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Title

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Permalink

<https://escholarship.org/uc/item/2gk5d6j7>

Journal

CSW Update, Winter(2015)

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Publication Date

2015

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Health, Immunity, and the Pursuit of Happiness

The Relationship between Positive Emotions and Inflammation in Breast Cancer Survivors

A RECENT STUDY conducted by UCLA researchers examines the relationship of positive emotions and inflammation in women diagnosed with breast cancer, a disease that affects 1 in 8 women in the United States.

Although the field of psychology has traditionally focused on the study of negative psychological experiences (for example, depression, anxiety, and stress), more recent evidence supports the importance of positive emotions for both psychological and physical wellbeing. In cancer patients and survivors, the experience of positive emotions is associated with improved adjustment, including lower anxiety, depressive symptoms, pain, and fatigue as well as better quality of life (Baker, Denniston, Zabora, Poland, & Dudley, 2002; Guadagnoli

& Mor, 1989; Schroevers, Sanderman, Sonderer, & Ranchor, 2000). Not only are positive emotions important for psychological adjustment, they also predict important physical health outcomes. Positive emotions prospectively predict improved outcomes for a wide variety of diseases (Cohen & Pressman, 2006) as well as longer survival in both cohorts of initially healthy populations and patient populations (Chida & Steptoe, 2008). Moreover, limited preliminary evidence suggests that positive emotions may predict improved cancer survival (Levy, Lee, Bagley, & Lippman, 1988; Prinsloo et al., 2014).

Despite accumulating evidence supporting the association of positive emotions with improved psychological and physical health,

the mechanisms that underlie this relationship have not been determined. The overarching aim of our research was to better understand the relationship of positive emotions with intermediate biological processes that may underlie its association with improved health over time. More simply, we wanted to know: how do positive emotions “get under our skin” to influence health?

One plausible mechanism may be inflammation. The immune system is comprised of a variety of cells and organs that function to protect us from threats, including pathogens (for example, bacteria) and altered host cells (for example, cancer cells). One of the primary processes by which the immune system responds to threats is inflammation. Inflammation is the

process by which immune cells are brought to an affected area so that threats are prevented from spreading and subsequent tissue repair can take place. Macrophages, a class of immune cells, play a particularly important role in the inflammatory process by both destroying pathogens and releasing signaling proteins called cytokines that coordinate immune responses. Cytokines that promote inflammation are classified as proinflammatory and are often assessed as markers of inflammation. Well studied proinflammatory cytokines include interleukin 1 (IL-1), C-reactive protein (CRP), and tumor necrosis factor (TNF- α).

Although inflammation is an adaptive and necessary response of the immune system, chronic low-grade inflammation in the absence of an activating agent is maladaptive. This form of unremitting inflammation is associated with all-cause mortality (Harris et al., 1999) and a variety of diseases (Papanicolaou, Wilder, Manolagas, & Chrousos, 1998; Pradhan, Manson, Rifai, Buring, & Ridker, 2001), including the development and progression of tumors (Mantovani, Allavena, Sica, & Balkwill, 2008). Importantly, inflammation is regulated by other physiological systems, including the sympathetic nervous system and HPA axis, which are sensitive to psychological experiences—providing a plausible pathway by which psychological processes may influence inflammation.

Examining predictors of inflammation in breast cancer survivors

is of particular interest given that inflammation in the cancer context is associated with behavioral symptoms, including fatigue and depression (for example, Bower et al., 2011; Seruga, Zhang, Bernstein, & Tannock, 2008; Soygur et al., 2007), and also predicts cancer progression and mortality. Thus, we wanted to examine the association of positive emotions and markers of inflammation in women with early-stage breast cancer who were followed for a year after treatment with surgery, radiation, and/or chemotherapy.

Although some evidence suggests that positive emotions are associated with lower levels of inflammation (Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008; Steptoe & Wardle, 2005), results have been mixed (Constanzo et al., 2004; Lutgendorf et al., 2001; Ryff, Singer, & Dienberg Love, 2004; Sepah & Bower, 2009). Therefore, our research group decided to more closely examine a less-studied dimension of positive emotions: level of arousal (Russell, 1980). High arousal positive emotions are more activated and involve more energy, such as excitement and enthusiasm, while lower arousal positive emotions are less activated and involve less energy, such as contentment and serenity. Importantly, affective arousal has consequences for physiological arousal (Dockray & Steptoe, 2010; Pressman & Cohen, 2005) and the sympathetic nervous system is differentially sensitive to high versus low arousal positive emotions. Indeed, evidence suggests that

high arousal positive emotions are associated with greater activation than low arousal positive emotions (Pressman & Cohen, 2005). Given that the sympathetic nervous system regulates the immune system (Irwin & Cole, 2011), these differences in turn could have implications for inflammatory processes.

Method

Women who participated in our study came for an in-person appointment at UCLA at three time points: within three months of completing their primary breast cancer treatment (that is, surgery, radiation therapy, and/or chemotherapy) for a baseline assessment and 6 and 12 months after baseline for follow-up assessments. Our sample of 181 women completed psychosocial questionnaires at baseline and provided blood samples at each time point to be analyzed for markers of inflammation. The experience of high arousal positive emotions during the past month was assessed using the positive affect subscale of the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988) and the experience of low arousal positive emotions during the past week with the PANAS-X, an expansion of the original PANAS questionnaire (Watson & Clark, 1999). Given previous research establishing the relationship of both negative emotions and fatigue with inflammation, validated measures of negative emotions (PANAS; Watson et al., 1988) and fatigue (Fatigue Symptom Inventory; Hann et al.,

1998) were also included in order to determine whether any associations between positive emotions and inflammatory markers were independent (that is, not simply driven by a lack of negative emotions or fatigue). Inflammation was assessed by downstream markers of proinflammatory cytokine activity, including the interleukin-1 receptor antagonist (IL-1ra), a marker of IL-1 β activity; the soluble tumor necrosis factor (TNF) receptor type II (sTNF-RII), a marker of TNF- α activity; and C-reactive protein (CRP), a correlate of IL-6 activity.

Results

We found that higher levels of high arousal positive emotions predicted lower levels of the soluble tumor necrosis factor receptor type II (sTNF-RII), one month after primary treatment completion and at 6 and 12-month follow-ups. Importantly, effects of high arousal positive emotions were observed in analyses controlling for negative emotions, indicating that the effects of high arousal positive emotions are independent of negative emotions and are not merely driven by the absence of negative emotions. However, the relationship of high arousal positive emotions with sTNF-RII did not hold over and above fatigue. Thus, women's endorsement of high arousal positive emotions (for example, "active," "alert," "excited") may highly overlap with energy and vigor, the absence of which is associated with elevated inflammatory activity in breast cancer survivors (Bower et al., 2011; Bower, Ganz, Aziz, & Fahey,

2002). Furthermore, we found that higher levels of low arousal positive emotions predicted lower levels of the C-reactive protein (CRP) one month after primary treatment completion and at 6 and 12-month follow-ups. The relationship of low arousal positive affect and CRP remained significant in analyses controlling for negative emotions and fatigue, indicating that low arousal positive emotions may have distinct associations with CRP.

Although positive emotions have been postulated to exert influences on health and physiology (Pressman & Cohen, 2005), our finding that fatigue accounted for the association of high arousal positive emotions with sTNF-RII in this sample of early-stage breast cancer survivors may suggest an important qualification. It is well documented that proinflammatory cytokines act on the brain and can induce a specific constellation of behavioral symptoms termed sickness behavior (Dantzer & Kelley, 2007; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008), including fatigue. Thus, it is possible that the inverse association of high arousal positive emotions with sTNF-RII in this and other studies may reflect higher levels of inflammation acting on the brain—leading to both greater fatigue and lower high arousal positive emotions. Indeed, the induction of inflammatory cytokines leads to reductions in high arousal positive emotions (Späth-Schwalbe et al., 1998).

On the other hand, given the association of lower arousal

positive emotions with dampened sympathetic activation as well as the influence of sympathetic activation on inflammation (Irwin & Cole, 2011), our finding that low arousal positive emotions were uniquely associated with lower levels of CRP independent of fatigue is noteworthy. It is plausible that lower arousal positive emotions exert an influence on CRP by reducing engagement of stress-response systems, like the sympathetic nervous system, given strong evidence that stress is associated with increased levels of CRP (Glaser & Kiecolt-Glaser, 2005; Hänsel, Hong, Cámara, & von Känel, 2010; Miller & Blackwell, 2006). In light of the current findings as well as mixed results produced by previous studies examining positive emotions and inflammatory markers, we strongly encourage researchers in the future to consider possible bidirectional associations between positive emotions and inflammation.

Conclusions

Our results indicate that the relationship of high arousal positive emotions (for example, "active," "alert") with sTNF-RII may be driven by the overlap of high arousal positive emotions with fatigue while the association of low arousal positive emotions and CRP may be unique. Future research should consider affective arousal when examining the association of positive emotions with inflammation as this facet of positive emotions may have important implications for interpretation of results. Specifically,

bidirectional associations between both high and low arousal positive emotions and inflammation should be considered and is an important topic for future research.

Author's note: This article was based on research conducted by Patricia Moreno, Andrew Moskowitz, Patricia Ganz, and Julienne Bower that is currently under review for publication. This research was supported by the National Cancer Institute (R01 CA 109650) and the Breast Cancer Research Foundation. Patricia also received a CSW Travel Grant to support this research.

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