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Trajectories of Sleep Disturbance in Men with Prostate cancer before, during ,and after radiation therapy

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Trajectories of Sleep Disturbance in Men with Prostate Cancer Before, During, and After Radiation Therapy

by

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Abstract

Trajectories of Sleep Disturbance in Men with Prostate Cancer

Before, During, and After Radiation Therapy

Jia-Ni Liu

This study of prostate cancer patients who underwent radiation therapy (RT) examined how total sleep time changed from the time of simulation to four months after the completion of RT and investigated whether specific variables predicted initial levels of sleep disturbance and characteristics of the trajectories of sleep disturbance. Eighty-two men completed a number of measures (i.e., wrist actigraphy, General Sleep Disturbance Scale, Center for Epidemiologic Studies-Depression scale, Spielberger State-Trait Anxiety Inventories, Brief Pain Inventory) over six months. Descriptive statistics and hierarchical linear modeling were used for data analysis. Large amounts of inter-individual variability were found in the trajectories of sleep disturbance. At baseline, sleep disturbance were associated with ethnicity, KPS score, total dose of RT, pain at baseline. The trajectories of sleep disturbance in this group of men with prostate cancer were associated with total dose of RT, pain at baseline, total sleep time at baseline, state anxiety at baseline. This study is the first using actigraphy to identify predictors of inter-individual variability in sleep disturbance in men with prostate cancer undergoing RT. Additional research is warranted to confirm this study's findings and to develops and test interventions in this vulnerable group of oncology patients.

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Introduction

Recent data and clinical experience suggest that cancer patients experience a variety of sleep problems. In fact, in one study (Sarvard & Morin, 2001) 30 % of patients with a variety of cancer diagnoses had insomnia compared to only 20% of the general population. Precipitating factors for sleep disturbance in oncology patients include the stress associated with the diagnosis of cancer, the type and stage of disease, pain, and the side effects of treatment (Roscoe et al., 2007).

Prostate cancer is the second most common cancer diagnosis in men (American Cancer Society, 2009) and the incidence rates in African Americans are significantly higher compared to whites (American Cancer Society, 2009). While several studies have evaluated for sleep disturbance in patients with prostate cancer (Choo et al., 2007; Davidson, MacLean, Brundage, & Schulze, 2002; Dirksen, Epstein, & Hoyt, 2009; Gore, Kwan, Lee, Reiter, & Litwin, 2009; Greenberg, Gray, Manix, Eisenthal, & Carey, 2003; Korbblith, Herr, Ofman, Scher, & Holland, 1994; Lilleby, 1999; Penedo, Dahn, Shen, Schneiderman, & Antoni, 2006; Roeloffzen et al., 2010; Savard et al., 2005; Savard, Villa, Ivers, Simard, & Morin, 2009; Stepanski et al., 2008; Thomas, Bower, Hoyt, & Sepah, 2009; Uma, Kerrigan, Thronby, Monga, & Zimmermann, 2005); the majority included sleep as part of an evaluation of patients' quality of life (QOL) (Choo et al., 2007; Gore et al., 2009; Korbblith et al., 1994; Penedo et al., 2006; Roeloffzen et al., 2010; Uma et al., 2005). Findings from these studies suggest that patients with prostate cancer are at increased risk for sleep disturbance because of the disease itself and its treatments, particularly radiation therapy (RT) which can result in bowel and bladder problems. For example, RT can produce bladder irritation, which results in urinary

frequency and urgency (Savard & Morin, 2001). Hormonal therapy produces hot flashes and night sweets, which results in sleep disturbance (Savard & Morin, 2001). However, previous studies of patients with prostate cancer used primarily cross-sectional designs and did not use an objective measure (i.e., actigraphy) to evaluate for sleep disturbance.

Longitudinal studies that assess patients before, during, and after cancer therapy are necessary to determine the severity of sleep disturbance and how this symptom changes over time. In addition, studies are needed to evaluate for predictors of inter-individual differences in the trajectories of sleep disturbance. These studies require valid and reliable subjective and objective measures of sleep disturbance, as well as more sophisticated statistical methods that take repeated measures over time into account. These types of longitudinal studies will facilitate the identification of patients who are at greater risk for severe and persistent sleep disturbance may help to determine the underlying mechanisms for sleep disturbance, and guide the development and testing of targeted interventions.

Given the paucity of longitudinal studies on sleep disturbance in patients with prostate cancer, the purposes of the study were: to examine how total sleep time (TST) measured using wrist actigraphy, changed from the time of the simulation visit to four months after the completion of RT and to investigate whether specific demographic, clinical, and symptom characteristics predicted inter-individual differences in the trajectories of sleep disturbance.

Methods

Patients and Settings

This descriptive, correlational study is part of a larger, longitudinal study that evaluated multiple symptoms in patients who underwent primary or adjuvant RT (Aouizerat et al., 2009; Dhruva et al., 2010; Fletcher et al., 2009; Miaskowski et al., 2008). Patients were recruited from two RT departments located in a Comprehensive Cancer Center and a community-based oncology program at the time of the patient's simulation visit.

Patients were eligible to participate if they were ≥18 years of age; were scheduled to receive primary or adjuvant RT for one of four cancer diagnoses (i.e., breast, prostate, lung, brain); were able to read, write, and understand English; gave written informed consent; and had a Karnofsky Performance Status (KPS) score of ≥ 60. Patients were excluded if they had metastatic disease; more than one cancer diagnosis; or a diagnosed sleep disorder.

Instruments

The study instruments included a demographic questionnaire, the KPS scale (Karnofsky, Abelmann, Craver, & Burchenal, 1948), the General Sleep Disturbance Scale (GSDS) (Lee, 1992), the Center for Epidemiologic Studies-Depression (CES-D) Scale (Radloff, 1977), and the Spielberger State-Trait Anxiety Inventories (STAI-S and STAI-T) (Spielberger, Gorsuch, Suchene, Vagg, & Jacobs, 1983). Pain was evaluated using a modification of the Brief Pain Inventory (Daut, Cleeland, & Flanery, 1983). Objective data on sleep-wake circadian activity rhythms were obtained by continuous noninvasive monitoring of activity over 48 hours using a wrist motion sensor (Mini Motionlogger Actigraph, Ambulatory Monitoring, Inc., Ardsley, NY) (Ancoli-Israel et al., 2003; Berger, et al., 2008; Morgenthaler, et al., 2007).

The demographic questionnaire obtained information on age, gender, marital status, education, ethnicity, employment status, and the presence of a number of co-morbid conditions.

The GSDS consists of 21-items designed to assess the quality of sleep in the past week. Each item was rated on a 0 (*never*) to 7 (*everyday*) numeric rating scale (NRS). The GSDS total score is the sum of the seven subscale scores (i.e., quality of sleep, quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, excessive daytime sleepiness) that can range from 0 (*no disturbance*) to 147 (*extreme sleep disturbance*). Each mean subscale score can range from 0 to 7. Higher total and subscale scores indicated higher levels of sleep disturbance. Subscales scores of > 3 and a GSDS total score of > 43 indicate a significant level of sleep disturbance (Fletcher, et al., 2008). The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV (Lee, 1992; Lee & DeJoseph, 1992; Miaskowski & Lee, 1999). In the current study, the Cronbach's alpha for the GSDS total score was 0.84.

The LFS consists of 13 items that are rated on 0 to 10 NRS. Severity of fatigue was calculated as the mean of the 13 items, with higher scores indicating greater 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 going to bed (i.e., evening fatigue). The LFS has been used with healthy individuals (Gay, Lee, & Lee, 2004; Lee, et al., 1991) and in patients with cancer and HIV (Lee, Portillo, & Miramontes, 1999; Miaskowski, et al., 2006; Miaskowski & Lee, 1999; Miaskowski, et al., 2008). Cutoff scores of $\geq$3.2 and $\geq$5.6 indicate significant levels of morning and

evening fatigue, respectively (Fletcher, et al., 2008). The LFS was chosen for this study because it is relatively short, easy to administer, and has well-established validity and reliability. In this study, Cronbach's alphas for evening and morning fatigue at baseline were 0.96 and 0.95, 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 of $\geq$ 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; Radloff, 1977; Sheehan, Fifield, Reisine, & Tennen, 1995). In the current study, the Cronbach's alpha for the CES-D was 0.88.

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 generally feels. The STAI-S measures an individual's transitory emotional response to a stressful situation. It evaluates the emotional responses of worry, nervousness, tension, and feelings of apprehension related to how a person feels "right now" in a stressful situation. Cuttoff scores of $\geq$ 31.8 and $\geq$ 32.2 indicate high levels of trait and state anxiety, respectively. The STAI-T and STAI-S inventories have well-established criterion and construct validity and internal consistency reliability coefficients (Bieling, Antony, & Swinson, 1998; Kennedy, Schwab, Morris, & Beldia, 2001; Spielberger et al., 1983). In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.95, respectively.

Pain was evaluated using a modification of the BPI. Patients were asked to indicate whether or not they had pain other than "every day kinds of pain". Patients who responded in the affirmative were asked to rate the intensity of average and worst pain using 0 (no pain) to 10 (worst possible pain) NRS. In addition, they rated the number of days per week and the number of hours per day they experienced significant pain, as well as the amount of relief they experienced from their current regimen (i.e., 0%=no relief to 100%= complete relief). A mean interference score was calculated based on patients' responses to the interference items or the BPI. Because the majority of the patients did not have pain (74.4%), for the subsequent longitudinal analysis, pain was coded as present or absent.

Objective data on sleep-wake circadian activity rhythms were obtained by continuous noninvasive monitoring of activity over 48 hours using wrist actigraphy. For the purpose of this study, analyses were done on total sleep time (TST). Wrist actigraphy is validated with EEG measures of sleep and awakenings on men and women with both healthy and disturbed sleep patterns (Ancoli-Israel, et al., 2003; Buysse, Ancoli-Israel, Edinger, Lichstein, Morin, 2006; Morgenthaler, et al., 2007). It provides continuous motion data using a battery-operated wristwatch-size microprocessor that senses motion with a piezo-electric beam and detects movement in all three axes. The accompanying Action 4® software (Ambulatory Monitoring Inc., Ardsley, NY) allows analysis of activity and nonactivity as well as automatic scoring of sleep and wake in one-minute intervals.

Patients were asked to use the event marker on the wrist actigraph to indicate "lights out" and "lights on" time. Patients reported no difficulties wearing the wrist

actigraph. Since the actual time is important in the calculation of the amount of sleep obtained in the amount of time designated for sleep, having an additional source of information about nap times, bed times, and wake times is important. This information was recorded by patients in a two-day diary. Upon awakening, the patients used the diary to indicate the number of awakenings during the night.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and at the second site. At the time of the simulation visit (i.e., approximately one week prior to the initiation of RT), patients were approached by a research nurse to discuss participation in the study. After obtaining written informed consent, patients completed the demographic questionnaire, KPS scale, GSDS, STAI-T, STAI-S, CES-D, and the modified version of the BPI. Medical records were reviewed for disease and treatment information.

In addition, patients were taught to complete the LFS (Lee, Hicks, & Nino-Murcia, 1991) before going to bed each night (i.e., evening fatigue) and upon arising each morning (i.e., morning fatigue) for 2 consecutive days. Patients wore the wrist actigraph to monitor sleep and activity continuously for two consecutive days. They completed the two day diary that included sleep and wake times, naps, meal times, and level of physical activity during the day. Patients were asked to return the questionnaires and actigraphs to the research nurse in the RT department at the completion of the two days of data collection. 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 following the

completion of RT, and once a month for two months of data collection. The majority of the patients completed 16 assessments.

Data Analysis

Data were analyzed using SPSS version 15. Descriptive statistics and frequency distributions were generated for the sample characteristics and symptom data. Actigraphy files in zero-crossing mode were analyzed using the Cole-Kripke algorithm in the Action 4® software (Ambulatory Monetary Inc., Ardsley, NY, Cole & Kripke, 1992) by two of the researchers (Cole & Kripke, 1992). The file was first scanned for missing data. If more than four hours of day data or two hours of night data were missing that day's or night's data were not used in the analyses. Time limits were set for the 48-hour period. The file was reviewed and intervals were individually set for each day and night period using, in order of priority as decision guides, the event marker, dairy data, channel data, and cascading movement data.

To evaluate for changes in sleep disturbance over time, 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 sleep disturbance (i.e., TST) 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 patient was to be assessed on a prespecified schedule, the actual number of assessments was not the same for all of the patients 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 (Raudenbush et al., 2002).

With HLM, the repeated measures of the outcome variable (i.e., TST) are nested within individuals and the analysis of change in TST 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 (Raudenbush et al., 2002; Raudenbush, 2001).

The HLM analysis proceeded in two stages. First, intraindividual variability in TST over time was examined. In this study, time in weeks 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 patients' TST (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 effect) 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 aim and identified the change parameters that best described individual changes in TST.

The second stage of the HLM analysis, which answered the second aim, examined interindividual differences in the trajectories of TST 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 sleep disturbance in men with prostate cancer who underwent RT (Savard, Villa, Irvers, Simard, Morin, 2009; Dirksen et al., 2009). To improve estimation efficiency and construct a model that was parsimonious, an exploratory Level 2 analysis was done in which each potential predictor was assessed to see if it would result in a better fitting model if it alone was added as a Level 2 predictor. Predictors with a *t*-value of <2.0, which indicates a lack of a significant effect, 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 <0.05 indicates statistical significance.

Results

Patient Characteristics

The demographic, disease, and treatment characteristics of the 82 patients with prostate cancer are presented in Table 2. These men were approximately 67 years of age, were well educated, and had a KPS score of 95.7. Most of the patients were married or partnered (69.5%), White (76.8%), and not employed (53.7%). The distribution of clinical stage was 48.8% with T1, 42.5% with T2, and 8.8% with T3. Over 50% of the patients received hormonal therapy prior to the initiation of RT. The mean symptom severity scores for the 82 patients, at the time of the simulation visit, are listed in Table 2.

Individual and Mean Changes in TST

The first HLM analysis investigated how TST changed from the time of the simulation visit to four months after the completion of RT. Two models were estimated in which the function of time was linear and quadratic. The goodness-of-fit test of the deviance between the linear and quadratic models indicated that a quadratic model fit the data significantly better than a linear model.

The estimates of the quadratic change model are presented in Table 3 (unconditional model). Because the model had no covariates, the intercept represents the estimated amount of TST (i.e., 379.662 minutes) at the time of the simulation visit. The estimated linear rate of change in TST for each week was -2.282 minutes (p=0.004), and the estimated quadratic rate of change was 0.104 minutes (p=0.002). Figure 1A illustrates the trajectory of TST from the time of the simulation visit to four months after the completion of RT. TST decreased over the course of RT and then increased after the completion of RT.

Although the results indicate a sample-wide decrease followed by an increase in TST, they do not imply that all patients exhibited the same trajectory. The variance in individual change parameters estimated by the model (i.e., variance components, Table 3) suggested that substantial interindividual differences existed in the trajectories of TST, which are illustrated in Figure 1B. These results suggested that further examination of inter-individual differences in the individual change parameters were warranted.

Inter-individual Differences in the Trajectories of Sleep Disturbance

The second stage of the HLM analyses tested the hypothesis that the pattern of change over time in TST varied based on specific person, disease, treatment, and symptom variables that were found to influence the sleep of patients who underwent RT

for prostate cancer. As shown in the final model in Table 3, the four variables that predicted interindividual differences in the intercept for TST were ethnicity (i.e., White versus Nonwhite), KPS score, total dose of RT received, and the presence of pain at baseline. Baseline sleep disturbance was entered in Level 2 as a predictor of the slope parameters to control for individual differences in sleep disturbance at baseline. The four variables that predicted interindividual differences in the slope parameters for TST were total dose of RT received, baseline STAI-S score, presence of pain of baseline, and TST at baseline.

The effects of the six different predictors on patients' trajectories of TST are illustrated in Figures 2 and 3. Figure 2 displays the adjusted change curves in TST only for the two variables that predicted differences in baseline levels of TST (i.e., intercepts). Estimates are based on differences in ethnicity (white versus non-white) and KPS score (i.e., lower/higher calculated based on one standard deviation (SD) above and below the patients' mean KPS score).

Figure 3 displays the adjusted change curves for TST for the four variables that predicted differences in both baseline levels of TST (i.e., intercepts) and the trajectories of TST (i.e., linear and quadratic slopes). Estimates are based on differences in presence of pain at initiation of RT (i.e., yes versus no), total dose of RT received (i.e., lower/higher calculated based on one SD above and below the mean dose of RT received), baseline level of state anxiety (i.e., lower/higher calculated based on one SD above and below the mean baseline STAI-S score), and baseline level of TST (i.e., lower/higher calculated based on one SD above and below the mean baseline TST). It should be noted that mean TST scores for the various groups depicted in all of the figures

are estimated or predicted means based on the HLM analysis.

Discussion

This study is the first to evaluate for inter-individual differences in and predictors of the trajectories of sleep disturbance in men with prostate cancer who underwent RT using an objective measure of TST and a novel method of longitudinal data analysis. Consistent with previous reports of sleep disturbance in patients with prostate cancer (Savard et al, 2005; Dirksen et al, 2009), the patients in the study experienced a significant amount of sleep disturbance prior to, during, and for four months following the completion of RT. Based on the actigraphy data, these men slept between 66.50 minutes (i.e., 1.1 hours) and 592.00 minutes (i.e., 9.9 hours) per night prior to the initiation of RT. Approximately 65.47% of these patients slept less than the recommended minimum of 420 minutes (7.0 hours) per night prior to the initiation of RT which is higher than the 31.5% (Savard et al., 2009) to 53.0% (Dirksen et al., 2009) reported in previous studies. One of the reasons for these inconsistent findings may be that the previous studies relied on self-reports of sleep disturbance rather than actigraphy. Previous studies have shown that male oncology patients as well as men in the general population tend to report lower levels of symptoms than females (Valeberg et al., 2008). An additional reason for the inconsistent findings may be the stage in the disease trajectory patients were assessed for sleep disturbance. While this study evaluated patients prior to, during, and following RT, previous studies evaluated patients following radical prostatectomy (Savard et al., 2005) or at any point in the course of their treatment (Dirksen at al., 2009). Findings from this study suggest that men who are about to undergo RT are at particularly high risk group for sleep disturbance who warrant and variant careful assessments and treatment.

One of the major advantages of HLM is the ability to identify predictors that place patients at higher risk for sleep disturbance. In this study, Nonwhites were found to sleep on average 81.9 minutes (1.4 hours) less than Whites. Of the Nonwhites in this study (n=19), 78.9% self-identified as Black/African American, 15.8% as mixed ethnic background, and 5.3% as other. Previous researches on ethnic differences in sleep disturbance have produced conflicting results. In a comparative review of sleep in African Americans (Durrence & Lichstein, 2006), Durrence and Lichstein concluded that although the limited data were somewhat inconsistent, findings suggest that African American sleep worse than Caucasian Americans. While no studies were found that evaluated the relationship between ethnicity and sleep disturbance in patients with prostate cancer, a recent report of a heterogeneous sample of a heterogeneous of 823 patients receiving cancer chemotherapy found that nonwhites were 44% less likely to report insomnia than whites (Palesh et al., 2010). Reasons for these inconsistent findings may be related to a numbers of factors. First, in the study by Palesh and colleagues (Palesh et al., 2010), none of the patients had a diagnosis of prostate cancer and all of the patients were receiving chemotherapy. In addition, the assessment of insomnia was made using six questions on the frequency and duration of sleep problems from the Hamilton Depression Inventory compared to actigraphy in this study. The relationship between ethnicity and sleep disturbance in oncology patients warrants additional investigation because findings from a large population-based study suggest that in Nonwhites comorbid health conditions appear to moderate the relationship between sleep disturbance and worse physical function (Baldwin et al., 2010).

While only 25.6% of this sample indicated that they were experiencing pain, the presence of pain at baseline predicted a decrement in TST of 49.3 minutes and was associated with a worse trajectory of sleep disturbance over the course of RT (see Figure 3A). The pain characteristics of these 21 patients are summarized in Table 4. Based on their ratings of worst pain, this subset of patients reported moderate to severe pain for about 50% of the week. The finding of worse sleep being associated with chronic pain is consistent with findings from two cross-sectional studies of oncology patients (Savard et al., 2005, Stepanski et al., 2009). In addition, the men with prostate cancer and pain in this study reported lower TST (i.e., 280.5 minutes) at the initiation of RT than a sample of patients with chronic low back pain (i.e., TST = 381.7 minutes) (O'Donoghue, Fox, Heneghan, and Hurley, 2009).

Consistent with a study of insomnia in patients who underwent prostatectomy (Savard et al., 2005), higher levels of anxiety were associated with a worse trajectory of sleep disturbance over the 6 months of this study. However, unlike previous studies of heterogeneous samples of oncology patients (Stepanski et al., 2008) and patients with prostate cancer (Dirksen et al., 2009), depression was not a predictor of baseline levels of TST or changes in TST. This difference may be related to the relatively low CES-D scores in this sample. In addition, previous reports (Stepanski et al., 2008; Dirksen et al., 2009) evaluated the relationship between self-reported sleep disturbance and depression which maybe more related than an objective measure of sleep disturbance to a self-report measure of depression.

The only two clinical characteristics that predicted interindividual differences in sleep disturbance in this sample were KPS score and the total dose of RT received. While

mean KPS scores were high (i.e., 95.7 ± 6.9), findings from this study suggest that patients with lower KPS scores had worse TST scores at the initiation of RT that persisted over the 6 months of this study. In addition, patients who received a higher dose of RT had a worse sleep disturbance trajectory. However, it should be noted that the effects of radiation dose on the trajectory of sleep disturbance, while significant was relatively small.

Several study limitations need to be acknowledged. The sample size is relatively small. While the single cancer diagnosis limits the generalizability of the study findings, the homogeneity of this sample provides useful information on sleep disturbance in this high-risk group of patients. Because the refusal rate in the study was relatively high (43.6%), and the main reasons for refusal were being overwhelmed or too busy. Findings from this study may underestimate the amount of sleep disturbance in patients with prostate cancer. In addition, according to establish guidelines, actigraphy data should be collected for a minimum of three consecutive 24-hour periods (Littner et al., 2003). However, the 48-hour time frame used in this study was chosen to reduce respondent burden (Littner et al., 2003).

In summary, HLM is a useful statistical approach to analyze longitudinal data on inter-individual differences in symptom trajectories. The identification of predictors of this variability can be used to identify high risk patients who warrant interventions to decrease sleep disturbance and improve quality of life. Additional research is warranted to confirm this study's findings and to develops and test interventions in this vulnerable group of oncology patients.

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Table 1 Potential Predictors of Intercept, Linear Coefficient, and Quadratic Coefficient for Total Sleep Time

Predictors	Intercept	Linear Coefficient	Quadratic Coefficient
Person characteristics			
Age			
Education			
Employment status			
Lives alone			
Marital status	■		
White	■	■	■
Disease and treatment characteristics			
Gleason score			
Hormonal therapy prior to RT			■
KPS score	■		
Number of comorbidities	■		
Prescribed dosage of RT	■		■
Pretreatment PSA			
Total dose of RT	■	■	■
Symptoms			
Baseline CES-D score		■	
Baseline GSDS score			■
Baseline evening fatigue score			
Baseline morning fatigue score			
Baseline State Anxiety score		■	
Baseline Trait Anxiety score			
Presence of pain at baseline	■	■	■

CES-D= Center for Epidemiologic Studies Depression Scale; KPS= Karnofsky Performance Status; PSA= prostate-specific antigen; RT= radiation therapy; GSDS= General Sleep Disturbance Scale

Table 2 Demographic, Disease, and Treatment Characteristics of the Patients (n=82)

Characteristic	Mean (Standard Deviation)
Age (years)	67.1 (7.8)
Education (years)	16.0 (3.2)
Karnofsky Performance Status Score	95.7 (6.9)
Number of comorbidities	4.6 (2.5)
Lives alone (%)	23.2
Marital status (%)	
Married/partnered	69.5
Divorced/separated	13.4
Other	17.1
Ethnicity (%)	
Black	18.3
White	76.8
Other	4.9
Employed (%)	
Yes	46.3
No	53.7
Pre-treatment PSA level (nanograms/milliliter)	10.9 (7.9)
Gleason score (%)	
5 or 6	39.1
7	47.70
>8	13.40
Mean Gleason score	6.8 (0.9)
Clinical stage (%)	
T1	48.8

T2	42.5
T3	8.8
Prostatectomy prior to RT (%)	9.8
Hormonal therapy (%)	51.2
RT treatment plan (%)	
Whole pelvis + conformal boot after surgery	9.8
Whole pelvis + conformal boot	75.6
Whole pelvis + high dose RT	4.9
Whole pelvis + seed implant	9.8
Total dose of RT (cGys)	6,902 (958.2)
Mean symptom severity scores at baseline	
LFS score for evening fatigue	3.5 (2.1)
LFS score for morning fatigue	1.8 (1.8)
GSDS score	33.4 (16.3)
CES-D score	5.9 (5.7)
Trait Anxiety Inventory score	31.3 (7.9)
State Anxiety Inventory score	27.8 (7.8)

CES-D = Center for Epidemiologic Studies Depression Scale, cGYs=, GSDS = General Sleep Disturbance Scale, LFS = Lee Fatigue Scale, PSA = Prostate Specific Antigen, RT = radiation therapy

Table 3 Hierarchical Linear Model of Total Sleep Time

Total Sleep Time	Coefficient (SE)	
Variable	Unconditional Model	Final Model
Fixed effects		
Intercept	379.662 (8.850) [b]	329.753 (14.444) [b]
Time[a] (linear rate of change)	-2.282 (0.758) [c]	-1.801 (0.784) [d]
Time^2 (quadratic rate of change)	0.104 (0.031) [c]	0.070 (0.033) [d]
Time invariant covariates		
Intercept		
White		81.901 (15.701) [b]
KPS score		2.296 (0.991) [d]
Total dose of RT received		-0.016 (0.007) [d]
Presence of pain at baseline		-49.289 (15.651) [c]
Linear		
Total dose of RT received × time		-0.001 (0.001) [d]
Baseline STAI-S score × time		-0.316 (0.090) [c]
Presence of pain at baseline × time		-2.360 (1.643) [NS]
TST at baseline × time		-0.037 (0.009) [b]
Quadratic		
Total dose of RT received × time^2		0.000 (0.000) [d]
Baseline STAI-S score × time^2		0.011 (0.004) [c]
Presence of pain at baseline × time^2		0.145 (0.070) [d]
TST at baseline × time^2		0.002 (0.000) [b]
Variance components		
In intercept	5859.683[b]	3056.905[b]
In linear rate	20.062[b]	10.401[b]
In quadratic fit	0.034[b]	0.022[b]

Goodness-of-fit deviance (parameters estimated)	11998.793 (10)	11927.681 (22)
Model comparison (χ^2 [df])		71.111(12)

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

[b]$p < 0.0001$, [c]$p < 0.01$, [d]$p < 0.05$

KPS= Karnofsky Performance Status; RT= radiation therapy; STAI-S= Spielberger State Anxiety Inventory score; TST= total sleep time

Table 4 Characteristics of Pain in Prostate Cancer Patients Who Had Pain at the Baseline of Radiation Therapy (n=21)

Pain Characteristics	Mean (S.D.)
Average pain (0 to 10)	3.06 (1.52)
Worst pain (0 to 10)	6.40 (2.47)
Days per week in significant pain (0-7)	3.68 (2.89)
Hours per day in significant pain (0-24)	6.48 (6.38)
Percent pain relief (0% to 100%)	51.88 (35.82)
Mean pain interference score (0 to 10)	3.01 (2.09)

Figure 1-A. Trajectories of total sleep time measured using actigraphy over the 25 weeks of the study.

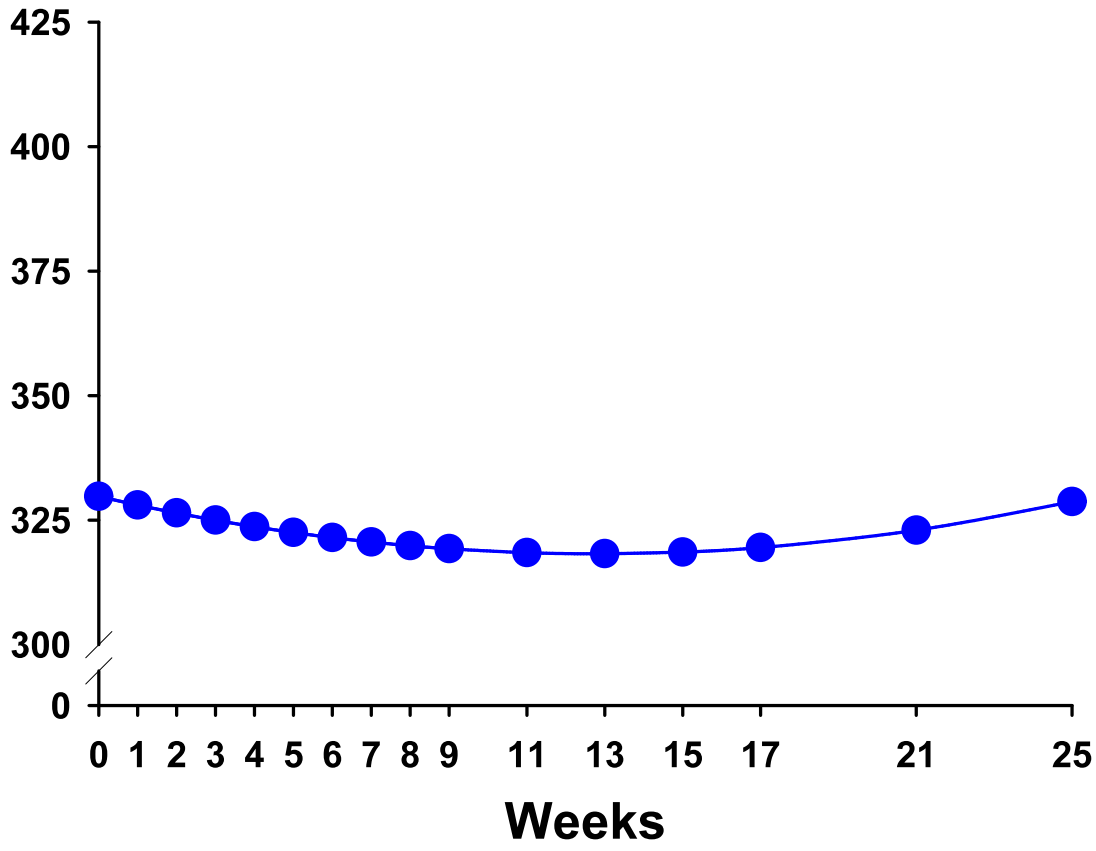


Figure 1-B. Spaghetti plot of the 82 patients' individual trajectories of total sleep time (TSTAVE) over the 25 weeks of the study.

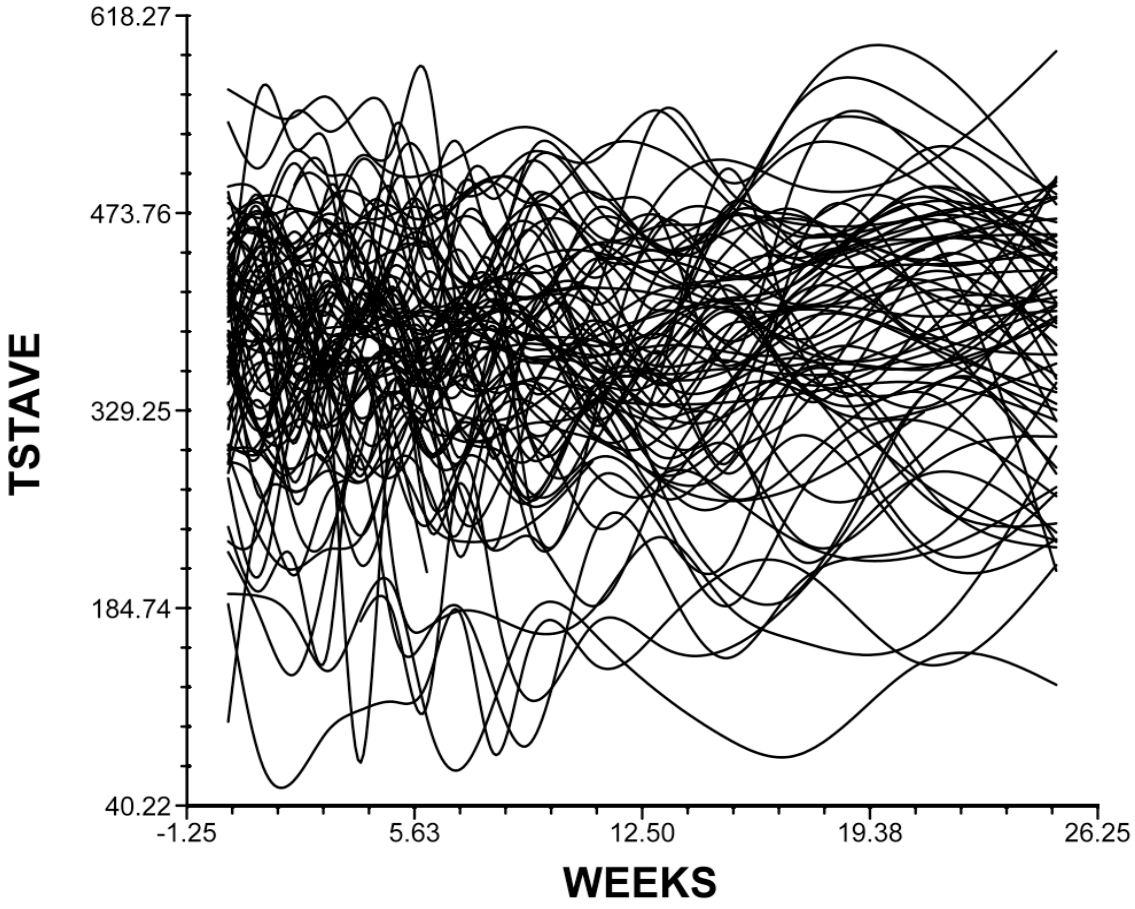


Figure 2. Trajectories of total sleep time measured using actigraphy by ethnicity (A; white versus nonwhite) and Karnofsky Performance Status (KPS) score (B; i.e., lower/higher KPS score)

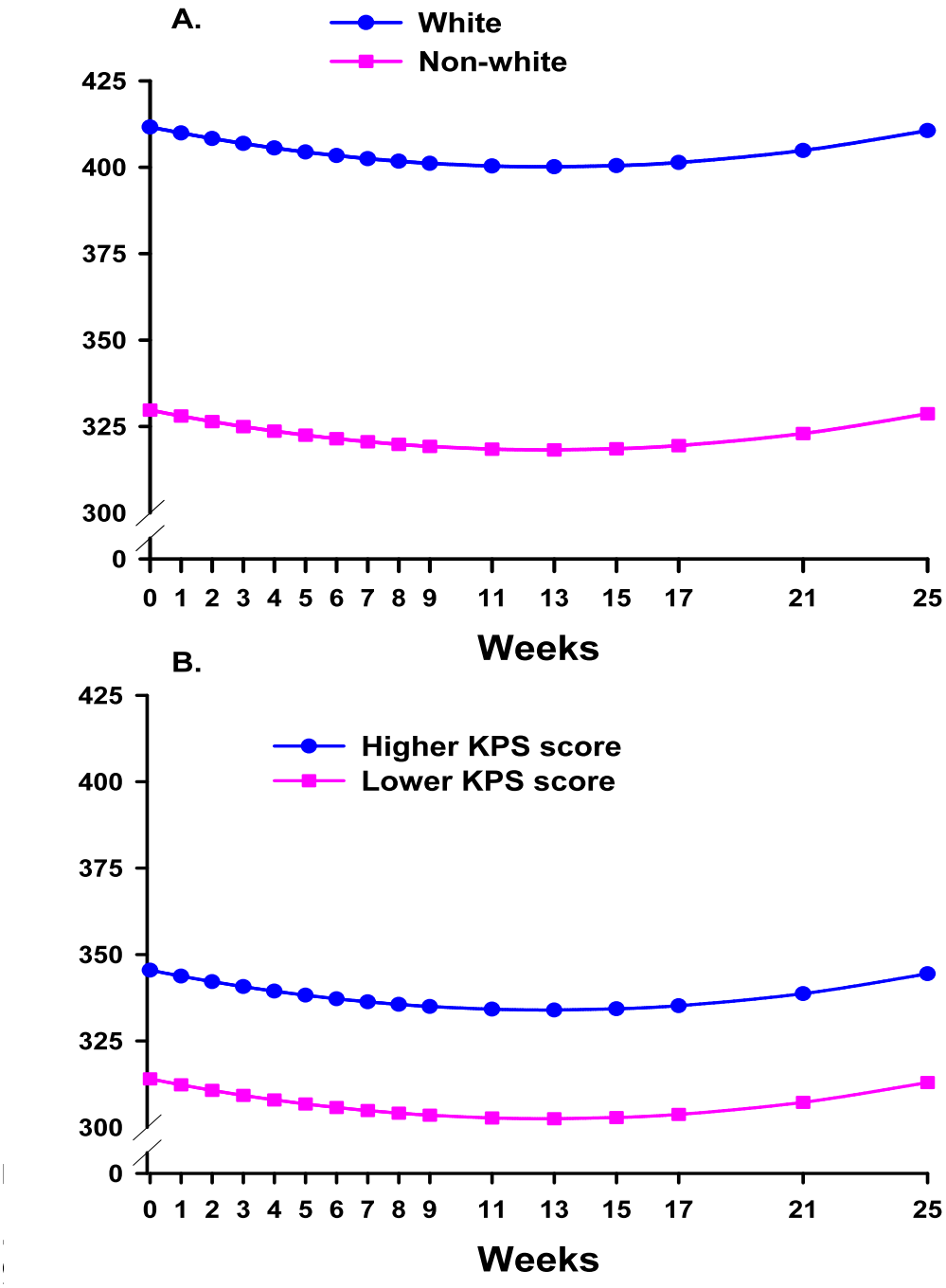
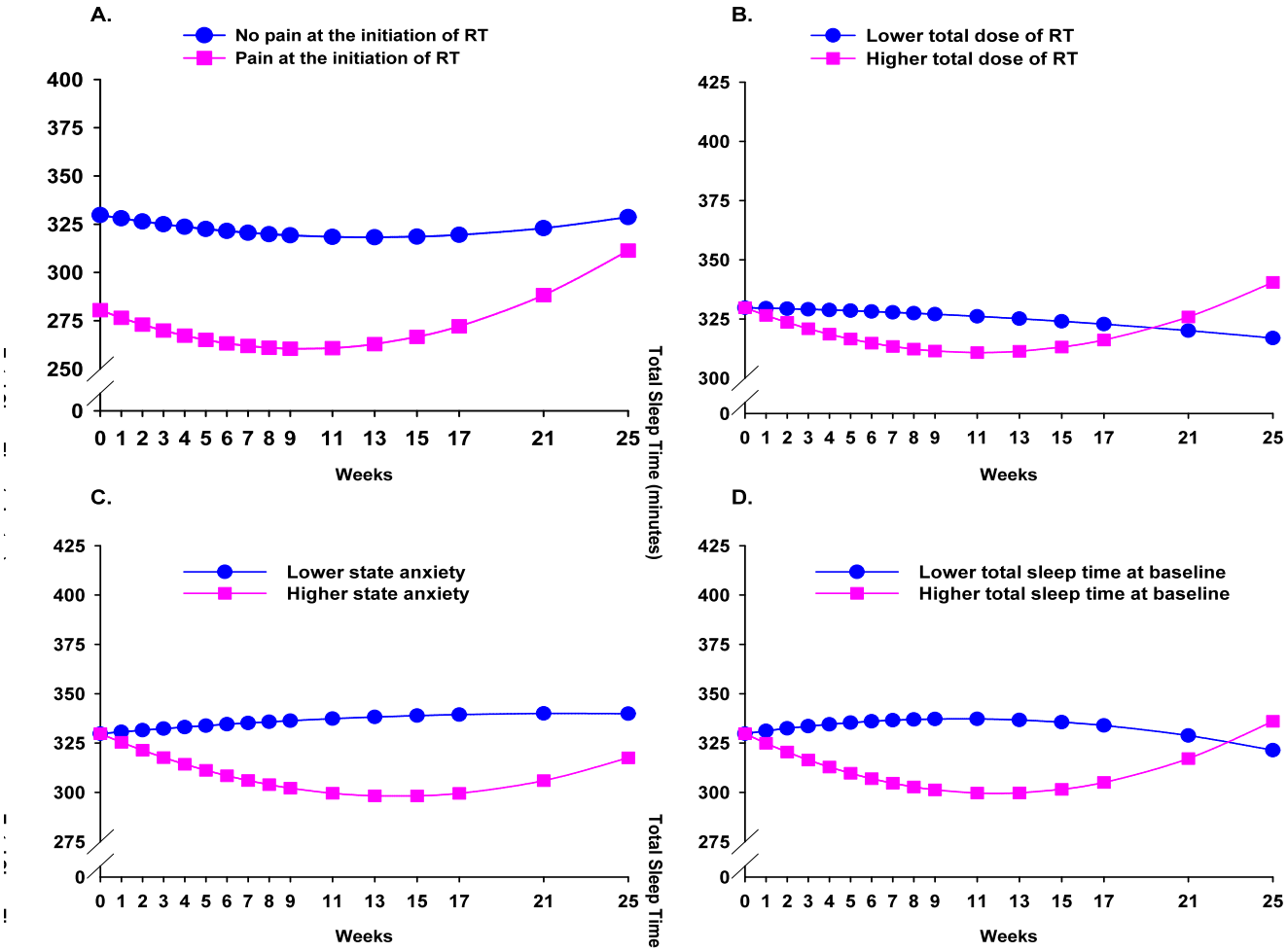


Figure 3. Trajectories of total sleep time (TST) measured by actigraphy by pain (A; i.e., pain at the initiation of RT versus no pain), total dose of radiation therapy (RT) administered (B; i.e., lower/high total dose of RT received); level of state anxiety (C; lower state anxiety versus higher state anxiety), and amount of TST at baseline (D; lower versus higher TST).



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