



Positive affect and inflammation during radiation treatment for breast and prostate cancer [☆]

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ABSTRACT

There is growing evidence that positive affect may influence health and immune function, although few studies have examined links between positive affect and immune processes in clinical populations. The purpose of this study was to examine whether positive affect is associated with changes in proinflammatory cytokines in cancer patients undergoing radiation treatment. Subjects were 50 individuals with early-stage breast and prostate cancer who completed psychosocial questionnaires and provided blood samples at seven time points before, during, and after radiation treatment. Positive affect was assessed before treatment onset using the CES-D (Center for Epidemiological Studies Depression Scale). Blood samples were assayed for serum levels of proinflammatory cytokines IL-1 β and IL-6. Patients with higher levels of positive affect before treatment exhibited higher mean levels of IL-1 β and IL-6 during radiation treatment (all $ps < .05$). Results suggest that positive affect enhances the acute inflammatory response to radiation treatment, perhaps facilitating tissue repair processes.

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1. Introduction

There is compelling evidence that emotions may influence immune system function and thus susceptibility to and severity of immune-related diseases (Glaser and Kiecolt-Glaser, 2005). This body of research has traditionally focused on negative affective states—such as depression, anxiety, and anger (Kiecolt-Glaser et al., 2002; Raison et al., 2006). However, there is growing interest in how positive psychological factors—such as positive affect, optimism, and benefit finding—affect health (Pressman and Cohen, 2005; Bower et al., 2008b) and the immunological pathways through which they exert their effects (Marsland et al., 2007).

To date, positive affect is the most commonly studied positive psychological factor relating to health and immune outcomes. For example, research has shown that positive affect predicts lower risk of HIV-related mortality (Moskowitz, 2003), enhanced antibody response to Hepatitis B vaccination (Marsland et al., 2006), decreased susceptibility to experimentally-exposed rhinovirus/influenza A virus (Cohen et al., 2006), fewer objective and subjective signs of illness following viral exposure (Doyle et al., 2006),

and faster skin wound healing (Robles et al., 2009). In the context of viral challenge, higher levels of positive affect are associated with lower levels of nasal proinflammatory cytokines, which appear to mediate effects on illness symptoms (Doyle et al., 2006; Janicki-Deverts et al., 2007). Effects of positive affect on these outcomes appear to be independent of, and in some cases, stronger than effects of negative affect (Cohen et al., 2006; Janicki-Deverts et al., 2007; Prather et al., 2007; Robles et al., 2009).

Naturalistic studies have shown more equivocal associations between positive affect and inflammatory markers. One such study found no association between positive affect and the soluble IL-6 receptor (sIL-6r) in healthy older women, but did find a positive association between eudemonic well-being (i.e. purpose in life) and sIL-6r (Ryff et al., 2004). A large longitudinal study of 2873 healthy adults found that positive affect was associated with lower circulating levels of C-reactive protein (CRP) and IL-6 for women, but not for men (Steptoe et al., 2008). Another study also found a negative association between positive affect and stimulated production of IL-6 and IL-10, but not IL-1 β or TNF- α (Prather et al., 2007).

To date, studies of positive affect and inflammation have primarily focused on healthy populations. However, inflammatory processes may have particular relevance in the context of cancer, as inflammation is increasingly recognized as a contributor to cancer development and progression (Coussens and Werb, 2002;

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Shacter and Weitzman, 2002) and may also play a role in cancer-related symptoms such as fatigue (Bower, 2008). In women with advanced ovarian cancer, positive psychological factors such as social support have been linked to lower levels of circulating IL-6 and VEGF, a cytokine involved with tumor angiogenesis (Costanzo et al., 2004; Lutgendorf et al., 2002). In contrast, depression is associated with elevations in proinflammatory cytokines in cancer populations (Jehn et al., 2006; Lutgendorf et al., 2008; Musselman et al., 2001).

To our knowledge, positive affect has not been examined in relation to inflammatory cytokines in cancer patients. We choose to examine this relationship among breast and prostate cancer patients undergoing radiation therapy. Radiation is a mainstay of cancer treatment, and works by interfering with tumor growth and metastasis by damaging the DNA of malignant cancer cells. Radiation therapy activates proinflammatory cytokine production as part of a coordinated response designed to control damage and promote tissue repair (Petrini et al., 1992; Barcellos-Hoff, 1998; Stone et al., 2003; Okunieff et al., 2008). To the extent that proinflammatory cytokines facilitate tissue recovery, increases in cytokine concentrations during treatment should have beneficial effects for patients undergoing radiation therapy. Indeed, acute wound healing studies have found that higher levels of IL-1 β and IL-6 at the wound site are associated with faster wound healing (Kiecolt-Glaser et al., 2005). However, radiation-induced elevations in proinflammatory cytokines may also have detrimental effects. For example, elevations in circulating levels of IL-6 predicted the development of radiation pneumonitis in lung cancer patients and acute proctitis in prostate cancer patients (Arpin et al., 2005; Hartsell et al., 2007; Christiansen et al., 2007). Cytokine activation might be particularly problematic if it persists beyond treatment completion, suggesting more chronic inflammation.

The current study was designed to test the association between positive affect and inflammation among breast and prostate cancer patients undergoing radiation treatment. Primary analyses focused on two key proinflammatory cytokines—IL-1 β and IL-6—that are known to be elevated during radiation therapy and have previously been associated with positive affective processes (Ryff et al., 2004; Prather et al., 2007; Steptoe et al., 2008). To investigate the impact of positive affect on inflammation, we examined whether individuals who reported higher levels of positive affect prior to treatment onset showed a differential cytokine response to treatment. To clarify the clinical significance of this response, we examined treatment-related side effects and followed patients after treatment completion.

2. Methods

2.1. Participants

Participants were breast and prostate cancer patients scheduled to undergo external beam radiation treatment at UCLA. They were recruited from the UCLA Radiation Oncology Clinic between January 2001 and September 2003. Eligibility criteria for participation in this study were as follows: (1) age 25–75; (2) newly diagnosed with localized breast cancer (stage 0–II) or prostate cancer (T1–T3, N0 and M0); (3) external beam radiation therapy as part of the primary treatment plan; (4) completion of definitive primary surgery (for breast cancer patients); and (5) ability to read and write English. Exclusion criteria included: (1) recurrent cancer; (2) prior or planned treatment with chemotherapy; and (3) regular use of immunosuppressive medication or tobacco.

A total of 107 patients were screened for study eligibility. Forty-one patients were not eligible due to medical conditions (e.g., previous cancer treatment) or use of tobacco, and 15 were eligible but refused participation due to concerns about blood draws, time de-

mands, or general lack of interest. A total of 51 patients were enrolled in the study and completed the baseline questionnaire. One prostate cancer patient withdrew immediately after treatment onset due to concerns about blood draws and was not included in analyses. The final sample included 50 patients ($n = 28$ breast cancer patients, $n = 22$ prostate cancer patients). The UCLA Institutional Review Board approved the study procedures and written informed consent was obtained from all participants.

2.2. Procedures

Potential participants were screened for eligibility during consultations at the UCLA Radiation Oncology Clinic. After determination of eligibility, subjects completed a baseline assessment prior to starting treatment. Patients with localized breast and prostate cancer typically receive daily radiation therapy, Monday through Friday, for a 6–8 week course of treatment. Study assessments occurred prior to treatment (Baseline), after 5 days of treatment (Treatment week 1), after 10 days of treatment (Treatment week 2), after 20 days of treatment (Treatment week 4), during the final week of treatment (Treatment week 6/8), and at two regularly scheduled follow-up visits targeted at 2 weeks and 2 months after treatment completion. Assessments were scheduled to coincide with treatment appointments and thus did not occur at the same time of day for all participants. However, appointments for individual participants typically did occur at the same time of day (e.g., some participants were routinely seen at 9AM, while others were routinely seen at 10AM). The majority of appointments were conducted in the morning (before noon), and all were completed by 3PM. Subjects completed self-report questionnaires and provided blood samples for immune analysis at each assessment. As part of the questionnaire, subjects indicated if they had experienced an illness, infection, or injury in the past week. If so, blood samples were not collected at that assessment to avoid confounding effects on cytokine levels.

2.3. Measures

Demographic and health information was collected at baseline, and presence of acute illnesses or infections was determined at each assessment by self-report questionnaire. Cancer and treatment-related information (e.g., cancer stage) was determined from chart reviews.

2.3.1. Positive affect

Positive affect was assessed at each assessment using the CES-D (Center for Epidemiological Studies Depression Scale), a 20-item measure with excellent reliability and validity (Radloff, 1977). This questionnaire assesses affect and symptoms experienced during the past week, and responses are on a scale from 0 = “rarely or none of the time” to 3 = “most or all of the time.” Previous factor analyses have indicated a four-factor structure to the CES-D that includes subscales for positive affect, negative affect, somatic, and interpersonal symptoms (Sheehan et al., 1995; Knight et al., 1997; Moskowitz, 2003; Bower et al., 2005). The positive affect subscale includes four items: “I felt hopeful about the future,” “I felt I was just as good as other people,” “I was happy,” “I enjoyed life.”

Each patient's positive affect score was computed solely from their baseline (pre-treatment) time point in order to minimize any confounds with direction of causality during radiation treatment (i.e. whether positive affect influences inflammation or vice-versa). Baseline positive affect was significantly correlated with positive affect at all subsequent time points (r 's = .908–.961, all p 's < .01). The single measures interclass correlation coefficient also indicated high reliability of positive affect over time (ICC = .882, p < .001).

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