the linear trend for time, and negative affect. This effect accounted for 1% of the residual intercept variance not accounted for by other covariates in the model. In contrast to effects for high-arousal positive affect, the association between low-arousal positive affect and CRP remained significant in analyses that also controlled for fatigue (Table 4; $b = -0.217$, $t(152) = -2.04$, $p = .043$). Thus, individuals with higher levels of low-arousal positive affect demonstrated lower levels of CRP across the three time points independent of negative affect and fatigue (Fig. 1). Low-arousal positive affect at baseline was not associated with sTNF-RII or IL-1ra at baseline or prospectively at 6- and 12-month follow-up assessments (p values > .05).

DISCUSSION

The aim of the current study was to determine the prospective association of high- and low-arousal positive affect with downstream markers of inflammation in women who had recently completed primary treatment of early-stage breast cancer. We found that higher levels of high-arousal positive affect ("excited," "active," "alert," "enthusiastic") predicted lower levels of the sTNF-RII, a marker of TNF activity, 1 month after primary treatment completion and at 6- and 12-month follow-ups, consistent with hypotheses. Importantly, effects of high-arousal positive affect were observed in analyses controlling for negative affect, indicating that the effects of high-arousal positive affect are independent of negative affect and are not merely driven by the absence of negative affect. However, the relationship of high-arousal positive affect with sTNF-RII did not hold over and above fatigue, suggesting that the association between sTNF-RII and high-arousal positive affect may be primarily driven by the "arousal" component of this affective state. There was no association between high-arousal positive affect and the other inflammatory markers assessed (i.e., CRP and IL-1RA).

A different pattern of results emerged for low-arousal positive affect. Specifically, we found that low-arousal positive affect ("calm," "relaxed") predicted lower levels of CRP 1 month after primary treatment completion and at 6- and 12-month follow-ups. The relationship of low-arousal

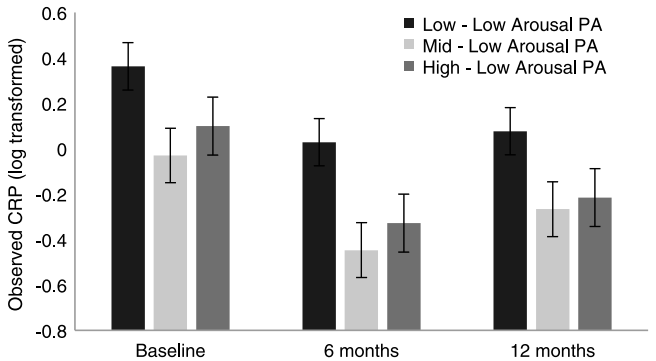

FIGURE 1. Relationship of low-arousal PA with CRP in the year after breast cancer treatment. Mean CRP shown at each tertile of low-arousal PA for the three assessment time points. Error bars represent standard errors. CRP = C-reactive protein; PA = positive affect.

positive affect and CRP remained significant in analyses controlling for negative affect *and* fatigue, indicating that low-arousal positive affect may have distinct associations with CRP (despite being significantly negatively correlated with fatigue, similar to high-arousal positive affect). There was no association with between low-arousal positive affect and either sTNF-RII or IL-1RA.

Previous research in noncancer samples has provided some support for the relationship of positive affect with reduced inflammation, including lower circulating levels of IL-6 and CRP (18) as well as lower reactivity and more efficient recovery of fibrinogen in response to a stress task (19). However, these studies aggregated ecological momentary assessments of participants' endorsement of feeling "happy" and therefore did not examine differences between low- and high-arousal positive affect. Other studies that have produced mixed results for the association of positive affect and inflammation have used measures that either do not capture level of arousal (22) or primarily capture high-arousal positive affect (20,21,48). Although research investigating differences in the association of high- versus low-arousal positive affect with inflammatory processes is lacking, previous studies examining the differential effects of high- versus low-arousal positive affect on other immune and physiological processes have also produced somewhat mixed results (4,27–31).

Our results indicate that high- and low-arousal positive affect have distinct inflammatory correlates, with implications for underlying pathways. Specifically, our finding that the association between high-arousal positive affect and levels of sTNF-RII was accounted for by fatigue may suggest a "sickness behavior" pathway for these effects. It is well documented that proinflammatory cytokines act on the brain and can induce a specific constellation of behavioral symptoms termed sickness behavior (49,50), including fatigue. We have previously shown that elevated levels of sTNF-RII are associated with fatigue in a subsample of participants from the current study (35) and in another samples of breast cancer survivors (51). Thus, it is possible that the inverse association of high-arousal positive affect with sTNF-RII in this study may reflect higher levels of inflammation acting on the brain—leading to both greater fatigue and lower high-arousal positive affect. Indeed, the induction of inflammatory cytokines leads to reductions in high-arousal positive affect, in addition to fatigue (52).

On the other hand, the finding that low-arousal positive affect was associated with lower levels of CRP, controlling for fatigue, may suggest a different underlying mechanism. States of low-arousal positive affect are associated with dampened sympathetic activation, which in turn modulates inflammatory activity. It is plausible that lower arousal positive affect exerts an influence on CRP by reducing engagement of stress-response systems, which would explain the current pattern of results. Indeed, individuals who are under chronic stress show elevated levels of CRP (53–55), whereas interventions, such as mindfulness meditation, yoga, and Qigong, that cultivate positively valenced low-arousal affective states (e.g., calmness and relaxation) have been shown to specifically reduce CRP (56). Furthermore, these mind-body interventions are also associated with decreases in inflammatory markers in cancer patients and survivors ((57–61); for review, see Ref. (62)). The specific mechanisms through which high- versus low-arousal positive affect is linked with inflammatory processes is an important question for future research.

Understanding the association of positive affect with inflammation is particularly important in the breast cancer context. Evidence suggests that low-grade inflammation is associated with cancer-related fatigue (35,51), depression (36,37), and health comorbidities like cardiovascular disease (38) that are elevated in breast cancer survivors and negatively affect quality of life. Furthermore, although survival rates for women with early-stage disease are high, there is evidence that high levels of CRP are associated with increased risk of all-cause mortality and breast cancer–specific mortality in early-stage breast cancer survivors (34). To the extent that low-arousal positive affective states are associated with lower levels of CRP in breast cancer survivors, strategies to enhance these affective states may have implications for their health and well-being, although the association with CRP was quite small.

Our results identified distinct inflammatory markers associated with high and low positive affect, as well as nonsignificant findings for several markers. Although inflammatory markers are often correlated, it is possible for markers to have distinct associations with the central nervous system, psychological states, and physical health, as observed in the current study. For example, sTNF-RII, but not IL-6, has been previously correlated with stress-induced changes in the central nervous system (63); CRP, but not IL-6 was correlated with daily family assistance in a sample of adolescents (64); and sTNF-RII has been shown to predict heart disease independent of CRP (65). Nevertheless, it is important to note that high- and low-arousal positive affect were each uniquely associated with only one inflammatory marker in this sample, and that several relationships we examined were nonsignificant (i.e., high-arousal positive affect with CRP and IL-1ra and low-arousal positive affect with sTNF-RII and IL-1ra). These specific effects were not predicted but are consistent with other findings from this sample. In particular, we have shown a specific association between fatigue and levels of sTNF-RII (35), which was not observed for other circulating markers. It is possible that activation of TNF may have particular relevance for neural processes related to arousal. Given the mixed nature of our results, these findings require replication in future research, with more focused investigation of the pathways linking behavioral states with specific inflammatory processes.

Other limitations of this study include the relatively homogenous patient population in terms of racial/ethnic composition and socioeconomic status, which limits the generalizability of the results. Furthermore, in addition to level of arousal, other dimensions of positive affect may also be important to disentangle. In particular, hedonic positive affect versus eudaimonic well-being has been associated with differing inflammatory gene expression profiles in leukocytes from healthy individuals (66) and may also have differential effects on inflammatory biology in cancer survivors. Although consistent with previous research, a major limitation of the current study is the use of abbreviated versions of positive affect subscale of the PANAS (32) and serenity subscale of the PANAS-X (42) that have not been validated; therefore, it is important that future research include a more focused assessment of high- and low-arousal positive affect using validated measures. Furthermore, much of the literature on positive affect and health focuses on the concept of happiness (67–71), which could be considered mid-arousal positive affect and is not included in either one of our measures. Future research should contrast the effects of high, mid, and low-arousal positive affect on immune processes. Because our study was observational in nature, we cannot draw conclusions regarding the direction of causality. Furthermore, it would be informative to have pretreatment measures of positive affect and inflammation to further probe the temporal dynamics of these systems and their interactions before, during, and after cancer treatment.

Our results indicate that the relationship of high-arousal positive affect (e.g., "excited," "active," "alert," and "enthusiastic") with sTNF-RII may be driven by the overlap of high-arousal positive affect with fatigue, whereas the association of low-arousal positive affect ("calm," "relaxed") and CRP may be unique. Of note, high- and low-arousal positive affect were each uniquely associated with one inflammatory marker and several of the relationships we examined were nonsignificant; therefore, these results await replication. Future research should consider affective arousal when examining the association of positive affect with inflammation as this facet of positive affect may have important implications for interpretation of results (particularly when using the commonly used positive affect subscale of the PANAS; (32)). Specifically, bidirectional associations between both high- and low-arousal positive affect and inflammation should be considered and is an important topic for future research.

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REFERENCES

1. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull 2004;130:601–30.
2. Chida Y, Steptoe A. Positive psychological well-being and mortality: a quantitative review of prospective observational studies. Psychosom Med 2008;70:741–56.
3. Cohen S, Pressman SD. Positive affect and health. Curr Dir Psychol Sci 2006;15:122–5.
4. Cohen S, Alper CM, Doyle WJ, Treanor JJ, Turner RB. Positive emotional style predicts resistance to illness after experimental exposure to rhinovirus or influenza A virus. Psychosom Med 2006;68:809–15.
5. Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. Fertil Steril 2001;76:675–87.
6. Middleton RA, Byrd KE. Psychosocial factors and hospital readmission status of older persons with cardiovascular disease. J Appl Rehabil Couns 1996;27:3–10.
7. Ostir GV, Markides KS, Peek MK, Goodwin JS. The association between emotional well-being and the incidence of stroke in older adults. Psychosom Med 2001;63:210–5.
8. Levy SM, Lee J, Bagley C, Lippman M. Survival hazards analysis in first recurrent breast cancer patients: seven-year follow-up. Psychosom Med 1988;50:520–8.
9. Prinsloo S, Wei Q, Scott SM, Tannir N, Jonasch E, Pisters L, Cohen L. Psychological states, serum markers and survival: associations and predictors of survival in patients with renal cell carcinoma. J Behav Med 2015;38:48–56.
10. Hooning MJ, Botma A, Aleman BMP, Baaijens MHA, Bartelink H, Klijn JGM, Taylor CW, van Leeuwen FE. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 2007;99:365–75.
11. Baker F, Denniston M, Zabora J, Polland A, Dudley WN. A POMS short form for cancer patients: psychometric and structural evaluation. Psychooncology 2002;11:273–81.
12. Guadagnoli E, Mor V. Measuring cancer patients' affect: revision and psychometric properties of the Profile of Mood States (POMS). Psychol Assess J Consult Clin Psychol 1989;1:150–4.
13. Schroevers MJ, Sanderman R, van Sonderen E, Ranchor AV. The evaluation of the Center for Epidemiologic Studies Depression (CES-D) scale: depressed and positive affect in cancer patients and healthy reference subjects. Qual Life Res 2000;9:1015–29.
14. Helgeson VS, Tomich PL. Surviving cancer: a comparison of 5-year disease-free breast cancer survivors with healthy women. Psychooncology 2005;14:307–17.
15. Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH Jr, Heimovitz H, Cohen HJ, Wallace R. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999;106:506–12.
16. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. Ann Intern Med 1998;128:127–37.
17. Pradhan A, Manson J, Rifai N, Buring J, Ridker P. C-reactive protein, interleukin 6, and risk of developing Type 2 diabetes mellitus. JAMA 2001;286:327–34.
18. Steptoe A, O'Donnell K, Badrick E, Kumari M, Marmot M. Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women: the Whitehall II Study. Am J Epidemiol 2008;167:96–102.
19. Steptoe A, Wardle J. Positive affect and biological function in everyday life. Neurobiol Aging 2005;26(Suppl 1):108–12.

20. Lutgendorf SK, Reimer TT, Harvey JH, Marks G, Hong S-Y, Hillis SL, Lubaroff DM. Effects of housing relocation on immunocompetence and psychosocial functioning in older adults. J Gerontol A Biol Sci Med Sci 2001;56:M97–105.
21. Ryff CD, Singer BH, Dienberg Love G. Positive health: connecting well–being with biology. Philos Trans R Soc Lond B Biol Sci 2004;359:1383–94.
22. Sepah SC, Bower JE. Positive affect and inflammation during radiation treatment for breast and prostate cancer. Brain Behav Immun 2009;23:1068–72.
23. Russell JA. A circumplex model of affect. J Pers Soc Psychol 1980;39:1161–78.
24. Dockray S, Steptoe A. Positive affect and psychobiological processes. Neurosci Biobehav Rev 2010;35:69–75.
25. Pressman SD, Cohen S. Does positive affect influence health? Psychol Bull 2005;131:925–71.
26. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol 2011;11:625–32.
27. Cohen S, Doyle WJ, Turner RB, Alper CM, Skoner DP. Emotional style and susceptibility to the common cold. Psychosom Med 2003;65:652–7.
28. Hoyt LT, Craske MG, Mineka S, Adam EK. Positive and negative affect and arousal: cross-sectional and longitudinal associations with adolescent cortisol diurnal rhythms. Psychosom Med 2015;77:392–401.
29. Pressman SD, Cohen S. Positive emotion word use and longevity in famous deceased psychologists. Health Psychol 2012;31: 297–305.
30. Marsland AL, Cohen S, Rabin BS, Manuck SB. Trait positive affect and antibody response to hepatitis B vaccination. Brain Behav Immun 2006;20:261–9.
31. Futterman AD, Kemeny ME, Shapiro D, Fahey JL. Immunological and physiological changes associated with induced positive and negative mood. Psychosom Med 1994;56:499–511.
32. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063–70.
33. Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhouser ML, Wener MH, Baumgartner KB, Gilliland FD, Sorensen BE, McTiernan A, Ulrich CM. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. J Clin Oncol 2009;27:3437–44.
34. Villaseñor A, Flatt SW, Marinac C, Natarajan L, Pierce JP, Patterson RE. Postdiagnosis C-reactive protein and breast cancer survivorship: findings from the WHEL Study. Cancer Epidemiol Biomarkers Prev 2013;23:189–99.
35. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? J Clin Oncol 2011;29:3517–22.
36. Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer 2008;8:887–99.
37. Soygur H, Palaoglu O, Akarsu ES, Cankurtaran ES, Ozalp E, Turhan L, Ayhan IH. Interleukin-6 levels and HPA axis activation in breast cancer patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1242–7.
38. Weaver KE, Foraker RE, Alfano CM, Rowland JH, Arora NK, Bellizzi KM, Hamilton AS, Oakley-Girvan I, Keel G, Aziz NM. Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: a gap in survivorship care? J Cancer Surviv 2013;7:253–61.
39. Ganz PA, Kwan L, Castellon SA, Oppenheim A, Bower JE, Silverman DHS, Cole SW, Irwin MR, Ancoli-Israel S, Belin TR. Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. J Natl Cancer Inst 2013;105:791–801.
40. Ganz PA, Bower JE, Kwan L, Castellon SA, Silverman DHS, Geist C, Breen EC, Irwin MR, Cole SW. Does tumor necrosis factor-alpha (TNF-α) play a role in post-chemotherapy cerebral dysfunction? Brain Behav Immun 2013;30:S99–108.
41. Ganz PA, Petersen L, Castellon SA, Bower JE, Silverman DHS, Cole SW, Irwin MR, Belin TR. Cognitive function after the initiation of adjuvant endocrine therapy in early-stage breast cancer: an observational cohort study. J Clin Oncol 2014;32: 3559–67.
42. Watson D, Clark LA. The PANAS-X: Manual for the Positive and Negative Affect Schedule–Expanded Form. Ames: The University of Iowa; 1999.
43. Hann DM, Jacobsen PB, Azzarello LM, Martin SC, Curran SL, Fields KK, Greenberg H, Lyman G. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. Qual Life Res 1998;7:301–10.
44. Diez-Ruiz A, Tilz GP, Zangerle R, Baier-Bitterlich G, Wachter H, Fuchs D. Soluble receptors for tumour necrosis factor in clinical laboratory diagnosis. Eur J Haematol 1995;54:1–8.
45. Ferrucci L, Ble A, Bandinelli S, Lauretani F, Suthers K, Guralnik JM. A flame burning within. Aging Clin Exp Res 2004;16:240–3.
46. O'Connor MF, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav Immun 2009;23:887–97.
47. Raudenbush SW, Bryk AS. Hierarchical Linear Models: Applications and Data Analysis Methods. Vol 1. Thousand Oaks, CA: Sage; 2002. Available at: https://books.google.com/books?hl=en&lr=&id=uyCV0CNGDLQC&oi=fnd&pg=PR17&dq=Hierarchical+linear+models:+Applications+and+data+analysis+methods+&ots=qA4LXp_8TG&sig=xXtePRdDEW4FZmbvnuGRuDpzU2I. Accessed November 16, 2015.
48. Constanzo ES, Lutgendorf SK, Kohut ML, Nisly N, Rozeboom K, Spooner S, Benda J, McElhaney JE. Mood and cytokine response to influenza virus in older adults. J Gerontol A Biol Sci Med Sci 2004;59:1328–33.
49. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 2007;21: 153–60.
50. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46–56.
51. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002;64:604–11.
52. Späth-Schwalbe E, Hansen K, Schmidt F, Schrezenmeier H, Marshall L, Burger K, Fehm HL, Born J. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. J Clin Endocrinol Metab 1998;83:1573–9.
53. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2005; 5:243–51.
54. Miller GE, Blackwell E. Turning up the heat inflammation as a mechanism linking chronic stress, depression, and heart disease. Curr Dir Psychol Sci 2006;15:269–72.
55. Hänsel A, Hong S, Cámara RJA, von Känel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci Biobehav Rev 2010;35:115–21.

56. Morgan N, Irwin MR, Chung M, Wang C. The effects of mind-body therapies on the immune system: meta-analysis. PLoS One 2014;9:e100903.
57. Rao RM, Nagendra HR, Raghuram N, Vinay C, Chandrashekara S, Gopinath KS, Srinath BS. Influence of yoga on mood states, distress, quality of life and immune outcomes in early stage breast cancer patients undergoing surgery. Int J Yoga 2008;1:11–20.
58. Oh B, Butow PN, Mullan BA, Clarke SJ, Beale PJ, Pavlakis N, Lee MS, Rosenthal DS, Larkey L, Vardy J. Effect of medical Qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial. Support Care Cancer 2012;20:1235–42.
59. Oh B, Butow P, Mullan B, Clarke S, Beale P, Pavlakis N, Kothe E, Lam L, Rosenthal D. Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized controlled trial. Ann Oncol 2010;21:608–14.
60. Bower JE, Crosswell AD, Stanton AL, Crespi CM, Winston D, Arevalo J, Ma J, Cole SW, Ganz PA. Mindfulness meditation for younger breast cancer survivors: a randomized controlled trial. Cancer 2015;121:1231–40.
61. Bower JE, Greendale G, Crosswell AD, Garet D, Sternlieb B, Ganz PA, Irwin MR, Olmstead R, Arevalo J, Cole SW. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial. Psychoneuroendocrinology 2014;43:20–9.
62. Bower JE, Irwin MR. Mind-body therapies and control of inflammatory biology: a descriptive review. Brain Behav Immun 2016;51:1–11.
63. Slavich GM, Way BM, Eisenberger NI, Taylor SE. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. Proc Natl Acad Sci 2010;107:14817–22.
64. Fuligni AJ, Telzer EH, Bower J, Cole SW, Kiang L, Irwin MR. A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. Psychosom Med 2009;71:329–33.
65. Shai I, Schulze MB, Manson JE, Rexrode KM, Stampfer MJ, Mantzoros C, Hu FB. A prospective study of soluble tumor necrosis factor-α receptor II (sTNF-RII) and risk of coronary heart disease among women with Type 2 diabetes. Diabetes Care 2005;28:1376–82.
66. Fredrickson BL, Grewen KM, Coffey KA, Algoe SB, Firestine AM, Arevalo JMG, Ma J, Cole SW. A functional genomic perspective on human well-being. Proc Natl Acad Sci 2013;110:13684–9.
67. Diener E, Chan MY. Happy people live longer: subjective well-being contributes to health and longevity. Appl Psychol Health Well Being 2011;3:1–43.
68. Lyubomirsky S, King L, Diener E. The benefits of frequent positive affect: does happiness lead to success? Psychol Bull 2005;131:803–55.
69. Veenhoven R. Healthy happiness: effects of happiness on physical health and the consequences for preventive health care. J Happiness Stud 2008;9:449–69.
70. Siahpush M, Spittal M, Singh GK. Happiness and life satisfaction prospectively predict self-rated health, physical health, and the presence of limiting, long-term health conditions. Am J Health Promot 2008;23:18–26.
71. Howell RT, Kern ML, Lyubomirsky S. Health benefits: meta-analytically determining the impact of well-being on objective health outcomes. Health Psychol Rev 2007;1:83–136.