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Symptoms in Family Caregivers of Patients Undergoing Radiation Therapy for Prostate Cancer

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Symptoms in Family Caregivers of Patients Undergoing Radiation Therapy for Prostate Cancer

by

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DISSERTATION

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Symptoms in Family Caregivers of Patients Undergoing Radiation Therapy for Prostate Cancer

Barbara Swore Fletcher

Abstract

Changes in the US health care system have resulted in increased numbers of patients with cancer being cared for at home by family caregivers (FCs). The prevalence, severity, and impact of five symptoms (depression, anxiety, sleep disturbance, fatigue, pain) were evaluated in 60 FCs of patients with prostate cancer at the initiation of radiation therapy (RT). A high percentage of FCs experienced clinically significant levels of a variety of symptoms, which had a negative effect on the FC's functional status and quality of life (QOL).

Two longitudinal studies were conducted that examined two of the most prevalent symptoms in FCs (i.e., fatigue, anxiety). Based on the results of hierarchical linear modeling (HLM), the trajectories and predictors of evening and morning fatigue were different. The model of evening fatigue was quadratic and the predictors of the intercept were baseline levels of FC sleep disturbance and baseline levels of patient evening fatigue, while the predictors for the slopes was baseline levels of FC evening fatigue. In contrast, the trajectories for morning fatigue were linear. The predictors of the intercept were baseline level of FC trait anxiety, baseline levels of patient morning fatigue, and level of family support.

Anxiety was a highly prevalent symptom in this sample of FCs. Based on the unconditional HLM model, these FCs reported clinically significant levels of anxiety at the time of the patients' simulation visit that decreased only slightly over the course of

the study. Higher levels of depression and morning fatigue in FCs at the time of the simulation visit as well as caring for a younger patient were associated with increased anxiety. In addition, the level of FC sleep disturbance at baseline had a significant impact on the trajectories of FC anxiety.

These studies revealed a high prevalence of symptoms which had a negative effect on functional status and QOL in FCs of patients undergoing RT for prostate cancer. HLM analyses highlighted the large amount of variability in fatigue and anxiety in these FCs. The symptoms of fatigue and anxiety in FCs evidenced the influence of the patient characteristics as predictors.

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Introduction

The body of this work consists of four papers. The first paper, titled "A Review of the Literature on the Symptom Experience of Family Caregivers (FCs) of Patients with Cancer", provided a synthesis and critique of the studies on five common symptoms (i.e., depression, anxiety, sleep disturbance, fatigue, pain) in FCs of patients with cancer.

The second paper, titled "Prevalence, Severity, and Impact of Symptoms in Family Caregivers of Patients at the Initiation of Radiation Therapy (RT) for Prostate Cancer" determined the prevalence and severity of depression, anxiety, pain, sleep disturbance, and fatigue in FCs of patients at the initiation of RT. In addition, the relationships among these symptoms and between these symptoms and FC outcomes of functional status and quality of life (QOL) were examined. The third aim focused on an evaluation of differences in functional status and QOL between those FCs with low and high levels of these five symptoms. Findings from this study suggest that a high percentage of FCs experienced clinically significant levels of a variety of symptoms at the initiation of the patients' RT for prostate cancer. Based on established cutpoints for each symptom inventory, 12.2% of the FCs had clinically significant levels of depression, 40.7% anxiety, 15.0% pain, 36.7% sleep disturbance, 30.0% evening fatigue, and 33.3% morning fatigue. These symptoms had a negative effect on the FCs functional status and QOL.

These findings validated an interest in symptoms in FCs not only at the initiation of RT but during and after the course of RT. The trajectory of evening and morning fatigue in FCs during this six month time period was examined in the third paper titled, Trajectories of Fatigue in Family Caregivers of Patients Undergoing Radiation Therapy

for Prostate Cancer." The purposes of this study were to examine how ratings of evening and morning fatigue changed from the time of the simulation visit to four months after the completion of RT and to investigate whether specific personal, environmental, health and illness, and symptom characteristics in FCs as well as personal, disease, and symptom characteristics in the patient predicted the initial levels of fatigue and/or characteristics of the trajectories of evening or morning fatigue in FCs.

Hierarchical linear modeling (HLM) based on full maximum likelihood estimation was used to answer the study aims. Evening fatigue in FCs increased over the course of the patients' RT and then declined after the completion of RT. Baseline level of sleep disturbance in the FC and the baseline level of evening fatigue in the patient predicted the inter-individual differences in the intercept for evening fatigue. Of note, even after controlling for FCs' level of fatigue at the beginning of RT, evening fatigue in the FC predicted inter-individual variability in both the linear and the quadratic components of the evening fatigue trajectories.

Changes in morning fatigue over the course of the patients' RT fit a linear model with fatigue scores decreasing over time. The three variables that predicted inter-individual differences in the intercept for morning fatigue were levels of trait anxiety in FCs, levels of perceived family support, and levels of morning fatigue in the patient at the beginning of RT. Eight morning fatigue trajectories were identified based on these three predictors of inter-individual variability.

The fourth paper, titled Trajectories of Anxiety in Family Caregivers of Patients Undergoing Radiation Therapy for Prostate Cancer" was undertaken because anxiety was found to be a highly prevalent symptom in this group of FCs. In addition, trait anxiety

was found to be a predictor of morning fatigue in FCs. Again, HLM was used to analyze the trajectories of anxiety in FCs over the course of RT and for four months following the completion of RT. Based on the unconditional HLM model, this sample of female FCs reported clinically significant levels of anxiety at the time of the patients' simulation visit (i.e., 33.865) that decreased only slightly to 32.535 over the six months of the study. When the final HLM model of anxiety was constructed, sixteen different anxiety trajectories were identified based on the predictors that were found to contribute to the model (i.e., levels of depression, morning fatigue, and sleep disturbance in FCs at the initiation of RT, as well as the patient's age). Higher levels of depression and morning fatigue in FCs at the time of the simulation visit as well as caring for a younger patient were associated with increased anxiety in these FCs. In addition, the level of sleep disturbance that the FCs reported at baseline had a significant impact on the trajectories of their anxiety. Specifically, FCs who reported higher sleep disturbance scores had anxiety scores that remained the same as their baseline scores across the six months of the study.

These studies are the first to examine the prevalence, trajectories, and predictors of symptoms in FCs of patients undergoing RT for prostate cancer Findings from these types of longitudinal studies will help to identify FCs who are at higher risk for severe symptoms and may facilitate the development of more targeted interventions for those at greatest risk.

A Review of the Literature on the Symptom Experience of Family Caregivers of Patients with Cancer

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A Review of the Literature on the Symptom Experience of Family Caregivers of Patients with Cancer

ABSTRACT

PURPOSE/OBJECTIVES: Review of the literature on depression, anxiety, sleep disturbance, fatigue, and pain in family caregivers (FCs) of oncology patients within the context of the Symptom Management Model (SMM) developed at the University of California, San Francisco.

DATA SOURCES: Published research studies and systematic reviews.

DATA SYNTHESIS: Studies of depressive symptoms in FCs of oncology patients were the most numerous; only a limited number of studies on anxiety, fatigue, sleep disturbance; and pain. Most studies focused on the symptom experience dimension of the UCSF SMM.

CONCLUSIONS: Based on the small sample sizes, cross-sectional nature of the studies, and lack of comparison groups, little is known about the prevalence and impact of symptoms on FCs of oncology patients.

IMPLICATIONS FOR NURSING: Additional research is needed to determine the prevalence, severity, and impact of symptoms on FCs. Better descriptive, correlational studies will lead to the development of interventions to improve symptom management in FCs of oncology patients.

INTRODUCTION

Recent reforms in the United States health care system, as well as advances in medical technology have resulted in increased numbers of patients with cancer being cared for at home by family members. In a recent survey by the National Alliance for Caregiving and the American Association of Retired Persons (Belden Russonello & Stewart, 2004), an estimated 44.4 million American caregivers (21% of the adult population) provided unpaid care to an adult. These family caregivers (FCs) fulfill an important role not only for the people they assist, but for society as a whole because their work results in a savings of $257 billion annually (Belden Russonello & Stewart, 2004; Moalosi et al., 2003). As medical management of cancer becomes more complex, FCs deal with extensive coordination of care which includes monitoring, problem solving, and supervision as well as with patients' physical and emotional needs.

In the face of these increasing challenges and responsibilities, FCs often report feeling depressed. However, little is known about the prevalence and severity of other symptoms in FCs of patients with cancer. One can hypothesize that the presence of pre-existing symptoms in FCs may interfere with their ability to assume a caregiving role and to carry it out effectively. In addition, FCs may develop new symptoms or have existing symptoms worsen during the course of their caregiving activities. Finally, unrelieved symptoms and the demands of caregiving may have an impact on the functional status and quality of life (QOL) of FCs.

A review of the literature failed to find any systematic evaluation of the symptom experience of FCs of oncology patients. Therefore, the purpose of this paper is to provide

a review and synthesis of the studies on five highly prevalent symptoms (i.e., depression, anxiety, sleep disturbances, fatigue, pain) in FCs of patients with cancer. Because of the large number of studies on depression in FCs of patients with cancer, this review focuses only on those studies. With regard to anxiety, recent reviews have summarized the prevalence and covariates for anxiety in FCs of patients with dementia (Cooper, Balamurali, & Livingston, 2006), as well as the effectiveness of interventions for anxiety with these FCs (Cooper, Balamurali, Selwood, & Livingston, 2007). Therefore, this paper summarizes the findings from these two reviews and synthesizes the findings from studies of anxiety in FCs of patients with cancer. Because of the limited amount of research on the other three symptoms that is specific to FCs of patients with cancer, studies of FCs of patients with dementia and Parkinson's disease (PD) are included in this review. The studies are reviewed and synthesized within the framework of the Symptom Management Model (SMM) that was developed at the University of California, San Francisco.

SYMPTOM MANAGEMENT MODEL

Briefly, the SMM is a multidimensional model embedded within the three domains of nursing (i.e., person, environment, health and illness) (Dodd et al., 2001; Larson et al., 1994)). The SMM consists of three dimensions (i.e., symptom experience, symptom management strategies, symptom outcomes) that interact within and between each other. This review examines the research on the symptoms of depression, anxiety, sleep disturbance, fatigue, and pain in FCs within the context of the symptom experience, the various components of the symptom management dimension, the impact of symptoms

on FC outcomes (i.e., functional status and QOL), and how the domains of person, environment, and health and illness influence the symptom experience. It is an ideal model to use for this review because it provides a comprehensive framework to synthesize and critique this literature.

METHODS

Comprehensive searches of PubMed and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases from 1990 to 2007 were done using the search terms of caregivers with symptoms, problems, depression, fatigue, sleep problems, anxiety, and pain. Over 75 abstracts were reviewed and a total of 49 studies were identified. These studies were evaluated and the reference lists were checked for additional studies. Five additional papers were identified in this way. A total of 54 studies met the following inclusion criteria: evaluated FCs from the adult cancer, dementia, or PD populations; evaluated some aspect of one of five symptoms (i.e., depression, anxiety, sleep disturbance, fatigue, pain); used a subjective or objective measure to assess one or more of these symptoms; and were published in English. Studies were excluded that evaluated: FCs of patients with end stage disease; bereavement in FCs; FCs of patients younger than 18 years of age; and FCs of patients with other chronic medical conditions. Tables 1 to 5 summarize the study data for each symptom.

LITERATURE REVIEW

Depression

Prevalence and severity of depression – As shown in Table 1, depression was assessed in 36 of the 54 studies (67%) included in this review. Twenty-five of these 36

studies (69%) used the Center for Epidemiologic Studies-Depression (CES-D) Scale (Radloff, 1977) to measure depressive symptoms. A grand weighted mean CES-D score of 13.4 was found for 76% (19 of 25) of the studies that reported their mean CES-D score. This mean score is close to the CES-D cutoff score (i.e., $\geq$ 16) and indicates a relatively high level of depressive symptoms. Of note, in a study of the psychometric properties of the CES-D, Hann et al. (1999) compared cancer patients to healthy controls and reported a CES-D score of 7.8 for the healthy controls. Twelve studies reported the percentage of FCs who scored above the cutoff on the CES-D. These percentages ranged from 20% to 73%.

Only one of the 36 studies (3%) used the Beck Depression Inventory (BDI) (Beck & Steer, 1993) to measure depression in FCs of breast cancer patients undergoing autologous bone marrow transplant (Gaston-Johansson, Lachica, Fall-Dickson, & Kennedy, 2004). The mean score for the sample was 7.5, which is within normal limits for this instrument. However, some scores were as high as 26, which suggests that these FCs were experiencing high levels of depressive symptoms. Four studies (11%) used the Profile of Mood States (McNair, Lorr, & Dropplemenn, 1971) and three studies (8%) used the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) to measure depression in FCs of patients with cancer.

Changes in severity and duration of depression – As shown in Table 1, the duration of the 14 descriptive studies that assessed for changes in the severity and duration of depressive symptoms ranged from 4 weeks (Passik & Kirsh, 2005) to 12 months (M. E. Kurtz, Kurtz, Given, & Given, 2004; Langer, Abrams, & Syrjala, 2003).

In 4 studies, FCs were followed for 6 months. All but one study (B. Given & Given, 1992) reported that depressive symptoms in FCs decreased over time.

Relationship between depression and other symptoms – Eight of the 36 studies (22%) examined the association between depression and other symptoms in FCs (Table 1). Both Carter and Chang (2000) and Cho et al. (2006) found that FCs who reported higher levels of depression reported higher levels of sleep disturbance. In a qualitative study (Carter, 2002), FCs stated that chronic sleep disturbance led them to feel irritable and then led to anger, guilt, and depressive symptoms. Three studies (Flaskerud, Carter, & Lee, 2000; Gaston-Johansson et al., 2004; Iconomou, Viha, Kalofonos, & Kardamakis, 2001) found positive correlations between depression and anxiety. One study (Cho et al., 2006) found a positive correlation between depression and fatigue. Finally, Kozachik (2001) found that the FCs' baseline depression score was a significant predictor of depression in subsequent weeks.

Management of depression – Only 6 of the 36 studies (17%) tested an intervention to decrease depressive symptoms in FCs (Table 1). In a randomized clinical trial (RCT) that examined changes in the psychological status of FCs of patients surgically treated for cancer (Jepson, McCorkle, Adler, Nuamah, & Lusk, 1999), the overall psychosocial status of FCs improved from baseline to 3 months and remained the same at 6 months in both the intervention and control groups. No differences in any of the outcome measures were found between the two groups except in those FCs with physical problems. Among those FCs with physical problems, the psychosocial status of the treatment group declined at 3 months compared to the control group and the opposite

pattern was seen at 6 months. The authors concluded that FCs with physical problems were at increased risk for psychological morbidity, which may have a delayed onset. In addition, the home care intervention may have been an extra burden to those FCs with physical problems.

In a RCT that tested the effects of a psychoeducational intervention for depressive symptoms in FCs of patients with cancer (Kozachik et al., 2001), no differences in CES-D scores were found between the experimental and control groups. In both groups, depressive symptoms decreased over time. FC depression at baseline and the number of nursing interventions was regressed on FC depression at 3 and 6 months in separate regression models. At 6 months, a non-significant inverse relationship was found between the number of nursing interventions and the FC's level of depression. This finding suggests that the nursing intervention had started to have an affect on FC's level of depression.

In another study (M.E. Kurtz, Kurtz, Given, & Given, 2005), the use of a nursing intervention that focused on teaching both FCs and patients the skills to better manage the patients' symptoms did not reduce depressive symptoms in FCs. In a fourth study that evaluated the effects of a problem solving intervention (Toseland, Blanchard, & McCallion, 1995), no significant differences in levels of depressive symptoms were found between the experimental and control groups. In the only study that focused on patients who underwent a bone marrow transplant (Langer et al., 2003), a recovery workshop conducted in a group format did not effect FC depression scores. Finally, in a

pilot study of a brief behavioral sleep intervention (Carter, 2006), no improvements were noted in the depression scores of FCs in the intervention group.

Depression and symptom outcomes – Only five of the 36 studies (14%) evaluated the relationship between depression and one of the eight outcomes from the SMM in FCs of patients with cancer (Table 1). Four of these studies focused on QOL as the outcome measure and found that higher levels of depressive symptoms were associated with lower QOL scores. In another study (Ferrario, Zotti, Massara, & Nuvolone, 2003a), higher levels of depression were associated with less satisfaction with life.

Depression and the person domain – As shown in Table 1, 19 of the 36 studies (53%) evaluated the relationship between some aspect of the person domain and depression. The relationships between depression and various demographic characteristics were assessed in 10 studies. Only one study (M.E. Kurtz et al., 2005) examined the relationship between age and depression and found that younger FCs had higher depression scores. In 5 studies (Cho et al., 2006; Hagedoorn, Buunk, Kuijer, & Wobbes, 2000; Iconomou et al., 2001; Langer et al., 2003; Tuinstra et al., 2004), female FCs reported higher depression scores than male FCs, while in one study (Kozachik et al., 2001), the exact opposite was found. Findings on the relationship between education and depression are contradictory. Three studies found that lower levels of education were associated with higher levels of depression (Iconomou et al., 2001; Nijboer, Triemstra, Tempelaar, Sanderman, & Van den Bos, 1999a; Raveis, Karus, & Siegel, 1998), while one study found that higher levels of education were associated with higher depression scores (M. E. Kurtz et al., 2004).

The relationship between depression and a number of personality characteristics of the FC was assessed in four studies (C.W. Given et al., 1993; Kim, Duberstein, Sorensen, & Larson, 2005; M. E. Kurtz, Kurtz, Given, & Given, 1995; Nijboer, Tempelaar, Triemstra, van den Bos, & Sanderman, 2001). FCs who were more optimistic reported lower levels of depressive symptoms (C.W. Given et al., 1993; M. E. Kurtz et al., 1995). In contrast, FCs with higher levels of neuroticism had more depressive symptoms (Kim et al., 2005; Nijboer et al., 2001). Four studies (Campbell et al., 2004; M. E. Kurtz et al., 2004; M.E. Kurtz et al., 2005; Nijboer et al., 2001) found that FCs with higher levels of self-esteem or a sense of mastery of care reported lower levels of depressive symptoms.

Two of the 36 studies (6%) (Carter, 2002; Iconomou et al., 2001) reported on how marital status influenced depression in FCs. Carter (2002) found that spouse FCs were significantly less depressed than non-spouse FCs. In contrast, Iconomou et al. (2001) found that partners were more depressed than non-partners.

Depression and the environmental domain – In this review, patients are seen as part of the environment in the sense that they make up a very large part of the caregiving environment and can influence the responses of the FCs. Twenty-five of the 36 studies (69%) assessed the relationship between a number of environmental variables and depressive symptoms in FCs (Table 1). Two studies found that FCs had higher depression scores than the general population or age-matched control groups (Clavarino, Lowe, Carmont, & Balanda, 2002; Hagedoorn et al., 2000). In one study (B. Given & Given, 1992), FCs of patients with recurrent cancer reported higher levels of depression than

FCs of patients with newly diagnosed cancer. Similar results were seen in a study that examined the relationship between the patients' stage of disease and depression in FCs (M.E. Kurtz et al., 2005).

In a study of the interaction of age, symptoms, and survival status of patients on the physical and mental health of FCs (M. E. Kurtz, Kurtz, Given, & Given, 1994), the patient variables of younger age, increased symptoms, and increased immobility were associated with increased depressive symptoms in FCs. These findings were replicated in a subsequent study (M. E. Kurtz et al., 2004) that assessed both patient variables and a variety of aspects of the FC experience (i.e., increased impact on schedule, increased sense of family abandonment, and decreased social function) and found that all of these variables were associated with increased levels of depressive symptoms in FCs of patients with cancer. Given et al. (1992; 1993) also reported that increased disruptions in the schedule of FCs were associated with increased levels of depressive symptoms.

Eleven studies shown in Table 1, found that a larger number of symptoms and increased symptom severity in patients were associated with increased depressive symptoms in FCs. Three studies assessed the patients' pain (Carter & Chang, 2000; Flaskerud et al., 2000; C. Miaskowski, Kragness, Dibble, & Wallhagen, 1997) and found that higher levels of pain in patients were associated with higher FC depression scores. One study examined the impact of the marital relationship on FC's level of depression (Williamson & Schulz, 1995a) and found that FCs who were in relationships with the patient prior to the onset of illness that were characterized by mutual demonstrations of concern and responsiveness to each other's needs reported lower levels of depression.

Finally, in five studies (Ferrario et al., 2003a; Flaskerud et al., 2000; Gaston-Johansson et al., 2004; Iconomou et al., 2001; Sherwood et al., 2006) higher levels of caregiver strain were associated with higher levels of depression in FCs.

Depression and the health and illness domain – As shown in Table 1, eight of the 36 studies (22%) examined the relationship between the health and illness domain and depressive symptoms in FCs. In general, these studies reported that higher depression scores were associated with increased numbers of comorbid conditions or poorer health status in FCs of oncology patients.

Anxiety

Systematic reviews of anxiety in FCs of patients with dementia – A synthesis of the thirty-three studies that evaluated the prevalence of and covariates for anxiety in FCs of patients with dementia (Cooper et al., 2006) found that clinically significant levels of anxiety were present in 25% of FCs and was more common than in age-matched controls. Covariates associated with higher levels of anxiety included confrontative and escape avoidance coping, higher FC burden, and poorer FC health. In a second systematic review, that focused on intervention studies for anxiety in these FCs (Cooper et al., 2007), a total of 24 studies were identified that met the authors' inclusion criteria. Of note, only one study had anxiety as the primary outcome variable; most of these intervention studies were focused on depression. The authors concluded that no cognitive-behavioral intervention was found to be effective for the treatment of anxiety in FCs of patients with dementia.

Prevalence and severity of anxiety – As shown in Table 2, anxiety was assessed in 14 of the 54 studies (26%) that examined the symptom experience of FCs of patients with cancer. Multiple instruments were used to evaluate anxiety in these FCs. Three studies (Campbell et al., 2004; Langer et al., 2003; C. Miaskowski et al., 1997) used the anxiety subscale of the Profile of Mood States (POMS) Short Form (Shacham, 1983). Anxiety scores ranged from 1.0 to 9.6 across these three studies. No interpretation of these levels of anxiety was given, although after allowing for differences in scoring, this range indicates mild to moderate anxiety.

Flaskerud et al. (2000) assessed a variety of symptoms including anxiety in FCs of patients with dementia and cancer using the three item anxiety subscale of the Symptom Checklist-90 Revised (Derogatis, 1994). A higher percentage of FCs of patients with cancer (85%) reported feeling nervous or shaky compared to only 38% of the FCs of patients with dementia ($p = 0.007$).

The State Anxiety Inventory (STAI-State) (Spielberger, Gorsuch, Suchene, Vagg, & Jacobs, 1983) was used to assess anxiety in three studies (Ferrario et al., 2003a; Gaston-Johansson et al., 2004; Toseland et al., 1995). The mean state anxiety scores were similar across these three studies and indicated a moderate level of state anxiety (Spielberger et al., 1983). Ferrell et al. (1999) used the Quality of Life-Family Tool (B. R. Ferrell, Dow, & Grant, 1995) to measure on a scale that ranged from 0 (“best outcome”) to 10 (“worst outcome”). FCs reported a mean anxiety score of 5.8, which was significantly higher than the scores reported by patients (i.e., 5.2, $p = 0.03$).

Three studies (Clavarino et al., 2002; Cliff & Macdonagh, 2000; Iconomou et al., 2001) used the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) to assess anxiety in FCs. In two studies (Clavarino et al., 2002; Cliff & Macdonagh, 2000), 20% to 40% of the FCs scored above the cutoff for clinically significant levels of anxiety.

Changes in severity and duration of anxiety – Only one of the 14 studies (7%) assessed for changes in anxiety over time (Walsh, Culpepper Martin, & Schmidt, 2004), as part of a pre-test/post-test design and found decreases in FC anxiety scores over time.

Relationship between anxiety and other symptoms – Twenty-one percent (3 of 14) of the studies that evaluated anxiety symptoms assessed for relationships with other symptoms (Flaskerud et al., 2000; Gaston-Johansson et al., 2004; Iconomou et al., 2001). All three found positive correlations between anxiety and depression. In addition, Flaskerud et al. (2000) found that higher anxiety scores were correlated not only with higher depression scores, but with higher anger scores and more sleep problems. Gaston-Johansson et al. (2004) reported that higher anxiety scores were correlated with higher fatigue scores.

Management of anxiety – Three of the 14 studies (21%) tested an intervention to decrease anxiety (Langer et al., 2003; Toseland et al., 1995; Walsh et al., 2004). In a group intervention with patients and FCs that focused on recovery after bone marrow transplantation (Langer et al., 2003), no differences in FCs anxiety scores were found between the intervention and the control groups. Positive results were reported by Walsh et al. (2004), who used a creative arts intervention to reduce anxiety in FCs. A significant

reduction in anxiety scores was found immediately after the intervention ($t = -5.0$, $p < 0.001$). However, in a six session intervention program that consisted of support, problem solving, and coping skills (Toseland et al., 1995), no significant changes in FCs anxiety scores were reported.

Anxiety and symptom outcomes – Only three of the 14 studies (21%) evaluated the relationship between anxiety and one of the eight outcomes from the SMM (Ferrario et al., 2003a; Gaston-Johansson et al., 2004; Iconomou et al., 2001). Two of these studies focused on QOL (Gaston-Johansson et al., 2004; Iconomou et al., 2001) and found that higher anxiety scores in FCs were associated with decreases in QOL. Ferrario et al. (2003a) reported that higher levels of trait and state anxiety were associated with less satisfaction with life.

Anxiety and the person domain – Eight of the 14 studies (57%) evaluated the relationship between some aspect of the person domain and anxiety (Table 2). Campbell et al. (2004) found that lower anxiety scores were reported by FCs who reported greater overall confidence in assisting patients with symptom control and in FCs who reported greater confidence in helping patients to cope with their symptoms. In four studies (Gaston-Johansson et al., 2004; Iconomou et al., 2001; Langer et al., 2003; Matthews, 2003), higher anxiety scores were reported by female FCs. In addition, FCs who were not married and had lower incomes reported higher anxiety scores (Gaston-Johansson et al., 2004). In one study (Segrin, Badger, Dorros, Meek, & Lopez, 2006), FCs with higher anxiety scores reported a poorer quality relationship with the patient.

Anxiety and the environmental domain – Seven of the 14 studies (50%) assessed anxiety levels and some aspect of the environmental domain (Table 2). Two studies (Clavarino et al., 2002; Langer et al., 2003) found that FCs of patients with cancer had higher anxiety scores than non-FCs. In the only comparison study of two patient samples (Flaskerud et al., 2000), FCs of patients with cancer reported higher anxiety scores than FCs of patients with dementia. In two studies (Flaskerud et al., 2000; C. Miaskowski et al., 1997), FCs who cared for patients with cancer pain reported higher anxiety scores than FCs of pain free patients. Finally, two studies (Ferrario et al., 2003a; Iconomou et al., 2001) found that higher anxiety scores were associated with higher levels of caregiver strain.

Anxiety and the health and illness domain – Only one study of the 14 (7%) evaluated the relationship between anxiety and the health and illness domain. Iconomou et al. (2001) found that higher anxiety scores were associated with FC's reports of poorer health status.

Sleep Disturbance

Prevalence and severity of sleep disturbance – As shown in Table 3, sleep disturbance was assessed in 20 of the 54 studies (37%) that examined a variety of symptoms in FCs of patients with cancer, dementia, or PD.

Ten of these 20 studies (50%) used the Pittsburg Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) to measure sleep disturbance. A grand weighted mean PSQI score of 8.5 was found for 8 of these 10 studies that reported their sample's score (Carter, 2002, 2006; Carter & Chang, 2000; Cho et al., 2006;

McCurry, Logsdon, Vitiello, & Teri, 1998; McKibbin et al., 2005; Pal et al., 2004; Wilcox & King, 1999). This mean score is higher than the PSQI cutoff of 5 that indicates a moderate level of sleep disturbance in these FCs of patients with cancer, dementia, or PD.

The 10 remaining studies used different instruments to evaluate sleep. Four studies (Hosaka & Sugiyama, 2002; Mizuno, Hosaka, Ogihara, Higano, & Mano, 1999; Secker & Brown, 2005; Woods, Wills, Higginson, Hobbins, & Whitby, 2003) used various versions of the General Health Questionnaire (GHQ), which is a widely used 28 to 30 item scale that evaluates psychiatric morbidity. Sleep disturbance scores on the GHQ ranged from 1.5 to 12.7.

In another study of sleep disturbance in FCs of elderly Japanese patients with dementia (Sato, Kanda, Anan, & Watanuki, 2002), EEG patterns as well as perceptions of sleep disturbance were assessed using the Sleep Evaluation Questionnaire (SEQ) (Parrott & Hindmarch, 1980). The sleep quality ratings for FCs (i.e., more restless versus more restful, more periods of wakefulness versus fewer periods of wakefulness) were significantly lower than those for non-FCs. EEG testing showed that FCs had a significantly higher percentage of Stage 1 sleep and a lower percentage of Stage 2 sleep with more awake time during the second cycle, and higher percentages of Stages 3 and 4 sleep during the third cycle than non-FCs. These data suggest that changes in sleep EEGs of FCs were associated with higher perceived sleep disturbance scores and higher sleep needs.

The percentage of self-rated sleep disturbance in patients with PD and their FCs (Smith, Ellgring, & Oertel, 1997) was compared to healthy controls in a study that used the Zung Self-Rating Depression Scale (SDS) (Zung, 1976). One sleep question (i.e., "I cannot sleep well at night") taken from the SDS along with one other question (i.e., "I can no longer sleep through the night because my partner needs help") were used to assess sleep disturbance. FC sleep disturbance scores were higher than those reported by patients with PD and significantly higher than the scores for healthy controls. In another study of FCs of patients with PD (Happe & Berger, 2002), a single item from the CES-D about having a bad night's sleep in the past week was used to assess the prevalence of sleep disturbance. Twenty-seven percent of the FCs were categorized as having a significant amount of sleep disturbance. Despite the number of different instruments used, all of the studies that assessed sleep disturbance found moderate to severe sleep problems in 25% to 95% of FCs.

Changes in severity and duration of sleep disturbance – Only one descriptive study of the 20 (5%) assessed for changes in sleep disturbance over time (Carter, 2003) and found that PSQI sleep disturbance scores were highly variable from week to week. Of note, FCs typically underrated their sleep disturbance when compared with actigraphic measures. FCs reported a mean sleep duration of 6.1 hours, whereas by actigraphy it was estimated to be 4.8 hours. Likewise, self-reports of sleep efficiency were at 80%, but when measured by actigraphy, were found to be 74%. Sleep latency was highly variable across time.

Relationship between sleep disturbance and other symptoms – Nine of the 20 studies (45%) examined the associations between sleep disturbance and other symptoms in FCs. Eight of these studies found that FCs who reported higher sleep disturbance scores reported higher levels of depression (Table 3). Two studies (Cho et al., 2006; Sato et al., 2002) found that higher sleep disturbance scores were associated with higher levels of fatigue. A similar relationship was found between sleep disturbance and anxiety (Flaskerud et al., 2000; Pal et al., 2004) and sleep disturbance and anger (Carter, 2002; Flaskerud et al., 2000).

Management of sleep disturbance – Six of the 20 studies (30%) tested an intervention to decrease sleep disturbance in FCs (Table 3). Three intervention studies demonstrated significant improvements in sleep disturbance scores (McCurry et al., 1998; Secker & Brown, 2005; Woods et al., 2003). The first study (McCurry et al., 1998), tested two interventions to improve sleep quality in FCs of patients with dementia. The first intervention was given over a 6 week period and consisted of group sessions regarding sleep hygiene, stimulus control, and sleep compression strategies. The second intervention covered the same information on an individual basis over 4 weeks. Data from both intervention studies were pooled and the results showed significant improvements in sleep scores from baseline. In a study of FCs of patients with dementia (Woods et al., 2003), referral to a specialist in mental health nursing services resulted in a significant reduction in sleep disturbance scores in these FCs 8 months after the intervention. Finally, the use of a cognitive behavioral therapy (CBT) intervention (Secker & Brown, 2005), given over 12 to 14 weeks, resulted in significant

improvements in insomnia in FCs of patients with dementia 3 months after the intervention. The three negative intervention studies evaluated a structured 5 week psychoeducational intervention (Mizuno et al., 1999), an intervention that consisted of education, relaxation training, and group discussion (Hosaka & Sugiyama, 2002), and a brief behavioral sleep intervention (Carter, 2006).

Sleep disturbance and symptom outcomes – Only two studies (Cho et al., 2006; McKibbin et al., 2005) examined the relationship between sleep disturbance and FC outcomes. Cho (2006) found that higher levels of sleep disturbance were associated with lower QOL scores in FCs of patients with cancer. McKibbin (2005) found that increased levels of sleep disturbance were associated with decreased functional status in FCs of patients with dementia.

Sleep disturbance and the person domain – Five of the 20 studies (25%) evaluated the relationship between some aspect of the person domain and sleep disturbance (Cho et al., 2006; McCurry et al., 1998; McKibbin et al., 2005; Smith et al., 1997; Wilcox & King, 1999). Conflicting results were reported on gender differences in sleep disturbance. In a study of FCs of patients with cancer (Cho et al., 2006), no differences in sleep disturbance scores were found between males and females. In contrast, in a study of FCs of patients with PD (Smith et al., 1997), women reported significantly higher sleep disturbance scores than men.

In terms of age differences, one study found that older FCs of patients with dementia (McKibbin et al., 2005) reported lower levels of sleep efficiency, less slow wave sleep, and more Stage 1 sleep than younger FCs. Wilcox (1999) found higher levels

of daytime dysfunction in younger FCs of patients with dementia. One intervention study (McCurry et al., 1998) found that FCs of patients with dementia who responded to the intervention were younger and more adherent with treatment procedures.

Sleep disturbance and the environmental domain – Nine of the 20 studies (45%) assessed the relationship between the environmental domain and sleep disturbance (Table 3). In three studies that evaluated FCs of patients with dementia (Sato et al., 2002; Smith et al., 1997; Wilson, 1989), FCs of these patients had higher sleep disturbance scores than non-FCs. In four studies that evaluated FCs of patients with cancer (Passik & Kirsh, 2005), PD (Wilcox & King, 1999), and dementia (McKibbin et al., 2005; Wilcox & King, 1999), FCs who cared for sicker patients reported more sleep disturbance. In the only study that compared two groups of FCs (Flaskerud et al., 2000), FCs of patients with cancer reported more sleep disturbance than FCs of patients with dementia.

Sleep disruption and the health and illness domain – No studies assessed the relationship between the health and illness domain and sleep disturbance in FCs of patients with cancer, dementia, or PD.

Fatigue

Prevalence and severity of fatigue – As shown in Table 4, fatigue was assessed in 11 of the 54 studies (20%) that examined the symptom experience of FCs of patients with cancer, dementia, or PD.

Three studies used the Piper Fatigue Scale (PFS) (Piper et al., 1998) to measure fatigue severity (Clark, 2002; Gaston-Johansson et al., 2004; S. Jensen & Given, 1991). It was not possible to calculate a grand weighted mean PFS score because these studies

used different versions of PFS. On average, FCs reported moderate levels of fatigue. However, wide variability in fatigue scores was noted in these three studies. Three studies (Campbell et al., 2004; Hosaka & Sugiyama, 2002; C. Miaskowski et al., 1997) used the Profile of Mood States (POMS) (McNair, Lorr, & Droppleman, 1992) to evaluate fatigue in FCs. The grand weighted mean fatigue score was 8.8, which reflects a moderate level of fatigue (moderate = 7.1 to 11.0).

Five studies each used a different instruments to assess fatigue in FCs (Cho et al., 2006; B.R. Ferrell et al., 1999; Passik & Kirsh, 2005; Sato et al., 2002; Teel & Press, 1999). All of these studies found moderate levels of fatigue in FCs of patients with cancer, PD, and dementia.

Changes in severity and duration of fatigue – No studies assessed changes in the severity or duration of fatigue in FCs over time.

Relationship between fatigue and other symptoms – Three of the 11 studies (27%) evaluated the relationships between fatigue severity and other symptoms (Cho et al., 2006; Clark, 2002; Gaston-Johansson et al., 2004). In these three studies, higher fatigue scores were associated with higher depression scores. Similar relationships were found between fatigue and anxiety (Gaston-Johansson et al., 2004) and fatigue and sleep disturbance (Cho et al., 2006) scores.

Management of fatigue – Only one of the 11 studies (9%) evaluated the impact of an intervention for FCs of patients with dementia (Hosaka & Sugiyama, 2002). The use of a 5 week intervention that consisted of education, progressive relaxation, and group discussion resulted in a significant decrease in FCs' levels of fatigue.

Fatigue and symptom outcomes – Two of the 11 studies (18%) evaluated the relationship between fatigue and one of the eight outcomes from the SMM (Cho et al., 2006; Gaston-Johansson et al., 2004). Both of these studies found that higher levels of fatigue were associated with lower QOL scores in FCs.

Fatigue and the person domain – Four of the 11 studies (36%) evaluated the relationship between some aspect of the person domain and fatigue (Campbell et al., 2004; Cho et al., 2006; Clark, 2002; Gaston-Johansson et al., 2004). In one study (Cho et al., 2006), higher fatigue scores were reported by female FCs of cancer patients. In another study of FCs of patients with cancer (Gaston-Johansson et al., 2004), higher fatigue scores were found in FCs with lower incomes.

The relationships between fatigue and some personality characteristics of the FC were assessed in two studies (Campbell et al., 2004; Clark, 2002). FCs with greater overall confidence in their ability to assist patients with symptom control or with coping reported lower levels of fatigue (Campbell et al., 2004). FCs of patients with dementia who reported higher levels of individual hardiness reported lower fatigue scores (Clark, 2002).

Fatigue and the environmental domain – Five of the 11 studies (45%) assessed the relationship between fatigue and some aspect of the environmental domain. Two studies (Sato et al., 2002; Teel & Press, 1999) found that FCs of patients with cancer, dementia, and PD had higher fatigue scores than non-FCs. FCs who cared for patients with a higher number of memory and behavior problems reported higher levels of fatigue (Clark, 2002). Finally, two studies found that FCs who reported higher levels of caregiver strain

(Passik & Kirsh, 2005) or a greater impact of caregiving on their schedule (S. Jensen & Given, 1991), reported higher levels of fatigue.

Fatigue and the health and illness domain – No studies were found that assessed the relationship between the health and illness domain and fatigue in FCs.

Pain

As shown in Table 5, only one study of the 54 (2%) evaluated pain in FCs of patients with cancer, dementia, or PD (Kuzu et al., 2005). In this study of FCs of patients with dementia, the FCs mean pain intensity score was 37.5 using the Duke Pain Scale. An educational intervention that included structured and tailored components focused on patients and FCs problems had no effect on the FCs pain.

In addition, two studies were found that mentioned pain in FCs. In a study of FCs and cancer pain management (B.R. Ferrell et al., 1999), FCs reported their concerns about their QOL and about the management of cancer pain. Their own pain was rated as one of the top 5 symptoms on the physical well-being subscale of the FC-QOL (B. R. Ferrell et al., 1995). In a study of sleep in older women FCs of patients with dementia (Wilcox & King, 1999), the most common reasons for sleep difficulties among FCs were "needing to use the bathroom" (83%), "feeling too hot" (39%), and "having pain" (34%).

SUMMARY AND CRITIQUE

This paper is the first to provide a comprehensive review of five highly prevalent symptoms in FCs of patients with cancer, dementia, or PD within the context of the UCSF SMM (Dodd et al., 2001). Despite the large number of FCs currently providing care to adults in the United States, little is known about their symptoms. Only 54 studies

were found that examined symptoms in FCs of patients with cancer, dementia, or PD. Given the fact that the burden of caregiving will increase as the population ages, more research is needed on these symptoms in FCs.

Of note, studies of depressive symptoms in FCs of oncology patients were the most numerous (i.e., a total of 36 studies). In contrast only 14 studies evaluated anxiety, 9 evaluated sleep disturbances, and 8 evaluated fatigue in FCs of oncology patients. No studies were found that examined pain in this group of FCs.

Across the five symptoms, the majority of the studies focused on some aspect of the symptom experience dimension of the SMM. However, based on the cross-sectional nature of the studies, the relatively small sample sizes, the lack of comparison groups, little is known about the incidence or prevalence rates of these five symptoms in FCs of patients with cancer. In addition, virtually no information is available on the multiple dimensions of each symptom and changes in the symptom experience over time.

Thirteen studies have tested interventions to decrease symptoms in FCs of patients with cancer, dementia, or PD. Six of these studies tested psychoeducational interventions to decrease depressive symptoms (Hosaka & Sugiyama, 2002; Jepson et al., 1999; Kozachik et al., 2001; M.E. Kurtz et al., 2005; Toseland et al., 1995; Woods et al., 2003). The total number of FCs enrolled in these studies ranged from 30 to 161 and evaluations occurred following one session or after 12 months. Five of the interventions had no effect on FCs depression scores (Carter, 2006; Kozachik et al., 2001; M.E. Kurtz et al., 2005; Langer et al., 2003; Toseland et al., 1995) and one study reported worsening

and improvements in depression scores based on specific FC characteristics (Jepson et al., 1999).

Only one study was found that tested a creative arts intervention to for anxiety (Walsh et al., 2004) and found that this intervention decreased anxiety in the 40 FCs who used it. Only six studies were found that attempted to test interventions to improve sleep in FCs of patients with cancer (Carter, 2006), dementia (Hosaka & Sugiyama, 2002; McCurry et al., 1998; Mizuno et al., 1999; Woods et al., 2003) and PD (Secker & Brown, 2005). Findings from four of these studies suggest that a variety of interventions were effective in improving sleep (Carter, 2006; McCurry et al., 1998; Secker & Brown, 2005; Woods et al., 2003). Interestingly, one study tested the effectiveness of an intervention on three symptoms (i.e., fatigue, anxiety, and sleep disturbance) simultaneously (Hosaka & Sugiyama, 2002). This intervention, which had both psychosocial and psychoeducational components, reduced anxiety and fatigue but had no effect on sleep disturbance.

A minimum of eight outcomes (i.e., functional status, symptom status, self-care, costs, QOL, morbidity and comorbidity, mortality, emotional status) can be evaluated within the context of the SMM. Of the 7 studies (13%) that examined the relationship between a symptom and an outcome, only QOL (Cho et al., 2006; Gaston-Johansson et al., 2004; Hagedoorn et al., 2000; Iconomou et al., 2001; Nijboer et al., 1999a), functional status (McKibbin et al., 2005) and satisfaction with life (Ferrario et al., 2003a) were evaluated.

As one examines the various components of the SMM in relationship to the symptom studies of FCs, it is interesting to note that the vast majority of these 54 studies

examined one or more interdependent factors that affect the various dimensions of the SMM (i.e., person, environment, health and illness). In the 28 studies (52%) that examined some aspect of the person domain, the most common FC characteristics that were evaluated included gender, education, income, and a variety of personality characteristics (i.e., self-esteem, optimism, self-efficacy). However, because the majority of these studies evaluated rather disparate characteristics from the person domain, no definitive conclusions can be drawn about the relationships between these person characteristics and the symptom experiences of FCs of patients with cancer, dementia, or PD.

Thirty-five studies (65%) examined some aspect of the environmental domain and the symptoms of FCs of patients with cancer, dementia, or PD. The two aspects of the environmental domain that were examined most frequently were some characteristic of the patient as the FCs' environment or some aspect of the FC experience (i.e., caregiver burden, demands of caregiving on schedule). One consistent finding across the various studies was that FCs who cared for patients who were sicker (i.e., more symptoms, advanced stage disease) reported higher symptom scores. In addition, in most of these studies, higher symptom scores were associated with higher burden scores.

Only 8 studies (15%) examined the relationship between symptoms in FCs and their health or illness (C.W. Given et al., 1993; Iconomou et al., 2001; Jepson et al., 1999; M. E. Kurtz et al., 1994; M.E. Kurtz et al., 2005; Nijboer et al., 1999a; Raveis et al., 1998; Sherwood et al., 2006). All of these studies focused on the symptom of depression.

Again, based on this limited amount of research no definitive conclusions can be drawn at the present time.

METHODOLOGIC ISSUES IN THE STUDIES OF SYMPTOMS IN FAMILY CAREGIVERS

In terms of the demographic characteristics of the FCs evaluated in the 54 studies of symptoms in FCs (two studies had more than one publication on the same sample), a total of 5,645 participants were included in these studies with sample sizes that ranged from 10 to 491. The mean age of the FCs was 56.3 years and approximately 66% of the participants were female. In addition, the majority of the FCs were Caucasian and well-educated and had middle-income levels. The number of FCs included in these studies is extremely small given the fact that an estimated 44.4 million Americans are FCs (Belden Russonello & Stewart, 2004). In addition, the demographic characteristics of these FCs limit the generalizability of the study findings.

In terms of study design, 32 of the 54 studies (59%) used a cross-sectional design and 22 (41%) used a longitudinal design to obtain information on symptoms experienced by FCs of patients with cancer, dementia, or PD. Due to the limited number of studies on the symptoms of depression, anxiety, fatigue, and sleep disturbance in FCs, no definitive conclusions can be drawn on the prevalence rates for these symptoms, the demographic characteristics of FCs who are at higher risk of experiencing these symptoms, the negative consequences associated with these symptoms, and the relationship between symptoms in FCs and other aspects of the FC experience. In addition, with the exception of depression, very little is known about changes in FCs symptoms over time.

Only 13 of the 54 studies (24%) were intervention studies. Three of the intervention studies focused only on depression (Jepson et al., 1999; Kozachik et al., 2001; M.E. Kurtz et al., 2005), one only on anxiety (Walsh et al., 2004), four only on sleep (McCurry et al., 1998; Mizuno et al., 1999; Secker & Brown, 2005; Woods et al., 2003), and one only on pain (Kuzu et al., 2005). One study evaluated the effects of the intervention on sleep and depression (Carter, 2006), two on depression and anxiety (Langer et al., 2003; Toseland et al., 1995) and one on anxiety, sleep, and fatigue (Hosaka & Sugiyama, 2002).

Five used a pre-test post-test design (Hosaka & Sugiyama, 2002; Kuzu et al., 2005; Mizuno et al., 1999; Toseland et al., 1995; Walsh et al., 2004) and the remainder were RCTs. In terms of the types of interventions that were evaluated to improve symptoms, ten tested education and support based interventions (Hosaka & Sugiyama, 2002; Jepson et al., 1999; Kozachik et al., 2001; M.E. Kurtz et al., 2005; Kuzu et al., 2005; Langer et al., 2003; McCurry et al., 1998; Mizuno et al., 1999; Secker & Brown, 2005; Toseland et al., 1995), one evaluated the effect of referral to an advanced practice nurse to improve sleep (Woods et al., 2003), and one tested a creative arts intervention to decrease stress and anxiety in FCs (Walsh et al., 2004). Five of the trials demonstrated improvements in FC symptoms (McCurry et al., 1998; Mizuno et al., 1999; Secker & Brown, 2005; Walsh et al., 2004; Woods et al., 2003), four failed to demonstrate improvements in FC outcomes (Kozachik et al., 2001; M.E. Kurtz et al., 2005; Kuzu et al., 2005; Langer et al., 2003), and three trials (Carter, 2006; Jepson et al., 1999;

McCurry et al., 1998) produced mixed results (i.e., some symptoms improved, while others did not improve).

FUTURE DIRECTION FOR RESEARCH

This review demonstrates the paucity of research on symptoms in FCs. Almost any research study would add to the body of knowledge in this emerging field of inquiry. The UCSF SMM provides an excellent conceptual framework to begin to develop descriptive, cross-sectional studies to examine the prevalence, characteristics, management strategies, and outcomes of symptoms in FCs of patients with cancer. In addition, longitudinal studies of both male and female FCs are needed to determine how symptoms in FCs change over time, as well as in relationship to changes in the patients' condition or course of treatment. One critical question that needs to be addressed is the impact of the caregiver role on symptoms in FCs. Without these descriptive studies, and the data they provide, it will be difficult to design intervention studies to improve outcomes in FCs.

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Table 1 - Studies That Evaluated Depression in Family Caregivers of Patients with Cancer

First author, Year, Characteristics of FCs	Symptom Experience	Symptom Management Strategies	Association with other symptoms	Outcomes	Domains of Person, Environment, and Health and Illness
Campbell, 2004 N = 40 Age = 57.6 ± 10.2 Female = 97.5% Design: Cross-sectional	POMS depression score = 3.8 ± 5.1	Not evaluated	Not evaluated	Not evaluated	Person: Lower depression scores were found in FCs who reported greater overall confidence in assisting patients with symptom control and in FCs who reported greater confidence in helping patients to cope with their symptoms.
Carter and Chang, 2000 N = 51 Age = 53.7 ± 14.3 Female = 80.4% Design: Cross-sectional	CES-D score = 18.6 ± 10.9; 52.9 % of FCs had a CES-D score ≥ 16	Not evaluated	Higher depression scores were significantly correlated with higher sleep disturbance scores.	Not evaluated	Environment: Higher patient pain intensity scores were associated with more depressive symptoms in FCs.
Carter, 2002 Subset of the sample from Carter and Chang, 2000 N = 47 Design: Cross-sectional	CES-D score = 19.3 ± 11.1 57% of FCs had a CES-D score ≥ 16	Not evaluated	Chronic sleep loss led to irritability and anger, then guilt, and finally depression.	Not evaluated	Person: Spouse FCs reported significantly lower CES-D scores than non-spouse FCs.
Carter, 2003 N = 10 Mean age = 61.0 Female = 80% Design: Longitudinal, 10 week	In weeks 1-7, 50% of FCs had CES-D scores ≥ 16 In weeks 8-10, 20% of FCs had CES-D scores ≥ 16	Not evaluated	Depressive symptoms and sleep disturbance fluctuated over time.	Not evaluated	Not evaluated
Carter, 2006 N = 30	CES-D scores for the control group at	Brief behavioral	Not evaluated	Not evaluated	Not evaluated

Age = 53.0 ± 17.0 Female = 63% Design: Longitudinal, 4 month	baseline = 17.3 ± 9.5, at 3 weeks = 12.9 ± 9.2, at 5 weeks = 11.8 ± 10.0 For the intervention group at baseline = 16.6 ± 13.0, at 3 weeks = 13.9 ± 8.8, at 5 weeks = 12.7 ± 9.0	sleep intervention that lasted one hour plus a booster did not improve FC depression scores.			
Cho, 2006 N = 103 Age = 48.3 ± 11.4 Female = 78% Design: Cross-sectional	CES-D score = 18.1 ± 8.4 55% of FCs had CES-D scores ≥ 16.	Not evaluated	Higher depression scores were associated with higher levels of fatigue and sleep disturbance.	Higher levels of depression were associated with lower QOL scores.	Person: Female FCs had significantly higher depression scores than male FCs.
Clavarino, 2002 N = 19 Age = 49.5 ± 9.9 Female = 42% Design: Cross-sectional	HADS depression score not reported Non-cases = 76% Borderline cases = 6% Cases = 18%	Not evaluated	Not evaluated	Not evaluated	Person: No differences in depression scores between patients and FCs. Environment: The prevalence of depression in FCs was higher than in the general population (15%).
Cliff, 2000 N = 135 Age = 73.9 ± 7.4 Female = 100% Design: Cross-sectional	HADS mean depression score = 3.6 ± 3.0; 3.0% of FCs had a score of >11	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Ferrario, 2003 N = 50 Age = 46.7 ± 15.0 Female = 56% Design: Cross-sectional	DQ score of validation sample = 6.7 ± 4.8; FC sample = 6.3 ± 5.0	Not evaluated	Not evaluated	Higher levels of depression were associated with less satisfaction with life.	Environment: Higher depression scores were associated with higher levels of caregiver strain and greater need for knowledge of the patient's disease.
Ferrell, 1999	FC QOL tool mean	Not evaluated	Not evaluated	Not evaluated	Not evaluated

N=231 Age = 56 Female = 72% Design: Cross-sectional	depression score = 4.7 ± 2.9				
Flaskerud, 2000 N = 41 Age = 51.5 ± 14.2 Female = 100% Design: Cross-sectional	Mean CES-D score not reported; 50% of the FCs had CES-D scores ≥ 16	Not evaluated	Higher depression scores correlated with higher anxiety, anger, and sleep disturbance scores.	Not evaluated	Environment: Higher patient pain scores were associated with higher depression scores in FCs. Increased number of years of caregiving associated with increased depression in FCs.
Gaston-Johansson, 2004 N = 102 Age = 47.6 ± 10.8 Female = 25% Design: Cross-sectional	BDI score = 7.5 ± 5.5 Maximum score = 26 Severe depression scores for some of participants; exact numbers not reported.	Not evaluated	Higher depression scores correlated with higher state and trait anxiety scores.	Not evaluated	Environment: Higher FC depression scores were correlated with higher subjective and objective burden scores.
Given & Given, 1992 N = 49 New disease (ND) = 21, Recurrent disease (RD) = 28 ND age = 54.0 ± 13.0 RD age = 55.0 ± 12 Female = 20% Design: Longitudinal, 6 months	CES-D score at enrollment for FCs of patients with ND = 4.9 ± 4.6; for FCs of patients with RD = 6.9 ± 4.8 Depression in both groups of FCs increased over time	Not evaluated	Not evaluated	Not evaluated	Environment: FCs of patients with recurrent disease reported higher levels of depression than FCs of ND patients at intake and at 6 months. Higher FC depression scores were associated with worse function and more symptom distress in patients.
Given, 1993 N = 196 Age = 55.5 ± 12.7 Female = 63%	CES-D score = 1.7 ± 0.4; Range 1 to 4	Not evaluated	Not evaluated	Not evaluated	Person: FCs who scored higher on optimism scored lower on depression. Environment: FC depression scores correlated with patient variables of immobility, symptom

Design: Cross-sectional					distress, and dependencies in ADLs and with increased disruption in FCs' schedule. Health and Illness: Higher depression scores were associated with an increased impact on FC health.
Hagedoorn, 2000 N = 253 Age = 53.5 Female = 58% Design: Cross-sectional	CES-D scores for female FCs of patients from a patient association = 11.8 ± 7.9; for male FCs of patients from a patient association = 8.1 ± 6.1; for female FCs of patients seen in hospital setting = 12.5 ± 8.4; and for male FCs of patients seen in hospital setting = 7.6 ± 6.2 CES-D score ≥ 16 for females = 34.8%, for males = 12.3%	Not evaluated	Not evaluated	Female FCs perceived more psychological distress and a poorer QOL than women in healthy couples.	Person: Higher depression scores reported by female FCs. Wives of cancer patients reported higher depression scores than husbands of cancer patients. Environment: FCs of patients with cancer reported higher depression scores than FCs of healthy individuals.
Iconomou, 2001 N = 65 Age = 47.6 ± 15.7 Female = 56.9% Design: Cross-sectional	HADS depression score = 12.1 ± 5.2	Not evaluated	Depression and anxiety scores were positively correlated.	Higher depression scores were associated with a poorer QOL.	Person: Female FCs reported significantly more depression than male FCs. FCs with higher education were significantly less depressed. Partners were more depressed than non-partners. Environment: Positive correlations were found between depression scores and impact of caregiving scores. Health and Illness: Higher depression scores were associated with poorer health status scores.
Jepson, 1999 N = 161	Mean CES-D score = not reported in tables.	Depression decreased over	Not evaluated	Not evaluated	Health and Illness: FCs, in the intervention group who had physical problems, reported

Age = 62.3 Female = 67.7% Design: Longitudinal, 6 months	Generally, depression scores tended to decrease from baseline to 3 months and then to increase slightly from 3 months to 6 months.	time in both the intervention and control groups.			increased depression scores over the first 3 months and then decreased depression scores over the next 3 months of the intervention, while the control group with physical problems showed the opposite pattern.
Kim, 2005 N = 120 Age = 63.1 ± 10.0 Female = 66% Design: Cross-sectional	CES-D score = 11.3 ± 9.1 Range 0 to 40 30% of FCs had CES-D score ≥ 16 Hamilton Depression Rating Scale = 8.1 ± 6.4 Range 0 to 26	Not evaluated	Not evaluated	Not evaluated	Person: Higher FC depression scores were associated with increased levels of neuroticism and decreased levels of interpersonal self-efficacy.
Kozachik, 2001 N = 91 Age control group = 53.0 ± 14.6 Female = 48% Age treatment group = 51.3 ± 12.8 Female = 53% Design: Longitudinal, 24 weeks	Baseline CES-D score = 9.9 ± 7.6 for control group and 12.0 ± 8.3 for treatment group Over time, CES-D scores decreased in both the control (9.3 ± 8.0 at 9 weeks, 7.8 ± 7.0 at 24 weeks) and treatment groups (9.6 ± 8.2 at 9 weeks, 9.0 ± 7.4 at 24 weeks)	Educational intervention had no effect on depression scores.	Baseline depression score was a significant predictor of depression at 9 and 24 weeks.	Not evaluated	Person: Higher depression scores reported by male FCs (average of 2 points higher) than female FCs. Environment: Number of patient symptoms at baseline and at 9 and 24 weeks were significant predictors of FCs' depression scores.
Kurtz, 1994 N = 208 Age = 55.0 Female = 63.5% Design: Longitudinal, 12 months	CES-D scores of FCs of survivors of greater than 12 months (n = 111) = 1.6; FCs of survivors of 6 to 12 months (n = 35) = 1.7; and FCs of survivors of less than 6 months (n =	Not evaluated	Not evaluated	Not evaluated	Environment: FCs of older patients were less depressed. Higher depression scores were found in FCs with shorter survival times. Higher depression scores in FCs were associated with increased number of patient symptoms, patient depression, immobility, and dependence. Health and Illness: As stage of illness

	62) = 1.8				progressed, FCs experienced increased levels of depression and greater impact on health.
Kurtz, 1995 N = 150 Age = 55.1 Female = 62% Design: longitudinal, 6 months	Baseline CES-D score = 1.6 ± 0.4, Range 1 to 4 At 6 months, change scores of -0.04 ± 0.3	Not evaluated	Not evaluated	Not evaluated	Person: FCs who were more optimistic reported lower levels of depression. Environment: Patient symptoms were strong predictors of patient depression which in turn predicted FC depression.
Kurtz, 2004 N = 491 > 65 years = 64% Female = 76.2% Design: Longitudinal, 12 months	Baseline CES-D score = 10.9 ± 7.4 After 12 months = 8.5 ± 7.2	Not evaluated	Not evaluated	Not evaluated	Person: Higher levels of depression in FCs were associated with more education, increased feelings of abandonment, and worse FC social functioning. Environment: Higher levels of FC depression were associated with patient depression, more severe patient symptoms, greater impact on FC schedule, and FCs who lived with the patient.
Kurtz, 2005 N = 237 Age = 55.2 ± 13.7 Female = 53.4% Design: Longitudinal, 20 weeks	CES-D score for control group at baseline = 11.3 ± 10.2, at 10 weeks = 7.4 ± 8.4, at 20 weeks = 8.1 ± 10.1 CES-D score for treatment group at baseline = 10.8 ± 9.2, at 10 weeks = 9.7 ± 9.7, at 20 weeks = 7.7 ± 9.1	No differences in FCs' depression scores as a result of an educational intervention.	Not evaluated	Not evaluated	Person: FCs who were younger, had less sense of mastery of care tasks, and with worse social functioning had higher levels of depression. Environment: FCs who provided more symptom assistance and FCs of patients with late stage disease had higher levels of depression. Health and Illness: FCs who reported a higher number of comorbid conditions had higher levels of depression.
Langer, 2003 N = 131 FCs of patients with cancer Age = 48.1 ± 9.8 Female = 50.4%	POMS mean depression scores at baseline = 0.92 ± 0.82. POMS mean depression score at 1 year = 0.85 ± 0.77.	No differences in depression scores in FCs assigned with patients to a 90	Not evaluated	Not evaluated	Person: FCs depression scores decreased over 12 months. Prior to transplant, FCs reported higher depression scores than patients. Female FCs reported higher depression scores than male FCs.

N = 88 FCs in a normative sample Age = 45.9 ± 9.2 Female = 55%		minute group format recovery workshop compared to standard care.			Environment: FCs compared to a normative sample, reported elevated levels of depression prior to and 6 months post-transplant.
Miaskowski, 1997 N = 128 Age = 52.9 ± 14.1 for FCs of patients with pain; 54.9 ± 13.8 for FCs of pain free patients Female = 64% for FCs of patients with pain; 52% for FCs of pain free patients Design: Cross-sectional	POMS depression score was 8.0 ± 6.2 for FCs of patients with pain and 5.6 ± 5.7 for FCs of pain free patients.	Not evaluated	Not evaluated	Not evaluated	Environment: FCs of patients with pain had significantly higher depression scores than FCs of pain free patients.
Nijboer, 1999 N = 148 Age = 63.0 ± 11.0 Female = 64% Design: Longitudinal, 6 months	CES-D score at 6 months after patient's discharge from hospital = 9.0 ± 8.2 20% of FCs had CES-D score ≥ 16	Not evaluated	Not evaluated	Higher levels of depression were associated with poorer QOL.	Person: FCs initial levels of depression, lower educational status, and lower self esteem were associated with higher levels of depression at 6 months. Environment: FCs of a patient with a stoma and those with a poorer quality relationship with the patient had higher levels of depression at 6 months. More disruptions in schedule, financial problems, and lack of family support were associated with higher levels of depression at 6 months. Health and Illness: FCs who reported a loss of physical strength had higher levels of depression at 6 months.

Nijboer, 2001 Same sample as Nijboer, 1999 Design: Longitudinal, 6 months	Baseline CES-D score = 13.8 ± 9.4;at 6 months after patient's discharge from hospital = 9.0 ± 8.3	Not evaluated	Not evaluated	Not evaluated	Person: FCs initial levels of depression, higher levels of neuroticism, and lower levels of mastery and self-esteem were associated with higher levels of depression at 6 months. Environment: Higher FC depression scores at 6 months correlated with higher levels of patient depression, increased number of care tasks, increased negative interactions, and decreased emotional and social support.
Passik, 2005 N = 25 Age = 54.5 ± 12.5 Female = 16% Design: Longitudinal, 1 month	ZSDS scores at baseline = 36.3 ± 9.3; at one month follow-up = 35.6 ± 7.9	Not evaluated	Not evaluated	Not evaluated	Person: FCs ratings of depression were lower than patients at baseline and at the 1 month follow-up. Environment: Higher fatigue scores in patients were correlated with higher FC depression scores.
Raveis, 1998 N = 164 Age = 38.6 ± 7.6 Female = 100% Design: Cross-sectional	CES-D score = 12.0 ± 10.6 30% of FCs had CES-D score ≥ 16	Not evaluated	Not evaluated	Not evaluated	Person: FCs with less education, fewer additional roles, an increased sense of filial obligation, and less favorable attitudes toward the caregiving experience reported higher depression scores. Environment: Increased number of patient symptoms and fewer domains of patient need were associated with higher depression scores in FCs. Health and Illness: A report of a limiting health condition in the FC was associated with higher depression scores.
Schumacher, 1993 N = 75 Age = 43.8 ± 14.7 Female = 51% Design: Cross-sectional	Within 3 weeks of initiation of CTX, POMS depression score = 10.1 ± 10.7	Not evaluated	Not evaluated	Not evaluated	Person: FCs who perceived that their coping strategies were less efficacious were more depressed. Environment: FCs of male patients and FCs with less social support were more depressed.
Sherwood, 2006	CES-D score = 14.9 ±	Not evaluated	Not evaluated	Not evaluated	Environment: Higher levels of neuropsychiatric

N = 95 Age = 51.0 ± 12.0 Female = 74% Design: Cross-sectional	8.9				symptoms in patients were associated with higher levels of depression and higher levels of burden in FCs. Higher levels of depression in FCs were associated with higher levels of caregiver burden. Health and Illness: Higher levels of FC burden were associated with a higher impact on FCs health.
Stetz, 2004 N = 11 patients with cancer and 15 patients with AIDS Age = 51.0 for patients with cancer and 39.0 for patients with AIDS Female = 91% for patients with cancer and 80% for patients with AIDS Design: Cross-sectional	CES-D score for FCs of patients with cancer = 15.9 ± 10.6 and 20.7 ± 12.6 for patients with AIDS 73% had CES-D scores ≥ 16.	Not evaluated	Not evaluated	Not evaluated	Environment: FCs of patients with cancer reported that the work of caregiving disrupted their ability to socialize to a greater degree than FCs of patients with AIDS. FCs of patients with cancer experienced a greater impact on their normal ADLs than FCs of patients with AIDS. FCs of patients with AIDS reported more rewards from caregiving than FCs of patients with cancer.
Toseland, 1995 N = 78, 38 in control group; 40 in treatment Age = 53.5 Female = 50% Design: Longitudinal, pre and post 6 week intervention	Baseline CES-D score = 16.2 ± 6.0 for control group and 15.8 ± 5.2 for treatment group Post-intervention CES-D score = 17.7 ± 6.7 for control group and 16.3 ± 6.2 for treatment group	A six session intervention of support, problem solving, and coping skills did not decrease depression scores in FCs.	Not evaluated	Not evaluated	Not evaluated
Tuinstra, 2004	Baseline CES-D score	Not evaluated	Not evaluated	Not evaluated	Person: Female FCs reported higher depression

N = 137 Age of females = 58.8 ± 11.3 Age of males = 59.4 ± 10.6 Female = 65% Design: Longitudinal, 6 months	= 14.1 ± 9.2 for females and 13.6 ± 9.3 for males 3 month CES-D score = 11.3 ± 10.3 for females and 7.8 ± 6.9 for males 6 month CES-D score = 10.3 ± 8.7 for females and 7.3 ± 7.4 for males				scores at three and six months after the patients' surgery than male FCs. At the time of the patients' surgery, male FCs reported higher depression scores than male patients.
Williamson, 1995 N = 82 Age = 60.2 ± 11.3 Female = 67.1% Design: Cross-sectional	CES-D = 11.6 ± 8.7 30.5% of FCs had CES-D score ≥ 16	Not evaluated	Not evaluated	Not evaluated	Environment: FCs, in relationships with the patient prior to the onset of illness that were characterized by mutual demonstrations of concern and responsiveness to each others' needs, reported lower levels of burden and depression. FCs who cared for patients with more severe symptoms reported higher levels of depression.
Williamson, 1998 N = 75 Age = 62.2 ± 8.6 Female = 68% Design: Cross-sectional	CES-D score = 11.2 ± 8.5 29.3% of FCs had CES-D score ≥ 16	Not evaluated	Not evaluated	Not evaluated	Environment: Activity restrictions in FCs totally mediated associations between FC stress (operationalized as the severity of the patients' symptoms) and FC resentment and depressed affect. In other words, the severity of the patients' symptoms was associated with negative affective outcomes for FCs largely to the extent that it disrupted the FCs normal activities.

Abbreviations: ADLs = activities of daily living, BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies- Depression Scale; CTX = chemotherapy; DQ = Depression Questionnaire; FC = Family caregiver; HADS = Hospital Anxiety and Depression Scale; POMS = Profile of Mood States; ZSDS = Zung Self Rating Depression Scale

Table 2 - Studies that Evaluated Anxiety in Family Caregivers of Patients with Cancer

First author, Year Characteristics of FC	Symptom Experience	Symptom Management Strategies	Association with other symptoms	Outcomes	Domains of Person, Environment, and Health and Illness
Campbell, 2004 N =40 Age = 57.6 ± 10.2 Female = 97.5% Design: Cross-sectional	POMS anxiety score = 4.3 ± 4.6	Not evaluated	Not evaluated	Not evaluated	Person: Lower anxiety scores were found in FCs who reported greater overall confidence in assisting patients with symptom control and in FCs who reported greater confidence in helping patients to cope with their symptoms.
Clavarino, 2002 N = 19 Age = 49.5 ± 9.9 Female = 42% Design: Cross-sectional	HADS mean anxiety score not reported Non-cases = 44% Borderline cases = 17% Cases = 39%	Not evaluated	Not evaluated	Not evaluated	Person: No differences in anxiety scores were found between patients and FCs. Environment: The prevalence of anxiety was higher in FCs than in the general population (i.e., 9.7%).
Cliff, 2000 N = 135 Age = 73.9 ± 7.4 Female = 100% Design: Cross-sectional	HADS mean anxiety score = 7.2 ± 4.7; 20.7% of FCs had a score of >11	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Ferrario, 2003 N = 50 Age = 46.7 ± 15.0 Female = 56% Design: Cross-sectional	STAI – trait score of validation sample = 42.7 ± 9.9; FC sample = 43.2 ± 10.7 STAI – state score of validation sample = 40.4 ± 9.7; FC sample = 44.6 ± 12.0	Not evaluated	Not evaluated	Higher levels of trait and state anxiety were associated with less satisfaction with life.	Environment: Higher trait and state anxiety scores were associated with higher levels of FC strain and a greater need for knowledge about the patient's disease.
Ferrell, 1999	FC QOL tool mean	Not evaluated	Not evaluated	Not	Person: FCs' anxiety was higher than patients' anxiety.

N = 231 Age = 56 Female = 72% Design: Cross-sectional	anxiety score =5.8 ± 3.0			evaluated	
Flaskerud, 2000 N = 41 Age = 51.5 ± 14.2 Female = 100% FCs of patients with cancer or dementia Design: Cross-sectional	SCL -90 Revised 3-item anxiety scale Fearful = 68% Nervous/shaky = 85% Tense = 90%	Not evaluated	Higher anxiety scores were correlated with higher depression, anger, and sleep disturbance scores.	Not evaluated	Environment: Higher anxiety scores correlated with higher patient pain scores. FCs of cancer patients experienced more anxiety than FCs of patients with dementia.
Gaston-Johansson, 2004 N = 102 Age = 47.6 ± 10.8 Female = 25% Design: Cross-sectional	STAI state score = 40.3 ± 10; STAI trait score = 37.4 ± 7.9	Not evaluated	Positive correlations were found between anxiety, depression, and fatigue.	Decreased QOL associated with increased anxiety and increased burden.	Person: Higher anxiety scores reported by female FCs. Higher anxiety scores reported by non-married FCs. Higher anxiety scores associated with lower reported income.
Iconomou, 2001 N = 65 Age = 47.6 ± 15.7 Female = 56.9% Design: Cross-sectional	HADS anxiety score = 12.9 ± 5.6	Not evaluated	Depression and anxiety scores were positively correlated.	Higher anxiety scores were associated with a poorer QOL.	Person: Female FCs reported significantly more anxiety than male FCs. FCs with higher education were significantly less anxious. Environment: Positive correlations were found between anxiety scores and impact on caregiving scores. Health and Illness: Higher anxiety scores were associated with poorer FC health status scores.
Langer, 2003 N = 131 FCs of patients with cancer Age = 48.1 ± 9.8	POMS mean anxiety score at baseline = 1.40 ± 0.88. POMS mean anxiety score at 1 year = 1.39 ± 0.87.	No differences in anxiety scores in FCs assigned with patients to a 90	Not evaluated	Not evaluated	Person: FCs anxiety scores decreased over 12 months. FCs reported higher anxiety scores than patients prior to- and 12 months post-transplant. Female FCs reported higher anxiety scores than male FCs. Environment: FCs compared to a normative sample,

Female = 50.4% N = 88 FCs in a normative sample Age = 45.9 ± 9.2 Female = 55% Design: Longitudinal, 12 months		minute group format recovery workshop compared to standard care.			reported elevated levels of anxiety prior to and 6 and 12 months post-transplant.
Matthews, 2003 N = 135 Age = 55.2 ± 11.6 Female = 47% Design: Cross-sectional	Anxiety measured by a single item from the QOL-F questionnaire = 4.5 ± 2.9 for all FCs; 4.0 ± 2.6 for male FCs; 5.6 ± 3.0 for female FCs	Not evaluated	Not evaluated	Not evaluated	Person: Female FCs reported higher anxiety scores than male FCs.
Miaskowski, 1997 N = 128 Age = 52.9 ± 14.1 for FCs of patients with pain; 54.9 ± 13.8 for FCs of pain free patients Female = 64% for FCs of patients with pain; 52% for FCs of pain free patients Design: Cross-sectional	POMS anxiety score was 9.3 ± 5.5 for FCs of patients with pain and 6.8 ± 4.6 for FCs of pain free patients	Not evaluated	Not evaluated	Not evaluated	Environment: FCs of patients with pain had significantly higher anxiety scores than FCs of pain free patients.
Segrin, in press N = 96 Age = 51.7 ± 14.8 Female = 26% Design: Cross-sectional	Composite measure of anxiety scores not reported	Not evaluated	Not evaluated	Not evaluated	Person: FCs with higher anxiety scores reported a poorer quality relationship with the patient. Environment: FCs' anxiety scores were significantly correlated with patients' anxiety scores.

Toseland, 1995 N = 80 Age = 53.5 Female = 50% Design: Longitudinal, pre and post 6 week intervention	Baseline STAI state anxiety = 38.4 ± 9.6 for control group and 36.1 ± 11.5 for intervention group Post-intervention STAI state anxiety = 38.9 ± 11.4 for control group and 36.8 ± 11.9 for intervention group	A 6 session program of support, problem solving, and coping skills resulted in no change in FC anxiety scores.	Not evaluated	Not evaluated	Not evaluated
Walsh, 2004 N = 40 Age = 51.4 ± 15.4 Female = 75% Design: Longitudinal, pre and post test after single intervention session	BAI = 32.8 ± 9.4 at baseline and 27.8 ± 7.7 post the intervention	Creative arts intervention resulted in significant decreases in anxiety scores.	Not evaluated	Not evaluated	Not evaluated

Abbreviations: BAI = Beck Anxiety Inventory; FC = Family caregiver; GHQ-30 = General Health Questionnaire-30; HADS = Hospital Anxiety and Depression Scale; MOS-SF-36 = Medical Outcomes Study-Short Form-36; POMS = Profile of Mood States; QOL = Quality of life; QOL-F = Quality of Life-Family; SCL = Symptom Checklist; STAI = Spielberger Anxiety Inventory

Table 3 - Studies that Evaluated Sleep Disturbance in Family Caregivers of Patients with Cancer, Dementia, or Parkinson's disease

First author, Year Characteristics of FC	Symptom Experience	Symptom Management Strategies	Association with other symptoms	Outcomes	Domains of Person, Environment, and Health and Illness
Carter & Chang, 2000 N = 51 Age = 53.7 ± 14.3 Female = 80.4% FCs of patients with cancer Design: Cross-sectional	PSQI global score = 11.3 ± 4.4; 95% of FCs reported sleep problems	Not evaluated	Higher sleep disturbance scores were significantly correlated with higher depression scores.	Not evaluated	Not evaluated
Carter, 2002 Subset of the sample N = 47 from Carter and Chang, 2000 FCs of patients with cancer Design: Cross-sectional	PSQI global score = 11.4 ± 4.4; 95% of FCs reported severe overall sleep problems	Not evaluated	Chronic sleep loss led to irritability and anger, then guilt and finally depression.	Not evaluated	Not evaluated
Carter, 2003 N = 10 Mean age = 61 Female = 80% FCs of patients with cancer Design: Longitudinal, 10 week	PSQI global score was above the cutoff of 5 for normal sleep for all 10 weeks of the study	Not evaluated	Sleep disturbance and depressive symptoms fluctuated over time.	Not evaluated	Not evaluated
Carter, 2006	PSQI score for the	Brief	Not evaluated	Not	Not evaluated

N = 30 Age = 53.0 ± 17.0 Female = 63% FCs of patients with cancer Design: Longitudinal, 4 months	control group at baseline = 9.3 ± 5.5, at 3 weeks = 7.9 ± 5.0, at 5 weeks = 7.6 ± 5.0 For the intervention group at baseline = 9.9 ± 4.6, at 3 weeks = 7.9 ± 3.0, at 5 weeks = 7.2 ± 3.0 SE by actigraphy for the control group at baseline = 84% ± 9%, at 3 weeks = 86% ± 8%, at 5 weeks = 87% ± 7; For the intervention group at baseline = 89% ± 8%, at 3 weeks = 88% ± 10%, at 5 weeks = 86% ± 13%	behavioral sleep intervention that lasted one hour plus a booster demonstrated some efficacy in improving sleep quality.		evaluated	
Cho, 2006 N = 103 Age = 48.3 ± 11.4 Female = 78% FCs of patients with cancer Design: Cross-sectional	Global PSQI score = 5.8 ± 2.2	Not evaluated	Higher sleep disturbance scores were correlated with higher levels of depression and fatigue.	Higher levels of sleep disturbance were associated with lower QOL scores.	Person: No differences in sleep disturbance scores between male and female FCs.
Ferrell, 1999 N = 231 Age = 56 Female = 72% FCs of patients with cancer	FC QOL tool mean sleep disturbance score = 5.1 ± 3.2	Not evaluated	Not evaluated	Not evaluated	Not evaluated.

Design: Cross-sectional					
Flaskerud, 2000 N = 41 Age = 51.5 ± 14.2 Female = 100% FCs of patients with cancer or dementia Design: Cross-sectional	PSQI-3 items assessed: Trouble falling asleep = 46%. Restless sleep = 82% Trouble staying asleep = 76%	Not evaluated	Higher sleep disturbance scores correlated with higher depression, anger, and anxiety scores.	Not evaluated	Environment: FCs of cancer patients experienced more difficulty staying asleep and more restless sleep than FCs of patients with dementia.
Happe, 2002 N = 101 Age = 62.3 ± 10.0 Female = 63% FCs of patients with PD Design: Cross-sectional	Single item of the CES-D about having bad night-time sleep in the past week Bad night-time sleep was reported by 27% of FCs	Not evaluated	Higher sleep disturbance scores correlated with higher depression scores.	Not evaluated	Environment: Bad night-time sleep in FCs was correlated with motor symptom severity and bad sleep in patients, male gender of the patients, and the frequency of caregiving.
Hosaka, 2003 N = 20 Age = 54.7 ± 4.4 Female = 100% FCs of patients with dementia Design: longitudinal, pre and post 5 90 minute intervention sessions	Sleep disturbance score from GHQ-30 = 1.5 ± 1.5 pre- and 1.0 ± 1.0 post-intervention	Intervention of education, relaxation training, and group discussion did not improve sleep.	Not evaluated	Not evaluated	Not evaluated
McCurry, 1998 N = 36 Age = 68.7 ± 10.6 Female = 78%	PSQI score for control group pre-treatment = 11.9 ± 4.5, post treatment = 10.6 ± 4.4, and 3-	Data from an individual and a group intervention	Not evaluated	Not evaluated	Person: FCs who were treatment responders tended to be younger and more adherent with procedures.

FCs of patients with dementia Design: Longitudinal, 3 months	month = 10.2 ± 4.2 For intervention group pre-treatment = 10.8 ± 3.4, post-treatment = 7.8 ± 3.3, and 3-months = 6.2 ± 3.6	(i.e., standard sleep hygiene, stimulus control, and sleep. compression strategies) were combined. FCs in the treatment group showed significant improvements in sleep scores after treatment and at the 3-month follow-up.			
McKibbin, 2005 N = 113 Age = 73.5 ± 9.4 for FCs of patients with moderate to severe dementia Female = 66.7% 71.1 ± 8.3 for FCs of patients with mild dementia Female = 75.0% 67.6 ± 6.8 for non-FC controls Female = 71.2% Design:	PSQI total score for FCs of patients with moderate to severe dementia = 9.1 ± 5.4 for those < 71 years and 2.2 ± 5.4 for those > 71 years For FCs of patients with mild dementia = 4.4 ± 3.4 for those < 71 years and 4.4 ± 4.7 for those > 71 years For non-FC controls = 2.2 ± 4.4 for those < 71 years and 5.6 ± 3.8 for those > 71 years	Not evaluated	Not evaluated	Increased sleep disturbance was associated with decreased functional status.	Person: Older FCs of patients with moderate to severe dementia slept less than older non-FCs. Older FCs had lower sleep efficiency, less slow wave sleep, and more Stage 1 sleep than younger FCs. Environment: FCs of patients with moderate to severe dementia reported significantly more sleep problems than non-FCs.

Cross-sectional	Polysomnography used to measure sleep.				
Mizuno, 1999 N = 42 Age = 56.7 ± 9.7 Female = 90.5% FCs of patients with dementia or disability Design: Longitudinal, pre and post 5 90 minute intervention sessions	GHQ-30 sleep subscales scores for control group = 2.01 ± 1.00 and 2.13 ± 1.27. GHQ-30 sleep subscale scores for the exercise and relaxation group = 1.86 ± 1.21 and 2.09 ± 0.82.	Structured 5-week psycho-educational intervention program had no effect on sleep disturbance scores.	Not evaluated	Not evaluated	Not evaluated
Pal, 2004 N = 23 Age = 65.2 ± 11.3 Female = 65.2% FCs of patients with PD Design: Cross-sectional	PSQI global score = 5.5 ± 3.8 ; 60% of FCs had a global score of > 5	Not evaluated	Significant correlations were found between anxiety and depression and sleep disturbance.	Not evaluated	Environment: FCs had significantly lower PSQI global scores than patients with PD.
Passik, 2005 N = 25 Age = 54.5 ± 12.5 Female = 16% FCs of patients with cancer Design: Longitudinal, 1 month	Caregiver NRS of insomnia at baseline = 2.6 ± 2.9; at one month follow-up = 3.2 ± 2.9	Not evaluated	Not evaluated	Not evaluated	Environment: Higher fatigue scores in patients were correlated with higher sleep disturbance scores in FCs.
Sato, 2002 N = 18 Age = 66	SEQ quality of sleep score in FCs was significantly lower than	Not evaluated	Poorer quality sleep was associated with increased levels of morning	Not evaluated	Environment: FCs reported poorer quality sleep than non-FCs.

Female = 100% FCs of patients with dementia Design: Cross-sectional	non-FCs with more items of restless sleep and more periods of wakefulness		fatigue.		
Secker, 2005 N = 15 in the control and 15 in the intervention group Age = 58.9 ± 11.4 for the control and 59.1 ± 12.2 for the intervention group Female = 40% for control and 46.7% for intervention group FCs of patients with PD Design: Longitudinal, 6 months	GHQ-28 anxiety and insomnia subscale score at baseline = 11.1 ± 4.9 for control and 12.7 ± 2.9 for the intervention group At 3 months, = 8.5 ± 4.3 for control and 5.8 ± 3.9 for the intervention group At 6 months = 8.6 ± 4.6 for control and 5.2 ± 3.3 for the intervention group	12 to 14 sessions of CBT over 12 to 14 weeks resulted in improvements in anxiety and insomnia at 3 months compared to standard care.	Not evaluated	Not evaluated	Not evaluated
Smith, 1997 N = 256 Age = 64.8 Female: 63.7% FCs of patients with PD and healthy controls Design: Cross-sectional	Sleep disturbance item from the ZSDS = 2.3 ± 1.0 for FCs and 1.8 ± 0.9 for controls	Not evaluated	Not evaluated	Not evaluated	Person: Overall, women reported higher sleep disturbance scores than men. Environment: Female FCs reported higher sleep disturbance scores than female controls. The strongest predictor of disrupted sleep in FCs was the disease severity of the patient.
Teel, 1999 N = 125	VSH sleep disturbance subscale = 3.9 for FCs	Not evaluated	Not evaluated	Not evaluated	Environment: All three groups of FCs reported higher levels of sleep disturbance and lower

Age = 72.3 Female = 52.0% FCs of patients with cancer, dementia, and PD Design: Cross-sectional	and 3.0 for non-FCs VSH sleep effectiveness subscale = 6.8 for FCs and 8.0 for non-FCs				levels of sleep effectiveness than non-FCs.
Wilcox, 1999 N = 90 Age = 62.8 ± 9.5 Female = 100% FCs of patients with dementia Design: Cross-sectional	PSQI score = 7.7 ± 3.8 65.6% had a global score of > 5	Not evaluated	Higher levels of sleep disturbance were correlated with higher levels of depression and lower levels of internalized anger.	Not evaluated	Person: Higher levels of sleep disturbance were found in FCs with less education. Higher levels of daytime dysfunction were found in younger FCs. Environment: Higher levels of sleep disturbance were found in FCs than in the general population. Higher levels of sleep disturbance were associated with more night-time disruptions by the patient.
Woods, 2003 N = 128 Age = 58.8 ± 13.2 in control and 62.4 ± 15.9 in the intervention group Female = 20% in the control and 74% in the intervention group FCs of patients with dementia Design: Longitudinal, 8 months	Insomnia and anxiety were measured together using the GHQ-30 subscale B pretreatment score = 6.5 ± 4.4 for control and 7.3 ± 5.1 for the intervention group Post-treatment score = 6.0 ± 4.0 for the control and 5.1 ± 3.3 for the intervention group	FCs referred to a specialist in mental health nursing service reported significant decreases in sleep disturbance at 8 months compared to FCs in the standard care group.	Not evaluated	Not evaluated	Not evaluated

Abbreviations: CBT = cognitive behavioral therapy, FC = Family caregiver; GHQ-30 = General Health Questionnaire-30; NRS = Numeric rating scale; PD = Parkinson's Disease; PSQI = Pittsburgh Sleep Quality Index; SE = sleep efficiency; SEQ = Sleep Evaluation Questionnaire; VSH = Verran and Snyder-Halpern Sleep Scale; ZSDS = Zung Self Rating Depression Scale

Table 4 - Studies that Evaluated Fatigue in Family Caregivers of Patients with Cancer, Dementia, or Parkinson's Disease

First author, Year Characteristics of FC	Symptom Experience	Symptom Management Strategies	Association with other symptoms	Outcomes	Domains of Person, Environment, and, Health and Illness
Campbell, 2004 N = 40 Age = 57.6 ± 10.2 Female = 97.5% FCs of patients with cancer Design: Cross-sectional	POMS fatigue score = 6.8 ± 5.3	Not evaluated	Not evaluated	Not evaluated	Person: Lower fatigue scores were found in FCs who reported greater overall confidence in assisting patients with symptom control and in FCs who reported greater confidence in helping patients to cope with their symptoms.
Cho, 2006 N = 103 Age = 48.3 ± 11.4 Female = 78% FCs of patients with cancer Design: Cross-sectional	LFS score = 4.7 ± 2.0	Not evaluated	Higher fatigue scores were correlated with higher levels of depression and higher levels of sleep disturbance.	Higher levels of fatigue were associated with lower QOL scores.	Person: Female FCs had higher fatigue scores than male FCs.
Clark, 2002 N = 67 Age = 55 ± 12.6 Female = 91% FCs of patients with dementia Design: Cross-sectional	PFS score = 3.9 ± 2.0 23% of FCs reported experiencing fatigue for months	Not evaluated	Higher fatigue scores were correlated with higher depression scores.	Not evaluated	Person: Lower FC fatigue scores were correlated with higher individual hardiness scores. Environment: Higher occurrence of memory and behavior problems in the care recipient were associated with increased fatigue in FCs.
Ferrell, 1999 N = 231 Age = 56	FC QOL score for fatigue = 4.9 ± 2.8	Not evaluated	Not evaluated	Not evaluated	Not evaluated

Female = 72% FCs of patients with cancer Design: Cross-sectional					
Gaston-Johansson, 2004 N = 102 Age = 47.6 Female = 25% FCs of patients with cancer Design: Cross-sectional	PFS score = 28.5 ± 18.5 High PFS scores in some participants	Not evaluated	Higher fatigue scores were correlated with higher depression and anxiety scores.	Higher levels of fatigue were associated with lower QOL scores.	Person: Higher FC fatigue scores correlated with lower income levels.
Hosaka, 2003 N = 20 Age = 54.7 ± 4.4 Female = 100% FCs of patients with dementia Design: Longitudinal, pre and post 5 90 minute intervention sessions	POMS fatigue score pre-intervention = 11.2 ± 7.2 ; post-intervention = 8.2 ± 5.3	Intervention of education, relaxation training, and group discussion completed over 5 weeks resulted in a significant decrease in fatigue.	Not evaluated	Not evaluated	Not evaluated
Jensen, 1991 N = 248 Age = 54.8 ± 12.6 Female = 65% FCs of patients with cancer Design: Cross-sectional	PFS score = 8.0 45% reported slight fatigue (1-7 on PFS), 25% reported moderate fatigue (7.01-11.0), and 28% reported severe fatigue (11.01-16.4)	Not evaluated	Not evaluated	Not evaluated	Environment: Higher FC fatigue scores were correlated with higher impact on schedule scores.

Miaskowski, 1997 N = 128 Age = 52.9 ± 14.1 for FCs of cancer patients with pain; 54.9 ± 13.8 for FCs of pain free cancer patients Female = 64% for FCs of patients with pain; 52% for FCs of pain free patients Design: Cross-sectional	POMS fatigue score was 8.3 ± 5.4 for FCs of patients with cancer pain and 6.2 ± 5.6 for FCs of pain free patients	Not evaluated	Not evaluated	Not evaluated	
Passik, 2005 N = 25 Age = 54.5 ± 12.5 Female = 16% FCs of patients with cancer Design: Longitudinal, 1 month	FSI score at baseline = 41.4 ± 23.5; at one month follow-up = 35.4 ± 23.3	Not evaluated	Not evaluated	Not evaluated	Environment: FCs with higher levels of caregiver strain reported higher levels of fatigue at baseline.
Sato, 2002 N = 18 Age = 66.1 Female = 100% FCs of patients with dementia Design: Cross-sectional	Perceived Symptoms of Fatigue score = 1.4 ± 0.9 for FCs versus 0.3 ± 0.4 for non-FCs.	Not evaluated	Not evaluated	Not evaluated	Environment: Higher levels of perceived and physiologic fatigue reported by FCs compared to non-FCs.
Teel, 1999 N = 125	VAS-F score for FCs = 3.5; for non FCs = 2.1	Not evaluated	Not evaluated	Not evaluated	Environment: All three groups of FCs reported more fatigue and less energy than an age matched

Age = 72.3 Female = 52.0% FCs of patients with cancer, dementia, and PD Design: Cross-sectional	POMS fatigue score for FCs = 2.6; for non-FCs = 1.8				control group.

Abbreviations: FC = Family caregivers; FSI = Fatigue Symptom Inventory; LFS = Lee Fatigue Scale; PD = Parkinson's disease; PFS = Piper Fatigue Scale; POMS = Profile of Mood States; QOL = Quality of Life; VAS-F = Visual Analogue Scale-Fatigue

Table 5 - Studies That Evaluated Pain in Family Caregivers of Patients with Dementia

First author, Year, Characteristics of FCs	Symptom Experience	Symptom Management Strategies	Association with other symptoms	Outcomes	Domains of Person, Environment, and Health and Illness
Kuzu, 2005 N = 32 Age = 49.6 ± 12.9 Female = 65.6% FCs of patients with dementia Design: Longitudinal, pre and post a 50 minute educational intervention	Duke Pain Scale – pre-intervention score = 37.5 ± 31.3; post-intervention score = 25.0 ± 25.4	Educational intervention that included structured and tailored components that focused on patient and FC problems had no effect on FCs' pain.	Not evaluated	Not evaluated	Not evaluated

Abbreviations: FC = Family caregivers

Prevalence, Severity, and Impact of Symptoms in Family Caregivers of Patients at the Initiation of Radiation Therapy for Prostate Cancer

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Running head: SYMPTOMS IN FAMILY CAREGIVERS

Abstract

PURPOSE - In a sample of family caregivers (FCs) of patients with prostate cancer who were to begin radiation therapy (RT), the purposes were to: determine the prevalence and severity of depression, anxiety, pain, sleep disturbance, and fatigue; determine the relationships among these symptoms and between these symptoms and FC outcomes of functional status and quality of life (QOL); and evaluate for differences in functional status and QOL between FCs with low and high levels of these symptoms.

METHODS - FCs were recruited before the patient initiated RT and completed Center for Epidemiological Studies-Depression Scale, Spielberger State Trait Anxiety Inventory, Lee Fatigue Scale, General Sleep Disturbance Scale, and a numeric rating scale for worst pain intensity.

RESULTS - Sixty female FCs participated in the study (mean age = 64.2 years; average Karnofsky Performance Status score = 94.0). Based on established cutpoints for each instrument, 12.2% of the FCs had clinically significant levels of depression, 40.7% anxiety, 15.0% pain, 36.7% sleep disturbance, and 33.3% morning fatigue and 30.0% evening fatigue. Over 30% of FCs had clinically significant levels of anxiety, sleep disturbance, and fatigue. FCs with clinically significant levels of trait anxiety, pain, sleep disturbance, and morning fatigue had significantly lower functional status scores. FCs with clinically significant levels of depression, anxiety, pain, and fatigue had significantly lower QOL scores.

CONCLUSIONS - A high percentage of FCs experience clinically significant levels of a variety of symptoms. These symptoms have a negative effect on the FC's functional status and QOL.

Introduction

An estimated 44.4 million Americans provide some level of care to an adult family member and this number is likely to increase.[1] While several studies have found higher levels of depressive symptoms and mental health problems in family caregivers (FCs) of patients with dementia,[2,3] little is known about the prevalence and severity of symptoms of FCs of patients with cancer.

In a comprehensive review of the symptom experience in FCs of patients with cancer (Fletcher, Dodd, Schumacher, and Miaskowski, in review), only 25 descriptive studies were identified. The most frequently assessed symptom was depression (92% of the studies), followed by anxiety (32%), fatigue (24%), and sleep disturbance (20%). No studies were found that evaluated pain in FCs of patients with cancer. Of note, higher symptom severity scores in FCs were associated with decreases in quality of life (QOL),[4-8] health status,[6,8-11] and life satisfaction.[12] However, because of the paucity of research, no definitive conclusions can be drawn about the prevalence, severity, and impact of each of these symptoms in FCs of patients with cancer.

Therefore, the purposes of this study, in a sample of FCs of patients with prostate cancer who were to begin radiation therapy (RT) were to: determine the prevalence and severity of depression, anxiety, pain, sleep disturbance, and fatigue; determine the relationships among these symptoms and between these symptoms and FC outcomes of functional status and QOL; and evaluate for differences in functional status and QOL between those FCs with low and high levels of depression, anxiety, pain, sleep disturbance, and fatigue.

Methods

Participants and Settings - This descriptive, correlational study is part of a longitudinal study that evaluated multiple symptoms in patients who underwent primary or adjuvant RT and their FCs. The patients and their FCs were recruited from two RT departments at the time of the patient's simulation visit. Patients had been diagnosed with prostate cancer for 9.7 + 15.1 months (range 1.9 to 93.3 months). The study was approved by the Committee on Human Research at each of the study sites.

Following recruitment of the patients with prostate cancer, they were asked to identify the person most involved in their care (i.e., their FC). If the FC was with the patient, the research nurse explained the study and obtained written informed consent from the FC. FCs who were not with the patient were contacted by phone to determine their interest in study participation. The research nurse visited those FCs at home, obtained informed consent, and had them complete the baseline questionnaires.

FCs were eligible to participate if they: were an adult (≥ 18 years of age); were able to read, write, and understand English; gave written informed consent; had a Karnofsky Performance Status (KPS) score of > 60; were living with the patient; and did not have a diagnosed sleep disorder.

Instruments - The study instruments included a demographic questionnaire, the KPS scale,[13] the Center for Epidemiological Studies-Depression Scale (CES-D),[14] the Spielberg State Trait Anxiety Inventory (STAI-T and STAI-S),[15] a descriptive numeric rating scale (NRS) for worst pain intensity,[16] the General Sleep Disturbance Scale

(GSDS),[17] the Lee Fatigue Scale (LFS),[18] and the Quality of Life Scale-Family Version (QOL-FV).[19]

The demographic questionnaire provided information on age, gender, marital status, education, ethnicity, employment status, and the presence of a number of comorbid conditions. In addition, FCs completed the KPS scale.[13]

The CES-D consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores ≥ 16 indicating the need for participants to seek a clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity.[20,21] In the current study, the Cronbach's alpha for the CES-D was 0.84.

The STAI-T and STAI-S each consist of 20 items that are rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. A higher score indicates greater anxiety. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality make up. The STAI-S measures an individual's transitory emotional response to a stressful situation. The STAI-T and STAI-S have well-established criterion and construct validity and internal consistency reliability coefficients.[22-24] For this study, the Cronbach's alphas for the STAI-T and the STAI-S were 0.89 and 0.93, respectively.

Worst pain intensity was evaluated using a descriptive NRS that ranged from 0 (no pain) to 10 (excruciating pain). A descriptive NRS is a valid and reliable measure of pain intensity.[16]

The GSDS consists of 21 items that evaluate various aspects of sleep disturbance. Each item was rated on a NRS that ranged from 0 (never) to 7 (every day), and the 21 items were summed to yield a total score that could range from 0 (no disturbance) to 147 (extreme disturbance). The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV.[17,25-29] In the current study, the Cronbach's alpha for the GSDS total score was 0.79.

A fatigue severity score was calculated as the mean of the 13 items from the LFS and could range from 0 to 10, with higher scores indicating higher levels of fatigue severity. The LFS has been used to measure the severity of fatigue in healthy individuals,[18,28] as well as in patients with cancer,[30] and HIV.[27] The LFS was chosen as the fatigue measure for this study because it is relatively short and easy to administer. In addition, it does not focus on cancer fatigue, and as such, is appropriate for FCs. The LFS has established validity and internal consistency reliability coefficients.[18] In this sample, the Cronbach's alphas for the fatigue scale were 0.96 (morning) and 0.95 (evening).

The QOL-FV consists of 37 items that measure four dimensions of QOL in FCs of patients with cancer using 0 to 10 NRSs.[31] A total QOL score as well as subscale scores were calculated, with higher scores indicating a better QOL. In the present study, the Cronbach's alpha for the total QOL score was 0.95.

After obtaining written informed consent, FCs completed all of the study questionnaires. The LFS was completed in the evening prior to bed (i.e., evening fatigue) and again upon awakening (i.e., morning fatigue) for two consecutive days. This

assessment coincided with the patients' simulation visit and was considered the baseline assessment for the larger longitudinal study.

Statistics - Data were analyzed using SPSS version 14. Descriptive statistics and frequency distributions were generated for the sample characteristics and symptom severity scores. Pearson Product Moment correlation coefficients were calculated to determine the relationships between each of the symptom severity scores and KPS and QOL scores. In order to determine the prevalence rates for the various symptoms, cutpoints were chosen for each of the symptom inventories based on published reports of clinically meaningful differences. The cutpoints for each of the instruments were: CES-D ≥ 16,[14] STAI-T ≥ 31.8, STAI-S ≥ 32.2,[15] worst pain ≥ 7.0,[32] GSDS ≥ 43.0,[17] morning fatigue LFS ≥ 3.2,[18] and evening fatigue LFS ≥ 5.6.[18] In addition, independent Student's t-tests were used to evaluate for differences in functional status (KPS score) and QOL (total QOL-FV and subscale scores) between those FCs with low and high levels of each symptom. A p-value of less than 0.05 was considered statistically significant.

Results

Family Caregiver Characteristics - As summarized in Table 1, the majority of the FCs were older (64.2 ± 8.8 years), Caucasian (80.0%), married/partnered (93.3%), and well educated (15.2 ± 2.8 years). Twenty-three different comorbid conditions were identified by at least one FC. The mean number of comorbid conditions was 4.8 ± 3.0.

Prevalence and Severity of Symptoms in FCs - The mean symptom severity scores for the total sample, as well as the percentage of FCs in the low and high symptom groups and their mean symptom severity scores, are listed in Table 2.

Depression – The mean CES-D score for the total sample was 8.4 ± 6.5. Twelve percent of FCs had CES-D scores of ≥ 16. The mean CES-D score for the high symptom group was 21.0 ± 5.2.

Anxiety – The mean trait and state anxiety scores for the total sample were 35.3 ± 9.9 and 32.6 ± 10.6, respectively. Both of these scores are above the cutpoint for clinically significant levels of anxiety. Approximately 57.8% of the FCs were categorized in the high group based on their mean trait anxiety scores and 40.7% were categorized in the high group based on their mean state anxiety scores.

Pain – The mean worst pain intensity score for the total sample was 1.3 ± 3.1. Only 15% of the FCs reported a worst pain score of ≥ 7 (mean score was 8.2 ± 1.0).

Sleep Disturbance – The mean GSDS score for the total sample was 39.9 ± 16.2. Over 36% of the FCs reported GSDS scores that were above the cutpoint of 43.0.

Fatigue – In the total sample, scores for morning fatigue (2.5 ± 2.1) were lower than those reported for evening fatigue (4.3 ± 2.3). Approximately 30% of the FCs reported morning and evening fatigue scores that were above the cutpoints for clinically significant levels of fatigue.

Relationships among the various symptoms - Table 3 lists the correlations among the various symptoms. Significant moderate to strong positive correlations were found among the majority of symptoms. Of note, ratings of evening fatigue were not correlated with the majority of the other symptoms.

Relationships among symptoms and functional status and QOL - As shown in Table 4, significant negative correlations were found between KPS scores and the symptoms of

depression, trait anxiety, worst pain, sleep disturbance, and morning fatigue. A similar trend was found with all of the subscale scores as well as the total QOL score. As the severity of most of the symptoms increased, the majority of the QOL subscale scores decreased.

Differences in functional status and QOL scores between FCs in the low and high symptom groups

KPS Score - The mean KPS score for the entire sample of FCs was high (mean 94.0 $\pm$ 10.5). As shown in Figure 1A, significantly lower KPS scores were reported by FCs in the high symptom group compared to the low group for trait anxiety ($t = 2.3$, $p = 0.025$), worst pain ($t = 2.8$, $p = 0.007$), sleep disturbance ($t = 2.1$, $p = 0.047$), and morning fatigue ($t = 2.2$, $p = 0.037$).

QOL-FV Total and Subscale Scores - The mean total QOL-FV score for the entire sample was 7.2 $\pm$ 1.4. As shown in Figure 1B, significantly lower total QOL scores were reported by FCs in the high symptom group compared to the low symptom group for depression ($t = 3.7$, $p = 0.001$), trait anxiety ($t = 4.8$, $p < 0.0001$), state anxiety ($t = 4.5$, $p < 0.0001$), worst pain ($t = 2.1$, $p = 0.04$), morning fatigue ($t = 5.2$, $p < 0.0001$), and evening fatigue ($t = 2.5$, $p = 0.014$).

QOL-FV Physical Subscale – The mean QOL-FV physical subscale score for the entire sample was 8.1 $\pm$ 1.7. As shown in Figure 2A, significantly lower physical subscale scores were reported by FCs in the high symptom group compared to the low symptom group for depression ($t = 2.0$, $p = 0.05$), trait anxiety ($t = 3.8$, $p < 0.0001$), state

anxiety (t = 3.6, p = 0.001), worst pain (t = 2.3, p = 0.05), sleep disturbance (t = 3.0, p = 0.006), morning fatigue (t = 3.7, p = 0.001), and evening fatigue (t = 4.1, p < 0.0001).

QOL-FV Psychological Subscale – The mean QOL–FV psychological subscale score for the entire sample was 6.5 $\pm$ 1.7. As shown in Figure 2B, significantly lower psychological subscale scores were reported by FCs in the high symptom group compared to the low symptom group for depression (t = 3.1, p = 0.003), trait anxiety (t = 5.7, p < 0.0001), state anxiety (t = 4.6, p < 0.0001), morning fatigue (t = 5.6, p < 0.0001), and evening fatigue (t = 2.0, p = 0.05).

QOL-FV Social Subscale – The mean QOL–FV social subscale score for the entire sample was 7.6 $\pm$ 1.7. As shown in Figure 2C, significantly lower social subscale scores were reported by FCs in the high symptom group compared to the low symptom group for depression (t = 3.1, p = 0.003), trait anxiety (t = 3.3, p = 0.002), state anxiety (t = 3.2, p = 0.002), morning fatigue (t = 4.2, p = 0.0001), and evening fatigue (t = 2.9, p = 0.005).

QOL-FV Spiritual Subscale – The mean QOL–FV spiritual subscale score for the entire sample was 7.4 $\pm$ 1.4. As shown in Figure 2D, a significantly lower spiritual subscale score was reported by FCs in the high symptom group compared to the low symptom group only for state anxiety (t = 2.2, p = 0.031).

Discussion

This study is the first to evaluate the prevalence and severity of five common symptoms in the same sample of FCs of patients with prostate cancer. Of note, for state and trait anxiety and morning fatigue, the mean symptom severity scores for the total

sample were above the established cutoffs for clinically significant symptom severity. In addition, for trait and state anxiety, as well as for sleep disturbance and morning and evening fatigue, 30% to 58% of the sample was found to have clinically significant symptom severity scores. As noted in Table 2, all of the prevalence rates for these five symptoms in the high group are higher than the lowest prevalence rates reported for depression,[33-36] anxiety,[33] chronic pain,[37-41] sleep disturbance,[42-45] and fatigue,[46] in the general population.

In addition to the high prevalence rates for these symptoms, findings from this study suggest that these symptoms have negative effects on FC's functional status and QOL. Higher levels of depression, trait anxiety, worst pain, sleep disturbance, and morning fatigue were associated with lower KPS scores even in this relatively small sample of women who reported high levels of function. Even stronger negative correlations were found among all of the symptom severity scores except worst pain, and the total and subscale scores of the QOL-FV. Taken together, these findings confirm those of two previous studies of the negative impact of symptoms on the functional status of FCs.[5,6]

One of the advantages of the symptom scales used in this study is that they have established cutpoints for clinically significant scores. Therefore, we were able to evaluate the impact of clinically significant levels of each of these symptoms on FC outcomes. FCs with high levels of trait anxiety, worst pain, sleep disturbance, and morning fatigue reported significantly lower KPS scores. It is important to note that the differences in KPS scores between the high and low groups for each symptom represent not only

statistically but clinically significant differences in functional status based on calculations of effect sizes (i.e., d = 0.59 for trait anxiety, d = 1.06 for worst pain, d = 0.68 for sleep disturbance, d = 0.80 for morning fatigue, where d = mean of the low group – mean of the high group/standard deviation of the total sample or the difference between the two means in standard deviation units). Similarly, the differences in the total QOL scores between the high and low groups based on a calculation of effect size were clinically meaningful for depression (d = 1.3), trait anxiety (d = 1.1), state anxiety (d = 1.1), worst pain (d = 0.7), morning fatigue (d = 1.1), and evening fatigue (d = 0.7). This conclusion is based on reports that suggest that minimally important differences in QOL are in the range of 0.20 to 0.50 standard deviation units.[47-49]

A surprising finding in this study is the relatively low prevalence of pain (only 15%) in this sample of older women. This finding may be attributed to the fact that the cutoff for pain was relatively high (worst pain score of 7). However, this cutpoint was chosen because in a previous study it was associated with deleterious effects on function.[32] However, in the group of FCs who reported pain, 82% had pain at or above this cutpoint. In addition, the most common comorbidities reported by this group of FCs were back problems (100%), headaches (64%), and arthritis (55%).

Several limitations of this study are worth noting. The generalizability of the study findings is limited by inclusion of only female FCs and because the majority of these FCs were Caucasian and well-educated. In addition, these FCs were caring for patients who had early stage prostate cancer who were relatively well. Therefore, these

findings may be an underestimate of the symptom experience of FCs of patients with cancer.

Despite these limitations, the findings from this relatively small sample of female FCs suggest that clinically significant levels of anxiety, sleep disturbance, and fatigue occur in over 30% of FCs. In addition, these symptoms as well as depression and pain have negative effects on FC outcomes. Additional research is warranted to determine the co-occurrence of multiple symptoms and symptom clusters in FCs, as well as how these symptoms change over time and in relationship to the patient's disease trajectory. In the meantime, oncology clinicians need to be aware of the symptom burden of the FCs of their patients and the potential impact that these symptoms may have on the FC's ability to provide care to the patient.

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Table 1. Demographic characteristics and comorbid conditions of the family caregivers (n = 60) of men with prostate cancer

Characteristics	Mean (SD)
Age (years)	64.2 (8.8)
Education (years)	15.2 (2.8)
Karnofsky Performance Status Score	94.0 (10.5)
Gender	%
Female	100.0
Ethnicity	
African American	11.7
Asian or Pacific Islander	3.3
Caucasian	80.0
Other	5.0
Marital Status	
Married/partnered	93.3
Other	6.7
Employment Status	
Work for pay	36.7
Other	63.3
Lives with patient	
Yes	98.3
No	1.7
Comorbid Conditions	
Back problems	49.2
Arthritis	43.1
Hypertension	36.2
Headaches	35.6
Hemorrhoids	28.8

SD = standard deviation

Table 2. Prevalence of and differences in the mean symptom severity scores between the low and high symptom groups

Symptom Inventory and Cutpoint	Total Sample Symptom Severity Score	Low Group (below cutpoint)			High Group (above cutpoint)			Prevalence of symptoms in general population
	Mean (SD)	% (n)	Mean	(SD)	% (n)	Mean	(SD)	%
Depression (CES-D) High ≥ 16	8.4 (6.5)	87.9 (51)	6.7	(4.4)	12.1 (7)	21.0	(5.2)	2.6-9.6
Trait Anxiety (STAI-T) High ≥ 31.8	35.3 (9.6)	42.4 (25)	26.3	(3.1)	57.6 (34)	42.0	(6.9)	16.9-19.5
State Anxiety (STAI-S) High ≥ 32.2	32.6 (10.6)	59.3 (35)	26.0	(3.8)	40.7 (24)	42.2	(9.9)	
Worst pain High ≥ 7.0	1.4 (3.1)	85.0 (51)	0.2	(1.0)	15.0 (9)	8.2	(1.0)	10.8-24.4 chronic pain
Sleep Disturbance (GSDS) High ≥ 43.0	39.9 (16.2)	63.3 (38)	30.0	(7.9)	36.7 (22)	56.8	(12.1)	27.7-37.2 insomnia
Morning Fatigue (LFS) High ≥ 3.2	2.5 (2.1)	66.7 (40)	1.2	(1.0)	33.3 (20)	5.0	(1.2)	22.0-38.0
Evening Fatigue (LFS) High ≥ 5.6	4.3 (2.3)	70.0 (42)	3.1	(1.7)	30.0 (18)	6.9	(0.8)	

Abbreviations: CES-D = Center for Epidemiological Studies - Depression, GSDS = General Sleep Disturbance Scale, LFS = Lee Fatigue Scale, SD = standard deviation, STAI-S = Spielberger State Anxiety Inventory, STAI-T = Spielberger Trait Anxiety Inventory

Table 3. Correlations among the symptom severity scores for depression, anxiety, pain, sleep disturbance, and fatigue

	Depression	Trait Anxiety	State Anxiety	Worst Pain	Sleep Disturbance	Morning Fatigue	Evening Fatigue
Depression	1	**.75** **< 0.0001** **n = 58**	**.78** **< 0.0001** **n = 58**	.22 0.10 n = 58	**.31** **0.02** **n = 58**	**.44** **< 0.0001** **n = 58**	.23 0.08 n = 58
Trait Anxiety		1	**.69** **< 0.0001** **n = 58**	**.35** **0.01** **n = 59**	**.33** **0.01** **n = 59**	**.48** **< 0.0001** **n = 59**	.20 0.12 n = 59
State Anxiety			1	.14 0.30 n = 59	**.30** **0.02** **n = 59**	**.44** **< 0.0001** **n = 59**	.18 0.18 n = 59
Worst Pain				1	**.30** **0.02** **n = 60**	**.35** **0.01** **n = 60**	.23 0.08 n = 60
Sleep Disturbance					1	**.44** **< 0.001** **n = 60**	**.43** **< 0.0001** **n = 60**
Morning Fatigue						1	**.54** **< 0.0001** **n = 60**
Evening Fatigue							1

Significant correlations are in bold

Table 4. Correlations among symptom severity scores and Karnofsky Performance Status score (KPS) and Quality of Life Inventory (QOL-FV) scores

	KPS	QOL-FV				
		Total Score	Physical Subscale	Psychological Subscale	Social Subscale	Spiritual Subscale
Depression	**-.32** **0.02** **n = 53**	**-.70** **< 0.0001** **n = 55**	**-.52** **< 0.0001** **n = 57**	**-.69** **< 0.0001** **n = 54**	**-.58** **< 0.0001** **n = 56**	**-.39** **0.004** **n = 54**
Trait Anxiety	**-.36** **0.01** **n = 54**	**-.63** **< 0.0001** **n = 56**	**-.42** **0.001** **n = 58**	**-.67** **< 0.0001** **n = 55**	**-.45** **<0.0001** **n = 57**	**-.32** **0.02** **n = 55**
State Anxiety	-.08 0.55 n = 54	**-.65** **< 0.0001** **n = 56**	**-.39** **0.002** **n = 58**	**-.66** **< 0.0001** **n = 55**	**-.48** **< 0.0001** **n = 57**	**-.46** **< 0.0001** **n = 55**
Worst Pain	**-.39** **0.01** **n = 60**	**-.30** **0.02** **n = 57**	**-.42** **0.001** **n = 59**	**-.28** **0.04** **n = 56**	-.21 0.12 n = 58	-.03 0.83 n = 56
Sleep Disturbance	**-.32** **0.02** **n = 55**	**-.40** **0.002** **n = 57**	**-.42** **0.0001** **n = 59**	**-.36** **0.007** **n = 56**	**-.34** **0.009** **n = 58**	-.16 0.24 n = 56
Morning Fatigue	**-.28** **0.04** **n = 55**	**-.62** **< 0.0001** **n = 57**	**-.66** **< 0.0001** **n = 59**	**-.59** **< 0.0001** **n = 56**	**-.52** **< 0.0001** **n = 58**	**-.28** **0.04** **n = 56**
Evening Fatigue	-.08 0.55 n = 55	**-.31** **0.02** **n = 57**	**-.55** **< 0.0001** **n = 59**	**-.28** **0.04** **n = 56**	**-.27** **0.04** **n = 58**	.06 0.66 n = 56

Significant correlations are in bold

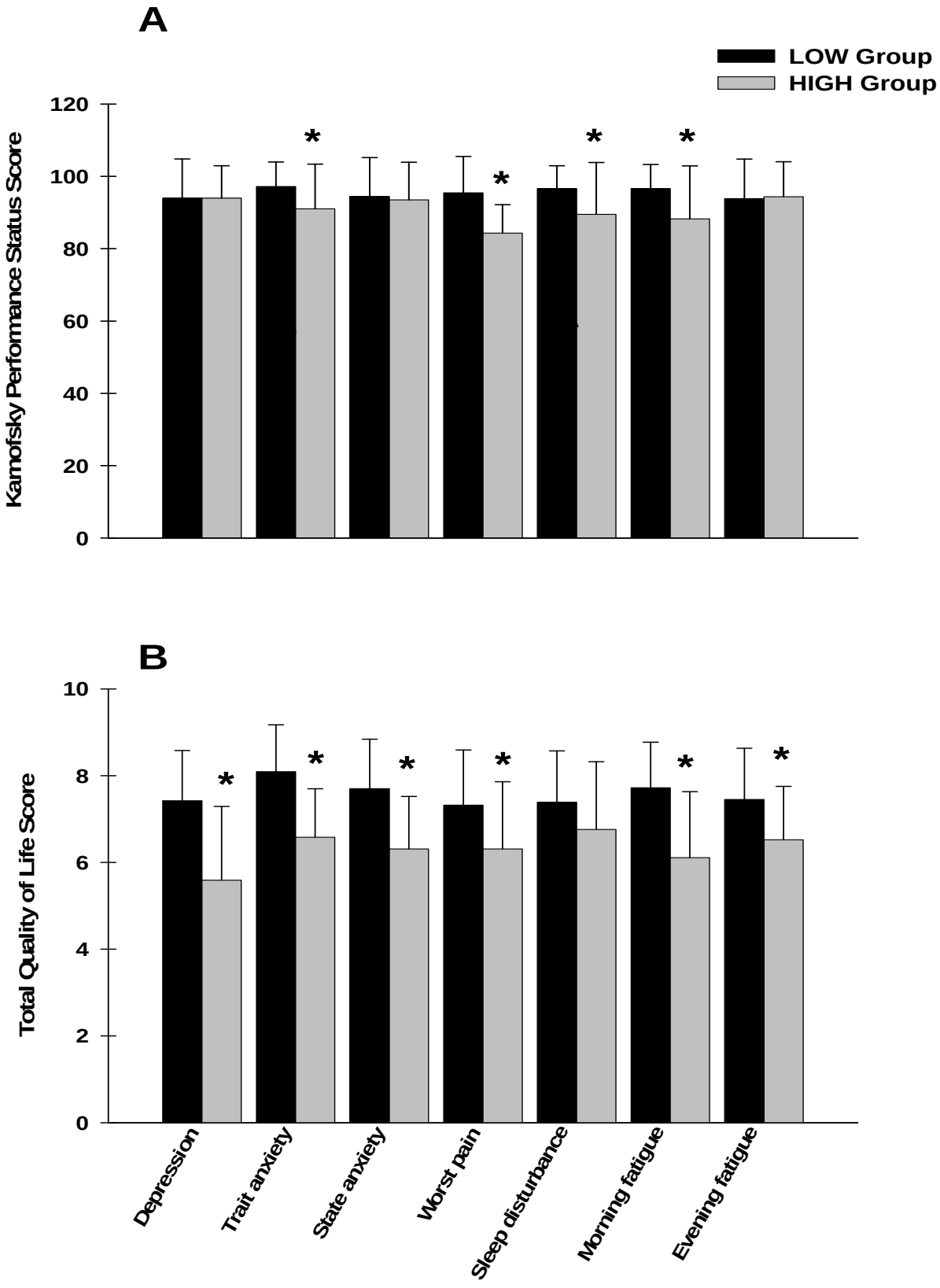
Figure Legends

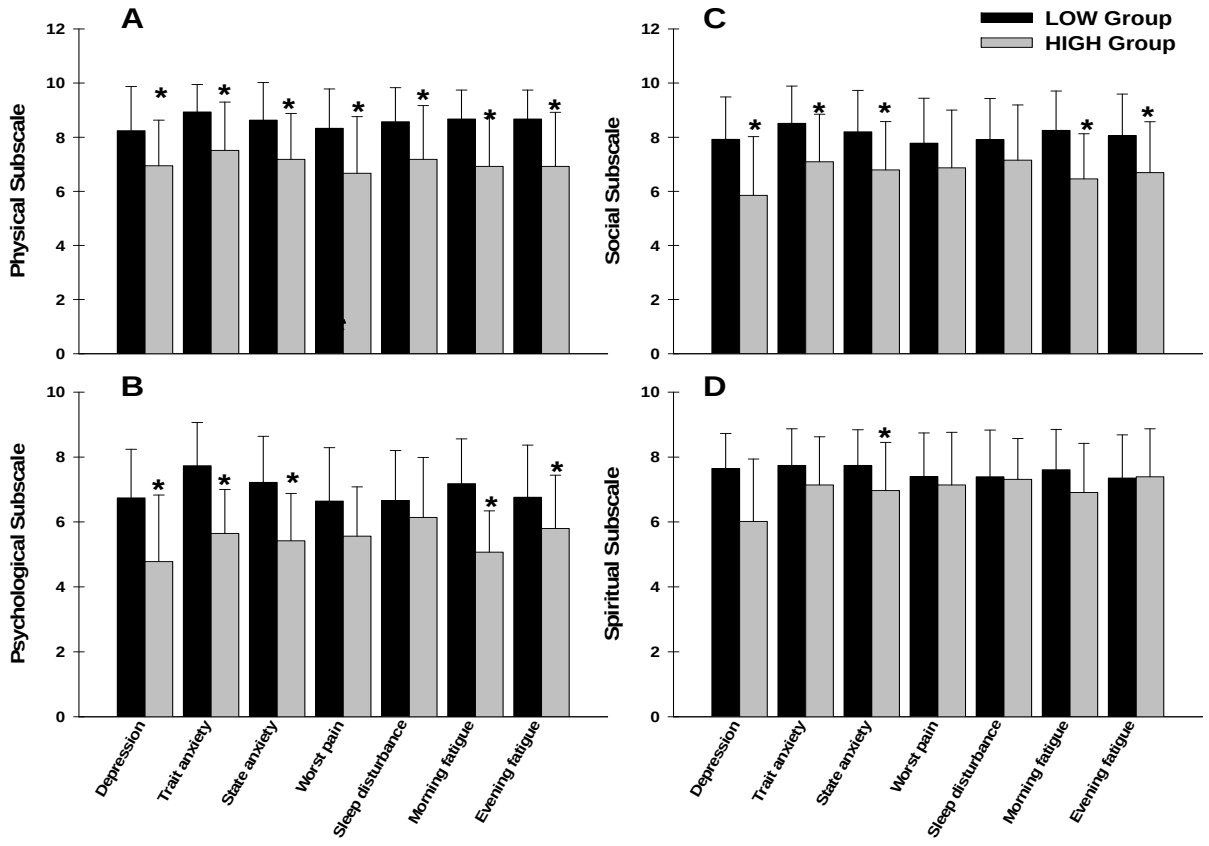
Figure 1. Differences in Karnofsky Performance Status and Quality of Life scores between family caregivers with low and high symptoms

For each symptom, differences in Karnofsky Performance Status (A) and total Quality of Life (B) scores between family caregivers in the low and high symptom groups are shown. Values are expressed as means and standard deviations. The * represents significant differences between the groups at a p–value of ≤ 0.05.

Figure 2. Differences in Quality of Life subscale scores between family caregivers with low and high symptoms

For each symptom, differences in the physical (A), psychological (B), social (C), and spiritual (D) subscale scores of the Quality of Life Scale – Family Version between family caregivers in the low and high symptom groups are shown. Values are expressed as means and standard deviations. The * represents significant differences between the groups at a p–value of ≤ 0.05.


A
LOW Group
HIGH Group
Karnofsky Performance Status Score
120
100
80
60
40
20
0
B
Total Quality of Life Score
10
8
6
4
2
0
Depression
Trait anxiety
State anxiety
Worst pain
Sleep disturbance
Morning fatigue
Evening fatigue


A
B
C
D
LOW Group
HIGH Group
Physical Subscale
Psychological Subscale
Social Subscale
Spiritual Subscale
0
2
4
6
8
10
12
*
Depression
Trait anxiety
State anxiety
Worst pain
Sleep disturbance
Morning fatigue
Evening fatigue

Trajectories of Fatigue in Family Caregivers of Patients Undergoing Radiation Therapy for Prostate Cancer

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Abstract

Purpose: In a sample of FCs of patients who underwent radiation therapy (RT) for prostate cancer, the purposes were to examine how ratings of evening and morning fatigue changed from the time of the simulation visit to 4 months after the completion of RT and to investigate whether specific personal, environmental, health and illness characteristics, and/or symptoms in FCs as well as personal, disease, and/or symptom characteristics in the patient predicted the initial levels of fatigue and/or changes in the characteristics of the trajectories of evening and morning fatigue in FCs.

Methods: FCs were recruited before the patient initiated RT and completed Center for Epidemiologic Studies – Depression Scale, Spielberger State Trait Anxiety Inventory, Lee Fatigue Scale, General Sleep Disturbance Scale, and a numeric rating scale for worst pain intensity. Descriptive statistics and frequency distributions were generated on the sample characteristics using SPSS TM Version 14.0. Hierarchical linear modeling (HLM), based on full maximum likelihood estimation, was performed to evaluate the trajectories of fatigue.

Results: Evening fatigue in FCs increased over the course of the patients' RT and then declined after the completion of RT. Baseline level of sleep disturbance in the FC and baseline level of evening fatigue in the patient predicted the inter-individual differences in the intercept for evening fatigue. Of note, even after controlling for FCs' level of fatigue at the beginning of RT, this variable predicted inter-individual variability in both the linear and quadratic components of the evening fatigue trajectories.

Changes in morning fatigue over the course of the patients' RT fit a linear model with fatigue scores decreasing over time. The three variables that predicted inter-individual differences in the intercept for morning fatigue were levels of trait anxiety in FCs, levels of perceived family support, and levels of morning fatigue in the patient at the beginning of RT. Eight morning fatigue trajectories were identified based on these three predictors of inter-individual variability.

Conclusions: Findings from this study demonstrate the large amount of inter-individual variability in the trajectories of evening and morning fatigue in FCs of patients with cancer. Of note, the trajectories and predictors of evening and morning fatigue were different. These types of analyses provide insights into subgroups of FCs who are at risk for higher levels of symptoms and may provide insights that will guide the development of more targeted interventions. (391 words)

Introduction

In the last decade, the number of family caregivers (FCs) caring for a patient with cancer has grown and at the same time the complexity of that care has increased tremendously. With cancer treatment routinely being delivered in the outpatient setting, FCs are frequently called upon to give care that requires problem solving and clinical judgment, as well as organizational and communication skills for which they have received little or no training (Schumacher, Beck, & Marren, 2006).

In the face of these increasing challenges and responsibilities, FCs report feelings of stress, burden, or depression (for review see (Blanchard, Albrecht, & Ruckdeschel, 1997; B. A. Given & Given, 1994; B. A. Given, Given, & Kozachik, 2001; B. A. Given & Sherwood, 2006; Nijboer, Triemstra, Tempelar, Sanderman, & van den Bos, 1998; Pitceathly & Maguire, 2003; Weitzner, Haley, & Chen, 2000)). Given the physical and mental demands of caregiving, it is reasonable to hypothesize that FCs would experience significant levels of fatigue. However, in a recent review of symptom prevalence (Fletcher, Dodd, Schumacher, & Miaskowski, in review), only eight studies were found that evaluated fatigue in FCs of patients with cancer (Campbell et al., 2004; Cho et al., 2006; B.R. Ferrell et al., 1999; Gaston-Johansson et al., 2004; S. Jensen & Given, 1991; C. Miaskowski et al., 1997; Passik & Kirsh, 2005; Teel & Press, 1999). Two studies (Cho et al., 2006; Gaston-Johansson et al., 2004) found that higher fatigue scores were associated with higher depression and anxiety scores and two studies (S. Jensen & Given, 1991; Passik & Kirsh, 2005) found that higher fatigue scores were associated with increased FC burden. In addition, recent work from Fletcher et al. (in review), found that

30.0% of FCs of patients with prostate cancer reported clinically significant levels of evening fatigue, and 33.3% reported clinically significant levels of morning fatigue at the initiation of the patients' radiation therapy (RT). In addition, these FCs reported significantly lower functional status and QOL scores compared to those FCs with low levels of fatigue. Of note, only one study (Passik & Kirsh, 2005) has assessed changes in the severity of fatigue and found that increased levels of patient fatigue were associated with increased levels of FC fatigue. In addition, spouses who reported higher levels of burden experienced more fatigue, had worse dyadic adjustment, reported poor energy levels, and tended to engage in fewer work and social activities.

Given the preliminary evidence that fatigue is a problem for FCs, as well as the paucity of longitudinal studies on fatigue in FCs of patients with cancer, the purposes of this study, in a sample of FCs of patients who underwent RT for prostate cancer, were: to examine how ratings of evening and morning fatigue changed from the time of the simulation visit to four months after the completion of RT and to investigate whether specific personal, environmental, health and illness, and/or symptom characteristics in the FCs as well as personal, disease, and symptom characteristics in the patients predicted the initial levels of fatigue and/or characteristics of the trajectories of evening and morning fatigue in FCs.

Methods

Participants and Settings

This descriptive, longitudinal study is part of a larger study that evaluated multiple symptoms in patients who underwent primary or adjuvant RT and in their FCs.

The participants were recruited from two RT departments at the time of the patient's simulation visit.

Following recruitment of the patients with prostate cancer, they were asked to identify the person most involved in their care (i.e., their FC). If the FC was with the patient, the research nurse explained the study and obtained written informed consent from the FC. FCs who were not with the patient were contacted by phone to determine their interest in study participation. The research nurse visited those FCs at home, obtained written informed consent, and enrolled them in the study.

FCs were eligible to participate if they: were an adult (≥ 18 years of age); were able to read, write, and understand English; gave written informed consent; had a Karnofsky Performance Status (KPS) score of > 60; were living with the patient who was receiving primary or adjuvant RT for prostate cancer; and did not have a diagnosed sleep disorder. This study was approved by the Human Subjects Committee at the University of California, San Francisco and at the second study site.

One hundred and eighty-eight patients with prostate cancer were approached and 82 consented to participate in this study (43.6% response rate). Of these 82, 60 had a female FC who agreed to participate. The major reasons why patients refused were: being too overwhelmed with their cancer experience or too busy. No differences were found in any of the demographic characteristics between the patients who did and did not choose to participate in this study.

Instruments

The study instruments included a demographic questionnaire, the Karnofsky Performance Status Scale (KPS) (Karnofsky, 1977), the Lee Fatigue Scale (LFS) (Lee, Hicks, & Nino-Murcia, 1991), the General Sleep Disturbance Scale (GSDS) (Lee, 1992), the Center for Epidemiological Studies-Depression Scale (CES-D) (Radloff, 1977), the Spielberg State-Trait Anxiety Inventories (STAI-S and STAI-T) (Spielberger et al., 1983), a descriptive numeric rating scale (NRS) for worst pain intensity, and the Caregiver Reaction Assessment (CRA) (C. W. Given et al., 1992).

The demographic questionnaire provided information on age, marital status, years of education, living arrangements, ethnicity, and employment status. In addition, patients and FCs completed a checklist of comorbidities and the KPS.

Fatigue severity was measured using the 13-item LFS. Each item was rated using a 0 to 10 NRS and a total score was calculated as the mean of the 13 items that can range from 0 to 10, with higher scores indicating higher levels of fatigue severity. Respondents were asked to rate each item based on how they felt "right now", within 30 minutes of awakening (i.e., morning fatigue) and prior to bed (i.e., evening fatigue). The LFS has been used with healthy individuals (Gay, Lee, & Lee, 2004; Lee et al., 1991) as well as in patients with cancer (C. Miaskowski & Lee, 1999) and HIV (Lee, Portillo, & Miramontes, 2001). It was chosen for this study because it is relatively short and easy to administer. The LFS has well established validity and reliability (Lee et al., 1991). In this sample, the Cronbach's alphas for the LFS for FCs' and patients' evening and morning ratings were .95 and .96, respectively.

The GSDS consists of 21 items that evaluate various aspects of sleep disturbance. Each item was rated on a NRS that ranged from 0 (never) to 7 (every day). The 21 items were summed to yield a total score that could range from 0 (no disturbance) to 147 (extreme sleep disturbance). The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV (Dorsey, Lee, & Scharf, 2004; Gay et al., 2004; Lee, 1992; Lee & Gay, 2004; C. Miaskowski & Lee, 1999). In the current study, the Cronbach's alphas for the GSDS total score were .79 and .81 for FCs and patients, respectively.

The CES-D consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores ≥ 16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity (Carpenter et al., 1998; Sheehan, Fifield, Reisine, & Tennen, 1995). In the current study, the Cronbach's alphas for the CES-D were .84 and .83 for FCs and patients, respectively.

The STAI-T and STAI-S inventories consist of 20 items each that are rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. A higher score indicates greater anxiety. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality and estimates how a person feels generally. The STAI-S measures an individual's transitory emotional response to a stressful situation. It evaluates the emotional response of worry, nervousness, tension, and feelings of apprehension related to how people feel "right now" in a stressful situation. The STAI-S and STAI-T inventories have well-established criterion and construct validity and internal

consistency reliability coefficients (Bieling, Antony, & Swinson, 1998; Kennedy, Schwab, Morris, & Beldia, 2001; Stanley, Novy, Bourland, Beck, & Averill, 2001). In this study, the Cronbach's alphas for the STAI-T and STAI-S for FCs were .89 and .93, respectively. The Cronbach's alphas for the STAI-T and STAI-S for patients were .86 and .91, respectively.

Worst pain intensity was evaluated using a descriptive NRS that ranged from 0 (no pain) to 10 (excruciating pain). A descriptive numeric rating scale is a valid and reliable measure of pain intensity (M. P. Jensen, 2003).

The CRA is a 24-item instrument used to evaluate the FC's experience of caregiving. Each item is rated on a Likert scale that ranges from 1 (strongly agree) to 5 (strongly disagree). Five subscale scores (i.e., caregiver's health problems – 4 items, impact of caregiving on self-esteem – 7 items, disrupted schedule – 5 items, financial problems – 3 items, and lack of family support – 5 items) are created as the mean of the responses to the items in the subscale. The CRA has well established validity and reliability in FCs of patients with dementia (C. W. Given et al., 1992) and cancer (B. Given & Given, 1992; C.W. Given et al., 1993; M. E. Kurtz et al., 1994; M. E. Kurtz et al., 1995, 2004; Nijboer et al., 2001; Nijboer, Triemstra, Tempelar, Sanderman, & van den Bos, 1999; Sherwood et al., 2006). In this sample, Cronbach's alpha for the CRA was .84.

Study Procedures

At the time of the simulation visit (i.e., approximately 1 week prior to the start of RT), patients were approached by a research nurse to discuss participation in the study.

After obtaining written informed consent, patients and their FCs were asked to complete the baseline study questionnaires. They were taught to complete the LFS before going to bed each night (i.e., evening fatigue) and upon arising each morning (i.e., morning fatigue) for two consecutive days. Assessments were done at the time of the simulation visit (i.e., baseline), weekly during the course of RT, every two weeks for two months, and once a month for two months following the completion of RT. The majority of FCs completed 16 assessments.

Data Analysis

Descriptive statistics and frequency distributions were generated on the sample characteristics using SPSS™ Version 14.0. For each of the 16 assessments, a mean for each of the LFS scores (i.e., evening and morning) was calculated for use in the subsequent statistical analyses. Hierarchical linear modeling (HLM), based on full maximum likelihood estimation, was done using the software developed by Raudenbush and colleagues (Raudenbush & Bryk, 2002). The repeated measures of fatigue were conceptualized as being nested within individuals. Compared with other methods of analyzing change, HLM has two major advantages. First, HLM can accommodate unbalanced designs which allows for the analysis of data when the number and the spacing of the assessments vary across respondents. Although every FC was to be assessed on a pre-specified schedule, the actual number of assessments was not the same for all of the FCs because some patients had longer periods of RT and some had scheduling conflicts. Second, HLM has the ability to model individual change, which

helps to identify more complex patterns of change that are often overlooked by other methods.

With HLM, the repeated measures of the outcome variable (i.e., evening or morning fatigue in FCs) is nested within individuals and the analysis of change in fatigue scores has two levels: within persons (Level 1) and between persons (Level 2). At Level 1, the outcome is conceptualized as varying within individuals and is a function of person-specific change parameters plus error. At Level 2, these person-specific change parameters are multivariate outcomes that vary across individuals. These Level 2 outcomes can be modeled as a function of demographic or clinical characteristics that vary between individuals, plus an error associated with the individual. Combining Level 1 with Level 2 results in a mixed model with fixed and random effects.

Separate HLM analyses were done to evaluate changes over time in ratings of evening and morning fatigue in FCs. Each HLM analysis proceeded in two stages. First, intra-individual variability in fatigue over time was examined. In this study, time refers to the length of time from the simulation visit to four months after the completion of RT (i.e., six months with a total of 16 assessments). Three Level 1 models, which represented that the FCs' fatigue levels (a) did not change over time (i.e., no time effect), (b) changed at a constant rate (i.e., linear time effect), and (c) changed at a rate that accelerates or decelerates over time (i.e., quadratic term) were compared. At this point, the Level 2 model was constrained to be unconditional (i.e., no predictors) and likelihood ratio tests were used to determine the best model. These analyses answered the first research

question and identified the change parameters that best described individual changes in evening and morning fatigue over time.

The second stage of the HLM analysis, which answered the second research question, examined inter-individual differences in the trajectories of evening and morning fatigue in FCs by modeling the individual change parameters (i.e., intercept, linear, and quadratic slopes) as a function of proposed predictors at Level 2. Table 1 presents a list of the proposed predictors that was developed based on a review of the literature on fatigue in FCs and patients with cancer. To improve estimation efficiency and construct a model that was parsimonious, an exploratory Level 2 analysis was done and predictors with a t-value of < 2.0 were dropped from subsequent model testing. All of the potentially significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a significant contribution in conjunction with other variables were retained in the final model. A p-value of <.05 indicates statistical significance.

Results

Family Caregiver and Patient Characteristics

The demographic characteristics and comorbid conditions of the FCs are presented in Table 2a. The FCs were approximately 64 years of age, well educated, and had a baseline KPS score of 94.0. Ninety-three percent were married, 80% Caucasian, and approximately 37% were employed at the time of the study. Over 35% of the FCs reported back problems, arthritis, hypertension, or headaches at the baseline visit.

The demographic, disease, and treatment characteristics of the patients are presented in Table 2a and 2b. The men with prostate cancer were approximately 68.1 years of age and had a KPS score of 96.8. The distribution of clinical stage was 46.7% with T1, 40.0% with T2, and 10.0% with T3. Over 50% of the patients received hormonal therapy prior to the initiation of RT. The mean time since diagnosis was 9.7 + 15.1 months.

Individual and Mean Change in Evening and Morning Fatigue in Family Caregivers

Changes in evening and morning fatigue from the time of the simulation visit to 4 months after the completion of RT were examined in the first HLM analysis. Two models were estimated in which the function of time was linear and quadratic. Table 3 presents the two nested models. For evening fatigue, the likelihood ratio tests indicated that a quadratic model fit the data significantly better than a linear model. For morning fatigue, the linear model was a better fit than the quadratic model.

Evening Fatigue – The estimates of the quadratic change model are presented in Table 4 (unconditional model). Because the model has no covariates (i.e., unconditional), the intercept represents the estimate of the amount of evening fatigue in FCs (i.e., 4.335 on a 0 to 10 scale) at the time of the patient's simulation visit. The estimated linear rate of change in evening fatigue at each assessment time was 0.126 ($p < 0.0001$) and the estimated quadratic change was -0.004 ($p < 0.0001$).

Figure 1 displays the trajectory for evening fatigue in FCs from the time of the patient's simulation visit to 4 months after the completion of RT. Evening fatigue in FCs

increased over the course of the patients' RT and then declined after the completion of RT.

Morning Fatigue – The unconditional model is shown in Table 4 and the intercept represents the estimated amount of morning fatigue in FCs (i.e., 2.636) at the time of the simulation visit. The estimated linear rate of change at each assessment time was -0.0180 ($p = 0.005$).

Figure 1 displays the trajectory for morning fatigue in FCs from the time of the patient's simulation visit to 4 months after the completion of RT. Morning fatigue gradually decreased over time.

Although these sample wide results indicate uniform changes over time, they do not imply that all FCs exhibited the same trajectory. The variance in individual change parameters estimated by the models (i.e., variance components, Table 4) suggested that substantial inter-individual differences existed in the trajectories of evening and morning fatigue. These differences in evening and morning fatigue are illustrated in Figures 2A and 2B. Such results suggested that further examination of the inter-individual differences in the individual change parameters was warranted.

Inter-individual Differences in the Trajectories of Evening and Morning Fatigue in Family Caregivers

The hypothesis that characteristics of the FC (i.e., personal, environmental, health and illness, symptoms) as well as of the patient (i.e., personal, disease, symptoms) might influence the trajectories of evening and morning fatigue in FCs was tested in the next HLM analyses. Exploratory analyses were completed with all of the potential predictor

variables listed in Table 1. To improve estimation efficiency and construct models that were parsimonious, exploratory Level 2 analyses were done and predictors with a t-value of < 2.0 were dropped from the model testing. All of the significant predictors from these exploratory analyses were entered into the models to predict each individual change parameter (i.e., intercepts and/or slopes). Only predictors that maintained a significant contribution in conjunction with other variables were retained in the final models of evening and morning fatigue in FCs.

Evening Fatigue in FCs – Table 4 shows the final model for evening fatigue in FCs. The two variables that predicted the inter-individual differences in the intercept for evening fatigue were baseline level of sleep disturbance in the FC and baseline level of evening fatigue in the patient. Baseline level of evening fatigue in the FC was entered in Level 2 as a predictor of the slope parameters to control for intra-individual differences in evening fatigue at baseline. Baseline level of evening fatigue in the FC was the one variable that predicted inter-individual differences in the slope parameters for evening fatigue. In order to illustrate the effects of the different predictors on the trajectories of evening fatigue in FCs, Figure 3 was compiled to display the adjusted change curves of evening fatigue according to differences in baseline levels of sleep disturbance (i.e., high or low FC baseline sleep disturbance based on 1 standard deviation above and below the mean GSDS score), baseline levels of evening fatigue in patients (i.e., high or low baseline patients' evening fatigue based on 1 standard deviation above or below the mean evening LFS score), and baseline level of FC evening fatigue (i.e., high and low baseline

fatigue based on 1 standard deviation above and below the FC's mean evening LFS score).

Morning Fatigue in FCs – Table 4 shows the final model for morning fatigue in FCs. The three variables that predicted inter-individual differences in the intercept for morning fatigue were baseline levels of trait anxiety in FCs, baseline levels of family support, and baseline levels of morning fatigue in patients. Baseline levels of morning fatigue in FCs were entered in Level 2 as a predictor of the slope parameters to control for inter-individual differences in morning fatigue at baseline. No predictors were found that predicted the change in morning fatigue over time (i.e. slope). In order to illustrate the effects of the different predictors on the FCs' trajectories of morning fatigue, Figure 4 was compiled to display the adjusted change curves of morning fatigue according to differences in baseline levels of trait anxiety in FCs (i.e., high or low trait anxiety based on 1 standard deviation above and below the mean trait anxiety score for FCs), baseline levels of family support (i.e., high or low levels of family support based on 1 standard deviation above and below the mean CRA - lack of family support score), and baseline levels of morning fatigue in patients (i.e., high or low levels of morning fatigue based on 1 standard deviation above or below the patients' mean baseline morning LFS score).

Discussion

This longitudinal study is the first to examine inter-individual differences in the trajectories of evening and morning fatigue in FCs of patients undergoing RT for prostate cancer, as well as to determine the predictors for these trajectories. While direct comparisons are not possible because previous research did not distinguish between

evening and morning fatigue, our findings are consistent with studies of fatigue in patients with prostate cancer (Choo et al., 2006; Hickok et al., 2005; C Miaskowski, in review; Monga, Kerrigan, Thornby, Monga, & Zimmermann, 2005), that demonstrated that fatigue increased during RT and then decreased following the completion of RT. In addition, these findings are consistent with the only longitudinal study of fatigue in FCs (Passik & Kirsh, 2005) that demonstrated a decrease in FC fatigue at a one month follow-up. However, given the fact that this study is, to our knowledge, only the second longitudinal study of fatigue in FCs of patients with cancer, additional research is warranted to determine if similar fatigue trajectories occur in other groups of FCs where patients have different cancer diagnoses, are receiving different types of cancer treatments, or are in different stages of their disease process.

Consistent with previous cross-sectional studies (Lee et al., 1991; Lee, Portillo, & Miramontes, 1999) as well as the findings from one longitudinal study of the patients from this sample with prostate cancer (C Miaskowski, in review), ratings of evening fatigue were higher than ratings of morning fatigue across the six months of the study. While in the study of patients with prostate cancer, both evening and morning fatigue trajectories best fit a quadratic model, the morning fatigue trajectory of the FCs was linear. Reasons for these differences, while not readily apparent, may relate to the fact that different patient and FC characteristics were found to predict inter-individual differences in the trajectories of evening and morning fatigue. An alternative hypothesis is that the mechanisms that produce fatigue in patients and FCs may be different.

As shown in Figure 2A and 2B, the individual trajectories of evening and morning fatigue were extremely variable in this sample of FCs. In terms of evening fatigue, the levels of sleep disturbance in the FC at baseline, as well as the baseline level of evening fatigue in the patient predicted the inter-individual differences in the severity of evening fatigue at the time of the simulation visit (.e., intercept). These evening fatigue scores ranged from 2.69 to 6.57, holding the other predictors constant. It is interesting to note that for every one unit increase in patient's evening fatigue scores, FC's level of fatigue increased by 0.354 units. This finding is consistent with a previous report (Passik & Kirsh, 2005), that increased levels of fatigue in patients were associated with increased levels of fatigue in FCs. While the patient's level of fatigue did not predict the slope of the trajectories of evening fatigue in FCs, the patients' level of morning fatigue at baseline predicted the baseline level of morning fatigue in FCs. Taken together, these two findings suggest that studies of symptoms in FCs need to include an evaluation of symptom intensity in the patients, particularly if the purpose of the studies is to determine the predictors of symptom intensity in FCs.

As in our study of the patient cohort (C Miaskowski, in review), baseline levels of sleep disturbance in FCs predicted the inter-individual differences in the levels of evening fatigue in FCs at the time of the simulation visit. This finding is congruent with work by Cho and colleagues (2006), who reported a positive correlation between sleep disturbance and fatigue in a cross-sectional study of FCs of oncology patients. Of note, even after controlling for FCs' baseline levels of evening fatigue, this variable predicted inter-individual variability in both the linear and quadratic components of the trajectories.

When the final HLM model of evening fatigue was constructed, eight different fatigue trajectories were identified based on three predictors of inter-individual variability. As illustrated in Figure 3, two distinct groups of trajectories are evident that are influenced by baseline levels of fatigue in the FCs. Those FCs with lower levels of evening fatigue at baseline exhibited trajectories that gradually increased during the course of the patients' RT and then decreased following the completion of RT. Those FCs with higher levels of evening fatigue at baseline exhibited trajectories of evening fatigue that gradually increased over the course of the patients' RT. The predictor that influenced the overall severity of the fatigue trajectories was the FCs level of sleep disturbance at baseline. FCs with higher levels of sleep disturbance with either high or low levels of patient or FC evening fatigue at baseline had the higher evening fatigue scores over time.

An important finding from this study is that the trajectories and predictors of morning and evening fatigue in FCs were not identical. As shown in Table 4, the predictors of inter-individual variability in morning fatigue scores in FCs at the time of the simulation visit were: baseline trait anxiety in FCs, baseline level of family support, and patient's level of morning fatigue at baseline. No predictors of the linear slope were identified in this analysis. Of note, the predictors of the intercept for morning fatigue in FCs differed completely from those found to predict morning fatigue in the patients in this cohort (i.e., age, baseline level of sleep disturbance, and baseline level of depression). Reasons for these differences are not readily apparent and warrant evaluation in future studies. One potential reason for the differences in these predictor variables may

relate to the fact that the FC sample was all women, while the patient sample was men with prostate cancer.

As shown in Figure 4, all of the eight trajectories for morning fatigue decreased over time. Those FCs with the highest levels of morning fatigue reported higher levels of trait anxiety, lower levels of family support, and cared for patients with higher levels of morning fatigue at baseline. The morning fatigue scores reported by these FCs (i.e., 4.63) were above the cutpoint for clinically significant levels of morning fatigue of $\geq$ 3.2 (Fletcher, Paul et al., in review). Only one other study of FCs of cancer patients (Gaston-Johansson et al., 2004) found that higher anxiety scores were associated with higher fatigue scores in FCs.

Limitations of this study include the small sample size, the homogenous sample characteristics (i.e., all female, all FCs of patients with prostate cancer), and the focus on a single treatment modality (i.e., RT). Therefore, the findings may not generalize to other FC populations. Additional research is warranted to replicate these findings as well as to evaluate the fatigue trajectories of other groups of FCs of patients with cancer.

Based on the results of this study, FCs who report higher levels of sleep disturbance and baseline evening fatigue and whose patient partners report higher levels of baseline evening fatigue at the start of RT will be more likely to report higher levels of evening fatigue. In addition, FCs who report higher levels of baseline trait anxiety, lower levels of family support, and whose patient partners reported higher levels of morning fatigue at the start of RT will be more likely to report higher levels of morning fatigue.

Future research studies will need to confirm these findings as well as explore the trajectories of morning and evening fatigue in other samples of FCs.

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Table 1 - Potential Predictors of Intercept, Linear Coefficient, and Quadratic Coefficient for Evening and Morning Fatigue

Potential Predictors	Evening Fatigue			Morning Fatigue		
	Intercept	Linear Coefficient	Quadratic Coefficient	Intercept	Linear Coefficient	Quadratic Coefficient
Family Caregiver						
Person						
Age						
Relationship						
Marital status						
Education						
Ethnicity					●	
Environment						
CRA Impact on Schedule						
CRA Caregiver's Esteem						
CRA Lack of Family Support				●		
CRA Impact on Health						
CRA Impact on Finances						
Health and Illness						
KPS Score						
Number of comorbidities						
Symptoms						
Baseline GSDS score	●		●			
Baseline CES-D score	●		●	●		
Presence of pain at baseline						
Baseline trait anxiety score				●		

Baseline state anxiety score				●
Baseline evening fatigue score		●		
Baseline morning fatigue score	●			
Patient				
Person				
Age	●			●
Ethnicity				
Education				
Employment				
Health and Illness				
KPS score				
Number of comorbidities				
Symptoms				
Baseline GSDS score	●	●	●	●
Baseline CES-D score	●	●	●	●
Presence of pain at baseline				
Baseline trait anxiety score				●
Baseline state anxiety score				●
Baseline evening fatigue score	●			●
Baseline morning fatigue score				●

● = From exploratory analyses had a t-value > 2.00

Abbreviations: CES-D = Center for Epidemiologic Studies- Depression; CRA = Caregiver Reaction Assessment, GSDS = General Sleep Disturbance Score; KPS = Karnofsky Performance Status

Table 2a – Demographic Characteristics and Comorbid Conditions of the Family Caregivers and Patients (n=60)

Characteristic	Family Caregivers	Patients
	Mean (Standard Deviation)	Mean (Standard Deviation)
Age (years)	64.2 (8.8)	68.1 (7.9)
Education (years)	15.2 (2.8)	16.6 (3.2)
Karnofsky Performance Status Score	94.0 (10.5)	96.8 (5.45)
	%	%
Marital status		
Married/partnered	93.3	93.3
Other	6.7	6.7
Ethnicity		
Black	11.7	13.3
White	80.0	81.7
Other	8.3	5.0
Employed		
Yes	36.7	44.1
Comorbid Conditions		
Back problems	49.2	59.3
Arthritis	43.1	36.2
Hypertension	36.2	32.8
Headaches	35.6	19.0
Hemorrhoids	28.8	31.0

Table 2b – Patient Disease and Treatment Characteristics

	%
Gleason score	
5 or 6	40.0%
7	46.7%
$\geq$ 8	5.0%
Clinical stage	
T1	46.7%
T2	40.0%
T3	10.0%
Prostatectomy prior to RT	11.7%
Hormonal therapy prior to RT	51.7%
RT treatment plan	
Whole pelvis + conformal boost after surgery	11.7%
Whole pelvis + conformal boost	70.0%
Whole pelvis + high dose RT	5.0%
Whole pelvis + seed implant	13.3%
	Mean (standard deviation)
Total dose of RT (cGys)	6851 (1024.2)
Time since diagnosis (months)	9.7 (15.1)

Abbreviations: cGys = dose of RT in centigray units, RT = radiation therapy,

Table 3 - Comparison of Linear and Quadratic Models for Evening and Morning Fatigue

FATIGUE	VARIABLE	LINEAR MODEL	QUADRATIC MODEL
Evening	Goodness-of-fit deviance (# of parameters estimated)	2932.292 (6)	2886.014(10 46.278 (4)*
	Model comparison (χ^2 [*df*]) versus linear model	--------	
Morning	Goodness-of-fit deviance (# of parameters estimated)	2838.733 (6)	
	Model comparison (χ^2 [*df*]) versus linear model	--------	

*p < .0001

Table 4 - Hierarchical Linear Models of Evening and Morning Fatigue in Family Caregivers

Evening Fatigue	**Coefficient (SE)**	
Variable	Unconditional Model	Final Model
Fixed Effects		
Intercept	4.335 (0.249)*	4.335 (0.211)*
Time[a] (linear rate of change)	0.1256 (0.025)*	0.126 (0.027)*
Time^2 (quadratic rate of change)	-0.004 (0.001)*	-0.004 (0.001)*
Time invariant covariates[b]		
Baseline sleep disturbance in FC		-0.056 (0.012)*
Baseline evening fatigue in patient		0.354 (0.092)*
Baseline evening fatigue in FC x time		-0.043 (0.012)**
Baseline evening fatigue in FC x time^2		0.002 (0.000)**
Variance components		
In intercept	3.318*	2.276*
In linear rate	0.018*	0.025*
In quadratic fit	0.000*	0.000*
Goodness-of-fit deviance(parameters estimated)	2886.014 (10)	2854.033 (14)
Model comparison (χ^2 [*df*])		5.511 (5)+++

Morning Fatigue	Coefficient (SE)	
Variable	Unconditional Model	Final Model
Fixed Effects		
Intercept	2.636 (0.242)*	2.637 (0.190)*
Time[a] (linear rate of change)	-0.018 (0.006)***	-0.018 (0.006)***
Time invariant covariates[b]		
Baseline trait anxiety in FCs		0.090 (0.200)*
Baseline lack of family support		0.567 (0.266)****
Baseline morning fatigue in patients		0.408 (0.104)*
Variance components		
In intercept	3.289*	1.958*
In linear rate	0.001 ++	0.001++
Goodness-of-fit deviance(parameters estimated)	2838.733 (6)	2809.358 (10)
Model comparison (χ^2 [*df*])		4.35 (2)+

*p < 0.0001, **p = 0.001, ***p = 0.005. ****p = 0.037, +p ≤ 0.05, ++p = 0.02, +++p = 0.357

[a]Time was coded 0 at the time of the simulation visit

[b]Time invariant covariates taken from predictors of FC and patient fatigue in the literature

Figure legends

Figure 1 – Trajectories of evening and morning fatigue over the 25 weeks of the study

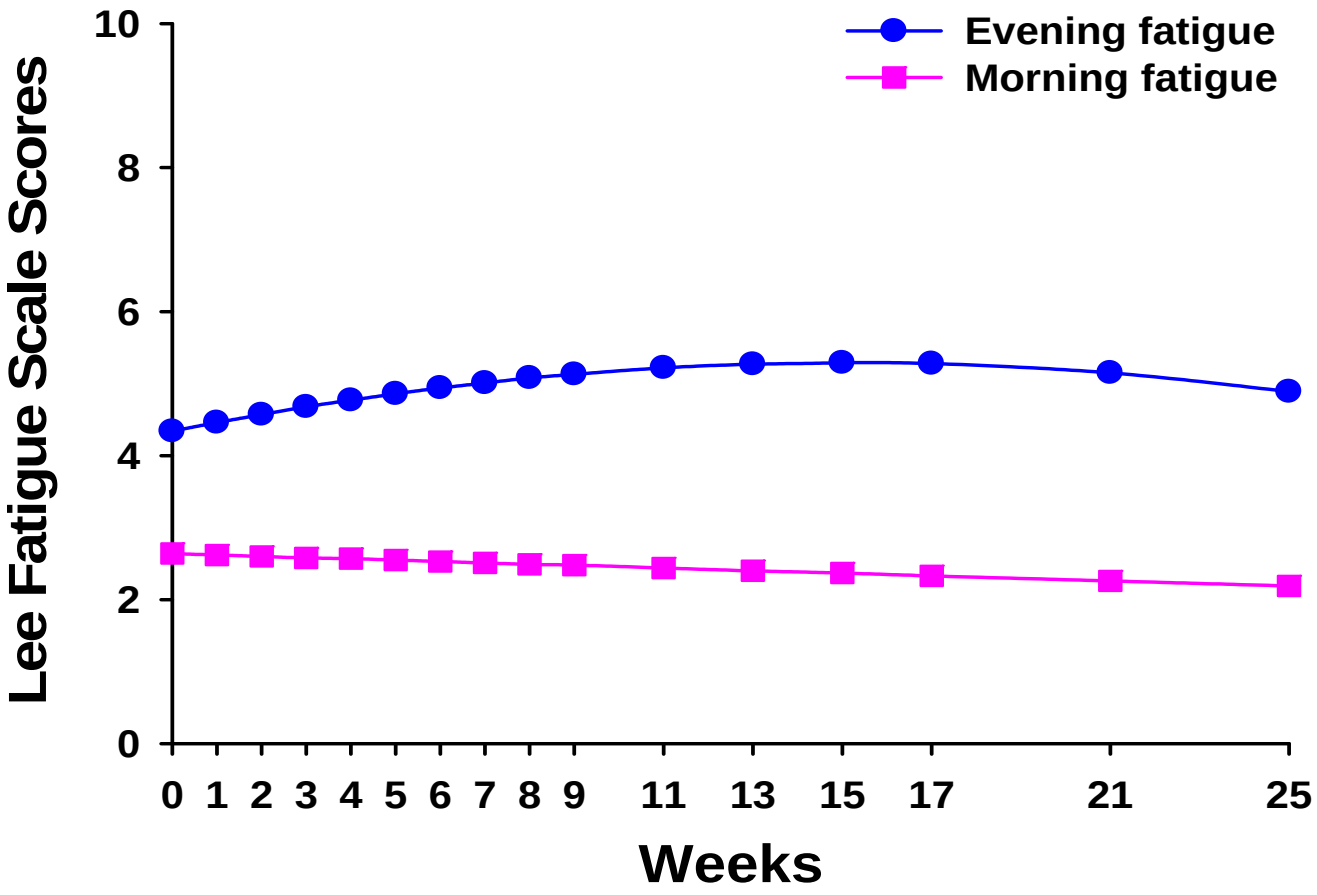
Figure 2 – Spaghetti plots of individual trajectories of evening (A) and morning (B) fatigue over the 25 weeks of the study

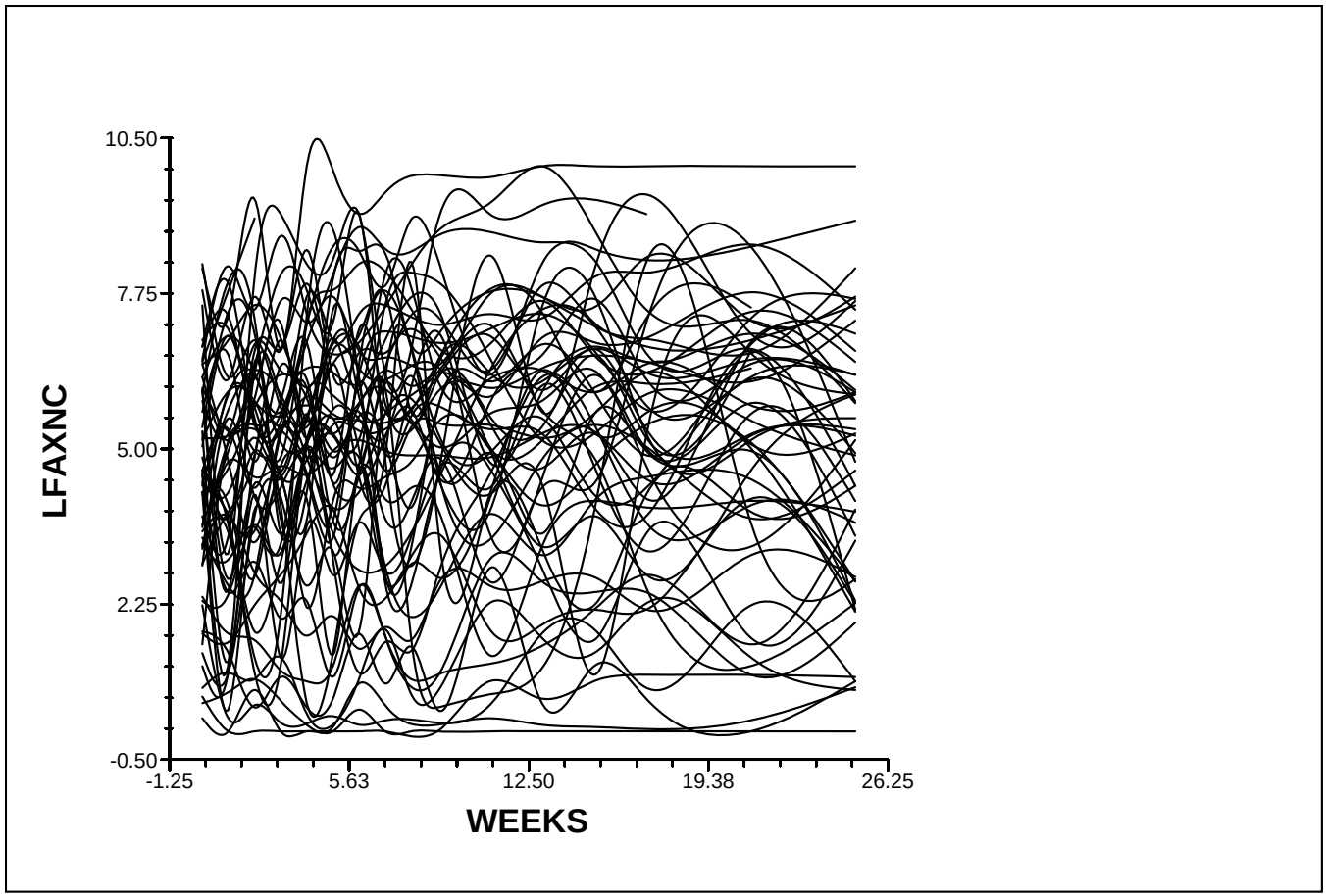
Figure 3 – Trajectories of evening fatigue

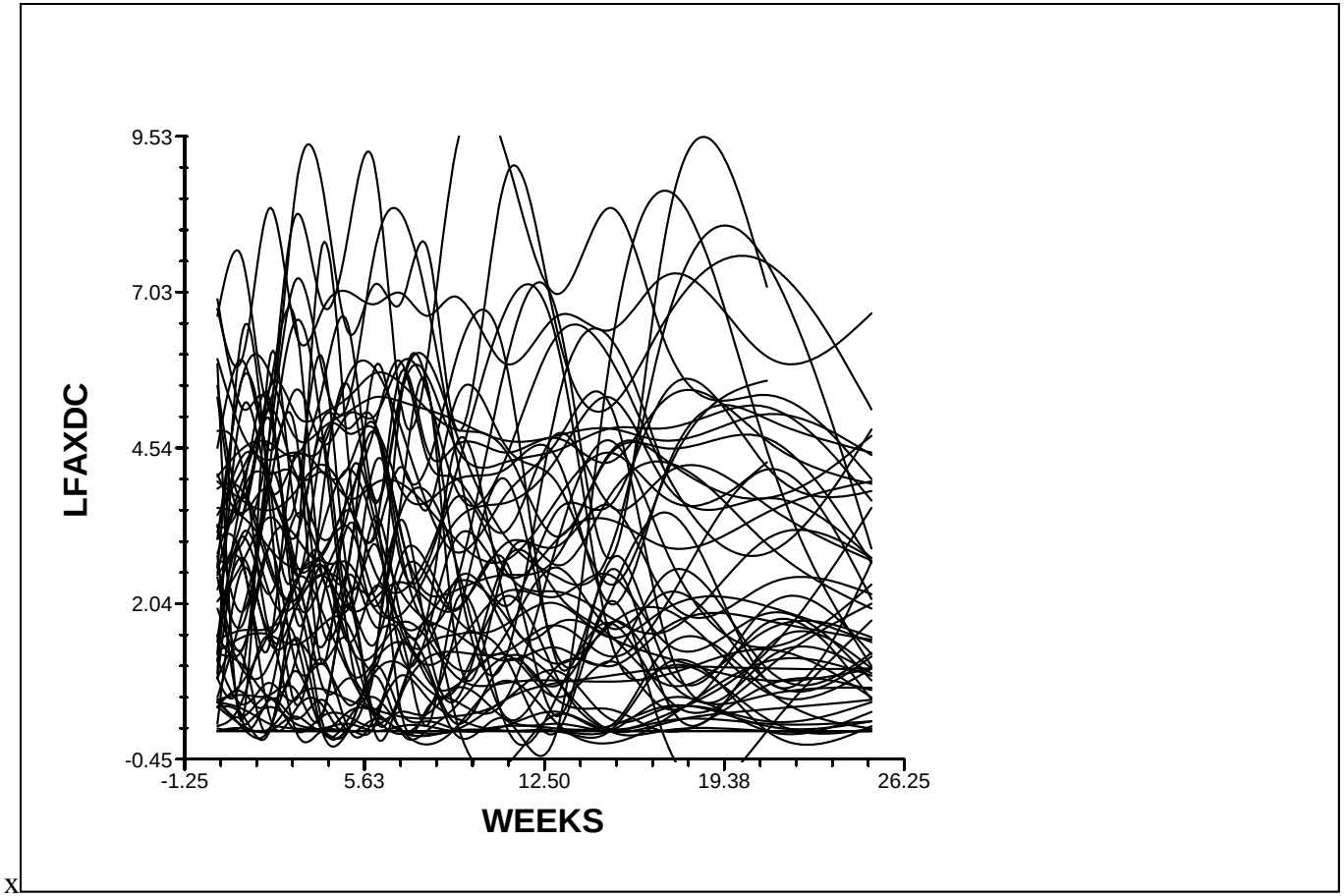
Trajectories of evening fatigue by level of sleep disturbance at baseline (i.e., low sleep/high sleep), level of evening fatigue in patients at baseline (low PT fatigue/high PT fatigue), and level of FC evening fatigue at baseline (i.e., low FC fatigue/high FC fatigue)

Figure 4 – Trajectories of morning fatigue

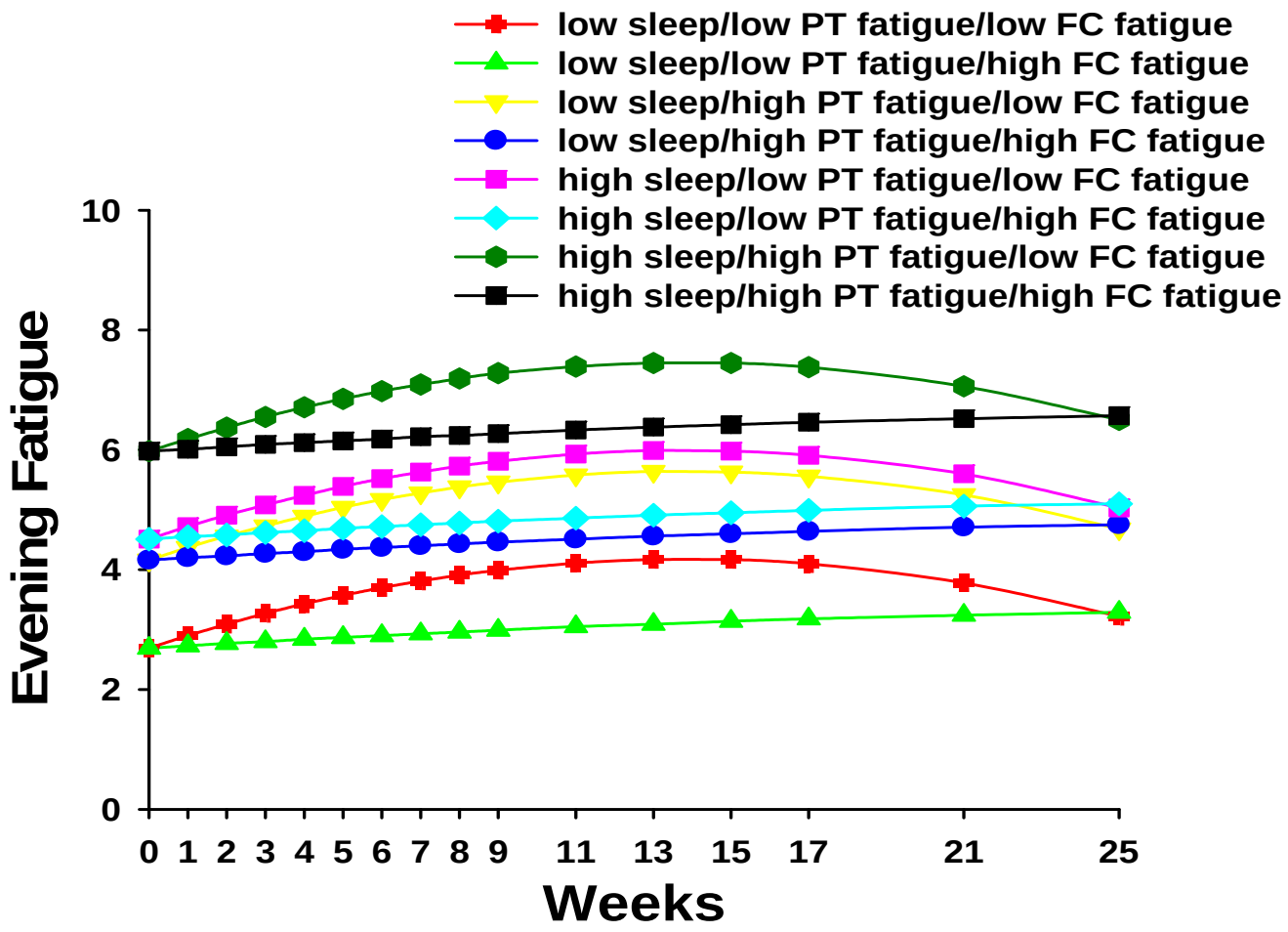
Trajectories of morning fatigue by level of FC trait anxiety at baseline (i.e., low FC anxiety/high FC anxiety), level of morning fatigue in patients at baseline (i.e., low. PT fatigue/high PT fatigue), and level of FC morning fatigue at baseline (i.e., low FC fatigue/high FC fatigue)

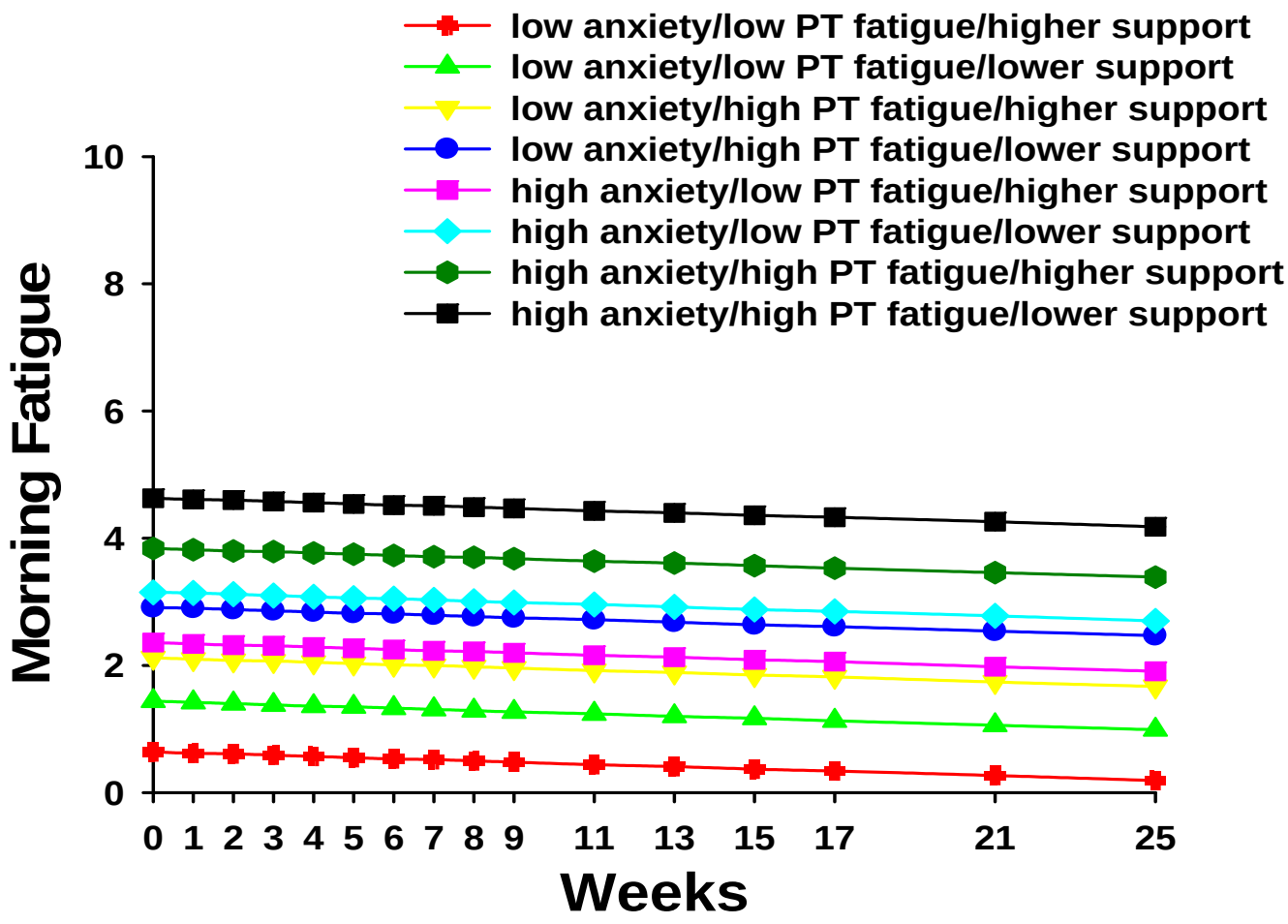

Evening fatigue
Morning fatigue
Lee Fatigue Scale Scores
10
8
6
4
2
0
0 1 2 3 4 5 6 7 8 9 11 13 15 17 21 25
Weeks


10.50
7.75
5.00
2.25
-0.50
LFAXNC
-1.25
5.63
12.50
19.38
26.25
WEEKS



x


low sleep/low PT fatigue/low FC fatigue
low sleep/low PT fatigue/high FC fatigue
low sleep/high PT fatigue/low FC fatigue
low sleep/high PT fatigue/high FC fatigue
high sleep/low PT fatigue/low FC fatigue
high sleep/low PT fatigue/high FC fatigue
high sleep/high PT fatigue/low FC fatigue
high sleep/high PT fatigue/high FC fatigue
Evening Fatigue
0
2
4
6
8
10
0 1 2 3 4 5 6 7 8 9 11 13 15 17 21 25
Weeks


low anxiety/low PT fatigue/higher support
low anxiety/low PT fatigue/lower support
low anxiety/high PT fatigue/higher support
low anxiety/high PT fatigue/lower support
high anxiety/low PT fatigue/higher support
high anxiety/low PT fatigue/lower support
high anxiety/high PT fatigue/higher support
high anxiety/high PT fatigue/lower support
Morning Fatigue
10
8
6
4
2
0
0 1 2 3 4 5 6 7 8 9 11 13 15 17 21 25
Weeks

Trajectories of Anxiety in Family Caregivers of Patients Undergoing Radiation Therapy for Prostate

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Abstract

Purpose: In a sample of FCs of patients who underwent RT for prostate cancer, the purposes of this study were to examine how ratings of state anxiety changed from the time of the simulation visit to four months after the completion of RT and to investigate whether specific personal, environmental, health and illness, and symptom characteristics in FCs as well as personal, disease, and symptom characteristics in the patients predicted the initial levels of anxiety and/or characteristics of the trajectories of anxiety in FCs.

Methods: FCs were recruited before the patient initiated RT and completed Center for Epidemiologic Studies – Depression Scale, Spielberger State Trait Anxiety Inventory, Lee Fatigue Scale, General Sleep Disturbance Scale, and a numeric rating scale for worst pain intensity. Descriptive statistics and frequency distributions were generated on the sample characteristics using SPSS TM Version 14.0. Hierarchical linear modeling (HLM), based on full maximum likelihood estimation, was performed to evaluate the trajectories of fatigue.

Results: Based on the unconditional HLM model, this sample of female FCs reported clinically significant levels of anxiety at the time of the patients' simulation visit (i.e., 33.85) that decreased only slightly (i.e., 32.54) over the 6 months of the study. When the final HLM model was constructed sixteen different anxiety trajectories were identified based on the predictors that were found to contribute to the model (i.e., levels of depression, morning fatigue, and sleep disturbance in the FCs at the initiation of RT, sleep disturbance in the FCs over time, as well as the patient's age). Higher levels of depression and morning fatigue in FCs at the time of the simulation visit as well as caring

for a younger patient were associated with increased anxiety in these FCs. In addition, the level of sleep disturbance that the FCs reported at baseline had a significant impact on the trajectories of their anxiety. Specifically, FCs who reported higher sleep disturbance scores had anxiety scores that remained the same as their baseline scores across the six months of the study.

Conclusions: Findings from this study highlighted the large amount of inter-individual variability in anxiety that was reported by this group of FCs of patients undergoing RT for treatment of prostate cancer. In addition, the results suggest that FCs need to be evaluated for the co-occurrence of anxiety and depression. (383 words).

Introduction

Caregiving for patients has consistently been linked with psychological problems, particularly in terms of caregiver burden, psychological distress, and depressive symptoms (Cooper et al., 2006; Fletcher, Dodd et al., in review; B. A. Given & Sherwood, 2006). In contrast, anxiety, a constant and exaggerated sense of worry (Cooper et al., 2006), has not been investigated in detail.

In a recent review of symptoms in family caregivers (FCs) of oncology patients (Fletcher, Dodd et al., in review), only 14 studies were identified that evaluated anxiety in FCs. Included in the review was the work of Ferrario and colleagues that compared the FCs of cancer patients to the general population and found higher anxiety levels in the FCs (2003a). Several studies (Clavarino et al., 2002; Cliff & Macdonagh, 2000; Iconomou et al., 2001) have reported clinically significant levels of anxiety in 20.7% to 39.0% of FCs of patients with cancer. In addition, FCs of patients with cancer were found to have higher anxiety scores than those FCs of patients with AIDS or dementia (Flaskerud et al., 2000).In a recent study of depression and anxiety in patients with prostate cancer and their FCs (Couper et al., 2006), the FCs had rates of depression and generalized anxiety disorder that were twice as high as those of Australian women in the community.

Recent work from our research group on the prevalence, severity, and impact of symptoms on FCs of patients with prostate cancer (Fletcher, Paul et al., in review), found that mean trait and state anxiety scores of the FCs (Spielberger et al., 1983) were above the cutpoint for clinically significant levels of anxiety. In addition, FCs with clinically

significant levels of anxiety reported significantly lower functional status scores as well as lower QOL scores. Finally, in a study of the trajectories and predictors of fatigue in FCs of patients undergoing radiation therapy (RT) for prostate cancer (Fletcher, unpublished-b), trait anxiety was found to be a significant predictor of the trajectories of morning fatigue in FCs.

Recent though limited evidence suggests that anxiety is a prevalent symptom that has a significant impact on FCs and that it may influence the severity of other symptoms. Given these relatively recent findings, it is important to evaluate for changes in anxiety in FCs over time. Therefore, the purposes of this study, in a sample of FCs of patients who underwent RT for prostate cancer, were to examine how ratings of anxiety changed from the time of the simulation visit to four months after the completion of RT and to investigate whether specific personal, environmental, health and illness, and symptom characteristics in FCs as well as personal, disease, and symptom characteristics in the patients predicted the initial levels of anxiety and/or characteristics of the trajectories of anxiety in FCs.

Methods

Participants and Settings

This descriptive, longitudinal study is part of a larger study that evaluated multiple symptoms in patients who underwent primary or adjuvant RT and their FCs. The participants were recruited from two RT departments at the time of the patient's simulation visit.

Following recruitment of the patients with prostate cancer, they were asked to identify the person most involved in their care (i.e., their FC). If the FC was with the patient, the research nurse explained the study and obtained written informed consent from the FC. FCs who were not with the patient were contacted by phone to determine their interest in study participation. The research nurse visited those FCs at home, obtained written informed consent, and enrolled then in the study.

FCs were eligible to participate if they: were an adult (≥ 18 years of age); were able to read, write, and understand English; gave written informed consent; had a Karnofsky Performance Status (KPS) score of ≥ 60; were living with the patient who was receiving primary or adjuvant RT for prostate cancer; and did not have a diagnosed sleep disorder. This study was approved by the Human Subjects Committee at the University of California, San Francisco and at the second study site.

One hundred and eighty-eight patients with prostate cancer were approached and 82 consented to participate in this study (43.6% response rate). Of these 82, 60 had a female FC who agreed to participate. The major reasons why patients refused were being too overwhelmed with their cancer experience or too busy. No differences were found in any of the demographic characteristics between the patients who did and did not choose to participate in this study.

Instruments

The study instruments included a demographic questionnaire, the Karnofsky Performance Status Scale (KPS) (Karnofsky, 1977), the Lee Fatigue Scale (LFS) (Lee et al., 1991), the General Sleep Disturbance Scale (GSDS) (Lee, 1992), the Center for

Epidemiological Studies-Depression Scale (CES-D) (Radloff, 1977), the Spielberg State-Trait Anxiety Inventories (STAI-S and STAI-T) (Spielberger et al., 1983), a descriptive numeric rating scale (NRS) for worst pain intensity, and the Caregiver Reaction Assessment (CRA) (C. W. Given et al., 1992).

The demographic questionnaire provided information on age, marital status, years of education, living arrangements, ethnicity, and employment status. In addition, patients and FCs completed a checklist of comorbidities and the KPS.

Anxiety was evaluated using the STAI-T and STAI-S inventories consist of 20 items each that are rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. A higher score indicates greater anxiety. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality and estimates how a person feels generally. The STAI-S measures an individual's transitory emotional response to a stressful situation. It evaluates the emotional response of worry, nervousness, tension, and feelings of apprehension related to how people feel "right now" in a stressful situation. The STAI-S and STAI-T inventories have well-established criterion and construct validity and internal consistency reliability coefficients (Bieling et al., 1998; Kennedy et al., 2001; Stanley et al., 2001). In this study, the Cronbach's alpha for the STAI-T for FCs was .89 and for the STAI-S was .93. The Cronbach's alpha for the STAI-T for patients was .86 and for the STAI-S was .91.

Fatigue severity was measured using the 13-item LFS. Each item was rated using a 0 to 10 NRS and a total score was calculated as the mean of the 13 items that can range from 0 to 10, with higher scores indicating higher levels of fatigue severity. Respondents

were asked to rate each item based on how they felt "right now", within 30 minutes of awakening (i.e., morning fatigue) and prior to bed (i.e., evening fatigue). The LFS has been used with healthy individuals (Gay et al., 2004; Lee et al., 1991) as well as in patients with cancer (C. Miaskowski & Lee, 1999) and HIV (Lee et al., 2001). It was chosen for this study because it is relatively short and easy to administer. The LFS has well established validity and reliability (Lee et al., 1991). In this sample, the Cronbach's alphas for the LFS for both the FC's and patient's evening and morning ratings were .95 and .96, respectively.

The GSDS consists of 21 items that evaluate various aspects of sleep disturbance. Each item was rated on a NRS that ranged from 0 (never) to 7 (every day). The 21 items were summed to yield a total score that could range from 0 (no disturbance) to 147 (extreme sleep disturbance). The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV (Dorsey et al., 2004; Gay et al., 2004; Lee, 1992; Lee & Gay, 2004; C. Miaskowski & Lee, 1999). In the current study, the Cronbach's alphas for the GSDS total score for FCs and patients were .79 and .81, respectively.

The CES-D consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores ≥ 16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity (Carpenter et al., 1998; Sheehan et al., 1995). In the current study, the Cronbach's alphas for the CES-D for FCs and patients were .84 and .83, respectively.

Worst pain intensity was evaluated using a descriptive NRS that ranged from 0 (no pain) to 10 (excruciating pain). A descriptive numeric rating scale is a valid and reliable measure of pain intensity (M. P. Jensen, 2003).

The CRA is a 24-item instrument used to evaluate the FC's experience of caregiving. Each item is rated on a Likert like scale that ranges from 1 (strongly agree) to 5 (strongly disagree). Five subscale scores (i.e., caregiver's health problems – 4 items, impact of caregiving on self-esteem – 7 items, disrupted schedule – 5 items, financial problems – 3 items, and lack of family support – 5 items) are created as the mean of the responses to the items in the subscale. The CRA has well established validity and reliability in FCs of patients with dementia (C. W. Given et al., 1992) and cancer (B. Given & Given, 1992; C.W. Given et al., 1993; M. E. Kurtz et al., 1994; M. E. Kurtz et al., 1995, 2004; Nijboer et al., 2001; Nijboer et al., 1999; Sherwood et al., 2006). In this sample, Cronbach's alpha for the CRA was .84.

Study Procedures

At the time of the simulation visit (i.e., approximately 1 week prior to the start of RT), patients were approached by a research nurse to discuss participation in the study. After obtaining written informed consent, patients and their FCs were taught to complete the baseline study questionnaires. The STAI-T and the STAI-S were completed at the first assessment. Subsequent assessments of anxiety were completed every other week for 4 weeks (i.e., 2, 4, 6, 8), at the end of RT (week 9), every other week for 4 weeks (i.e., 11, 13, 15, 17), and once a month for 2 months (i.e., 21, 25) following the completion of RT. The majority of FCs completed 12 assessments.

Data Analysis

Descriptive statistics and frequency distributions were generated on the sample characteristics using SPSS™ Version 14.0. For each of the 12 assessments, a mean for the STAI-S score was calculated for use in the subsequent statistical analyses. Hierarchical linear modeling (HLM), based on full maximum likelihood estimation, was done using the software developed by Raudenbush and colleagues (Raudenbush & Bryk, 2002). The repeated measures of anxiety were conceptualized as being nested within individuals. Compared with other methods of analyzing change, HLM has two major advantages. First, HLM can accommodate unbalanced designs which allows for the analysis of data when the number and the spacing of the assessments vary across respondents. Although every FC was to be assessed on a pre-specified schedule, the actual number of assessments was not the same for all of the FCs because some patients had longer periods of RT and some had scheduling conflicts. Second, HLM has the ability to model individual change, which helps to identify more complex patterns of change that are often overlooked by other methods.

With HLM, the repeated measures of the outcome variable (i.e., anxiety in FCs) are nested within individuals and the analysis of change in anxiety scores has two levels: within persons (Level 1) and between persons (Level 2). At Level 1, the outcome is conceptualized as varying within individuals and is a function of person-specific change parameters plus error. At Level 2, these person-specific change parameters are multivariate outcomes that vary across individuals. These Level 2 outcomes can be modeled as a function of demographic or clinical characteristics that vary between

individuals, plus an error associated with the individual. Combining Level 1 with Level 2 results in a mixed model with fixed and random effects.

The HLM analysis proceeded in two stages. First, intra-individual variability in anxiety over time was examined. In this study, time refers to the length of time from the simulation visit to four months after the completion of RT (i.e., six months with a total of 12 assessments). Three Level 1 models, which represented that the FCs' anxiety levels (a) did not change over time (i.e., no time effect), (b) changed at a constant rate (i.e., linear time effect), and (c) changed at a rate that accelerates or decelerates over time (i.e., quadratic term) were compared. At this point, the level 2 model was constrained to be unconditional (i.e., no predictors) and likelihood ratio tests were used to determine the best model. These analyses answered the first research question and identified the change parameters that best described individual changes in anxiety over time.

The second stage of the HLM analysis, which answered the second research question, examined inter-individual differences in the trajectories of anxiety in FCs by modeling the individual change parameters (i.e., intercept, linear, and quadratic slopes) as a function of proposed predictors at Level 2. Table 1 presents a list of the proposed predictors that was developed based on a review of the literature of anxiety in FCs of patients with cancer and a review of the literature of anxiety in men with prostate cancer who underwent RT. To improve estimation efficiency and construct a model that was parsimonious, an exploratory Level 2 analysis was done and predictors with a t-value of < 2.0 were dropped from subsequent model testing. All of the potentially significant predictors from the exploratory analyses were entered into the model to predict each

individual change parameter. Only predictors that maintained a significant contribution in conjunction with other variables were retained in the final model. A p-value of <.05 indicates statistical significance.

Results

Family Caregiver and Patient Characteristics

The demographic characteristics and comorbid conditions of the FCs (n = 60) are presented in Table 2A. The FCs were approximately 64 years of age, well educated, and had a baseline KPS score of 94.0. Ninety-three percent were married, 80% Caucasian, and approximately 37% were employed at the time of the study. Over 35% of the FCs reported back problems, arthritis, hypertension, or headaches at the baseline visit.

The demographic, disease, and treatment characteristics of the patients are presented in Tables 2A and 2B. The men with prostate cancer were approximately 68.1 years of age and had a KPS score of 96.8. The distribution of clinical stage was 46.7% with T1, 40.0% with T2, and 10.0% with T3. Over 50% of the patients received hormonal therapy prior to the initiation of RT. The mean time since diagnosis was 9.7 $\pm$ 15.1 months.

Individual and Mean Changes in Anxiety in Family Caregivers

Changes in anxiety from the time of the simulation visit to 4 months after the completion of RT were examined in the first HLM analysis. Two models were estimated in which the function of time was linear and quadratic. For anxiety, the likelihood ratio tests indicated that a linear model fit the data significantly better than a quadratic model.

The unconditional model is shown in Table 4 and the intercept represents the estimated amount of anxiety in FCs (i.e., 33.865) at the time of the simulation visit. The estimated linear rate of change in anxiety at each assessment was -0.111 ($p \leq 0.02$).

Figure 1A displays the trajectory for anxiety in FCs from the time of the patient's simulation visit to 4 months after the completion of RT. Anxiety gradually decreased over time.

Although these sample wide results indicate uniform changes over time, they do not imply that all FCs exhibited the same trajectory. The variance in individual change parameters estimated by the model (i.e., variance components, Table 4) suggested that substantial inter-individual differences existed in the trajectories of anxiety. These differences in anxiety are illustrated in Figure1B. Such results suggested that further examination of the inter-individual differences in the individual change parameters was warranted.

Inter-individual Differences in the Trajectories of Anxiety in Family Caregivers

The hypothesis that characteristics of the FC (i.e., personal, environmental, health and illness, symptoms) as well as of the patient (i.e., personal, disease, symptoms) might influence the trajectories of anxiety in FCs was tested in the next HLM analyses. Exploratory analyses were completed with all of the potential predictor variables listed in Table 1. To improve estimation efficiency and construct models that were parsimonious, exploratory Level 2 analyses were done and predictors with a t-value of < 2.0 were dropped from the model testing. All of the significant predictors from the exploratory model were entered into the models to predict each individual change parameter (i.e.,

intercepts and/or slope). Only predictors that maintained a significant contribution in conjunction with other variables were retained in the final model of anxiety in FCs.

Table 3 shows the final model for anxiety in FCs. The three variables that predicted inter-individual differences in the intercept for anxiety were baseline depression scores in FCs, baseline levels of morning fatigue in FCs, and the age of the patient. Baseline levels of sleep disturbance in the FCs predicted changes in anxiety over time (linear slope). Baseline level of anxiety in FCs was entered in Level 2 as a predictor of the slope parameter to control for intra-individual differences in anxiety at baseline. In order to illustrate the effects of the different predictors on the FCs' trajectories of anxiety, Figure 2 (lower levels of FC depression) and 3 (higher levels of FC depression) were compiled to display the adjusted change curves of anxiety according to differences in baseline levels of depression in FCs (i.e., high or low levels of depression in FCs based on 1 standard deviation above and below the mean CES-D score for FCs). The CES-D score was chosen to dichotomize the data as it was the most robust predictor based on the t value and significance in the model. Also, the literature demonstrates that depression is often present with anxiety (Beekman et al., 2000; Regier, Rae, Narrow, Kaelber, & Schatzberg, 1998; Schoevers, Deeg, van Tilburg, & Beekman, 2005). Figure 2 and 3 show the sixteen adjusted change curves of anxiety according to differences in, baseline patient age (i.e., younger or older patient age based on 1 standard deviation above or below the mean age for the patient), baseline morning fatigue levels for the FC (i.e., low or high levels of morning fatigue based on 1 standard deviation above or below the mean baseline LFS score of morning fatigue for FCs), and baseline FC sleep disturbance (i.e.,

low or high levels of sleep disturbance based on 1 standard deviation above and below the mean GSDS score for FCs).

Discussion

This longitudinal study is the first to examine inter-individual differences in anxiety in FCs of patient undergoing RT for prostate cancer as well as to determine the predictors of those inter-individual differences. As shown in Figure 1, the unconditional model demonstrated that this sample of female FCs reported clinically significant levels of anxiety at the time of the patients' simulation visit (i.e., 33.865; cutoff score for the STAI-S $\geq$ 32.2) that decreased only slightly to 32.535 over the six months of the study. These results differ somewhat from the one other longitudinal study of anxiety in FCs of patients who underwent a hematopoietic stem cell transplant (Langer et al., 2003). Anxiety in FCs was high at the initiation of the study, dropped dramatically by 6 months and remained stable at 1 year, although the FC's anxiety scores were above those of the general population norm at all three time points. Differences in trajectories for anxiety between the two studies could be due to a number of different factors including: the patients' diagnosis and treatments, age of the FC, gender of the FCs, instruments used to measure anxiety, or number of assessments. However, given the fact that there are so few longitudinal studies of FC anxiety, additional research is warranted to determine if similar anxiety trajectories occur in other groups of FCs whose patients have different cancer diagnoses, undergo different treatment regimens. or are in different stages of their disease process.

One of the major findings from this study is that the baseline depression scores of these FCs made a significant contribution to the FCs' baseline level of state anxiety. For every one point increase in the CES-D score, FCs' state anxiety score increased by 0.75 points, when all other variables were held constant. In addition, FCs with higher depression scores (i.e., one standard deviation above the mean CES-D score of 8.41 $\pm$ 6.39) had baseline state anxiety scores that ranged from approximately 34 to 43 (See Figure 3). In contrast, FCs with lower depression scores at baseline (Figure 2) had baseline state anxiety scores that ranged from approximately 24.5 to 33.8. These findings are in concert with previous cross-sectional studies (B. Given & Given, 1992; C.W. Given et al., 1993; Nijboer et al., 1999a), that found significant correlations between anxiety and depression in FCs of patients with cancer. Additional research is warranted on the relationship between anxiety and depression in FCs because of the growing body of literature that suggests that most depressed FCs are also anxious and that the co-occurrence of depression and anxiety is associated with significant morbidity (B. Given & Given, 1992; M. E. Kurtz et al., 1994; M. E. Kurtz et al., 1995).

Another important finding from this study is the impact that FC sleep disturbance at baseline had on the trajectories of anxiety in these FCs. Of note, the FC baseline GSDS score was the only significant predictor of the slope of anxiety. As shown in Figures 2 and 3, FCs who reported higher sleep disturbance scores (i.e., one standard deviation above the mean baseline GSDS score of 39.85 $\pm$ 16.17) had anxiety trajectories that remained high (i.e., approximately the same as their baseline anxiety levels) across the six months of the study. In contrast, FCs who reported lower GSDS scores at baseline

demonstrated anxiety trajectories that gradually decreased over the six months of the study and in every case were below the FC's baseline level of anxiety. While no studies have approached the examination of the relationships between anxiety and sleep disturbance in FCs using HLM analyses, findings from this study are consistent with previous reports that found positive correlations between anxiety and sleep disturbances in FCs of patients with cancer (Flaskerud et al., 2000).

Of note, baseline levels of morning (i.e., 2.31 $\pm$ 1.94), but not evening, fatigue of FCs were associated with state anxiety scores such that for every one point increase in the morning LFS score, FCs state anxiety scores increased by 0.88 points when all other variables were held constant. While no studies have reported specifically on the relationship between anxiety and morning fatigue, one study suggested that anxiety and fatigue scores were positively correlated in FCs of patients with cancer (Gaston-Johansson et al., 2004). In addition, it is known that one of the hallmarks of clinically significant depression is reports of morning fatigue (Gelenberg & Hopkins, 2007; Maurer & Colt, 2006). Perhaps a similar relationship exists between an anxiety disorder and morning fatigue that warrants investigation in future studies.

Consistent with our previous study of the trajectories of fatigue in FCs of patients with prostate cancer (Fletcher, unpublished-b), the fact that the patients' age predicted FCs' baseline levels of state anxiety suggests that patient characteristics need to be considered in studies of FCs' symptom trajectories. In this study, FCs who cared for younger patients (i.e., one standard deviation below the mean patient age of 68.10 $\pm$ 7.94) had higher baseline state anxiety scores than those who cared for older patients. It is not

readily apparent why younger patient age was associated with increased anxiety in FCs. However, previous studies have found that FCs who cared for younger patients reported higher levels of symptoms and increased burden (M. E. Kurtz et al., 1994; Schumacher, Dodd, & Paul, 1993). This finding warrants investigation in future studies.

Several limitations of this study need to be acknowledged including the relatively small sample size and homogeneous sample characteristics (i.e., all female, all FCs of patients with prostate cancer). Therefore, the findings from this study may not be generalized to other FC populations. It is important to replicate these findings using a larger sample of FCs of patients with a variety of cancer diagnoses, different cancer treatments, and different stages of the disease trajectory.

This study highlighted the large amount of inter-individual variability in the levels of state anxiety in a sample of FCs of patients with prostate cancer at the initiation and over the course of RT. In addition, FCs with higher depression scores reported higher levels of anxiety. In fact, based on the results of this study, FCs who report high levels of baseline depression and higher levels of morning fatigue at the time of the simulation visit, and whose patient partner was younger were the most likely group to report the highest levels of state anxiety. In contrast, those FCs who reported lower levels of depression and lower levels of morning fatigue at baseline and who cared for an older patient reported the lowest state anxiety scores. Of note, the trajectories of state anxiety between these two FC groups were different. In the former group, state anxiety scores remained at the same high level over the six months of the study. In the latter group, state anxiety scores decreased gradually over the course of the study.

Future studies could utilize HLM analysis to evaluate the predictors for and patterns of change in both anxiety and depression to determine which symptom influences the trajectory of the other symptom. These types of studies may enable us to identify high risk groups of FCs and to develop more targeted interventions for high risk FCs and/or patient-FC dyads.

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Table 1 - Potential Predictors of Intercept and Linear Coefficient for Anxiety

Potential Predictors	Family Caregivers		Patients	
Demographics	**Intercept**	**Linear Coefficient**	**Intercept**	**Linear Coefficient**
Person				
Age			●	
Relationship				
Marital status				
Education				
Ethnicity			●	
Employment				
Environmental				
CRA impact on schedule				
CRA caregiver's esteem				
CRA lack of family support				
CRA impact on health				
CRA impact on finances				
CRA fear of second cancer				
CRA fear of metastasis				
CRA fear of cancer spreading				
Health and Illness				
KPS score				
Number of comorbidities	●			
Stage of disease	NA	NA		
Type of treatment	NA	NA		
Received hormone treatment prior to RT	NA	NA		
Time since diagnosis				
Symptoms				
Baseline GSDS score	●	●		
Baseline CES-D score	●	●	●	
Presence of pain at baseline				
Baseline trait anxiety score	●			
Baseline morning fatigue score	●			
Baseline evening fatigue score	●			

●= From exploratory analyses had a t-value > 2.00

Abbreviations: CES-D = Center for Epidemiologic Studies- Depression; CRA = Caregiver Reaction Assessment; GSDS = General Sleep Disturbance Score; KPS = Karnofsky Performance Status; NA = Not applicable, RT = Radiation Therapy

Table 2a – Demographic Characteristics and Comorbid Conditions of the Family Caregivers and Patients (n=60)

Characteristic	Family Caregivers	Patients
	Mean (Standard Deviation)	Mean (Standard Deviation)
Age (years)	64.2 (8.8)	68.1 (7.9)
Education (years)	15.2 (2.8)	16.6 (3.2)
Karnofsky Performance Status Score	94.0 (10.5)	96.8 (5.45)
	%	%
Marital status		
Married/partnered	93.3	93.3
Other	6.7	6.7
Ethnicity		
Black	11.7	13.3
White	80.0	81.7
Other	8.3	5.0
Employed		
Yes	36.7	44.1
Comorbid Conditions		
Back problems	49.2	59.3
Arthritis	43.1	36.2
Hypertension	36.2	32.8
Headaches	35.6	19.0
Hemorrhoids	28.8	31.0

Table 2b – Patient Disease and Treatment Characteristics

	%
Gleason score	
5 or 6	40.0%
7	46.7%
$\geq$ 8	5.0%
Clinical stage	
T1	46.7%
T2	40.0%
T3	10.0%
Prostatectomy prior to RT	11.7%
Hormonal therapy prior to RT	51.7%
RT treatment plan	
Whole pelvis + conformal boost after surgery	11.7%
Whole pelvis + conformal boost	70.0%
Whole pelvis + high dose RT	5.0%
Whole pelvis + seed implant	13.3%
	Mean (standard deviation)
Total dose of RT (cGys)	6851 (1024.2)
Time since diagnosis (months)	9.7 (15.1)

Abbreviations: cGys = dose of RT in centigray units, RT = radiation therapy

Table 3 - Hierarchical Linear Models of State Anxiety in Family Caregivers

State Anxiety	**Coefficient (SE)**	
Variable	Unconditional Model	Final Model
Fixed Effects		
Intercept	33.865 (1.168)*	33.903 (0.797)*
Time[a] (linear rate of change)	-0.111 (0.0485)****	-0.113 (0.045)+
Time invariant covariates[b]		
Baseline CES-D score in FC		0.747 (0.126)*
Baseline LFS score in FC		0.978 (0.412)+
Patient's age		-0.306 (0.093)***
Baseline GSDS in FC x time		0.007 (0.003)+
Baseline STAI-S score in FCs x time		-0.006 (0.004)+++
Variance components		
In intercept	66.057*	22.368*
In linear rate	0.049++	0.031+
Goodness-of-fit deviance(parameters estimated)	4339.599398 (6)	4281.184097 (11)
Model comparison (χ^2 [*df*])		58.4193 (5)**

Abbreviations: CES-D = Center for Epidemiological Studies – Depression Scale, GSDS = General Sleep Disturbance Scale, LFS = Lee Fatigue Scale, STAI-S = Spielberg State Trait Anxiety Inventory-State

*$p < 0.0001$, **$p < 0.001$, ***$p \leq 0.002$, ****$p = 0.026$, +$p = 0.02$, ++$p = 0.003$, +++$p = 0.17$

[a]Time was coded 0 at the time of the simulation visit

[b]Time invariant covariates taken from predictors of FC and patient fatigue in the literature

Figure legends

Figure 1A – Trajectories of anxiety over 25 weeks of the study

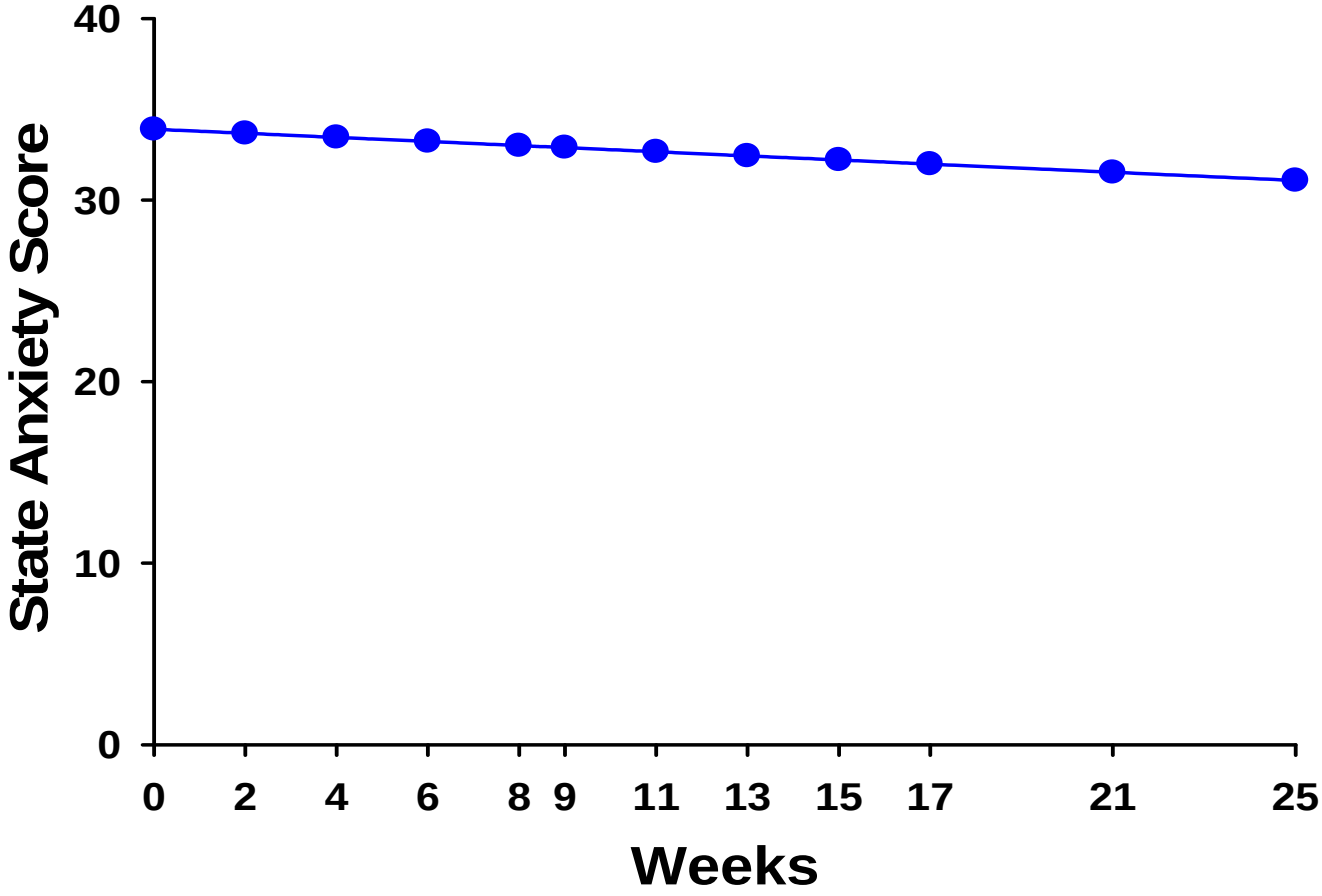
Figure 1B - Spaghetti plot of individual trajectories of anxiety over the 25 weeks of the study

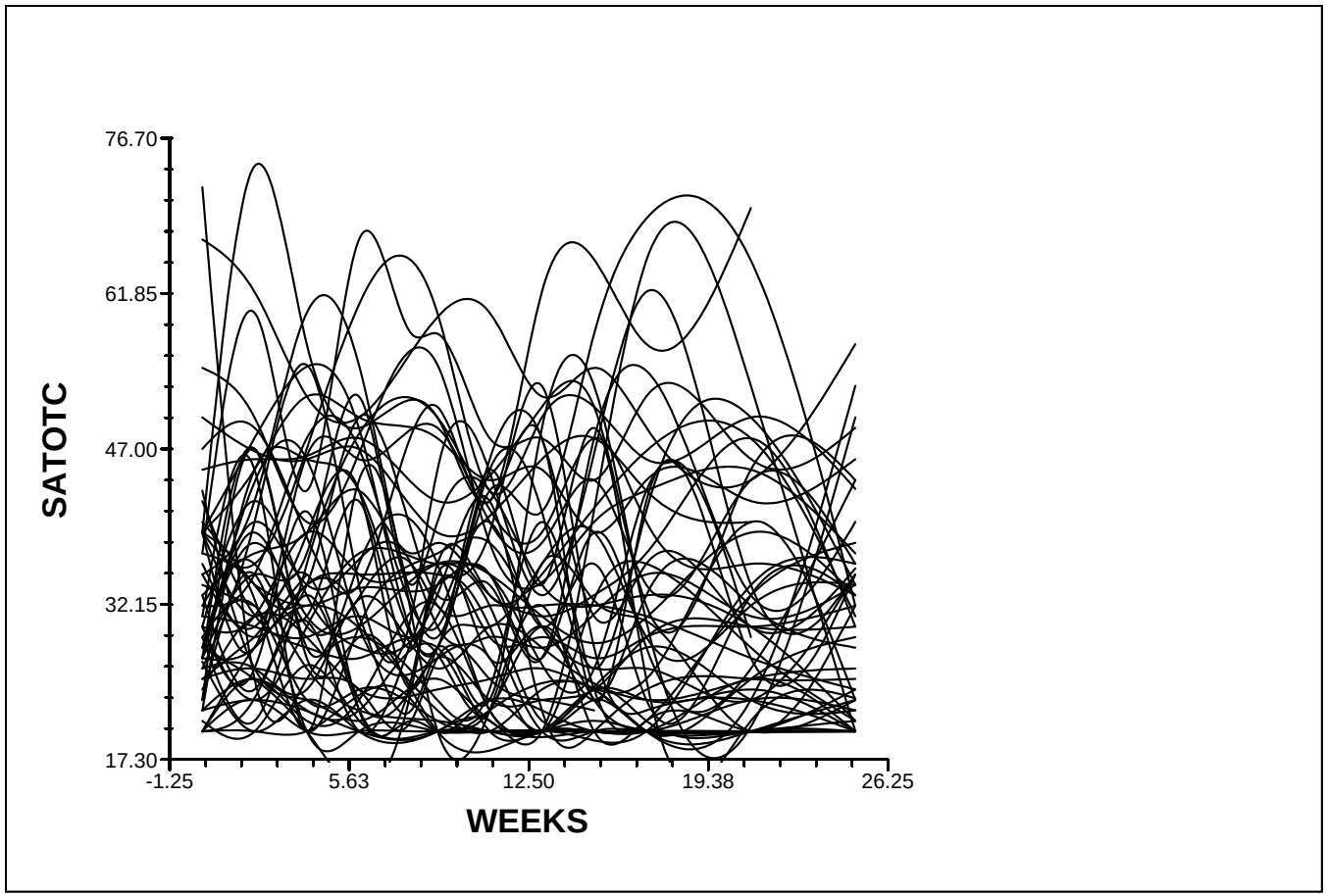
Figure 2 – Trajectories of anxiety by lower level of depression

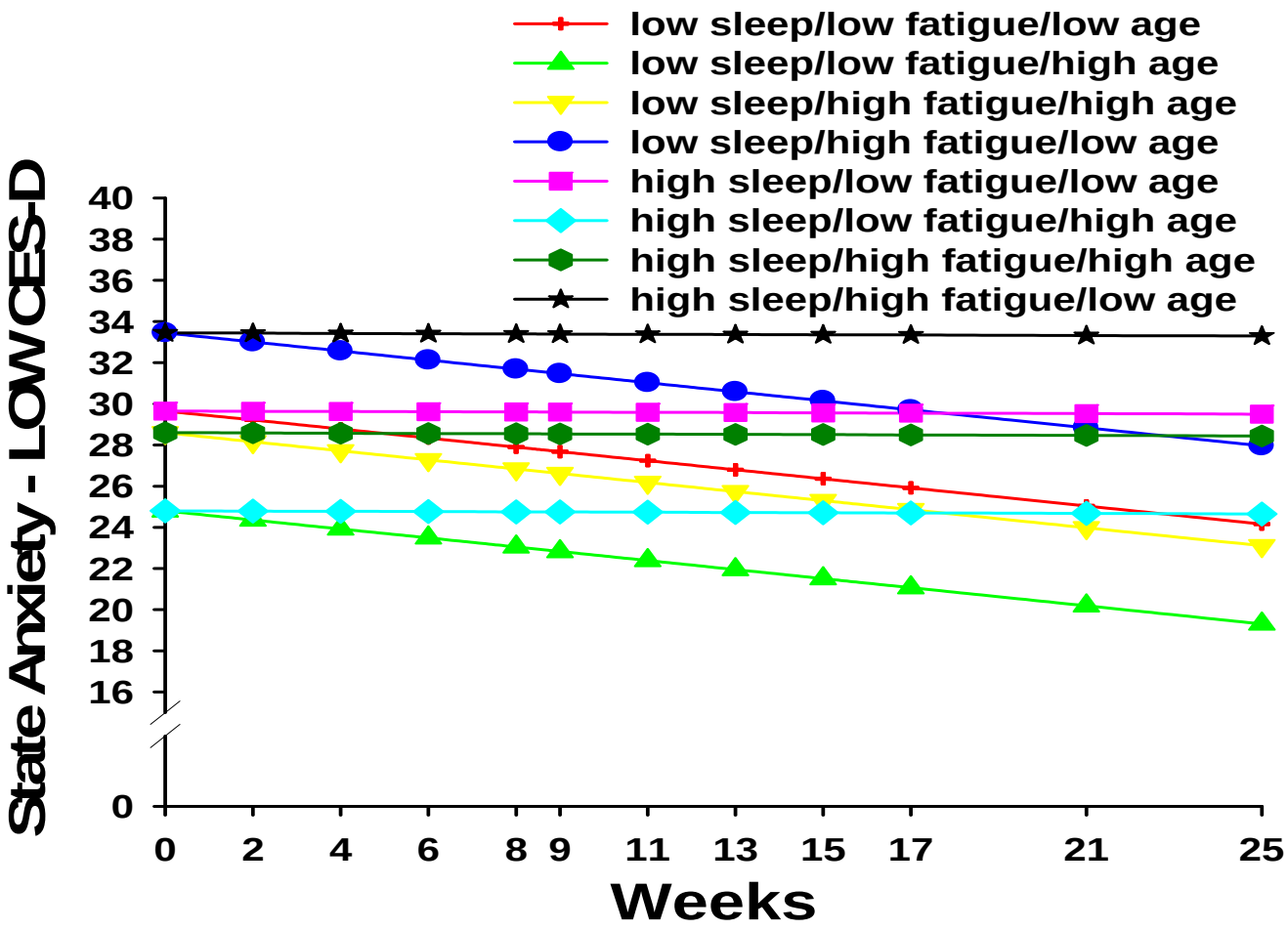
Trajectories of anxiety by lower level of depression in FCs at baseline (i.e., low CES-D) and by level of sleep disturbance in FCs at baseline (i.e., low sleep/high sleep), level of FC morning fatigue at baseline (i.e., low fatigue/high fatigue), and by patient age (i.e., PT low age/PT high age)

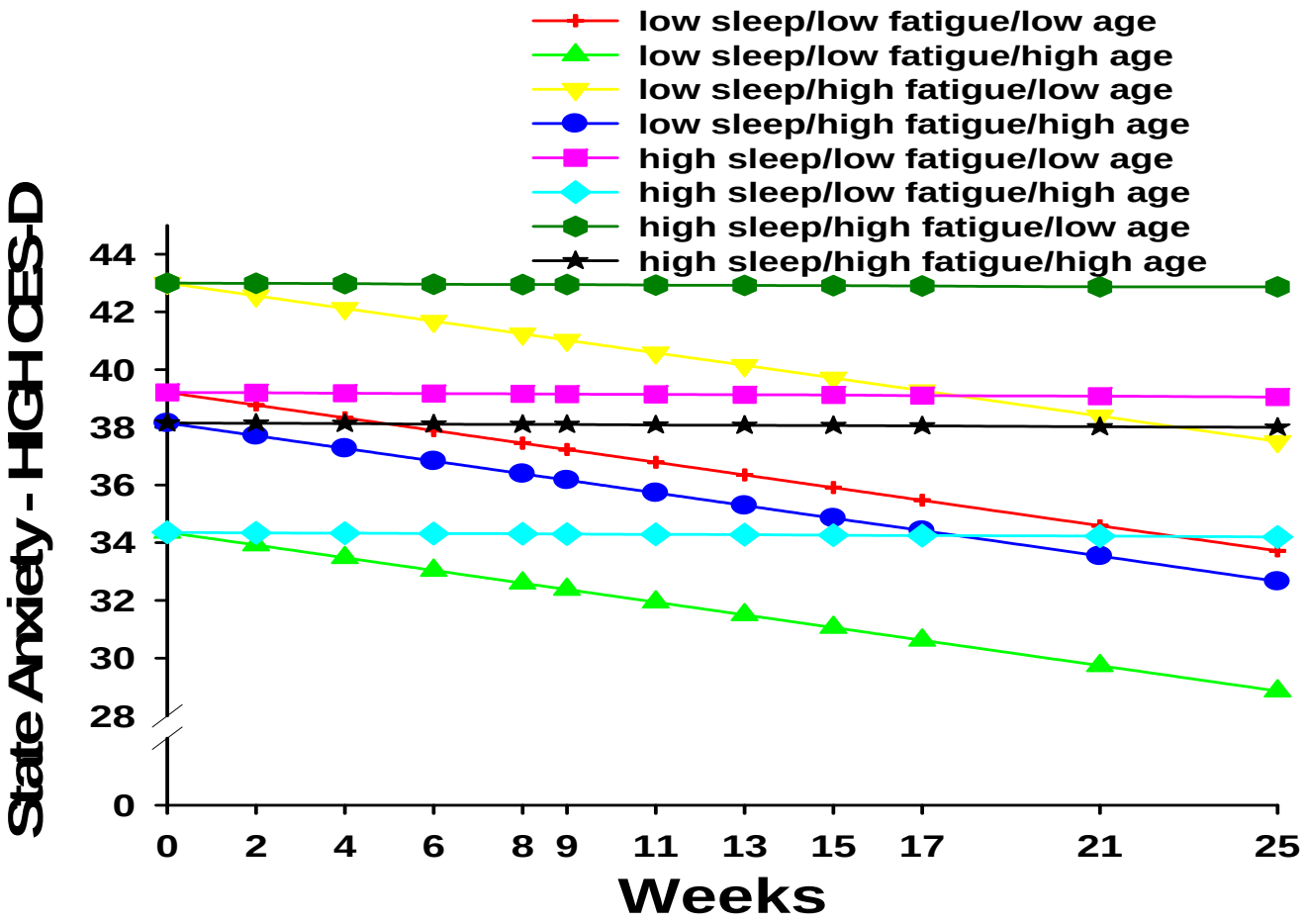
Figure 3 – Trajectories of anxiety by higher level of depression

Trajectories of anxiety by higher level of depression in FCs at baseline (i.e., high CES-D) and by level of sleep disturbance in FCs at baseline (i.e., low sleep/high sleep), level of FC morning fatigue at baseline (i.e., low fatigue/high fatigue), and by patient age (i.e., PT low age/PT high age)


State Anxiety Score
40
30
20
10
0
0
2
4
6
8
9
11
13
15
17
21
25
Weeks


76.70
61.85
47.00
32.15
17.30
SATOTC
-1.25
5.63
12.50
19.38
26.25
WEEKS


low sleep/low fatigue/low age
low sleep/low fatigue/high age
low sleep/high fatigue/high age
low sleep/high fatigue/low age
high sleep/low fatigue/low age
high sleep/low fatigue/high age
high sleep/high fatigue/high age
high sleep/high fatigue/low age
State Anxiety - LOW CES-D
40
38
36
34
32
30
28
26
24
22
20
18
16
0
0
2
4
6
8
9
11
13
15
17
21
25
Weeks


low sleep/low fatigue/low age
low sleep/low fatigue/high age
low sleep/high fatigue/low age
low sleep/high fatigue/high age
high sleep/low fatigue/low age
high sleep/low fatigue/high age
high sleep/high fatigue/low age
high sleep/high fatigue/high age
State Anxiety - HGHCES-D
44
42
40
38
36
34
32
30
28
0
0
2
4
6
8
9
11
13
15
17
21
25
Weeks

Conclusion and Directions for Future Research

Despite the large numbers of family caregivers (FCs) currently providing care to adults in the United States (Belden Russonello & Stewart, 2004) (i.e., estimated at 44.4 million), little is known about their symptoms. In a review of the literature on symptoms of FCs of oncology patients (Fletcher, Dodd et al., in review) only 42 studies were found that evaluated five common symptoms. The most well-studied symptom was depression (36 studies), followed by anxiety (14 studies), sleep disturbance (9 studies), and fatigue (8 studies). Of note, no studies were found that evaluated pain in FCs of patients with cancer. Due to the diverse nature of this limited number of studies, no definitive conclusions can be drawn about the prevalence rates for these symptoms, the demographic characteristics of the FCs who were at highest risk of experiencing these symptoms, the negative consequences associated with these symptoms, or the relationship among symptoms in FCs and other aspects of their FC experience.

The purposes of the current studies were to explore and describe symptoms in FCs of patients at the initiation of, during, and four months after the completion of radiation therapy (RT) for prostate cancer. The first study (Fletcher, Paul et al., in review) assessed prevalence rates for five common symptoms (i.e., depression, anxiety, pain, sleep disturbance, fatigue) in FCs at the time that the patient initiated RT. Further, the relationship between symptoms in FCs and functional status and their quality of life (QOL) was examined. For trait and state anxiety, sleep disturbance, and evening and morning fatigue, 30% to 58% of the FCs had clinically significant symptom severity scores. In addition to the high prevalence rates for these symptoms, findings from this

study suggested that these symptoms had negative effects on FC's functional status and QOL.

Hierarchal linear modeling (HLM) (Raudenbush & Bryk, 2002) was used in the next two studies (Fletcher, unpublished-a, unpublished-b) to evaluate the trajectories of evening and morning fatigue and state anxiety over time. Generally, intra-individual levels of symptom severity were very stable, changing little over time, while inter-individual variability was high. In fact, findings from this study suggested that the symptoms of fatigue and anxiety in some FCs do not always improve with the passage of time. Different predictors were associated with higher levels of evening fatigue compared to morning fatigue. In addition, their trajectories were dissimilar. These results provide additional evidence that evening and morning fatigue are distinct constructs and should be studied independently. The two predictors that influenced the baseline severity of the evening fatigue were the FC's level of sleep disturbance at baseline and the patients' level of evening fatigue at baseline. FCs with higher levels of sleep disturbance with either high or low levels of patient or FC evening fatigue at baseline had higher evening fatigue scores over the six months of the study. For morning fatigue, those with the highest trait anxiety symptoms had the highest levels of morning fatigue over time.

The predictor that influenced the overall severity of the anxiety trajectory was the FC's level of depressive symptoms at baseline. For every one point increase in the Center for Epidemiologic Studies–Depression Scale (CES-D) score, FCs' state anxiety scores increased by 0.75 points, when all other variables were held constant. Additional research is warranted to evaluate the relationship between anxiety and depression in FCs because

of the growing body of literature that suggests that most depressed FCs are also anxious and that the co-occurrence of depression and anxiety is associated with significant morbidity. The FC baseline General Sleep Disturbance Scale (GSDS) score in these FCs was the only significant predictor of the slope of state anxiety. FCs who reported higher sleep disturbance scores had anxiety trajectories that remained high across the six months of the study.

It is interesting to note that the significant predictors of evening and morning fatigue and anxiety were other symptoms (i.e., sleep disturbance, trait anxiety, depression) in FCs. These findings support the concept of the co-occurrence of multiple symptoms or symptom clusters that are related to and/or interact with each other to influence the trajectories of a specific symptom. Additional research is needed to determine how changes over time in one symptom influence the trajectories of another symptom.

The large amount of inter-individual variability seen in the levels of evening and morning fatigue, as well as in anxiety, suggest that these phenotypic differences may be associated with genetic variability. This hypothesis warrants testing in future studies.

The aforementioned studies were the first to examine the prevalence of five common symptoms as well as the first to evaluate for inter-individual differences in the trajectories of three symptoms (i.e., evening and morning fatigue, anxiety) in FCs of patients undergoing RT for prostate cancer. They used a relatively small homogenous sample (i.e., older, female FCs of patients with prostate cancer) with the focus on a single treatment modality. Therefore, the results, although important, are preliminary.

Additional research is warranted to replicate these findings in a larger sample, as well as to evaluate symptom trajectories of other groups of FCs of patients with different cancer diagnoses, where patients are receiving different types of treatments, or where patients are in different stages of their disease. Future studies could include an analysis of symptom clusters, particularly with regard to the psychological symptoms, as well as the genetic basis for these highly prevalent symptoms in FCs of oncology patients. Further analyses using HLM will need to evaluate not only baseline characteristics of the patient as predictors (as done in the current studies), but also how changes in the patients' over time affect FC trajectories. These types of investigations should assist with the identification of high risk groups of FCs and with the development of more targeted interventions that can be evaluated in FCs who are at high risk and/or patient – FC dyads.

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