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Inflammatory biomarkers and emotional approach coping in men with prostate cancer

Michael A. Hoyt [a,*], Annette L. Stanton [b,c,d], Julienne E. Bower [b,c,d], KaMala S. Thomas [e], Mark S. Litwin [d,f,g], Elizabeth C. Breen [c], Michael R. Irwin [b,c,d]

[a] Department of Psychology, Hunter College, City University of New York, United States
[b] Department of Psychology, University of California, Los Angeles, United States
[c] Cousins Center for Psychoneuroimmunology, Semel Institute, University of California, Los Angeles, United States
[d] Jonsson Comprehensive Cancer Center, University of California, Los Angeles, United States
[e] Department of Psychology, Pitzer College, Claremont University Consortium, United States
[f] Department of Urology, David Geffen School of Medicine, University of California, Los Angeles, United States
[g] Department of Health Policy & Management, Fielding School of Public Health, University of California, Los Angeles, United States

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ABSTRACT

Objective: Emotion-regulating coping is associated with improvements in psychological and physical health outcomes. Yet in the context of prostate cancer-related stressors, limited research has characterized associations of emotion-regulating coping processes (emotional expression, emotional processing) and inflammatory processes that are related to disease risk. This investigation examined the relation of Emotional Approach Coping (EAC) with markers of inflammation to test the hypothesis that higher EAC scores at study entry (T1) would be associated with lower proinflammatory markers four months later (T2), specifically sTNF-RII, CRP, and IL-6.

Methods: Forty-one men (M age = 66.62 years; SD = 9.62) who had undergone radical prostatectomy or radiation therapy for localized prostate cancer within two years completed questionnaires, including assessments of EAC, at T1, and provided blood samples for immune assessments at T2.

Results: When controlling for relevant biobehavioral controls, emotional processing predicted lower IL-6 ($B = -.66$, $p < .01$), sTNF-RII ($B = -.43$, $p < .05$), and CRP ($B = -.43$, $p < .10$), whereas emotional expression was significantly associated with higher levels of sTNF-RII ($B = .55$, $p < .05$). Associations of emotional expression and IL-6 ($B = .38$, $p < .10$), and CRP ($B = .44$, $p < .10$) approached significance. Probing interactions of emotional processing and expression (though only approaching significance) suggested that expression of emotion is associated with higher inflammation (CRP and sTNF-RII) only in the context of low emotional processing.

Conclusions: Attempts at emotion regulation via emotional processing appear to modulate inflammatory processes. Understanding, making meaning of, and working through emotional experience may be a promising target of intervention to reduce inflammation with potential effects on psychological and cancer outcomes in men with prostate cancer.

1. Introduction

The experience of cancer diagnosis and treatment exposes individuals to numerous physical and emotional stressors and accounts for increased risk of emotional distress and depression. The first one to two years following radical prostatectomy or completion of radiation treatment for prostate cancer are markedly demanding and characterized by relatively rapid changes in physical functioning (Litwin et al., 2001; Stanford et al., 2000), increased risk for depression (Jayadevappa et al., 2011), sleep disturbance (Savard et al., 2005), worry and anxiety (Sharpley et al., 2008), and declining health-related quality of life (Gore et al., 2009). Emotional perturbations and chronic negative affective states associated with stressors can invoke potent negative effects on inflammatory and other cellular immune processes (Irwin, 2002; Kemeny, 2007; Reiche et al., 2004; Segerstrom and Miller, 2004; Steptoe et al., 2007), which can compound the burden associated with cancer and have a direct and indirect impact on mental and physical health outcomes (Grivennikov et al., 2010; Mantovani et al., 2008; see also Irwin and Cole, 2011 on behavior and inflammation). Coping through avoidance has typically been associated

* Corresponding author. Address: Hunter College, City University of New York, Department of Psychology, 695 Park Avenue, Room HN-611, New York, NY 10065, United States. Tel.: +1 212 396 6690; fax: +1 212 772 5620.
E-mail address: michael.hoyt@hunter.cuny.edu (M.A. Hoyt).

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with suppression of cellular immune function, as seen in individuals with HIV and cancer (Fawzy et al., 1990; Futterman et al., 1996; Goodkin et al., 1992a,b); however, effects of approach coping on immune parameters have rarely been assessed (see Goodkin et al., 1992a). Use of coping strategies that lead one to focus on and regulate difficult emotions (e.g., emotional approach coping) related to one's cancer experience has potential for modifying the affective response, reducing inflammation (Master et al., 2009), and improving psychological (Hoyt, 2009) and physical (Hoyt et al., 2013) health outcomes in men with cancer.

Emotional approach coping (EAC) (Stanton et al., 1994) is comprised of two distinct but related emotion-regulating strategies: emotional processing and emotional expression. In the case of prostate cancer, emotional processing includes purposive attempts to acknowledge, explore, and understand one's emotions related to prostate cancer; emotional expression represents active verbal and non-verbal efforts to communicate or symbolize cancer-related emotional experiences (Stanton et al., 2000b). Research with breast cancer survivors has characterized a benefit of EAC on physical health and psychological adjustment, including increased vigor, fewer medical visits for cancer-related morbidities, and improved self-reported health (Stanton et al., 2000a, 2002). However, research in men with mixed cancer types (Hoyt, 2009) found that greater use of emotional expression in response to cancer-related stressors was associated with lower levels of psychological distress, whereas emotional processing demonstrated a positive relationship with distress. In an expanded cohort of the current study, Hoyt et al. (2013) found an opposite pattern, with emotional processing associated with improved prostate-specific functioning, but no relationship with emotional expression. Such disparate associations might be better understood by distinguishing the interactions of expressing and processing cancer-related emotions. Expressing emotions without attempts to understand or make meaning from emotional experience might exacerbate affective dysregulation and promote rumination, persistent worry, or other maladaptive repetitive thought patterns.

Little work has attempted to identify biological mechanisms by which EAC operates, including markers of inflammation. In fact, only one study (Master et al., 2009) has examined inflammatory markers in association with dispositional use of EAC. In a sample of young adults undergoing an acute laboratory stressor, higher levels of EAC, particularly emotional processing, were associated with a less pronounced increase in soluble tumor necrosis factor-receptor type-II (sTNF-RII) in oral mucosal transudate (and interleukin-6, though non-significant after controlling for behavioral factors). Those who are less likely to focus on emotions as a means of coping may be at heightened risk for chronic elevations in inflammation and health-related consequences.

To examine whether coping with cancer-related stressors via emotion-regulatory coping processes was associated with markers of inflammation, this study tested the hypothesis that EAC processes would correlate with circulating levels of proinflammatory cytokines within a clinically relevant period following prostate cancer treatment. Prior work supports a benefit to psychological and physical outcomes of emotional expression (Hoyt, 2009) and emotional processing (Hoyt et al., 2013) in men with cancer. Thus, we hypothesized that EAC processes would predict lower inflammation levels during this time period. The interaction of EAC processes (emotional processing $\times$ emotional expression) was also examined. We expected that emotional expression in the presence of emotional processing would exhibit a more pronounced effect on biomarkers.

There is growing evidence that activation of the proinflammatory cytokine network underlies negative psychological states in cancer patients (Irwin and Miller, 2007; Lee et al., 2004; Miller et al., 2008; Musselman et al., 2001). We focus on three inflammatory markers, interleukin-6 (IL-6), C-reactive protein (CRP), and sTNF-RII, which can be reliably assessed in plasma and have been linked to behavioral and cancer-related outcomes in previous research with cancer survivors (Bower et al., 2011, 2009; Collado-Hidalgo et al., 2002; Orre et al., 2009). Evidence from non-cancer populations implicates these markers in emotional disturbance and depression (Dowlati et al., 2010; Howren et al., 2009; O'Brien et al., 2007), and elevations in IL-6 (Jehn et al., 2006; Musselman et al., 2001; Seruga et al., 2009) and TNF-a (Seruga et al., 2009) have been linked to depression in cancer patients. Notably, sTNF-RII reflects TNF-a activity (Spinas et al., 1992) and tends to be more reliably measured than TNF-a (Diez-Ruis et al., 1995). Experimentally induced immune activation with the release of sTNF-RII leads to increased emotional disturbance (Reichenberg et al., 2001) and in cancer samples has been connected to behavioral symptoms including fatigue (Bower et al., 2011). Because IL-6 induces CRP, this biomarker can provide a measure of the cumulative activity of IL-6 and systemic inflammation.

2. Method

2.1. Participants

Men who completed radical prostatectomy or radiation therapy for localized prostate cancer within the prior two years were recruited to take part in a larger study on "health-related quality of life after prostate cancer." Forty-one participants were recruited via physician/clinic referrals ($n = 2$), community outreach and advertisement ($n = 15$), and from an institutional tumor registry database ($n = 24$). Participants were screened to exclude individuals not meeting entrance criteria (e.g., localized disease, time since treatment, English speaking) and those with any cognitive debilitating co-morbidity (e.g., dementia). Participants were also excluded for presence of medical conditions or medications that would likely confound immune evaluation (e.g., autoimmune disorder, inflammatory disease, uncontrolled thyroid disease, active infection, recent myocardial infarction); regular smoker (daily use); or heavy alcohol use (more than 14 drinks per week). Participants were re-screened at each study visit for acute infection, recent vigorous exercise, recent caffeine or cigarette use, and changes in medications, and rescheduled as appropriate.

Participants were English-speaking men who ranged in age from 51 to 87 years ($M = 66.62$, $SD = 9.62$) and on average, completed treatment 15.63 months prior ($SD = 7.53$; range = 2 to 24 months) to study completion. Clinical and socio-demographic variables are reported in Table 1. No men were on active hormonal therapy at the time of participation. Notably, an additional three men completed the initial assessment but not the T2 session (not reported on here). These men did not differ significantly from those who completed the T2 assessment on sociodemographic or cancer-related variables.

2.2. Procedures

After providing written informed consent, participants attended an individual session (T1) to complete questionnaire and interview assessments and returned for a follow-up session 4 months later (T2) where they provided blood samples. Their height and weight as well as other relevant biobehavioral variables were recorded at each session. All assessments were conducted in the morning (before 11 am). Participants received $25 after each session. The institutional review board at the University of California, Los Angeles approved study procedures.