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Childhood Adversity and Cumulative Life Stress: Risk Factors for Cancer-Related Fatigue

Julienne E. Bower[1,2], Alexandra D. Crosswell[1], and George M. Slavich[2]

[1]Department of Psychology and [2]Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles

Abstract

Fatigue is a common symptom in healthy and clinical populations, including cancer survivors. However, risk factors for cancer-related fatigue have not been identified. On the basis of research linking stress with other fatigue-related disorders, we tested the hypothesis that stress exposure during childhood and throughout the life span would be associated with fatigue in breast cancer survivors. Stress exposure was assessed using the Stress and Adversity Inventory, a novel computer-based instrument that assesses for 96 types of acute and chronic stressors that may affect health. Results showed that breast cancer survivors with persistent fatigue reported significantly higher levels of cumulative lifetime stress exposure, including more stressful experiences in childhood and in adulthood, compared to a control group of nonfatigued survivors. These findings identify a novel risk factor for fatigue in the growing population of cancer survivors and suggest targets for treatment.

Keywords

child trauma, health, stressful life events, fatigue, breast cancer

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Fatigue is common in healthy individuals and among individuals with clinical disorders, including major depression, chronic fatigue syndrome (CFS), and autoimmune disease (Pawlikowska et al., 1994; Ramsey-Goldman & Rothrock, 2010). Fatigue also is an important side effect of cancer treatment (Bower et al., 2000). Cancer-related fatigue has been described as a subjective state of overwhelming and sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest (Cella, Peterman, Passik, Jacobsen, & Breitbart, 1998). Fatigue afflicts almost all individuals who undergo standard cancer therapies and may persist for years after successful treatment, degrading quality of life and possibly presaging shorter survival (Bower et al., 2000; Cella, Davis, Breitbart, & Curt, 2001; Groenvold et al., 2007). Despite the prevalence and impact of this symptom, risk factors for cancer-related fatigue remain unknown. Disease and treatment-related factors are not strong predictors of fatigue in cancer survivors, and examination of psychological factors may be a more promising approach.

Stress is thought to play an important role in many disorders characterized by fatigue, although evidence for this link varies by condition and by how stress is conceptualized and assessed. Research on stress and fatigue-related disorders typically has conceptualized stress as an acute trigger for the onset of disease and associated symptoms. For example, major life events are known to be strongly associated with the onset and severity of depression (Harkness et al., 2010; Kendler, Karkowski, & Prescott, 1999; Kessler, 1997), including somatic symptoms of depression, such as fatigue (Muscatell, Slavich, Monroe, & Gotlib, 2009). Acute stress also is related to

Corresponding Author:
Julienne E. Bower, Department of Psychology, University of California, Los Angeles, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095
E-mail: jbower@ucla.edu

the onset of CFS, although research on this topic is more limited (Hatcher & House, 2003; Theorell, Blomkvist, Lindh, & Evengard, 1999). At the symptom level, daily diary studies have shown that daily stressors are associated with elevated fatigue (Parrish, Zautra, & Davis, 2008).

Investigators recently have adopted a life-course perspective to studying links between stress and disease. This perspective emphasizes the importance of sensitive periods during the life span and the impact of repeated or cumulative stress exposure on health. One critical stress-sensitive period is childhood (Lupien, McEwen, Gunnar, & Heim, 2009). Compelling evidence has shown that stress occurring in childhood is a major risk factor for mental and physical health problems later in life (e.g., Felitti et al., 1998), including fatigue-related disorders, such as depression, CFS, and autoimmune disease (Chapman et al., 2004; Dube et al., 2009; Heim et al., 2006). In population-based studies, childhood stress has been associated with symptoms of fatigue among otherwise healthy adults (Cho, Bower, Kiefe, Seeman, & Irwin, 2012). Together, these studies have suggested that childhood stress may be a common risk factor for fatigue across different conditions.

Another life-course perspective focuses on cumulative stress exposure as a predictor of poor health. Indeed, cumulative exposure to adversity has been associated with psychiatric disorders in young adults (e.g., Turner & Lloyd, 1995). However, few investigators have attempted to quantify stress exposure throughout the course of the life span to evaluate links with behavioral disturbances in later adulthood, including fatigue. In fact, in only one study have researchers examined the association between lifetime stress exposure and CFS (Nater, Maloney, Heim, & Reeves, 2011). In that study, patients with CFS reported higher levels of traumatic events throughout the course of the life span and severe (but not traumatic) events during the past year relative to nonfatigued individuals. However, the association between cumulative stress and fatigue in other contexts, including cancer, has not been examined.

One challenge to understanding links between cumulative stress exposure and fatigue involves the assessment of cumulative life stress. Although several interview-based systems have been developed for measuring stress exposure (e.g., Adrian & Hammen, 1993; Brown & Harris, 1978; Dohrenwend, Raphael, Schwartz, Stueve, & Skodol, 2013; Kendler, Karkowski, & Prescott, 1998), these systems generally assess for many different stressors occurring during a relatively short period (e.g., 1–2 years). Once a stressor is endorsed, interviewers conduct a thorough probe to collect detailed information about the contextual features of the stressor, as well as its precise timing, duration, and severity. These systems thus are ideal for measuring stress exposure in high resolution during a short period of time, but given the depth of assessment involved, they do not adapt well to measuring longer stress-assessment windows.

In this study, we applied a life-course perspective to the study of stress and fatigue in cancer survivors through the use of an innovative computer-based system for assessing cumulative life stress. The Stress and Adversity Inventory (STRAIN) is based on gold-standard methods for assessing stress and measures a person's lifetime exposure to 96 types of acute and chronic stressors that may affect health (Slavich & Epel, 2010). The stressors cover all major life domains (e.g., health, relationships, education, work, and finances) and focus on experiences that have a moderate base rate in child and adult populations. The use of the STRAIN facilitated the second novel feature of this study, which was the detailed examination of stress both in childhood and throughout the life span. In previous studies, researchers typically have looked at either childhood or adulthood life stress. However, each of these approaches provides an incomplete picture of a person's total stress exposure. For example, early life stress may become embedded in the body through its effects on developing neural, endocrine, and immune systems, resulting in poor health later in life independent of adult stress exposure (Miller, Chen, & Parker, 2011). Alternatively, childhood stress may be mediated by continued stress exposure throughout the course of the life span, and it may be the cumulative toll of these stressors that increases risk for disease (e.g., Turner & Lloyd, 1995).

The third novel aspect of this study was the examination of stress and fatigue in the context of cancer. Despite links between stress and fatigue in other contexts, surprisingly few researchers have examined the association between stress and cancer-related fatigue. In two previous studies, childhood abuse/neglect was associated with elevated fatigue in women with breast cancer (Fagundes, Lindgren, Shapiro, & Kiecolt-Glaser, 2012; Witek-Janusek, Tell, Albuquerque, & Mathews, 2013). However, there has been no examination of the full range of childhood experiences that may be associated with fatigue, nor have researchers examined cumulative or adulthood life stress exposure as predictors of cancer-related fatigue.

To advance our understanding of links between childhood stress exposure, cumulative stress exposure, and fatigue in the context of cancer, we administered the STRAIN to breast cancer survivors with persistent fatigue and to a control group of nonfatigued survivors. On the basis of research that has shown links between early life stress and fatigue in CFS and other populations (Cho et al., 2012; Heim et al., 2006), we hypothesized that fatigued breast cancer survivors would report higher levels of childhood stress than would nonfatigued breast cancer survivors. Next, drawing from research on

cumulative stress exposure and fatigue (Nater et al., 2011), we hypothesized that fatigued survivors would report elevated levels of lifetime stress exposure. In addition, we examined associations among childhood stress, adulthood stress, and fatigue to determine whether continued stress exposure might explain any link between childhood stress and fatigue status.

Method

Participants

Breast cancer survivors with cancer-related fatigue and nonfatigued control participants were identified from previous studies (Bower, Ganz, Irwin, Arevalo, et al., 2011; Bower, Ganz, Irwin, Kwan, et al., 2011; Bower, Garet, et al., 2011). To be eligible for the present study, participants had to meet the following criteria: (a) diagnosed with early stage breast cancer within 5 years of initial study participation; (b) completed all cancer treatments, with the exception of hormonal therapy, at the time of initial study participation; and (c) currently disease free.

Fatigue status was determined at the time of initial study participation using scores on the Short Form (SF)-36 vitality scale, a reliable and valid measure of energy/fatigue in the general population (Ware & Sherbourne, 1992). This scale consists of four items assessing how much of the time the individual "felt full of pep," "had a lot of energy," "felt worn out," and "felt tired" during the past 4 weeks. Scores range from 0 to 100, with higher scores indicating more energy/less fatigue. This scale is bipolar in nature, with scores above the midpoint of 50 representing relative well-being and scores below 50 representing limitations or disability related to fatigue (Ware & Sherbourne, 1992). Consistent with our prior research (e.g., Bower, Ganz, Irwin, Arevalo, et al., 2011), our procedure used a classification system in which women who scored at or below 50 at the time of initial study participation were classified as fatigued and women who scored at or above 70 were classified as nonfatigued. In addition, women in the control group were excluded if they scored above 16 on the Center for Epidemiologic Studies Depression Scale to minimize confounding effects of depression.

Procedure

Recruitment letters were sent to 89 potential participants; 64 women responded, 52 were eligible and interested, and 50 provided STRAIN interview data for analysis (33 fatigued, 17 nonfatigued). All study procedures were approved by the institutional review board of the University of California, Los Angeles.

Measures

STRAIN. The STRAIN is an online stress-assessment system that measures individuals' lifetime exposure to 96 types of acute and chronic stressors that may have implications for health (Slavich & Epel, 2010). The STRAIN is based on state-of-the-art, interview-based methods for assessing life stress, including the Life Events and Difficulties Schedule (Brown & Harris, 1978), and assesses all major life domains that are covered by these systems, including housing, education, work, treatment/health, marital/partner, reproduction, financial, legal/crime, other relationships (e.g., confidants and other friendships), accidents, deaths, and possessions. For each stressor that is endorsed, participants are asked a series of tailored follow-up questions that determine the stressor's severity, frequency, timing, and duration.

Stressors were originally identified for possible inclusion in the STRAIN on the basis of four strategies: (a) an exhaustive literature search for major life stressors that have been linked with health; (b) individual and group consultation sessions with external experts who specialize in the conceptualization and assessment of life stress; (c) consensus judgments from a team of life stress rating experts trained in a gold-standard, interview-based system for assessing life stress (i.e., the Life Events and Difficulties Schedule; Brown & Harris, 1978); and (d) a comprehensive review of all existing state-of-the-art, interview-based measures of life stress (e.g., Adrian & Hammen, 1993; Brown & Harris, 1978; Dohrenwend et al., 2013; Kendler et al., 1998). All questions underwent extensive review and revision to translate them into the language format of the STRAIN. In the end, this iterative process yielded 96 core questions. The validity of this question set has been demonstrated in the context of predicting metabolic health (Kurtzman et al., 2012) and mental and physical health (Slavich & Epel, 2013). In addition, a large literature exists that has shown the reliability and validity of the core questions and interviewing procedures on which the STRAIN is based (for reviews, see Dohrenwend, 2006; Hammen, 2005; Monroe, 2008; Monroe, Slavich, & Georgiades, 2009).

In the present study, the STRAIN was administered by an advanced graduate student interviewer who was trained in the STRAIN by G. M. Slavich. Participants were asked to think about all of the stressors that occurred prior to their cancer diagnosis and treatment to determine how lifetime stress exposure before cancer affected their postcancer fatigue. The average administration time was 42 min.

Childhood Trauma Questionnaire. We supplemented our assessment of childhood stress with questions from

the Emotional Neglect subscale of the Childhood Trauma Questionnaire, a commonly used self-report inventory with strong psychometric properties (Fink, Bernstein, Handelsman, Foote, & Lovejoy, 1995).

Demographic characteristics. Information on race/ethnicity, marital status, education, and income was obtained from self-report questionnaires completed at initial study participation.

Statistical analyses

In our preliminary analyses, we used *t* tests and chi-square analyses to compare fatigued and nonfatigued survivors on demographic characteristics. Next, we tested for possible differences in stress exposure using the following stress summary scores: (a) an index of exposure to childhood adversity that included physical abuse, emotional abuse, sexual abuse by someone in the family or close social network, parental divorce or separation, separation from parents, harsh discipline from parents, ongoing physical fights or violence between parents, serious relationship problems between parents, and no stable place to live, all occurring before age 18; (b) an index of exposure to adulthood stress, based on the number and the cumulative severity of life events and chronic difficulties experienced in all life domains after age 18; (c) an index of total lifetime stress exposure, based on the number and the cumulative severity of life events and difficulties experienced in all life domains at any age. In the primary analyses, we used analyses of covariance to compare fatigued and nonfatigued survivors on these indices, controlling for relevant confounds.

Results

Preliminary analyses

Participants were primarily White, college graduates with an average age of 57.8 years (see Table 1 for participants' demographic statistics). Fatigued survivors were less likely to be married than nonfatigued survivors (45% vs. 88%; $p = .003$) and were approximately 1 year further postdiagnosis (6.7 vs. 5.7 years), although this difference was not significant ($p = .26$). The difference in time since diagnosis is attributable to the different studies from which participants were drawn (i.e., in our earlier studies, we deliberately enrolled a higher percentage of fatigued survivors and, thus, yielded more fatigued participants for the current study). Given these differences, we controlled for marital status and time since diagnosis in analyses.

Differences in stress exposure for fatigued and nonfatigued women

We first tested the hypothesis that fatigued survivors would have higher levels of childhood stress exposure than nonfatigued control participants would. As predicted, fatigued survivors reported significantly more childhood stressors, $F(1, 46) = 5.3$, $p = .025$, $\eta_p^2 = .10$, and significantly higher levels of childhood emotional neglect, $F(1, 46) = 14.9$, $p < .001$, $\eta_p^2 = .25$, than nonfatigued survivors (see Table 2 for differences in stress exposure). To further probe the association between childhood stress and fatigue, we conducted exploratory analyses comparing fatigued and nonfatigued survivors on the nine dimensions of childhood stress. On every dimension, fatigued survivors reported higher rates of exposure, and these differences reached or approached significance for parental violence (reported by 27% of fatigued vs. 0% of nonfatigued participants; $p = .017$, $\phi = 0.34$), no stable place to live (reported by 15% of fatigued vs. 0% of nonfatigued participants; $p = .09$, $\phi = 0.24$), and parental divorce (reported by 24% of fatigued vs. 6% of nonfatigued participants; $p = .11$, $\phi = 0.23$).

We next tested the hypothesis that fatigued survivors would have elevated levels of lifetime stress exposure. As predicted, fatigued breast cancer survivors reported more acute life events and chronic difficulties throughout the life span than nonfatigued survivors, $F(1, 46) = 6.7$,

Table 1. Demographic Characteristics of Study Participants by Fatigue Group Status

Characteristic	Fatigued ($n = 33$)	Nonfatigued ($n = 17$)
Mean age, years (range)	57.1 (46–74)	59.2 (47–80)
Race/ethnicity, *n* (%)		
White	28 (85)	14 (82)
Other	5 (15)	3 (18)
Married, *n* (%)	15 (45)**	15 (88)**
Education status, *n* (%)		
High school graduate/some college	14 (42)	5 (29)
College graduate/graduate degree	19 (58)	12 (71)
Mean time since cancer diagnosis, years (*SD*)	6.7 (2.8)	5.7 (3.0)

**$p < .01$.

Table 2. Differences in Stress Exposure Throughout the Life Span by Fatigue Group Status

Characteristic	Fatigued (n = 33)	Nonfatigued (n = 17)
Cumulative life events and chronic difficulties		
Count	25.1 (7.9)*	20.3 (7.9)*
Severity	103.4 (38.9)*	78.7 (37.6)*
Childhood life events and chronic difficulties		
Count	2.15 (2.1)*	0.88 (1.0)*
Emotional neglect (CTQ)	2.45 (1.1)***	1.56 (0.6)***
Adulthood life events and chronic difficulties		
Count	21.5 (7.1)*	17.6 (6.2)*
Severity	90.1 (35.3)*	69.3 (30.6)*

Note: Data are mean (*SD*). CTQ = Childhood Trauma Questionnaire.
*p < .05. ***p < .001.

p = .013, η_p^2 = .13, and greater severity of those events and difficulties, $F(1, 46) = 7.0$, p = .01, η_p^2 = .13 (see Table 2). These stressors appeared to be distributed across the life course; in addition to the elevated childhood stress exposure reported earlier, fatigued survivors reported experiencing significantly more life events and chronic difficulties in adulthood than did nonfatigued survivors, $F(1, 46) = 5.5$, p = .024, η_p^2 = .11, as well as significantly greater severity of those experiences compared to nonfatigued survivors, $F(1, 46) = 5.7$, p = .021, η_p^2 = .11.

To determine whether childhood stress was associated with elevated stress exposure in adulthood (i.e., stress continuity), we examined the correlation between stressors occurring in childhood and adulthood. Results showed a significant positive correlation between number of childhood and adulthood stressors, r = .38, p = .007, and between number of childhood stressors and severity of adulthood stressors, r = .47, p = .001.

Discussion

This study was designed to examine associations between lifetime stress exposure and symptoms of fatigue in breast cancer survivors. As hypothesized, women with persistent posttreatment fatigue reported significantly higher levels of stress exposure, both in childhood and in adulthood, than did nonfatigued control participants. To our knowledge, these data are the first to show that cumulative stress exposure is associated with cancer-related fatigue.

These findings are consistent with a life-course perspective on stress and health and provide a bridge between this work and research on cancer-related fatigue. Life-course models emphasize the importance of childhood experiences as a predictor of mental and physical health in adulthood. Consistent with this approach, our results showed that fatigued breast cancer survivors reported significantly higher levels of childhood stress exposure than nonfatigued survivors. Previous studies have documented an association between traumatic childhood experiences and fatigue outside the context of cancer (Heim et al., 2006) and more recently, in breast cancer survivors (Fagundes et al., 2012; Witek-Janusek et al., 2013). Our data replicate and extend these findings in several ways. Although in previous studies researchers have focused only on childhood trauma (specifically, abuse and neglect), we assessed a broader range of early life experiences that included more moderate stressors. Indeed, although fatigued survivors in our study reported higher levels of all types of childhood stress, these differences were strongest for divorce and ongoing fights or violence between parents. Thus, our findings suggest that exposure to conflict and disruption in the home, in addition to neglect and abuse, may set the stage for subsequent symptoms of cancer-related fatigue.

Fatigued survivors in this study also reported significantly higher levels of stress in adulthood, which included both acute life events (e.g., being fired and death of a close friend or relative) and chronic difficulties (e.g., being overwhelmed at work and caregiving). Researchers assessing cumulative stress exposure and mental health primarily have focused on traumatic events, and their results have shown links with depression, anxiety, and other outcomes (e.g., Turner & Lloyd, 1995, 2004). Our findings are consistent with this work and suggest that nontraumatic stressors occurring throughout the life span also may be relevant for symptoms of fatigue in the aftermath of cancer. Finally, these results demonstrate a link between stressors occurring in childhood and adulthood and suggest that continuity of stress exposure may contribute to fatigue in the aftermath of cancer. Relations between childhood and adulthood stress exposure have been investigated in other disorders, such as depression

(e.g., Hammen, Hazel, Brennan, & Najman, 2012), but never in the context of cancer.

One of the key unanswered questions from this study concerns the mechanisms that link stress and fatigue in cancer survivors. Childhood adversity influences physiological systems associated with cancer-related fatigue, including the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, and immune system (Lupien et al., 2009; Miller et al., 2011). In particular, inflammation is a plausible biological pathway linking childhood stress and fatigue because inflammatory processes are elevated among adults with a history of early life stress (Miller et al., 2011) and among fatigued cancer patients and survivors (Bower & Lamkin, 2013). Early life stress may prime innate immune cells to produce higher levels of proinflammatory cytokines in response to challenge, including the challenge of cancer diagnosis and treatment, leading to elevated symptoms of fatigue. In addition, childhood stressors may enhance neuroimmune signaling, leading to elevated symptoms of fatigue following an inflammatory stimulus. There also is evidence that chronic stress in adulthood is associated with elevated inflammatory activity (e.g., Kiecolt-Glaser et al., 2003; Miller et al., 2008), which may set the stage for heightened inflammation and fatigue after cancer.

Longitudinal studies that follow cancer patients from diagnosis into survivorship and include detailed assessments of lifetime stress exposure, immune and inflammatory status, and fatigue, as well as other potential contributing factors, are needed to elucidate the pathways linking stress throughout the life span and fatigue. For example, both early life stress and chronic stressors in adulthood are associated with alterations in glucocorticoid sensitivity (Miller et al., 2008; Miller et al., 2009), which may drive elevated levels of inflammation and associated symptoms of fatigue in the cancer context (Bower, Ganz, Irwin, Arevalo, et al., 2011). However, the possibility that premorbid differences in glucocorticoid sensitivity may set the stage for cancer-related inflammation and fatigue has not been assessed, nor have epigenetic underpinnings of these differences been examined. Psychological pathways also may play an important role. For example, childhood adversity is associated with deficits in coping strategies and psychosocial resources that may increase risk for postcancer fatigue, such as catastrophizing (Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007) and social isolation (Jaremka et al., 2013). Elucidating the biological and psychological risk factors that influence cancer-related fatigue, and the mechanisms through which they act, will inform our understanding of fatigue in the context of cancer and potentially other medical conditions as well.

Our findings provide initial evidence that stress throughout the course of the life span may represent a risk factor for posttreatment fatigue in cancer survivors. Strengths of the study include the focus on breast cancer survivors who were well characterized with respect to fatigue and health status and the use of an innovative computer-based system for assessing lifetime stress exposure. Several limitations also should be noted. First, our findings are based on a relatively small sample and require replication in a larger, more representative group. Second, our stress assessment was retrospective and occurred several years after cancer diagnosis. Participants' stress reports possibly may have been biased by their experiences with cancer or by their symptoms of fatigue. Of note, the classification of women as fatigued or nonfatigued was based on fatigue reports obtained at least 1 year prior to the stress interview, reducing the likelihood that current fatigue symptoms were driving reports of precancer stress. Still, prospective studies are needed.

On a more general level, there are concerns about participants' ability to report reliably on past life events (Maughan & Rutter, 1997), although the issue of unreliable retrospective reporting may be exaggerated because many life events can be recalled reliably when trained interviewers are used and life histories are probed in a systematic manner (Brewin, Andrews, & Gotlib, 1993; Kessler & Wethington, 1991). In addition, stress reports may serve as a proxy for other types of exposures, such as socioeconomic status and living conditions, which were not assessed in this report.

In conclusion, cancer-related fatigue is a common and important problem in the growing population of cancer survivors in the United States, currently estimated at 13.7 million individuals (Siegel et al., 2012). Our findings suggest that cumulative stress exposure may represent a risk factor for persistent fatigue in women with a history of breast cancer. Furthermore, these results build on a broader stress-and-health literature to demonstrate that exposure to stress throughout the life span is associated not only with clinical disorders such as depression and CFS but also with symptoms of fatigue in somatic conditions such as cancer.

Author Contributions

J. E. Bower developed the study concept. All authors contributed to the study design. Data collection was performed by A. D. Crosswell under the supervision of G. M. Slavich. J. E. Bower conducted the primary analyses and drafted the initial version of the manuscript, which was revised by A. D. Crosswell and G. M. Slavich. All authors approved the final version of the manuscript for submission.

Declaration of Conflicting Interests

The authors declare that they have no conflicts of interest with respect to their authorship or the publication of this article.

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