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Sleep problems in advanced cancer patients and their caregivers: Who is disturbing whom?

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Abstract *Background* The aims of the study were to understand sleep problems and their effects in advanced cancer patients and spousal and intimate partner caregivers and to examine the directionality of the link between patients' and caregivers' sleep problems. *Methods* Fifty-four advanced cancer patients and their spousal and intimate partners were administered a battery of questionnaires that included the Pittsburgh Sleep Quality Index and the Center for Epidemiological Studies at the patients' cancer diagnosis and at 2, 4, and 6 months after diagnosis. *Results* Patients' and caregivers' sleep duration was significantly related. Using cross-lagged panel analyses, caregivers' sleep quality significantly predicted patients' sleep quality and patients' sleep quality subsequently predicted caregivers' sleep quality. Patients' sleep latency significantly was found to significantly predict caregivers' sleep latency. *Conclusion* Patients diagnosed with cancer and their intimate partners have poor sleep quality and sleep patterns are related.

Keywords Cancer · Sleep quality · Caregiver · Sleep latency · Sleep problem

Introduction

Sleep symptoms are common in patients with cancer. Although studies of cancer patients often include the assessment of individual symptoms of insomnia rather than full diagnostic criteria, prevalence rates of sleep disturbances are consistently high (59–79%) (Davidson et al., 2002; Savard & Morin, 2001; Theobald, 2004). Rates of insomnia and subclinical symptoms and of insomnia in patients with cancer appear to be at least two to three times higher than in the general population (Savard & Morin, 2001). Longitudinal studies have found that sleep problems such as insomnia often begin or worsen during cancer treatment, and follow a chronic course in up to 95% patients (Savard & Morin, 2001). The rate of sleep problems also rises in more advanced cancer patients (85%), whose significant symptom burdens and uncontrolled physical symptoms can contribute to poor sleep quality (Collins et al., 2017).

Sleep plays a vital role in physical and psychological health, and inadequate sleep may further compound illness and impair recovery (Collins et al., 2017). Chronic sleep problems can have negative effects on outcomes as diverse as quality of life, physical symptoms, adherence to treatments, interpersonal relationships, accidents and falls, pro-inflammatory cytokines, and healthcare utilization (Davidson et al., 2002; Berger, 2003; Bjørngaard et al., 2011; Engstrom et al., 1999; Kochar et al., 2007; Manabe

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et al., 2000; Manocchia et al., 2001; Palesh et al., 2012). Among cancer patients, sleep disturbance is associated with aberrant patterns of cortisol secretion, which in turn can impair the cellular immunity responsible for mounting a defense against tumors (Theobald, 2004).

Intimate partners are frequently the primary caregivers for cancer patients, often providing around-the-clock care and incurring physical, emotional, and financial burden (Northouse et al., 2012; Pellegrino et al., 2010). Most research on the sleep of intimate partner caregivers has been conducted in caregivers of patients with dementia. However, recent studies have also shown high rate of sleep problems among intimate partner caregivers of patients with cancer (Carter & Chang, 2000; Carter, 2003; Stenberg et al., 2010). A systematic review of ten sleep studies found that as much as 72% of caregivers reported moderate to severe sleep disturbance (Maltby et al., 2017). Intimate partner caregivers also reported significantly greater sleep problems compared to the general population (Zhang et al., 2014). Specifically, problems with insomnia, sleep latency, wake after sleep onset (WASO), night awakenings, and daytime fatigue are common among intimate partner caregivers of cancer patients (Kotronoulas et al., 2013). Despite the high prevalence of sleep problems, some findings suggest caregivers may underestimate the extent of their problem. Sleep measured across a 10-week span showed caregivers reported an average of 6.05 h of sleep a night, yet objective assessment indicated an average sleep duration of only 4.83 h a night (Carter & Chang, 2000). A qualitative study of caregivers of advanced cancer patients found caregivers minimized the significance of their sleep problems (Hearson & McClement, 2007). Carney and colleagues measured sleep using actigraphy and found that cancer patients and their caregivers had approximately 18 awakenings, each lasting 3–4 min, over the course of the night (Carney et al., 2011). These findings are consistent with a study of 60 caregivers of advanced cancer patients, in which 90% had sleep fragmentation (Gibbins et al., 2009). However, it is still not clear that if the severity of the sleep fragmentation in cancer caregivers is different from the general population.

Sleep problems can lead to negative mental and physical health outcomes among cancer caregivers. For instance, sleep problems have been associated with increased depression, poorer coping, lower optimism, less mastery, and higher neuroticism among caregivers (Northouse et al., 2012; Carter & Acton, 2006). Specifically, sleep fragmentation can lead to excessive daytime sleepiness, cognitive impairment and mood disorders (Martin et al., 1996; Stepanski & Perlis, 2000), and has also been associated with metabolic syndrome, diabetes, and increased risk of cardiovascular disease (CVD) (Mullington et al., 2001, 2009, 2010; Vgontzas et al., 2009). These risks may be compounded by the fact that many caregivers must provide care for months or even years. Carter found that caregivers of advanced cancer patients reported providing care an average of 16 h of care per day for 2 years. Of these caregivers, 95% reported severe sleep problems with moderate-severe daytime impairment (Carter & Chang, 2000).

While sleep problems are common and have negative consequences for both patients and caregivers, little is known about how these problems differ among partners, or how sleep in one partner may affect sleep in the other. Two separate studies found that 40–50% of cancer patients and caregivers reported sleep problems (Carney et al., 2011; Gibbins et al., 2009). The primary difference between cancer patients and intimate partner caregivers was that patients had more frequent awakenings and used significantly more sleep aids than their intimate partner (Carney et al., 2011). Cancer patients also reported poorer sleep efficiency compared to caregivers, but sleep, rest and wake and activity parameters were highly correlated among partners. A recent study found that interdependence in couples' sleep (sleep–wake concordance) is associated with CVD risk, raising the possibility that dyadic sleep patterns may also affect health outcomes in cancer patients (Gunn et al., 2016). Further research is needed to compare intimate partner sleep patterns in cancer patients and their caregivers versus the general population.

Sleep disturbance in cancer patients is a crucial area of clinical and research focus, as sleep loss can affect one's physical and emotional health. These factors can impact the caregivers' ability to safely and effectively perform caregiving duties. Further research is needed to examine the extent and nature of sleep problems in cancer caregivers, as well as explore potential demographic and emotional predictors to identify those cancer caregivers at a higher risk for developing sleep problems. To address the gap in cancer caregivers' sleep research, this study aimed to: (1) describe the sleep problems of advanced cancer spousal and intimate partner caregivers, (2) investigate the association between sleep problems and depression in advanced cancer patients and intimate partner caregivers, and (3) examine the directionality of the link between patients' and their caregivers' sleep problems.

Methods

Design and participants

We conducted a prospective observational study in patients with cancer and their intimate partners. The Liver Cancer Center evaluates and treats patients with advanced cancers related to the hepatobiliary-pancreatic system. Patients and intimate partners were enrolled between January 2008 to June 2012 (K07CA118576 and R21CA127046). Patients were required to have a biopsy or radiographic-proven diagnosis of cancer affecting the hepatobiliary or pancreatic system. Additional inclusion and exclusion criteria for patients and intimate partners were: (1) age 21 years or older; (2) fluent in English, and (3) no evidence of thought disorder, hallucinations, or delusions.

Instruments

Sociodemographic, disease, and treatment specific factors

Sociodemographic data including patients' age, gender, BMI, race, ethnicity, religious preference, educational level, occupation, income, and health insurance status were collected on a self-reported questionnaire designed specifically for this study. Disease-specific and treatment-related information including diagnosis, presence or absence of cirrhosis, maximum tumor size, number of lesions, vascularity of lesions, and vascular invasion was gathered from the patients' electronic medical record. Survival was measured from the time of diagnosis of cancer until death.

Sleep

The Pittsburgh Sleep Quality Index (PSQI) is an 18-item self-rated questionnaire which assesses sleep quality and disturbance over a one-month time interval (Buysse et al., 1989). The PSQI was used to describe sleep problems in seven components: sleep duration, sleep disturbances, sleep latency ($\geq$ 30 min indicates poor latency), daytime dysfunction, sleep efficiency (time asleep divided by time spent in bed, $<$ 85% indicates poor efficiency), subjective sleep quality, and use of sleep medication. Each component is scored on a 0–3 scale. The seven component scores are summed to yield a global score of ranging from 0 to 21 (higher scores indicate worse sleep quality and scores greater than 5 indicate poor sleep quality) (Buysse et al., 1989). Acceptable measures of internal consistency (Cronbach $\alpha = 0.83$), test–retest reliability ($r = 0.85$, $p < 0.001$), and validity using clinical interview and polysomnographic (Hotelling's TL = 2.62, $p < 0.001$), have been reported for the PSQI (Buysse et al., 1989).

Depressive symptoms

The Center for Epidemiologic Studies-Depression (CES-D) is a 20-item self-report questionnaire designed to assess depressive symptoms. Each item is answered on a four-point scale by reporting weekly frequency of depressive symptoms ("rarely," "some days," "occasionally," "most days") (Radloff, 1977). The CES-D has a range of 0–60 for the summed item scores (Radloff, 1977). A total score of 16 or greater represents depressive symptoms in the clinical range (Radloff, 1977). The CES-D has demonstrated adequate construct validity with higher scores among cancer patients than healthy adults prior to treatment ($p < 0.05$) and midway through treatment ($p < 0.001$); positive correlation with the Profile of Mood States-Fatigues and the State-Trait Anxiety Inventory-Anxiety and negative correlations with the Mental Health Summary Scale of the Short Form-36 ($p < 0.001$ for all correlations) (Hann et al., 1999). It is also found to have acceptable reliability ($\alpha = 0.89$) and test–retest reliability ($r = 0.57$, $p < 0.001$) in cancer patients (Hann et al., 1999).

Procedure

The study was approved by the University of Pittsburgh Institutional Review Board prior to the enrollment of patients. Patients were referred to the study team by their attending physician. If the patient agreed to speak to the study team, study staff would explain the risks and benefits of the study and obtain informed consent from the patient prior to administering the questionnaires.

Data analysis

All data were entered, verified and analyzed with SPSS version 25 (IBM Corp, Armonk, NY). Descriptive statistics were performed to obtain measures of central tendency, distribution, and percentages for each variable. Kendal tau-c coefficients were computed to assess agreement between patients and caregivers sleep problems at each time point. Next, the longitudinal relationships among patient and caregivers sleep problems were examined by constructing four constrained cross-lagged panel models using EQS software (version 6.2, Multivariate Software, Inc.). The panel design allowed for the estimation of autocorrelations (correlations between the same variables measured at different times) and cross-lagged correlations (correlations between different variables measured at different times) (Kenny, 1975). Model fit was assessed using goodness of fit indices, including root mean square error of approximation (RMSEA; values $\leq$ .07 were considered appropriate); standardized root mean square residual (SRMSR; values $\leq$ .08 were considered good fit); and the comparative fit index (CFI; values $\geq$ .95 were considered good fit) (Lt & Bentler, 1999). Cross-lagged panel analyses were used to examine relationships in patient and caregivers' sleep quality, latency, and duration over time. Analyses were conducted with EQS (Multivariate Software, Inc., version 6.2) using maximum likelihood estimation.

Results

Sociodemographic characteristics of 54 advanced cancer patients and their intimate partner are shown in Table 1. The majority of the patients were male (65%), Caucasian (80%) and the mean age was 62 (SD = 11). The majority of patients were diagnosed with hepatocellular or cholangiocarcinoma (67%) and most were treated with regional chemotherapy or radiation (76%). The family caregivers were primarily female (71%), Caucasian (91%), and had a mean age of 55 (SD = 12) years. Forty-three percent of intimate partner caregivers were working full or part-time and 24% of patients were employed.

Sleep of advanced cancer patients

The patients reported a mean sleep duration of 6.47 h (SD = 2.1) and an average sleep latency of 21.9 min (SD = 25.9); 12% reported a sleep latency of > 30 min three or more times per week. Sixty-four percent of patients reported taking a sleep aid in the past month and 8.1 percent reported taking a sleep aid three or more times per week. Patients reported a mean sleep efficiency of 85.6%.

Table 1 Sociodemographic characteristics of patients and caregivers

	Caregivers N = 54	Patients N = 54
Gender (n, %)		
Male	15 (29)	35 (65)
Female	39 (71)	19 (35)
Age (mean, SD)	55 (12)	62 (11)
Race (n, %)		
Caucasian	49 (91)	43 (80)
Non-Caucasian	5 (9)	11 (20)
Marital status		
Married (n, %)	38 (73)	38 (70)
Cohabitating or significant other	16 (27)	16 (27)
Educational level (n, %)		
Less than high school	2 (4)	3 (6)
Completed high school	15 (28)	31 (58)
College	37 (68)	15 (28)
Employed (n, %)	23 (43)	13 (24)
Diagnosis	–	
Hepatocellular or Cholangio Carcinoma	–	36 (67)
Colorectal with liver metastases	–	6 (11)
Other	–	12 (22)
Treatment	–	
Regional chemo/90Y (radiation)	–	41 (76)
Radiofrequency ablation/resection	–	13 (24)

Table 2 Kendall's Tau-c coefficients for patients and caregivers at each time point

PSQI component	Time 1	Time 2	Time 3	Time 4
Global sleep quality	.18	−.25	.12	.31
Duration	.28**	.27	.11	.15
Daytime dysfunction	−.05	.12	−.17	.02
Latency	.01	−.24	−.12	−.11
Disturbance	−.02	−.03	.18	.12

*$p < .05$; **$p < .01$; ***$p < .001$

Table 3 Model fit indices for Figs. 1, 2, 3 and 4

PSQI component	χ^2	SRMSR	CFI
Global sleep quality	141.44, $df = 28$, $p < .001$	.019	.98
Duration	105.90, $df = 28$, $p < .001$	.064	.92
Latency	118.38, $df = 28$, $p < .001$	.048	.93
Disturbance	67.34, $df = 28$, $p = .013$	.012	.95

Sleep of Spousal or Intimate Partner Caregivers

Caregivers reported on average sleeping 6.0 h per night (SD = 2.1; range 1–9 h) and a mean sleep latency of 24 min (SD = 21.8); 27% reported a sleep latency of greater than 30 min. Thirty percent of family caregivers reported using a sleep aid in the last week and 22% of caregivers reported using a sleep aid more than 3 times per week. Caregivers reported a mean sleep efficiency of 83%.

Concordance between cancer patients and spousal/intimate partner caregivers sleep problems

Kendall's tau-c was performed to examine the concordance between 54 patient and family caregivers with regard to the components of the PSQI. Patient and intimate partner sleep duration were significantly related (Kendall's tau-c = 0.301, $p = 0.02$). The patient and intimate partner agreement for the PSQI Daytime Dysfunction was not significant (Kendall's tau-c = 0.027, $p = 0.86$). The patient and intimate partners' sleep latency also was not significantly related at diagnosis (Kendall's tau-c = 0.115, $p = 0.458$), however, patients and intimate partner had approximately the same latency (patients 29.9; SD = 25.9 min and = 24.0; SD = 21.8 min). The use of medication between the patients and intimate partner was not significant (Kendall's tau-c = 0.182, $p = 0.119$). A total of 30% of intimate partner reported using a sleep aid within the last week and 22% of intimate partner reported using a sleep aid more than 3 times per week (Table 2).

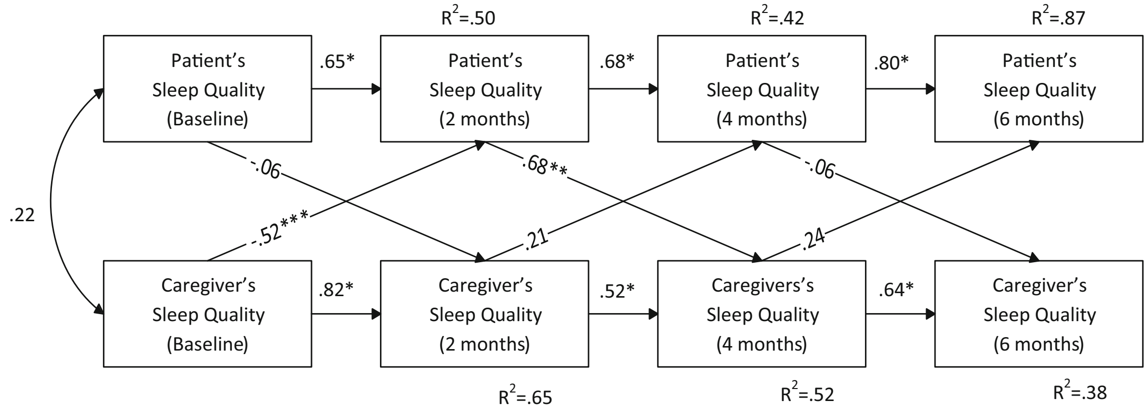

Fig. 1 Cross-lagged panel analyses of patient and caregiver sleep quality

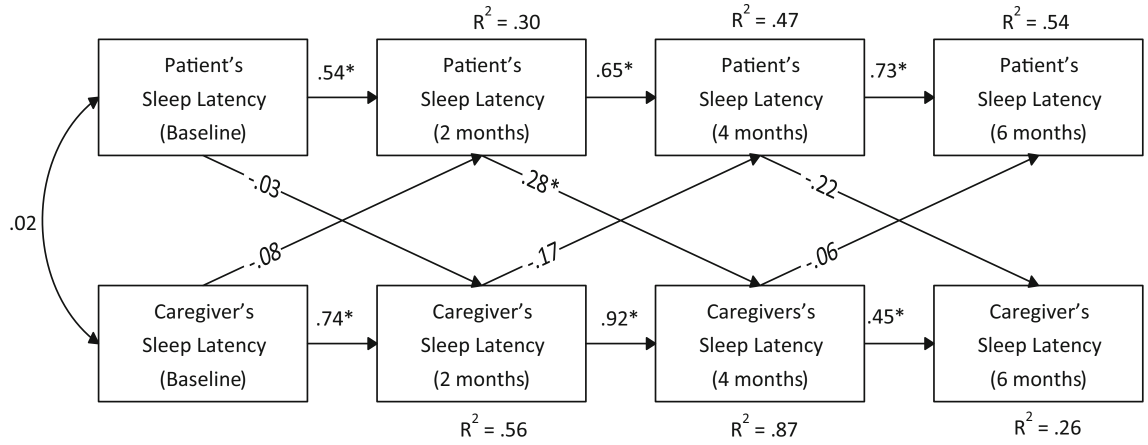

Fig. 2 Cross-lagged panel analyses of patient and caregiver sleep latency

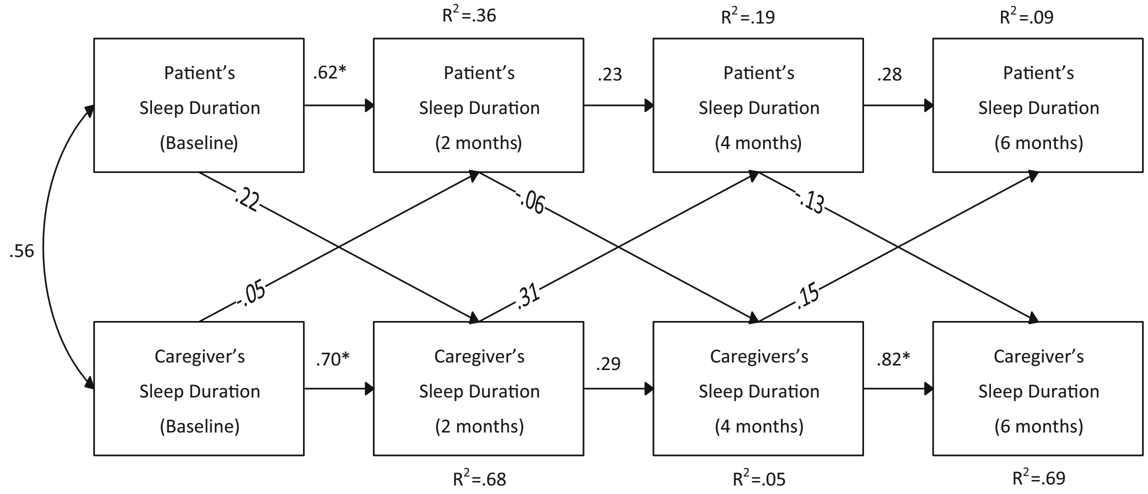

Fig. 3 Cross-lagged panel analyses of patient and caregiver sleep duration

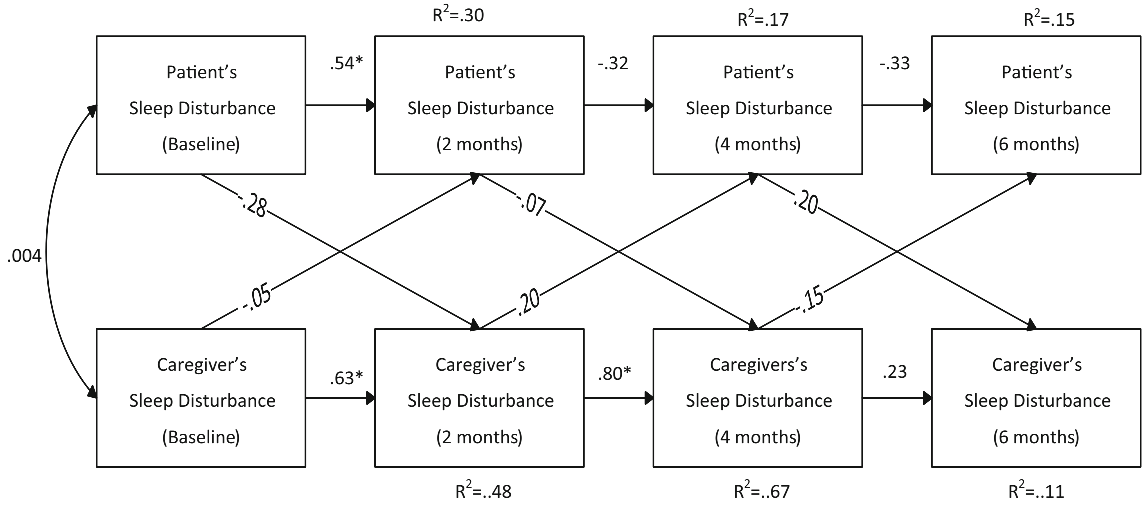

Fig. 4 Cross-lagged panel analyses of patient and caregiver sleep disturbance

Patients' and caregivers' sleep problems: who is disturbing whom?

Using cross-lagged panel analyses, partners' sleep quality significantly predicted patients' sleep quality (r = 0.52, $p < 0.001$) from baseline to the 2-month evaluation; patients' sleep quality then significantly predicted partners' sleep quality from the 2 months to the 4-month evaluation (r = 0.68, $p = 0.01$). Similarly, patients' sleep latency significantly predicted partners' sleep latency from 2 to 4 months (r = 0.28, $p = 0.05$). Although sleep duration was highly correlated between patients and partners between baseline to 6-months, neither patients' nor partners' sleep duration significantly predicted the other's (Table 3 and Figs. 1, 2, 3, 4).

Sleep and depression

No significant relationships were found between the caregivers' sleep parameters on the PSQI and depression. Sleep duration [F(1,26) = 0.646, $p = 0.533$], sleep latency [F(1,25) = 1.824, $p = 0.184$], and sleep quality [F(1,26) = 0.681, $p = 0.573$] were not related to depressive symptoms.

Similarly, we did not observe significant relationships between sleep duration [F(1,19) = 1.543, $p = 0.242$], sleep latency [F(1,18) = 0.546, $p = 0.590$], or sleep quality [F(1,19) = 0.715, $p = 0.557$] and depressive symptoms in the advanced cancer patients.

Discussion

Consistent with previous studies(Carter & Chang, 2000; Carter, 2006; McCurry et al., 2007; Nijboer et al., 1999), our study found that sleep problems, such as poor sleep quality and short sleep duration, were common among cancer patients and their intimate partner caregivers. We observed short sleep duration for patients and caregivers that is less than the recommended 7 h per night of sleep (Hirshkowitz et al., 2015). Further, since self-report often overestimates the duration of sleep compared to actigraphy (Lauderdale et al., 2008), the hours of sleep estimated by patients and caregivers in this study are likely overestimated. Inconsistent with prior research, intimate partner caregivers had shorter sleep duration, longer sleep latency, and poorer sleep efficiency compared to their loved ones diagnosed with cancer (Carney et al., 2011). Additionally, cancer caregivers reported a higher frequency of using sleep aids.

Poor sleep in patients with cancer has been increasingly tied to increased risk of psychological symptoms and mortality. For instance, Palesh has recently found a link between sleep efficiency and increased mortality in a sample of patients diagnosed with breast cancer (Kakizaki et al., 2008; Palesh et al., 2014). We also found a curvilinear relationship between sleep duration and mortality. Further studies are needed to examine whether treatment of sleep problems improves symptoms and survival in the context of cancer (Collins et al., 2017).

Similarly, sleep problems in cancer caregivers should not be neglected and will need further investigation as they may explain caregivers' increased risk of CVD. Several large epidemiological studies have shown a link between caregiving and increased risk for CVD (Ji et al., 2012; Lee et al., 2003; Schulz & Beach, 1999), but the mechanisms underlying this link have not been elucidated. A recent meta-analysis found that insomnia is associated with a 45% increased risk of developing and dying from CVD (Cappuccio et al., 2011). Risk factors for CVD also include metabolic abnormalities (e.g., low high-density lipoprotein and high levels of triglycerides and glucose levels) (Cappuccio et al., 2011) and sleep problems are precisely found to be one of the significant predictors of the development of metabolic abnormalities (Gottlieb et al., 2005, 2006; Troxel et al., 2010). Sleep fragmentation, poor sleep efficiency and quality, and insomnia have been associated with increased risk of developing metabolic syndrome, diabetes, and CVD in the general population (Fernandez-Mendoza et al., 2012; Mullington et al., 2009; Vgontzas et al., 2009). Thus, sleep problems may be one pathway that links caregiving and development of the CVD.

Prior research has investigated demographic, genetics, and psychosocial predictors of poor caregiver sleep quality. Few studies have addressed whether partners affect each other's sleep quality. For example, a cross-sectional study of cancer caregivers found less functional coping, mastery, neuroticism, and depression predicted sleep problems(Carter, 2006), and a longitudinal study of cancer patients and caregivers identified age and genotype as predictors of both baseline sleep disturbances and subsequent trajectories(Miaskowski et al., 2010). A study on Parkinson's disease patients and their caregiving partners also found a relationship between spouses' and patients' self-perceived sleep, but this cross-sectional study could not address directionality (Happe & Berger, 2002). Few studies have assessed sleep over time, particularly in dyads. We found agreements between patients and family caregivers in sleep quality, sleep duration, sleep latency and the use of sleep aids. Although limited, we observed some bidirectional relationships between patients' and caregivers' sleep patterns. One of the partner's sleep quality and sleep latency predicted the other partners at 2 months' intervals. This suggests that if one of the partners has sleep disturbance, the other partner is affected.

Although the current study has provided insight to cancer patients and caregivers' sleep problems and bidirectional association, there are several potential limitations. First, the sample size is small, but the study begins to show trends that may be important for future study. Second, we collected only self-reported sleep data, which might underestimate sleep disturbance compared to actigraphy. Third, the patients in this study were diagnosed with advanced cancers (stage III and IV) and were primarily male and Caucasian. A more diverse sample with regard to types and stages of cancer, gender, and race is recommended.

Even with the acknowledged limitations, this study presents pragmatic implications for future sleep research on cancer patients and caregivers. To our knowledge, this is the first prospective study examining the link between cancer patients and their caregivers' sleep problems. Specifically, it investigated four different major parameters of sleep and followed up for 6 months to explore the relationship of each of them between cancer patients and their caregivers, which provided sufficient evidence on the similar sleep patterns and bi-directional relationship. In addition, this study is an important supplement to the cancer caregiver sleep research.

The results from the current study together with the findings discussed above suggest that clinical trials testing dyadic sleep interventions are warranted. Targeted interventions may improve sleep and mental health outcomes on a short-term basis and serve as a prevention tool for reducing the risk of long-term poor mental and physical health outcomes in cancer patients and intimate partner caregivers.

We believe that there are at least two directions for future research. First, effective interventions specifically targeted to cancer patients and caregivers are warranted to help improve outcomes. There are only a few options for treatment for cancer patient population and their caregivers. In our study, we found that caregivers use sleep aids to minimize the negative effects of sleep problem, but sleep aids' sedative effects impact the caregiver's ability to respond to the needs of the patient during the night (Carter, 2003). Treatment of the intimate partners sleep problems, either through the downstream treatment of the patient or dyadic treatment, may improve sleep, quality of life, and potentially the health of the caregiver. Currently, cognitive behavioral therapy is widely applied to treating sleep disorders with cancer patients and that can significantly improve subjective sleep outcomes in patients with cancer (Garland et al., 2014). Mindfulness-based stress reduction was also tested as a sleep intervention to treat cancer patient (Carlson et al., 2016; Shapiro et al., 2003). A multi model psychological sleep management program combining relaxation techniques, sleep hygiene, cognitive techniques, and advice in stimulus control technique was found effective in enhancing various sleep parameters and well-being of cancer patients (Simeit et al., 2004). There are even fewer studies discussed sleep intervention for cancer caregivers. However, dyadic treatment of sleep, rather than individual treatment with either the cancer patient or caregiver, could potentially establish a more sustainable, healthy sleep pattern based on our study result that one of the partner's sleep problem will affect the other. Studies also found the sleep of partners has been shown to improve when the identified person with sleep problems was treated (McArdle et al., 2001).

Second, prospective studies with more racially diverse samples, longer follow up, and use of actigraphy are warranted to further confirm the reliability and validity of the bidirectional relationship in sleep patterns between cancer patients and caregivers. Prior studies found that the sleep of partners improves when the identified person with sleep problems was treated; however, not all parameters of sleep show improvement (McArdle et al., 2001). Further research is needed to understand the sleep patterns of cancer patients and their intimate partners to develop effective dyadic sleep interventions. Given that some of the correlations and nuanced changes in sleep patterns are not easy to detect, a design with more precise and objective measurements looking at sleep at a micro level will allow for more sophisticated analyses. A recent study found couples had higher concordance in sleep–wake patterns throughout the night using actigraphy to measure minute-by-minute sleep for 10 days (Gunn et al., 2015). This method could be one possibility to further explore the dyadic sleep pattern in the future.

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Compliance with ethical standards

Conflict of interest Qi Chen, Lauren Terhorst, Amy Lowery-Allison, Hannah Cheng, Allan Tsung, Mikhaila Layshock, Daniel J. Buysse, David A. Geller, James W. Marsh, Yisi Wang and Jennifer L. Steel declare that they do not have conflict of interest.

Human and animal rights and Informed consent All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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