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Long lasting effects of smoking: Breast cancer survivors' inflammatory responses to acute stress differ by smoking history☆

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Summary Cigarette smoking continues to be the most preventable cause of illness and death and has been linked to the development and prognosis of cancer. Current smokers have higher levels of inflammation than nonsmokers, and inflammation can remain elevated in former smokers even years following cessation. Inflammation can also be enhanced by stress. This study examined cortisol and inflammatory responses to a laboratory stressor in breast cancer survivors who formerly smoked compared to their counterparts who had never smoked. Participants included 89 women (age = 51.6 ± 8.9 years) who had completed treatment for stage 0—IIIA breast cancer within the past three years and were at least two months post surgery, radiation or chemotherapy, whichever occurred last. Cortisol and interleukin-6 (IL-6) were evaluated in response to a standardized laboratory speech and mental arithmetic stressor. Former (n = 25) and never (n = 64) smokers did not differ by cancer stage, cancer treatment, comorbidities, time since cancer treatment, depression, or stress. Despite having similar cortisol responses to the stressor, former smokers had exaggerated IL-6 responses two hours post-stressor compared to never smokers. This effect persisted after controlling for age, BMI, time since treatment, education, and antidepressant

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use. An exaggerated and prolonged inflammatory response to stress could be one mechanism underlying the persistent inflammation observed in former smokers.

1. Introduction

Cigarette smoking continues to be the most preventable cause of illness and death and has been linked to the development and prognosis of cancer. Between 1997 and 2001, more than 450,000 deaths resulted from cigarette smoking each year (Center for Disease Control and Prevention, 2005). On average, adults who smoke cigarettes die 14 years earlier than nonsmokers (Doll et al., 2004). Dysregulated immune function, including chronic inflammation, may underlie the increased risk of developing smoking-related chronic diseases such as cancer and premature death (Cross et al., 1999).

Cigarette smoking boosts systemic inflammation (Das, 1985). For example, current smokers have higher basal levels of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α) compared to individuals who have never smoked (Bermudez et al., 2002; Bo et al., 2005; Haddy et al., 2005; Wannamethee et al., 2005; Nazmi et al., 2008). Furthermore, CRP and IL-6 levels increase with greater smoking exposure as indexed by number of cigarettes smoked per day or pack years (Mendall et al., 2000; Bazzano et al., 2003; Helmersson et al., 2005; Wannamethee et al., 2007).

Some data suggest that inflammation may remain elevated even years after smoking cessation. For example, compared to never smokers, CRP levels were higher in former smokers 10—20 years following smoking cessation (Frohlich et al., 2003; Wannamethee et al., 2005). Similarly, past smokers had elevated IL-6 levels compared to nonsmokers (Wannamethee et al., 2007). Reasons behind persistent inflammation remains unclear; it has been suggested that systemic hypoxia and tissue damage may continue driving elevated inflammation as the body recovers from chronic exposure to over 7000 inhaled chemicals (Agusti et al., 2003; United States Department of Health and Human Services, 2010).

This study addressed an additional possibility, the hypothesis that inflammatory responses to acute stress may be enhanced among former smokers. Cortisol, a primary stress hormone, inhibits immune cell activity by binding to glucocorticoid receptors and reducing cytokine production (Brattsand and Linden, 1996; Barnes, 1998). However, chronically elevated cortisol can lead to glucocorticoid resistance, such that immune cells down-regulate the expression of glucocorticoid receptors (Webster and Cidlowski, 1994; Webster et al., 2002). In turn, this down-regulation leads to increased inflammation because cortisol cannot effectively dampen excessive cytokine production (Miller et al., 2002).

Cigarette smoking has been linked to the alterations in hypothalamic-pituitary-adrenal (HPA) activity. Nicotine, the addictive component in tobacco, can stimulate the HPA axis and result in greater cortisol release (Balfour, 1989; Mendelson et al., 2005). Among smokers, both basal cortisol levels and the cortisol awakening response were greater than nonsmokers' cortisol levels (Rohleder and Kirschbaum, 2006; Steptoe and Ussher, 2006). Smokers exhibited a blunted cortisol response to a laboratory stressor compared to nonsmokers (Kirschbaum et al.,1993b, 1994; al'Absi et al., 2003; Childs and de Wit, 2009). Furthermore, smokers can develop glucocorticoid resistance (Pedersen et al., 1996; Barnes and Adcock, 2009).

However, despite the evidence of HPA dysregulation in current smokers, it is unclear whether these alterations continue after smoking cessation. The current study investigates this possibility by comparing responses of former and never smokers to a laboratory stressor. To our knowledge, this investigation is the first study to compare HPA responses to an acute stressor in former and never smokers.

A breast cancer diagnosis and its treatment are typically stressful, and many breast cancer survivors continue to report significant distress following treatment (Härtl et al., 2003; McGregor and Antoni, 2009). Prior stress exposure and/or depression may enhance stress-induced inflammatory responses (Glaser et al., 2003; Pace et al., 2006). Thus, using a sample of breast cancer survivors to examine acute stress responses may offer an opportunity to investigate how past smoking may affect physiology. Accordingly, we investigated cortisol and IL-6 responses to an acute laboratory stressor in former and never smokers. We hypothesized that former smokers would have a reduced or blunted cortisol response to the acute stressor compared to never smokers. In addition, we expected that the IL-6 response would be larger in former smokers than never smokers.

2. Methods

2.1. Participants

The study data were drawn from the baseline sample (prior to randomization) of a clinical trial assessing the impact of yoga on fatigue and inflammation in breast cancer survivors. We used all available participants who had provided baseline data, except for 9 current smokers because the group was too small to make meaningful conclusions, 2 participants who did not have baseline IL-6 levels, and 5 participants were removed due to lack of both IL-6 assessments post-stressor. In addition, one never smoker had IL-6 levels 3 standard deviations above the mean at all three time points; therefore, this participant's data were dropped from all analyses.

Women were recruited through breast cancer clinics, community fliers, and media announcements. Eligible women completed treatment for stage 0—IIIA breast cancer within the past three years (except for selective estrogen receptor modulators or aromatase inhibitors) and were at least two months post surgery, radiation, or chemotherapy, whichever occurred last. Screening exclusions included a prior history of breast or any other cancer except basal or squamous cell, more than five hours a week of vigorous physical exercise, current yoga practice, diabetes, uncontrolled hypertension, evidence of liver or kidney failure, and symptomatic ischemic heart disease. The Ohio State Biomedical Cancer Research Review Committee approved the project; all subjects gave written informed consent prior to participation.