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The Symptom Cluster Experience Profile Framework

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Abstract

Purpose—To present the novel Symptom Cluster Experience Profile (SCEP) Framework for guiding symptom research in adult-survivors of childhood cancers (ACC-survivors) and other subgroups at risk for high symptom burden.

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

Data Synthesis—In a previous study, we generated a preliminary model to characterize subgroups of ACC-survivors with high-risk symptom cluster profiles. We developed the SCEP Framework that depicts symptom cluster experiences as subgroup-specific profiles that are driven by multiple sets of risk and protective factors. These risk and protective factors may directly and indirectly --through their effects on systemic stress -- contribute to or alleviate symptoms. Systemic stress instigates and sustains the symptom experience, which 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 ACC-survivors and other subgroups at risk for high symptom burden, further development and validation of the SCEP Framework will occur.

Implications for Nursing Research and Practice—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.

Today, with 5-year survival rates for most childhood cancers at 80% (Horner et al., 2009), there are more than 225,000 adult survivors of childhood cancers (ACC-survivors) in the United States (Mariotto et al., 2009). According to emerging evidence, these ACC-survivors are highly vulnerable to late effects, i.e., physical and psychological complications, disabilities, and 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; Bowers et al., 2006; Mertens et al., 2001; Mertens et al., 2002; Mertens et al., 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 ACC-survivors 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).

Though understudied in ACC-survivors and not necessarily linked empirically to specific organ system impairments, it is also important to identify subgroups of ACC-survivors who are high risk for excess symptom burden. Alarming, unrelieved symptoms in ACC-survivors 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 attempt (Recklitis, Lockwood, Rothwell, & Diller, 2006), and actual suicide rates for cancer survivors are twice that of the general population nationally (Misono et al., 2008). Among ACC-survivors 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; Mulrooney et al., 2008); 12%-16% problems sleeping (Mulrooney et al., 2003; Mulrooney et al., 2008); 5%-17% psychological distress (i.e., anxiety, depression, somatic distress) (Zeltzer et al., 2009); and 14% difficulty concentrating (Ness et al., 2008). In a previous study, we generated a preliminary model to characterize subgroups of ACC-survivors with high-risk symptom cluster profiles (Finnegan et al., 2009). Using data from over 7000 CCSS participants, we are now refining and testing this model in the Symptom Cluster Experience Profile study. In this paper, we present 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 (Figure 1), and are empirically derived based on clustering of five cardinal symptoms (pain, fatigue, sleep disturbance, psychological distress, and difficulty concentrating) within subgroups. We

derive the subgroup-specific profiles using a sophisticated analytic modeling method – latent variable mixture modeling (Finnegan et al., 2009). However, the subgroups can also be derived 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 in Figure 1. We selected these risk and protective factors from symptom studies of ACC-survivors and the general population and categorized them as: 1) person vulnerability/resilience and 2) environmental risks/resources (Heitkemper & Shaver, 1989). These risk and protective factors may directly and indirectly -- through their effects on systemic stress -- contribute to or alleviate symptoms. Systemic stress instigates and sustains the symptom experience, which 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

Person vulnerability/resilience—Multiple factors may influence personal vulnerability and resilience to stress. Among ACC-survivors, these factors include: 1) cancer exposure variables (e.g., cancer type, treatment history, age at cancer diagnosis, survival time); 2) co-morbid conditions (e.g., number, severity, and types); 3) lifestyle behaviors (e.g., physical activity, healthy eating, tobacco use, and alcohol/substance use); and 4) negative affect propensity (enduring tendency to experience negative affect).

Cancer exposure variables: Due to rapid evolving knowledge of the disease and treatment of childhood cancers, wide variability exists across ACC-survivors in their exposure to various cancer disease types, treatments, and survival factors. There is conflicting evidence that such factors are related to symptom experiences. Across six population-based studies (sample size ranged from 691 to 9535), no firm conclusions can be drawn about whether specific types of cancer predisposed ACC-survivors to experiencing symptoms (see Table 1). For example, as compared to ACC-survivors of leukemia, ACC-survivors of bone tumors were more likely to experience psychological distress in one study (Hudson et al., 2003) but 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 were also highly variable and inconclusive (see Table 2). For example, in two U.S. studies radiation therapy in ACC-survivors 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 ACC-survivors also precludes us from drawing conclusions about how age at and survival time since cancer diagnosis may impact 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 ACC-survivors to psychological distress and difficulty concentrating. In summary, from these data it can be argued 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.

Co-morbid conditions: Logically, it might be expected that chronic co-morbid conditions would amplify symptom experiences. In two separate nationally representative samples of adults who reported a cancer history (n=1904 and n=2161), the odds of reporting multiple symptoms (pain/insomnia/psychological distress and pain/fatigue/depression) increased substantially with the number of co-morbid conditions (Mao et al., 2007; Reyes-Gibby et al., 2006). In our preliminary study of symptom cluster experience profiles, members of the subgroup with the most intensive symptom cluster experience profile were six times more likely to report at least one co-morbid condition than the subgroup with the least intensive symptom cluster experience profile (Finnegan et al. 2009). In question is whether the so-called co-morbid conditions emerge (a) independently, (b) as late disease/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 co-morbid 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 this evidence shows that chronic health conditions and various clusters of symptoms are positively related regardless of cancer status, we posit in our SCEP framework that the relationships are bound in synchrony and involve complex undetermined heterogeneity resulting from multiple person vulnerability/resilience factors and environmental risks/resources.

Lifestyle behaviors: Among ACC-survivors, 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 ACC-survivors, tobacco use (Emmons et al., 2003), heavy alcohol use (Lown et al., 2008), physical inactivity (Ness et al., 2009), and obesity (Meeske et al., 2005) were associated with psychological distress. Obesity was also associated with greater likelihood of reporting fatigue and sleep disturbance (Meeske et al., 2005; Mulrooney et al., 2003; Mulrooney et al., 2008). Recently, Cox et al. (2009) identified pain, fatigue, and psychological distress as significant predictors of lack of participation in regular physical activity. Moreover, in our empirically-derived symptom cluster subgroup model, we showed that a healthy lifestyle specifically characterized the ACC-survivor 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 (e.g., Courneya et al., 2004; Segar et al., 1998). Likewise, in a recent pilot study of ACC-survivors, a 10-week home-based exercise counseling program with feedback from a pedometer intervention was effective in increasing physical activity and decreasing fatigue, with improvements lasting up to 36 weeks (Blaauwbroek et al., 2008). Among ACC-survivors, 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, life-long 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, 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 ACC-survivors 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 ACC-survivors has the potential to reveal those at high risk for persistent or debilitating symptoms as a target for interventions to modulate this vulnerability/resilience factor.

Environmental Risks/Resources—In the SCEP framework, key environmental risks and resources that we see as contributing to complex heterogeneity in symptom experiences among ACC-survivors are depicted as overall life strain, interpersonal social relationships, and neighborhood social and physical environments. Very little is known about how these environmental risks and resources impact the symptom experience in ACC-survivors.

Life strain: Data from multiple studies of chronic disorders, including cancer survivors, support the connection between exposure to stressful life events (life strain) and somatic symptoms. This research includes somatic functional disorders with multi-symptom manifestations such as fibromyalgia (FM), irritable bowel, and chronic fatigue (CFS) syndromes. For example, based on European data, predisposition to FM 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 who have irritable bowel (Hertig, Cain, Jarrett, Burr, & Heitkemper, 2007), and 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 (PTSS), above and beyond demographics, cancer factors and levels of parental PTSS (Currier, Jobe-Shields, & Phipps, 2009). Although we found no studies of life strain and symptoms in ACC-survivors, based on the evidence in other chronic illness groups, it is likely that the cumulative effect of

stressful life events has a major impact on subgroup-specific symptom experience profiles in ACC-survivors.

Interpersonal social relationships: It has been well documented that social integration, social networks (due to the opportunities for interaction, engagement, and influence as well as access to resources), and multiple forms of social support (e.g., emotional, instrumental, informational) can promote well-being and buffer the effects of stress in some circumstances (Berkman & Glass 2000). Moreover, 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 ACC-survivors may be at higher risk for social isolation than others. In a large population-based Canadian study, child and adolescent survivors of 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 have also found peer relationship problems in CNS tumor survivors, as well as children who received CNS-directed treatments for leukemia, lymphoma, and solid tumors outside the CNS (e.g., cranial radiation therapy and 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.

Neighborhood social and physical environments: Though understudied in ACC-survivors, aspects of neighborhood social environment and physical environment may directly and indirectly --through their effects on stress -- contribute to or alleviate symptoms. 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 system such as transportation networks, design, air and water quality, and noise (Committee on Physical Activity, Health, Transportation, and Land Use 2005; Klitzman et al. 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., 2008; 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/

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 have also found that pain is greater or more disabling among residents of socioeconomically disadvantaged neighborhoods (Davies et al., 2008; Jordan et al., 2008) and that fewer pharmacies carry opioid analgesics in non-white and higher poverty neighborhoods than in white 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). Whereas, not well studied in general and among ACC-survivors in particular, it is quite plausible that the stressors and resources described above for psychological distress and pain may also affect fatigue, sleep disturbance, and mental clouding symptoms as well.

Systemic Stress

Overview—Novel, uncontrollable and unpredictable negative events are linked to heightened emotional arousal (Deary et al., 2007; Overmier & Murison, 2005), which drives physiological ‘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 pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF 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 will only provide short-term adaptation. When activation is frequent or chronic, over time the reserve for adapting to excess challenges is dampened. 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 pro-inflammatory 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, these 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 ACC-survivors, 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 ACC-survivors 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 ACC-survivors uncertainty has been linked to PTSD symptoms as well as lower levels of health promotion behaviors (Lee, Santacroce, & Sadler, 2007; Lee, Gau, Hsu, & Chang, 2009; Santacroce & Lee, 2006). For

example, adolescent survivors who worried about cancer and treatment effects were likely to smoke and drink (Cox, McLaughlin, Rai, Steen, & Hudson, 2005). In our study of ACC-survivors, 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 ACC-survivors, we posit that ‘distress’ physiological activation in vulnerable individuals occurs at a relatively sub-clinical level and is evident in circulating cortisol changes and relative dominance of pro-inflammatory cytokines. This provokes or amplifies symptoms, particularly pain, fatigue, sleep disturbance, psychological distress, and difficulty concentrating. For example, in their extensive studies of fatigue in breast cancer survivors, Bower and colleagues have repeatedly shown that relative to “non-fatigued” breast cancer survivors, “fatigued” breast cancer survivors had significant alterations in fatigue-related immune and neuroendocrine parameters, i.e., pro-inflammatory cytokines and cortisol levels (e.g., 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 thereby influence other quality of life components, such as functional status, general health perceptions, and overall quality of life (see Figure 1). In our study of 100 ACC-survivors, overall quality of life differentiated the three subgroup-specific symptom cluster experience profiles (Finnegan et al., 2009). As expected, ACC-survivors 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 these symptoms alone, had a negative synergistic effect on quality of life. Although other investigators have not examined symptom clusters and quality of life in ACC-survivors, a negative impact of individual symptoms on the three quality of life components has been documented in this population (Helder et al., 2003; Mulrooney et al., 2008; Ness et al., 2008; Sharp, Kinahan, Didwania, & Stolley, 2007).

Conclusions

Along with organ toxicities and secondary cancers, subgroups of ACC-survivors are at risk for experiencing a high symptom burden. We 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 ACC-survivors. Further development and validation of the SCEP Framework will occur in our study of over 7000 participants from the CCSS.

Implications for Nursing Research and Practice

Since clustering of these five cardinal symptoms is not unique to ACC-survivors, the SCEP framework can also be applied to nursing research and practice in other populations at risk for high symptom burden. Three, four, or five of the five cardinal symptoms have clustered together in multiple studies of survivors of adult-onset cancers, regardless of their cancer survivor status (e.g., 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 (e.g., Bender et al., 2008; Mao et al., 2007; Reyes-Gibby, Aday, Anderson, Mendoza, & Cleeland, 2006). These 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 these five cardinal symptoms, it is likely that multiple person-level and environmental-level factors that are outside of obvious disease-specific or typical organ dysfunction processes contribute to mechanisms underlying symptom cluster experiences. The SCEP framework can be used in future studies to specify these 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 ACC-survivors as well as other subgroups at risk for experiencing high symptom burden.

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Figure 1. Symptom Cluster Experience Profile Framework

Table 1
Cancer Types and Likelihood of Reporting Five Cardinal Symptoms (reference group = Leukemia)

Studies by Symptom	Cancer Types						
	CNS	HD	NHL	WT	NB	STS	Bone
Pain							
Alessi et al., 2007	More likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Cancer type not studied	Cancer type not studied	Equally as likely to report symptom	More likely to report symptom
Hudson et al., 2003	Equally as likely to report symptom	Less likely to report symptom	Equally as likely to report symptom	Cancer type not studied	Cancer type not studied	More likely to report symptom	More likely to report symptom
Pogany et al., 2006	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Cancer type not studied	Cancer type not studied	Equally as likely to report symptom	Equally as likely to report symptom
Shimoda et al., 2008)	Cancer type not studied	Cancer type not studied	Equally as likely to report symptom	Cancer type not studied	Cancer type not studied	Cancer type not studied	Equally as likely to report symptom
Fatigue							
Mulrooney et al., 2003	Equally as likely to report symptom	More likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	More likely to report symptom	Equally as likely to report symptom
Mulrooney et al., 2008	Equally as likely to report symptom	Equally as likely to report symptom	Cancer type not studied	Cancer type not studied	Cancer type not studied	Equally as likely to report symptom	Equally as likely to report symptom
Sleep Disturbance							
Mulrooney et al., 2003	Equally as likely to report symptom	More likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Less likely to report symptom	More likely to report symptom	More likely to report symptom
Mulrooney et al., 2008	More likely to report symptom	Equally as likely to report symptom	Cancer type not studied	Cancer type not studied	Cancer type not studied	More likely to report symptom	Equally as likely to report symptom
Psychological Distress							
Alessi et al., 2007	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom
Hudson et al., 2003	Cancer type not studied	More likely to report symptom	Cancer type not studied	Cancer type not studied	Cancer type not studied	More likely to report symptom	More likely to report symptom
Pogany et al., 2006	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom
Difficulty Concentrating							
Alessi et al., 2007	More likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom
Pogany et al., 2006	Equally as likely to report symptom	Less likely to report symptom	Less likely to report symptom	Equally as likely to report symptom	Less likely to report symptom	Equally as likely to report symptom	Equally as likely to report symptom

More likely to report symptom

Equally as likely to report symptom

Less likely to report symptom

Cancer type not studied

CNS – Central Nervous System

HD – Hodgkin Disease

NHL – Non-Hodgkin Lymphoma

WT – Wilm's Tumor

NB – Neuroblastoma

STS – Soft Tissue Sarcoma

Bone – Bone Tumors

Table 2
Cancer Treatments and Associations with Five Cardinal Symptoms

Studies by Symptom	Cancer Treatments							
	S	C	R	S+C	S+R	C+R	S+C+R	Cr R
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

S – Surgery
 C – Chemotherapy

R – Radiation
 Cr R – Cranial Radiation

Table 3
Cancer Time-related Variables and Associations with Five Cardinal Symptoms

Studies by Symptom	Cancer Time-related Variables	
	Older age at cancer diagnosis	Survival time since cancer 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		
Mental Clouding		
Alessi et al., 2007		
Pogany et al., 2006		
<div> <div></div> Positively associated with symptom <div></div> Negatively associated with symptom <div></div> Time variable not studied <div></div> Not associated with symptom </div>		