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The Symptom Cluster Experience Profile Framework

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Five-year survival rates for most childhood cancers are approaching 82% (Altekruse et al., 2010), and more than 225,000 adult survivors of childhood cancers were living in the United States in 2009 (Mariotto et al.). According to emerging evidence, adult survivors are highly vulnerable to late effects (e.g., physical and psychological complications, disabilities, adverse outcomes) that persist or arise after completion of cancer treatments (Children's Oncology Group, 2008; Hewitt, Weiner, & Simone, 2003). Many late effects are life threatening (e.g., recurrence of primary cancers, secondary cancers, cardiovascular and pulmonary complications) (Bowers et al., 2005, 2006; Mertens et al., 2001, 2002, 2008; Neglia et al., 2001; Oeffinger et al., 2006) and clearly result from previous cancer therapies. Other late effects are chronic health conditions (e.g., hypothyroidism, diabetes, coronary artery disease) that result from complex interactions among previous cancer therapies, stressors, lifestyle behaviors, and family history (Geenen et al., 2007; Oeffinger et al., 2006). As part of the Childhood Cancer Survivor Study (CCSS), numerous investigators have identified subgroups of adult survivors of childhood cancers who are at high risk for organ toxicities and secondary cancers, and risk-based screening recommendations have been developed to optimize outcomes in these high-risk subgroups (Hudson et al., 2009).

Although understudied in adult survivors of childhood cancers and not necessarily linked empirically to specific organ-system impairments, subgroups of adult survivors who are at high risk for excess symptom burden should be identified. Alarming, unrelieved symptoms in adult survivors of childhood cancers have been associated with negative and potentially fatal consequences. For example, the combination of unrelieved pain and psychological distress was significantly associated with suicidal ideation or past suicidal attempts (Recklitis, Lockwood, Rothwell, & Diller, 2006), and actual suicide rates for cancer survivors are twice that of

Purpose/Objectives: To present the novel Symptom Cluster Experience Profile (SCEP) framework for guiding symptom research in adult survivors of childhood cancers and other subgroups at risk for high symptom burden.

Data Sources: Empirically derived model of symptom cluster experience profiles, existing theoretical frameworks, and data-based literature on symptoms and quality of life in adult survivors of childhood cancers.

Data Synthesis: In a previous study, the authors generated a preliminary model to characterize subgroups of adult survivors of childhood cancers with high-risk symptom cluster profiles. The authors developed the SCEP framework, which depicts symptom cluster experiences as subgroup-specific profiles that are driven by multiple sets of risk and protective factors. The risk and protective factors may directly and indirectly contribute to or alleviate symptoms through their effects on systemic stress. Systemic stress instigates and sustains the symptom experience that, in turn, is expressed through negative diffusion into other components of quality of life, such as functional status, general health perceptions, and overall quality of life.

Conclusions: The SCEP framework is an initial approach to unbundle the complex heterogeneity that underlies the clustering of symptoms. By measuring a wide range of risk and protective factors in future studies of adult survivors of childhood cancers and other subgroups at risk for high symptom burden, further development and validation of the SCEP framework will occur.

Implications for Nursing: The SCEP framework can be used to specify mechanisms underlying symptom cluster profiles and derive interventions targeted to high-risk symptom profiles. Findings from future studies can be translated to risk-based surveillance and symptom management clinical practice guidelines.

the general population nationally (Misono, Weiss, Fann, Redman, & Yueh, 2008).

Among adult survivors of childhood cancers from the CCSS, 10%–23% reported moderate to extreme pain (Hudson et al., 2003; Lu, Tsao, Leisenring, Robison, & Zeltzer, 2007), 16%–40% significant fatigue (Hudson et al., 2003; Mulrooney et al., 2003, 2008), 12%–16% problems sleeping

(Mulrooney et al., 2003, 2008), 5%–17% psychological distress (e.g., anxiety, depression, somatic distress) (Zeltzer et al., 2009), and 14% difficulty concentrating (Ness et al., 2008). In a previous study, the authors generated a preliminary model to characterize subgroups of adult survivors of childhood cancers with high-risk symptom cluster profiles (Finnegan et al., 2009). By using data from more than 7,000 CCSS participants, the authors are refining and testing the model in the Symptom Cluster Experience Profile (SCEP) study. This article presents a theoretical framework to guide the development of subgroup-specific symptom cluster experience profiles.

Symptom Cluster Experience Profile Framework

Overview

Symptom cluster experience profiles are central to the SCEP framework (see Figure 1) and are derived empirically based on clustering of five cardinal symptoms

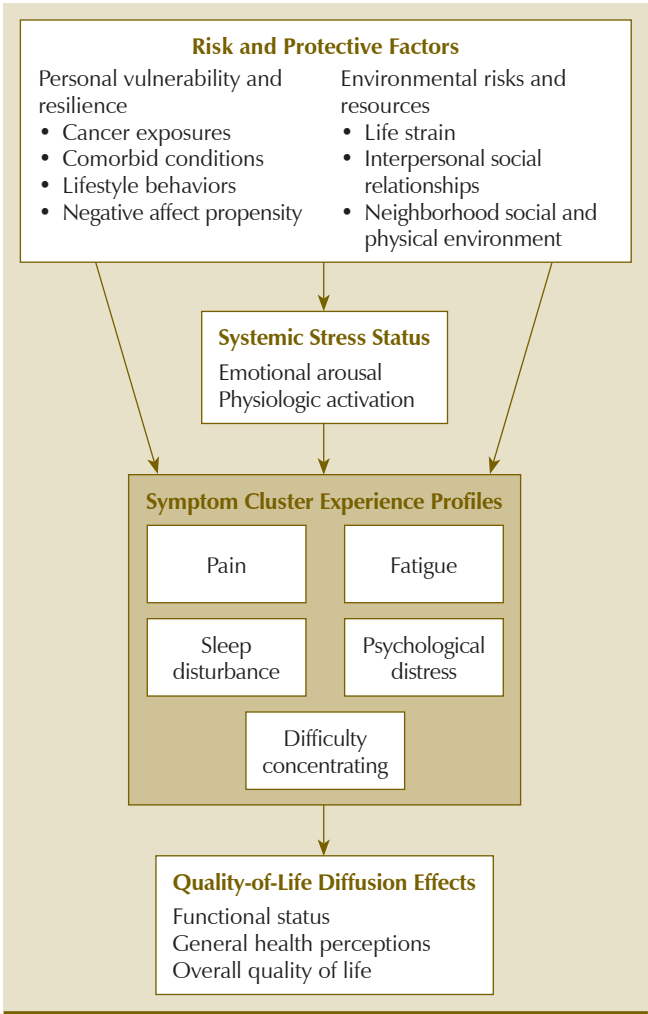


Figure 1. Symptom Cluster Experience Profile Framework

(pain, fatigue, sleep disturbance, psychological distress, and difficulty concentrating) within subgroups. The authors derived the subgroup-specific profiles by using a sophisticated analytic modeling method—latent variable mixture modeling (Finnegan et al., 2009). However, the subgroups also can be derived by using other statistical approaches, such as cluster analysis (Miaskowski, Aouizerat, Dodd, & Cooper, 2007).

The subgroup-specific profiles vary depending on manifestations of systemic stress and multiple sets of known and potential risk and protective factors. The arrows indicate the dominant causal associations. Reciprocal relationships might exist but are not characterized. The authors selected these risk and protective factors from symptom studies of adult survivors of childhood cancers and the general population and categorized them as personal vulnerability and resilience and environmental risks and resources (Heitkemper & Shaver, 1989). The risk and protective factors may directly and indirectly contribute to or alleviate symptoms through their effects on systemic stress. Systemic stress instigates and sustains the symptom experience that, in turn, has a negative impact on other components of quality of life.

The conceptualization of quality of life in terms of functional status, general health perceptions, and overall quality of life, all directly affected by symptoms, is adapted from the revised Wilson and Cleary Framework for Health-Related Quality of Life (Ferrans, Zerwic, Wilbur, & Larson, 2005). Functional status is the ability to perform tasks in physical, psychological, social, and role domains. General health perceptions are personal evaluations of one's own comparative health status made operational through a subjective overall health rating. Overall quality of life is assessed as subjective well-being (i.e., how happy or satisfied someone is with life as a whole) (Ferrans et al., 2005).

Risk and Protective Factors

Personal vulnerability and resilience: Multiple factors may influence personal vulnerability and resilience to stress. Among adult survivors of childhood cancers, the factors include (a) cancer exposure variables (e.g., cancer type, treatment history, age at cancer diagnosis, survival time), (b) comorbid conditions (e.g., number, severity, types), (c) lifestyle behaviors (e.g., physical activity; healthy eating; tobacco, alcohol, or substance use), and (d) negative affect propensity (e.g., enduring tendency to experience negative affect).

Cancer exposure variables: Because of rapidly evolving knowledge of the disease and treatment of childhood cancers, wide variability exists across adult survivors of childhood cancers in their exposure to various cancer disease types, treatments, and survival factors. Conflicting evidence suggests that such factors are related to symptom experiences. Across six population-based

studies (sample sizes ranged from 691–9,535), no firm conclusions could be drawn about whether specific types of cancer predisposed adult survivors of childhood cancers to experiencing symptoms (see Table 1). For example, as compared to adult survivors of childhood leukemia, adult survivors of childhood bone tumors were more likely to experience psychological distress in one study (Hudson et al., 2003) but were equally as likely to experience psychological distress in two other studies (Alessi et al., 2007; Pogany et al., 2006).

As with cancer types, the effects of cancer treatments during childhood on symptom experiences during adulthood also were highly variable and inconclusive (see Table 2). For example, in two U.S. studies, radiation therapy in adult survivors of childhood cancers was linked to pain (Hudson et al., 2003; Zeltzer et al., 2008), whereas radiation therapy was not associated with pain in two international studies (Alessi et al., 2007; Pogany et al., 2006).

Variability in the results from extant studies of adult survivors of childhood cancers also precluded the authors from drawing conclusions about how age at and survival time since cancer diagnosis may affect the symptom experience (see Table 3). For example, Zeltzer et al. (2008) found that older age at childhood cancer diagnosis and longer survival time were associated with pain, but Alessi et al. (2007) showed that younger age at diagnosis predisposed adult survivors of childhood cancers to psychological distress and difficulty concentrating. In summary, one can argue from these data

that not only cancer types, treatments, survival time, and age at cancer diagnosis but also other factors likely contribute to the heterogeneity underlying the observed clustering of symptoms.

Comorbid conditions: Logically, one might expect that chronic comorbid conditions would amplify symptom experiences. In two separate nationally representative samples of adults who reported a cancer history (N = 1,904 and 2,161, respectively), the odds of reporting multiple symptoms (e.g., pain, insomnia, and psychological distress; pain, fatigue, and depression) increased substantially with the number of comorbid conditions (Mao et al., 2007; Reyes-Gibby, Aday, Anderson, Mendoza, & Cleeland, 2006). In the authors' preliminary study of symptom cluster experience profiles, members of the subgroup with the most intensive profile were six times more likely to report at least one comorbid condition than the subgroup with the least intensive profile (Finnegan et al., 2009). In question was whether the so-called comorbid conditions emerge (a) independently, (b) as late disease or treatment effects, or (c) as manifestations of the "stress" (physical or mental) of having had childhood cancer as survivors age. Bender et al. (2008) compared symptom clusters in cancer survivors with comorbid conditions versus individuals who had chronic health problems but no history of cancer. Three symptoms (pain, fatigue, and sleep disturbance) clustered together in both groups. Although the evidence shows that chronic health conditions and various clusters of symptoms are positively related regardless of

Table 1. Likelihood of Reporting Five Cardinal Symptoms by Cancer Type

Studies by Symptom	Central Nervous System	Hodgkin Disease	Non-Hodgkin Lymphoma	Wilms Tumor	Neuroblastoma	Soft Tissue Sarcoma	Bone Tumors
Pain							
Alessi et al., 2007	▲	■	■	◆	◆	■	▲
Hudson et al., 2003	■	●	■	◆	◆	▲	▲
Pogany et al., 2006	■	■	■	◆	◆	■	■
Shimoda et al., 2008	◆	◆	■	◆	◆	◆	■
Fatigue							
Mulrooney et al., 2003	■	▲	■	■	■	▲	■
Mulrooney et al., 2008	■	■	◆	◆	◆	■	■
Sleep disturbance							
Mulrooney et al., 2003	■	▲	■	■	●	▲	▲
Mulrooney et al., 2008	▲	■	◆	◆	◆	▲	■
Psychological distress							
Alessi et al., 2007	■	■	■	■	■	■	■
Hudson et al., 2003	◆	▲	◆	◆	◆	▲	▲
Pogany et al., 2006	■	■	■	■	■	■	■
Difficulty concentrating							
Alessi et al., 2007	▲	■	■	■	■	■	■
Pogany et al., 2006	■	●	●	■	●	■	■

▲—more likely to report symptom; ●—less likely to report symptom; ■—equally as likely to report symptom; ◆—cancer type not studied

Note. The reference group was leukemia.

Table 2. Associations Between Five Cardinal Symptoms and Surgery, Chemotherapy (Chemo), and Radiation

Studies by Symptom	Surgery	Chemo	Radiation	Surgery + Chemo	Surgery + Radiation	Chemo + Radiation	Surgery + Chemo + Radiation	Cranial Radiation
Pain								
Alessi et al., 2007	■	■	■	◆	▲	◆	▲	◆
Hudson et al., 2003	■	■	▲	◆	◆	◆	◆	▲
Pogany et al., 2006	◆	■	■	■	▲	■	▲	◆
Zeltzer et al., 2008	■	■	▲	◆	◆	◆	◆	■
Fatigue								
Mulrooney et al., 2003	◆	■	▲	◆	◆	◆	◆	◆
Mulrooney et al., 2008	◆	■	▲	◆	◆	◆	◆	◆
Sleep disturbance								
Mulrooney et al., 2003	◆	■	■	◆	◆	◆	◆	◆
Mulrooney et al., 2008	◆	■	■	◆	◆	◆	◆	◆
Psychological distress								
Alessi et al., 2007	■	■	■	◆	▲	◆	▲	◆
Hudson et al., 2003	■	■	■	◆	◆	◆	◆	◆
Pogany et al., 2006	◆	■	■	■	▲	■	▲	◆
Zebrack et al., 2002	◆	◆	◆	◆	◆	◆	◆	■
Zebrack et al., 2004	◆	■	◆	◆	◆	◆	◆	■
Zebrack et al., 2007	◆	■	■	◆	◆	◆	◆	▲
Zeltzer et al., 2008	■	■	▲	◆	◆	◆	◆	■
Difficulty concentrating								
Alessi et al., 2007	■	■	■	◆	■	◆	▲	▲
Pogany et al., 2006	◆	■	■	■	■	■	▲	▲

▲—symptom associated with treatment; ■—symptom not associated with treatment; ◆—treatment not studied

cancer status, the authors posit in the SCEP framework that the relationships are bound in synchrony and involve complex, undetermined heterogeneity, resulting from multiple personal vulnerability and resilience factors and environmental risks and resources.

Lifestyle behaviors: Among adult survivors of childhood cancers, in addition to influencing the emergence and natural course of some chronic illnesses, lifestyle behaviors are related to symptom burden and, potentially, to its alleviation. In separate studies of adult survivors of childhood cancers, tobacco use (Emmons et al., 2003), heavy alcohol use (Lown et al., 2008), physical inactivity (Ness et al., 2009), and obesity (Meeske, Siegel, Globe, Mack, & Bernstein, 2005) were associated with psychological distress. Obesity also was associated with greater likelihood of reporting fatigue and sleep disturbance (Meeske et al., 2005; Mulrooney et al., 2003, 2008). Cox et al. (2009) identified pain, fatigue, and psychological distress as significant predictors of lack of participation in regular physical activity. In addition, the authors showed in their empirically derived symptom cluster subgroup model that a healthy lifestyle specifically characterized the adult survivor of childhood cancer subgroup with the least intensive symptom cluster experience profile (Finnegan et al., 2009). The efficacy of physical activity in reducing fatigue and psychological distress symptoms has been

demonstrated in studies of survivors of adult-onset cancers (Courneya et al., 2004; Segar et al., 1998). Likewise, in a pilot study of adult survivors of childhood cancers, a 10-week home-based exercise counseling program with feedback from a pedometer was effective in increasing physical activity and decreasing fatigue, with improvements lasting up to 36 weeks (Blaauwbroek et al., 2009). Among adult survivors of childhood cancers, a better understanding of subgroup-specific sets of lifestyle behaviors may translate to effective targeted interventions to relieve symptoms and improve quality of life.

Negative affect propensity: In the general population, the enduring, lifelong tendency to experience negative affect, often measured as neuroticism (Deary, Chalder, & Sharpe, 2007), has been related to heightened reactivity to stressors (Bolger & Schilling, 1991), increased objectively measured negative life events (Magnus, Diener, Fujita, & Pavot, 1993), more physical illness (Huovinen, Kaprio, & Koskenvuo, 2001; Matthews, Yousfi, Schmidt-Rathjens, & Amelang, 2003), poorer prognosis and untoward events in chronic illness (Denollet & Van Heck, 2001), and compromised immune function (Marsland, Cohen, Rabin, & Manuck, 2001). Several investigators have found that adult survivors of childhood cancers who met criteria for diagnosis of post-traumatic stress disorder (PTSD) had higher

scores on negative affect measures than those without PTSD (Bruce, 2006; Rourke, Hobbie, Schwartz, & Kazak, 2007; Schwartz & Drotar, 2006). Better understanding of propensity for negative affect in adult survivors of childhood cancers has the potential to reveal those at high risk for persistent or debilitating symptoms as a target for interventions to modulate this vulnerability and resilience factor.

Environmental risks and resources: In the SCEP framework, key environmental risks and resources contributing to complex heterogeneity in symptom experiences among adult survivors of childhood cancers are depicted as life strain, interpersonal social relationships, and neighborhood social and physical environments. Very little is known about how these environmental risks and resources affect the symptom experience in adult survivors of childhood cancers.

Life strain: Data from multiple studies of chronic disorders that included cancer survivors support the connection between exposure to stressful life events (life strain) and somatic symptoms. This research includes somatic functional disorders with multisymptom manifestations such as fibromyalgia, irritable bowel, and chronic fatigue syndromes. For example, based on European data, predisposition to fibromyalgia was related to reports of high exposure or high perceived negativity related to life events, including major or daily hassles; sexual, physical, or emotional abuse; and a driven lifestyle (Deary et al., 2007). Life strain has been associated with subsequent symptom severity in clinic patients with irritable bowel (Hertig, Cain, Jarrett, Burr, & Heitkemper, 2007); in regression analysis using a community-based sample, total life stress was independently related to functional gastrointestinal disorders (Levy, Cain, Jarrett, & Heitkemper, 1997). Finally, in children who were undergoing active treatment for cancer, cumulative life strain uniquely contributed to levels of post-traumatic stress symptoms beyond demographics, cancer factors, and levels of parental post-traumatic stress symptoms (Currier, Jobe-Shields, & Phipps, 2009). Although the authors found no studies of life strain and symptoms in adult survivors of childhood cancers, based on the evidence in other chronic illness groups, the cumulative effect of stressful life events likely has a major impact on subgroup-specific symptom experience profiles in adult survivors of childhood cancers.

Interpersonal social relationships: Social integration, social networks (because of the opportunities for interaction, engagement, and influence as well as access to resources), and multiple forms of social support (e.g., emotional, instrumental, informational) have been well documented to promote well-being and buffer the effects of stress in some circumstances (Berkman & Glass 2000). In addition, in a recent national needs assessment, support from family and friends, opportunities

to meet other survivors, and encouragement to pursue social activities were the most highly ranked supportive care needs among young adult cancer survivors (Zebrack, Mills, & Weitzman, 2007). Unfortunately, certain subgroups of adult survivors of childhood cancers may be at higher risk for social isolation than others. In a large population-based Canadian study, child and adolescent survivors of central nervous system (CNS) tumors, leukemia, and neuroblastoma were less likely to have close friends or to use friends as confidants than population controls of the same age and gender (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005). Likewise, in the CCSS cohort, adolescent survivors of CNS tumors, leukemia, and neuroblastoma were more likely to display antisocial behaviors and report symptoms of psychological distress than a sibling comparison group (Schultz et al., 2007). Others also have found peer-relationship issues in CNS tumor survivors, as well as in children who received CNS-directed treatments for leukemia, lymphoma, and solid tumors outside the CNS (e.g., cranial radiation therapy, intrathecal chemotherapy) (Vannatta, Gartstein, Short, & Noll, 1998; Vannatta, Gerhardt, Wells, & Noll, 2007). During childhood, targeting high-risk survivors with programs to build social skills may lead to enhanced social support during adulthood and protection against stress and symptoms.

Table 3. Associations Between Five Cardinal Symptoms and Cancer Time-Related Variables

Studies by Symptom	Older Age at Diagnosis	Survival Time Since Diagnosis
Pain		
Alessi et al., 2007	■	◆
Pogany et al., 2006	■	◆
Zeltzer et al., 2008	▲	▲
Fatigue		
Mulrooney et al., 2003	■	■
Mulrooney et al., 2008	■	■
Sleep disturbance		
Mulrooney et al., 2003	■	■
Mulrooney et al., 2008	■	■
Psychological distress		
Alessi et al., 2007	●	◆
Pogany et al., 2006	■	◆
Zebrack et al., 2002	■	■
Zebrack et al., 2004	■	◆
Zebrack et al., 2007	■	■
Zeltzer et al., 2008	■	■
Difficulty concentrating		
Alessi et al., 2007	●	◆
Pogany et al., 2006	■	◆

▲—positively associated with symptom; ●—negatively associated with symptom; ■—not associated with symptom; ◆—time variable not studied

Neighborhood social and physical environments:

Although understudied in adult survivors of childhood cancers, aspects of neighborhood social environment and physical environment may directly and indirectly contribute to or alleviate symptoms through their effects on stress. The neighborhood social environment includes social norms and values as well as the structure and characteristics of social interactions within neighborhoods (Coutts & Kawachi, 2006). The neighborhood physical environment includes land use, physical infrastructure systems such as transportation networks, design, air and water quality, and noise (Committee on Physical Activity, Health, Transportation, and Land Use, Transportation Research Board, Institute of Medicine of the National Academies, 2005; Klitzman, Matte, & Kass, 2006).

In the general population, the salutogenic and pathogenic effects of neighborhood social and physical environments on physical and mental health are of growing interest (Davies et al., 2009; Jordan, Thomas, Peat, Wilkie, & Croft, 2008; Kim, 2008; Mair, Roux, & Galea, 2008; Stockdale et al., 2007; Truong & Ma, 2006). Whereas neighborhood positive social dynamics (e.g., cohesion, trust, reciprocity, collective efficacy, sense of community), aesthetic quality, pedestrian friendliness, density of supportive services (e.g., churches), and green space are protective against psychological distress (Kim, 2008; Mair et al., 2008; Truong & Ma, 2006), some neighborhood features may act as stressors. Independent of individual characteristics, higher levels of psychological distress have been associated with residing in neighborhoods characterized by few economic resources; high levels of violence (or low safety), disorder (e.g., vandalism, drug selling, prostitution, litter), physical deterioration or decay (e.g., abandoned buildings), traffic, crowding, or noise; population instability or turnover; social isolation; or close proximity to industrial land use (Kim, 2008; Mair et al., 2008; Stockdale et al., 2007; Truong & Ma, 2006). Investigators also have found that pain is greater or more disabling among residents of socioeconomically disadvantaged neighborhoods (Davies et al., 2009; Jordan et al., 2008) and that fewer pharmacies carry opioid analgesics in non-Caucasian and higher poverty neighborhoods than in Caucasian and lower poverty neighborhoods, which may contribute to unrelieved pain (Green, Ndao-Brumblay, West, & Washington, 2005; Mayer, Kirlin, Rehm, & Loeser, 2008; Morrison, Wallenstein, Natale, Senzel, & Huang, 2000). Although not well studied in general and among adult survivors of childhood cancers in particular, the stressors and resources described for psychological distress and pain also may affect the symptoms of fatigue, sleep disturbance, and difficulty concentrating.

Systemic Stress

Overview: Novel, uncontrollable, and unpredictable negative events are linked to heightened emotional arousal (Deary et al., 2007; Overmier & Murison, 2005),

which drives physiologic stress activation. The hypothalamic-pituitary-adrenal (HPA) and sympathetic nervous system axes are turned on, leading to the release of cortisol and catecholamines. To further prepare, a low grade inflammatory activation occurs, and proinflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor- α are released (Chrousos, 2000; Denollet et al., 2003; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). Although this stress-inflammatory activation is adaptive in the context of bodily threat, it only will provide short-term adaptation. When activation is frequent or chronic, the reserve for adapting to excess challenges is dampened over time. Triggered by emotional arousal, with or without actual tissue injury or infection, the low grade inflammatory activation may incite symptoms such as pain, fatigue, or sleep disturbance (Kronfol & Remick, 2000).

One view of chronic stress activation is that the initial up-regulation of the HPA axis and cortisol release eventually converts to a down-regulation, indicated by low cortisol (Fries, Hesse, Hellhammer, & Hellhammer, 2005). Hypocortisolism may be the context for proinflammatory cytokine predominance to drive fatigue, other symptoms, and so-called illness behavior characterized by behavioral withdrawal. However, another view suggested by Dantzer (2005) is that rather than up-regulation and down-regulation occurring sequentially, the two profiles may represent two different groups: one group has a propensity to anxious arousal and up-regulation of the HPA axis, and the other group is predisposed to anergic arousal and down-regulation of the HPA axis.

Emotional arousal: Among adult survivors of childhood cancers, past cancer experiences and worries about the future may result in chronic emotional arousal in the context of enduring certainty (Koocher & O'Malley, 1981; Parry, 2003). Some adult survivors of childhood cancers embrace this uncertainty, find new meaning in life, and actually move to a higher level of life satisfaction (post-traumatic growth) (Parry & Chesler, 2005). In other adult survivors of childhood cancers, uncertainty has been linked to PTSD symptoms as well as lower levels of health promotion behaviors (Lee, Gau, Hsu, & Chang, 2009; Lee, Santacroce, & Sadler, 2007; Santacroce & Lee, 2006). For example, adolescent survivors who worried about cancer and treatment effects were more likely to smoke and drink (Cox, McLaughlin, Rai, Steen, & Hudson, 2005). In the authors' study of adult survivors of childhood cancers, those who had high levels of worry and perceived many physical activity barriers were less likely to be physically active (Finnegan et al., 2007).

Physiologic activation: Although not yet explored to any extent as a possible systemic mechanism underlying symptom burden in adult survivors of childhood cancers,

the authors posit that distress physiologic activation in vulnerable individuals occurs at a relatively subclinical level and is evident in circulating cortisol changes and relative dominance of proinflammatory cytokines. This provokes or amplifies symptoms, particularly pain, fatigue, sleep disturbance, psychological distress, and difficulty concentrating. For example, extensive studies of fatigue in breast cancer survivors have repeatedly shown that relative to nonfatigued survivors, fatigued survivors had significant alterations in fatigue-related immune and neuroendocrine parameters (i.e., proinflammatory cytokines and cortisol levels) (Bower, Ganz, & Aziz, 2005; Bower et al., 2006; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006).

Quality-of-Life Diffusion Effects

The five cardinal symptoms in the SCEP framework have a negative valence in experience and, therefore, influence other quality-of-life components such as functional status, general health perceptions, and overall quality of life. In the authors' study of 100 adult survivors of childhood cancers, overall quality of life differentiated the three subgroup-specific symptom cluster experience profiles (Finnegan et al., 2009). As expected, adult survivors of childhood cancers in the subgroup with the most intense symptom cluster profile had the lowest mean quality-of-life scores, and the differences among the subgroups in quality-of-life scores were large enough to be clinically meaningful. In a study of 166 leukemia survivors, Meeske et al. (2005) reported that fatigue and psychological distress together, rather than either of the symptoms alone, had a negative synergistic effect on quality of life. Although other investigators have not examined symptom clusters and quality of life in adult survivors of childhood cancers, a negative impact of individual symptoms on the three quality-of-life components has been documented in this population (Helder et al., 2004; Mulrooney et al., 2008; Ness et al., 2008; Sharp, Kinahan, Didwania, & Stolley, 2007).

Conclusions

Subgroups of adult survivors of childhood cancers are at risk for experiencing a high symptom burden along with organ toxicities and secondary cancers. The authors developed a theoretical framework for deriving subgroup-specific symptom cluster experience profiles as prerequisites for targeted symptom management interventions. The SCEP framework is a beginning and evolving approach for unbundling the complex heterogeneity that underlies the clustering of five cardinal symptoms among adult survivors of childhood cancers. Further development and validation of the SCEP framework will occur in the authors' study of more than 7,000 participants from the CCSS.

Implications for Nursing Research and Practice

Because clustering of the five cardinal symptoms is not unique to adult survivors of childhood cancers, the SCEP framework also can be applied to nursing research and practice in other populations at risk for high symptom burden. Three, four, or five of the cardinal symptoms have clustered together in multiple studies of survivors of adult-onset cancers, regardless of their cancer survivor status (Barsevick, 2007; Bender, Ergyn, Rosenzweig, Cohen, & Sereika, 2005; Kim, Barsevick, Tulman, & McDermott, 2008) and in studies of adults with chronic health conditions other than cancer (Bender et al., 2008; Mao et al., 2007; Reyes-Gibby et al., 2006). The symptoms also clustered in other functional syndromes, such as fibromyalgia, chronic fatigue syndrome, and multiple chemical sensitivity syndromes (McFarlane, Ellis, Barton, Browne, & Van Hooff, 2008).

Given the diversity of populations presenting with clustering of the five cardinal symptoms, multiple person-level and environmental-level factors that are outside of obvious disease-specific or typical organ dysfunction processes likely contribute to mechanisms underlying symptom cluster experiences. The SCEP framework can be used in future studies to specify the mechanisms and derive interventions targeted to high-risk symptom profiles. Finally, the SCEP framework can be used to translate research findings to clinical practice. Based on subgroup-specific symptom cluster experience profiles, risk-based surveillance and intervention guidelines can be targeted to subgroups of adult survivors of childhood cancers as well as other subgroups at risk for experiencing high symptom burden.

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